New Aspects of Excimer Laser Coronary Angioplasty
Physical aspects and clinical results

Front cover : Homogeneous light distribution at the tip of a 1.6 mm modified laser catheter (thermographic image)

Back cover : "Lang, héél lang geleden..."
Melody Hamburger, December, 1998

Additional financial support for publication of this thesis was generously provided by:
Arrow bv, Biosense, Boston Scientific Corporation, Cordis Johnson & Johnson Med bv, DATA Scope, Eli Lilly Nederland, Endosonics bv, Guidant Nederland bv, Jomed Netherlands bv, Medinol Ltd, Medtronic bv, Novoste Europe sa/nv, Revolving fund, Sorbo fonds, Spectranetics bv, St. Jude Medical, TD Medical bv, Terumo Europe nv

ISBN 90-73235-27-8
Printed by Optima Grafische Communicatie, Rotterdam

New Aspects of Excimer Laser Coronary Angioplasty Physical aspects and clinical results

Nieuwe aspecten van excimer laser coronaire angioplastiek Fysische aspecten en klinische resultaten

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. dr P.W.C. Akkermans M.A.
en volgens Besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
3 september 1999 om 13.30 uur

door

Jaap Nico Hamburger

geboren te Amsterdam

PROMOTIECOMMISSIE

PROMOTOR	:	Prof. dr P.W. Serruys
OVERIGE LEDEN	:	Prof. dr M.B. Leon Prof. dr ir N. Bom Prof. dr P.D. Verdouw Prof. dr R. Beyar Prof. dr J.R.T.C. Roelandt
CO-PROMOTORES	:	dr P.J. de Feyter dr ir G.H.M. Gijsbers

At the Yad Vashem holocaust memorial in Jerusalem it is written,

"Remembrance is the secret of redemption. Forgetfulness leads to exile"

(Baal Shem Tov, 1698-1760).

Therefore, this thesis is dedicated to memory of
alov ha-shalom Jaap, Nico and Martha Bolle

CONTENTS

Introduction and overview of the thesis

INTRODUCTION AND OVERVIEW OF THE THESIS

Cardiac death is the leading cause of mortality in the Western world. The major contributor to cardiac death is coronary artery disease.[1-3] Coronary atherosclerosis is a chronic disease of the vessel wall of the artery, resulting in a progressive narrowing of its lumen.[4] The advancing process of luminal narrowing is responsible for a progressive diminution of blood flow to the myocardium, resulting in a myocardial perfusion defect with subsequently, a reduction in cellular oxygenation. Myocardial ischemia, through a not yet fully explained mechanism, is usually the cause of a significant (typically exercise induced) discomfort, known as angina pectoris. The final stage in the progression of coronary artery disease is a complete interruption of blood flow to the myocardium. The interruption can also occur suddenly, as a result of atherosclerotic plaque rupture and/or blood clot formation.[5,6] Unless restored promptly, the absence of antegrade blood flow will lead to tissue necrosis, or in other words, myocardial infarction. It is usually the ensuing electrical instability of the myocardium that is related with cardiac sudden death.[7,8] Whatever the cause of the interruption of the coronary blood flow may be, in due time nature finds a way around: small vascular branches connect the coronary artery distal to the closure with the other, (non-diseased) coronary arteries. These connections, or collaterals, allow for a limited perfusion of the myocardial segment distal to the closure of the parent coronary artery. In a teleological sense, one could argue that these collaterals - given their limited capacity - succeed in supplying the myocardium just enough to keep it "alive and suffering" (Fig 1A,B). It is the patient with this very condition - a total blockage of a coronary artery, a partly "undernourished" myocardium and angina pectoris during physical activity – who plays a central role in the current thesis.

What are the options for this patient? We could chemically reduce the activity of the heart muscle, thereby reducing its oxygen demand and subsequently the patient will not have his/her chest discomfort too often.[9] In other words, we keep the patient on medication for the remainder of his life. Another option is to refer the patient to the cardiac surgeon, who will open the patient's chest and leg in order to trans-

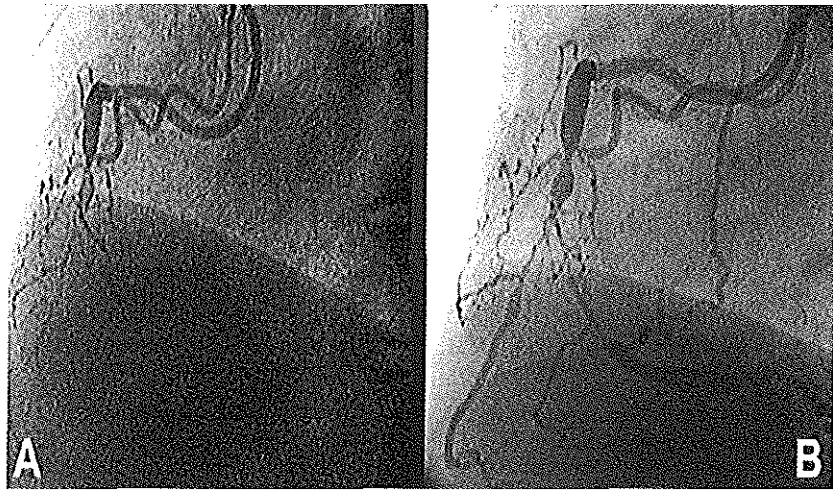


Figure 1 Total occlusion of a right coronary artery. A left Amplatz guiding catheter is positioned in the ostium of the right coronary artery and a 7 French diagnostic catheter in the ostium of the left coronary artery. A. Antegrade injection showing the occlusion stump B. Bilateral simultaneous injection of contrast medium, showing the occlusion stump (antegrade flow) and the distal parent lumen through both bridging and contralateral collateral branches (retrograde flow).

plant a vein from the leg to the heart, thus bypassing the problem.[10] If however we wish to deal with the heart of the matter, we should try to open the blockage in an attempt to restore the blood flow through the original channel. Three questions are of importance in this matter. First, is it technically feasible to recanalize a chronic total coronary occlusion? Second, if technically possible, can we expect a clinical benefit from reopening a blood vessel which supplies a potentially damaged myocardial area and third, if there is a clinical benefit, how does this compare to the results achieved with conservative (medical) therapy? These questioned will be addressed in detail in Part II of this thesis.

XeCl-Excimer Laser Technology

In a mechanistic approach to coronary artery disease, there are two basic options. First, there is a "classical" approach in which the obstructing material is pushed aside, for instance by using dilatation balloons and/or intra-coronary stents.[11-15] Within several years of its introduction, balloon dilation developed into a reliable, non-surgical technique with acute success rates well over 90%. However, a limiting factor to a lasting result was the phenomenon of restenosis, a healing response of the vessel wall occurring four to six months after treatment in approximately 40% of patients. The necessity of reducing restenosis rates was the rationale for a second strategy: the development of new devices designed to enlarge the vessel lumen by removing the obstructing material.[16-18] One of these new techniques for tissue removal (or atherectomy) was XeCl-excimer laser coronary angioplasty

(ELCA). A decade has passed since the introduction of ELCA in the arena of interventional cardiology. During this time, many patients - often with complex coronary artery disease - have been treated with this therapeutic modality.[19-30] The publication of the results from the U.S. ELCA Registry,[24] the European Registry[25] and the randomized AMRO trial,[26] allowed for an initial evaluation of the clinical ELCA experience. Although the earlier reports mainly emphasized favorable acute results, a general impression emerged that ELCA was associated with coronary dissection, early recoil and restenosis rates at least as high as those following balloon angioplasty.[21,27-28] As initial expectations were based on the results of "free beam in air experiments" (using a free laser beam focussed by a set of mirrors to ablate dry tissue samples),[31] the somewhat disappointing clinical results were not fully understood. Therefore, it was of paramount importance to achieve a better understanding of basic excimer laser - tissue interactions in fluids, and to use this knowledge in an attempt to improve the safety and efficacy of laser atherectomy. Geert HM Gijsbers, PhD and Anton van Leeuwen, PhD, at the University Hospital of Utrecht, The Netherlands, did much of the original work in the field of physical mechanisms in excimer laser-tissue interaction. From their pioneering work it emerged that the basic mechanism responsible for tissue removal is a combination of photochemical dissociation of organic molecules and vaporization of tissue water.[32,33] At an early stage, it was recognized that these phenomena could be responsible for the efficacy of ELCA, but most likely were responsible for the negative side effects (e.g. dissection, acute closure, and perforation) as well. In an effort to apply insights acquired in the experimental laboratory to a clinical setting, we touched upon a third physical phenomenon which stood at the basis of much of the work reported in this thesis: the influence of the configuration of a laser catheter on the efficacy and quality of tissue ablation.[34]

This Thesis

This thesis consists of two parts. In the first, the concept of XeCl-excimer laser tissue ablation is described, based on the results of experiments performed between January, 1991 and December, 1997. From these experiments it emerged, that tissue irradiation by UV photons resulted in the formation of insoluble gas due to photochemical dissociation of molecular bonds in lipids. It was calculated, that photochemical dissociation accounted for less than 10% of the applied photon energy (see: Chapter 5). It was therefore assumed that the majority of photon energy was

either reflected, or transformed into heat. It has been shown that thermal accumulation is responsible for the formation of rapidly expanding and imploding water vapor bubbles and pressure waves after each laser pulse. The density of water vapor is 0.81 kg/m^3, which translates to 1235 liter vapor per liter of vaporized water. As a result, the evaporation of tissue, which consists for approximately 70% of water, leads to an increase of volume by a factor of 1235 x 0.7=864. Likewise, the photochemical dissociation of lipids will further add to volume expansion. It is therefore likely, that tissue ablation is a result of forceful tissue disruption due to volume expansion in addition to evaporation and photochemical dissociation. This combined mechanism is reflected in the histology of tissue samples (Chapter 2), with the occurrence of lobes (incomplete tissue removal), splits and vacuoles. Van Leeuwen et al. demonstrated this phenomenon to be responsible for the induction of deep injury of the vessel wall, with dissection of the media.[33] Of importance, was our finding that the extent of these events was related to the fluence (or energy density) at the tip of a laser catheter. Increasing the fluence at the catheter tip resulted in the removal of more tissue. However, a higher fluence also gave rise to higher insoluble gas yields and larger water vapor bubbles, which in turn resulted in an increase in mechanical damage to surrounding

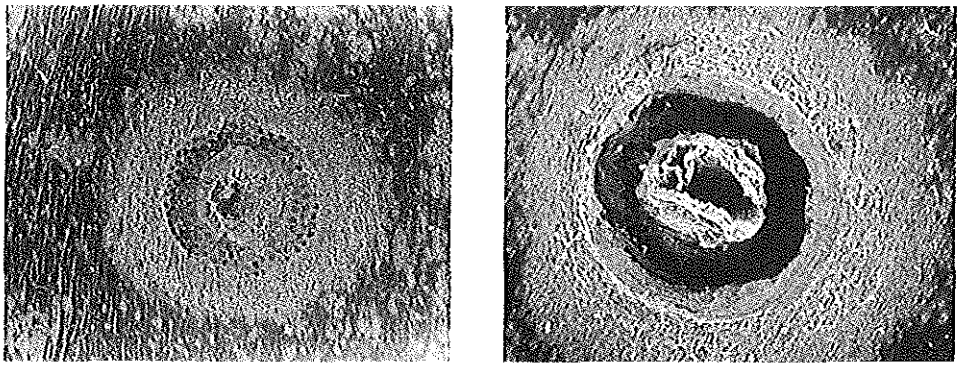


***Figure 2** A. Scanning electron micrograph of a lesion after 50 laser pulses at a fluence of 45 mJ/mm^2 and a pulse repetition rate of 25 Hz . The porcine aortic tissue sample was immersed in saline (0.9 NaCl). A pressure equivalent of 10 grams was exerted on the catheter tip during ablation. Note that the tissue in front of the catheter tip is only partially ablated ("Swiss cheese phenomenon"). B. Scanning electron micrograph of a lesion after 50 laser pulses at a fluence of 60 mJ/mm2 and a pulse repetition rate of 25 Hz . The porcine aortic tissue tissue sample was immersed in saline (0.9 NaCl). A pressure equivalent of 10 grams was exerted on the catheter tip during ablation. Ablation at a high fluence resulted in a more thorough removal of tissue, but also in more damage to the surrounding endothelium.*

(non-ablated) tissue (Fig 2A,B). Also, we learned to appreciate the influence of the composition of the experimental fluid medium on ablation efficacy and quality.[35] Absorption of UV light by hemoglobin resulted in a marked decrease in ablation efficacy. The interaction of UV light with iodide containing radiographic contrast media resulted in a marked increase in collateral tissue damage, while replacement of fluid media by a CO_2 flush resulted in histology qualities comparable to the results of earlier "free-beam-in-air experiments" (Fig 3). The results from these experiments compared well with those achieved in other studies, using a saline flush method.[36,37] Consequently, the saline flush method is systematically applied during ELCA procedures. As it was hypothesized that a decrease in mechanical strain of the vessel wall would improve clinical results, the aim was to find ways of increasing the system's ablation efficacy in order to allow for ablation at lower energy densities.

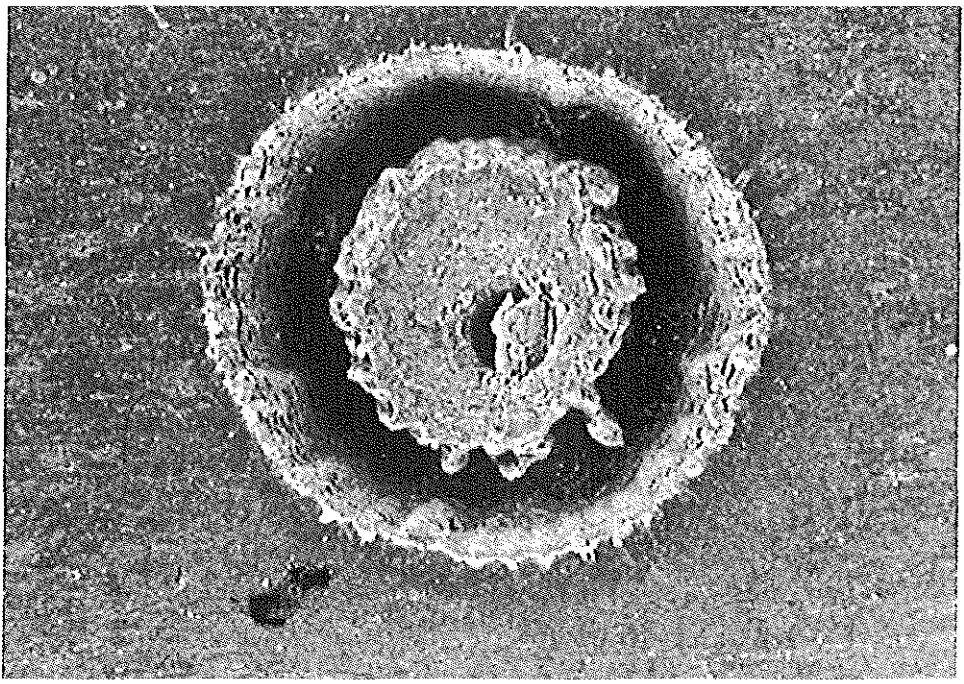


Figure 3 *Scanning electron micrograph of a lesion after 50 laser pulses at a fluence of 60 mJ/mm² and a pulse repetition rate of 25 Hz. The porcine aortic tissue tissue sample was pierced by a 0.014" guide wire to facilitate the laser catheter movement and immersed in CO_2 gas. A pressure equivalent of 10 grams was exerted on the catheter tip during ablation. Note the relative absence of damage to the surrounding endothelium.*

The efforts to achieve this goal focussed on three strategies. A limitation of ablation efficacy could be the result of a catheter advancement speed beyond its capacity to ablate tissue. Therefore, in a series of experiments we evaluated the speed of tissue removal for different sets of laser parameters. These experiments led to the development of an automated catheter advancement device (AcAD, see Chapter 3). Spectranetics International, a US based excimer laser manufacturer, followed-up on this concept by designing a catheter advancement device suitable for clinical use. A description of the Spectranetics motorized advancement device is given in Appendix 1.

Second, the transport of light from the laser into the human body is based on multifiber technology: a large number of small, flexible silica fibers grouped together into one catheter. The distance between the individual fibers inside a catheter is such that the light coming from the individual fibers does not overlap at the catheter - tissue interface. For this reason, each individual fiber acts as a single source of laser energy. Subsequently, any tissue situated in between individual fibers would not be directly ablated. Therefore, we evaluated the possibility of improving ablation efficacy by increasing the number of silica fibers within one laser catheter. Again, this concept was implemented by the industry, through the clinical introduction of the so-called High-Density catheter (see Chapter 4). Finally, as the ablation efficacy of a multifiber catheter is limited by the presence of a non-light emitting area at the catheter tip ("dead space") we evaluated the possibility of ablation at significantly reduced energy densities by completely eliminating catheter tip dead space. The ensuing concept of homogeneous light distribution (HLD, Chapter 5 and Appendix 2) however, has not (yet?) been implemented in the clinical arena.

The second part of this thesis provides the clinical experience with excimer laser coronary angioplasty at the Rotterdam Thoraxcenter as of August 1993. The emphasis was on the experience with the Spectranetics laser guidewire for percutaneous treatment of patients with myocardial ischemia due to chronic total coronary occlusion. The technique of the laser guidewire procedure is described (Chapter 6), signs of early left ventricular functional recovery following successful laser recanalization (Chapter 7), the acute results of registries performed in our center (Chapter 8), Europe (Chapter 9) and the United States (Chapter 10), as well as the final outcome of a European randomized trial (Chapter 11). All patients treated with the laser guidewire at the Rotterdam Heartcenter had clinical follow-up for a period of up to five years,

the results of which are described in Chapter 12. Finally, we described the results of the use of excimer laser for the treatment of patients with diffuse intra stent restenosis (Chapter 13).

The hypotheses in this thesis were

1. Damaging side-effects during excimer laser coronary angioplasty are related to intrinsic mechanisms of excimer laser tissue ablation
2. Optimization of excimer laser coronary angioplasty can be achieved by elimination of UV-absorbing media, reduction of catheter advancement speeds and by reduction of the non-light emitting area at the tip of a laser catheter
3. Percutaneous recanalization of chronic total coronary occlusions by using laser guidewire is feasible and safe
4. Revascularization therapy is superior to medical therapy in patients with chronic total coronary artery occlusions

SUMMARY OF THE INDIVIDUAL CHAPTERS:

PART I

In PART I, "Physical aspects of excimer laser-tissue interaction", we describe some of the studies performed at the Laser Laboratory Thoraxcenter.

Chapter 1

"Excimer laser coronary angioplasty: A physical perspective to clinical results" contains the findings from our early experimental work, initiated at the Laser Center of the Academic Medical Center Amsterdam, under guidance of Prof. MJC van Gemert. The chapter provides an introduction to some physical mechanisms responsible for excimer laser - tissue interaction, the influence of UV absorption by hemoglobin on ablation efficacy and it contains the first description of the concept of homogeneous light distribution.

Chapter 2

"Method for the assessment of ablation performance: a novel technique for direct evaluation of *in vitro* excimer laser tissue ablation" describes a methodology for on-line evaluation of tissue samples used for excimer laser experiments. The method introduces a practical alternative for time and resource consuming standard histology of a large series of tissue samples. The method was designed by the Laser Laboratory of the Thoraxcenter Rotterdam in cooperation with the department of Pathology of the medical faculty at the Erasmus University, Rotterdam.

Chapter 3

"The usefulness of slow-speed automated catheter advancement for optimization of excimer laser-tissue debulking" provides the results of experiments per-

formed to assess the speed of ablation by using standard laser catheters and laser parameters typical for ELCA. This is the first study in which the speed of ablation - under those conditions typical for ELCA - is quantified. Of importance, was the finding that for typical ELCA parameters (50-60mJ/mm^2, 25 Hz pulse repetition rate) optimal ablation was achieved at a catheter advancement speed of no more than 0.06 mm/s. The outcome of this study provided the platform for the development of an automated catheter advancement device.

Chapter 4

"Ablation properties of a new 2.0 mm high density excimer laser catheter for coronary angioplasty." This chapter contains the results of the *in vitro* evaluation of a new type of catheter technology, the "high density catheter (HD catheter)". As compared to experiments with conventional catheters, the use of the HD catheter resulted in more efficient tissue removal. In these experiments it was possible to increase the catheter advancement speed to values higher than 0.06 mm/s by increasing the pulse repetition rate to 40 Hz or 80 Hz. However, the volumes of insoluble gas as measured under *in vitro* conditions of optimal ablation, could prove to be inhibitive in a clinical setting. This *in vitro* study preceded the clinical introduction of the HD catheter at the Rotterdam Thoraxcenter.

Chapter 5

"The influence of homogeneous light distribution on excimer laser ablation of vascular tissue" concludes the first part of this thesis. In this chapter we discuss the relation between energy density at the tip of a laser catheter and the physical phenomena which occur during tissue ablation. As a homogeneous light distribution at the catheter tip increases its ablation efficacy, tissue could be ablated at lower energy densities. As a result, less adjacent tissue trauma occurred. However, it perspired that ablation with HLD at low energy densities and slow device advancement speeds resulted in significant tissue temperature rises, which could negatively influence clinical results.

PART II

In PART II, "Clinical aspects of excimer laser coronary angioplasty", we describe our clinical experience with excimer laser coronary angioplasty in the 1993-1998 period. This part of the thesis contains both the Thoraxcenter Rotterdam single-center experience, as well as results of international, multicenter studies in which the Thoraxcenter participated. The emphasis is in particular on the experience with the Spectranetics laser guidewire for recanalization of chronic total coronary occlusions.

Chapter 6

"Laser guidewire for recanalization of chronic total occlusions" provides a technical introduction to the laser guidewire procedure. The technique of this procedure evolved as a result of an effort to further the feasibility of percutaneous techniques for revascularization of coronary chronic occlusions.

Chapter 7

"Early recovery of wall motion abnormalities after recanalization of chronic totally occluded coronary arteries: a dobutamine-atropine stress echocardiographic prospective single center experience" is the first dobutamine stress echocardiography study to report improvement of left ventricular function within 48 hours after successful recanalization of chronic total coronary occlusions. Surprisingly, we found a significant improvement of the contralateral myocardial area in addition to an improvement of the myocardial area supplied by the recanalized coronary artery.

Chapter 8

"Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study" was the first publication in the literature of a consecutive series of patients with laser guidewire facilitated recanalization of chronic total occlusions.

Chapter 9

"Recanalization of total coronary occlusions using a laser guide wire: The European TOTAL Surveillance Study" is the report on the final results of the European TOTAL Surveillance Study, in which 345 patients were treated with the laser guidewire. In this study - as well as in the US registry, described in the next Chapter -, the advantage of the use of the laser guidewire in those coronary occlusions refractory for conventional guidewires was clearly demonstrated.

Chapter 10

"Laser wire for crossing chronic total occlusions - 'Learning phase' results from the U.S. TOTAL Trial" is the report on the final results of the US TOTAL Surveillance Study. The author of this thesis participated as co-operator in eight of the participating clinical sites and as co-author of the manuscript.

Chapter 11

"Total Occlusion Trial with Angioplasty by using Laser guidewire: the TOTAL Trial" is the report on the final results of a European multicenter randomized trial, evaluating the safety and efficacy of the laser guidewire as compared to conventional guidewires. This study confirmed the safety and feasibility of the laser guidewire procedure.

Although the results of the registries described in the previous two chapters suggested an advantage of the laser guidewire over conventional guidewires, this advantage was not sustained in the randomized TOTAL trial.

Chapter 12

"Recanalization of chronic total coronary occlusions using a laser guidewire: long-term follow-up" provides the long-term follow-up (range 12 – 54 months) of patients with chronic total coronary occlusions either successfully revascularized (percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or medically treated. There was a significant difference in the occurrence of serious adverse events at clinical follow-up in favor of those patients successfully revascularized.

Chapter 13

"Six-month outcome after excimer laser coronary angioplasty for diffuse in-stent restenosis: a single center experience" is a chapter in which we report patients who had excimer laser coronary angioplasty for treatment of diffuse in-stent restenosis. The exceptional length of the treated segments is reflected in the relative lack of response to therapy.

Chapter 14

"Conclusions." In this chapter the results of this thesis are summarized and discussed. Some areas for future research are indicated.

Appendix 1

"Spectranetics Catheter Advancement Device (CAD), a device description" is an industrial description of a device which was developed following the results of experiments described in Chapter 4.

Appendix 2

"Methode voor het verkrijgen van een homogene lichtdistributie (HLD) bij intravasculaire bestraling met laserlicht, alsmede daarbij te gebruiken lasercatheter, en werkwijze voor het vervaardigen daarvan" is the original text of the Dutch patent application no. 9300064 concerning the concept of homogeneous light distribution.

REFERENCES

1. Hart en Vaatziekten in Nederland 1998. Cijfers over ziekte en sterfte. Uitgave van de Nederlandse Hartstichting
2. American Heart Association Cardiovascular Disease Statistics, 1998
3. Stone NJ. The clinical and economic significance of atherosclerosis. *Am J Med* 1996;101(4A):4A6S-9S
4. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, Rosenfeld ME, Schwartz CJ, Wagner

WD, Wissler RW. A defenition of advanced atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1995;92(5):1355-74

5. Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, Cheseboro JH. Atherosclerotic plaque rupture and thrombosis. Evolving concepts. *Circulation,* 1990;82(3 Suppl):1147-59
6. Cheseboro JH, Rauch U, Fuster V, Badimon JJ. Pathogenesis of thrombosis in coronary artery disease. *Haemostasis,* 1997;27 (Suppl)1:12-8
7. Mehta D, Curwin J, Gomes JA, Fuster V. Sudden death in coronary artery disease: acute ischemia versus myocardial substrate. *Circulation* 1997;96(9):3215-23
8. Hurwitz JL, Josephson ME. Sudden cardiac death in patients with chronic coronary heart disease. *Circulation* 1995;85(1 Suppl):143-9
9. Leon MB, Rosing DR, Bonow RO, Epstein SE. Combination therapy with calcium-channel blockers and beta blockers for chronic stable angina pectoris. *Am J Cardiol* 1985; 55(3):69B-80B
10. Favaloro R. Critical analysis of coronary artery bypass graft surgery: a 30-year journey. *J Am Coll Cardiol* 1998;31(4 Suppl B)1B-63B
11. Grüntzig AR, Senning A, Segenthale WE. Nonoperative dilatation of coronary artery stenosis: percutaneous transluminal angioplasty. *N Engl J Med* 1979;301:61-68
12. Serruys PW, de Jaegere P, Kiemeney F, Macaya C, Rutsch W, Heyndrikx G, Emanuelson H, Morco J, Legrand V, Materne P, Belardi MA, for the BENESTENT Study Group. A comparison of balloon expandable-stent implantation with balloon angioplasty in patients with coronary artery disease: Benestent Study Group. *N Engl Med J* 1994;331:489-95
13. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Deter K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shacknovich A, Hirschfeld J, Bailey S, Ellis S, Rake R, Goldberg S, for the Stent Restenosis Study Investigators. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease: Stent Restenosis Study Investigators. *N Engl Med J* 1994;331:496-501
14. Serruys PW, Sousa E, Belardi J, Nobuyoshi M, Probst P, Gulba DC, Brachmann J, Almagor Y, Bos HS,

van den Heuvel P. BENESTENT-II trial: subgroup analysis of patients assigned either to angiographic or clinical follow-up or clinical follow-up alone. *Circulation* 1997;96 (Suppl I): I-653

15. Versaci F, Gaspardone A, Tomai F, Crea F, Chiarello L, Gioffrè P. A comparison of coronary artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *New Engl J Med* 1997;336: 817-22
16. Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, Lansky AJ, Popma JJ, Kuntz RE. Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). *Circulation* 1997;3; 97(4):309-11
17. Simonton CA, Leon MB, Baim DS, Hinohara T, Kent KM, Bersin RM, Wilson BH, Mintz GS, Fitzgerald PJ, Yock PG, Popma JJ, Ho KK, Cutlip DE, Senerchia C, Kuntz RE. Optimal directional atherectomy: final results of the Optimal Atherectomy Restenosis Study (OARS). *Circulation* 1997;97(4):332-9
18. Reisman M, Harms V, Whitlow P, Feldman T, Fortuna R, Buchbinder M. Comparison of early and recent results with rotational atherectomy. *J Am Coll Cardiol* 1997;29(2):353-7
19. Litvack F, Grundfest W, Eigler N, Tsoi D, Goldenberg T, Laudenslager J, Forrester J, Percutaneous excimer laser coronary angioplasty. *Lancet* 1989;2(8654):102-103 (letter)
20. Reeder GS, Bresnahan JF, Holmes DR, Litvack F. Excimer laser coronary angioplasty: results in restenosis versus de novo coronary lesions. Excimer Laser Coronary Angioplasty Investigators. *Cathet Cardiovasc Diagn* 1992; 25:195-199
21. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser angioplasty. *Am J Cardiol* 1992; 70:1533-1539
22. Margolis JR, Mehta S. Excimer laser coronary angioplasty. *Am J Cardiol* 1992; 69:3F-11F
23. Strikwerda S, Koolen JJ, Feyter de PJ, Sprangers RLH, Tijssen JGP, Serruys PW. Excimer laser coronary angioplasty in the Netherlands: preamble for a randomized study. *Am Heart J* 1993; 125:838-847
24. Litvack F, Eigler N, Margolis J, Rothbaum D, Bresnahan JF, Holmes D, Untereker W, Leon M, Kent K, Pichard A. Percutaneous excimer laser coronary angioplasty: results in the first consecutive 3,000 patients. The ELCA Investigators. *J Am Coll Cardiol* 1994; 23:323-329
25. Bittl JA, Sanborn TA, Yardley DE, Tcheng JE, Isner JM, Chokshi SK,

Strauss BH, Abela GS, Walter PD, Schmidhofer M. Predictors of outcome of percutaneous excimer laser coronary angioplasty of saphenous vein bypass graft lesions. The Percutaneous Excimer Laser Coronary Angioplasty Registry. *Am J Cardiol* 1994; 74:144-148

26. Baumbach A, Oswald H, Kvasnicka J, Fleck E, Geschwind HJ, Ozbek C, Reifart N, Bertrand ME, Karsch KR. Clinical results of coronary excimer laser angioplasty: report from the European Coronary Excimer Laser Angioplasty Registry. *Eur Heart J* 1994; 15:89-96
27. Strikwerda S, Montauban-van Swijndregt E, Melkert R, Serruys PW. Quantitative angiographic comparison of elastic recoil after coronary excimer laser assisted balloon angioplasty and balloon angioplasty alone. *J Am Coll Cardiol* 1995; 25: 378-388
28. Appelman YEA, Piek JJ, de Feyter PJ, Tijssen JGP, Strikwerda S, David GK, Serruys PW, Margolis JR, Koelemay MJ, van Swijndregt E, Koolen JJ. Excimer Laser Coronary Angioplasty versus Balloon Angioplasty in the Treatment of Obstructive Coronary Artery Disease: a Randomized Clinical Trial. *Lancet* 1996, 347:79-84
29. Appelman YEA, Piek JJ, Redekop K, de Feyter PJ, Koolen JJ, David GK, Strikwerda S, Tijssen JG, Serruys PW, van Swijndregt E, van Gemert MJ, Lie KI. Clinical events following excimer laser angioplasty or balloon angioplasty for complex coronary lesions: sub analysis of a randomized trial. *Heart* 1998;79(1): 34-8
30. Appelman YEA, Koolen JJ, Piek JJ, Redekop K, de Feyter PJ, Strikwerda S, David GK, Serruys PW, Tijssen JG ,van Swijndregt E, Lie KI. Excimer laser angioplasty versus balloon angioplasty in functional and total coronary occlusions. *Am J Cardiol* 1996;78(7):757-62
31. Grundfest WS, Litvack F, Forrester JS, Goldenberg T, Swan HJC, Morgenstern L, Fishbein M, McDermid IS, Rider DM, Pacala TJ, Laudenslager JB. Laser ablation of human atherosclerotic plaque without adjacent tissue injury. *J Am Coll Cardiol* 1985; 5:929-33
32. Gijsbers GHM, Sprangers RLH, Van Gemert MJC. Excimer laser coronary angioplasty: laser-tissue interactions at 308 nm. in: *Primer on Laser Angioplasty*, 2nd edition. Ginsburg R, Geschwind H. (Eds.), Futura Publishing Co., Inc. Mount Kisco NY, 1992. Chapter 13, pp. 217-241
33. Leeuwen van TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced

by excimer laser pulse causes microsecond arterial dilation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993; 87:1285-1263

34. Hamburger JN, Gijsbers GH, Lijmer JG, Oei F, Sprangers RL, van Gemert MJ, Dunning AJ. 308 nm excimer laser tissue interaction using a modified multifiber catheter. *J Am Coll Cardiol* 1993; 21: 385A
35. Van den Broecke D, Hamburger JN, Gijsbers G, Serruys PW. The influence of CO_2 flush on the quality of excimer laser-tissue ablation. *J Interv Cardiol* June,1995;233(A)
36. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264-9
37. Baumbach A, Haase KK, Rose C, Oberhoff M, Hanke H, Karsch KR. Formation of Pressure Waves During *in vitro* Excimer Laser Irradiation in Whole Blood and the Effect of Dilution With Contrast Media and Saline. *Lasers Surg Med* 1994; 14:3-6

New Aspects of Excimer Laser Coronary Angioplasty

PART I

Physical aspects of excimer laser-tissue interaction

"Let him who seeks, continue seeking until he finds. When he finds, he will become troubled. When he becomes troubled, he will be astonished, and he will rule over the all."

From: The Gospel of Thomas, Nag Hammadi Library

CHAPTER 1

Excimer laser coronary angioplasty: A physical perspective to clinical results

Jaap N. Hamburger, Geert H.M. Gijsbers,

Geert G.A.M. Verhoofstad, Jan van Marle,

Duco G. van den Broecke, Clara E.E. Hanekamp,

Patrick W. Serruys, Martin J. C. van Gemert

In: Topol E, Serruys PW (eds), Current Review of Interventional Cardiology, 2nd edn (Philadelphia: Current Medicine, 1995); 159-172

EXCIMER LASER CORONARY ANGIOPLASTY: A PHYSICAL PERSPECTIVE TO CLINICAL RESULTS

It was Albert Einstein's publication in 1917 on the concept of stimulated emission of radiation, which eventually led to the development of lasers (Light Amplification by Stimulated Emission of Radiation).[1] It still took 43 years before Maiman[2] succeeded in constructing the first operating Ruby laser in 1960. During the following decade, many different types of lasers were developed for a wide range of applications. The unique property of laser radiation, being a parallel monochromatic light beam, allows for localized energy deposition with very high energy densities into irradiated material. It was specifically this feature that ultimately gave rise to the application of lasers in the field of medicine.

The type of laser-tissue interaction is determined by the wavelength of the laser beam, the mode of light emission (continuous or pulsed), and the mode of application (ie, focused, defocused, or fiber delivery). Currently, a wide variety of pulsed and continuous wave lasers are available with wavelengths in either the infrared, visible, or ultraviolet range of the electromagnetic spectrum. As a result, many different types of laser-tissue interaction, such as thermal, photochemical, photo-mechanical, photoablative or photo-biostimulative are being used for different medical applications.

LASERS IN CARDIOLOGY

THERMAL LASERS

In the early 1980s the first attempts were made to use laser energy for cardiovascular applications. Making use of continuous wave lasers such as the carbon dioxide and neodymium-yag (infrared) or Argon laser (visible light), the laser was used as a thermal source by which intravascular devices such as the metal "hot tip", the "hot balloon", or a sapphire-tipped catheter were heated in order to weld or ablate atherosclerotic tissue. However, extensive thermal damage such as coagulation, vacuolization and carbonization of the endovascular tissue, gave rise to poor clinical results and high complication rates.[3,4]

XENON-CHLORIDE EXCIMER LASER

It was only after the introduction of the pulsed xenon chloride (XeCl) excimer laser, emitting ultraviolet light at a wavelength of 308 nm, that laser angioplasty established itself as a feasible technique for the treatment of sympto-

matic coronary artery disease. The process of excimer laser-induced tissue removal was attributed to photo-chemical dissociation of molecular bonds. In this process heat generation was considered to be of minor importance. The early *in vitro* studies with the excimer laser, in which a free laser beam was focused through air on tissue samples, indeed showed very accurate removal of tissue without adjacent tissue injury.[5-7] Next, the development of excimer lasers with long pulse duration allowed for coupling of the high energy laser bundle into flexible multifiber catheters.[8]

The clinical introduction of excimer laser coronary angioplasty (ELCA) in 1988 was accompanied by high expectations with regard to its efficacy and the possible reduction of angioplasty related restenosis rates. Since then, thousands of patients with symptomatic coronary artery disease have been treated by means of ELCA, both in the United States and in Europe.[9-15] Although several reports have confirmed the efficacy of ELCA, particularly in saphenous vein graft lesions, long lesions, ostial lesions, calcified stenoses, and unsuccessful balloon dilatations (so-called "alpha lesions"),[11] reported restenosis rates vary from 42 to 48%, thereby being quite comparable to rates associated with balloon angioplasty.[10-12] ELCA related complications, such as perforation, acute closure, and arterial wall dissection, have been reported as well.[12,13] The only prospective randomized study of the immediate and long-term results of ELCA versus balloon angioplasty in long diffuse coronary lesions, the "AMRO trial", has been conducted in the Netherlands.[15] In this study, 308 patients with 325 type-C lesions were randomized to ELCA or conventional balloon angioplasty. In 98% of the laser cases, laser angioplasty was followed by adjunctive balloon angioplasty. The following items were analyzed: procedural success, defined as < 50% residual stenosis at the end of the procedure; the net gain in minimal lumen diameter at 6-month follow-up angiography relative to the pre-procedural baseline; clinical endpoints (death, myocardial infarction, coronary artery bypass graft surgery [CABG] or repeat percutaneous transluminal coronary angioplasty [PTCA] of the randomized segment within six months); and the functional status at six months. Statistical analysis of these parameters failed to demonstrate a significant difference between the two treatment modalities.

These somewhat disappointing clinical results could not be explained by the findings of the previously mentioned free beam in air experiments. The physical reality of ELCA, however, is a multifiber catheter delivering a laser beam

to tissue in a liquid surrounding. Therefore, in an attempt to elucidate the mechanisms which are responsible for tissue removal and side effects in ELCA we performed *in vitro* experiments using multifiber catheters, simulating intravascular phenomena by using fresh tissue samples or tissue phantoms immersed in liquid.[17,18] Based on these experiments, in the next section we will describe physical phenomena responsible for tissue removal in ELCA. As will be described in the third section, ablation with currently used multifiber catheters results in an incomplete removal of tissue at low laser energy densities and in severe mechanical damage to the adjacent vascular tissue at higher energy densities. In the fourth section, we will combine our findings in an attempt to explain the results of the current clinical application of the excimer laser. Finally, some new technical developments aimed at the reduction of ELCA related vascular wall damage will be discussed. These techniques hopefully will lead to improved clinical results, making better use of the unique forward debulking properties of laser radiation.

PHYSICAL PHENOMENA DURING ELCA

INSOLUBLE GAS FORMATION

Ablation of organic polymers by ultraviolet (UV) radiation is usually attributed to photo-chemical dissociation of molecular bonds by UV photons. Due to the absorption of photon energy, large molecules are divided into smaller components. Some of these small molecules will be in the gaseous phase. Indeed, abundant gas production was seen during XeCl excimer laser tissue ablation in a liquid environment.[18,19]

GAS YIELD MEASUREMENTS

We determined the dependency of insoluble gas yield on laser pulse energy density using a gas sample chamber based on a design by Davis and coworkers.[20] A sample of fresh porcine aorta was put on a spring to keep the tissue in contact with a multifiber catheter. The chamber was filled with saline. Gas production during laser ablation was determined from the rise of the liquid level in a capillary (Figure 1). The LAIS PC4010 (1.3-mm diameter) and PC4021 (1.6-mm diameter) multifiber catheters were used, coupled to a LAIS Dymer 200+ (LAIS, Irvine, CA) excimer laser. The force provided by the spring was equivalent to 6 g for the PC4010 catheter and to 9 g for the PC4021 catheter. The ratio of the applied weights was equal to the ratio of the overall diameter of the two catheters, in order to exert equal pressures during ablation. Pulse energy densities were used in the range of 30 mJ/mm^2 to 60 mJ/mm^2 with a pulse repetition rate of 20 Hz, to reflect those

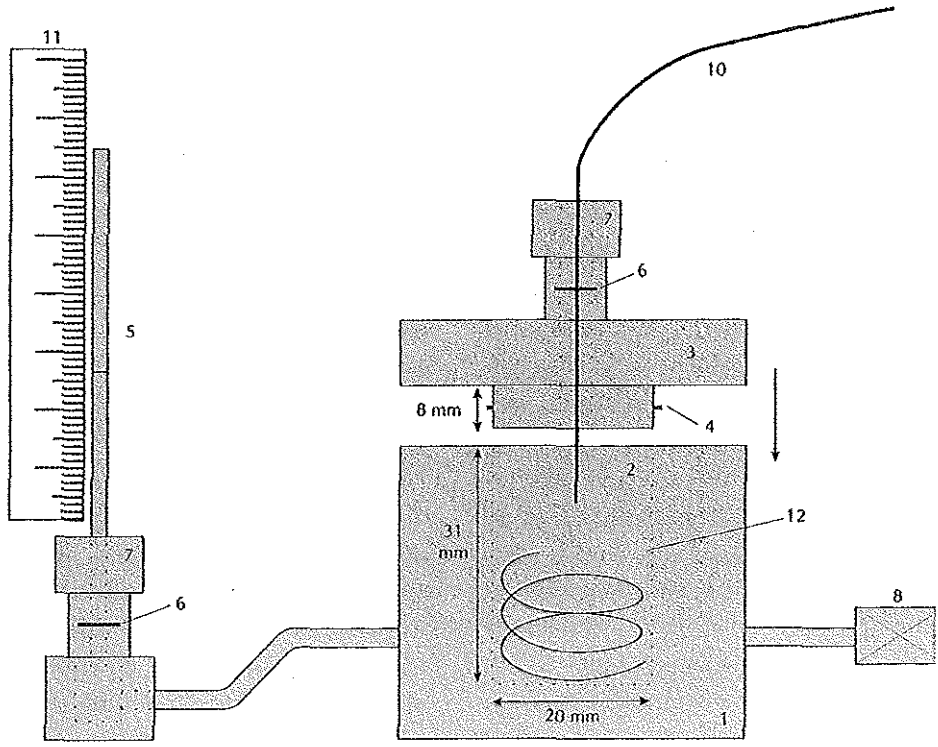


Figure 1 *Gas sample chamber. 1: Perspex cylinder; 2: hole; 3: Perspex cap; 4 and 6: rubber rings; 5: glass capillary, the rise of the level of liquid is proportional to the gas volume increase in the chamber; 7: screw caps; 8: valve; 9: attachment for syringe; 10: fiber or catheter; 11: ruler; 12: spring with table.*

laser parameters typically used in ELCA over the years. After applying a maximum of 120 pulses, the average gas production was determined. As shown in Figure 2, it is clear that an increase of the energy density from 30 to 60 mJ/mm^2 resulted in an increase of the average gas production by a factor of 10. At 60 mJ/mm^2 the gas production was about 0.25 µl per pulse per mm^2 at the distal tip of the catheter. Therefore, per pulse approximately 0.06 µl of gas for the PC4010 and 0.1 µl of gas for the PC4021 were created. For a typical pulse train of 60 pulses, this means a total gas volume of 4 µl and 6 µl, respectively. Since the diameter of a single gas bubble of 4 µl and 6 µl is 2 mm and 2.3 mm, respectively, these are large volumes as related to the size of a

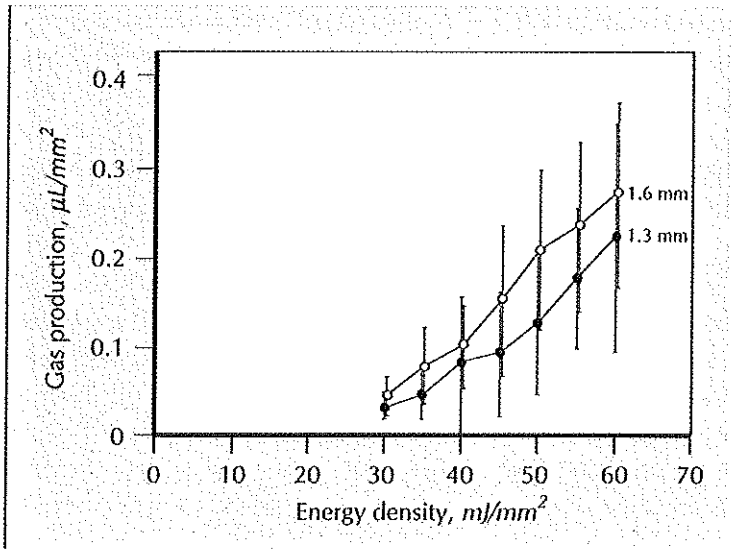


figure 2 Gas production on porcine aortic tissue per unit of light emitting area as a function of pulse energy density. An AIS PC4010 laser catheter (1.3 mm) and an AIS PC4021 laser catheter (diameter 1.6 mm) were used with forces equivalent to 6 g and 9 g, respectively, to push the catheters against the tissue. The values are determined over a complete pulse train of maximum 120 pulses. The data are presented as average ± SD (n=10).

stenosed coronary artery.

Given a gas production of 0.25 µl/mm² per pulse at 60 mJ/mm², it can be calculated that less than 7% of all photons are actually used for photo-chemical dissociation. Therefore, the vast majority of photon energy is either reflected or otherwise will be transformed into heat.

During ablation experiments we noted that in blood a substantial amount of gas was produced as well (Figure 3). Gas formation was always observed, both in porcine aorta and in blood, and also at energy densities below 30 mJ/mm². Even at energy densities just above zero fluence the production of insoluble gas was observable. In order to determine the substance

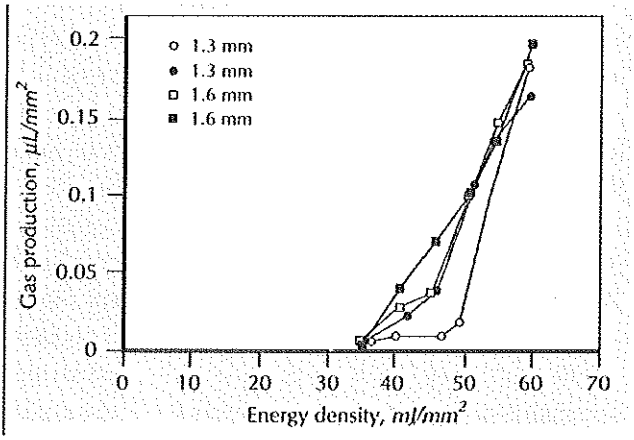


Figure 3 Gas production per unit of light emitting area per pulse in fresh heparinized human blood as a function of pulse energy density. An AIS PC4010 laser catheter (1.3 mm) and an AIS PC4021 laser catheter (diameter 1.6 mm) were used. The data are the results of single measurements.

responsible for the detected gas formation in blood, we separated hemoglobin (a strong absorber in the UV spectrum) from the blood cell membranes. Although the excimer laser light was strongly absorbed in this purified hemoglobin solution, no gas production could be measured. However, when the cell membranes were brought in suspension it was observed that for a given energy density, gas was created in similar amounts as in whole blood. From this we inferred that lipids, being the main component of cell membranes, are responsible for gas formation by XeCl excimer laser pulses. In accordance with this observation were the following findings. When excimer laser pulses were delivered to gelatin consisting of 30 % collagen-protein and water, there was an absence of gas production. Likewise, in a saturated solution of bovine thymus DNA gas formation did not occur. Thus, we concluded that proteins and DNA do not contribute to gas formation by 308-nm excimer laser radiation, and therefore play no role in the process of photo-chemical dissociation.

To study the behavior of gas in a tight coronary artery stenosis, we simulated conditions during ELCA by using a tissue phantom. The phantom consisted of a polyacrylamide gel containing a high concentration of glycerin, a material of which the gas producing potential had previously been established. The polyacrylamide gel had tissue-like mechanical properties and was optically transparent, thus allowing for on-line video registration. A PC4021 catheter was placed perpendicular on the gel surface. A weight of 20 grams was added to the catheter to compensate for the friction between the gel and the catheter. Laser pulses were applied with an energy density of 60 mJ/mm^2 and a pulse repetition rate of 20 Hz. During the first several pulses a gas-filled spherical region was created under the catheter tip. After approximately 60 pulses, catheter penetration occurred into the space that was previously formed by the gas. From this moment we recorded continuous penetration until cessation of the laser pulse train. Due to gas formation there was a constant creation of space in front of the catheter tip, thus allowing the catheter to proceed. Although some gas was noted to escape in the liquid above the polyacrylamide gel, the major portion of it stayed around the catheter, as can be seen in Figure 4. Furthermore, the accumulation of gas was responsible for the creation of small radial fissures in the gel, alongside the catheter. If this model is indeed representative of phenomena occurring during ELCA, it suggests that the abundant gas formation during ablation mechanically dilates a stenosed artery, thereby facilitating the crossing of the lesion by the catheter. Consequently, this might cause a reduc-

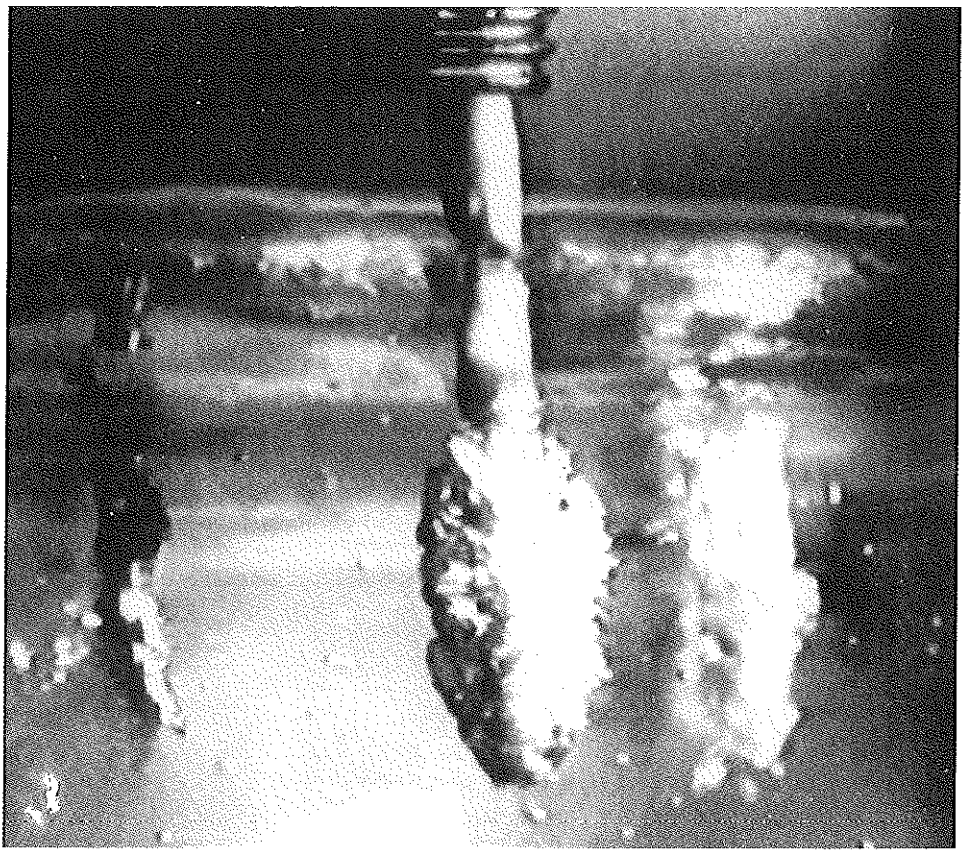


Figure 4 Close-up video recording of an envelope of gas produced in polyacrylamide (PAA) with glycerin around a PC4021 catheter delivering excimer laser pulses at 60mJ/mm² at 20 Hz. The situation after approximately 1000 pulses is shown. A weight of 20 g was added to the catheter. The catheter tip was at the bottom of the envelope and moved steadily downward during application of the laser pulses. The other lesions in the PAA are from previous experiments.

tion of the system's ablation efficiency, since the atherosclerotic material that is pushed aside most likely will not be ablated.

FAST EXPANDING WATER VAPOR BUBBLES

During the process of tissue ablation the major part of laser energy is transformed into heat. Due to the short pulse duration a substantial increase in temperature is reached within a very short time span. This mechanism results in the formation of rapidly expanding and imploding water vapor bubbles (within 250 µs) after each laser pulse. We described fast expanding and collapsing water vapor bubbles that were created after each laser pulse in an UV absorb-

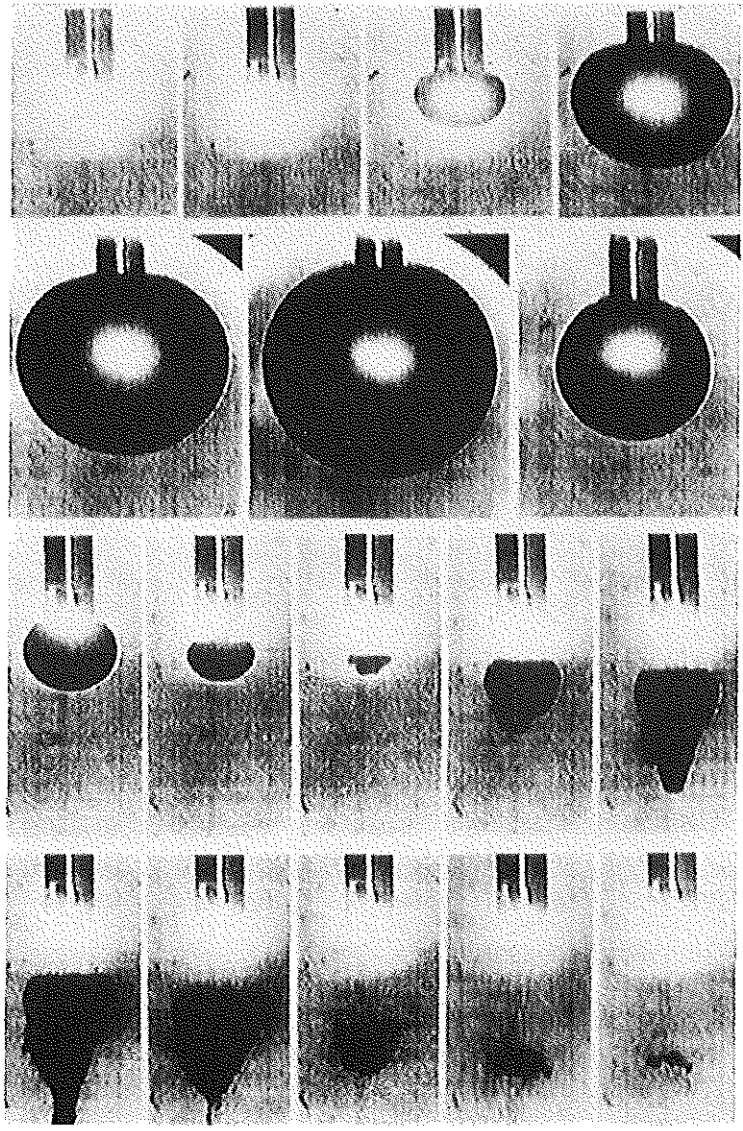


Figure 5 Temporal development of a fast expanding and collapsing water vapor bubble created by a xenon chloride (XeCl) excimer laser pulse delivered by a single optical fiber in a solution of ultraviolet-absorbing oxybuprocaine-HCL. The vertical bar is the fiber tip, the spot of white light at the tip is fluorescence light. The pulse energy was 40 mJ/mm². The time after the pulse for each picture is, first row: before the pulse, 0.75, 6, 20 μs; second row: 45, 105, 155 μs; third row: 160, 170, 175, 185, 205 μs; fourth row: 235, 265, 295, 325, 335 μs.

ing medium (Figure 5).[18] Likewise, Van Leeuwen and co-workers[21] observed these fast expanding bubbles on porcine aortic tissue when XeCl excimer laser pulses were applied by means of a single fiber. When the fiber was allowed to penetrate the tissue they observed tissue surface elevation, which was attributed to fast expanding bubble formation inside the tissue. Histology of the tissue

samples showed dissection of the intima and media, presumably caused by dilatation of the fast expanding bubbles. Elsewhere, Van Leeuwen and co-workers[22] proved that in rabbit femoral and iliac arteries fast expanding bubbles, having a maximum diameter of approximately three times the catheter diameter, caused microsecond dilation and invagination of the adjacent vascular wall. Histologic examination showed extensive damage, characterized by rupture and abrasion of parts of the internal elastic lamina with extensive smooth muscle cell necrosis. Furthermore, red blood cells stained medial dissections that ran parallel to the arterial wall. In addition, these authors presume water vapor to be the major component of the fast bubbles.

The threshold energy density for fast bubble formation in porcine aorta was found to be 20 mJ/mm^2. This means that at energy densities in ELCA, fast bubble formation occurs always. Given the dynamics of this process, we consider the combination of the fast bubble and insoluble gas formation to be responsible for most of the above described collateral damage.

EVALUATION OF TISSUE ABLATION EFFICIENCY AND QUALITY USING MULTIFIBER CATHETERS

In the previous section we described the process of excimer laser tissue ablation with the emphasis on UV photon-tissue interaction. From a clinical point of view we were interested in the evaluation of the specific influence of multifiber catheter configuration on the efficacy and quality of ablation.[23] From Monte Carlo computer simulations of photon behavior in tissue,[18] it follows that no matter how tightly packed together, inevitably there is a certain amount of dead space between fibers in a multifiber catheter configuration. Therefore, it can be expected that due to the configuration of the multifiber catheters currently used in ELCA, there is no light overlap between the fibers at the catheter-tissue interface. Furthermore, it has been shown that light intensity distribution in tissue is related to fiber diameter. In short this means that by increasing the laser beam (or fiber) diameter, the maximum fluence under the surface of irradiated tissue will increase as well (Figure 6). This mechanism is caused by the fact that the chance of absorption of a scattered photon in tissue within the diameter of a light bundle increases by the increase of the light bundle diameter. Given the absence of light overlap between fibers at the tip of a multifiber catheter, only the tissue directly beneath the individual fibers would be ablated.

To confirm the hypothesis of the increase of ablation efficiency by increasing fiber diameter, we compared

the former available LAIS multifiber catheters PC 4021, containing 200 fibers of 50 µm, the PC 4020, containing 12 fibers of 200 µm, and a modified catheter with a single beam diameter of 1600 µm. The modified catheter consisted of a PC 4021 catheter with a flat polished distal tip and a silica window with a 1600 µm diameter and a 0.5-mm central guidewire lumen. The silica tip was used to diffuse the light coming from the fibers in order to obtain a homogeneous light distribution at the window-tissue interface. The window was fixed to the catheter tip by means of a Teflon plug in the guide wire lumen. The laser was the LAIS 200+ Dimer. The catheters were vertically fixed in a shaft. The distal end of the catheter was free to be in contact with the tissue. The shaft moved freely in the vertical direction and was kept in vertical position by means of a thin wire, guided by pulleys and a counter weight. On a table fixed on the shaft, a weight of 12 grams was added to control the force with which the catheter was pushed onto the tissue. This weight was chosen based on previously published experiments.[19] The tissue was fixed on a holder in a glass reservoir and immersed in either saline or blood

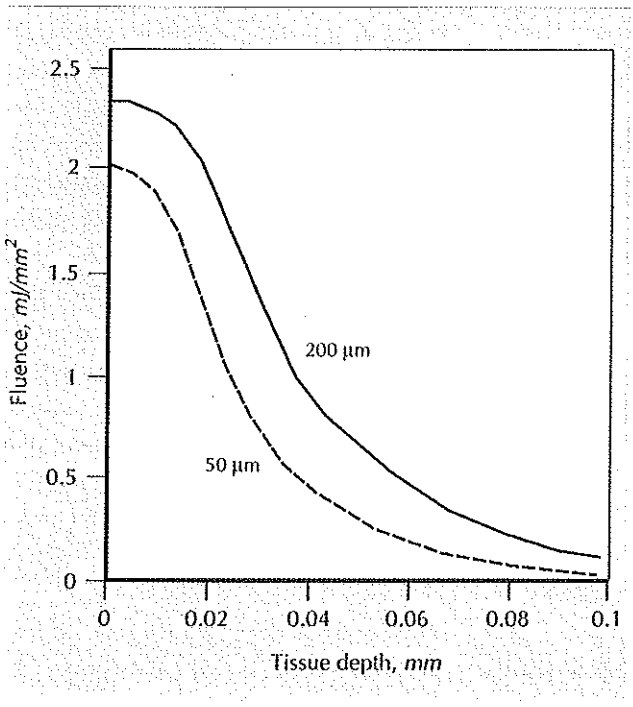


Figure 6 Light distribution of 308 nm light as a function of depth below the central part of a single fiber of 50 µm in diameter and a single fiber of 200 µm in diameter as a result of a Monte Carlo simulation. It is assumed that 1 mJ/mm² is incident on the tissue. At the surface the energy density is higher than the incident energy density due to scattering. This effect is more pronounced for the 200 µm fiber.

(human packed cells). Fresh porcine aorta was used as a tissue sample.

In order to evaluate the ablation efficiency and quality under several clinically relevant conditions, the following experimental set-ups were used: a non-contact mode, in which the catheter tip was positioned 0.5 mm above the tissue surface during ablation; a contact mode, in which a weight was added to the catheter to ensure a continuous pressure of the catheter tip on the tissue during ablation.

The craters were made delivering 40 pulses with energy densities of 30 mJ/mm^2 (total energy per pulse = 12.5 mJ) or 60 mJ/mm^2 (total energy per pulse = 25 mJ). Pulse frequencies were 5 and 20 Hz. Since blood is known to be a strong absorber at 308 nm, all experiments were performed both in saline and in a blood environment. For each setting of parameters ten craters were made. For statistical analysis we used a χ^2 test.

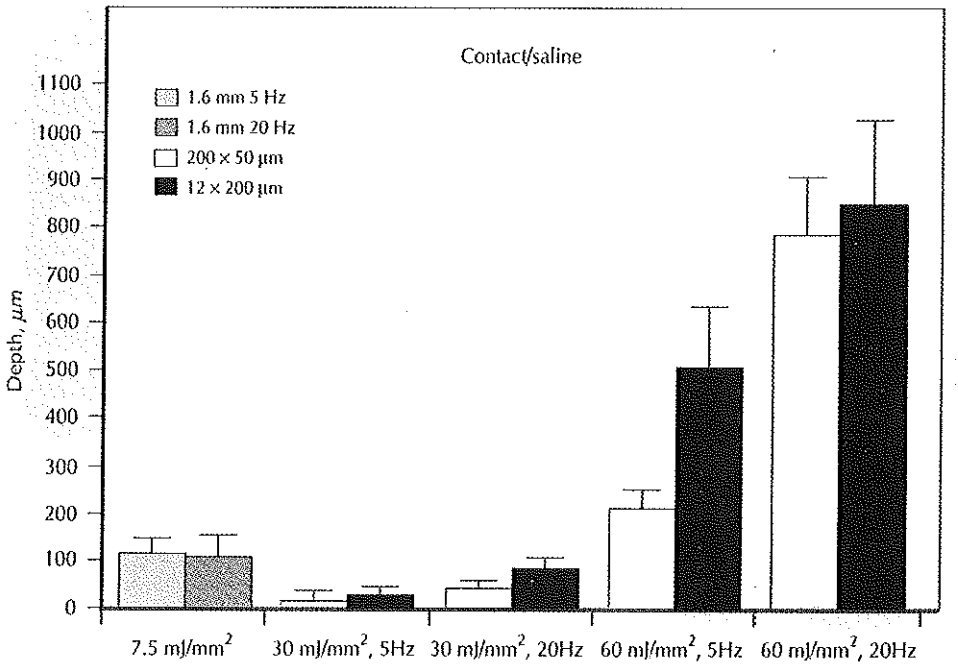


Figure 7 Average crater depths in porcine aorta after 40 xenon chloride (XeCl) excimer laser pulses using different catheters in contact with the tissue. A weight of 12 g was added to the catheters. The tissue was immersed in saline. The catheters used were the LAIS PC4020 (consisting of 12x200 µm fibers), the LAIS PC4021 (consisting of 200x50 µm fibers), and a modified catheter having a homogenized light distribution over a diameter of 1.6 mm. The bars indicate the average values, the SD is indicated by the thin bars (n=10).

We assessed crater depth, morphology, thermal, and mechanical damage by light and electron microscopy. The crater depths (mean ± SD) for the PC4020, the PC 4021, and the modified multifiber catheter are given in Figures 7 through 9. As can be appreciated from the results, the ablation efficiency of the conventional multifiber catheters increased by

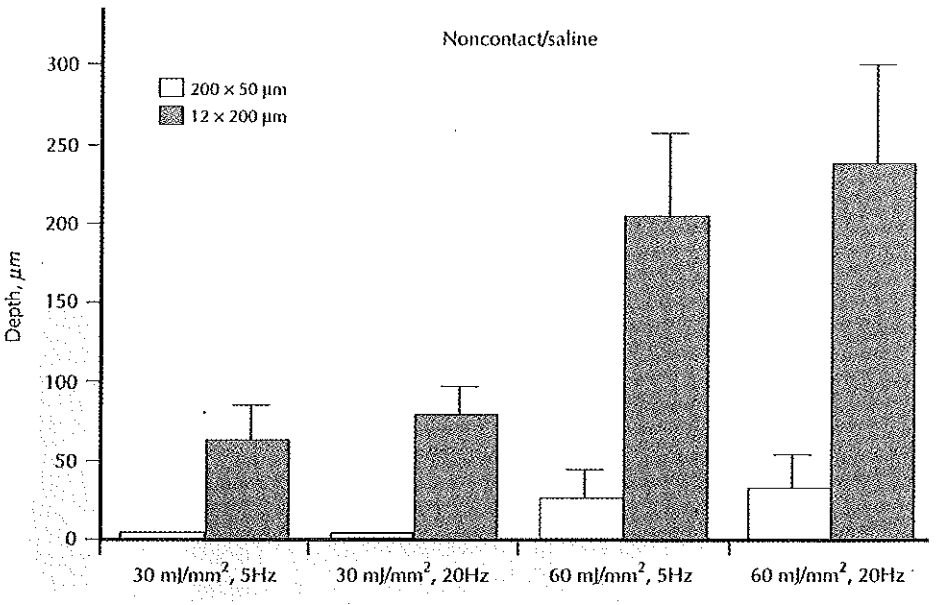


Figure 8 *Average crater depths in porcine aorta after 40 xenon chloride (XeCl) excimer laser pulses using different catheters positioned 0.5 mm above the tissue. The tissue was immersed in saline. The catheters used were the LAIS PC4020 (consisting of 12x200 µm fibers) and the LAIS PC4021 (consisting of 200x50 µm fibers). The bars indicate the average values, the SD is indicated by the thin bars (n=10).*

increasing the fluence ($p<0.0001$). As can be seen in Figure 7, the pulse repetition rate had a significant influence on the ablation efficiency as well, but only when the tip of the catheter was in contact with the tissue ($p<0.0001$). Likewise, the ablation efficiency increased considerably when the catheter was in contact with the tissue as compared to the noncontact mode ($p<0.0001$). The histology of the 50-µ fiber catheters in the noncontact mode revealed a picture which more resembles superficial erosion than real crater formation.

Striking was the absence of tissue ablation in the noncontact mode in blood, even at a fluence of 60 mJ/mm² for both types of catheters. Figure 9 shows the results of ablation in a blood environ-

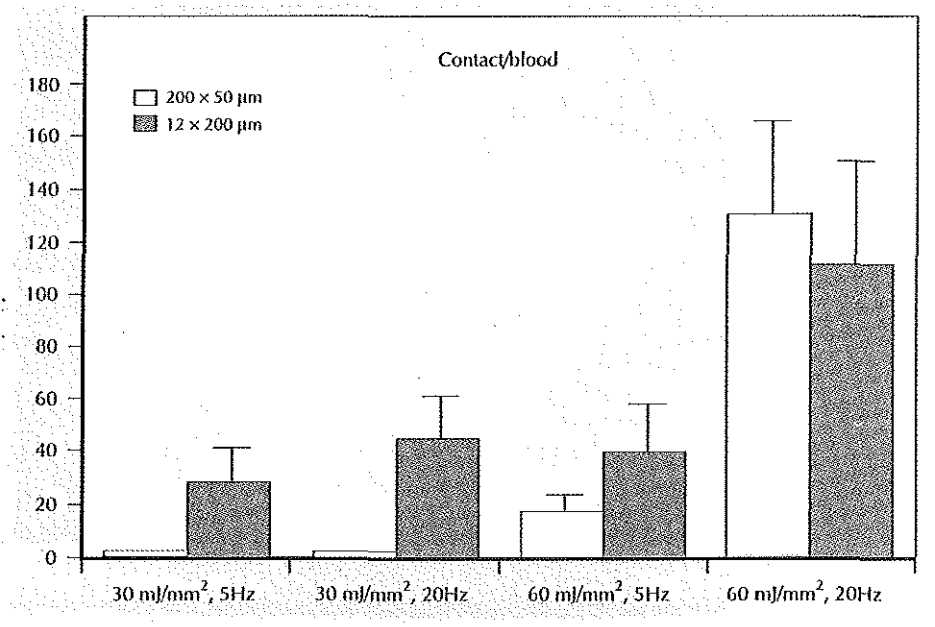


Figure 9 Average crater depths in porcine aorta after 40 xenon chloride (XeCl) excimer laser pulses using different catheters in contact with the tissue. A weight of 12 g was added to the catheters. The tissue was immersed in blood (human packed cells). The catheters used were the LAIS PC4020 (consisting of 12x200 µm fibers) and the LAIS PC4021 (consisting of 200x50 µm fibers). The bars indicate the average values, the SD is indicated by the thin bars (n=10).

ment, with the catheter tip being in contact with the tissue sample. From these results it can be appreciated that even when the catheter during ablation is pressed against the tissue, the absorption of 308 nm in hemoglobin still results in a significant reduction of the ablation efficiency as compared with the experiments in saline ($p<0.0001$). To validate the Monte Carlo computer simulations, we analyzed crater depth for any given set of parameters, comparing the 50-µ fiber with the 200-µ fiber catheter. As predicted by the Monte Carlo computer simulations, the 200-µ fiber craters were always deeper under all circumstances ($p<0.0001$), with the exception of the experiments at 60 mJ/mm², 20 Hz ($p=0.38$). Figures 10 and 11 show typical examples of crater formation at a low fluence. As it shows, part of the tissue in front of the catheter tip is not illuminated and therefore not ablated (the "Swiss cheese phenomenon"). The nonablated tissue or "tissue bridges", prevented a continuous catheter advancement through the tissue. As can be seen in Figure 12, abla-

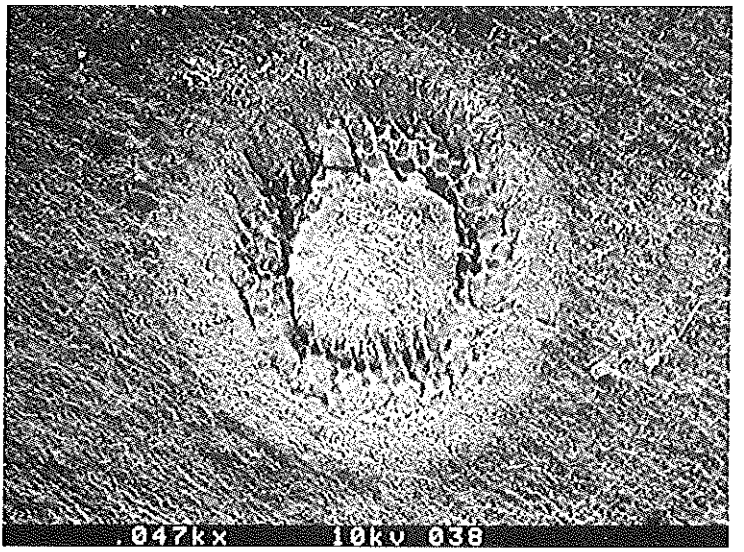


Figure 10 *Scanning electron microscopy of an ablation lesion in porcine aorta made by 40 xenon chloride (XeCl) excimer laser pulses delivered by a LAIS PC4021 catheter (200x50 µm fibers) in contact with the tissue. The pulse energy density was 30 mJ/mm². Note the strands of unablated tissue and a circular area of endothelial damage surrounding the area of ablation.*

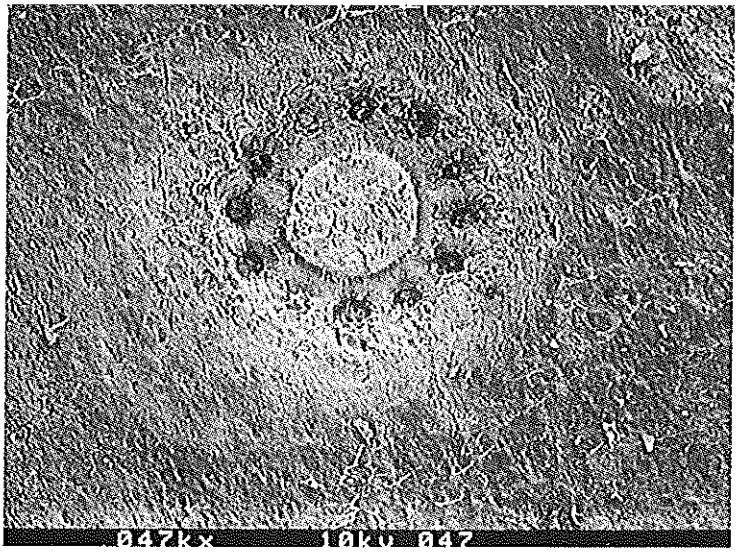


Figure 11 *Scanning electron microscopy of an ablation lesion in porcine aorta made by 40 xenon chloride (XeCl) excimer laser pulses delivered by a LAIS PC4020 catheter (12x200 µm fibers) in contact with the tissue. The pulse energy density was 30 mJ/mm². Again, there is no ablation of tissue between the individual fibers, and a circular area of endothelial damage is present.*

tion at a high fluence resulted in a more thorough removal of tissue. However, this invariably gave rise to extensive circumferential damage of the surrounding endothelium.

In Figure 13 we see a light microscopic detail of a crater wall showing an absence of cell nuclei and a confluent

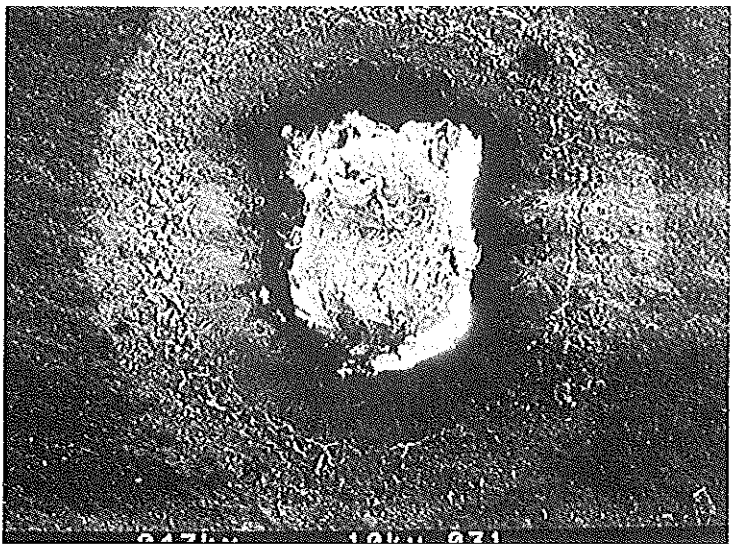


Figure 12 *Scanning electron microscopy of an ablation lesion in porcine aorta made by 40 xenon chloride (XeCl) excimer laser pulses delivered by a LAIS PC4021 catheter (200x50 μm fibers) in contact with the tissue. The pulse energy density was 60 mJ/mm². A deep ablation crater is made without residual unablated tissue. However, a larger zone of endothelial damage is created than is present around the lesions made at 30 mJ/mm². The bright spot in the center of the lesion is due to absence of a sputtered gold layer needed to prevent the build-up of electrostatic charge.*

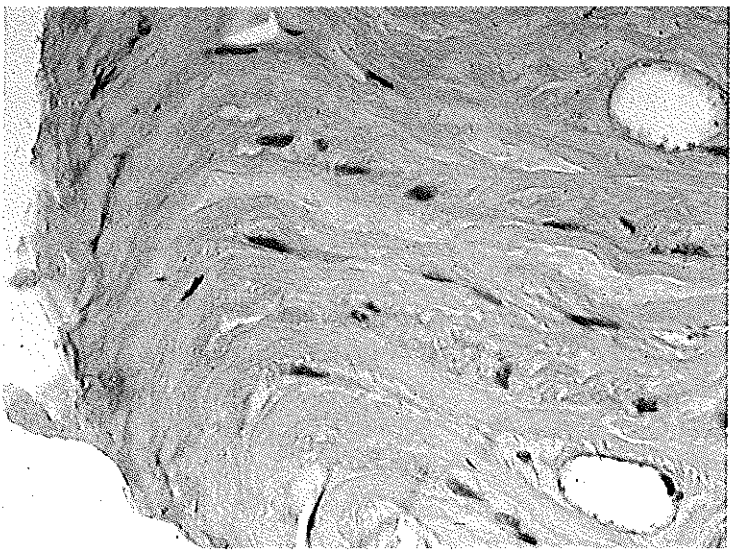


Figure 13 *Light microscopic detail of an ablation crater wall made in porcine aorta by 40 xenon chloride (XeCl) excimer laser pulses delivered by a LAIS PC4021 catheter (200x50 μm fibers) in contact with the tissue. The pulse energy density was 60 mJ/mm². Along the crater edge an absence of cell nuclei and melting of collagen fibers can be observed, which indicates thermal injury.*

aspect of the collagen fibers. These microscopic findings are generally considered to be a reflection of thermal injury.

To assess the possible further increase in ablation efficiency by an additional enlargement of the beam diameter and a reduction of the dead space at the

catheter tip, the effects of the modified multifiber catheter in porcine aorta were compared with standard multifiber catheters. The same laser pulse energies (12.5 mJ and 25 mJ, respectively) were used. The active ablating surface was calculated to be 0.38 mm^2 for the PC 4020, 0.39 mm^2 for the PC 4021, and 1.8 mm^2 for the modified catheter. The crater depths resulting from ablation with the modified multifiber catheter are given in Figure 7. The results show that the ablation depths at an energy density of 7.5 mJ/mm^2 for the modified multifiber catheter were a factor three to six larger than for the PC4021 at an energy density of 30 mJ/mm^2.

Contrary to the standard multifiber catheters that produced different clusters of separate craters according to their design with ragged crater walls and extensive damage to the surrounding endothelium, the modified multifiber catheter produced single smooth craters. In accordance with the theory of an increase of ablation efficiency by increasing the beam diameter, the average ablation efficiency further increased using the modified catheter. Surprisingly, no damage to the surrounding endothelium was seen (Fig 14a, 14b). In addition, electron microscopic signs of thermal damage such as carbonization or melting of collagen fibers in the crater wall were absent when a modified multifiber catheter with a homogeneous light distribution was used. Thus, we concluded that homogeneous light distribution not only improves ablation efficacy, but also reduces damage to the adjacent vascular tissue.

DISCUSSION

In the late 1980s the XeCl excimer laser was introduced in the arena of interventional cardiology as a nonthermal forward debulking device. It came with the promise of smooth ablation and subsequently, lower restenosis rates. All these promises and hopes were mostly based on experiments with a free laser beam focused on tissue samples in air. Based on the above described experiments with multifiber catheters on tissues and tissue phantoms immersed in saline and blood, we obtained more insight in the mechanisms of excimer laser-induced tissue removal during ELCA.

Two different physical mechanisms were shown to be responsible for the ablation of vascular tissue with the current multifiber catheters. These mechanisms are, first, nonthermal UV-light induced dissociation of molecules and, second, the thermal process of water vaporization. The described physical phenomena imply that tissue removal results from the disruption of tissue by gas and water vapor formation. The debris consisting of tissue remnants and

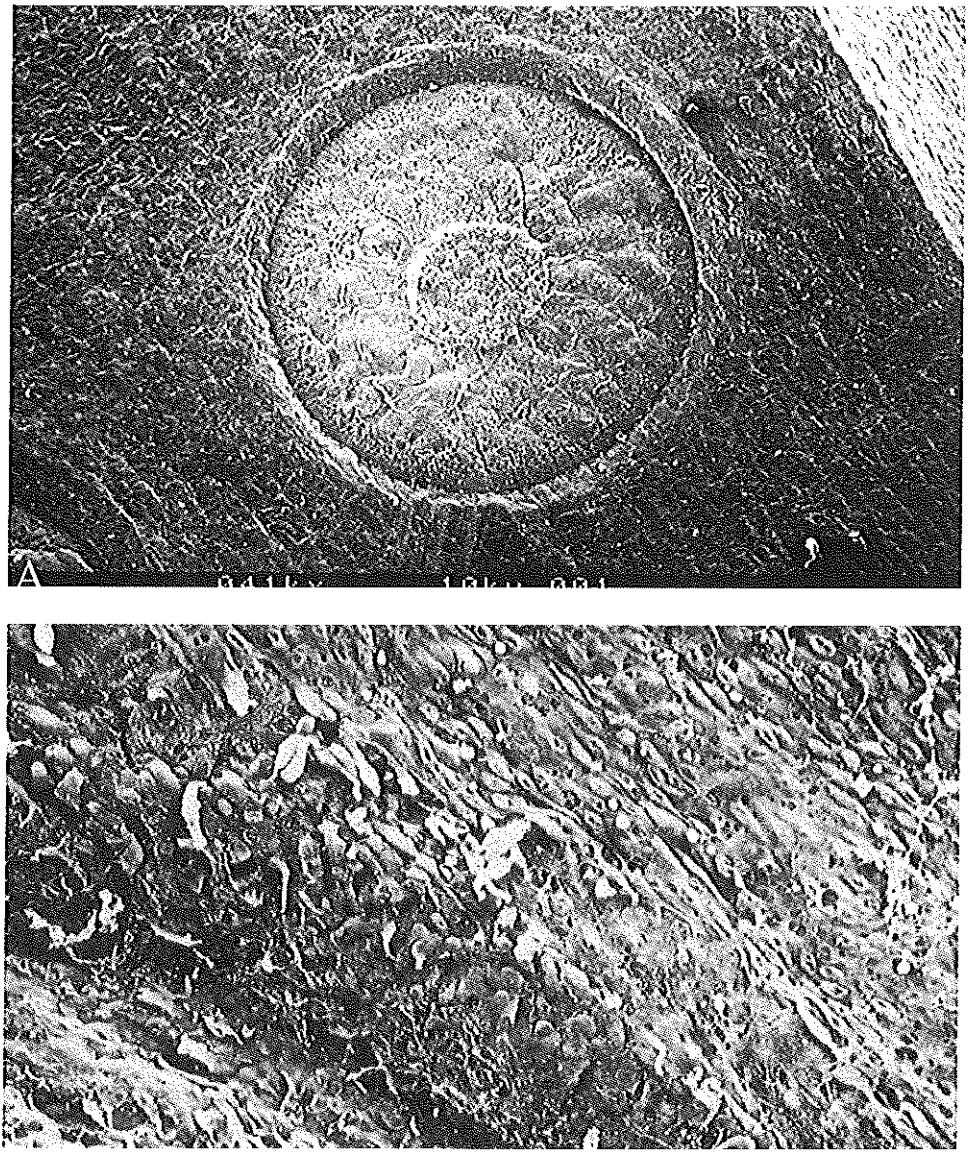


Figure 14 A, Scanning electron microscopy of an ablation lesion in porcine aorta made by 40 xenon chloride (XeCl) excimer laser pulses delivered by a modified LAIS PC4021 catheter in contact with the tissue. Through this modification the light distribution incident on the tissue was homogenized. The pulse energy density was 7.5 mJ/mm². The central part is unablated tissue due to a Teflon plug used to mechanically attach the silica window on a LAIS PC4021 catheter. B, Detail of the lesion shown in A. Note the intact endothelial cells up to the crater edge.

water is subsequently forced away by both the fast bubble and accumulated gas. In ELCA, these phenomena will occur in narrowed arteries. In contrast to balloon angioplasty, atherosclerotic plaque will be removed. However, it can be envisaged that especially in tight lesions part of the plaque will not be ablated, but be pushed aside by the accumulating nondissoluble gas. The fact that in ELCA the post-ELCA luminal diameter is usually smaller than the diameter of the catheter, is consistent with this hypothesis.[19]

From light and electron microscopic evaluation of ablation with the multifiber catheters it followed that complete removal of tissue at low fluences was prevented by a substantial amount of dead space at the catheter tip. Tissue present at the location of dead space between the individual fibers was not removed, resulting in the occurrence of so called "tissue bridging". Subsequently, the catheter movement into the tissue was halted by these tissue remnants. Indeed, it was also the clinical experience that fluences of 30 to 45 mJ/mm^2 were not sufficient to obtain an efficient debulking, especially in type C lesions. Only by increasing the fluence to values of 50 mJ/mm^2 and up could most lesions effectively be crossed. However, an increase of fluence does not result in light overlap between individual fibers. Therefore, the mechanism of successful crossing in this setting is not as much an increase in tissue ablation but an increase of the size and the mechanical impact of the water vapor bubble and a sharp increase in the production of insoluble gas. As was discussed, at those fluences currently used for ELCA, the dynamics of the water vapor bubble and accumulating indissoluble gas are large enough to remove mechanically any nonablated tissue. As a result, the ablation at high fluences led to extensive collateral vessel wall damage. Subsequently, removal of tissue by the mechanical impact of both the water vapor bubble and accumulating indissoluble gas is probably responsible for most of the clinically reported complications, such as dissection and perforation.

From the above described experiments we may conclude that ablation is more efficient when the tip of the catheter is in contact with the tissue, exerting a certain amount of pressure. Furthermore, the ablation will be more efficient, and less damaging to the surrounding arterial wall when the blood interface between the catheter tip and the tissue is effectively removed.[22] Clinically this could be achieved by flushing the coronary artery with saline during the laser procedure. The finding that with a 0.5-mm blood interface even at a fluence of 60 mJ/mm^2 no ablation occurred contradicts the so-called "Moses-effect" as described by

Isner and coworkers.[24] From the ablation rates as deducted from the results in the previous section, it is clear that tissue is ablated at a rate of approximately 0.5 mm per second. Therefore, only a slow pass of the catheter through the coronary artery can be effective. Any attempt to make a "fast pass" will probably only lead to a manual dottering of the lesion, thereby increasing the chance of dissection formation.

Based on Monte Carlo computer simulations of light distribution in tissue, we expected an increase of ablation efficiency by increasing the laser beam diameter. Measuring crater depth resulting from individual fiber activity this hypothesis was verified by comparing 200-μ fiber catheters with 50-μ fiber catheters. Except for the "in contact / saline" measurements at 60 mJ/mm^2 the difference in crater depth, and thereby ablation efficiency, was highly significant in favor of the catheter with the larger fiber diameter. The absence of a significant difference at maximum fluence and repetition rate during in contact ablation, is possibly caused by the fact that at these parameters the size of the fast bubble is large enough to be responsible for most of the tissue removal, thereby masking any other phenomenon. By using the modified multifiber catheter, having a homogeneous light distribution with a beam diameter of 1600 μm, a further increase of the ablation efficiency could be obtained. Besides the Monte Carlo effect, this can also be contributed to the absence of dead space at the catheter tip. The fact that the laser pulse energy was kept at the same level for experiments with the modified multifiber catheters, but the ablative surface of this catheter was much larger, the resulting energy density at the tip of this catheter was much lower. Nevertheless, with a homogeneous light distribution at a fluence of 7.5 mJ/mm^2, the crater depth increased by more than a factor of six compared with the conventional multifiber catheter at 30 mJ/mm^2. Since ablation with the modified catheter occurred at a fluence well below the threshold for fast bubble formation, no collateral damage to the surrounding endothelium was seen.

Another approach to the reduction of collateral damage is the concept of "Multiplexing" (Spectranetics, Colorado Springs, Colorado), or SELCA ("smooth excimer laser coronary angioplasty", Medolas, Munich, Germany). By selective activation of catheter sections, a significant reduction of energy per pulse can be achieved at the same fluence levels. Thereby the overall size of the fast expanding and collapsing water vapor bubble is reduced. This technical option for a possible improvement of the ablation quality, is currently under investigation at our laboratories.

In conclusion, a model was presented for the ablation of vascular tissue with the XeCl excimer laser. In this model, ablation is based on insoluble gas formation due to photo-chemical dissociation of lipids and water vapor formation due to photon energy conversion into heat. We have shown that with the design of current multifiber catheters these phenomena are a necessary evil for an efficient recanalization of a diseased coronary artery. In our opinion, the mechanical interaction with the arterial wall of water vapor bubbles and insoluble gas explains both the effectivity and the complications seen during ELCA.
The initial experiments with a modified laser catheter with a homogeneous light distribution indicate that vascular tissue indeed can effectively be removed by excimer laser at energy densities below the threshold for water vapor bubble formation. Hopefully, the further development and evaluation of this new technique will improve the clinical results of ELCA, which is potentially still the only true forward debulking technique available in coronary angioplasty.

REFERENCES

1. Einstein A. Zur quantentheorie der strahlung. *Phys Zeitschrift* 1917, 18: 121-128
2. Maiman Th.Stimulated optical radiation in ruby. *Nature* 1960, 187:493-494
3. Oomen A, Van Erven L, Vandenbroucke WVA, Verdaasdonk RM, Slager CJ, Thomsen SL, Borst C. Early and late arterial healing response to catheter induced laser, thermal, and mechanical wall damage in the rabbit. *Lasers Surg Med* 1990; 10:363-374
4. Deckelbaum LI. Coronary Laser Angioplasty *Lasers Surg Med* 1994; 14:101-110
5. Grundfest WS, Litvack IF, Goldenberg T, Sherman T, Morgenstern L, Carroll R, Fishbein M, Forrester J, Margitan J, McDermid S, Pacala TJ, Rider DM, Laudenslager JB. Pulsed ultraviolet lasers and the potential for safe laser angioplasty. *Am J Surg* 1985; 150:220-226
6. Grundfest WS, Litvack IF, Forrester J, Goldenberg T, Swan HJC, Morgenstern L, Fishbein M, McDermid IS, Rider DM, Pacala TJ, Laudenslager JB. Laser ablation of human atherosclerotic plaque without adjacent tissue injury. *J Am Coll Cardiol* 1985; 5:929-933
7. Litvack F, Grundfest WS, Goldenberg T, Laudenslager J, Pacala T, Segalowitz J, Forrester JS. Pulsed laser angioplasty: wavelength power and energy dependencies relevant to clinical application. *Lasers Surg Med* 1988; 8:60-65
8. Laudenslager JB. Excimer lasers

adapt to angioplasty. *Laser Focus World*, May 1988

9. Karsch KR, Haase KK, Voelker W, Baumbach A, Mauser M, Seipel L. Percutaneous coronary excimer laser angioplasty in patients with stable and unstable angina pectoris. Acute results and incidence of restenosis during 6-month follow up. *Circulation* 1990; 81:1849-1859
10. Cook SL, Eigler NL, Shefer A, Goldenberg T, Forrester JS, Litvack F. Percutaneous excimer laser coronary angioplasty of lesions not ideal for balloon angioplasty. *Circulation* 1991; 84:632-643
11. Litvack F, Margolis JR, Cummins F, Bresnahan J, Goldenberg T, Rothbaum D, Leon MB, Untereker W, Kent KM, King SB, Holmes DR, Block PC, Douglas J, Forrester J. for the ELCA investigators: Excimer coronary (ELCA) registry: report of the first consecutive 2080 patients. *J Am Coll Cardiol* 1992; 19:276A (abstract)
12. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser angioplasty. *Am J Cardiol* 1992; 70:1533-1539
13. Bittl JA, Sanborn TA. Excimer laser-facilitated coronary angioplasty. Relative risk analysis of acute and follow-up results in 200 patients. *Circulation* 1992; 86:71-80
14. Margolis JR, Mehta S. Excimer laser coronary angioplasty. *Am J Cardiol* 1992; 69:3F-11F
15. Oswald H, Schernikau U, Baumbach A, Geschwind HJ, Karsch K, Fleck E. for the investigators of the European Registry. Quantitative results of the European coronary excimer laser angioplasty registry. *Eur Heart J* 1993; 14:2296 (abstract)
16. Excimer laser coronary angioplasty versus balloon angioplasty used in long coronary lesions: the AMRO-trial Piek JJ, Appelman Yj, Strikwerda S, Koolen JJ, David G, de Feyter PJ, Serruys PW, Montauban van Swijndregt E, Koelemay MJ, Tyssen JG. *Eur Heart J* 1994; (abstract)
17. Gijsbers GHM, Sprangers RLH, Keijzer M, De Bakker JMT, Van Leeuwen TG, Verdaasdonk RM, Borst C, Van Gemert MJC. Some laser-tissue interactions in 308 nm excimer laser coronary angioplasty. *J Interven Cardiol.* 1990;3:231-241
18. Gijsbers GHM, Sprangers RLH, Van Gemert MJC. Excimer laser coronary angioplasty: laser-tissue interactions at 308 nm. In: *Primer on Laser Angioplasty*, 2nd edition. Ginsburg R, Geschwind H. (Eds.), Futura Publishing Co, Inc. Mount Kisco NY, 1992. Chapter 13, pp. 217-241
19. Gijsbers GHM, Van den Broecke

DG, Sprangers RLH, Van Gemert MJC. Effect of force on ablation depth for a XeCl excimer laser beam delivered by an optical fiber in contact with arterial tissue under saline. *Lasers Surg Med.* 1992;12: 576-584

20. Davis GS, Bott-Silverman C, Goormastic M, Gerrity RG, Kittrell C, Feld M, Kramer JR. Gas volume quantitation during argon ion laser ablation of atheromatous aorta in blood and 0.9 % saline media with an optically shielded catheter. *Lasers Surg Med* 1988;8:72-76
21. Van Leeuwen TG, Van Erven L, Meertens JH, Motamedi M, Post MJ, Borst C. Origin of arterial wall dissections induced by pulsed excimer and mid-infrared laser ablation in the pig. *J Am Coll Cardiol.* 1992; 19:1610-1618
22. Van Leeuwen TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced by excimer laser pulse causes microsecond arterial dilatation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993;87:1258-1263
23. 308 Excimer Laser Tissue Interaction Using a Multi Fiber Catheter. J. Hamburger, G. Gijsbers, R. Sprangers, M. van Gemert, A. Dunning. *J Am Coll Cardiol*, 21;2: 385 A, 938-69 (Abstract)
24. Isner JM, DeJesus SR, Clarke RH, Gal D, Rongione AJ, Donaldson RF. Mechansism of laser ablation in an absorbing fluid field. *Lasers Surg Med* 1988; 8:543-554

CHAPTER 2

Method for the assessment of ablation performance: a novel technique for direct evaluation of *in vitro* excimer laser tissue ablation

Geert H.M. Gijsbers, Jaap N. Hamburger,

Jeannette H.A.M. Wonders, Pieter E. Zondervan,*

Patrick W. Serruys

(Submitted for publication to *Circulation*)

METHOD FOR THE ASSESSMENT OF ABLATION PERFORMANCE: A NOVEL TECHNIQUE FOR DIRECT EVALUATION OF *IN VITRO* EXCIMER LASER TISSUE ABLATION

ABSTRACT

Background-Light microscopy (LM) forms an integral part of *in vitro* evaluation of laser-tissue interaction. However, LM - and the making of LM preparations - is in general a time consuming and costly affair. Direct Microscopy (DM) was designed as a relatively quick and less costly alternative method for the direct evaluation of excimer laser-tissue interaction.

Methods and Results-Using a XeCl 308 nm excimer laser and standard 1.7 mm coronary laser catheters, ablation craters were made in porcine aortic tissue samples. Images were visualized and digitally sampled using a color CCD video camera mounted on a microscope, and stored on CD-ROM for off-line analysis. Crater dimensions (in number of pixels) were assessed using standard image processing software. Following fixation in 10 % formalin, ablation craters were cut in the medial plane. One series of crater halves were prepared for standard LM reference, while the opposite halves were immersed in a toluidin-blue solution and repositioned under the microscope. We defined six items related to ablation efficacy (quantitative assessment) and seven items related to collateral tissue damage (semi-quantitative scale; 0 = absence of an item, 2 = worst case). To test the relative accuracy of DM vs. LM, randomly chosen craters were analyzed by an independent reviewer who was blinded for the experimental parameters of crater formation. The concordance for presence or absence of a phenomenon was: false positive 2.5%, false negative 5% (DM vs. LM, intra-observer concordance of 92.5%, Cohen's Kappa=0.68, 95% Confidence Interval 0.35-1.02). When the presence of a phenomenon was specified (the "severity score"), the concordance was 70% (Cohen's Kappa=0.43, 95% Confidence Interval 0.23-0.63).

Conclusion-Although LM remains the "golden standard" these results justify the use of DM as a routine technique for rapid evaluation of large quantities of tissue samples in the setting of applied research.

Excimer laser coronary angioplasty (ELCA) was introduced in 1987.[1] Since, several studies have been published reporting on the clinical benefits and complications of this treatment modality.[2-4] As the removal of atherosclerotic plaque was originally attributed to photochemical dissociation of illuminated tissue only,[5] later publications stressed the importance of explosive tissue water vaporization as an essential part of the ablation process.[6,7] It transpired that the very nature of this ablation process was not only responsible for the effectiveness of ELCA, but also for its complications.[8,9] Previously, we described the influence of catheter configuration and various laser parameters on the efficacy and quality of *in vitro* laser tissue ablation.[7,10-12] The evaluation of these variables and their impact on tissue ablation invariably involves the assessment of large quantities of tissue samples on a routine basis. Standard methods for *in vitro* evaluation include histology for light microscopy (LM) and scanning- or transmission electron microscopy.[5-7,13-18] However, these methods are both costly and time consuming. Therefore, we developed a new, less elaborate and less expensive *m*ethod for *a*ssessment of *a*blation *p*erformance (MAAP). The purpose of this paper is to describe this practical tool in the evaluation of excimer laser tissue interaction.

METHODS

CRATER FORMATION

All experiments were performed using fresh thoracic porcine aortic tissue samples. Any loose connective tissue attached to the adventitia was removed using tweezers and a pair of surgical

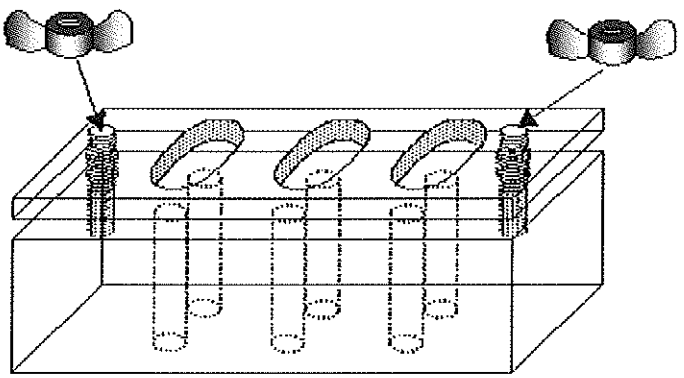


Figure 1 Tissue holder. The tisue samples were positioned between the upper and the bottom part. A laser catheter was positioned perpendicularly on the tissue through the oval opening in the upper part of the tissue holder. The channels in the bottom part allowed for unhampered progression of the catheter after perforation of the tissue sample.

scissors. The aorta was cut in segments of approximately 5 cm length. These segments were then cut lengthwise, spread open with the intima facing upwards and placed in a tissue holder (Fig 1). The tissue holder was positioned in a container, and immersed in saline (0.9% NaCl). The proximal part of a standard 0.014" coronary guidewire was cut in 10 segments of approximately 5 cm each. Subsequently, tissue samples were pierced with these guide wire segments. Excimer laser multifiber catheters (Spectranetics Inc, USA) were connected to a Spectranetics CVX-300 XeCl-excimer laser system, emitting ultra violet light at a wavelength of 308 nm. The catheters were positioned in a specially designed set-up that allowed for a stabile perpendicular position of the catheter tip on the tissue sample (Fig 2). The proximal part of the 0.014" guidewire was inserted in the distal guidewire lumen after which the laser catheter was placed in a perpendicular position on the aorta intima. Penetration of the catheter into the tissue during laser activation was controlled by means of a weight, placed on a shaft weight table. This experimental set-up has previously been described in detail.[11] For the purpose of statistical analysis, 10 ablation craters were made for each set of laser parameters.

IMAGE PROCESSING

The samples were observed using a microscope (Olympus BH-2) and NeoPlan 5x objective and visualized using a color CCD video camera (Sony DXC-151P) mounted on the microscope. Images were sampled in a PC using a

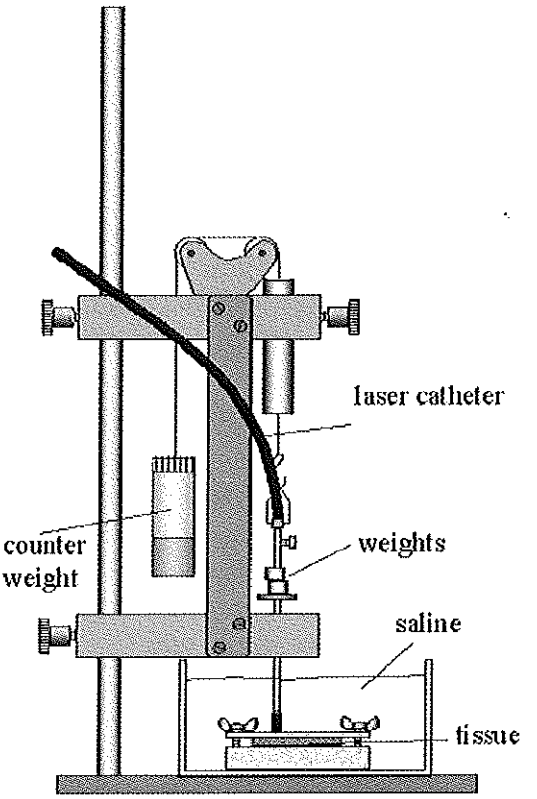


Figure 2 Set-up for laser tissue ablation at a constant pressure. A laser catheter was mounted in a shaft that could move freely in vertical direction. Weights were added to the shaft to control the pressure of the catheter on the tissue.

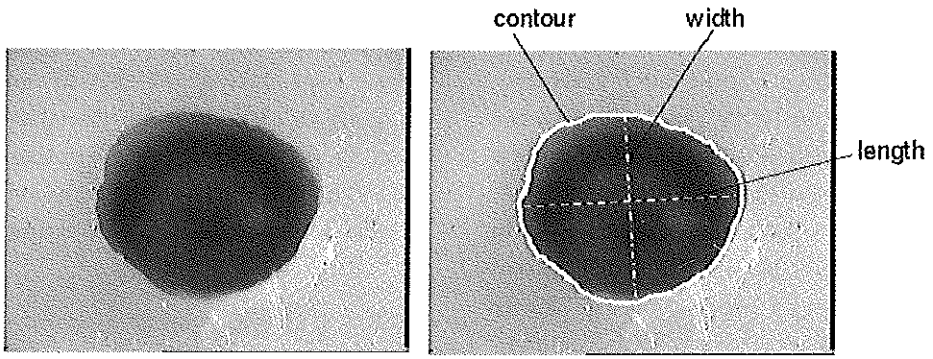


Figure 3 Example of an unfixed microscopic crater top view. The left image is the unprocessed image; the right image indicates the width and length of the crater and the crater contour that was used to determine the crater cross-sectional area.

frame grabber (Iris video digitizer, Inside Technology, The Netherlands). Twenty-four bit RGB pictures of 768 x 574 pixel size were obtained in which 296 pixels corresponded to 1 mm of physical length. Dimensions in number of pixels were assessed using standard image processing software (Adobe Photoshop 4.0, Adobe Systems, USA). Finally, the images were stored on CD-ROM for off-line data analysis.

TISSUE SAMPLE PREPARATION

Immediately following the creation of ablation craters, the catheter was pulled-back and the tissue sample was removed from the holder. The tissue samples were placed on a microscopy glass slide. Excess saline was gently removed using an absorbing tissue after which the slide was positioned on the stage of a microscope. As the samples were too thick to allow for illumination from below, they were illuminated from above using a fiberoptic bundle halogen light source (Schott KL 1500, Germany). The light bundle was adjusted such that it was incident under a grazing angle. Using the microscope mounted CCD video camera, images were taken from the crater top circumference to measure the crater length, width and cross-sectional area as indicated in Figure 3. Then, the tissue samples were fixed in 10 % formalin (aqueous solution of formaldehyde) at room temperature, for a 24 hour period. Following fixation, the tissue was rinsed with distilled water to remove any formaldehyde remains. With the ablation craters facing upwards, the samples were placed on paper tissue sheets providing a suitable support. The craters were cut in the medial plane into two halves using

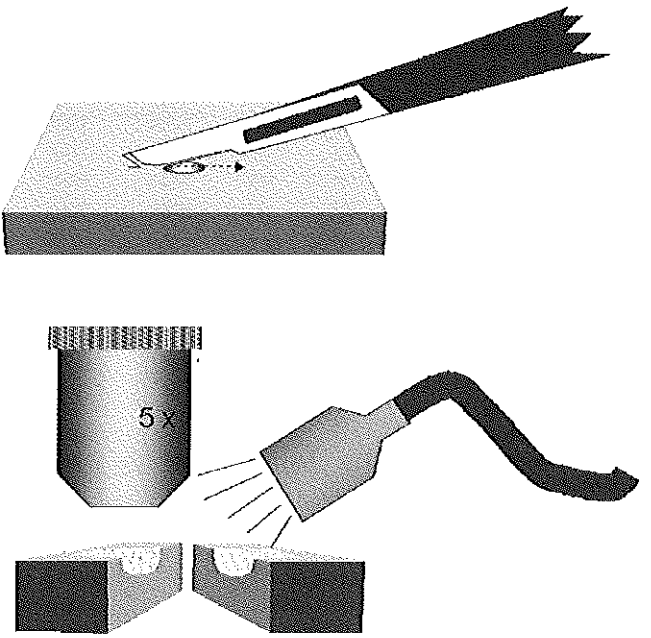


Figure 4 Tissue preparation for Direct Microscopy. A fixed ablation crater was cut in half by a scalpel. The two halves were colored by a Toluidin-Blue solution and subsequently observed under a microscope as indicated in the bottom drawing. A light beam from a fiberoptic, halogen light source (Schott KL 1500, Germany), illuminated the halves.

a scalpel no. 15 (Swann-Morton, UK) (Fig 4). Subsequently, the crater halves were removed from the aortic tissue sample, leaving a tissue rim of approximately 2 millimeters. In order to reduce the chance of making cutting artifacts, a new scalpel was used for every 10 craters. To assess the accuracy of MAAP as compared to standard histological techniques, one series of crater halves (randomly selected) were imbedded in paraffin. These tissue samples were cut in 4 mm slides and stained with a hematoxylin-eosin dye for light microscopic reference. The remaining series of crater halves (or "direct microscopic samples (DM)") were immersed in a toluidin-blue solution for approximately 10 seconds in order to enhance contrast. The colored halves were repositioned under the microscope (Fig 4). In order to obtain sharp images of all parts of the sample, the cutting plane of the samples was placed parallel to the microscope stage. As drying of the tissue samples could potentially cause some tissue shrinkage, images were taken immediately after coloring. As the average tissue shrinkage due to formalin-fixation was measured to be less than 2%, this was not considered to be a relevant cause of artifact (Table 1).

TABLE 1. Tissue crimp due to fixation in formalin

Crater	length before fixing (pix)	Length after Fixing (pix)	change %	width before fixing (pix)	Width after Fixing (pix)	change %	area before fixing (pix)	area after fixing (pix)	change %
240601	302	313	3.6	230	222	-3.5	51200	51600	0.8
240602	360	354	-1.7	290	303	4.5	71900	72100	0.3
240631	350	339	-3.1	282	257	-8.9	79000	69000	-12.7
240638	388	377	-2.8	298	297	-0.3	90600	85800	-5.3
250611	423	458	8.3	349	350	0.3	113800	125300	10.1
250615	421	434	3.1	342	344	0.6	115000	115800	0.7
Average			1.2			-1.2			-1.0

MICROSCOPIC EVALUATION

The ablation craters were analyzed with regard to the efficiency of tissue removal and the extent of collateral mechanical damage. These two groups were subdivided in six items related to the quantification of tissue removal (including the length, width, and crater area mentioned above) and seven items related to collateral tissue damage. The item characteristics are schematically depicted in Figures 5 and 6. The items of the first group were measured in pixels (quantitative assessment) and the items of the second group were determined semi-quantitatively. For this purpose we used a scale from 0 to 2, with 0 being the absence of a given item and 2 its maximum appearance (worst case). It

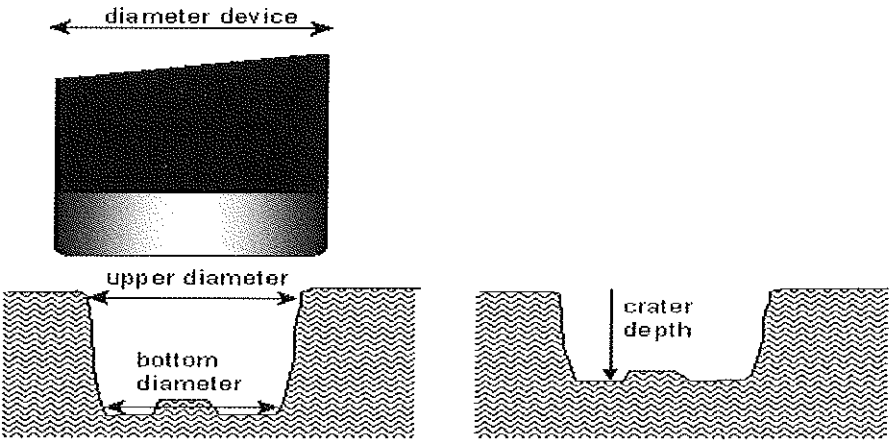
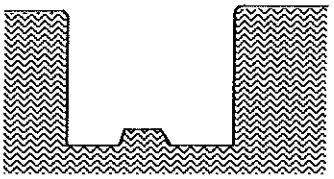
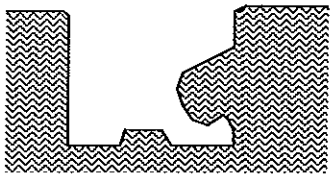


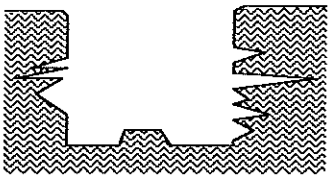
Figure 5 Using Direct Microscopy, the upper diameter, the bottom diameter and the crater depth were determined and compared with the diameter of the laser catheter device.



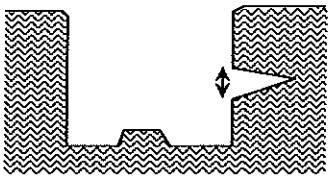
Straight hole, no observable mechanical damage



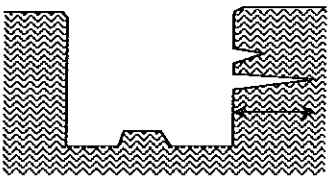
Lobe presence:
0: absence
1: a lobe up to 1/2 hole diameter
2: a lobe larger than 1/2 hole diameter



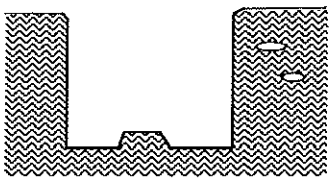
Torn appearance:
0: absence
1: a few tears (1-3)
2: many (>3)



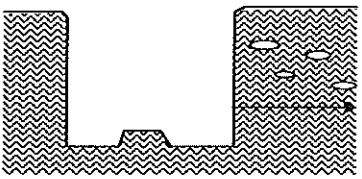
Tear width:
0: absence
1: clearly present/not very large
2: large



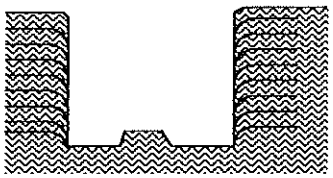
Tear depth:
0: absence
1: depth < 1/2 hole diameter
2: depth > 1/2 hole diameter



Vacuole amount:
0: absence
1: a few (1-5)
2: many (>5)



Vacuole depth (distance to crater wall)
0: absence
1: depth < 1/2 hole diameter
2: depth > 1/2 hole diameter



Pressed appearance:
0: fibers straight
1: fiber ends pressed less than 45 deg.
2: fiber ends pressed between 45 and 90 deg.

Figure 6 The scores of different tissue damage characteristics, schematically depicted.

must be noted that "tear width" and "tear depth" were not independent from "torn appearance", just as "vacuole depth" was not independent from "vacuole presence" (Fig 6).

MAAP EVALUATION

To test the relative accuracy of the MAAP method, ten craters (both DM samples and their LM counterparts) were randomly chosen. Examples are shown in Figures 7 and 8. Subsequently, an independent reviewer (*) who was blinded to the experimental parameters of crater formation, analyzed the samples. Also, the order in which the samples were reviewed was such that the laser parameters for any LM preparation did not correspond with the laser parameters of the ensuing DM preparation, in order to avoid any bias.

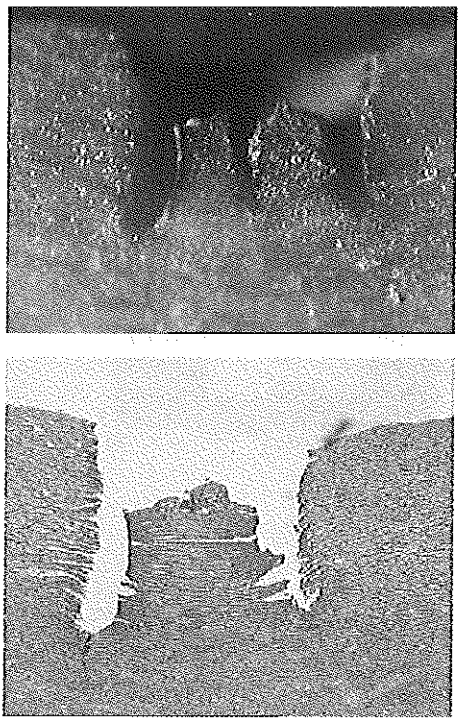


Figure 7 Example of Direct Microscopy (upper image) and corresponding Light Microscopy (bottom image) of a laser ablation crater. The intact adventitia indicated that the laser catheter had not perforated the tissue samples (porcine aorta).

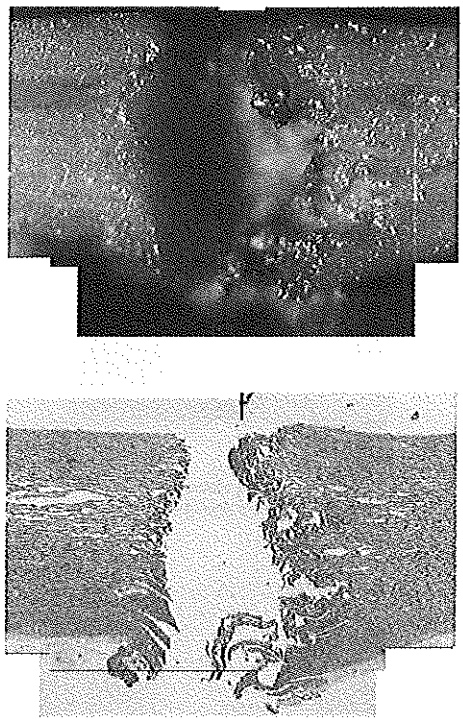


Figure 8 Example of Direct Microscopy (upper image) and corresponding Light Microscopy (bottom image) of a laser ablation crater. The laser catheter perforated the tissue samples, causing extensive collateral damage. Note the presence of lobes, tears, vacuoles, and pressed fibers.

TABLE 2A.

DM\LM

Frequency	+	-	Total
+	33	1	34
-	2	4	6
Total	35	5	40

Kappa=0.68, 95% Confidence Interval 0.35-1.02

DM= direct microscopy, LM= light microscopy

TABLE 2B.

DM\LM

Frequency	0	1	2	Total
0	4	2	0	6
1	1	11	13	25
2	0	5	34	39
Total	5	18	47	70

Kappa=0.43, 95% Confidence Interval 0.23-0.63

DM= direct microscopy, LM= light microscopy

STATISTICAL ANALYSIS

The results are presented in a 2 x 2 and a 3 x 3 table. A Cohen's Kappa coefficient was calculated to determine the level of agreement between the two evaluation methods.

RESULTS

The average time needed for tissue preparation, image acquisition and microscopic assessment of a crater was approximately 4 minutes. The results of the LM and DM evaluation are given in Tables 2A and B. Comparing both assessment techniques we first calculated the concordance for presence or absence of a given phenomenon using the results of LM as the "golden standard". The results were: false positive 2.5%, false negative 5% (DM vs. LM, intra-observer concordance of 92.5%, Kappa=0.68, 95% CI 0.35-1.02, Table 2A). When the presence of a phenomenon was further specified (the "severity score"), the concordance was 70% (Kappa=0.43, 95% CI 0.23-0.63, Table 2B).

DISCUSSION

The aim of the proposed method was to allow for a relatively quick and low-cost assessment of *in vitro* excimer laser ablation efficiency and laser induced mechanical trauma of vascular tissues. In addition, the digital storing of images using MAAP allowed for off-line analysis of histology data. Notwithstanding these advantages, it was by no means the intention to replace light microscopy as the golden standard. Besides the possible advantages, a few limitations of MAAP were noted. First, MAAP provides information about one single plane only. Also, the resolution of this system is approximately 3 micron, while the resolution of LM is approximately 1 micron. Finally, the number of tissue samples evaluated for

this report was limited to a set of ten craters (i.e. ten sets of different laser parameters) only. However, we believe that an intra-observer concordance of 93% was sufficiently high to justify the use of MAAP as a routine technique for rapid evaluation of large quantities of tissue samples in the setting of applied research.

REFERENCES

1. Litvack F, Grundfest W, Eigler N, Tsoi D, Goldenberg T, Laudenslager J, Forrester J, Percutaneous excimer laser coronary angioplasty. *Lancet* 1989; July 8:102-103
2. Litvack F, Eigler N, Margolis J, Rothbaum D, Bresnahan JF, Holmes D, Untereker W, Leon M, Kent K, Pichard A, King S, Ghazzal Z, Cummins F, Krauthamer D, Palacios I, Block P, Hartzler GO, O'Neill W, Cowley M, Roubin G, Klein LW, Frankel PS, Adams C, Goldenberg T, Laudenslager J, Grundfest WS, Forrester JS for the ELCA Investigators. Percutaneous Excimer Laser Coronary Angioplasty: Results in the First Consecutive 3,000 Patients. *J Am Coll Cardiol* 1994; 23:323-329
3. Appelman YEA, Piek JJ, de Feyter PJ, Tijssen JGP, Strikwerda S, David GK, Serruys PW, Margolis JR, Koelemay MJ, van Swijndregt E, Koolen JJ. Excimer Laser Coronary Angioplasty versus Balloon Angioplasty in the Treatment of Obstructive Coronary Artery Disease: a Randomized Clinical Trial. *Lancet* 1996, 347:79-84
4. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol*, 1997;30:649-56
5. Grundfest WS, Litvack F, Forrester JS, Goldenberg T, Swan HJC, Morgenstern L, Fishbein M, McDermid IS, Rider DM, Pacala TJ, Laudenslager JB. Laser ablation of human atherosclerotic plaque without adjacent tissue injury. *J Am Coll Cardiol* 1985; 5:929-33
6. Leeuwen van TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced by excimer laser pulse causes microsecond arterial dilation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993; 87:1285-1293
7. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, Van Marle J, Van den Broecke DG, Hanekamp CEE, Van Gemert MJC, Serruys PW. Excimer Laser Coronary Angio-plasty: A physical perspective to clinical results. In: Topol E, Serruys PW (eds), *Current Review of Interven-*

tional Cardiology, 2nd edn (Philadelphia: Current Medicine, 1995); 159-172.

8. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser angioplasty. *Am J Cardiol* 1992; 70:1533-1539
9. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264-9
10. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution to reduce vessel trauma during excimer laser angioplasty. *Semin Intervent Cardiol* 1996; 1: 143-148
11. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution and high-density laser techniques in excimer laser coronary angioplasty. In: *Current Review of Interventional Cardiology*, third edition (Holmes and Serruys Ed.) 1996, Current Medicine, Philadelphia
12. Appelman YEA, Piek JJ, Verhoofstad GGAM, Gijsbers GHM, van Gemert MJC. Tissue ablation and gas formation of two excimer laser systems: an *in vitro* evaluation on porcine aorta. *Lasers Surg Med* 1996; 18:197-205.
13. Grundfest WS, Litvack IF, Goldenberg T, Sherman T, Morgenstern L, Carroll R, Fishbein M, Forrester J, Margitan J, McDermid S, Pacala TJ, Rider DM, Laudenslager JB. Pulsed ultraviolet lasers and the potential for safe laser angioplasty. *Am J Surg* 1985; 150:220-226
14. Isner JM, Donaldson RF, Deckelbaum LI, Clarke RH, Laliberte SM, Ucci AA, Salem DN, Konstam MA. The excimer laser: gross, light microscopic and ultrastructural analysis of potential advantages for use in laser therapy of cardiovascular disease. *J Am Coll Cardiol* 1985; 6:1102-09
15. Furzikov NP, Karu TI, Letokhov VS, Beljaev AA, Ragimov SE. Relative efficiency and products of atherosclerotic plaque destruction by pulsed laser radiation. *Lasers Life Sci* 1987; 1:265-274
16. Higginson LAJ, Farrell EM, Walley VM, Taylor RS, Keon WJ. Arterial response to excimer and argon laser irradiation in the atherosclerotic swine. *Lasers Med Sci* 1989; 4:85-92
17. Van Leeuwen TG, Van Erven L, Meertens JH, Motamedi M, Post MJ, Borst C. Origin of arterial wall dissections induced by pulsed excimer and mid-infrared laser ablation in the pig. *J Am Coll Cardiol* 1992; 19:1610-1618
18. Jansen ED, Le TH, Welch AJ.

Excimer, Ho:YAG, and Q-switched Ho:YAG ablation of aorta: a comparison of temperatures and tissue damage *in vitro*. *Applied Optics* 1993; 32:526-534

CHAPTER 3

The usefulness of slow-speed automated catheter advancement for optimization of excimer laser-tissue debulking

Jaap N. Hamburger, Geert H.M. Gijsbers,

Jeannette H.A.M. Wonders, Ronald van der Putten,

Virgil H.C. Ansems, Thelma Witteveen, Patrick W. Serruys

(Submitted for publication to *Circulation*)

THE USEFULNESS OF SLOW-SPEED AUTOMATED CATHETER ADVANCEMENT FOR OPTIMIZATION OF EXCIMER LASER-TISSUE DEBULKING

ABSTRACT

Background-Clinical studies have thus far failed to prove the long-term advantage of excimer laser coronary angioplasty (ELCA) over PTCA alone. The efficacy of ELCA depends on the choice of laser parameters, the amount of pressure the catheter exerts on the lesion and the speed of catheter advancement. As these parameters are operator dependent, we tried to objectively define the relevance of each of these variables.

Methods and Results-A CVX-300 XeCl excimer laser (308 nm, 200 ns, 25 Hz) and standard 1.7 mm multifiber catheters (Spectranetics, USA) were used to ablate craters in fresh porcine aortic tissue. Experiments were performed in a pressure driven advancement mode (PDA, weights of 12-36 grams, duration of 30 seconds) or a speed driven advancement mode (SDA, predefined catheter travel of 1.7 mm, speeds of 0.06-0.51 mm/s). Tissue vaporization was monitored using high-speed videography. The insoluble gas production and temperature increase were measured on-line. Direct microscopy was used to measure the ablation efficacy and the surrounding tissue damage. In PDA, the ablation efficacy was inversely related to the amount of pressure applied and in SDA inversely related to catheter advancement speed. Tissue tearing was related to tissue vaporization, while vacuolization of the tissue seemed related to accumulation of insoluble gas. Parameters for optimal ablation efficacy (SDA, 60 mJ/mm^2 – 0.06 mm/s) resulted in the least tissue damage as well. In SDA at 60 mJ/mm^2, the gas yield increased by a factor of seven when decreasing catheter speed to 0.06 mm/s (74 ± 9 µl). The maximum temperature increase above ambient was 22 ± 3 °C.

Conclusions-In order to allow for an operator independent evaluation of optimal conditions for debulking (60 mJ/mm^2 - 0.06 mm/s) we introduce the concept of an automated catheter advancement device. However, when optimizing debulking conditions the possibility of arterial thermal damage and myocardial ischemia due to the accumulation of insoluble gas must be taken into account.

Since its introduction in 1988, a number of reports on the clinical experience with excimer laser coronary angioplasty (ELCA) have been published.[1-8] In these, ELCA did not seem to have a long-term clinical advantage over percutaneous transluminal coronary angioplasty (PTCA) alone.[2,3,6,8] Various mechanisms have been suggested as an explanation for the absence of a sustained clinical advantage, such as a limited debulking capacity, an excess of vessel wall trauma and/or a relatively high late luminal loss.[1,4,9,10-12] To better understand the clinical results of ELCA, a number of *in vitro* studies have been performed to elucidate basic laser-tissue interactions.[13-19] Currently, it is assumed that excimer laser tissue removal is the result of tissue vaporization due to thermal accumulation ("fast expanding vapor bubbles") and photochemical dissociation induced formation of insoluble gas. It emerged that the process of tissue vaporization can be influenced by varying the amount of pressure exerted on the catheter tip during ablation.[17] Also, adjusting the advancement speed of the catheter during ablation[1,19] could influence the extent of debulking. The efficacy of ELCA therefore, could be determined by the choice of laser parameters, the amount of pressure the catheter exerts on the obstructing tissue or the speed with which the catheter is advanced through the lesion. As these parameters are intrinsically operator dependent, we tried to objectify the relevance of each of these variables separately. For this purpose, the *in vitro* debulking capacity of a standard 1.7 mm ELCA catheter was investigated using two different experimental modes. The results of a "pressure driven advancement" (PDA) mode, in which during the application of laser pulses a constant weight was applied on the catheter, were compared with the results of a "speed driven advancement" (SDA) mode, in which a constant speed was applied to the catheter. Finally, to allow for an operator independent clinical evaluation of these *in vitro* results, we sug-gest the introduction of an "automated catheter advancement device (AcAD)".

METHODS

LASER AND LASER CATHETER

The laser was a CVX-300 XeCl excimer laser (Spectranetics Inc, Colorado Springs, CO) emitting ultraviolet light at a wavelength of 308 nm with a pulse duration of approximately 200 ns. For all experiments the pulse repetition rate was 25 Hz. A standard multifiber catheter (Vitesse-C 1.7 mm, Spectranetics Inc.) was used. The catheter contained 135 silica fibers of 61-µm diameter, concentrically distributed around a central guide wire lumen. The catheter outer

diameter was 1.62 ± 0.03 mm; the diameter of the outer rim of the fiber bundle was 1.29 ± 0.05 mm. The outer diameter of the guide wire channel was 0.52 ± 0.03 mm. The effective light emitting area was 0.39 ± 0.03 mm^2. The energy density used was 45 mJ/mm^2 or 60 mJ/mm^2. We chose these values based on earlier observations, suggesting that ablation at energy densities below 45 mJ/mm^2 was negligible, while 60 mJ/mm^2 is currently the clinically recommended maximum for this type of catheter.

TISSUE SAMPLES

Laser ablation lesions (henceforward called "craters") were made in fresh porcine thoracic aortic tissue samples. Loose connective tissue surrounding the adventitia was removed and the aorta was cut in tubular segments of 3 to 4 cm. The thickness of the samples chosen was approximately 2 mm. These segments were kept in an airtight container on ice. Just prior to use, a segment was cut longitudinally and spread with the intima faced upward, thus creating a rectangular tissue sample of approximately 4 x 3 cm. The segment was mounted in a holder, which was placed in a glass container (Fig 1) and immersed in saline (NaCl 0.9 %)

PRESSURE DRIVEN ADVANCEMENT (PDA)

PDA experiments were performed by means of a set-up as shown in Figure 2. A laser catheter was mounted in a shaft that could move freely in the vertical direction. A counter weight ensured zero pressure when no weights were added. Weights of 12, 24 or 36 grams were added to the shaft to vary the pressure of the catheter on the tissue. The movement of the catheter was recorded using a position transducer (model

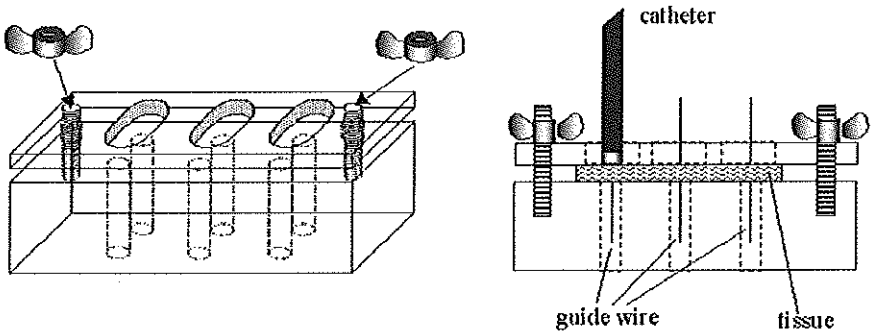


Figure 1 Tissue holder (base dimensions 7 x 3cm). A rectangular piece of tissue was mounted on the tissue holder. Three slots allowed for access to the tissue. Cut pieces of a 0.014" guide wire were pierced through the tissue providing guide wire guidance of a catheter. The catheter was free to perforate the tissue into channels in the bottom part of the holder.

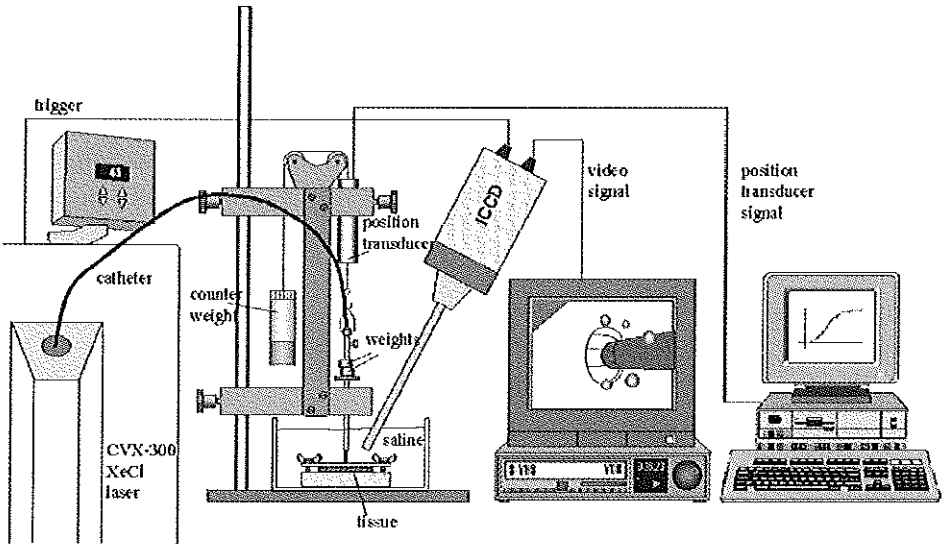


Figure 2 Set-up for pressure driven advancement.

MTN/DL12.5, Monitran Ltd., Penn, UK) sampled by an A/D converter in a personal computer (PC) (model DAS 1401, Keithley Metrabyte, Taunton, MA). An advancement recording started at the first laser pulse. The recording stopped if the catheter movement stopped, the catheter had perforated the tissue, or a maximum of 30 seconds of continuous laser activation had been reached. Fast expanding vapor bubbles were observed by means of an intensified CCD video camera (model 4Quik05, Stanford Computer Optics Inc. USA) equipped with a borescope (model F100, Olympus Optical Co. Japan) for close-up imaging in a saline environment. The image intensifier of the camera served as an electronic shutter and was triggered by an electronic pulse from the laser. Short exposure times were used to image the fast expanding bubbles at the moment of maximum expansion. The delay time between the laser trigger signal and the exposure time of the image intensifier was adjusted by means of a PC. Typical delay- and exposure times were 80 μs and 5 μs, respectively. Images were recorded using a S-VHS video recorder (Panasonic Model NV-FS200, Japan). Those video frames showing the largest bubble size were captured in a PC using a video frame grabber (Iris Video Digitizer, Inside Technology, Amersfoort, The Netherlands). The diameters of bubbles and catheter were determined by means of image analysis software (Photoshop,

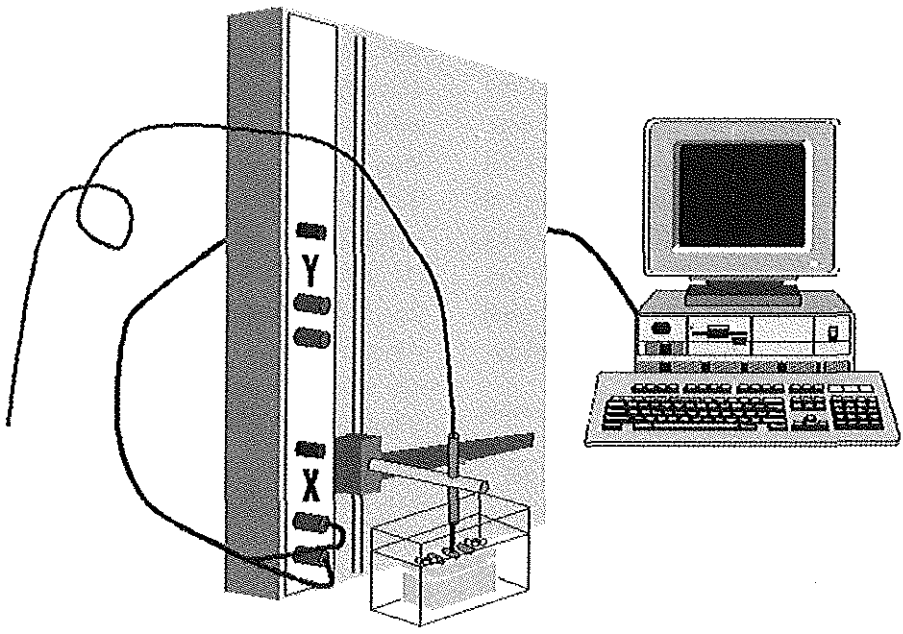


Figure 3 Set-up for speed driven advancement.

Adobe Inc., USA). For statistical purposes, 10 craters were made for each set of experimental parameters.

SPEED DRIVEN ADVANCEMENT (SDA)

To provide a constant speed, the catheter was fixed in a shaft that was mounted on the X-direction carriage of an XY recorder (Model BD 90, Kipp & Zonen, Delft, The Netherlands, Fig 3). The catheter was positioned on the tissue using the zero-adjust control of the recorder. The X-direction connector controlled the movement of the catheter, through a voltage provided by a D/A-converter (PC-LabCard PCL-711S, Advantech, Taipei, Taiwan). The voltage was varied by means of a Pascal program that allowed the choice of speed and the delay between the onset of laser activation and the start of catheter advancement. The applied speeds were 0.51 mm/s, 0.24 mm/s, 0.12 mm/s and 0.06 mm/s. The sequence started with 0.51 mm/s as preliminary experiments had shown that speeds in excess of this value resulted in relatively poor ablation. The remaining speeds were obtained by arbitrarily halving each previous speed. Speeds below 0.06 mm/s were not used as they were deemed to be impractical for clini-

cal use. To prevent perforation of the approximately 2.0 mm diameter tissue samples, the total advancement of the catheter during lasing was 1.7 mm. Typically, the laser pulse train started one second prior to the initiation of catheter movement. This was based on observations in previous PDA studies showing that invariably, it took several pulses before actual catheter advancement started. The total number of pulses applied at any speed is given in Table 1. The diameter of fast expanding bubbles was measured as described above. For statistical purposes, 10 craters were made for any combination of parameters.

Table 1. Number of pulses during a catheter advancement of 1.7mm, including a 1 second rest before catheter advancement.

Speed (mm/s)	0.51	0.24	0.12	0.06
Nr. of pulses	108	202	379	733

MICROSCOPIC ASSESSMENT OF ABLATION PERFORMANCE

Ablation efficacy and quality were determined using a method described in detail elsewhere.[20] In short, immediately following the creation of 10 ablation craters a microscopic image was made of the top-view of each unfixed crater by means of a microscope (BH-2 + NeoPlan 5 x objective, Olympus, Japan) equipped with a color CCD-camera (DXC-151P, Sony, Japan). The tissue sample with 10 craters was then fixed in formalin (10% formaldehyde) for 24 hours. Subsequently, each crater was cut in halves along the long axis. The halves were stirred in a diluted Toluidine-blue solution for image enhancement. All images were stored on PC hard disk using a video frame grabber (Iris Video Digitizer, Inside Technology, Amersfoort, The Netherlands). For analysis, standard image analysis software (Photoshop, Adobe Inc, USA) was used. From these images a number of quantitative and semi-quantitative features were scored. From the unfixed top-view image, the cross sectional area (in mm^2) and the ratio of the long- and short axis of the superior circumference were measured. From the fixed and stained crater halves were determined the presence or absence of perforation of the adventitia, the ratio of crater depth and 1.7 mm catheter travel (in SDA) and the ratio of crater bottom diameter and the catheter outer diameter. In a 0-2 classification (0 = absence of a phenomenon, 2 = worst case) the presence of residual tissue on the crater wall (lobes), the extent of tissue tears (torn appearance) and the extent of vacuolization in the crater wall were assessed. Also, the bending of tissue fibers adjacent to the crater wall (bending of 0°, 0 - 45° or 45 - 90°) was assessed. As a result, the score was inversely related to the quality of tissue ablation.

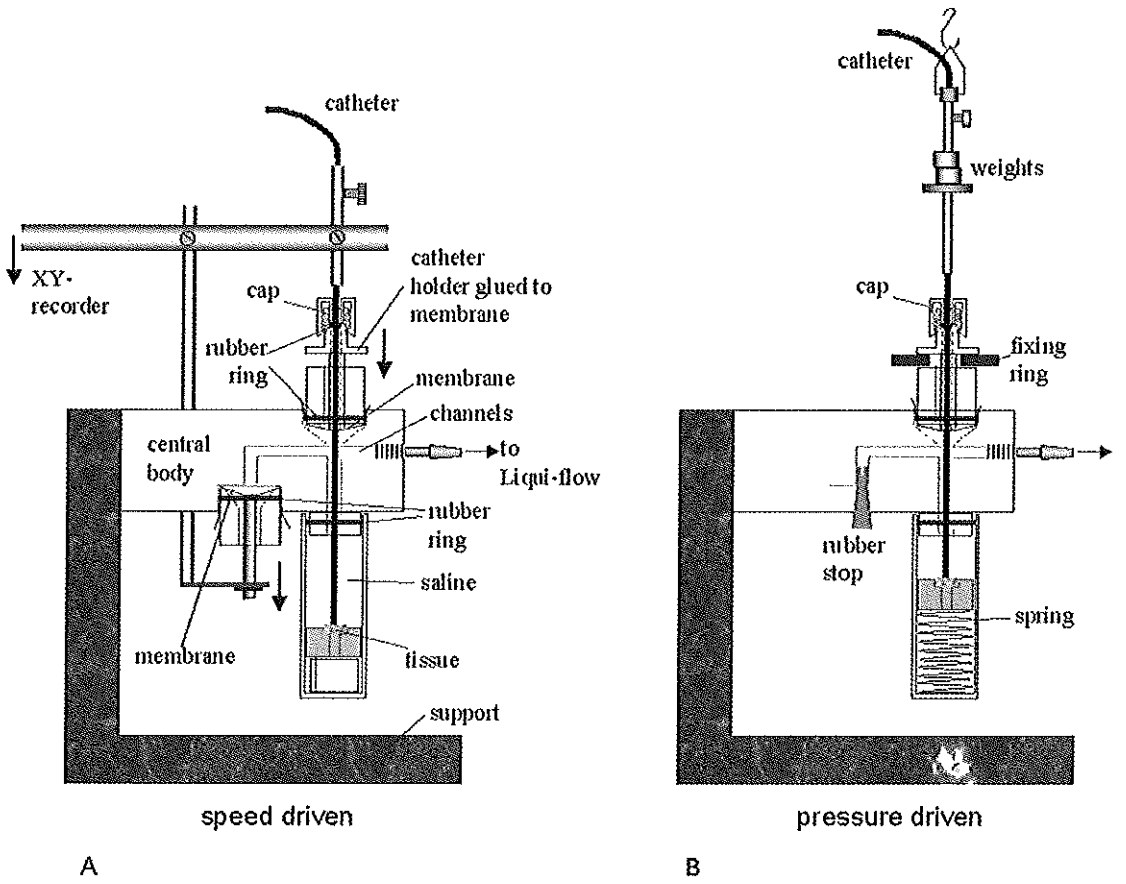


Figure 4 Gas volume sampler. A) Speed driven advancement B) Pressure driven advancement

GAS YIELD MEASUREMENT

For measurement of insoluble gas production, a 5 mm diameter disk was punched from a rectangular tissue segment and put in a gas sample chamber (Fig 4). Gas measurements were based on the displacement of saline by accumulating gas. The device was designed to compensate for the inherent saline displacement due to forward movement of the catheter during SDA experiments. A catheter was positioned on a circular piece of tissue in a tube that was fitted airtight to the central body by a rubber ring. The catheter was guided through a holder that was fitted airtight by tightening the cap. The tube and channels in

the central body of the device were filled with saline. Gas produced by excimer laser pulses caused a displacement of saline. The saline escaped through a flow-measuring device (LiquiFlow Model L1-FB-11-0, Bronkhorst Hi-Tec, Veenendaal, The Netherlands). The flow provided a proportional voltage in the range of 0 to 11 µl/s. The voltage was sampled and processed by means of a PC-based A/D converter (model DAS 1401, Keithley Metrabyte, Tounton, MA, USA).

A) SDA GAS MEASUREMENTS

The catheter holder was glued on a thin latex membrane. The catheter was guided through a central hole in the membrane, the purpose of which was to ensure unhampered movement of the catheter in the airtight cell. The XY recorder (Fig 3) advanced the catheter. To compensate for the inherent saline displacement by the forward movement of the catheter, a second membrane was simultaneously pulled downwards. The accuracy of the automated gas measurement system was better than 4% for total gas volumes, as determined by a 50-µl-calibration syringe. The residual volume due to the membrane-compensated movement of the catheter was determined after each individual gas yield measurement and subtracted from the measured gas volume. This residual gas volume was typically less than 1 µl.

B) PDA GAS MEASUREMENTS

As no compensation was necessary during pressure driven advancement, the second membrane was replaced by a rubber stop and the catheter holder was immobilized. To provide pressure, first the cap was loosened to allow free movement of the catheter and the required weights were added to the shaft. As a result, a spring positioned under the tissue holder was impressed thus providing a constant pressure. The cap was then tightened and gas yields were recorded until no further gas formation was measured (which indicated tissue perforation) or a maximum of 30 seconds laser activation (=750 pulses) had been reached.

TEMPERATURE MEASUREMENTS

Temperature measurements were performed using a thermocouple (Ceramo Type K, Thermo Electric International BV, Warmond, The Netherlands). To simulate recanalization of a coronary stenosis, an aortic tissue sample was tightly wrapped and put into a plastic cylinder (Fig 5). Through the center of the tissue sample a guide wire was inserted over which a catheter was positioned on the tissue. Through a small opening in the plastic tube a 0.25 mm diameter thermocouple was placed 2 mm below the surface of the tissue. The tip of the thermocouple was positioned such to have either a 0.5 mm or

1 mm minimum distance from the outer surface of the catheter during ablation. The thermocouple was connected to a Keithley DAS 1401 A/D-converter by means of a STP-37/C screw terminal connector (Keithley Metrabyte, Tounton, MA, USA) with on board cold junction compensation for on-line temperature registration.

DATA ANALYSIS

The results are given as the mean ± SD. Where appropriate results were compared using an unpaired Students t-test. A p-value <0.05 was considered as significant.

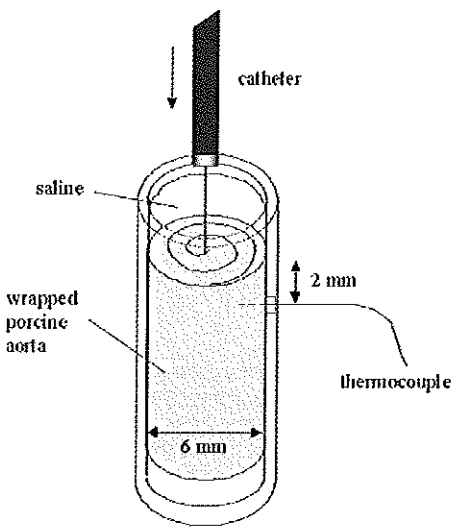


Figure 5 Temperature measurement set-up

RESULTS

MICROSCOPY

ABLATION EFFICACY

For the purpose of a direct comparison of PDA (presented as a function of weight) and SDA (presented as a function of speed), the results are presented side-by-side in Figures 6, 7 and 8. The number of perforations as a function of weight (PDA) is shown in Figure 6A. At twelve grams, the catheter usually halted in the media e.g. continued application of laser pulses did not result in additional catheter advancement. Increasing the fluence and/or applying higher pressures enhanced catheter progression. The ratios of SDA crater depth and catheter advancement as a function of speed are given in Figure 6B. At 60 mJ/mm^2, the average crater depth was equal to the catheter travel. At 45 mJ/mm^2, the crater depth was inversely related to catheter speed (crater depth/ catheter travel ratio at 0.51 mm/s vs. 0.06 mm/s: 0.43 ± 0.06 vs. 0.84 ± 0.10, $p<0.0001$). The ratio of the short and long axes (Figs 6C,D) was less than 1 in all experiments, indicating that the craters were elliptical and/or irregular, rather then circular. The cross sectional area for PDA (Figs 6E and 8) was inversely related to both the applied weight and energy density. Note that even the largest area, at 45 mJ/mm^2 - 12 grams, was less than 0.75 times the cross-sectional area of the outer rim of

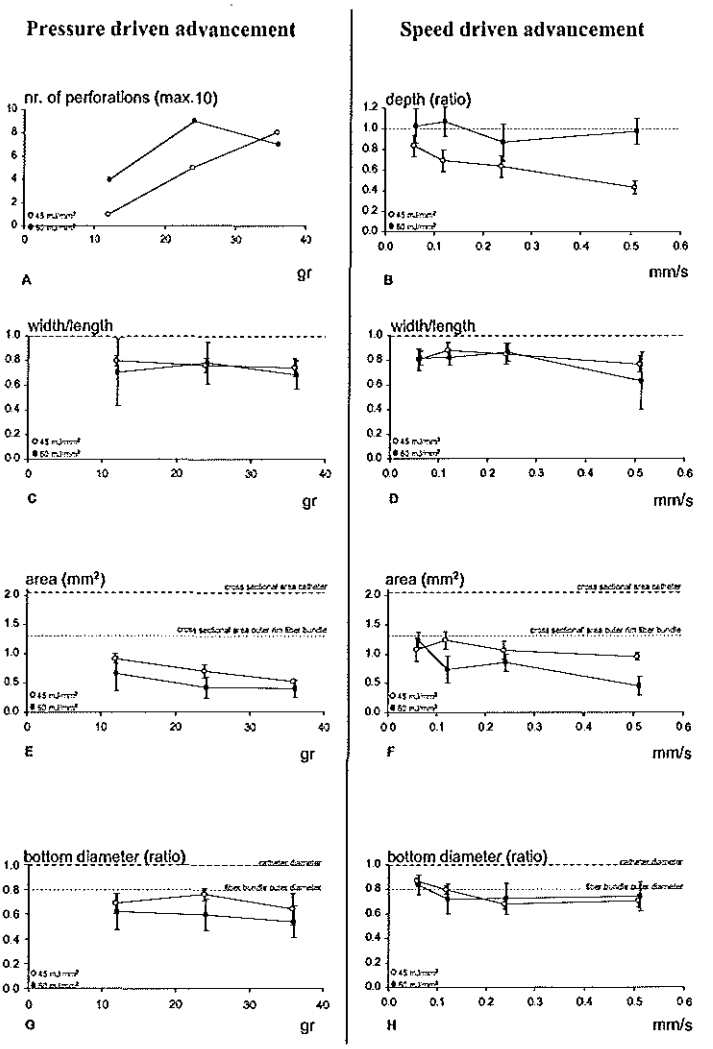


Figure 6 A. PDA, number of medial perforations in a series of 10 as a function of weight. B. SDA, ratio of crater depth and catheter advancement of 1.7 mm as a function of speed. A crater depth of 1.7 yields a value of 1. C. PDA, the ratio of the short (width) and long (length) axes of the minimal crater cross-sections as a function of weight. A ratio of 1, indicated by the dotted line, indicates a circular crater. D. SDA, the ratio of the short (width) and long (length) axes of the minimal crater cross-sections as a function of speed. E. PDA, minimal cross sectional area of freshly made ablation craters as a function of weight. For comparison, the cross sectional areas of the catheter and the outer rim of the fiber bundle are indicated. F. SDA, minimal cross sectional area of freshly made ablation craters as a function of speed. G. PDA, ratio of crater bottom diameter and catheter diameter as a function of weight. For comparison, the diameters of the catheter and the outer rim of the fiber bundle are indicated. H. SDA, ratio of crater bottom diameter and catheter diameter as a function of speed.

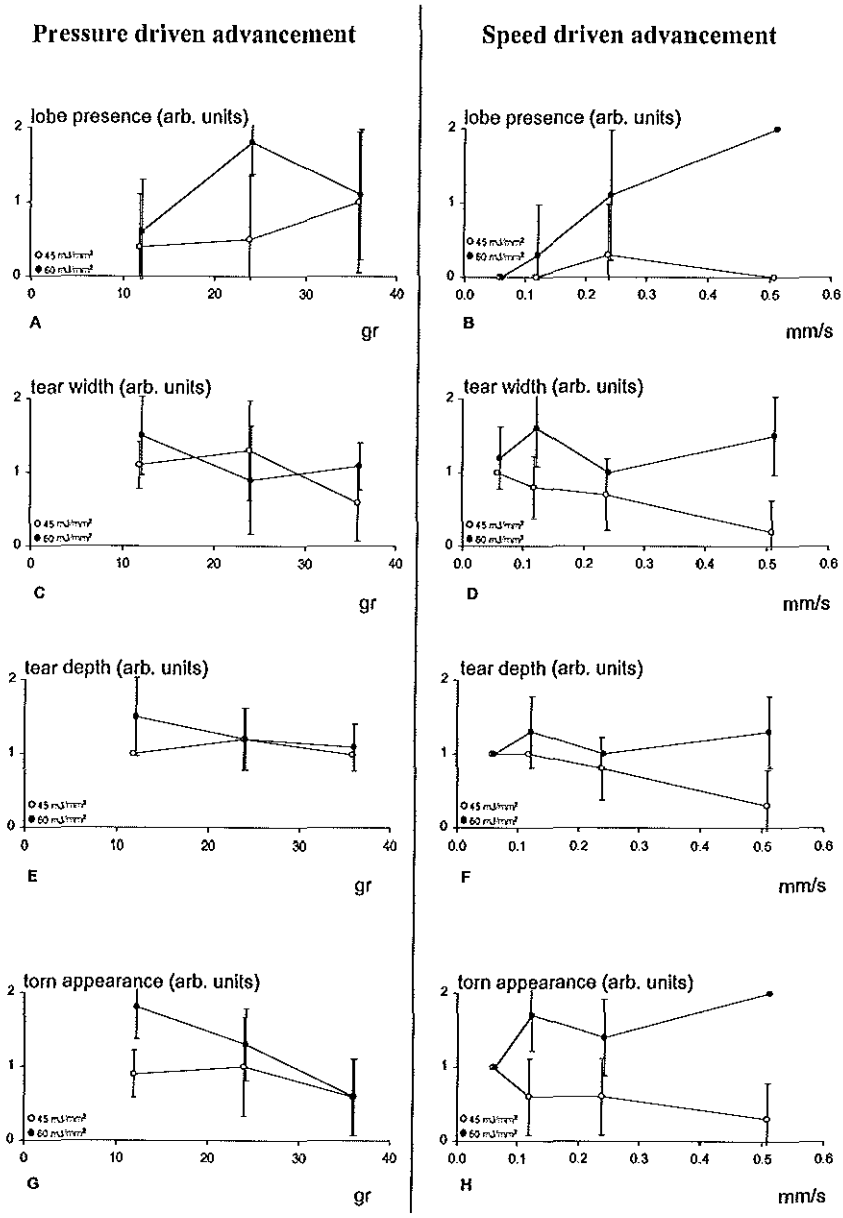


Figure 7 A. PDA, lobe presence as a function of weight. B. SDA, lobe presence as a function of speed. C. PDA, tear width as a function of weight. D. SDA, tear width as a function of speed. E. PDA, tear depth as a function of weight. F. SDA, tear depth as a function of speed. G. PDA, torn appearance as a function of weight. H. SDA, torn appearance as a function of speed.

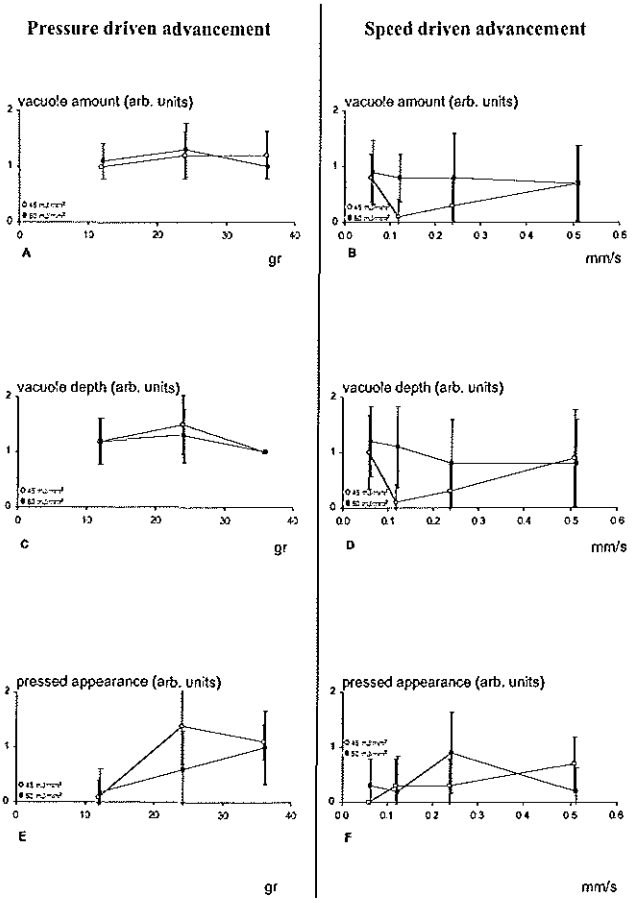


Figure 8 A. PDA, vacuole amount as a function of weight. B. SDA, vacuole amount as a function of speed. C. PDA, vacuole depth as a function of weight. D. SDA, vacuole depth as a function of speed. E. PDA, pressed appearance as a function of weight. F. SDA, pressed appearance as a function of speed.

the laser fibers. Also for SDA, the cross sectional area (Fig 6F) was smaller at 60 mJ/mm^2 than at 45 mJ/mm^2, except for its maximum value: SDA 1.24 ± 0.12 mm^2 (at 60 mJ/mm^2 - 0.06 mm/s) vs. PDA 0.94 ± 0.08 mm^2 (at 45 mJ/mm^2 - 12 grams, SDA>PDA, $p < 0.0001$). Conform cross sectional area measurements, PDA bottom diameters were always smaller than the diameter of the laser fiber outer rim (Fig 6G). The SDA bottom diameters (Fig 6H) were similar for both energy densities, but increased at lower speeds to diameters larger than the fiber bundle outer diameter.

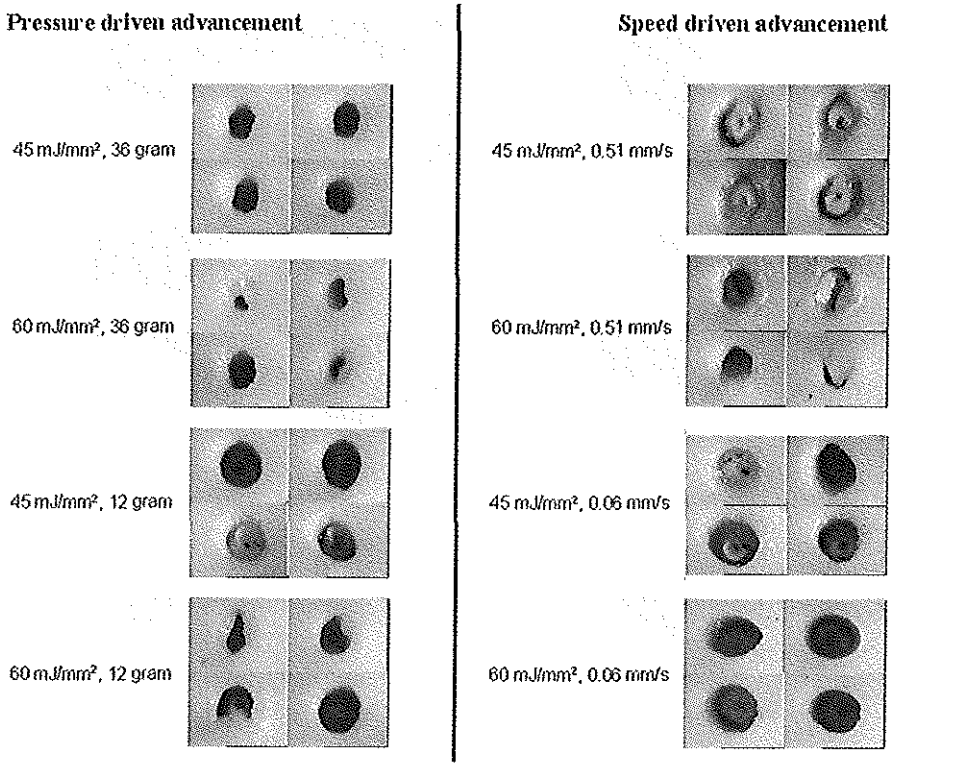


Figure 9 *Top view of unfixed craters of a series of 10, made at weights of 12 -, or 36 grams (PDA) and speeds of 0.06 -, to 0.51 mJ/mm² (SDA) for 45 and 60 mJ/mm2.*

ABLATION QUALITY

Tears (Figs 7A-H, 8A-F). Remarkable, was the presence of lobes blocking the crater lumen at 60 mJ/mm² - 0.51 mm/s, indicating inefficient ablation (Figs 7B,9). At 45 mJ/mm² very few lobes were seen. At 0.06 mm/s no lobes were observed for either energy density. Note (Figs 10,11) that especially at 45 mJ/mm² tissue remnants were seen around the guide wire punch hole in the center of the craters. These were not classified as lobes. It was observed that in those cases where a central tissue chunk was absent in the histology, a cylindrical piece of tissue was present around the guide wire over which the catheter had been advanced. The cross sectional area was inversely related to the presence of lobes. Tissue tears were observed under all experimental conditions (Figs 7C-H). At 60 mJ/mm², extensive tearing was observed for SDA speeds ≥0.12 mm/s. The smallest and

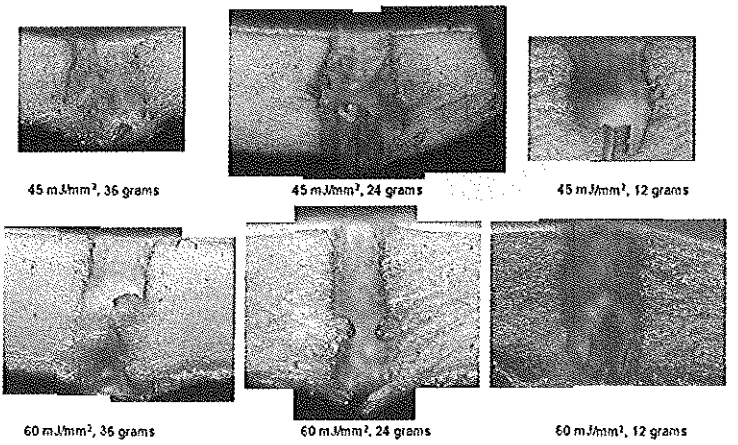


Figure 10 Typical examples of PDA crater morphology at energy densities of 45 and 60 mJ/mm² and weights of 12, 24 or 36 grams.

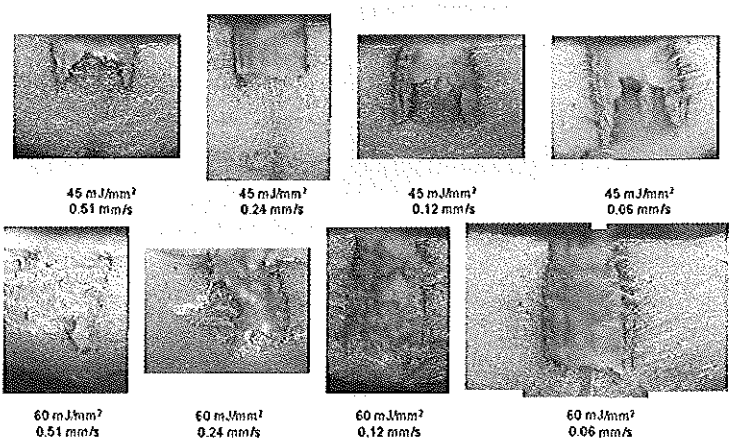


Figure 11 Typical examples of SDA crater morphology at energy densities of 45 and 60 mJ/mm² and speeds of 0.06 – 0.51 mm/s.

least amount of tears were found at 45 mJ/mm² and higher SDA speeds. Small numbers of vacuoles, usually close to the crater wall, were present in all PDA cases (Figs 8A,C) and (at 60 mJ/mm²) at all SDA speeds (Figs 8B,D). At 45 mJ/mm², hardly any vacuoles were observed at speeds of 0.12 and 0.24 mm/s. The tissue fibers were only mildly pressed using SDA (Fig 8F), while for PDA, fibers were increasingly pressed when using larger weights. To better appreciate the effects of pressure and applied speed, Figure 9 shows the superior views of craters made with the extreme upper and lower weights (36

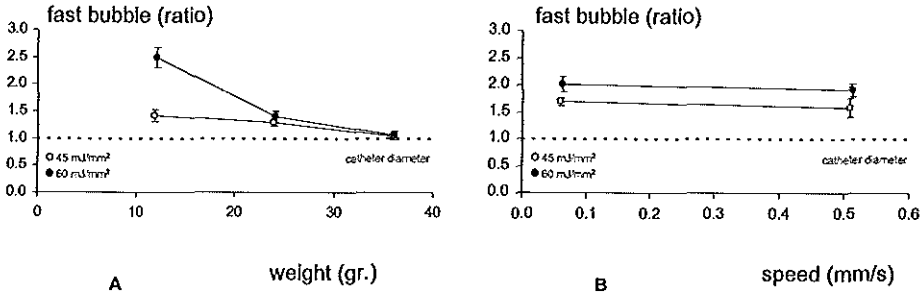


Figure 12 A. PDA, ratio of the maximum fast expanding bubble diameter and the catheter diameter as a function of weight. B. SDA, ratio of the maximum fast expanding bubble diameter and the catheter diameter as a function of speed.

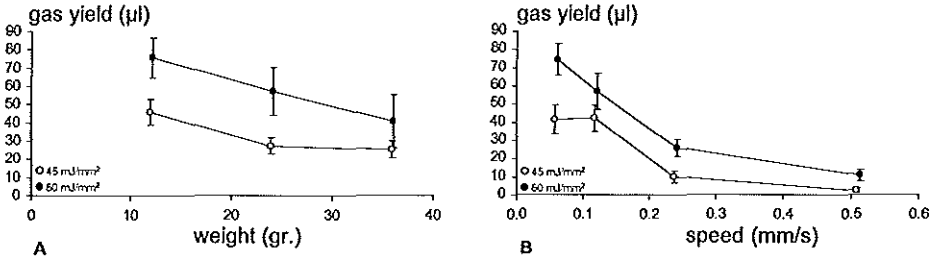


Figure 13 A. PDA, total gas yield after 750 pulses as a function of weight. B. SDA, total gas yield over a catheter travel of 1.7 mm as a function of speed.

and 12 grams) and speeds (0.51 and 0.06 mm/s). Representative examples of crater halves made at all weights and energy densities are shown in Figure 10, while examples made at all speeds and energy densities are shown in Figure 11.

TISSUE WATER VAPORIZATION

The maximum fast bubble size for PDA decreased by increasing weight (Fig 12A). At 36 grams fast bubbles were hardly observable. For SDA, the fast bubble diameter increased less than 6 % when going from 0.51 mm/s to 0.06 mm/s (Fig 12B). With SDA, the catheter was positioned in contact with the tissue with a presumed minimal pressure. Therefore, the maximum bubble size at PDA 60 mJ/mm^2 - 12 grams being much larger than any bubble observed for SDA, was an unexpected finding. Whenever present, the fast bubble lifted the tissue surface once the catheter entered the tissue, thus suggesting a potential for tissue disruption.

INSOLUBLE GAS MEASUREMENTS

During ablation, gas was forcefully ejected in a more or less constant stream of small bubbles from beneath the catheter tip. Sometimes gas bubbles escaped from previously made craters in the vicinity of the current catheter position. The PDA gas yields during a pulse train of 30 seconds (750 pulses) are shown in Figure 13A. As with maximum bubble diameter, the gas yield decreased considerably by increasing pressure. In SDA at 60 mJ/mm^2, the gas production increased by a factor of seven when decreasing catheter speed from 0.51 mm/s to 0.06 mm/s (Fig 13B).

TEMPERATURE MEASUREMENTS

Temperature increase above ambient temperature measured for a catheter speed of 0.06 mm/s is shown in Figure 14. In Figure 14A the pulse energy density was 45 mJ/mm^2 and the temperature curves were measured at 0.5-mm distance from the outer surface of the catheter. The catheter passed the thermocouple tip 35 seconds after activation of the laser. The total advancement was 6 mm in 101 seconds, during which 2525 pulses were delivered. The average maximum temperature increase measured in these experiments was 16 ± 6 °C. As is evident from these curves, there was a delay between the moment the catheter tip passed the thermocouple and the moment of maximum temperature. In measurements with the thermocouple tip positioned at 1 mm distance, the average maximum temperature increase reached was 14 ± 3 °C (Fig 14B). The temperature curves for experiments at 60 mJ/mm^2 and a thermocouple distance of 0.5 mm from the outer surface of the catheter are shown in Figure 14C. Here, the average maximum temperature increase was 22 ± 3 °C.

DISCUSSION

In ELCA a diseased coronary artery is recanalized by manually advancing a laser catheter. The catheter is pushed towards the lesion and during application of laser pulses gently advanced, usually at speeds in the range of 0.5-1 mm/s. In practice, neither speed nor pressure can be kept constant and it is unclear to what extent these parameters affect the process of plaque debulking. In this study, pressure and speed parameters were evaluated separately.

ABLATION EFFICACY

With PDA the crater cross sectional area increased for decreasing pressures. We hypothesized that once the first central layers of tissue were ablated, larger pressures allowed the catheter to cross the tissue by pushing the fibers aside, thus limiting the ablation efficacy. However, when the pressure applied to the catheter was decreased, the catheter's ability to penetrate the tissue

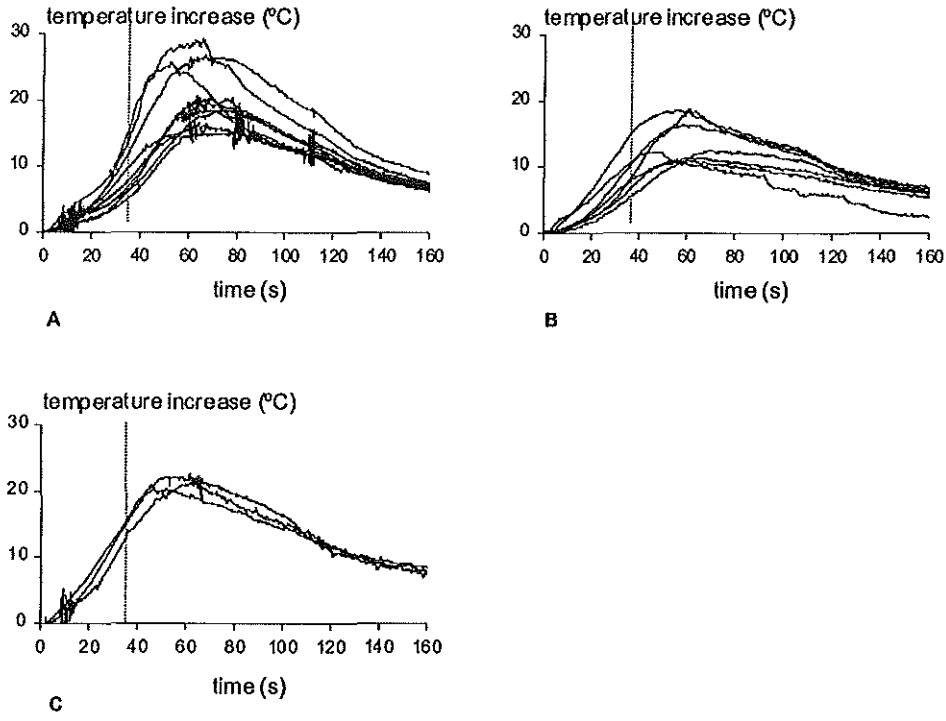


Figure 14 A. Temperature increase as a function of time (n=10). A laser pulse energy density of 45 mJ/mm² and a catheter advancement speed speed of 0.06 mm/s. Temperatures are measured at a fixed point 2 mm below the tissue surface. A minimum catheter to thermocouple distance of 0.5 mm. B. Temperature increase as a function of time (n=7). A laser pulse energy density of 45 mJ/mm² and a catheter advancement speed 0.06 mm/s. Temperatures are measured at a fixed point 2 mm below the tissue surface. A minimum catheter to thermocouple distance of 1.0 mm. C. Temperature increase as a function of time (n=4). A laser pulse energy density of 60 mJ/mm² and a catheter advancement speed 0.06 mm/s. Temperatures are measured at a fixed point 2 mm below the tissue surface. A minimum catheter to thermocouple distance of 0.5 mm. The dotted lines indicate the moment the catheter tip passes the thermocouple.

decreased as well. Therefore, when applying a constant pressure at the catheter tip, larger crater diameters are obtained at the cost of a limited penetration capacity. In agreement with this hypothesis was the finding that fiber bending at the crater wall was a feature predominantly seen in PDA experiments.

For SDA, the effect of speed on debulking efficiency and quality was profound. At 0.51 mm/s, the amount of ablation was limited. At 45 mJ/mm² - 0.51 mm/s the crater depth was less than half the catheter travel. Thus, the speed at which tissue was removed was less than the speed of the advancing

catheter tip i.e. the tissue was pushed forwards rather than ablated. When the catheter speed was reduced to 0.06 mm/s, the crater depth increased to more than 80 % of the catheter travel. At 60 mJ/mm^2 - 0.06 mm/s, the crater depth equaled the catheter travel, while the crater area nearly equaled the area of the outer rim of the fiber bundle. Furthermore, there were no lobes, while the bottom diameter was larger than the laser bundle outer diameter. Comparing PDA and SDA debulking properties, the latter was superior with regard to the amount of material removed: with SDA the maximum cross-sectional area was combined with a crater depth equal to the catheter travel and bottom diameters slightly larger than the fiber rim outer diameter.

ABLATION QUALITY

For SDA, in contrast to PDA, the least tear formation was found at those parameters responsible for optimal debulking (SDA, 60 mJ/mm^2 - 0.06 mm/s). Crater wall vacuolization was seen in most tissue samples, although with SDA there was an almost absence of vacuoles at 45 mJ/mm^2 and speeds of 0.24 and 0.12 mm/s. However, it should be noted there was a large spread in the vacuolization scores.

TISSUE VAPORIZATION

In PDA, the maximum diameter of fast expanding bubbles decreased with increasing weight. This phenomenon could be explained by an increase in water boiling temperature at increasing pressures. Once the catheter tip penetrated the tissue, the tissue surface was lifted, presumably by expansion of the fast expanding bubble. As we found a relatively large number of tears at 60 mJ/mm^2 - 12 grams, we believe that fast expanding bubbles are -at least partly- responsible for tear formation. Accordingly, it is likely that this phenomenon is related to ELCA-induced dissections.

INSOLUBLE GAS FORMATION

For both PDA and SDA, the gas yields increased with increasing tissue debulking. The forceful ejection of large quantities of insoluble gas could be responsible for crater wall vacuolization as seen in most tissue samples. In addition, tear formation (i.e. dissection following ELCA) could be enhanced by the same phenomenon. At optimal debulking parameters (SDA, 60 mJ/mm^2 - 0.06 mm/s), the gas yield was 74 ± 9 µl. If the observed gas yields are indicative of conditions during ELCA, such volumes could create a serious clinical challenge: a coronary lesion of 10 mm length would yield approximately 430 µl of insoluble gas, which is equivalent

to a single spherical bubble of 9.4 mm. For a person weighing 70 kg, this would be a gas load of 6-µl/kg-body weight. In a porcine model, a gas load of 2-µl/kg-body weight resulted in reversible myocardial motion abnormalities.[21]

TEMPERATURE MEASUREMENTS

The maximum temperature increase above ambient was 22 ± 3 ºC. Maximum temperature increases were measured only after the catheter tip had passed the position of the thermocouple. This delay could be related to diffusion of accumulated heat generated at the catheter tip during a prolonged laser pulse train. Also, the progression of insoluble gas created in deeper regions could add to this temperature increase time delay. In a coronary artery, a temperature increase of 22 °C above ambient (circa 37 °C) would lead to a vessel wall temperature of approximately 60 °C. Although temperature increases up to 60 °C have not been associated with significant thermal damage in post-mortem human aorta[22] other groups reported thermal damage following porcine in vivo studies.[17] Therefore, at slow catheter advancement speeds, especially in longer lesions, ELCA induced thermal necrosis of the vessel wall can not be ruled out.

CONCLUSIONS

Assuming that experiments on porcine aorta hold some relevance for ablation of human atherosclerotic plaque, the results of the current study may prove helpful in attempts to optimize debulking properties of ELCA. The PDA results suggest, that if progression is halted, further catheter advancement will only be achieved by applying more pressure, which however could cause the catheter to "Dotter" the lesion, rather then to improve the ablation process.

The SDA results indicate that in order to optimize plaque debulking, the catheter advancement speed should not exceed the speed at which the system is capable of ablating tissue. In the clinical practice of ELCA, catheter advancement speeds are usually ≥0.5 mm/s. The above findings however suggest that clinical results could benefit from a speed reduction by a factor of 5 to 10 in comparison. It is not likely that this could be achieved by a manually controlled catheter manipulation. Therefore, we suggest the introduction of an automated catheter advancement device (AcAD). The application of an AcAD could not only prove to be useful in optimizing coronary debulking, but may also be helpful in standardizing ELCA procedures. This could be of significance for renewed attempts to evaluate the clinical advantage of optimal

lesion debulking in coronary artery disease. It must be realized however, that by reducing catheter advancement speeds the total lasing time will increase. Consequently, improved tissue debulking at slow catheter advancement speeds might result in thermal necrosis of the vessel wall. In addition, it can be expected that the accumulation of gaseous debris will be substantial. Although *in vitro* and animal studies might not be directly applicable to the human heart in a clinical setting, it is likely that large volumes of insoluble gas could cause myocardial ischemia. Obviously, these effects should be anticipated when introducing AcAD in the clinical practice of ELCA.

REFERENCES

1. Bittl JA, Sanborn TA, Abela GS, Isner JM. Wire-guided excimer laser coronary angioplasty: instrument selection, lesion characterization, and operator technique. *J Interven Cardiol* 1992; 5:275-2911.
2. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser angioplasty. *Am J Cardiol* 1992; 70:1533-1539
3. Bittl JA, Sanborn TA. Excimer laser-facilitated coronary angioplasty. Relative risk analysis of acute and follow-up results in 200 patients. *Circulation* 1992; 86:71-80
4. Baumbach A, Oswald H, Kvasnicka J, Fleck E, Geschwind HJ, Ozbeck C, Reifart N, Bertrand ME, Karsch K. Clinical results of coronary excimer laser angioplasty: report from the European Coronary Excimer Laser Angioplasty Registry. *Eur Heart J* 1994; 15(1):89-96
5. Litvack F, Eigler N, Margolis J, Rothbaum D et al. Percutaneous excimer laser coronary angioplasty: results in the first consecutive 3,000 patients. The ELCA Investigators. *J Am Coll Cardiol* 1994; 23:323-329
6. Appelman YEA, Piek JJ, Strikwerda S, Tijssen JG, de Feyter PJ, David GK, Serruys PW, Margolis JR, Koelemay MJ, Montauban van Swijndregt EW, Koolen JJ. Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. *Lancet* 1996; 347: 79-84
7. Safian RD, Freed M, Reddy V, Kuntz RE, Baim DS, Grines CL, O'Neill WW. Do excimer laser angioplasty and rotational atherectomy facilitate balloon angioplasty? Implications for lesion-specific coronary intervention. *J Am Coll Cardiol* 1996; 27:552-559
8. Reifart N, Vandormael M, Krajcar M, Göhring S, Preusler W, Schwarz F, Störger H, Hofmann M, Klöpper J, Müller S, Haase J. Randomized

comparison of angioplasty of complex coronary lesions at a single center. Excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) study. *Circulation* 1997; 96:91-98.

9. Jain SP, Liu MW, Dean LS, Babu R, Goodsom, Yadav JS, Al-Shaibi KF, Mathur A, Iyer SS, Parks JM, Baxley WA, Roubin GS. Comparison of balloon angioplasty versus debulking devices versus stenting in right coronary ostial lesions. *Am J Cardiol* 1997; 79:1334-1338
10. Hoyne J, Mahon DJ, Nakamura S, Wallis J, Al-Zarka A, Saito S, Berns M, Tobis JM. Intravascular ultrasound imaging after excimer laser angioplasty. *Cath Card Diag* 1994; 32:213-222
11. Diethrich EB, Hanafy HM, Santiago OJ, Bahadir I. Angioscopy after coronary excimer laser angioplasty. *J Am Coll Cardiol* 1991; 18:643-644
12. Garcia-Cantu E, Corcos T, Faverau X, Toussaint M, Zimarino M, Guérin Y, Baget F. Early deterioration after excimer laser-assisted coronary angioplasty. *Am J Cardiol* 1997; 79: 1230-1232
13. Gijsbers GHM. Tissue ablation by CW lasers, and a pulsed XeCl excimer laser a used in excimer laser angioplasty. *Thesis*, University of Amsterdam, June 1992; pp. 107
14. Van Leeuwen TG, Van Erven L, Meertens JH, Motamedi M, Post MJ, Borst C. Origin of arterial wall dissections induced by pulsed excimer and mid-infrared laser ablation in the pig. *J Am Coll Cardiol* 1992;19:1610-1618
15. Leeuwen van TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced by excimer laser pulse causes microsecond arterial dilation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993; 87:1285-1293
16. Baumbach A, Haase KK, Rose C, Oberhoff M, Hanke H, Karsch KR. Formation of pressure waves during *in vitro* excimer laser irradiation in whole blood and the effect of dilution with contrast media and saline. *Lasers Surg Med* 1994; 14:3-6
17. Van Leeuwen TG, Jansen ED, Motamedi M, Welch AJ, Borst C. Excimer laser ablation of soft tissue: a study of the content of fast expanding and collapsing bubbles. *IEEE J Quantum Electron* 1994; 30:1339-1345
18. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, Van Marle J, Van den Broecke DG, Hanekamp CEE, Van Gemert MJC, Serruys PW. Excimer Laser Coronary Angioplasty: A physical perspective to clinical results. In: Topol EJ &

Serruys PW (eds) *Current Review of Interventional Cardiology*, 2nd edn. Philadelphia: Current Medicine 1995: 159-172

19. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution and high-density laser techniques in excimer laser coronary angioplasty. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, Philadelphia: Current Medicine 1996; 101-111
20. Gijsbers GHM, Hamburger JN, Wonders JHAM, Zondervan PE, Serruys PW. Method for the Assessment of Ablation Performance: a Novel Technique for Direct Evaluation of *In-Vitro* Excimer Laser Tissue Ablation. *Submitted for publication*
21. Van Blankenstein JH, Slager CL, Schuurbiers JCH, Strikwerda S, Verdouw PD. Heart function after injection of small air bubbles in coronary artery of pigs. *J Appl Physiol* 1993; 75: 1201-1207
22. Agah R, Pearce JA, Welch AJ, Motamedi M. Rate Process Model for Arterial Tissue Thermal Damage: Implications of Vessel Photocoagulation. *Lasers Surg Med* 1994; 15:176-184

CHAPTER 4

Ablation properties of a new 2.0 mm High Density excimer laser catheter for coronary angioplasty

Geert H.M.Gijsbers, Jaap N. Hamburger, Patrick W. Serruys

ABLATION PROPERTIES OF A NEW 2.0 MM HIGH DENSITY EXCIMER LASER CATHETER FOR CORONARY ANGIOPLASTY

ABSTRACT

Objectives-This *in vitro* study was designed to evaluate the ablation properties of a new design catheter for excimer laser coronary angioplasty (ELCA).

Background-The ablation efficacy of a laser catheter is determined by the ratio of the active surface area and the total surface area at the catheter tip. Therefore, a novel 2.0 mm High Density catheter (2.0 HD) with an increased number of fibers was introduced.

Methods-The laser was a CVX-300 XeCl excimer laser (308 nm, 200 ns, Spectranetics Inc., USA). A standard 2.0 mm multifiber catheter (2.0 C) and the new 2.0 HD catheter were used to ablate craters in porcine aorta. Experiments were performed in a speed driven catheter advancement mode (predefined catheter travel of 1.7 mm) at speeds of 0.06-0.51 mm/s. Energy densities ranging from 25 mJ/mm^2 to 60 mJ/mm^2 and pulse repetition rates of 25 Hz, 40 Hz, and 80 Hz were used. The insoluble gas production was measured on-line. Direct microscopy was used to assess ablation efficacy and surrounding tissue damage.

Results-Use of the 2.0 HD increased ablation efficacy (2.0 HD vs. 2.0 C, crater mouth cross sectional area 2.19 mm^2 ± 0.12 vs. 2.04 mm^2 ± 0.17, p=0.035, minimal crater diameter 1.83 ± 0.09 vs. 1.49 ± 0.12, p<0.0001). The extent of tissue damage was comparable for both catheter types. The lowest gas yield (ml ± SD) was measured at parameters resulting in optimal ablation (25 mJ/mm^2 - 40 Hz - 0.10 mm/s, 2.0 HD vs. 2.0 C, 65.1 ± 29 ml vs. 86.7 ± 16 ml, p=0.05). Increasing the repetition rate to 80 Hz significantly increased the insoluble gas yields.

Conclusion-Using the new 2.0 HD catheter improved *in vitro* ablation efficacy without increasing surrounding tissue damage.

Excimer laser coronary angioplasty (ELCA) has been demonstrated to be a safe therapeutic modality.[1-4] However, its capacity to ablate atherosclerotic plaque effectively has been questioned.[5-7] In addition, several studies failed to prove a long-term clinical benefit of ELCA over percutaneous transluminal coronary angioplasty (PTCA) alone.[8-10] In recent *in vitro* studies a number of explanations for sub-optimal clinical results have been suggested.[11,12] Typically, *in vitro* tissue ablation could be improved 1) by reducing the non-light emitting area at the tip of a catheter and 2) by reducing the catheter advancement speed to velocities of less than 0.5 mm/s.[11,13-15] Current multifiber laser catheters have a light emitting area that covers less than 30% of the total catheter tip surface area. Therefore, a new 2.0 mm High Density catheter (2.0 HD, Spectranetics Inc., USA) was designed with an increased number of fibers and subsequently, a reduced non-light emitting area. As catheter advancement speeds of <0.5 mm/s were considered not practical for the clinical setting, we evaluated the feasibility of tissue ablation at higher advancement speeds by increasing the laser pulse repetition rate from the currently used 25 Hz to 40 Hz and 80 Hz. Thus, in the present study the *in vitro* debulking properties of the new 2.0 mm HD-catheter at various pulse energy densities and pulse repetition rates were evaluated.

METHODS

LASER AND LASER CATHETERS

The laser was a CVX-300 XeCl excimer laser (Spectranetics Inc., USA) emitting ultraviolet pulses at a wavelength of 308 nm with a pulse duration of approximately 200 ns. The laser was adapted for the purpose of this study to reach a pulse repetition rate of 80 Hz. A prototype 2.0 HD multifiber catheter was used. The catheter contained 356 silica fibers of 61 µm diameter, concentrically distributed around a central guide wire lumen (Fig 1A,B). The ablation properties of the 2.0 HD were compared with those of a standard 2.0 mm catheter (2.0 Vitesse-C, Spectranetics Inc., USA), containing 238 fibers (Fig 1C,D). The physical properties of both catheters are summarized in Table 1.

PULSE ENERGY DENSITIES

When using a standard 1.7 mm catheter (active area 1.7C, 0.39 mm^2 = 21%), the typical energy density boundaries in ELCA were 45 mJ/mm^2 and 60 mJ/mm^2. As a higher fiber density in the 2.0 C resulted in a larger active area (active area 2.0 C, 0.70 mm^2 = 36%) we used 35 mJ/mm^2 as a lower limit for this catheter. Following a further increased active area (active area 2.0 HD, 1.94 mm^2 = 52%), pulse energy densities of 25, 30

and 45 mJ/mm^2 were used for the 2.0 HD.

AUTOMATED CATHETER ADVANCEMENT

To provide a constant speed to a catheter, the catheter was fixed in a shaft mounted on the X-direction carriage of an XY recorder (Model BD 90, Kipp & Zonen, Delft, The Netherlands, Fig 2). The X-direction connector controlled the movement of the catheter, through a voltage provided by a D/A-converter (PC-LabCard PCL-711S, Advantech, Taipei, Taiwan). The voltage was varied by means of a Pascal program that allowed the choice of speed and the delay between the onset of laser activation and the start of catheter advancement. To prevent perforation of the approximately 2.0 mm diameter tissue samples, the total predefined advancement of the catheter during lasing was 1.7 mm.

The catheter advancement speed currently advised for ELCA procedures is

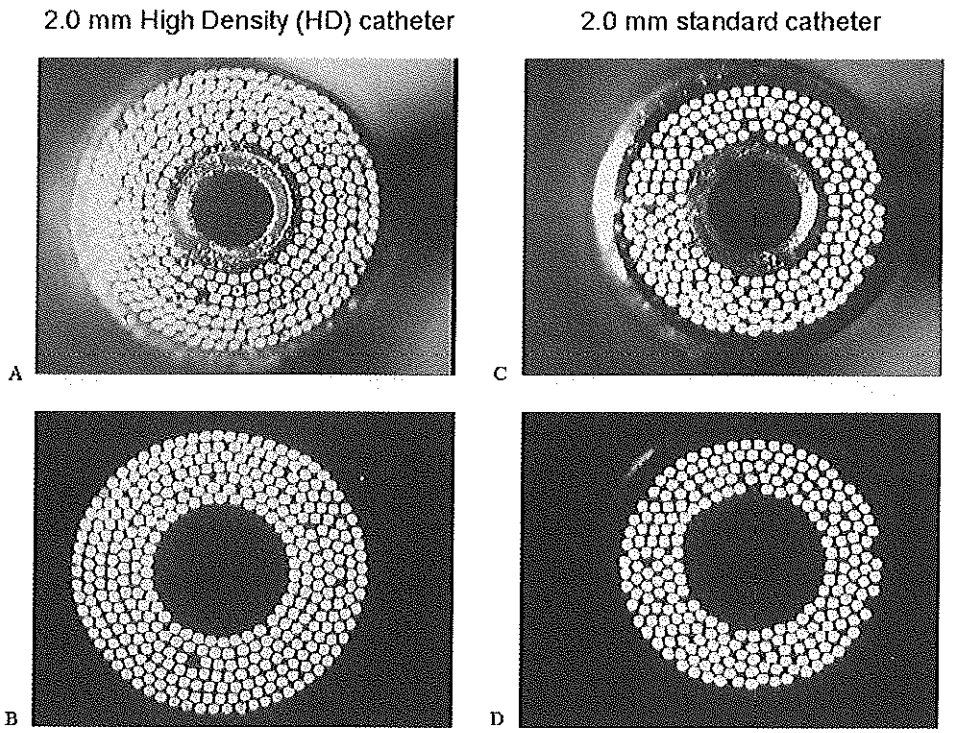


Figure 1 Front views of the 2.0 mm HD catheter (A,B) and the 2.0 mm standard catheter (C,D). The lower images show the fiber distribution, the upper images also show the outer dimensions and the dimensions of the inner tubing of the guide wire lumen.

device	#fibers	active area (mm^2)	Active OD (mm)	Passive ID (mm)	Device OD (mm)	Lumen diam. (mm)
2.0 mm HD cath.	356	1.04	1.80	0.83	2.02	0.52
2.0 mm stand. Cath.	238	0.70	1.55	0.86	1.94	0.57

Table 1. Catheter properties

Active area: light emitting area of all optical fibers. Active OD: diameter of outer rim of fiber bundle. Passive ID: diameter of inner rim of fiber bundle. Device OD: diameter of catheter. Lumen diameter: inner diameter of guide wire lumen.

0.5 – 1 mm/s.[16] However, in a previous study the speed of tissue removal (1.7 mm catheter, at 60 mJ/mm^2 – 25 Hz) was measured to be ≤0.06 mm/s.[15] ELCA at such low speeds could potentially cause clinical complications due to prolonged procedure times. Therefore, we comparatively used catheter advancement speeds of 0.5 mm/s, 0.12 mm/s and 0.06 mm/s at a pulse repetition rate of 25 Hz with proportionally increased advancement speeds of 0.10 and 0.19 mm/s for pulse repetition rates of 40 Hz and 80 Hz respectively (Table 2).

rep. rate (Hz)	Speed (mm/s)	Speed (mm/s)	speed (mm/s)
25	0.51	0.12	0.06
40			0.10
80			0.19

Table 2. Applied catheter advancement speeds

rep. rate = pulse repetition rate (Hz)

TISSUE SAMPLES

Laser ablation lesions (henceforward called "craters") were made in fresh porcine thoracic aortic tissue samples. Loose connective tissue surrounding the adventitia was removed and the aorta was cut in tubular segments of 3 to 4 cm. The thickness of the samples chosen was approximately 2 mm. These segments were kept in an airtight container on ice. Just prior to use, a segment was cut longitudinally and spread with the intima faced upward. The segment was mounted in a holder as previously described.[13-15] The holder was put in a glass container and immersed in saline (NaCl 0.9%). For gas measure-

ments, a 5 mm diameter disk was punched from a rectangular tissue segment and put in a gas sample chamber (see below). For statistical purposes, 10 craters were made for every defined combination of energy density, pulse repetition rate and catheter advancement speed.

MICROSCOPIC ASSESSMENT OF TISSUE DAMAGE

Ablation efficacy and quality were determined using a method described in detail elsewhere.[17] In short, immediately following ablation a microscopic image was made of each unfixed crater by means of a microscope (BH-2 + NeoPlan 5 x objective, Olympus, Japan) equipped with a color CCD-camera (DXC-151P, Sony, Japan). Tissue samples were fixed in formalin (10% formaldehyde) for 24 hours. Subsequently, each crater was cut along the long axis. The tissue halves were stirred in a Toluidine-blue solution for image enhancement. All images were stored on a personal computer (PC) hard disk using a video frame grabber (Iris Video Digitizer, Inside Technology, Amersfoort, The Netherlands). For analysis, standard image analysis software (Photoshop, Adobe Inc, USA) was used. From these images a number of quantitative and semi-quantitative features were scored. From the superior circumference were measured the cross sectional area (in mm^2) and the ratio of the long- and short axis. From the fixed and stained crater halves were determined the crater depth (in mm) and the minimal crater lumen diameter. In a 0-2 classification (0 = absence of a phenom-

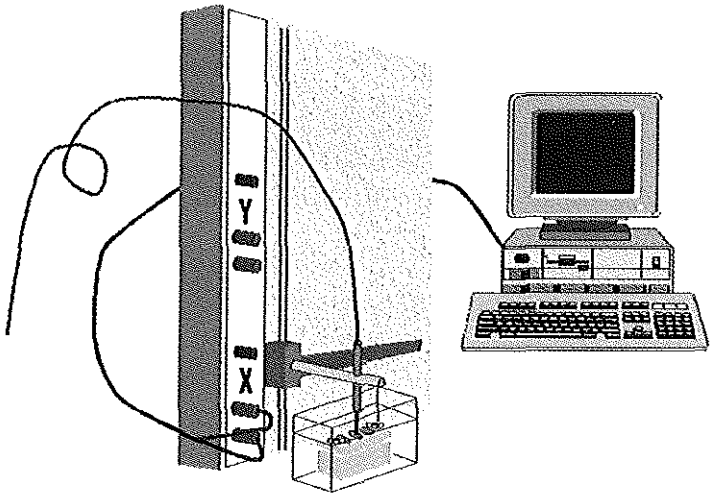


Figure 2 Set-up for speed driven advancement. A constant speed was applied to a catheter by means of an XY-recorder.

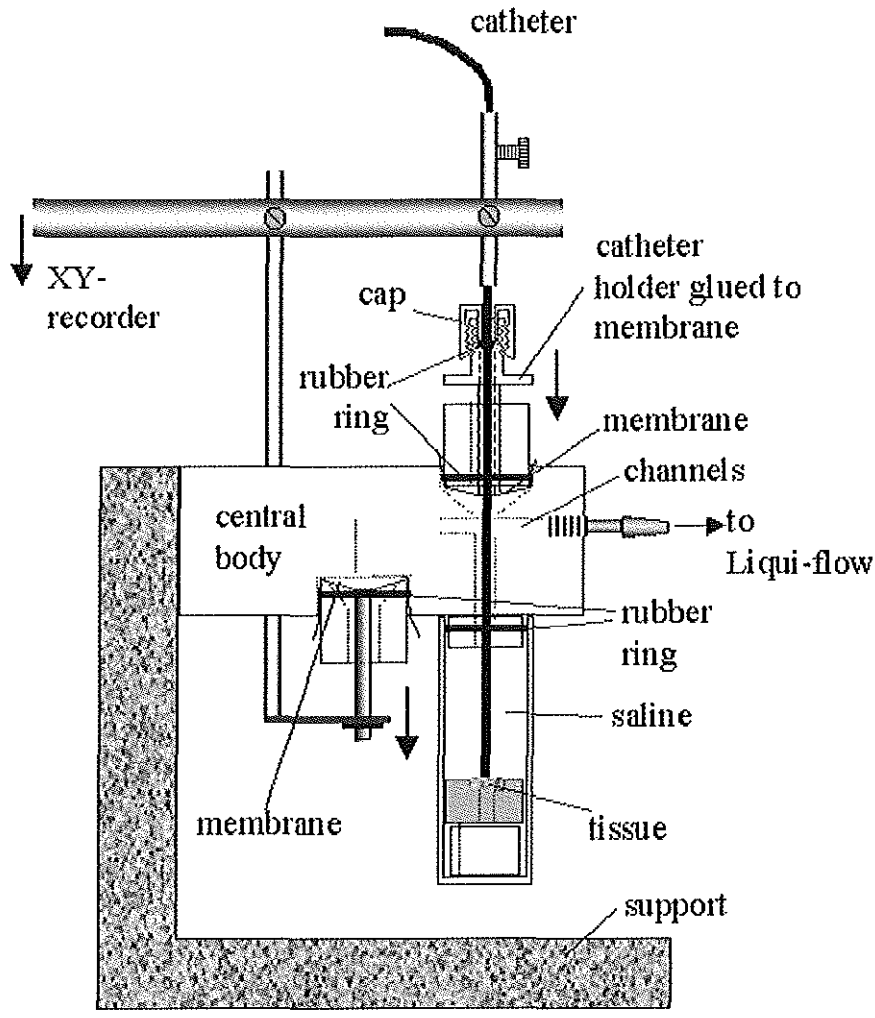


Figure 3 Gas volume sampler with catheter displacement compensation.

enon, 2 = worst case) the presence of residual tissue on the crater wall (lobes), the extent of tissue tearing (tear depth, tear width, number of tears) and the extent of vacuolization (number of vacuoles and distance to the crater wall) were assessed, as well as the bending of tissue fibers adjacent to the crater wall (bending of 0°, 0 - 45°, or 45 - 90°). The sum (average ± SD, n=10) resulted in an "injury score". As a result, the injury score was inversely related to the quality of tissue ablation. It should be noted that the injury score reflected the

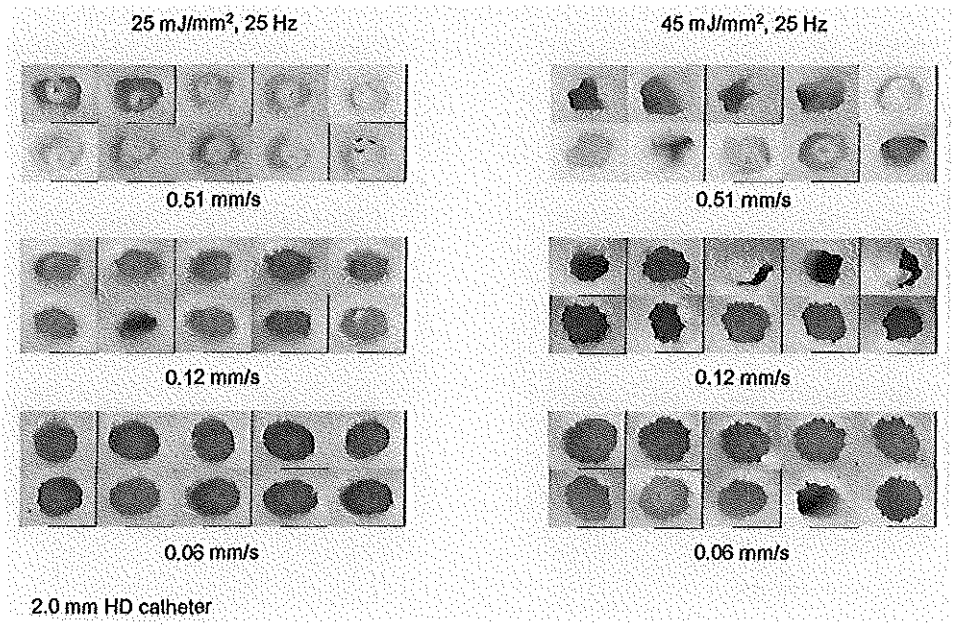


Figure 4 Top view of unfixed craters of a series of 10 created with a 2.0 mm HD catheter. Pulse energy densities of 25- and 45 mJ/mm² and a pulse repetition rate of 25 Hz were used. Catheter advancement speeds were 0.51 mm/s, 0.12 mm/s, and 0.06 mm/s.

assessment of damage in the tissue lateral to the movement of the catheter (the "crater wall"), analogous to a potential damage of the vessel wall during ELCA. Also, the possibility of perforation of tissue samples at higher energy densities and/or pulse repetition rates would preclude a systematic evaluation of the crater bottoms.

GAS YIELD MEASUREMENT

The device used for gas yield measurements was described in detail elsewhere [13,15]. In short, gas measurements were based on the displacement of saline by accumulating gas. The device was designed to compensate for the inherent saline displacement due to forward movement of the catheter during experiments (Fig 3). The saline escaped through a flow-measuring device (LiquiFlow Model L1-FB-11-0, Bronkhorst Hi -Tec, Veenendaal, The Netherlands) that provided a proportional voltage in the range of 0 to 11 µl/s. The voltage was sampled and processed by means of a PC-based A/D converter (model DAS 1401, Keithley Metrabyte, Tounton, MA, USA). The accuracy of the automated gas measurement system was better than 4 % for total gas volumes. The residual volume due to the membrane-

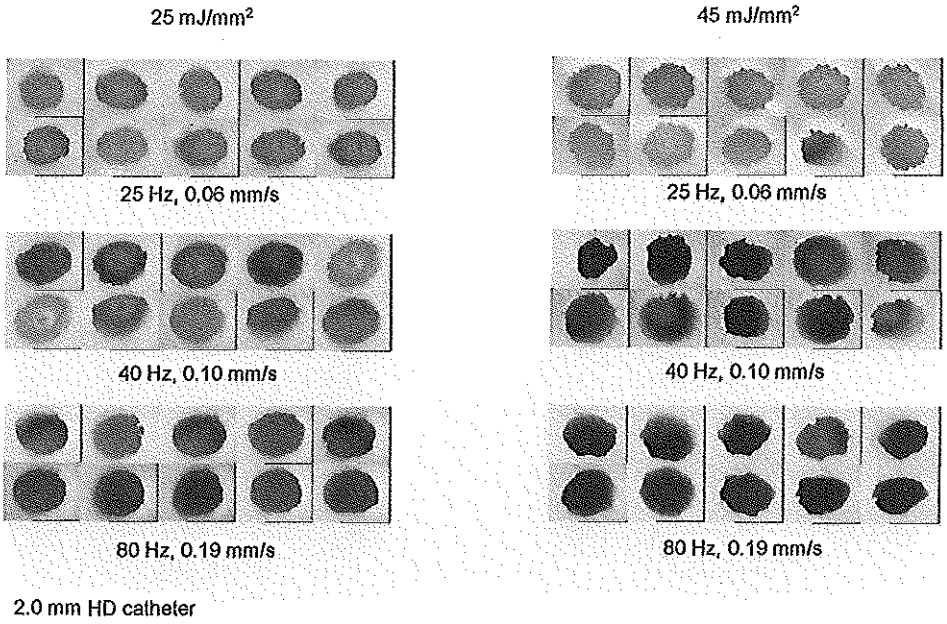


Figure 5a *Top view of unfixed craters of a series of 10 created with a 2.0 HD catheter. Pulse energy densities were 25- and 45 mJ/mm². The craters were made at 0.06 mm/s - 25 Hz, 0.10 mm/s - 40 Hz and 0.19 mm/s - 80 Hz*

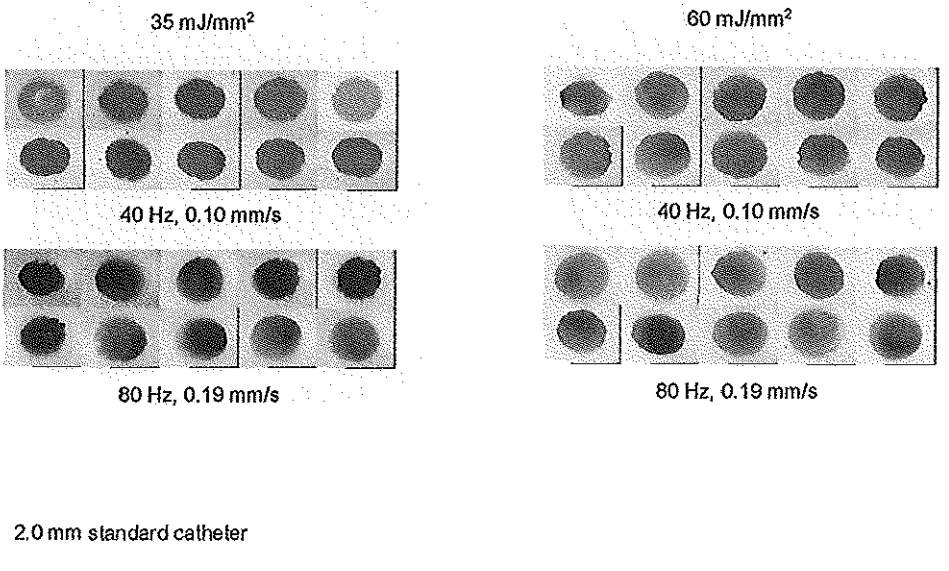


Figure 5b *Top view of unfixed craters of a series of 10 created with a 2.0 C catheter. Pulse energy densities were 35- and 60 mJ/mm². The craters were made 0.10 mm/s - 40 Hz and 0.19 mm/s - 80 Hz*

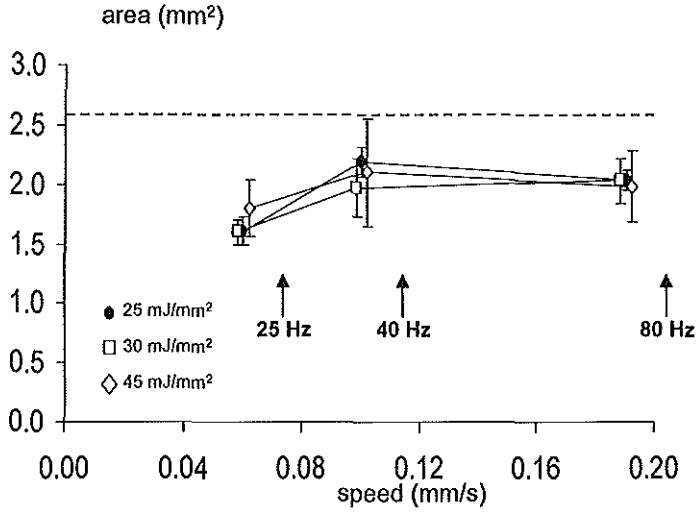


Figure 6 Minimal cross sectional area of craters made with a 2.0 mm HD-catheter as a function of pulse repetition rate. The energy densities were 25-, 30- and 45 mJ/mm². The dashed line indicates the area of the outer rim of the HD fiber distribution.

compensated movement of the catheter was determined after each individual gas yield measurement and subtracted from the measured gas volume. This residual gas volume was typically less than 1 µl.

STATISTICAL ANALYSIS

Continuous data were presented as mean ± SD. Comparisons of continuous variables were performed using unpaired two-tailed t tests. Incidents with a p value <0.05 were considered significant.

RESULTS

ABLATION EFFICACY

The top views of the 2.0 HD craters made at 25 Hz indicated that debulking efficacy was significantly affected by the catheter advancement speed (Fig 4). The craters made at speeds of 0.06 mm/s (25 Hz), and equivalent speeds of 0.10 mm/s (40 Hz) and 0.19 mm/s (80 Hz) were an illustration of the incremental effect of a higher pulse repetition rate on debulking efficacy (Fig 5a,b).

CROSS SECTIONAL AREA

At lower energy densities, the crater mouth cross sectional area significantly increased following an increase in pulse repetition rate (25 mJ/mm², 25 Hz vs. 40 Hz: 1.61 ± 0.12 mm² vs. 2.19 ± 0.12 mm², $p<0.0001$; at 30 mJ/mm², 25 Hz vs. 40 Hz: 1.60 ± 0.11 mm² vs. 1.97 ± 0.25 mm², $p=0.0004$). A subsequent increase in pulse repetition rate to 80 Hz did not further increase the crater area (Fig 6). At a fluence of 45 mJ/ mm², the effect of an increase in pulse repetition rate on crater

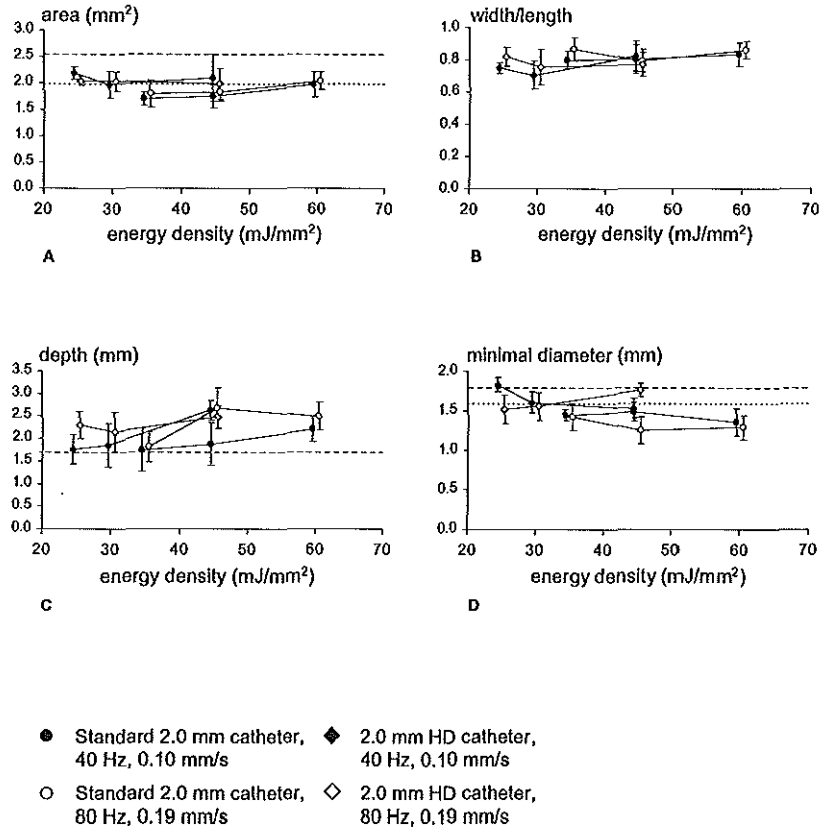


Figure 7 A. Crater mouth cross sectional area as a function of pulse energy density and catheter advancement speed. For comparison, the cross sectional areas of the outer rim of the fiber bundle of the HD-catheter (dashed line) and the standard catheter (dotted line) are indicated. B. The ratio of the short (width) and long (length) axes of the smallest crater cross-sections as a function of pulse energy and catheter advancement speed. C. Crater depth as a function of pulse energy and catheter advancement speed. The pre-defined catheter advancement was 1.7 mm and is indicated by the dashed line. D. Minimal crater diameter as a function of pulse energy and catheter advancement speed. The diameters of the outer rim of the fiber bundle of the 2.0 HD-catheter (dashed line) and the 2.0 C catheter (dotted line) are indicated.

area reached only border-line significance (45 mJ/mm², 25 Hz vs. 40 Hz: 1.79 ± 0.24 mm² vs. 2.10 ± 0.45 mm², p=0.071). Ablation with the 2.0 HD catheter resulted in a larger crater mouth cross sectional area (2.0 HD vs. 2.0 C: 2.19 ± 0.12 mm² vs. 2.04 ± 0.17 mm², p=0.035). Note, that when using the 2.0 HD, the crater area was smaller than the fiber area for all sets of parameters (dashed lines, Figs 6, 7a).

WIDTH/LENGTH RATIO

The width/length ratio was always smaller than 1, indicating an ellipsoid rather than a circular crater shape (Fig 7b). The larger ratios were seen following ablation with low energy densities and high pulse repetition rates (2.0 C at 35 mJ/mm^2 – 80 Hz: 0.87 ± 0.07; 2.0 HD at 25 mJ/mm^2 – 80 Hz: 0.82 ± 0.06, p=0.10).

CRATER DEPTH

The crater depth increased at greater energy densities and/or pulse repetition rates, regardless of what type of catheter was used. At either maximum energy density or an 80 Hz pulse repetition rate craters were deeper than the pre-defined 1.7 mm catheter travel (Fig 7c). For the maximum crater depth there was no significant difference between the two catheter types (2.0 HD vs. 2.0 C: 2.63 ± 0.21 mm vs. 2.68 ± 0.45 mm, p=0.48), possibly due to the fact that at 45 mJ/mm^2 - 80 Hz (2.0 HD) or 60 mJ/mm^2 – 80 Hz (2.0 C) most tissue samples were perforated, thus precluding a more precise comparison of the ablation efficacy.

CRATER MINIMAL LUMEN DIAMETER

As compared to the 2.0 C, using the 2.0 HD catheter resulted in a larger minimal diameter (2.0 HD vs. 2.0 C: 1.83 ± 0.09 mm vs. 1.48 ± 0.12 mm, p<0.0001). At 25 mJ/ mm^2 – 40 Hz, and 45 mJ/mm^2 – 80 Hz, the crater minimal lumen diameter equaled the active fiber outer diameter (Fig 7d).

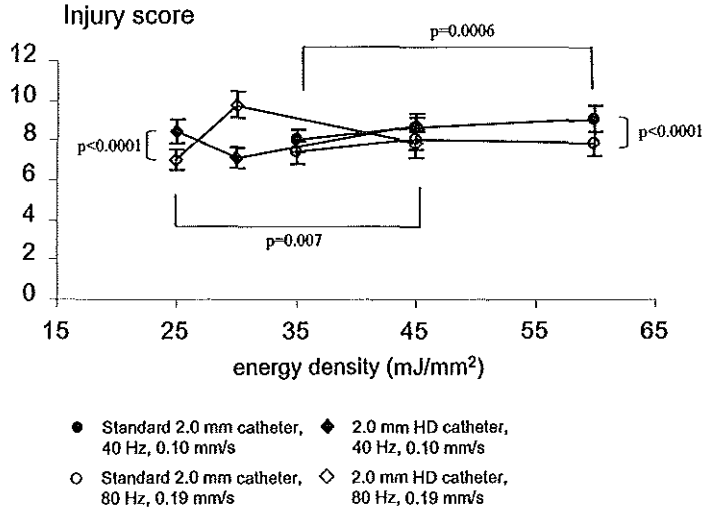


Figure 8 A graphic representation of the injury score.

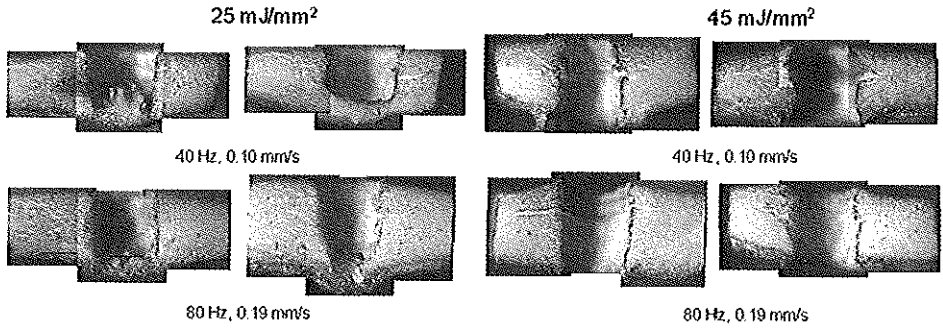


Figure 9 Examples of the morphology of craters made by the 2.0 HD-catheter at energy densities of 25- and 45 mJ/ mm² and pulse repetition rates of 40 Hz and 80 Hz

ABLATION QUALITY

Microscopically it was not possible to differentiate between the two catheter types, as all craters showed a considerable amount of surrounding tissue damage (Figs 8-10). The only negative exception was the presence of a maximum pressed appearance (fiber deflection of 45 - 90° at the crater rim) in all HD craters at 25 mJ/mm² – 40 Hz. In general, a higher energy density corresponded with a higher injury score. With the exception of 2.0 HD 30 mJ/mm² – 80 Hz, the injury scores at 80 Hz were significantly lower than at 40 Hz for all energy densities and pulse repetition rates (Fig 8).

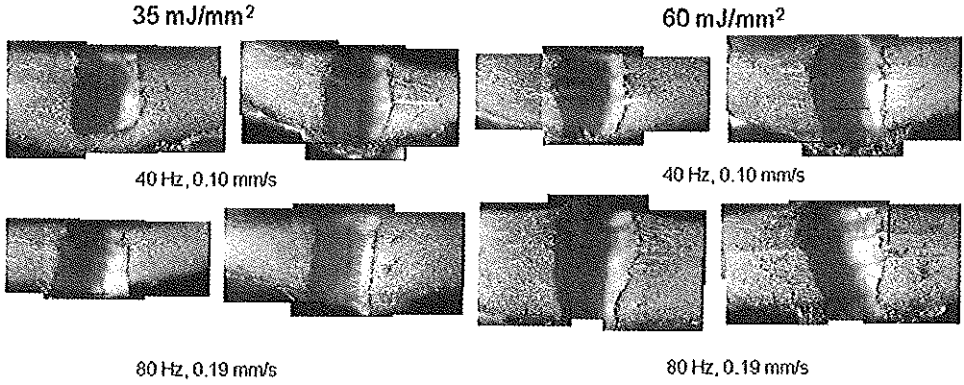


Figure 10 Examples of the morphology of craters made by the 2.0 C-catheter at energy densities of 35- and 60 mJ/ mm² and pulse repetition rates of 40- and 80 Hz

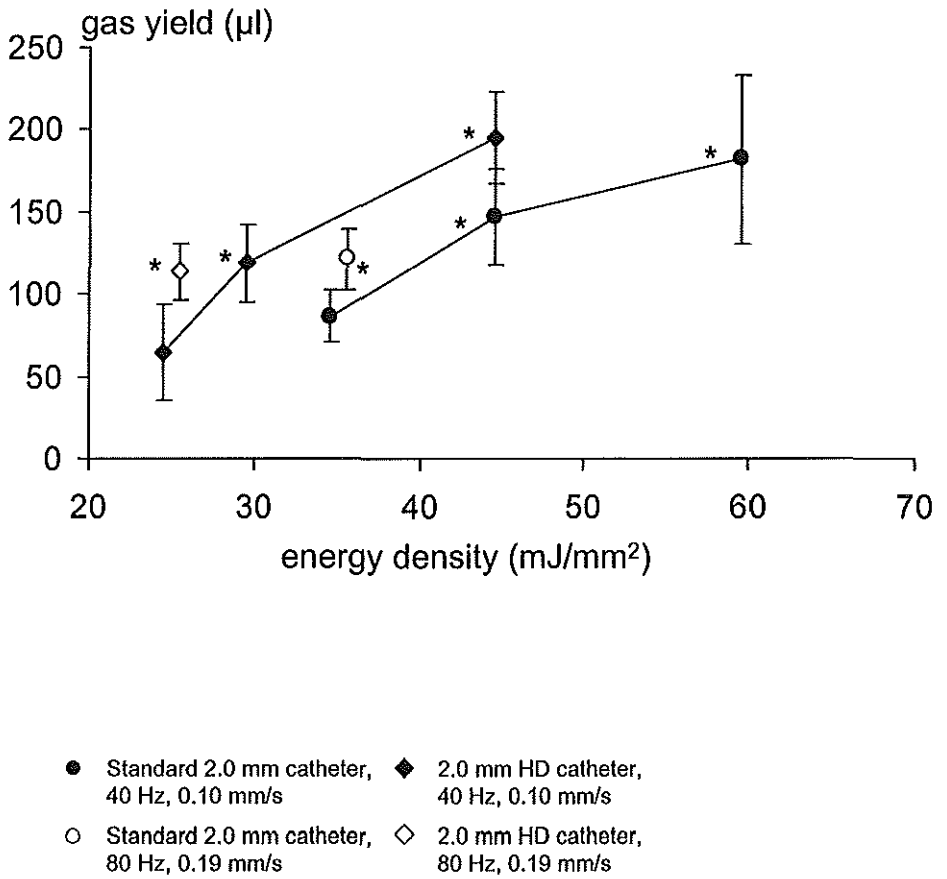


Figure 11 *Total gas yield as a function of pulse energy density and catheter advancement speeds. The asterixes indicate flow meter saturation during the pre-defined 1.7 mm catheter travel. As a result, for these situations the actual gas yield was higher than the indicated values.*

GAS YIELD

Total gas yields are shown in Figure 11. The maximum capacity of the gas flow meter used was 11 µl/s. At higher energy densities and 80 Hz excessive gas production caused an overload of the flow meter at the onset of the laser pulse train. Therefore, only those values given at 25 mJ/mm² - 40 Hz (2.0 HD) and 35 mJ/mm² - 40 Hz (2.0 C) were true yields, while the other values were an (under) estimation due to the limited maximum capacity of the flow meter (Fig 11, indicated by an asterix). Likewise, at 80 Hz only gas yields for lower energy densities could be deter-

mined. The gas yield measurements for the 2.0 HD ranged from 65 ± 29µl (25 mJ/mm² – 40 Hz) to 195 ± 28µl (45 mJ/mm² – 40 Hz, p<0.0001). For the 2.0 C the measurements ranged from 87 ± 16µl (35 mJ/mm² – 40 Hz) to 182 ± 52µl (60 mJ/mm² – 40 Hz, p<0.0001).

DISCUSSION

Previous clinical studies suggested ELCA to be of limited additional value in coronary angioplasty.[2,8-10] Both clinical- and *in vitro* studies have indicated that the moderate ablative capacity of currently available catheters could be responsible for sub-optimal clinical results.[5-7,11] However, it has been demonstrated that the *in vitro* ablation process can be enhanced by increasing the light emitting area at the catheter tip and by reducing the catheter advancement speed to values below 0.5 mm/s.[11,13-15] Therefore, a new 2.0 mm High Density excimer laser catheter with an increased number of fibers was designed and the current study was performed to evaluate its performance. An automated catheter advancement device was used to control the catheter movement at speeds <0.5 mm/s. In order to facilitate higher catheter advancement speeds, the 25 Hz pulse repetition rate - typical for ELCA - was increased to 40 Hz and 80 Hz.

ABLATION EFFICACY

Any definition of "optimal ablation" is arbitrary. However, from a clinical point of view one could argue that an optimal system should remove tissue effectively and predictably, while inflicting a minimum amount of damage to the surrounding vessel wall. As we used an automated catheter advancement device for all experiments, the post-ablation lumen should preferably have a diameter equal to the fiber area outer diameter ("maximum debulking") while the distance over which tissue was removed should equal the predefined advancement of the catheter ("predictable debulking").

The largest cross sectional area was obtained with the 2.0 HD at 25 mJ/mm² – 40 Hz – 0.10 mm/s (Fig 7a). Ablation with the same catheter and laser parameters also resulted in the largest crater minimal lumen diameter (Fig 7d). The largest cross sectional area for the 2.0 C was reached at 60 mJ/mm² and equaled the cross sectional area of the 2.0 C fiber area outer diameter. Although the top view at this energy density appeared to be smooth (Fig 5b), all dimensions were smaller than those found for the HD catheter.

In all experiments the width/length ratio of the crater tops was smaller than one, indicating an irregular or ellipsoid shape. This phenomenon could possibly be explained by splitting (rather

than ablation) of tissue along the direction of tissue fiber alignment in the media of the vessel wall. At lower energy densities (25 and 35 mJ/mm^2) and 80 Hz, craters were more circular than at 40 Hz. Also, craters made with the 2.0 C were more circular than those made with the 2.0 HD. This finding would thus favor the use of conventional catheters at laser parameters of 35 mJ/mm^2 and 80 Hz. However, at a pulse repetition rate of 80 Hz, craters were always deeper than the predefined 1.7 mm catheter travel, which could imply an increased risk of (coronary artery) perforation.

Despite the fact that the pre-defined catheter travel was shorter than the thickness of the tissue samples (as measured prior to ablation), perforation of the adventitia of the tissue samples occurred in most experiments when using a 80 Hz pulse repetition rate. Although the lateral damage -as expressed by the injury score- was less for 80 Hz than for 40Hz, the insoluble gas production at 80 Hz was factors higher, while the dimensional parameters for tissue removal were smaller. The excimer laser is predominantly a "contact laser". Nevertheless, it is possible to remove some tissue at a distance of the catheter tip, especially when using higher energy densities and pulse repetition rates in a saline environment.[11] Whether the perforation of tissue samples should be appreciated as a marker of improved ablation efficacy, or contrarily, should be regarded, as a reflection of increased tissue damage cannot be determined with certainty. The accumulation and ejection of large volumes of insoluble gas could be responsible for a forceful disruption of the distal tissue. This then would possibly explain the lower injury score, as an early distal perforation would eliminate the process of gas accumulation inside the tissue. In addition, if perforation would be a reflection of improved ablation efficacy, one would expect to find crater diameters at least equal to those created at 40 Hz. In contrast, they were smaller.

CATHETER ADVANCEMENT SPEED

The currently advised catheter advancement speed for ELCA is 0.5 – 1.0 mm/s.[15] At 0.51 mm/s and a pulse repetition rate of 25 Hz, tissue ablation was negligible for either catheter and/or energy density. Significant tissue removal occurred only at advancement speeds as low as 0.06 mm/s. If for example, an advancement speed of 0.06 mm/s would be used to cross a coronary lesion of 10 mm in length, this would take 167 seconds of lasing time. Such a long treatment time could result in myocardial ischemia due to a sustained obstruction of coronary flow. Therefore, the advancement speed was increased proportionally to an increase in pulse repetition rate, thus

maintaining the same advancement per pulse. Using the same example, at 80 Hz and 0.19 mm/s the lasing time to cross a 10 mm long lesion would be reduced from nearly 3 minutes to 53 seconds. However, as stated before, at 80 Hz the crater depth was always larger than the predefined catheter travel, thus introducing a potential risk of vessel wall perforation.

COLLATERAL TISSUE DAMAGE

An important finding was that although there were some minor differences, there was no set of parameters that allowed for ablation without collateral tissue damage. Tearing and vacuolization of adjacent tissue layers was a common feature in most tissue samples. These histologic phenomena probably reflected the mechanical impact of tissue vaporization and the accumulation and forceful ejection of insoluble gas. We also found a marked swelling of the tissue adjacent to the crater which resulted in an increased tissue sample diameter (Figs 7c,9,10). Unfortunately, it could not be determined with certainty whether this phenomenon was an expression of laser-tissue damage, or whether it resulted from friction between the catheter and the tissue.

INSOLUBLE GAS FORMATION

The formation of insoluble gas is most likely caused by excimer laser induced photochemical dissociation.[11,18,19] From previous experiments it emerged that photochemical dissociation occurs only as a result of the ablation of lipids.[11,19] As lipids are the predominant constituents of cell membranes we assume that although the current study was performed using porcine aorta, the results are indicative of the clinical setting of ELCA.

Even though gas yields exceeding 100 µl could not be measured directly (due to technical limitations), it was clear that increasing either energy density or the pulse repetition rate resulted in a significant increase in gas production. Increasing the pulse repetition rate from 40 Hz to 80 Hz resulted in a greater than 75% increase (>114 ml). As the crater depth increased only by 30% and the minimal crater diameter actually decreased, the 75% increase in gas yield could not be explained as a result of an increase in ablated volume. Following an increase in pulse repetition rate from 40 Hz to 80 Hz, using the 2.0 C at 35 mJ/mm^2, there was a 40% increase in gas yield without an increase in ablated volume. The possibility of an increase in pulse energy density per se being responsible for an increase in gas yields has been described before.[11,13,14, 18,19] Moreover, we previously observed a conversion of a linear to a non-linear increase in gas production, suggesting a second threshold for gas production occurring at (or

above) 35 mJ/mm^2. Therefore, the gas yields in this study could be a reflection of the applied energy density more then of the amount of tissue removed. Alternatively, an 80 Hz pulse repetition rate related increase of the catheter tip temperature could be responsible for this phenomenon as well. However, a direct relation between photochemical dissociation and ambient temperature has not been reported as yet. As distal embolization of insoluble gas could cause myocardial ischemia, the combination of a maximum debulking efficiency and a minimum gas yield would be preferable. The optimal result in this study was achieved using the HD catheter at 25 mJ/mm^2 – 40 Hz – 0.10 mm/s. Under these conditions, the crater depth was equal to the 1.7 mm catheter travel, the minimal crater diameter was equal to the fiber rim outer diameter, the cross sectional area approached the fiber cross sectional area, while these parameters resulted in the lowest gas yield as measured in this study.

Prior to a combined clinical introduction of the 2.0 HD and an automated catheter advancement device a word of caution seems appropriate. If the amounts of gas liberated on porcine aorta are indicative of gas yields during ELCA, treatment of a 10 mm length stenosis using a 2.0 mm HD-catheter at 25 mJ/mm^2 - 40 Hz - 0.1 mm/s would result in an insoluble gas yield of approximately 382 µl, which is equivalent to a single spherical bubble of 9.0 mm. For a person weighing 70 kg this would be a gas load of 5.5 µl/kg body weight. Animal experiments with a gas load of 2 µl/kg body weight injected directly into the LAD resulted in reversible myocardial motion abnormalities.[20]

STUDY LIMITATIONS

In all experiments, the catheter advancement was less than the measured thickness of the tissue samples. Nevertheless, perforation of tissue samples did occur and precluded the evaluation of a potential difference in ablation efficacy between the two catheter types at higher pulse repetition rates and/or energy densities. A second limitation was the capacity of the gas flow meter, which did not allow for flow measurements of >11 µl/s. Subsequently, the gas measurements at higher energy densities and pulse repetition rates were an underestimation of the true gas production. Finally, it is reasonable to assume that tissue ablation at 80 Hz will result in higher tissue temperatures than ablation at 25 Hz or 40 Hz. Therefore, it would be relevant to measure *in vitro* tissue temperatures prior to a clinical introduction of 80 Hz as a pulse repetition rate in ELCA.

CONCLUSION

Use of the 2.0 HD increased debulking efficiency as compared to ablation with standard 2.0 C catheters. This improvement was achieved without significantly increasing surrounding tissue damage and at relatively low gas yields. Increasing the repetition rate to 80 Hz resulted in a crater depth larger than the pre-defined catheter travel, a smaller cross sectional area and a smaller minimal crater diameter, while the gas yield increased by at least 75 %. If the results from this study can be extrapolated to a clinical setting of ELCA, a significant improvement in ablation efficiency of non-calcified atherosclerotic plaque could be achieved. It will however be difficult, if not impossible to reliably realize such slow catheter speeds by manually controlling the catheter advancement. Therefore, we suggest the introduction of an automated catheter advancement device [15]. Finally, as insoluble gas yields could increase secondary to improved debulking, potential ischemic effects should be anticipated.

REFERENCES

1. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser angioplasty. *Am J Cardiol 1992; 70:1533-1539*
2. Bittl JA, Sanborn TA. Excimer laser-facilitated coronary angioplasty. Relative risk analysis of acute and follow-up results in 200 patients. *Circulation 1992; 86:71-80*
3. Litvack F, Eigler N, Margolis J, Rothbaum D et al. Percutaneous excimer laser coronary angioplasty: results in the first consecutive 3,000 patients. The ELCA Investigators. *J Am Coll Cardiol* 1994;23:323-329
4. Baumbach A, Oswald H, Kvasnicka J, Fleck E, Geschwind HJ, Ozbeck C, Reifart N, Bertrand ME, Karsch K. Clinical results of coronary excimer laser angioplasty: Report from the European Coronary Excimer Laser Angioplasty Registry. *Eur Heart J* 1994; 15(1):89-96
5. Hoyne J, Mahon DJ, Nakamura S, Wallis J, Al-Zarka A, Saito S, Berns M, Tobis JM. Intravascular ultrasound imaging after excimer laser angioplasty. *Cath and Cardiovasc Diagn* 1994;32:213-222
6. Diethrich EB, Hanafy HM, Santiago OJ, Bahadir I. Angioscopy after coronary excimer laser angioplasty. *J Am Coll Cardiol* 1991;18:643-644
7. Garcia-Cantu E, Corcos T, Faverau X, Toussaint M, Zimarino M, Guérin Y, Baget F. Early deterioration after excimer laser-assisted coronary angioplasty. *Am J Cardiol* 1997;79:1230-1232
8. Karsch KR, Haase KK, Voelker W, Baumbach A, Mauser M, Seipel L.

Percutaneous coronary excimer laser angioplasty in patients with stable and unstable angina pectoris. Acute results and incidence of restenosis during 6-month follow up. *Circulation* 1990; 81:1849-1859

9. Appelman YEA, Piek JJ, Strikwerda S, Tijssen JG, de Feyter PJ, David GK, Serruys PW, Margolis JR, Koelemay MJ, Montauban van Swijndregt EW, Koolen JJ. Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. *Lancet* 1996; 347: 79-84
10. Reifart N, Vandormael M, Krajcar M, Göhring S, Preusler W, Schwarz F, Störger H, Hofmann M, Klöpper J, Müller S, Haase J. Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) study. *Circulation* 1997; 96:91-98.
11. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, Van Marle J, Van den Broecke DG, Hanekamp CEE, Van Gemert MJC, Serruys PW. Excimer Laser Coronary Angioplasty: A physical perspective to clinical results. In: Topol EJ & Serruys PW (eds) *Current Review of Interventional Cardiology*, 2nd edn. Philadelphia: Current Medicine 1995:159-172
12. Baumbach A, Haase KK, Rose C, Oberhoff M, Hanke H, Karsch KR. Formation of Pressure Waves During In Vitro Excimer Laser Irradiation in Whole Blood and the Effect of Dilution With Contrast Media and Saline. *Lasers Surg Med* 1994; 14:3-6
13. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution and high-density laser techniques in excimer laser coronary angioplasty. In: *Current Review of Interventional Cardiology*, 3nd edition. Chapter 12, pp. 101-111. Eds. D.R. Holmes, Jr., P.W. Serruys, Current Medicine, Philadelphia (Publisher), 1995
14. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution to reduce vessel trauma during excimer laser angioplasty. *Semin Intervent Cardiol* 1996; 1: 143-148
15. Gijsbers GHM, Hamburger JN, Wonders JHAM, Van der Putten R, Ansems VHC, Witteveen Th, Serruys PW. The Usefulness of Slow-Speed Automated Catheter Advancement for Optimization of Excimer Laser-Tissue Debulking. *Submitted for publication*, 1999
16. Bittl JA, Sanborn TA, Abela GS, Isner JM. Wire-guided excimer laser coronary angioplasty: instrument selection, lesion characterization,

and operator technique. *J of Interven Cardiol* 1992; 5:275-291

17. Gijsbers GHM, Hamburger JN, Wonders JHAM, Zondervan PE, Serruys PW. Method for the Assessment of Ablation Performance: a Novel Technique for Direct Evaluation of *In-Vitro* Excimer Laser Tissue Ablation. *Submitted for publication*, 1999
18. Appelman YEA, Piek JJ, Verhoofstad GGAM, Gijsbers GHM, van Gemert MJC. Tissue ablation and gas formation of two excimer laser systems: an *in vitro* evaluation on porcine aorta. *Lasers Surg Med* 1996;18:197-205
19. Gijsbers GHM, Jenniskens HG, van Wieringen N, Sprangers RLH, van Gemert M. Gas and cavitation bubble formation by XeCl excimer lasers used in laser angioplasty. In: Tissue ablation by CW lasers and a pulsed XeCl excimer laser as used in excimer laser angioplasty. *Thesis*, University of Amsterdam, 1992:89-138.
20. Van Blankenstein JH, Slager CL, Schuurbiers JCH, Strikwerda S, Verdouw PD. Heart function after injection of small air bubbles in coronary artery of pigs. *J Appl Physiol* 1993;75:1201-1207

CHAPTER 5

The influence of homogeneous light distribution on excimer laser ablation of vascular tissue

Jaap N. Hamburger, Geert H.M. Gijsbers, Patrick W. Serruys

(Submitted for publication to *Circulation*)

THE INFLUENCE OF HOMOGENEOUS LIGHT DISTRIBUTION ON EXCIMER LASER ABLATION OF VASCULAR TISSUE

ABSTRACT

Background - Excimer laser coronary angioplasty (ELCA) is associated with high restenosis rates. Improvement of results may be achieved by increasing ablation efficacy and/or reducing laser induced vessel wall trauma. The ablation efficacy of a laser catheter is determined by the ratio of the active surface area and the total surface area at the catheter tip. ELCA induced vessel wall trauma (dissection) is secondary to accumulation of insoluble gas and vaporization of tissue water. The extent of these processes is determined by the energy density at the catheter tip. Elimination of non-light emitting area at the catheter tip results in a homogeneous light distribution (HLD). This study was designed to evaluate the hypothesis that HLD allows for increased ablation efficacy at lower energy densities with as a result, less adjacent tissue trauma.

Methods and Results - The laser was a CVX-300 XeCl excimer laser. A 1.7 mm HLD device and a 1.8 mm High-Density multifiber device (HD) were used to ablate craters in porcine aorta. Experiments were performed using an automated catheter advancement device. The antegrade device travel was 1.7 mm, at speeds of 0.015-0.51 mm/s. Energy densities ranging from 9 mJ/mm^2 to 44 mJ/mm^2 and a pulse repetition rate of 25 Hz were used. Tissue vaporization was monitored using high-speed videography. The insoluble gas production and temperature increase at 0.5 mm distance from the HLD tip were measured on-line. Direct microscopy was used to measure ablation efficacy. The surrounding tissue damage was quantified using predefined parameters of mechanical damage and expressed as a compound injury score. Optimal ablation efficacy was defined as the crater mouth area being equal to the catheter light emitting area (a crater mouth area ratio of one). The crater mouth area ratio was inversely related to catheter advancement speed. The maximum values were reached at a device speed of 0.015 mm/s and energy densities of 11.4 mJ/mm^2 (0.8 ± 0.04, HLD) and 43.7 mJ/mm^2 (0.8 ± 0.09, HD) respectively. At these parameters, ablation with the HLD device resulted in significantly smaller vapor bubbles (HLD vs. HD: 3.01 ± 0.22 vs. 3.30 ± 0.31, p=0.027), less insoluble gas (HLD vs.

HD: 74 ± 19 ml vs. 178 ± 25 ml, $p<0.0001$) and a lower injury score (HLD vs. HD: 3.5 ± 0.43 vs. 6.1 ± 0.6, $p<0.0001$). The maximum temperatures measured ranged from 79 ± 9 °C (55 ± 9 °C above ambient, HLD at 11.4 mJ/mm^2) to 85 ± 9 °C (61 ± 8 °C above ambient, HLD at 20 mJ/mm^2). The fraction of photons contributing to insoluble gas production was less than 5%.

Conclusion – HLD at slow catheter advancement speeds and low energy densities results in optimal ablation efficacy and minimal mechanical tissue injury. However, both the increase in tissue temperature and the large volumes of insoluble gas could be the limiting factors of a clinical application of HLD-ELCA.

Since its introduction in 1977, percutaneous transluminal coronary angioplasty (PTCA) has increasingly been used for the treatment of coronary artery disease.[1] In order to improve both the acute and long-term results of balloon angioplasty, various catheter techniques for removal of atherosclerotic plaque have been evaluated.[2-7] The clinical introduction of 308 nm XeCl excimer laser coronary angioplasty (ELCA) was based on initial *in vitro* experiments, demonstrating vascular tissue removal without adjacent tissue damage. Initially, photochemical dissociation was thought to be the physical mechanism responsible for tissue ablation.[8] However, the occurrence of fast expanding and imploding vapor bubbles as demonstrated in subsequent experiments, stressed the relevance of thermal induced tissue evaporation as an important additional mechanism.[9-11]

In ELCA, the light emitted from the laser is transported to a coronary lesion by use of flexible, multifiber catheters. From Monte Carlo computer simulations it follows, that in a multifiber catheter configuration there is always a certain amount of space in between the fibers.[12] It can be calculated that given a multifiber configuration, there is no light overlap between the fibers at the catheter tip-tissue interface.[13] Due to the absence of light overlap between fibers (or the presence of "dead space"), only the tissue directly beneath the individual fibers will be ablated. This was confirmed in experiments showing the inability of ELCA catheters to penetrate vascular tissue at low energy densities, resulting in a "Swiss cheese" like pattern of ablation[10] (Fig 1). Only at energy densities of ≥45 mJ/mm^2, the physical forces (larger water vapor bubbles, increased insoluble gas yield) were strong enough to shatter and remove non-ablated tissue strands located between the individual micro craters. However, this increase in ablation efficacy was at the cost of an increase in

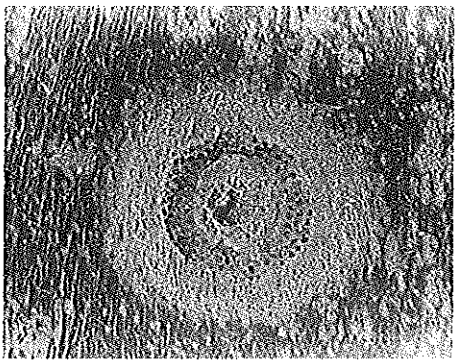


Figure 1 Scanning electron micrograph of a lesion after 50 laser pulses at a fluence of 45 mJ/mm² and a pulse repetition rate of 25 Hz. The porcine aortic tissue sample was immersed in saline (0.9 NaCl). A pressure equivalent of 10 grams was exerted on the catheter tip during ablation. Note that the tissue in front of the catheter tip is only partially ablated ("Swiss cheese phenomenon") due to a lack of light overlap at the catheter tip-tissue interface.

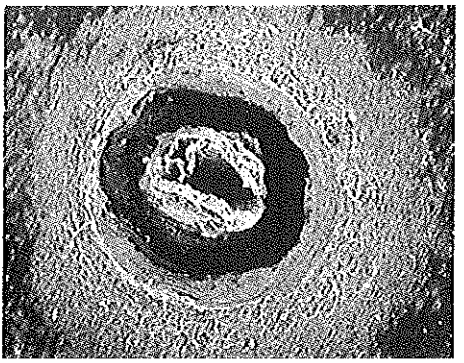


Figure 2 Improved catheter penetration at higher energy densities (60 mJ/mm²). Note the increase in collateral tissue damage. Scanning electron micrograph.

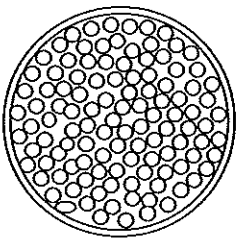
mechanical damage to adjacent tissue (Fig 2). We hypothesized that the elimination of dead space at the catheter tip would allow for efficient tissue ablation at lower energy densities and thus, result in less adjacent tissue damage. Therefore, in this study we evaluated the ablation properties of a multifiber High Density (HD) device in which a bundle of fibers, typically used in ELCA catheters, was packed as tight as possible in order to obtain a minimum amount of dead space. The results were compared with the ablation properties of a similar diameter single fiber with a homogeneous light distribution (HLD) at its tip. We measured tissue vaporization, insoluble gas volumes and tissue temperature increase during ablation of porcine aortic tissue samples. The morphology and dimensions of the ablated area ("ablation craters") and the adjacent tissue damage were subsequently evaluated.

METHODS

LASER AND LASER DEVICES

The laser was a Spectranetics CVX-300 XeCl excimer laser (Spectranetics, Colorado Springs, CO, USA) emitting ultraviolet light at a wavelength of 308 nm with a pulse duration of approximately 200 ns. For all experiments the pulse repetition rate was 25 Hz. A 1.8

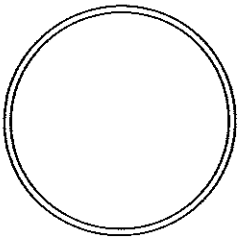
mm diameter High-Density device (1.8 HD, Spectranetics, USA) and a 1.7 mm diameter homogeneous light distribution device (1.7 HLD, Spectranetics, USA) were used. The 1.8 HD contained 288 concentrically distributed silica fibers of 61-μm diameter, while the 1.7 HLD contained a 1.52 mm diameter single fiber. The characteristics of both devices are given in Figure 3. The energy densities used for the 1.8 HD ranged from 19 to 44 mJ/mm^2, for the 1.7 HLD



HD 1.8 mm
outer diameter: 1.83 mm
outer rim fiber bundle: 1.49 mm

device surface area: 2.57 mm^2
fiber area: 1.74 mm^2
active area: 0.84 mm^2

fiber area/surface area = 69%
active area/fiber area = 48%
active area/surface area =33%



HLD 1.7 mm (cladding only)
outer diameter: 1.65 mm
outer rim fiber: 1.52 mm

device surface area: 2.19 mm^2
fiber area: 1.82 mm^2
active area: 1.82 mm^2

fiber area/surface area = 83%
active area/fiber area = 100%
active area/surface area =83%

Figure 3 *Characteristics of the 1.8 mm diameter High-Density device (288 concentrically distributed silica fibers of 61-μm diameter, top) and the 1.7 mm diameter homogeneous light distribution device (1.52 mm diameter single fiber, bottom).*

from 9 to 20 mJ/mm^2. We chose these values based on earlier observations, suggesting that ablation was negligible at energy densities below the given minimum values.[14] In addition to ablation at these minimum values, ablation properties at intermediate and maximum values were evaluated.

TISSUE SAMPLES

Laser ablation experiments were performed using fresh porcine thoracic aortic tissue samples. Loose connective tissue surrounding the adventitia was removed and the aorta was cut in tubular segments of circa 4 cm. The thickness of the samples chosen was approximately 2 mm. These segments were kept in an airtight container on ice. Prior to use, segments were cut longitudinally and spread with the intima faced upward, thus creating a rectangular tissue sample of approximately 4 x 3 cm. The segment was mounted in a holder, which was placed in a glass container and immersed in saline (NaCl 0.9 %).

SPEED DRIVEN ADVANCEMENT (SDA)

To provide a constant speed to a catheter, we used a system previously described.[15] In short, the catheter was fixed in a shaft that was mounted on the X-direction carriage of an XY recorder (Model BD 90, Kipp & Zonen, Delft, The Netherlands). The X-direction connector controlled the movement of the catheter, through a voltage provided by a D/A-converter (PC-LabCard PCL-711S, Advantech, Taipei, Taiwan). The voltage was varied by means of a Pascal program that allowed the choice of speed and the delay between the onset of laser activation and the start of catheter advancement. The catheter advancement speed currently advised for ELCA procedures is 0.5 – 1 mm/s.[16] However, in a previous study the progression of the ablation front (1.7 mm catheter, at 60 mJ/mm^2 – 25 Hz) was measured to be ≤0.06 mm/s.[15] Therefore, speeds of 0.51 mm/s and 0.06 mm/s were applied for the purpose of comparison, while in addition speeds of 0.03 mm/s and 0.015 mm/s were evaluated. To prevent mechanical perforation of the approximately 2.0 mm diameter tissue samples, the advancement of the catheter during lasing was programmed to be 1.7 mm. The laser pulse train started one second prior to the initiation of catheter movement. For statistical purposes, 10 craters were made for any combination of parameters.

MICROSCOPIC ASSESSMENT OF ABLATION PERFORMANCE

Prior to tissue fixation, images were made of the top-view of craters using a microscope (BH-2 + NeoPlan 5 x objective, Olympus, Japan) equipped with a color CCD-camera (DXC-151P, Sony, Japan). The tissue sample with 10

craters was then fixed in formalin (10% formaldehyde). Subsequently, each crater was cut in half along the long axis. The halves were stirred in a diluted Toluidine-blue solution for image enhancement. All images were stored on a personal computer (PC) hard disk using a video frame grabber (Iris Video Digitizer, Inside Technology, Amersfoort, The Netherlands). For analysis, standard image analysis software (Photoshop, Adobe Inc, USA) was used. From these images a number of quantitative and semi-quantitative features were scored. From the top-view image, the cross sectional area (in mm^2) and the long- and short axis (in mm) of the crater mouth circumference were measured. Ideally, the crater cross sectional area should equal the effective light emitting area (or "active area") at the tip of the laser device (crater mouth area/catheter core area ratio of 1). Also, the crater mouth circumference should be circular (crater circumference width/length ratio of 1). From the fixed and stained crater halves, measurements were made of the crater depth (in mm, as related to the pre-determined catheter travel of 1.7 mm), the minimal crater lumen diameter (in mm, as related to the device fiber outer diameter) and of the cross sectional area of the crater halves (in mm^2, as related to the product of 1.7 mm catheter travel times the device fiber outer diameter ≈ 2.5 mm^2). In a 0-2 classification (0 = absence of a phenomenon, 2 = worst case) the presence of residual tissue on the crater wall (lobes), the extent of tissue tearing (tear depth, tear width, number of tears) and the extent of vacuolization (number of vacuoles and distance to the crater wall) were assessed, as well as the bending of tissue fibers adjacent to the crater wall (bending of 0°, 0 - 45°, or 45 - 90°). The sum (average ± SD, n=10) resulted in an "injury score".

HIGH-SPEED VIDEOGRAPHY FOR MONITORING OF TISSUE VAPORIZATION

Fast expanding vapor bubbles were observed by means of an intensified CCD video camera (model 4Quik05, Stanford Computer Optics Inc. USA) equipped with a borescope (model F100, Olympus Optical Co. Japan) that allowed for close-up imaging in a saline environment. The image intensifier of the camera served as an electronic shutter and was triggered by an electronic pulse from the CVX-300 excimer laser. Short exposure times were used to image the fast expanding vapor bubbles at the moment of maximum expansion. The delay time between the laser trigger signal and the exposure time of the image intensifier was adjusted by means of a PC. Typical delay- and exposure times were 80 µs and 5 µs, respectively. Images were recorded using an S-VHS video recorder (Panasonic Model

NV-FS200, Japan). Those video frames showing the largest bubble size were captured in a PC using a video frame grabber (Iris Video Digitizer, Inside Technology, Amersfoort, The Netherlands). The diameters of bubbles and catheter were determined by means of image analysis software (Photoshop, Adobe Inc., USA).

GAS YIELD MEASUREMENTS

Measurements of insoluble gas production were performed using a previously described airtight gas sample chamber.[15] The method of this measurement was based on the principle of a displacement of saline due to accumulation of insoluble gas. The saline escaped through a flow-measuring device (LiquiFlow Model L1-FB-11-0, Bronkhorst Hi -Tec, Veenendaal, The Netherlands). The flow provided a proportional voltage in the range of 0 to 11 µl/s. The voltage was sampled and processed by means of a PC-based A/D converter (model DAS 1401, Keithley Metrabyte, Tounton, MA, USA). The accuracy of the automated gas measurement system was better than 4 % for total gas volumes, as determined by a 50-µl-calibration syringe. The device was designed to compensate for the inherent saline displacement due to forward movement of the laser device. The residual volume due to the membrane-compensated movement of the catheter was determined after each individual gas yield measurement and subtracted from the measured gas volume. This residual gas volume was typically less than 1 µl.

CALCULATION OF THE PHOTON FRACTION USED FOR GAS PRODUCTION

From previous experiments it emerged that tissue irradiation by UV photons resulted in the formation of insoluble gas due to photo-chemical dissociation of molecular bonds in lipids. In addition, photon energy could be either reflected or transformed into heat. In order to define the relative contribution of photo-chemical dissociation to the ablation process we calculated the fraction of photons used for gas production. The calculations are given in the Appendix.

TEMPERATURE MEASUREMENTS

Temperature measurements were performed using a thermocouple (Ceramo Type K, Thermo Electric International BV, Warmond, The Netherlands). To simulate recanalization of a tight stenosis, an aortic tissue sample was tightly wrapped and put into a plastic cylinder. Through the center of the tissue sample a guide wire was inserted over which a catheter was positioned on the tissue. Through a small opening in the plastic tube a 0.25 mm diameter thermocouple was placed 2 mm below the surface of the tissue. The tip of the thermocouple was positioned such to have either a

0.5 mm or 1 mm minimum distance from the outer surface of the catheter during ablation.[15] The thermocouple was connected to a Keithley DAS 1401 A/D-converter by means of a STP-37/C screw terminal connector (Keithley Metrabyte, Tounton, MA, USA) with on board cold junction compensation for on-line temperature registration. During temperature measurements, the laser device advancement speed was 0.015 mm/s. The predefined catheter travel was 4 mm, as a result of which 6717 pulses were delivered during 269 seconds (4 minutes, 29 seconds) of lasing time. Results are given as the maximum temperature increase above ambient (mean ± SD, n=10).

DATA ANALYSIS

The results are given as the mean ± SD. Where appropriate, results were compared using an unpaired, two-tailed Students t-test. A p-value <0.05 was considered as significant.

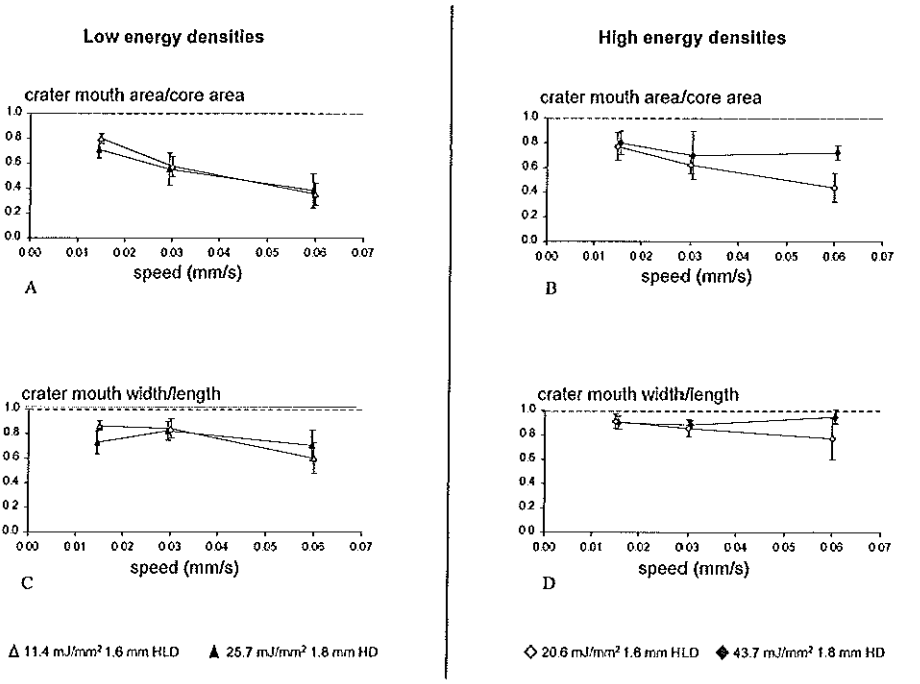


Figure 4 A. The ratio of the crater mouth and catheter core area. Ablation at intermediate energy densities B. The ratio of the crater mouth and catheter core area. Ablation at high energy densities. C. The ratio of the crater mouth circumference short (width) and long (length) axes. Ablation at intermediate energy densities. D. The ratio of the crater mouth circumference short (width) and long (length) axes. Ablation at high energy densities.

RESULTS

MICROSCOPIC ASSESSMENT OF ABLATION PERFORMANCE

CATHETER ADVANCEMENT SPEED

Similar to a catheter advancement speed typical for ELCA, we evaluated ablation efficacy at 0.5 mm/s. As ablation was fairly incomplete, further experiments were conducted by diminishing the advancement speed in a series of 0.12 mm/s, 0.06 mm/s, 0.03 mm/s and 0.015 mm/s.

CRATER MOUTH AREA/LIGHT EMITTING AREA RATIO

(Fig 4 A,B). The crater mouth area/light emitting area ratio was inversely related to the device advancement speed. The ratios were optimal at a speed of 0.015 mm/s and an energy density of 11.4 mJ/mm^2 (HLD), or 43.7 mJ/mm^2 (HD).

CRATER WIDTH/LENGTH RATIO

(Fig 4 C,D). At intermediate energy density levels, the crater mouth width/length ratio was significantly larger following HLD ablation (HLD 11.4 mJ/mm^2 vs. HD 25.7 mJ/mm^2, 0.87 ± 0.04 vs. 0.73 ± 0.09, p=0.0004). The width/length ratio was borderline significant larger in HD craters than in HLD craters only at both high energy density and high speed: (0.06 mm/s, HD 43.7 mJ/mm^2 vs. HLD 20.6 mJ/mm^2, 0.95 ± 0.06 vs. 0.77 ± 0.17, p=0.048).

CRATER DEPTH

(Fig 5 A,B). HLD crater depths varied from 1.35 ± 0.46 mm (9.1 mJ/mm^2- 0.06 mm/s) to 2.38 ± 0.19 mm (20.6 mJ/mm^2 – 0.06 mm/s), HD craters ranged from 1.17 ± 0.53 mm (19 mJ/mm^2 – 0.03 mm/s) to 2.33 ± 0.4 mm (43.7 mJ/mm^2 – 0.06 mm/s). At intermediate and high energy density levels, crater depths were always larger than the pre-determined 1.7 mm device travel. HD craters were deeper than HLD craters only at high energy density levels and a device speed of 0.015 mm/s (HD 43.7 mJ/mm^2 vs. HLD 20.6 mJ/mm^2, 2.17 ± 0.22 vs. 1.82 ± 0.06, p=0.0001). However, even at 9.1 mJ/mm^2 – 0.015 mm/s, the HLD device still had the capacity to perforate tissue samples and crater depths were significantly larger than HD craters at low energy density levels (HLD 9.1 mJ/mm^2 vs. HD 19 mJ/mm^2 – 0.015 mm/s, 2.27 ± 0.15 mm vs. 1.98 ± 0.24 mm, p=0.0046).

MINIMAL CRATER LUMEN DIAMETER

(Fig 5 C,D). A minimal crater lumen diameter equal to the fiber area outer diameter (HD 1.49 mm, HLD 1.52 mm) was considered optimal. Also for this parameter, the better results were achieved at lower device speeds (HLD

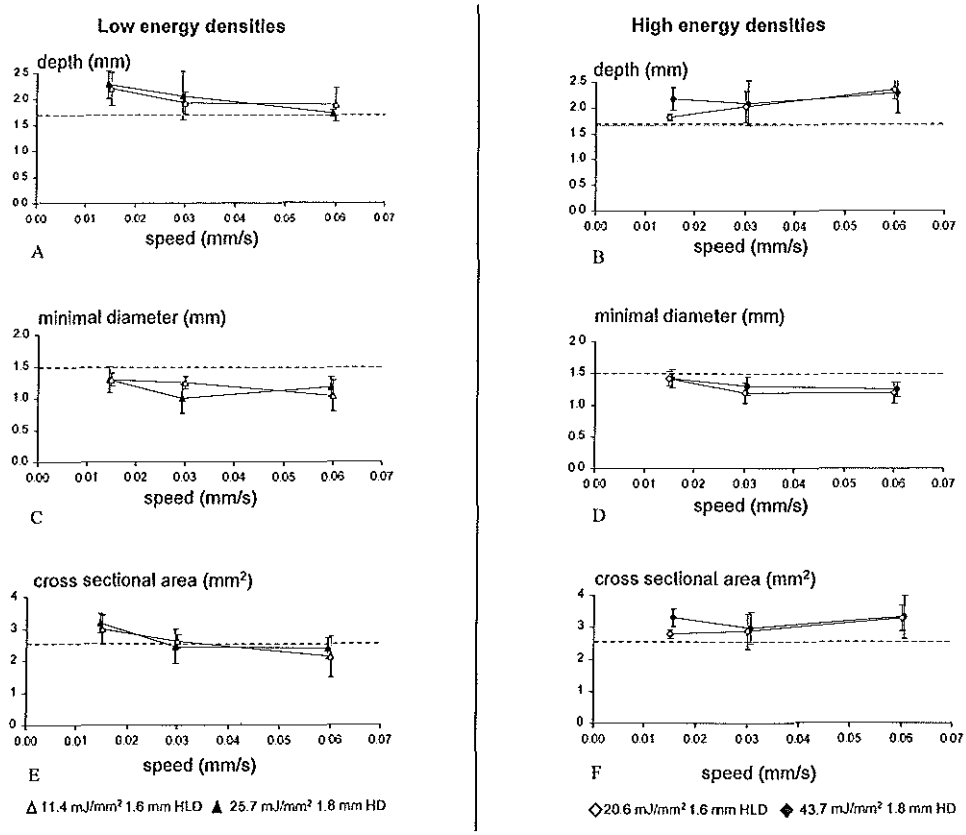


Figure 5 A. Crater depth as a function of pulse energy and catheter advancement speed. The pre-defined catheter advancement was 1.7 mm and is indicated by the dashed line. Ablation at intermediate energy densities B. Crater depth as a function of pulse energy and catheter advancement speed. The pre-defined catheter advancement was 1.7 mm and is indicated by the dashed line. Ablation at high energy densities C. Minimal crater diameter as a function of pulse energy and catheter advancement speed. The diameters of the outer rim of the fiber bundle of the HD and HLD-devices (dashed line) are indicated. Ablation at intermediate energy densities. D. Minimal crater diameter as a function of pulse energy and catheter advancement speed. The diameters of the outer rim of the fiber bundle of the HD and HLD-devices (dashed line) are indicated. Ablation at high energy densities. E. Crater mouth cross sectional area as a function of pulse energy density and catheter advancement speed. For comparison, the cross sectional areas of the outer rim of the fiber bundle of the HD-device and HLD-device are given (dashed line). Ablation at intermediate energy densities F. Crater mouth cross sectional area as a function of pulse energy density and catheter advancement speed. For comparison, the cross sectional areas of the outer rim of the fiber bundle of the HD-device and HLD-device are given (dashed line). Ablation at high energy densities

20.6 mJ/mm^2 vs. HD 43.7 mJ/mm^2 – 0.015 mm/s, 1.42 ± 0.12 mm vs. 1.42 ± 0.14 mm).

CRATER CROSS SECTIONAL AREA

(Fig 5 E,F). At low- and intermediate energy density levels, we found an inverse relationship between cross sectional area and device travel speed. At high energy density levels, the cross sectional area was always larger than the product of 1.7 (mm catheter travel) x 1.5 (mm the device fiber outer diameter, dotted line). Also for this parameter, HLD at low energy density resulted in significantly more tissue removal than the HD device (HLD 9.1 mJ/mm^2 vs. HD 19 mJ/mm^2, 2.78 ± 0.22 mm^2 vs. 2.46 ± 0.32 mm^2, p=0.017).

ABLATION QUALITY PARAMETERS

(Fig 6 A,B). On direct microscopy, some histology features were seen in the majority of samples and were considered as typical for excimer laser induced mechanical tissue damage. Among these were laceration, or tearing of tissue layers, the presence of vacuoles in various sizes and quantities and the protrusion in to the crater lumen of non-ablated tissue remnants ("lobes"). The downward deflection of fibers directly adjacent to the crater ("pressed appearance") was considered to reflect a mismatch between the device advancement speed and the actual speed of tissue removal. The HLD injury score ranged from 3.4 ± 0.44 to 11.1 ± 0.28, the HD score from 4.8 ±

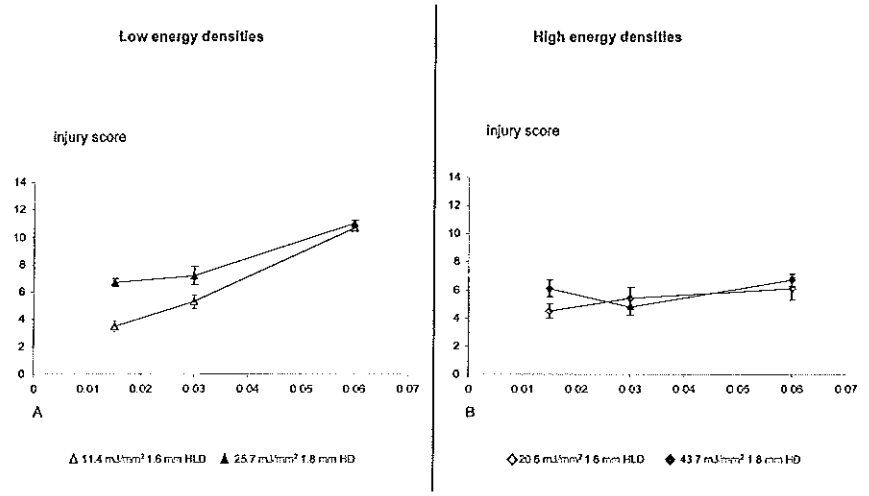


Figure 6 A graphic representation of the injury score. Ablation at intermediate energy densities (A) and ablation at high energy densities (B).

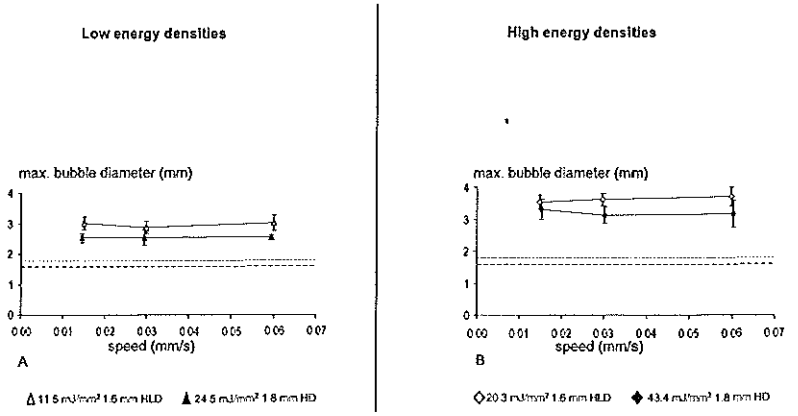


Figure 7 Maximum fast expanding bubble diameter (in mm) as a function of speed. Ablation at intermediate energy densities (A) and ablation at high energy densities (B).

0.59 to 11.56 ± 0.42. With the exception of HLD 20.6 mJ/mm^2 vs. HD 43.7 mJ/mm^2 at 0.03 mm/s (p=0.08), all HLD injury scores were significantly lower than the HD injury scores at the same device advancement speed. The HLD injury score at 11.4 mJ/mm^2 – 0.015 mm/s (3.5 ± 0.43) was significantly lower than any of the other values measured.

TISSUE VAPORIZATION

(Fig 7 A,B). For all experiments performed in this study, tissue ablation was invariably related to the occurrence of fast expanding vapor bubbles. For both the HD and HLD device, the vapor bubble diameters at a high energy density were significantly larger than those at intermediate energy density (at 0.015 mm/s, HLD 11.4 mJ/mm^2 vs. 20.6 mJ/mm^2, 3.01 ± 0.22 vs. 3.53 ± 0.22, p<0.0001. HD 25.7 mJ/mm^2 vs. 43.7 mJ/mm^2, 2.53 ± 0.16 vs. 3.3 ± 0.31, p<0.0001). Also, the vapor bubbles were larger with HLD than the with HD (at 0.015 mm/s, HLD 11.4 mJ/mm^2 vs. HD 25.7 mJ/mm^2, 3.01 ± 0.22 vs. 2.53 ± 0.16, p<0.0001).

GAS YIELD MEASUREMENTS

The results of the insoluble gas yield measurements are given in Fig 8 A,B. The HLD gas yields ranged from 39.4 ± 16 ml (at 10.7 mJ/mm^2, 0.06 mm/s) to 111.1 ± 30 ml (at 20.1 mJ/mm^2, 0.03 mm/s), while the HD gas yields ranged from 86.1 ± 20.8 ml (24.8 mJ/mm^2, 0.06 mm/s) to 178.4 ± 24.9 ml (43.8 mJ/mm^2, 0.015 mm/s). For all laser parameters, the HLD gas yields were significantly lower than the HD gas yields. Those laser parameters resulting in optimal tissue removal (HLD, 10.7 mJ/mm^2,

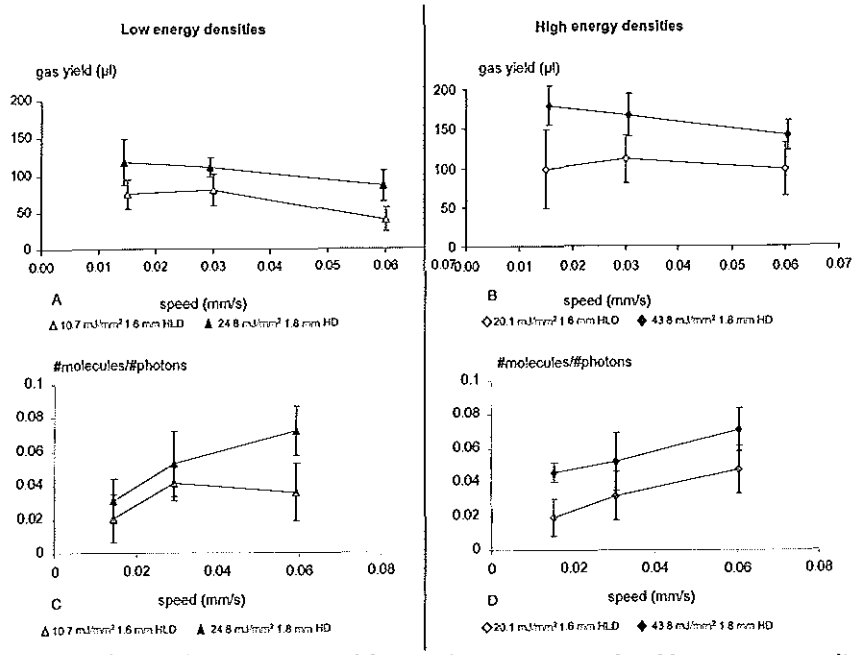


Figure 8 A. Total gas yield as a function of device advancement speeds. Ablation at intermediate energy densities. B. Ablation at high energy densities. C. The calculated number of gas molecules per number of incident photons at intermediate energy densities. D. At high energy densities.

0.015 mm/s) were associated with relatively low gas yields (74 ± 19.6 ml). Only at 10.7 mJ/mm², 0.06 mm/s the gas yields were lower, however these parameters were associated with incomplete tissue ablation. The calculated number of gas molecules per number of incident photons showed an almost linear decrease with decreasing energy densities (Fig 8 C,D). At device advancement speeds of ≤0.02 mm/s, less than 5% of the incident photon energy was transformed in insoluble gas.

TEMPERATURE MEASUREMENTS

The results of the temperature measurements during HLD ablation are shown in Fig 9. For experiments at 11 mJ/mm², the ambient temperature was 25 ± 0.5 °C. During ablation, the maximum temperature increase at 0.5 mm distance from the device tip was 55 ± 8 °C and at 1 mm distance 45 ± 6 °C. This resulted in a maximum temperature of 79 ± 9 °C. For experiments at 20 mJ/mm², the ambient temperature was 24 ± 0.9 °C, the maximum increase 61 ± 8° C (0.5 mm distance) and 51 ± 5 °C (1 mm distance), resulting in a maximum temperature of 85 ± 9 °C.

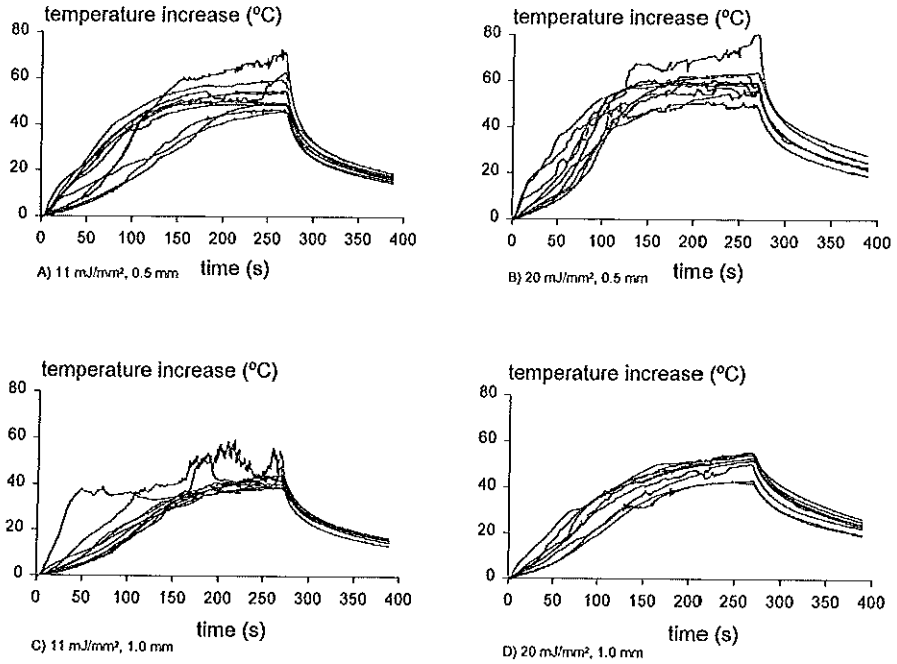


Figure 9 A. Temperature increase as a function of time for a laser pulse energy density of 11 mJ/mm² and a HLD device advancement speed speed of 0.015 mm/s. Temperatures are measured at a fixed point 2 mm below the tissue surface. A minimum catheter to thermocouple distance of 0.5 mm. Results are given as the maximum temperature increase above ambient (mean ± SD, n=10). B. Temperature increase as a function of time for a laser pulse energy density of 20 mJ/mm² and a HLD device advancement speed speed of 0.015 mm/s. A minimum catheter to thermocouple distance of 0.5 mm. C. Temperature increase as a function of time for a laser pulse energy density of 11 mJ/mm² and a HLD device advancement speed speed of 0.015 mm/s. A minimum catheter to thermocouple distance of 1.0 mm. D. Temperature increase as a function of time for a laser pulse energy density of 20 mJ/mm² and a HLD device advancement speed speed of 0.015 mm/s. A minimum catheter to thermocouple distance of 1.0 mm

COMBINED ANALYSIS

Optimal ablation efficacy was defined as the crater mouth area being equal to the catheter light emitting area (a crater mouth area ratio of one). This would translate to an ELCA catheter in a coronary atherosclerotic lesion, ablating a channel with a diameter equal to the diameter of its light emitting area. The maximum crater mouth area ratios were reached at a device speed of 0.015 mm/s and energy densities of 11.4 mJ/mm² (0.8 ± 0.04, HLD) and 43.7 mJ/mm² (0.8 ± 0.09, HD) respectively (Fig 10). At these parameters, the respective cross sectional areas were comparable as well (HLD vs. HD:

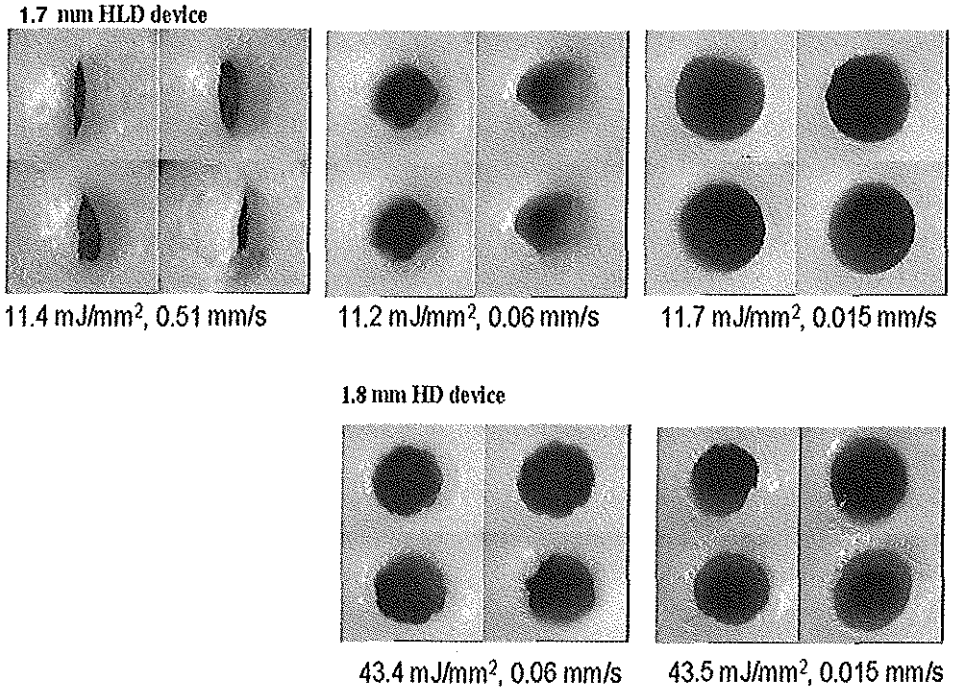


Figure 10 A. The maximum crater mouth area ratios were reached at a device speed of 0.015 mm/s and energy densities of 11.4 mJ/mm² (0.8 ± 0.04, HLD, top row) and 43.7 mJ/mm2 (0.8 ± 0.09, HD, bottom row)

2.99 ± 0.46 vs. 3.31 ± 0.27, p=0.07). However, ablation with the HLD device resulted in significantly smaller vapor bubbles (HLD vs. HD: 3.01 ± 0.22 vs. 3.30 ± 0.31, p=0.027), less insoluble gas (HLD vs. HD: 74 ± 19 ml vs. 178 ± 25 ml, p<0.0001) and a lower injury score (HLD vs. HD: 3.5 ± 0.43 vs. 6.1 ± 0.6, p<0.0001).

DISCUSSION

Historically, ablation of organic polymers by UV radiation is attributed to photo-chemical dissociation of molecular bonds by UV photons.[8,10] Due to the absorption of photon energy large molecules are divided into smaller components. Some of these small molecules will be in the gaseous phase. A second phenomenon which has been described, is the occurrence of rapidly (within 250 µs after each laser pulse) expanding and imploding vapor bubbles.[9] Similar to cavitation bubbles, a shock wave is generated at the moment of implosion. In previous studies, a correlation between the energy density at the tip of a laser delivery device, the volume of insoluble

gas and the dynamics of the fast expanding vapor bubble has been established.[10,15,16,18] Also, a direct relation between these physical phenomena and the severity of adjacent tissue damage has been postulated.[9,10,11,14-16]

For technical reasons, the application of laser energy in ELCA depends on the use of multifiber catheters. As the light rays emitted by individual fibers do not overlap, the catheter tip is partly light emitting, partly not ("dead space"). Obviously, this dead space at the catheter tip limits ablation efficacy, as tissue situated between the individual fibers is not directly ablated. By increasing the energy density at the tip of a laser catheter, non-ablated tissue remnants will be shattered and removed. Those energy densities typical for ELCA are sufficiently high to remove atherosclerotic plaque, but cause damage to the arterial wall as well.

In this study, we evaluated the hypothesis that an elimination of dead space at the catheter tip would increase ablation efficacy, therefore, allow for ablation at lower energy densities and subsequently, would result in a reduction of adjacent tissue damage. From the above presented experiments it emerged, that by using a homogeneous light distribution vascular tissue could indeed be ablated at significantly lower energy densities, with lower gas yields and significantly reduced collateral damage. Interestingly, even at the lowest energy densities evaluated, tissue ablation was always associated with the accumulation of insoluble gas and the occurrence of water vapor bubbles. In this study, the lowest gas yield measured was 74 ml (HLD, 0.015 mm/s and 11.4 mJ/mm^2), which was well in excess of gas yields in similar experiments with conventional ELCA catheters.[15,17,18] The accumulation of 74 ml of insoluble gas would result in a spheric bubble with a diameter of 5.2 mm. However, for those parameters typical of optimal ablation the calculated number of gas molecules per number of incident photons was less than 5%, while tissue temperatures of 85 ± 9 °C in the proximity of the laser device reflected tissue water vaporization. These findings suggest that thermal ablation rather than photochemical dissociation is the true mechanism of excimer laser tissue ablation at such low energy density levels.

FUTURE DIRECTIONS

With this set of experiments we made an attempt to describe some of the physical phenomena that occur during 308 nm XeCl-excimer laser ablation of vascular tissue. An additional evaluation of some laser parameters, i.e. an adjustment of the pulse repetition rate, could still further improve conditions for optimal ablation. On a more fundamental level, the question why the energy density controls the

balance between photo-chemical dissociation and water vaporization, needs to be clarified. Whether attempts to answer this question will provide us with the most optimal parameters for ELCA, or –on the contrary- will pave the way for the therapeutic use of other energy sources is an intriguing issue.

CONCLUSION

HLD allows for ablation at low energy densities. As a result, vapor bubbles were smaller, insoluble gas production was diminished (although gas yields were still not insignificant) and adjacent tissue damage was significantly reduced. Less than 5% of the calculated incident photon energy was transformed in insoluble gas while tissue temperatures increased up to 61 ± 8° C above ambient. Therefore, it can be concluded that under these conditions excimer laser tissue ablation is predominantly a thermal process. It is tempting, to suggest that HLD and slow catheter advancement speeds will improve clinical outcomes of ELCA by significantly reducing mechanically induced vessel wall damage. However, it is conceivable that the combined thermal strain, large volumes of insoluble gas and prolonged procedure times, rather than angiographic dissections could have a negative effect on the acute and long-term results of HLD-ELCA.

REFERENCES

1. Windecker S, Meyer BJ, Bonzel T, Fabian J, Heyndrickx G, Morice MC, Muhlberger V, Piscione F, Rothman M, Wijns W, van den Brand M, Meier B. Interventional Cardiology in Europe 1994. Working Group Coronary Circulation of the European Society of Cardiology. *Eur Heart J* 1998;19(1):40-54
2. Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, Lansky AJ, Popma JJ, Kuntz RE. Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). *Circulation* 1997;97 (4):309-11
3. Simonton CA, Leon MB, Baim DS, Hinohara T, Kent KM, Bersin RM, Wilson BH, Mintz GS, Fitzgerald PJ, Yock PG, Popma JJ, Ho KK, Cutlip DE, Senerchia C, Kuntz RE. Optimal directional atherectomy: final results of the Optimal Atherectomy Restenosis Study (OARS). *Circulation* 1997;97(4):332-9
4. Reisman M, Harms V, Whitlow P, Feldman T, Fortuna R, Buchbinder M. Comparison of early and recent results with rotational atherectomy. *J Am Coll Cardiol* 1997;29(2):353-7
5. Litvack F, Eigler N, Margolis J, Rothbaum D, Bresnahan JF, Holmes D, Untereker W, Leon M, Kent K, Pichard A. Percutaneous excimer

laser coronary angioplasty: results in the first consecutive 3,000 patients. The ELCA Investigators. *J Am Coll Cardiol* 1994; 23:323-329

6. Appelman YEA, Piek JJ, de Feyter PJ, Tijssen JGP, Strikwerda S, David GK, Serruys PW, Margolis JR, Koelemay MJ, van Swijndregt E, Koolen JJ. Excimer Laser Coronary Angioplasty versus Balloon Angioplasty in the Treatment of Obstructive Coronary Artery Disease: a Randomized Clinical Trial. *Lancet* 1996, 347:79-84
7. Reifart N, Vandormael M, Krajcar M, Göhring S, Preusler W, Schwarz F, Störger H, Hofmann M, Klöpper J, Müller S, Haase J. Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) study. *Circulation* 1997; 96:91-98.
8. Grundfest WS, Litvack F, Forrester JS, Goldenberg T, Swan HJC, Morgenstern L, Fishbein M, McDermid IS, Rider DM, Pacala TJ, Laudenslager JB. Laser ablation of human atherosclerotic plaque without adjacent tissue injury. *J Am Coll Cardiol* 1985; 5:929-33
9. Leeuwen van TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced by excimer laser pulse causes microsecond arterial dilation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993; 87:1285-1263
10. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, Van Marle J, Van den Broecke DG, Hanekamp CEE, Van Gemert MJC, Serruys PW. Excimer Laser Coronary Angioplasty: A physical perspective to clinical results. In: Topol EJ & Serruys PW (eds) *Current Review of Interventional Cardiology*, 2nd edn. Philadelphia: Current Medicine 1995: 159-172
11. Leeuwen van TG, Jansen ED, Welch AJ, Borst C. Excimer laser induced bubbles: dimensions, theory and implications for laser angioplasty. *Lasers in Surg Med* 1995;18:381-390
12. Keijzer M, Jacques SL, Prahl SA, Welch AJ. Light distributions in artery tissue: Monte Carlo simulations for finite-diameter laser beams. *Lasers Surg Med* 1989;9:148-154
13. Gijsbers GHM, Sprangers RLH, Van Gemert MJC. Excimer laser coronary angioplasty: laser-tissue interactions at 308 nm. in: *Primer on Laser Angioplasty*, 2nd edition. Ginsburg R, Geschwind H. (Eds.), Futura Publishing Co., Inc. Mount Kisco NY, 1992. Chapter 13, pp. 217-241
14. Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution and high-density laser

techniques in excimer laser coronary angioplasty. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, Philadelphia: Current Medicine 1996; 101-111

15. Gijsbers GHM, Hamburger JN, Wonders JHAM, van der Putten R, Ansems VHC, Witteveen Th, Serruys PWS. The Usefulness of Slow-Speed Automated Catheter Advancement for Optimization of Excimer Laser-Tissue Debulking. *Submitted for publication*
16. Bittl JA, Sanborn TA, Abela GS, Isner JM. Wire-guided excimer laser coronary angioplasty: instrument selection, lesion characterization, and operator technique. *J Interven Cardiol* 1992; 5:275-291
17. Gijsbers GHM, Hamburger JN, Serruys PW. Ablation Properties of a New 2.0 mm High Density Excimer Laser Catheter For Coronary Angioplasty. *Submitted for publication*
18. Appelman YEA, Piek JJ, Verhoofstad GGAM, Gijsbers GHM, van Gemert MJC. Tissue ablation and gas formation of two excimer laser systems: an *in vitro* evaluation on porcine aorta. *Lasers Surg Med* 1996; 18:197-205

APPENDIX

CALCULATION OF THE PHOTON FRACTION USED FOR GAS PRODUCTION

In order to calculate the fraction of photons used for gas production
we made the following assumptions:

1. Insoluble gas formation during excimer laser tissue ablation is the resultant of UV-photon induced dissociation of organic molecules
2. Photo-dissociation of one organic molecule is caused by the event of absorption of one single photon (multi-photon excitation was not taken into consideration)
3. The gas created as a result of photo-dissociation is an ideal gas at room temperature (20°C)

EXPERIMENT

Excimer laser pulses with a pulse energy density of x mJ/mm2 are used. The total light emitting area of a beam delivery device (fiber bundle in a catheter or a single HLD fiber) is A mm^2.
During application of n laser pulses a total gas amount of y µl is created.

To calculate the number of gas molecules in this volume, the ideal gas law is applied:

$$P\,V = N\,k\,T$$

P: pressure, assuming atmospheric pressure: p = 9.8·104 N/m2
V: volume; y µl equals y·10-9 m3
N: number of gas molecules
k: Boltzmann constant: 1.38·10-23 J/K
T: absolute temperature, T = 293 K (= 20°C)

This can be rewritten as
N = pV/kT

The number of molecules Ng in y µl of gas is (units are omitted):

$$N_g = \frac{9.8\cdot10^{4}\cdot y\cdot10^{-9}}{1.38\cdot10^{-23}\cdot293} = 2.4\cdot10^{16}\cdot y$$

The total energy E (in J) that is supplied to the tissue by n laser pulses is:

$$E = n\cdot x\cdot A\cdot10^{-3}\,J$$

The energy E_p of a single photon is given by

$$E_p = hc/\lambda$$

h: Planck's constant: $6.63\cdot10^{-34}$ Js
c: light speed: $3.0\cdot10^{8}$ m/s
λ: wavelength: 308 nm = $3.08\cdot10^{-7}$ m

The energy $E_{p,308}$ of a 308 nm photon is therefore $6.5\cdot10^{-19}$ J.

The number of photons N_p in the total delivered n pulses is

$$N_p = E/E_{p,308} = (n\cdot x\cdot A\cdot10^{-3})/6.5\cdot10^{-19} = 1.5\cdot10^{15}\cdot n\cdot x\cdot A$$

The number of gas molecules created per incident 308 nm photon, or the fractional gas production F_g, is

$$F_g = N_g/N_p = (2.4\cdot10^{16}\cdot y)/(1.5\cdot10^{15}\cdot n\cdot x\cdot A) = 16y/(n\cdot x\cdot A)$$

Example:
A 1.6 mm HLD single fiber with an advancement speed of 0.06 mm/s fires 884 pulses of 19.9 mJ/mm². The light emitting area is 1.82 mm². During this experiment 121.6 µl of insoluble gas was created.
The fractional gas production is:

$$F_g = 16\cdot121.6/(884\cdot19.9\cdot182) = 0.061$$

This indicates that per 100 incident UV photons 6.1 gas molecules were created. If all photons are absorbed and one event of photo-dissociation by one photon creates one gas molecule, then this number implies that only 6.1 % of all incident photons are used for gas production, while the remaining 93.9 % is dispersed in another form of energy (i.e. transformed into heat).

New Aspects of Excimer Laser Coronary Angioplasty

PART II

Clinical aspects of excimer laser coronary angioplasty

"If I do not help myself, who will help me?
But if I only help myself, who am I?"

From: The Pirkei Awot

CHAPTER 6

Laser guidewire for recanalization of chronic total occlusions

Jaap N. Hamburger, Patrick W. Serruys

In: Beyar, Keren, Leon and Serruys (eds) Frontiers in Interventional Cardiology, (Martin Dunitz Ltd, London 1997); 47-53

LASER GUIDEWIRE FOR RECANALIZATION OF CHRONIC TOTAL OCCLUSIONS

Since its introduction, percutaneous transluminal coronary angioplasty (PTCA) has established itself as an important alternative to coronary artery bypass surgery (CABG) in the treatment of coronary artery disease. A continuing development of techniques and tools, has led to a considerable increase in both the number and complexity of cases performed annually.[1] Once considered to be 'a temptation to resist', the percutaneous treatment of diseased saphenous vein bypass grafts, small diameter coronary arteries, and multivessel disease are becoming part of the routine rather than the exception in today's angioplasty practice. The recent explosive increase in the use of intracoronary stents has played a major role in this shift of the former boundaries of PTCA.[2] One of the last remaining bastions of CABG has been the treatment of chronic total coronary occlusions. Hampered by low initial success rates[3-8] and high recurrence rates,[9-11] it was only after the introduction of improved guidewire technology[12,13] in addition to the demonstration of a positive influence of stenting on long term vessel patency[14], that chronic total occlusion became a more acceptable indication for percutaneous treatment. The laser guidewire is an example of such new guidewire technology.[15] It was specifically designed for the recanalization of chronic coronary artery occlusions refractory to recanalization attempts using conventional guidewires. Earlier, our group reported on the initial clinical experience with the laser guidewire.[16] We report here on the technical aspects of laser guidewire assisted recanalization of total occlusions, a treatment modality for a potentially large group of patients.[17,18]

THE LASER GUIDEWIRE

The Spectranetics Prima Coronary Total Occlusion System (Model 018-003) (Spectranetics, Colorado Springs, CO), consists of an 0.018-inch laser guidewire and a support catheter and is designed to combine the mechanical attributes of a typical coronary guidewire with the ablative energy of the CVX-300 excimer laser in order to enable the initial crossing of total coronary occlusions (Fig 1). The wire consists of optical fibers with a 45 micron diameter, encased within a 0.018-inch diameter shaft. The distal 30 cm of the wire is relatively floppy and is treated

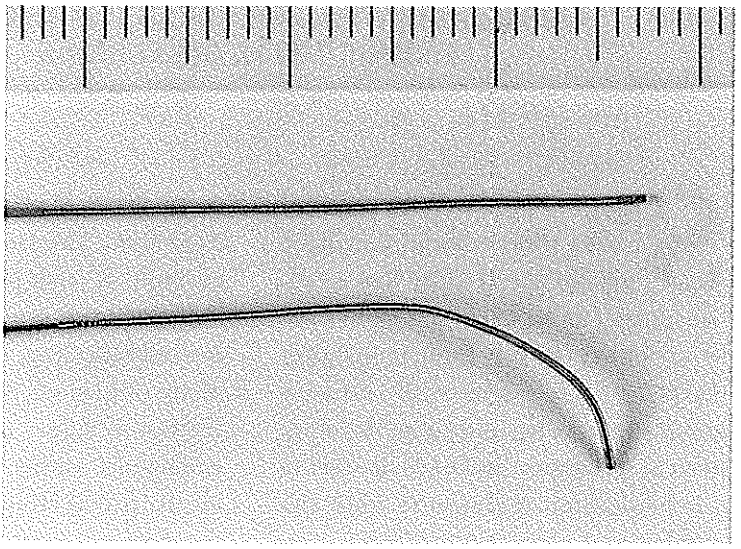


Figure 1 Total Occlusion System showing the tip of thelaser guidewire, unshaped (top) and shaped (bottom).

with a lubricious coating. The distal coil tip is radio-opaque for visualization under fluoroscopy. The wire tip is shapable and, if required, re-shapable during a procedure in order to meet specific anatomic circumstances. Furthermore, it has a torque device mounted on the proximal shaft. The support catheter, which comes with the laser guidewire is 135 cm long and has a single 0.018-inch wire compatible lumen. It has a radio-opaque marker mounted 1 mm proximal to a 2.5 French tapered tip. Finally, the system is supplied with a 15 cm long tapered 'peel-off' introducer to assist insertion of the laser guidewire into the support catheter.

The laser source compatible for the laser guidewire is the Spectranetics CVX-300 XeCl excimer laser, emitting at a wavelength of 308 nm. The physical phenomena which occur during tissue ablation at this wavelength are described elsewhere.[19]

THE LASER GUIDEWIRE PROCEDURE

The working mechanism of the laser guidewire is based on the ablation of diseased vascular tissue. Contrary to conventional guidewires that follow the path of least resistance, the laser guidewire will advance in whatever direction the wire tip is directed during activation of the laser beam. Consequently, a proper alignment of the laser guidewire is the most critical issue involved in this procedure. Therefore, to guide the steering of the wire through a missing segment, both a proximal entry point and a clear distal (anatomic) re-entry point leading to a visible true

distal lumen are an absolute pre-requisite for a successful procedure. As a rule, a complete distal opacification of the target vessel by collaterals (minimum: Rentrop[20] class 2) is required to assure the visibility of the target vessel during the procedure.

Currently, at the Thoraxcentre we use the approach described below in order to optimize the chances of a successful procedure. Puncturing of both femoral arteries with insertion of a second, smaller French-size catheter in the contralateral coronary artery is employed. By a combination of simultaneous bilateral injection of contrast medium into both coronary arteries, thus making use of the inter-coronary collateral circulation and (whenever available) biplane coronary angiography, optimal information is obtained about the anatomy of the missing segment (Fig 2). A monoplane system could be used, provided multiple views from different angles are made each time prior to the advancement of the laser guidewire.

A guiding catheter, minimum 8 French size, that provides good coaxial alignment and back up support is chosen. An example of a guiding catheter which supplies optimal back up support would be an Amplatz left, rather than a Judkins-type, guiding catheter for occlusions of either the left or right coronary artery. A large lumen Y-connector is mounted on the guiding catheter to allow for the potential introduction of a laser catheter, if crossing of the wire needs to be followed by an excimer laser coronary angioplasty (ELCA) procedure. Unless ipsilateral collaterals sufficiently supply the occluded segment, a 7 French diagnostic catheter introduced through the contralateral femoral artery is positioned in the ostium of the contralateral coronary artery.

To facilitate flushing of the support catheter during the procedure, a standard Y-connector with a three-way stop cock is mounted on the supplied support catheter. After flushing with a heparin solution, the support catheter is preloaded with the laser guidewire, using the peel-off introducer to avoid damage to the wire tip. Subsequently, the tip of the laser guidewire is shaped by rolling the tip gently between the first and second finger. Once positioned in the coronary artery, the tip of the wire tends to lose the imparted shape. It is therefore advisable to curve the wire tip to a larger extent than usually done with a conventional type guidewire for the same anatomical situation. After this, the laser guidewire is calibrated at a fluence of 60 mJ/mm^2 and a pulse repetition rate of 25 Hz. It should be noted that calibration of the wire is done only after shaping of the wire tip, since the tip shaping manoeuvre may damage the silica fibers inside the laser guidewire

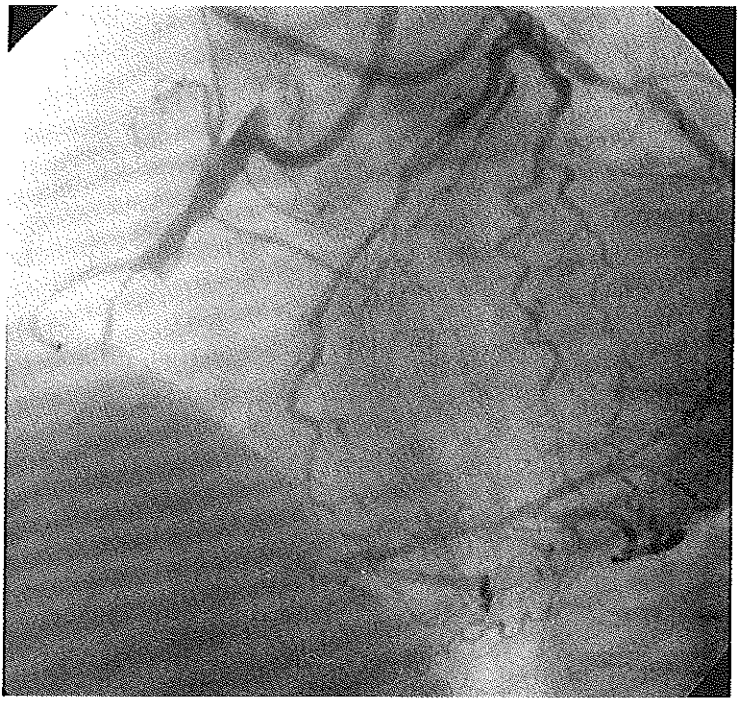


Figure 2 Total occlusion of a right coronary artery. A left Amplatz guiding catheter is positioned in the ostium of the RCA and a 7 French Judkins left diagnostic catheter in the ostium of the left coronary artery. Bilateral simultaneous injection of contrast medium, showing the occlusion stump and the distal lumen.

which would be manifest as a calibration failure. Once the calibration is completed, the laser guidewire is retrieved into the support catheter and both are introduced into the guiding catheter. The support catheter is advanced toward the tip of the guiding catheter, and the wire is advanced into the stump of the occlusion. When there is a sharp bend in the artery proximal to the target occlusion (e.g. an occlusion in the circumflex artery), prior to introduction of the laser guidewire, a mechanical guidewire can be used in order to position the tip of the support catheter in the funnel of the occlusion. In situations where there is an eccentric funnel, as an alternative to the support catheter, it may be helpful to use a balloon catheter and to inflate the balloon in the occlusion stump at a low pressure, for the creation of an entry point with a central location.

Initially, advancement of the laser guidewire without activation of the laser may be attempted. In the situation where it is not possible to advance the laser guidewire mechanically, the wire is moved forward during laser activation. The fluence typically used during a laser guidewire procedure is 60 mJ/mm^2, with a pulse repetition rate of

25 Hz. The corresponding pulse energy at the tip of the wire at this fluence, is approximately 1.2 mJ.

During pulse trains, with a maximum of 5 seconds, the wire is gently advanced at a rate of 0.5 - 1 mm per second. During advancement of the wire, continuous monitoring with biplane fluoroscopy of the position and alignment with the vessel segment to be crossed is strongly recommended. Each time the tip of the laser guidewire has reached a new position, the alignment with the distal lumen is checked by a contralateral injection of contrast medium. In case of misalignment, the advancement of the wire is discontinued and the laser guidewire is repositioned before further advancement.

If during laser activation the laser guidewire encounters intraluminal resistance which hampers its normal progression (e.g. plaque calcification), the pulse repetition rate should be increased to 40 Hz. In certain conditions, despite a pulse repetition rate of 40 Hz, wire progression can still be insufficient. This could be explained by:

- insufficient back up support, inability of the laser guidewire to ablate the tissue it is in contact with (e.g. calcium)
- a subintimal position of the wire tip (misalignment),
- mechanical damage of the wire tip with a subsequent drop in the energy output.

In these situations the following strategy is suggested. First, advance the support catheter in order to supply additional back up support. Although experience has taught us that nature is forgiving and staining of the occluded segment with contrast medium (intraluminal or perivascular) should not be a reason for terminating the procedure in general, pushing of the tip of the support catheter into the occluded segment should be avoided in order to prevent dissections.

Next, especially in case of fluoroscopically visible calcifications, a slight pullback of the tip of the wire can be tried. When readvancing the wire, the wire tip is steered around the obstruction, obviously staying within the boundaries of the arterial segment (Fig 3). Another option (especially if there are indications of a subintimal position of the wire tip) would be to withdraw the tip of the laser guidewire into the proximal stump of the occlusion, in order to make a new entry point. If, despite these efforts, wire progression is negligible, the tip of the support catheter should be positioned in the stump of the occlusion and the wire removed from the support catheter. Subsequently, the tip of the laser guidewire can be examined for mechanical damage, and the energy output can be measured.

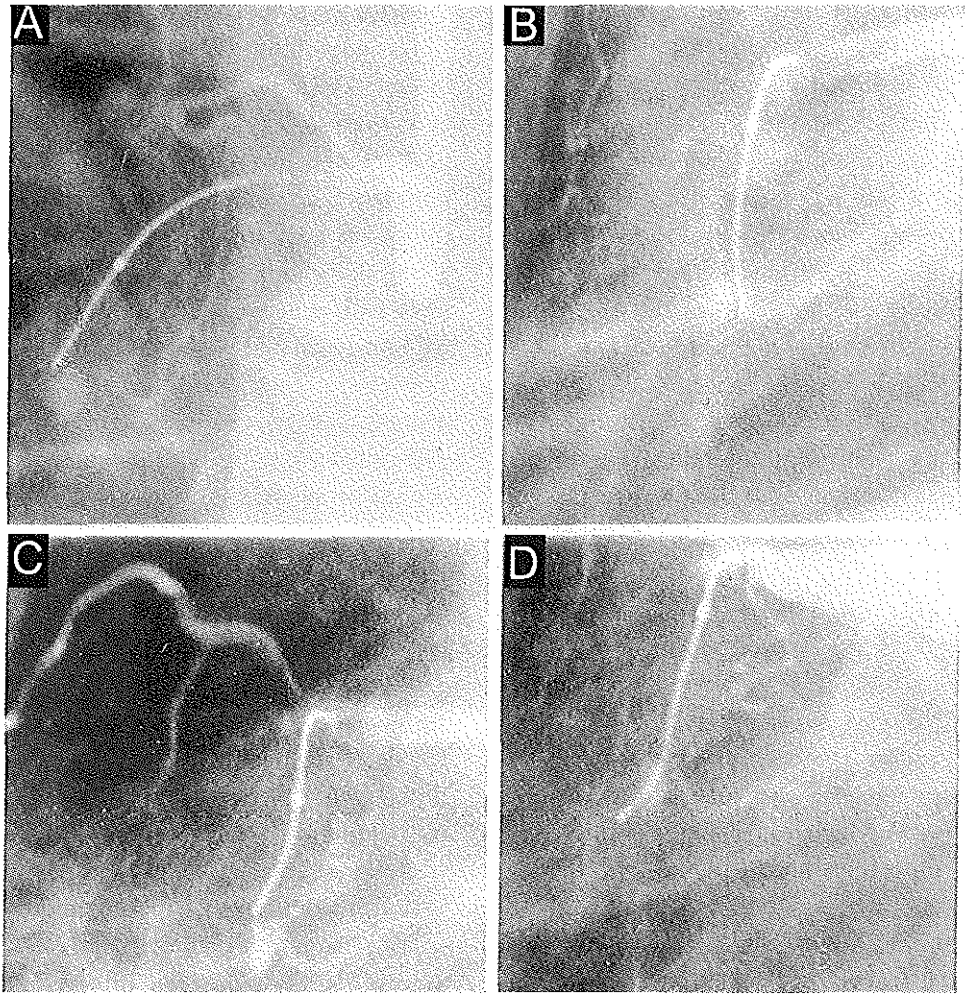


Figure 3 Total occlusion of the proximal right coronary artery. Panels A-C: the laser guidewire is steered around a calcified obstruction. D: angiographic confirmation of the intraluminal position of the distal tip of the laser guidewire

In case of reduced output, the laser guidewire should be recalibrated in an attempt to restore the original output. Obviously, if the distal part of the occluded segment could not be crossed with the laser guidewire, the laser guidewire can be exchanged for a conventional (i.e. mechanical) guidewire, while still making use of the support catheter.

If on fluoroscopy the wire tip projects outside the boundaries of the vessel, the wire should be withdrawn into the proximal part of the coronary artery. A proximal injection is used to check for possible leakage of contrast medium into the free pericardial space. Since there is usually no perfusion pressure inside the occluded segment, especially in longer segments, leakage into the free pericardial space is not likely. Nature seems to be forgiving in this situation and a so-called 'wire exit' is not necessarily a reason to abort the procedure.

Once the laser guidewire has crossed the occlusion, the intraluminal position of the wire in the distal true lumen must be confirmed by means of a contralateral injection of contrast medium. If there is doubt regarding the wire position the support catheter should never be advanced, nor should a balloon catheter be used, since it is this impatient manoeuvre which converts a benign wire exit into a perforation with tamponade introducing unnecessarily a major, potentially life threatening complication. Thus only after the intraluminal position of the wire has been confirmed, should the laser guidewire be used as an exchange wire for the ensuing interventional procedure.

ADJUNCTIVE ANGIOPLASTY

The aim of the adjunctive angioplasty is to remove as much obstructing material as possible, prior to 'dottering' of the remainder. Therefore, depending on lesion morphology and proximal reference diameter, either the 1.4 mm, 1.7 mm or 2.0 mm excimer laser catheter can be used, according to standard guidelines for the use of excimer laser equipment. Based upon the true ablation rate of the currently available multifiber catheters, the laser catheter should be advanced at a maximum speed of 0.5 mm per second at a fluence of 50 mJ/mm^2 and a pulse repetition rate of 25 Hz, for a maximum duration of five seconds. Both prior to and during activation of the laser, it is mandatory to flush the target vessel with saline. By removing any intraluminally present contrast medium as well as clearing most of the blood interface, the deleterious side-effects on the vessel wall of shock wave formation, due to absorption of 308 nm laser energy by contrast medium and haemoglobin, are minimized. The combination of a 'slow pass' with the use of saline flush has made excimer laser related coronary dissection an unnecessary complication.[21]

Finally, the issue remains whether or not the result achieved with balloon angioplasty should be optimized by means of the placement of one or more intracoronary stents. Violaris et al.[22] reported on the long-term restenosis rate following successful balloon dilatation of coronary occlusions. The study

population comprised 2950 patients (3549 lesions), which included 244 occlusive stenoses (6.9%). The six month angiographic restenosis rate (>50% stenosis at follow up) was significantly higher in the occlusion group at 45% compared to 33% in the non-occlusive group. Similarly the relative loss (mm, mean ± SD) in the occlusive group, 0.17 ± 0.3, n = 244 was significantly higher than in the non-occlusive group 0.12 ± 0.2, n = 3305, p<0.001. However, the higher restenosis rate in the occlusion group was entirely due to increased reocclusion: 18% (44/244 lesions) compared to 4.7% (156/3305 lesions) for the non-occlusive group (p<0.001). After exclusion of these reocclusions, the restenosis rate between the two groups was similar, 32.5 vs. 29.3% (p = 0.338), while the relative loss was even significantly lower in the occlusive group (0.07 ± 0.17, n = 200) than in the non-occlusive group (0.09 ± 0.16, n = 3149, p = 0.023). These results suggest that, other than what might be a population subgroup (18% early reocclusion), long-term results of successful angioplasty of total occlusions may be comparable with results of balloon angioplasty of non-occlusive coronary stenoses. Subsequent publications[14,15] have indicated that both the (early) reocclusion rate as well as the late restenosis rate after successful recanalization of total occlusions are favorably influenced by stent implantation. Therefore, it is our current policy to stent the occlusion site in all patients after successful recanalization has been achieved (Fig 4). The advantage of the use of intravascular ultrasound (IVUS), especially in optimizing the stent procedure, has been reported elsewhere.[23,24] Finally, all the patients in the Thoraxcentre are put on a medical regimen with ticlopidine and aspirin for two weeks and six months, respectively, in order to reduce the possibility of subacute reocclusion.

SUMMARY

With respect to the low success rate of PTCA for the treatment of chronic coronary total occlusions in general, and the clinical relevance of this condition to the practice of the (interventional) cardiologist, it seems justifiable to investigate new technologies aimed at increasing the opportunities of percutaneous intervention for this specific condition. Presently, the European registry with the laser guidewire, the European TOTAL Surveillance Study, has been completed.[25] From this experience, we have learned that following an initial failed attempt to mechanically re-establish flow, the success rate of the laser guidewire procedure is approximately sixty percent. Currently, the major limitation of the laser guidewire procedure is its technical complexity, resulting in

lengthy procedures with extensive use of fluoroscopic time and contrast medium. Development of alternative techniques for forward detection (e.g. ultrasound, fluorescence- or Raman spectroscopy) could prove to be essential in increasing the availability of the laser guidewire technology for general interventional practice. Although the preliminary European experience with the laser guidewire is encouraging, favorable success rates in recanalization of total coronary occlusions have been reported with new mechanical guidewires, such as the

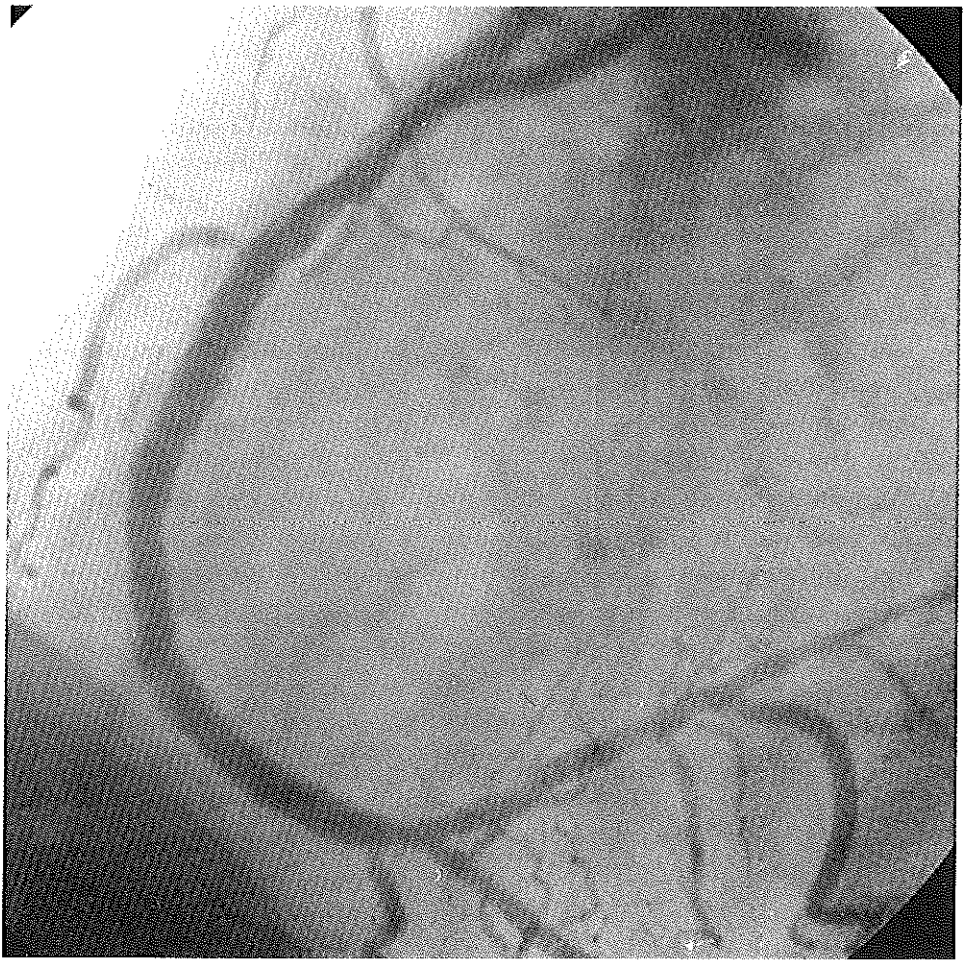


Figure 4 *Recanalization of a chronic totally occluded right coronary artery and reconstruction of the occluded segment using multiple stents. (Final result of the procedure in fig. 2).*

Choice PT plus wire (Scimed, BSC, Minesota, USA), the Crosswire (Terumo, Tokyo, Japan) and the Japanese Athlete guidewire (Asahi Intec, Co. Ltd, Tokyo, Japan). Consequently, the ongoing European-American multicenter randomized trial comparing the laser guidewire with the best available conventional mechanical guidewires (the 'TOTAL' trial) will answer the question whether this technique will obtain a definite place in the arena of interventional cardiology.

REFERENCES

1. Brand M van den. Utilization of angioplasty and cost of angioplasty disposables in 14 western European countries. *Eur Heart J* 1993;14, 391-397
2. Ruygrok PN, Serruys PW. Intra-coronary stenting, from concept to custom. *Circulation* 1996;94:882-890
3. Savage R, Hollman J, Gruentzig AR, Spencer King III, Douglas J, Tankersley R. Can percutaneous transluminal coronary angioplasty be performed in patients with total occlusion? *Circulation* 1982;66:1319 (A).
4. Heyndrickx GR, Serruys PW, van den Brand M, Vandormael M, Reiber JHC, Transluminal angioplasty after mechanical recanalization in patients with chronic occlusion of coronary artery. *Circulation* 1982;II-5/1319 (abstract)
5. Holmes DR, Vlietstra RE, Reeder GS, Bresnahan JF, Smith HC, Bove AA, Schaff HV. Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 1984;3:845-849
6. Meyer B, Gruentzig AR. Learning curve for percutaneous transluminal coronary angioplasty: skill, technology or patient selection. *Am J Cardiol* 1984;53:65C-66C
7. Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB. Angioplasty in total coronary artery occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985;6:526-533
8. Stone GW, Rutherford BD, McConahay DR, Johnson Jr. WL., Giorgi L.V, Ligon RW, Hartzler GO. Procedural outcome of angioplasty for total coronary artery occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15:849-65
9. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W, Jaski B, Hugenholtz PG. Elective P.T.C.A. of totally occluded coronary arteries not associated with acute myocardial infarction; short-term and long-term results. *Eur Heart J* 1985;6:2-12
10. DiScascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total coronary occlusion. *Am Heart J* 1986;111: 833-839

11. Ivanhoe RJ, Weintraub WS, Douglas Jr. JS, Lembo NJ, Furman M, Gershony G, Cohen CL, King III SB Percutaneous transluminal coronary angioplasty of chronic total occlusions: primary success, restenosis and long-term clinical follow-up. *Circulation* 1992;85:106-115
12. Serruys PW, Hamburger JN, de Feyter PJ, van den Brand M. Recanalization of Chronic Total Occlusions Using a Laser Guidewire: A Preliminary Experience. *Circulation* 1994 90,4, part 2:1776 A
13. Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T, Shibata N, Ishihara T. Ohsawa N. Coronary Angioplasty of Chronic Total Occlusions With Bridging Collateral Vessels: Immediate and Follow-Up Outcome From a Large Single-Center Experience. *J Am Coll Cardiol* 1995;26:409-15
14. Sirnes PA, Golf S, Myreng Y, Mølstad P, Emanuelsson H, Albertsson P, Brekke M, Mangschau A, Endresen K, Kjekshus J. Stenting in Chronic Coronary Occlusion (SICCO): A Randomized, Controlled Trial of Adding Stent Implantation After Successful Angioplasty. *J Am Coll Cardiol* 1996;28:1444-51
15. Hamburger JN, Serruys PW. Recanalization of chronic total occlusions using a laser guide wire. In: U Sigwart, M Bertrand and PW Serruys (eds) *Handbook of Cardiovascular Interventions*, (WB Saunders, London 1996); 493-500.
16. Hamburger JN, Airian S, Gijsbers GHM, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a single institution experience with the initial one-hundred cases. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, (Philadelphia: Current Medicine 1996); 101-111
17. Ruygrok PN, De Jaegere PPT, Verploegh J, van Domburg, De Feyter PJ. Immediate outcome following coronary angioplasty: a contemporary single center audit. *Eur Heart J* 1995;16 (Supp. L):24-29
18. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am Heart J* 1993;126:561-564
19. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, van Marle J, van den Broecke D G, Hanekamp CEE, van Gemert MJC, Serruys PW. Excimer Laser Coronary Angioplasty: A physical perspective to clinical results. In: Topol E, Serruys PW (eds), *Current Review of Interventional Cardiology*, 2nd edn (Philadelphia:

Current Medicine, 1995); 159-172.

20. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. *Circulation* 1986;74:469-476
21. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J and PELCA investigators. Effect of Intra-Coronary Saline Infusion on Dissection During Excimer Laser Coronary Angioplasty: A Randomized Trial. *Circulation* 1994 90,4, 2:1774 A
22. Violaris AG, Melkert R, Serruys PW. Longterm luminal renarrowing after successful elective coronary angioplasty of total occlusions: a quantitative angiographic analysis. *Circulation* 1995; 91:2140-2150
23. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL., Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995; 91(6): 1676-88
24. Prati F, Di Mario C, Hamburger JN, Gil R, von Birgelen C, Serruys PW. Guidance of multiple stent deployment in a chronic totally occluded coronary artery using three dimensional reconstruction of intra coronary ultrasound. *Am Heart J*, 130;6: 1286-1289, 1995
25. Hamburger JN, Seabra-Gomes R, Simon R, Mathey D, Sievert H, Koolen JJ, Fleck E, Rutsch W, Buchwald A, Serruys PW. Recanalization of Chronic Total Coronary Occlusions Using a Laser Guidewire: the European TOTAL Multicenter Surveillance Study. *Am J Cardiol* 1997;80:1419-1423

CHAPTER 7

Early recovery of wall motion abnormalities after recanalization of chronic totally occluded coronary arteries: a dobutamine-atropine stress echocardiographic prospective single center experience

Ricardo Rambaldi, Jaap N. Hamburger, Marcel M. Geleijnse, Geert-Jan Kimman, Aric A. Aiazian, Paolo M. Fioretti, Folkert J. Ten Cate, Jos R.T.C. Roelandt, Patrick W. Serruys

Am Heart J 1998 Nov;136(5):831-36

EARLY RECOVERY OF WALL MOTION ABNORMALITIES AFTER RECANALIZATION OF CHRONIC TOTALLY OCCLUDED CORONARY ARTERIES: A DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHIC PROSPECTIVE SINGLE CENTER EXPERIENCE

ABSTRACT

Background-Patients with symptomatic myocardial ischemia from a chronic totally occluded coronary (TOC) artery are usually referred for coronary artery bypass surgery. Because guidewire technology has improved in recent years, percutaneous coronary angioplasty has become a useful technique in opening chronic TOC arteries. We evaluated the early functional results of successful percutaneous recanalization by performing dobutamine stress echocardiography (DSE).

Methods-Fifteen patients with a chronic TOC artery who underwent a successful recanalization were prospectively studied. Each patient had a DSE within 24 h before and 48 h after the procedure. Wall motion was scored according to a 16 segments/5 points model. A clinical and angiographic follow-up of 6 months was obtained.

Results-The wall motion score index at rest improved from 1.26 ± 0.23 before to 1.22 ± 0.21 after the procedure ($p < 0.05$). Of those 10 segments that improved at rest, 7 were collateral-recipients and 3 were collateral-donors. The number of ischemic segments decreased from 46 before to 4 after the procedure ($p < 0.0001$). Wall motion score index at peak stress improved from 1.34 ± 0.20 pre- to 1.15 ± 0.12 post-procedure ($p < 0.05$). DSE was positive for ischemia in 15 patients before and 2 patients after the procedure ($p < 0.0001$). Angina was present in 12 patients before and in 2 patients after recanalization ($p < 0.0001$). Two patients (13%) had angiographic reocclusion and 5 (33%) restenosis after 6 months follow-up.

Conclusions-Successful percutaneous recanalization of chronic TOC artery results in an early improvement of both clinical status and resting or stress-induced wall motion abnormalities, as detected by DSE.

Angina pectoris is usually related to a significant stenosis of one or more coronary arteries.[1] Progression of a stenosis may lead to chronic total occlusion of the vessel, also in the absence of myocardial infarction.[2] Patients with a chronic totally occluded coronary (TOC) artery may experience exertional angina, possibly from an inverted shunt of coronary flow from the occluded segment(s) through collaterals to the non-occluded segments in times of increased blood flow requirements.[3] Therapeutic options are limited because medical treatment is not always sufficient, and coronary angioplasty is associated with both a high failure rate[4] and a high restenosis or reocclusion rate. Therefore, patients with significant symptoms are routinely referred for coronary bypass surgery.[5] However, various recent improvements in guidewire technology have considerably increased the success rates of percutaneous attempts at recanalization.[6-8] The efficacy of successful recanalization has been proven in the late follow-up by exercise test[9] and early after the procedure by cardiac pacing.[10,11] Dobutamine stress echocardiography (DSE), an established technique for the detection of myocardial ischemia,[12] has not been used to test the effects of recanalization of TOC artery early after a successful procedure. Therefore, we performed DSE to investigate whether a successful procedure results in an early reduction of myocardial ischemia in patients who underwent guidewire percutaneous recanalization of a chronic TOC artery.

METHODS

PATIENT POPULATION

Patients were prospectively included according to presence of angina pectoris and/or objective signs of ischemia in relation to a chronic TOC artery. An attempt was made to recanalize the target occlusion, by use of various guidewire technologies. This included the use of the excimer laser guide wire (Spectranetics Int., Colorado Springs, CO) in case of a failed attempt with conventional guide wires. An informed consent was obtained from all patients, according to the guidelines of the Medical Ethics Committee of the University Hospital Rotterdam.

ANGIOGRAPHIC DATA

A TOC artery was considered chronic if more than 4 weeks of angiographically proven duration[4] elapsed between the diagnostic coronary angiography and the date of the attempt at recanalization. For each patient the echocardiographic 16 segments model[13] was assigned to each coronary field and when collaterals were found, the corresponding echocardiographic segments were divided in either collateral donors or collateral recipients.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dobutamine stress echocardiography was performed within 24 hours before and 48 hours after the procedure. Dobutamine was administered as follows: 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. In submaximal nondiagnostic DSE, atropine was added: 0.25 mg repeated to a maximum of 1.0 mg in 4 minutes. Criteria for a positive DSE were stress-induced new or worsened wall motion abnormalities. Additional criteria were ST-segment elevation of 0.1 mV 80 ms after the J point in patients without prior myocardial infarction and horizontal or downsloping ST-segment depression of 0.1 mV 80 ms after the J point and angina. Pretest criteria for interruption of DSE were achieved 85 % of the maximal for sex- and age-predicted target heart rate, achieved maximal dose of both dobutamine and atropine, new significant wall motion abnormalities, horizontal or downsloping ST-segment depression >0.2 mV 80 ms after the J point compared with the baseline, ST-segment elevation >0.1 mV 80 ms after the J point in patients without prior myocardial infarction, severe angina, symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias and any serious side effect attributed to dobutamine infusion, such as headache, dizziness or a symptomatic vagal activation.[12]

ECHOCARDIOGRAPHIC IMAGING

The left ventricle was divided in 16 segments[13] and visually assessed for both systolic wall thickening and inward wall motion. Each segment was graded on a 5-point scoring system (1 = normokinesis or hyperkinesis; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis and 5 = dyskinesis) by an experienced observer blinded to both preprocedural and postprocedural data. The scoring was repeated by the same observer and in case of intra-observer disagreement the judgment of a second observer was obtained. Ischemia was defined as a deterioration in score at any stage of the test in one or more segments, unless an akinetic segment at rest and low dose dobutamine became dyskinetic at peak stress.[14] Wall motion score index was defined as the sum of the scores of the individual segments divided by the total number of segments. The medication used during the two DSE was not significantly different. The B-blocking agents were withdrawn 3 days before the first DSE and not reintroduced before the second DSE.

THE ANGIOPLASTY PROCEDURE

The attempt at recanalization was performed typically using either the Choice

PT wire (Scimed, Minneapolis, MN), Terumo Crosswire (Terumo, Japan) or the Prima laser wire (Spectranetics Corp., CO). The technique of the laser wire procedure has been extensively described elsewhere.[6,7,15] After successful crossing of the occlusion by the guidewire, angioplasty was performed either by balloon angioplasty, or a combination of excimer laser coronary angioplasty (ELCA) using the Spectranetics 1.4 mm or 1.7 mm Vitesse-C rapid exchange coronary catheters with adjunctive balloon angioplasty. Routinely, one or more intracoronary stents were implanted to obtain an optimal procedural result. After a successful angioplasty, patients were kept on a heparin infusion for 24 hours, maintaining the activated prothrombin time between 60 and 90 seconds.

FOLLOW-UP STUDY

All patients underwent a 6-month clinical and angiographic follow-up. Functional classification was performed according to the Canadian Cardiovascular Society. Restenosis was defined as >50% diameter stenosis at the treated coronary site, as determined by on-line quantitative angiographic analysis.

STATISTICAL ANALYSIS

Unless specified, values were expressed as mean ± SD. Comparison of variables was performed with two-tailed Student's t test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant.

RESULTS

PROTOCOL COMPLIANCE

Of 34 consecutive patients with a chronic TOC artery and a DSE before the procedure, 22 (65%) patients underwent successful recanalization. Of these, 2 patients were excluded due to poor echocardiographic image quality and 5 for no adherence to the protocol. Therefore, 15 patients fulfilled the study protocol, by undergoing two DSE's: before (<24 hours) and after (<48 hours) successful recanalization. The pretest baseline characteristics are given in Table I and confirm that the patient population is representative of current clinical practice with coronary angioplasty.

ANGIOGRAPHIC DATA

The angiographic data are given in Table II. The TOC artery was the right coronary artery in 7 patients (47%), left anterior descending coronary artery in 7 (47%) and left circumflex coronary artery in 1 (6%).

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

The hemodynamic data of preprocedure and postprocedure DSE are given in Table III. As shown, there was no significant difference between the pre proce-

Subject	Age (y)	Sex	AP (CCS)	Prior MI	Hyper-tension	Smoke	Diabetes	Hyper-cholesterolemia	FamHx
1	48	F	3	0	+	0	+	0	0
2	71	F	3	+	+	0	0	0	0
3	39	M	2	+	0	+	0	+	+
4	57	M	3	+	0	+	0	0	+
5	69	M	3	0	+	0	0	0	0
6	62	M	3	0	0	0	0	0	+
7	36	M	2	0	0	+	0	+	0
8	67	M	3	+	0	0	0	+	0
9	54	M	3	0	0	+	0	+	0
10	67	F	3	+	0	0	0	0	0
11	67	F	3	+	+	0	0	+	0
12	62	M	3	+	+	+	0	0	0
13	45	M	2	+	0	0	0	+	+
14	58	M	2	0	+	0	0	0	0
15	50	M	4	+	0	+	0	0	0
Mean ± SD	56 ± 11		2.8						
Total		11 M		9 MI	6	6	1	6	4

AP, Angina pectoris; COS Canadian Classification; FamHx, family history; MI, myocardial infarction

Table I *Pretest baseline characteristics of the patient population*

dural and postprocedural data. Wall motion score index (Table IV) at rest improved from 1.26 ± 0.23 before to 1.22 ± 0.21 after the procedure ($p < 0.05$). Of 10 segments (in 5 patients) that improved at rest, 7 were collateral recipients and 3 were collateral donors. DSE was positive for ischemia in 15 patients before and in 2 patients after the procedure ($p < 0.0001$). The number of ischemic segments decreased from 46 before to 4 after the procedure ($p < 0.0001$). The number of

Subject	Improved segments*	Occluded vessel	Collateral donor vessel(s)	Angina		ST-T	
				Pre	Post	Pre	Post
1	1	RCA	LAD	+	0	0	+
2	3	RCA	LAD	+	+	0	0
3	1	RCA	LAD, LCX	0	0	0	0
4	2	RCA	LAD	0	0	0	0
5	3	RCA	LAD, RCA	+	0	+	0
6	6	RCA	LAD, LCX	+	0	0	0
7	5	RCA	LAD	+	0	0	0
8	1	LAD	RCA	+	0	0	0
9	5	LAD	RCA	+	0	0	0
10	1	LAD	LCX, RCA	+	0	0	+
11	7	LAD	LCX, RCA	+	0	+	+
12	5	LAD	LCX, RCA	0	0	+	0
13	2	LAD	RCA	+	+	+	+
14	2	LAD	RCA	+	0	+	0
15	4	LCX	LAD	+	0	0	+

LAD, left anterior descending coronary artery; LCX, circumflex coronary artery; RCA, right coronary artery; post, postprocedure; pre, preprocedure
*Segments of the occluded coronary artery territory with improved wall motion after revascularization
†$P < 0.0001$ preprocedure vs postprocedure

Table II *Anatomic, angiographic, preprocedure, and postprocedure clinical data*

Table III Hemodynamic data at rest and peak dobutamine preprocedure and postprocedure

	Preprocedure							
Subject	HR rest	HR peak	SBP rest	SBP peak	DP rest	DP peak	HR rest	HR peak
1	64	116	140	125	8960	14,500	80	127
2	80	133	92	86	7360	11,438	90	130
3	75	135	147	163	11,025	22,005	85	130
4	90	143	153	153	13,770	21,879	80	137
5	61	105	142	124	8662	13,020	62	121
6	71	120	110	115	7810	13,800	70	120
7	74	117	145	180	10,730	21,060	80	133
8	70	130	163	144	11,410	18,720	76	131
9	70	138	112	107	7840	14,766	74	144
10	60	115	130	130	7800	14,950	72	113
11	74	142	137	103	10,138	14,626	88	115
12	70	132	98	100	6860	13,200	77	158
13	60	132	135	135	8100	17,820	84	142
14	59	91	145	151	8555	13,741	70	118
15	50	126	110	125	5500	15,750	50	117
Mean ± SD	68 ± 10	125 ± 14	130 ± 21	129 ± 25	8968 ± 2100	16,085 ± 3392	76 ± 10	130 ± 13

DP Double product (heart rate × systolic blood pressure) product in beats/min × Hg; HR heart rate / beats/min; SBP systolic blood pressure mm Hg.

segments with wall motion abnormality angiographically supplied by the occluded coronary artery that exhibited wall motion improvement after revascularization was 48 (Table II). Wall motion score index at peak stress improved from 1.34 ± 0.20 before to 1.15 ± 0.12 after the procedure ($p < 0.05$). Angina was experienced during DSE by 12 patients before and 2 patients after the procedure ($p < 0.0001$) (Table II).

FOLLOW-UP DATA

A 6-month clinical and angiographic follow-up was available for all patients. No major cardiac events such as death, myocardial infarction, coronary bypass

	WMA resting segments		Ischemic segments		Resting WMSI		Stress WMSI	
Subject	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0	0	1	0	1.00	1.00	1.13	1.00
2	3	1	3	1	1.19	1.06	1.19	1.06
3	5	5	1	0	1.31	1.31	1.25	1.19
4	3	3	2	0	1.31	1.31	1.19	1.13
5	2	0	2	0	1.13	1.00	1.13	1.00
6	3	3	6	0	1.31	1.31	1.50	1.25
7	0	0	5	0	1.00	1.00	1.38	1.00
8	8	7	1	0	1.75	1.69	1.81	1.25
9	7	7	5	0	1.50	1.50	1.38	1.31
10	0	0	1	0	1.00	1.00	1.06	1.00
11	4	4	7	0	1.25	1.25	1.56	1.25
12	4	3	4	0	1.25	1.19	1.50	1.13
13	4	4	5	3	1.25	1.25	1.31	1.25
14	0	0	2	0	1.00	1.00	1.31	1.19
15	6	2	1	0	1.63	1.38	1.38	1.31
Sum and means (±SD)	49	39	46	4*	1.26 ± 0.23	1.22 ± 0.21*	1.34 ± 0.20	1.15 ± 0.12*

Post, Postprocedure; Pre, preprocedure; WMA, wall motion abnormalities; WMSI, wall motion score index.
*$P < .05$ preprocedure vs postprocedure.

***Table IV** Preprocedure and postprocedure wall motion analysis*

Postprocedure			
SBP rest	SBP peak	DP rest	DP peak
90	66	7200	8382
86	80	7740	10,400
110	100	9350	13,100
132	162	10,560	22,194
141	107	8742	12,947
120	120	8400	14,400
125	150	10,000	19,950
126	109	9576	14,279
137	131	10,138	18,864
111	86	7992	9,718
115	95	10,120	10,925
112	129	8624	20,382
120	120	10,080	17,040
126	110	8820	12,980
108	125	5400	14,625
17 ±15	113 ± 26	8849 ± 1380	14,679 ± 4185

surgery, repeated PTCA or hospital admission for unstable angina occurred in this patient group. At six month follow-up 4 (27%) patients were in stable angina, whereas angiographycally 2 (13%) patients had a reocclusion and five (33%) had restenosis.

DISCUSSION

Shortly after the introduction of coronary angioplasty by Andreas Gruentzig in 1977, this technique was attempted in patients with chronic TOC arteries. Successive investigators reported on the relatively low procedural success rates and high restenosis rates following successful percutaneous recanalization.[16-18] However, the long-term clinical improvement,[19,20] the increased resting left ventricular function and the reduction of exercise-induced ischemic symptoms in the late follow-up of patients after successful recanalization,[7] supported the continuing effort in developing more effective technologies for percutaneous treatment of chronic TOC arteries. Typical examples of improved technology are the introduction of hydrophilic-coated guide wires and the excimer laser guide wire.

Thus far, no study documented the early functional impact of a successful percutaneous recanalization of a chronic TOC artery, in terms of resting regional left ventricular function and stress-induced myocardial ischemia. Obviously, a successful revascularization procedure should result in a reduction of myocardial ischemia. We used DSE, an established technique for the detection of myocardial ischemia, 24 hours before and within 48 hours after a successful revascularization to evaluate the immediate functional outcome of the procedure.

As a main result of our study, we found a significant improvement of stress-induced wall motion abnormalities. Therefore, DSE is helpful in documenting objectively the early functional outcome of a successful procedure. In addition, we also detected a significant improvement of resting wall motion abnormalities, involving 7 segments of the collateral-recipient coronary artery and 3 segments of the collateral-donor coronary artery. These results suggest the presence of dysfunctional but viable myocardium, which improves early after revascularization, consistent with

previous studies documenting an immediate functional recovery after revascularization.[21] Viable myocardium is also present in some collateral-donor segments (although supplied by a non-diseased coronary artery) possibly through a stealing effect resulting in repetitive stunning. The immediate increase of both coronary flow and flow reserve after revascularization, involving both collateral-recipient and collateral-donor segments, parallel with the angiographic disappearance of collaterals, may be the vascular substrate of the early functional recovery detected in our patients.[22]

Although not the aim of the present study, a reocclusion rate of 13% and a restenosis rate of 33% at six-month follow-up angiography appear significantly better than previously reported rates in the literature. The consequent use of intracoronary stents to stabilize the angioplasty results could be responsible for this favorable outcome.

STUDY LIMITATIONS

A possible limitation of the present study is the inclusion of patients after a successful revascularization only. However, the focus of this study was not the evaluation of the success rate of percutaneous revascularization in chronic TOC arteries, but the effectiveness of DSE to document the early functional and clinical impact of a successful revascularization. We believe that the demonstration of improvement of myocardial function early after a revascularization of a chronic TOC artery is important and may support further efforts to improve nonsurgical techniques for revascularization of TOC arteries.

CONCLUSIONS

In patients with symptoms or signs of myocardial ischemia resulting from a chronic TOC artery, DSE performed before and within 48 hours after a successful percutaneous recanalization documents a significant improvement of both clinical status and resting or stress-induced wall motion abnormalities.

REFERENCES

1. Braunwald E. Heart disease. In: *A textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 1992:1293-1295.
2. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am Heart J* 1993;126:561-564.
3. Meier B. Total coronary occlusion: a different animal ? *J Am Coll Cardiol* 1991;17 (Suppl B):50B-57B.
4. Puma JA, Sketch MH, Tcheng JE, Harrington RA, Phillips HR, Stack

RS. Percutaneous revascularization of chronic coronary occlusions: an overview. *J Am Coll Cardiol* 1995; 26:1-11.

5. Ruocco NA Jr, Ring ME, Holubkov R, Jacobs AK, Detre KK, Faxon DP. Results of coronary angioplasty of chronic total occlusions: the National Heart, Lung, and Blood Institute 1985-1986 Percutaneous Transluminal Angioplasty Registry. *Am J Cardiol* 1992;69:69-76.
6. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol*, 1997;30:649-656.
7. Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E. Recanalization Of Total Coronary Occlusions Using a Laser Guide Wire: The European TOTAL Surveillance Study. *Am J Cardiol* 1997;80:1419-1423
8. Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T. Coronary Angioplasty of Chronic Total Occlusions With Bridging Collateral Vessels: Immediate and Follow-Up Outcome From a Large Single-Center Experience. *J Am Coll Cardiol* 1995;26:409-415.
9. Melchior JP, Doriot PA, Chatelain P, Meier B, Urban P, Finci L. Improvement of left ventricular contraction and relaxation synchronism after recanalization of chronic total coronary occlusion by angioplasty. *J Am Coll Cardiol* 1987; 9:763-768.
10. Meier B. Coronary angioplasty for chronic total occlusion. In: Meier B, ed. *Interventional Cardiology*. Toronto: Hogrefe & Huber, 1990:145-174.
11. Meier B. Coronary angioplasty for chronic total occlusion. In: Topol EJ, ed. Textbook of *Interventional Cardiology*. Philadelphia: WB Saunders,1990:300-326.
12. Geleijnse ML, Roelandt JRTC, Fioretti PM. Methodology, feasibility, safety, and diagnostic accuracy of dobutamine stress echocardiography: a review. *J Am Coll Cardiol* 1997;30:595-606.
13. Bourdillon PDV, Broderik TM, Sawada SG, Armstrong WF, Ryan T, Dillon JC. Regional wall motion index for infarct and non-infarct region after reperfusion in acute myocardial infarction: comparison with global wall motion index. J *Am Soc Echo* 1989;2:398-407.
14. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AEM, Roelandt JRTC. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J*

Cardiol 1994;73:897-899.

15. Hamburger JN, Serruys PW. Laser guidewire for Recanalization of Chronic Total Occlusions. In: Frontiers in *Interventional Cardiology*, (R. Beyar, G. Keren, M. Leon and P.W. Serruys Editors). Chapter 4, 47-53. 1997, Martin Dunitz, London.
16. Heyndrickx GR, Serruys PW, van den Brand M, Vandormael M, Reiber JHC. Transluminal angioplasty after mechanical recanalization in patients with chronic occlusion of coronary artery (Abstr). *Circulation* 1982;II-5/1319.
17. Savage R, Hollman J, Gruentzig AR, King III S, Douglas J, Tankersley R. Can percutaneous transluminal coronary angioplasty be performed in patients with total occlusion? (Abstr). *Circulation* 1982;66:1319.
18. Roubin GS, Gruentzig AR. Percutaneous transluminal coronary angioplasty: state of the art and future directions (Review). *Int J Card Imag* 1985;1:143-154.
19. Ivanhoe RJ, Weintraub WS, Douglas Jr. JS, Lembo NJ, Furman M, Gershhony G. Percutaneous transluminal coronary angioplasty of chronic total occlusions: primary success, restenosis and long-term clinical follow-up. *Circulation* 1992;85: 106-115.
20. Finci L., Meyer B, Favre J, Righetti, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary artery occlusion. *Am J Cardiol* 1990;66: 660-662.
21. La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O. Echocardiography during infusion of dobutamine for identification of reversible dysfunction in patients with chronic coronary artery disease. *J Am Coll Cardiol* 1994;23:617-623.
22. Sambuceti G, Parodi O, Giorgetti A, Salvadori P, Marzilli M, Dabizzi P. Microvascular dysfunction in collateral-dependent myocardium. *J Am Coll Cardiol* 1995;26:615-623.

CHAPTER 8

Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study

Jaap N. Hamburger, Geert H.M. Gijsbers, Yukio Ozaki,

Peter N. Ruygrok, Pim J. de Feyter, Patrick W. Serruys

J Am Coll Cardiol, 1997;30:649-56

RECANALIZATION OF CHRONIC TOTAL CORONARY OCCLUSIONS USING A LASER GUIDE WIRE: A PILOT STUDY

ABSTRACT

Objectives-This study sought to prospectively evaluate the performance of a laser guide wire in crossing chronic total coronary occlusions in patients with a failed previous mechanical guide wire attempt.

Background-Despite continued refinement of mechanical hardware available for coronary angioplasty, restoration and maintenance of blood flow through a chronically occluded coronary artery remains a true challenge.

Methods-Fifty patients with a chronic total coronary occlusion and a previous failed attempt at recanalization using mechanical guide wires were included. A mec ıanical attempt to cross the occlusion was repeated. In case of failure, an additional attempt was made with the laser guide wire.

Results-The median age of occlusion was 22 weeks (range 5 to 200), and the occlusion length was 23 ± 11 mm (mean ± SD). A repeat mechanical attempt was successful in six cases (12%). Dissection occurred in five other cases, and device crossover was not attempted. Thus, in 39 patients an attempt was made with the laser guide wire, with successful recanalization in 23 (59%). Thereby the overall success rate increased from 12% to 58% (29 of 50 patients). The amount of contrast medium used was 515 ± 154 ml, fluoroscopy time was 99 ± 43 min, and total procedure time was 2 h 48 min (± 55 min). Procedural success was achieved in 26 cases and clinical success (procedural success without in hospital events) in 24. In-hospital events were two non-Q wave myocardial infarctions related to subacute reocclusion. In one patient, a balloon dilation after laser guide wire perforation resulted in tamponade requiring pericardiocentesis. After a successful procedure, the angina class decreased from 2.9 ± 0.2 to 1.4 ± 0.7 at 3 months of clinical follow-up. Six-month angiographic follow-up was completed in all 24 eligible patients and showed vessel patency in 20 (80%).

Conclusions-The use of the laser guide wire for recanalization of chronic total coronary occlusions refractory to treatment with mechanical guide wires is feasible and relatively safe and was successful in 59% of cases. This device must thus be considered a valuable addition to the interventional armamentarium and accordingly will be evaluated in a randomized clinical trial.

Abbreviations and Acronyms

CK = creatine kinase
ELCA = excimer laser coronary angioplasty
PTCA = percutaneous transluminal coronary angioplasty
QCA = quantitative coronary angiography
TIMI = Thrombolysis in Myocardial Infarction

Total coronary artery occlusion is estimated to be present in approximately one-third of the patient population undergoing diagnostic angiography for symptomatic coronary artery disease.[1] Despite a steady improvement in angioplasty tools to recanalize totally occluded vessels over the past decade, success rates have not dramatically increased.[2-7] A recently developed laser guide wire that combines the mechanical properties of a typical coronary guide wire with the ablative energy of a XeCl excimer laser may facilitate the recanalization of chronically occluded coronary arteries. Therefore, the primary goal of this study was to evaluate the performance of this new device in patients with symptomatic coronary artery disease due to a chronic total coronary occlusion.

METHODS

PATIENT SELECTION

From August 1993 to January 1995, a prospective observational pilot study was conducted at the Thoraxcenter of the University Hospital of Rotterdam to evaluate the performance of the Spectranetics Prima Total Occlusion System in crossing chronic total coronary occlusions. Inclusion criteria were a Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 coronary occlusion[8] and a failed previous attempt at recanalization using conventional guide wires. In all cases, a mechanical attempt to cross the total occlusion was repeated before (in case of failure) an ensuing attempt was made with the laser guide wire.

To evaluate the true potential of this new device, there were no exclusion criteria, with the exception of acute myocardial infarction within 2 weeks of the intervention. Thus, lesions that are typically considered unfavorable for a mechanical attempt at recanalization, including bridging collateral vessels, a major side branch originating from the stump of the occlusion, eccentric lesions or a nonvisible entry point, were intentionally not excluded (Fig 1). The age of occlusion was assessed in combination by angiographic data and from clinical history. The stump morphology was evaluated from the preprocedural angiogram. The distal vessel lumen was routinely visualized by a contrast medium injection in the contralateral coronary artery so that both femoral arteries were punctured in all cases. The length of occlusion was measured by quantitative coronary angiography (QCA) after

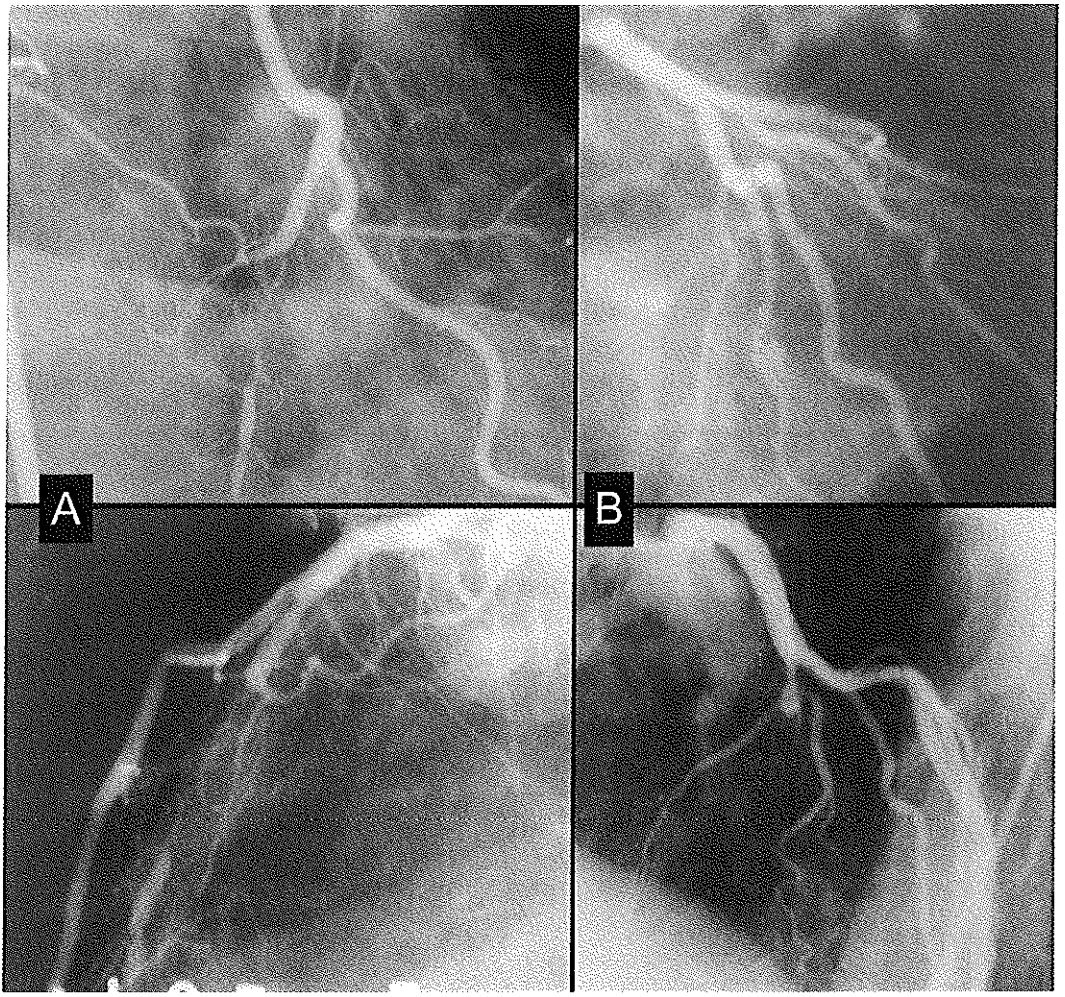


Figure 1 A, Total occlusion of the right coronary artery with a blunt stump, a major side branch originating in the stump and bridging collateral channels (top row, frontal view; bottom row, lateral view). B, Total occlusion of a proximal left coronary artery with a septal branch and a diagonal branch originating in the stump. There is a lesion in the ostium of the diagonal branch (top row: right inferior oblique view, bottom row: left superior oblique view).

visualization of both the occluded stump and the distal lumen by means of a simultaneous bilateral coronary injection at the commencement of the procedure. Fluoroscopic time, total procedure time and the amount of contrast medium used were recorded. Blood samples for creatine kinase (CK) analy-

sis were taken 12 h after the procedure. Because the first-generation laser guide wire was less steerable than most conventional guide wires, wire success was defined as angiographic evidence of reaching the true lumen of any branch distal to the occlusion. Procedural success was defined as an average diameter stenosis <50% in two orthogonal views by on-line QCA. Clinical success was defined as procedural success without death, myocardial infarction, coronary artery bypass graft surgery or repeat angioplasty during the index hospital stay.

LASER GUIDE WIRE

The laser guide wire (The Prima Total Occlusion System, model 018-003, Spectranetics) consists of an 0.018-inch guide wire containing 12 silica fibers with a 45-μm diameter. The supplied

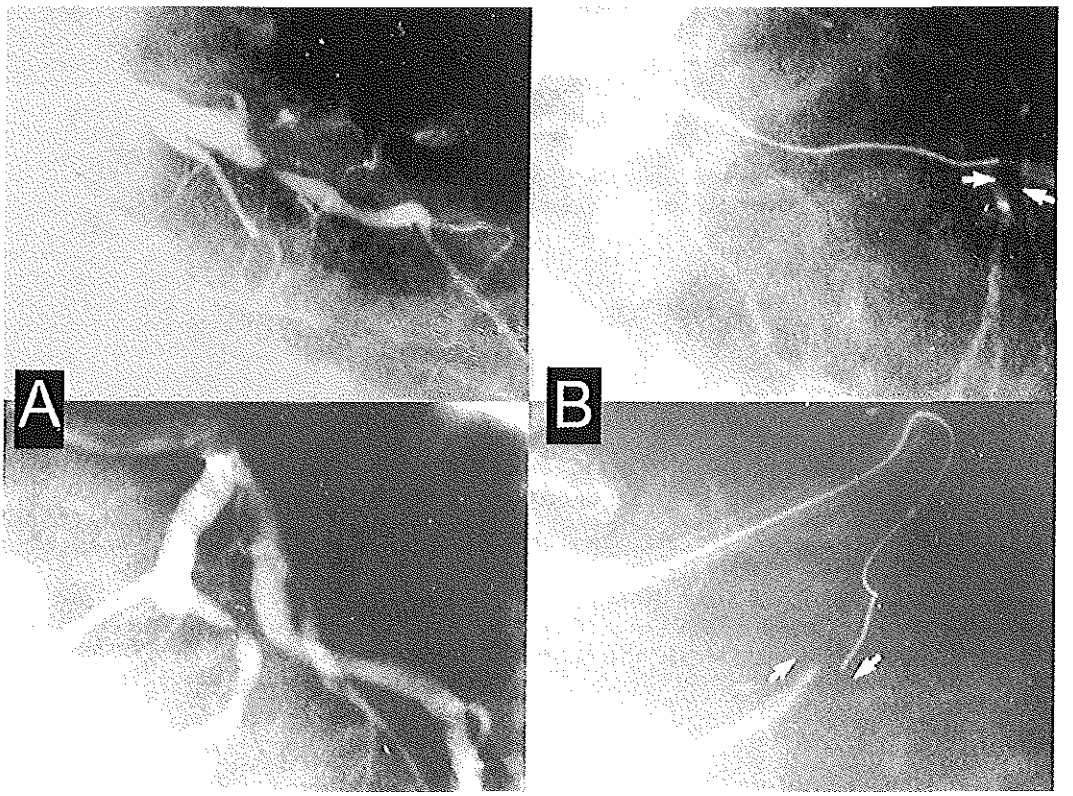


Figure 2 A, Total occlusion of the left anterior descending coronary artery. Top panel: right inferior oblique view. Bottom panel: left superior oblique view. B, Alignment of the guidewire tip with the distal lumen is suggested in the top panel. Due to simultaneous bilateral injection of the contrast medium and biplane angiography the malalignment of the guidewire is clearly visible in the bottom panel.

support catheter has a 2.5F tapered tip, providing additional coaxial backup support. The model 018-001 (Generation 1) had a nonshapable and subsequently nonsteerable tip that could only be advanced in straight coronary sections. The model 018-003 (Generation 2A) with a shapable steerable tip was introduced in December 1993. It was originally designed to function as an exchange guide wire. Because the floppy proximal part of the guide wire did not allow for an easy exchange, the Generation 2B with a stiffened proximal exchange section was introduced in April 1994.

The laser was the Spectranetics CVX 300 XeCl excimer laser. The fluence typically used during a laser guide wire procedure was 60 mJ/mm^2, with a pulse repetition rate of 25 Hz. On encountering resistance with the guide wire, the laser was activated in pulse trains for a maximum of 5 s. During laser activation, the laser guide wire was advanced at a rate of ~1 mm/s, usually during a simultaneous injection of contrast medium in the contralateral coronary artery. Biplane fluoroscopy was used to guide the alignment of the guide wire with the target segment (Fig 2). Whenever the laser guide wire encountered intraluminal resistance during laser activation (e.g., in more calcified lesions), the pulse repetition rate was increased to 40 Hz, thus increasing the ablation rate.

Table 1. Guide Wires Used in the Present Study

Conventional Guide wires	
Schneider 0.014" J-tip	32
ACS HTF 0.014"	5
ACS standard 0.018"	4
Schneider 0.012"	2
Scimed Roadrunner	1
Magnum wire	1
Not recorded	5
Laser Wires	
Generation 1	14
Generation 2A	19
Generation 2B	18

PROCEDURAL DATA

An initial attempt was made to cross the occlusion using conventional guide wires, typically using a balloon catheter (Medtronic 18 K) for additional backup support. If unsuccessful, a second attempt was made with the laser guide wire. Table 1 shows the various types of guide wires that were used. The conventional guide wire used most was the Schneider 0.014-in. guide wire (n = 32), whereas the currently used Generation 2B laser guide wire was available only in the last 18 cases. Because all these procedures were repeat percutaneous transluminal coronary angioplasty (PTCA) procedures, we avoided excessive use of very stiff guide wires, so as not to risk dissections that would preclude use of the laser guide wire. Moreover, because the distal end of the first-generation laser guide wire was extremely floppy, its potential to cross

an occlusion mechanically was somewhat limited. After successful guide wire crossing, angioplasty was usually performed using excimer laser coronary angioplasty (ELCA), using the Spectranetics 1.4- or 1.7-mm Vitesse-C rapid-exchange coronary catheter, and adjunctive balloon angioplasty. ELCA procedures were performed using a saline flush to facilitate removal of contrast medium and blood before and during laser activation to diminish vascular wall damage resulting from shock wave formation.[9] Occasionally, placement of one or more stents was required to obtain an optimal procedural result (n = 6). After successful angioplasty, patients received a heparin infusion for 24 h that maintained the activated partial thromboplastin time between 60 and 90 s.

PATIENT FOLLOW-UP

Patients were recalled after 3 months for a clinical assessment and after 4 to 6 months for a follow-up coronary angiogram. In case of a failed procedure, patients were referred for elective coronary artery bypass graft surgery.

STATISTICAL ANALYSIS

Results are expressed as mean value ± SD, unless otherwise indicated. Univariate logistic regression analysis was performed to determine whether clinical, angiographic or procedural factors were predictive of success. The predictive value was expressed as an odds ratio with corresponding 95% confidence interval.

INFORMED CONSENT

The study protocol had the approval of the University Hospital of Rotterdam Medical Ethics Committee. Written informed consent was obtained from all patients.

RESULTS

PROCEDURAL DATA

Data for 61 consecutive patients with a TIMI flow grade 0 total coronary occlusion in at least one coronary artery on diagnostic angiography and who were referred for a laser guide wire attempt at recanalization were prospectively collected. Of these, nine patients appeared to have TIMI flow grade 1, two TIMI flow grade 2 at the time of the procedure. These patients were consequently excluded from analysis. In the remaining group there were 51 occlusions in 50 patients. This patient cohort represented <20% of the total number of patients undergoing PTCA for a TIMI flow

Table 2. Baseline Clinical Characteristics of 50 Patients With 51 Occlusions

Age (yr)	58 ± 10
Male	43 (86%)
Previous MI	32 (64%)
CCS angina class	
II	4
III	46

Table 3. Baseline Lesion Characteristics

LAD	21 (41)
LCx	3 (6)
RCA	27 (53)
Age of occlusion (wk):	
Angiographic age	
Median	10
Range	2 - 200
Clinical age (n=42)	
Median	22
Range	5 - 200
Length of occlusion (mm)	23 ± 11
Stump morphology	
central funnel	24 (47)
eccentric funnel	11 (22)
blunt stump	15 (29)
Major side branch	19 (37)
Micro capillary refill	5 (8)
Non visible entry point	2 (4)

Data are presented as mean ± SD or number (%) of lesions, unless otherwise indicated. LAD=left anterior descending artery; LCx=left circumflex artery; RCA=right coronary artery

grade 0 total occlusion in our department during this period.[10] The baseline clinical characteristics are given in Table 2 and confirm that the patient group is representative of current clinical practice with percutaneous angioplasty. The baseline angiographic data are given in Table 3.

The duration (procedural time) of the initial attempt to cross the occlusion using a conventional guide wire was 33 ± 34 min. The duration of a subsequent attempt using the laser guide wire was 36 ± 28 min. The total fluoroscopic time was 99 ± 43 min, with a total procedural duration of 2 h 48 ± 55 min. The amount of contrast medium used was 515 ± 159 ml.

WIRE SUCCESS

Despite a previously failed mechanical attempt at recanalization, a repeat attempt to cross the occlusion with a mechanical guide wire was successful in six patients (12%). In five patients the procedure was terminated due to the presence of a mechanically induced dissection, considered to preclude the further use of a laser guide wire. With increasing experience it became evident that the occurrence of a dissection did not necessarily increase the risk or diminish the chance of success. In a number of cases with dissection, a new entry point could be created by steering the tip of the laser guide wire away from the site of the entry point of the dissection (Fig 3). Careful biplane angiography in several orthogonal projection combinations is accordingly an invaluable aspect of the procedure to facilitate reliable, precise and safe maneuvering of the laser guide wire.

Thus, in 39 patients (40 occlusions) an attempt was made with the laser guide wire, resulting in an additional 23 patients (24 occlusions) with a successfully crossed occlusion (59% laser guide wire success). As a result, the overall guide wire success rate increased from 12% to 58% (29 of 50 patients) (Fig 4).

Although longer and more tortuous occluded segments could be treated with the second-generation steerable

wire than the first-generation wire (25 ± 12 mm [n = 32] vs. 19 ± 6 mm [n = 7], p = 0.2), the difference in wire success did not reach statistical significance (53% vs. 86%, p = 0.11). As shown in Table 4, none of the variables normally associated with procedural outcome were predictive of failure or success.

PROCEDURE-RELATED COMPLICATIONS

Misalignment of the laser guide wire with the vessel wall boundaries was interpreted as laser guide wire perforation and occurred in seven patients. In one case, the guide wire position was mistakenly thought to be intraluminal. Without previous angiographic proof of

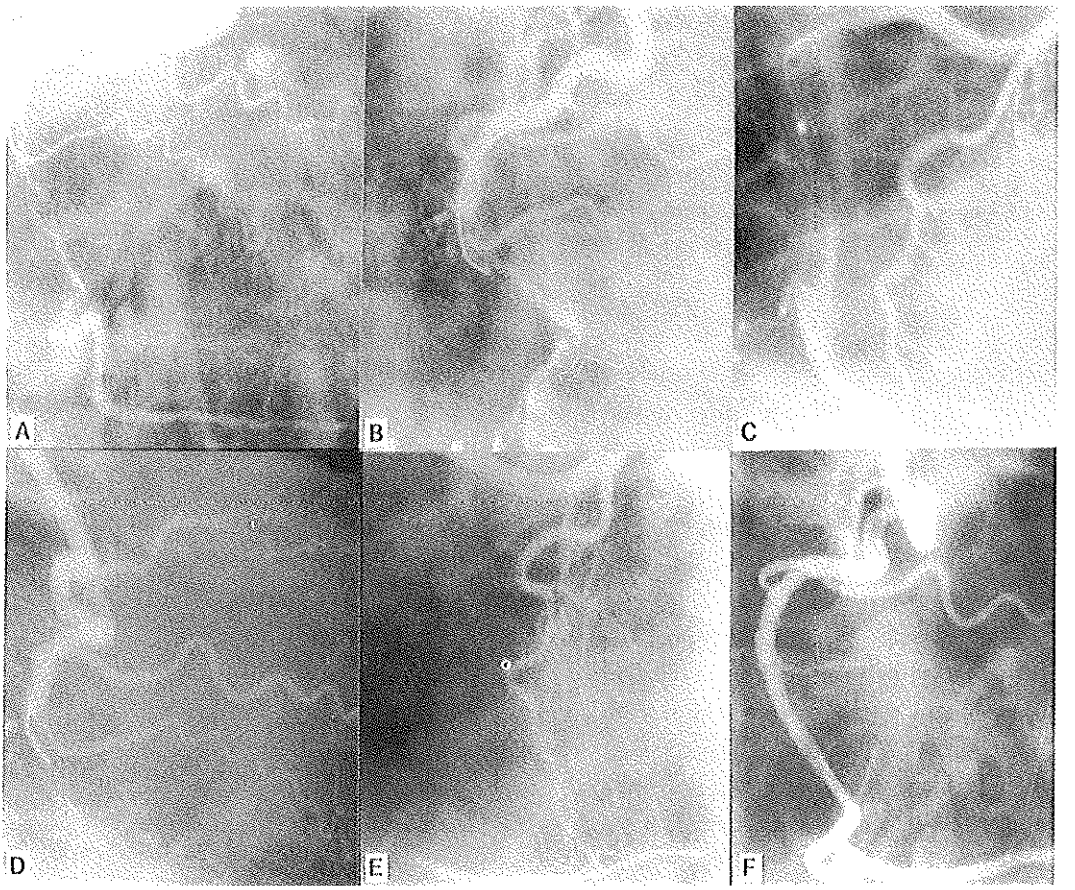


Figure 3 Laser guide wire attempt despite a mechanically induced dissection. A: Total occlusion of the right coronary artery (RCA) with a blunt stump and an ipsilateral collateral, filling the distal lumen. B: attempt with an 0.014" conventional guidewire to cross the occlusion. C: Spiral dissection of the RCA. D: Introduction of the laser guidewire creating a new entry point. E: The tip of the laser guidewire in the distal lumen of the RCA. F: Final results after balloon angioplasty.

the intraluminal localization of the laser guide wire, a 1.5-mm diameter balloon catheter was advanced and inflated. Extravasation of contrast medium occurred, leading to tamponade that was successfully managed by pericardiocentesis. In the remaining six cases, the laser guide wire perforation was the reason for terminating the procedure. Systemic anticoagulation was reversed, and the patients were monitored by transthoracic echocardiography and continuous hemodynamic assessment. There were no clinical sequelae in these patients.

Adjunctive angioplasty failed to restore TIMI flow grade 3 in three patients with distal dissection. As a result, procedural success was obtained in 26 patients.

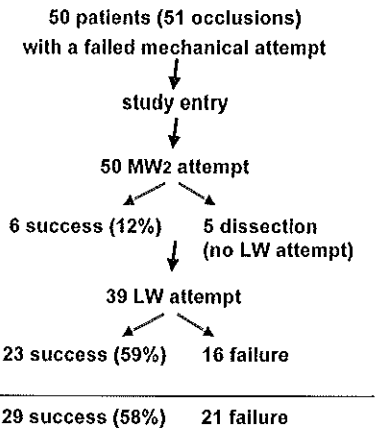


Figure 4 Breakdown of the results. All patients who entered the study had a previous failed attempt at recanalization using mechanical guide wires. MW2 = a repeat attempt using mechanical guide wires, LW = laser guide wire attempt.

Table 4. Angiographic predictors of succes

	OR (95% CI)	p value*
age of occlusion		
Angiographic	1.03 (0.97 - 1.1)	0.3
Clinical	0.99 (0.98 - 1.02)	0.7
Localization		
LAD vs. non - LAD	0.7 (0.2 - 2.5)	0.6
Morphology		
RD	0.5 (0.1 - 2.1)	0.4
Central funnel	0.9 (0.2 - 3.1)	0.8
Blunt funnel	1.9 (0.4 - 8.8)	0.4
Eccentric funnel	0.6 (0.1 - 3.01)	0.6
MSB	0.96 (0.2 - 3.8)	0.96
Bridging collateral channels	1.1 (0.6 - 7.1)	0.96
Length of occlusion	0.95 (0.9 - 1.01)	0.11

*Not significant for all comparisons. CI=confidence interval; OR=odds ratio; RD=proximal reference diamter; MSB=major side branch originating from the stump; other abbreviations as in Table 3.

CLINICAL EVENTS

Angina recurred within 48 h after an initially successful procedure in two patients (4%), leading to a non-Q wave myocardial infarction in both (CK 270 and 799 U/liter, respectively). A diagnosis of subacute reocclusion was confirmed angiographically, leading to successful repeat angioplasty in one patient and elective bypass surgery in the other. As a result, the overall clinical success rate was 48% (24 of 50 patients).

CLINICAL AND ANGIOGRAPHIC FOLLOW-UP

At 3-month clinical follow-up after a successful procedure, the mean angina class (Canadian Cardiovascular Society class) was reduced to 1.4 ± 0.7 versus 2.9 ± 0.3 before the procedure.

In 24 patients the occluded artery was successfully recanalized without occur-

rence of clinical events. Follow-up angiography was performed in all 24 patients, and 20 had a patent vessel (80%). Seven of these 20 patients (35%) had stenosis >50% by QCA (reference diameter 2.43 ± 0.52 mm, minimal lumen diameter 0.98 ± 0.21 mm, percent diameter stenosis 59 ± 8). As a result, late angiographic success (vessel patency in the absence of reocclusion or restenosis [defined as diameter stenosis >50% by QCA on the 6-month follow-up coronary angiogram]) was achieved in 54% of cases. Six patients (five with restenosis, one with reocclusion) underwent repeat intervention (25% reintervention rate) that was successful in all.

DISCUSSION

SUCCESS RATES

The past decade has not witnessed a substantial improvement in the success rate of recanalization of chronic totally occluded coronary arteries despite the advent of various new mechanical devices, such as the Magnum guide wire and the Rotacs system.[11] Using a meta-analysis of previously published reports, Meier[12] described an average success rate of 65% in recanalizing totally occluded vessels. The low success rate of 12% in our mechanical guide wire group is a reflection of the inclusion of only those patients with a TIMI grade 0 flow occlusion and at least one failed attempt using mechanical guide wires. Furthermore, angiographically unfavorable lesions were deliberately not excluded. Accordingly, a laser guide wire success rate of 59% in such a difficult lesion subset must be regarded as encouraging. Because the laser guide wire was used after a failed mechanical attempt at recanalization in this patient cohort, the question whether primary use of the laser guide wire will lead to higher success rates still needs to be answered. The Total Occlusion Trial With Angioplasty by Laser Guide Wire (TOTAL) trial, a randomized clinical trial evaluating the safety and efficacy of the laser guide wire, will address this question.

COMPLICATIONS

Laser guide wire perforation occurred in seven patients, without clinical sequelae. However, in one case balloon dilation after a laser guide wire perforation caused a tamponade that was managed by pericardiocentesis. Therefore, we strongly recommend not to advance any device over the laser guide wire before the intraluminal position of the guide wire tip has been angiographically con-

firmed. Furthermore, although we have not yet encountered such a situation, the possibility of reentry into the true distal lumen after laser guide wire perforation (especially in tortuous segments) must be kept in mind. However, the absence of clinical sequelae in all other cases of laser guide wire perforation suggests that guide wire perforation itself might be a benign phenomenon, allowing continuation of the procedure after with-drawal of the guide wire into the proximal part of the coronary artery (Figure 5). Although the issue of guide wire perforation should not be downplayed, and is a maneuver that must be avoided as much as possible, the term perforation with its ominous connotation could perhaps be replaced by a more benign term such as "guide wire exit." A change in terminology may be too early although, within this context, it seems relevant that the European Multicenter Surveillance Study,[13] with the laser guide wire has largely confirmed the benign character of these so-called laser guide wire perforations. Furthermore, the reporting of tamponade as a complication when using mechanical guide wires[14] suggests that this complication is not exclusively associated with the use of a laser guide wire.

In addition to these procedural complications, possible long-term complications due to prolonged fluoroscopy and the relatively large volume of contrast medium should also be considered.[15,16]

LONG-TERM FOLLOW-UP

In accordance with previous reports,[7,17,18] we found marked clinical improvement at follow-up in patients with successful recanalization. At 6-month angiographic follow-up, the reocclusion (20%) and restenosis rates (35%) in the remainder of our patient cohort are also in keeping with previously reported results.[19] As recently indicated[20–22], more liberal use of intracoronary stents will most likely lead to a significant reduction in the incidence of early and late reocclusion (Figure 6).

By undergoing recanalization of a total occlusion, a patient at no risk for restenosis is converted to a potential candidate for restenosis or reocclusion. However, the benefit of increasing the number of patent vessels should not be underestimated because the number of patent vessels has a strong bearing on the long-term prognosis of patients with coronary artery disease. However, the aim of the present pilot study was the primary evaluation of a laser guide wire. Whether use of a guide wire could affect 6-month restenosis rates is unlikely and beyond the scope of our study.

As the technology of the laser guide wire continues to evolve, it is conceivable that additional refinements, such

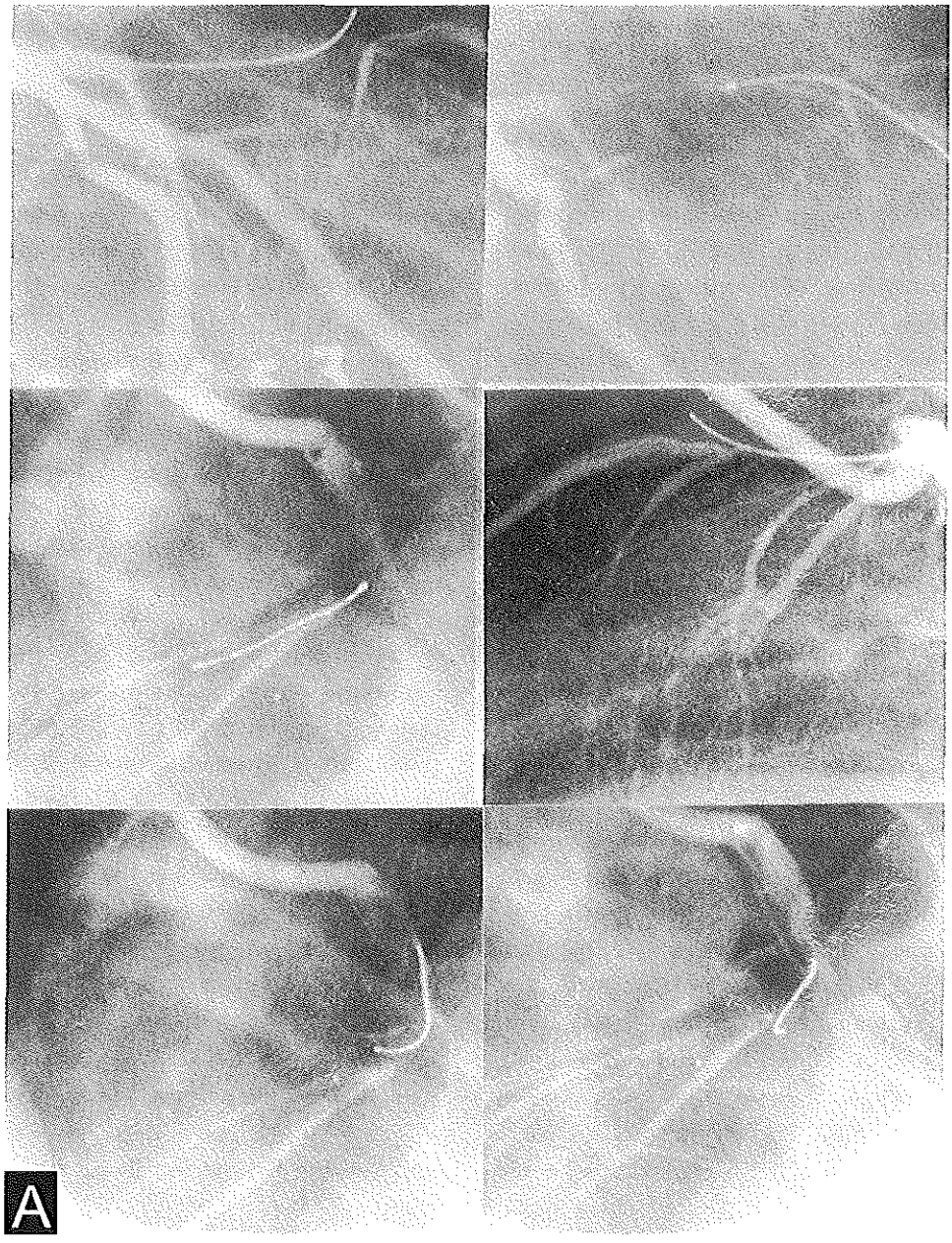
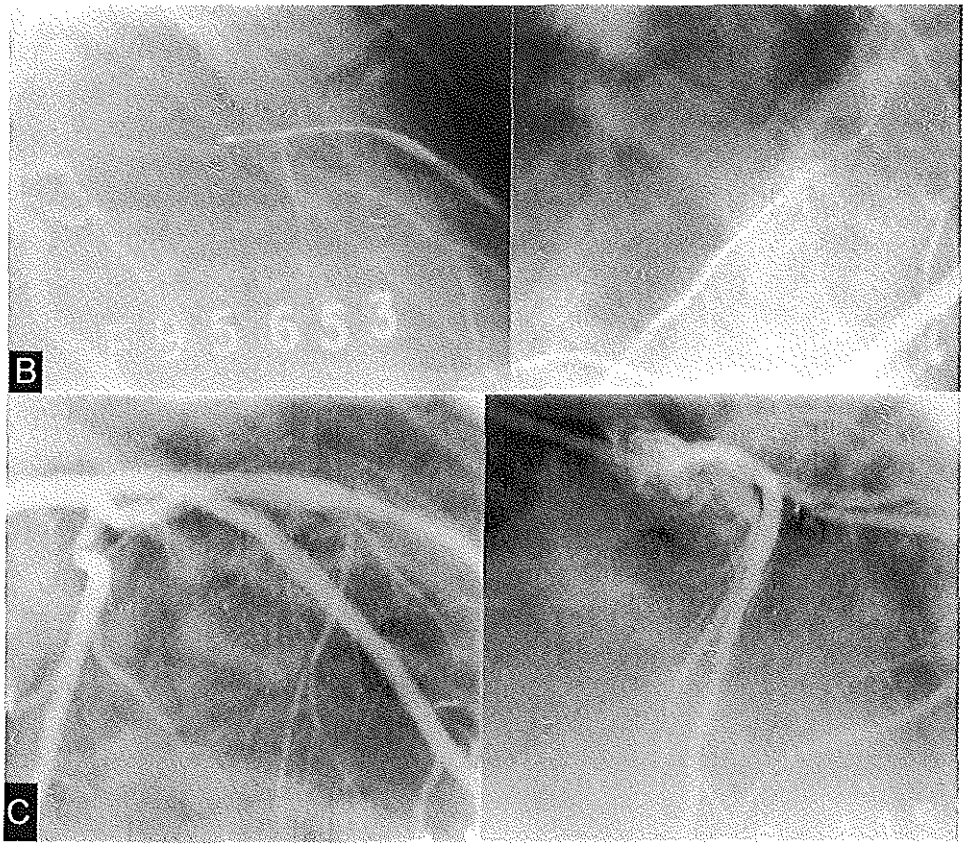


Figure 5abc *Laser guide wire "exit." A, Total occlusion of the proximal left anterior descending artery: numerous laser guide wire exits in different views. B, The laser guidewire positioned in the distal lumen. C, Final results after excimer laser coronary angioplsty and stenting.*



as remote tip control or simultaneous intravascular ultrasound to guide the procedure, will lead to a further increase in success rates and to a reduction of overall procedure time.

STUDY LIMITATIONS

This report describes our initial experience with a technology that was continually improving as our experience increased. We started with a new device that we deliberately tried to "push to the limit." However, soon it became apparent that to be successful, both a visible entry point and visualization of the distal lumen through collateral circulation were mandatory. In addition, the technical changes in the guide wire during this pilot phase possibly interfered with a uniform analysis of the results because two-thirds of procedures were performed with the less ideal earlier versions of the laser guide wire. Furthermore, only a relatively

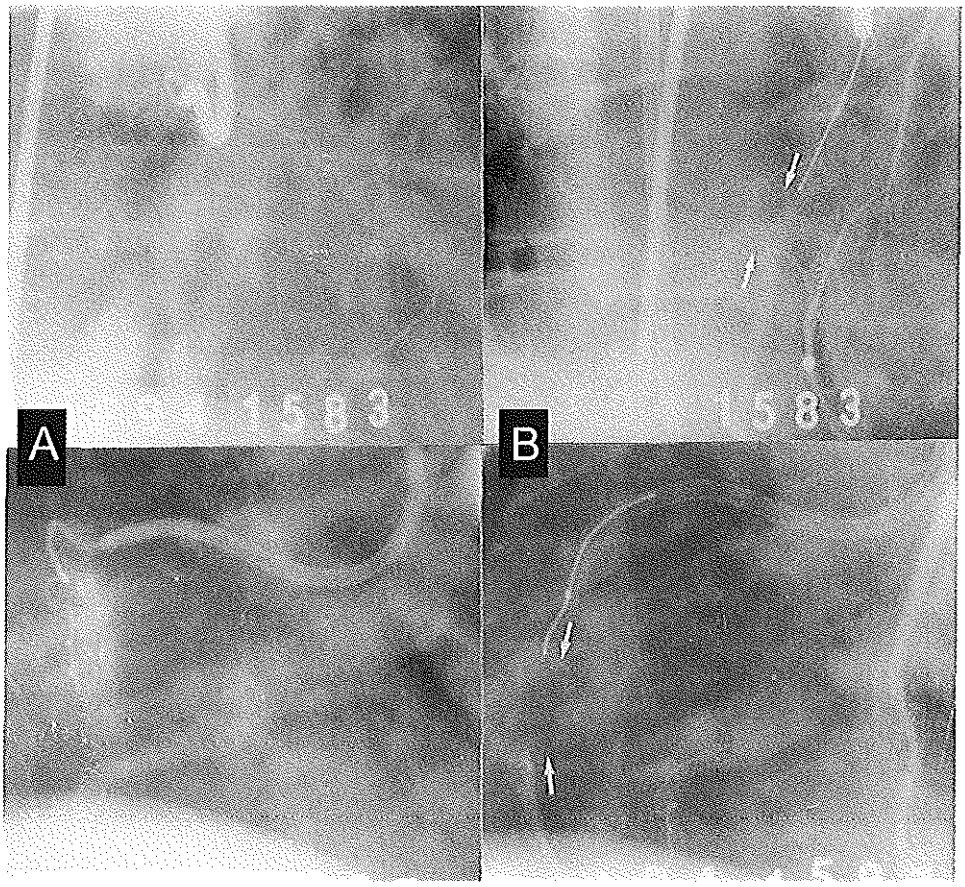
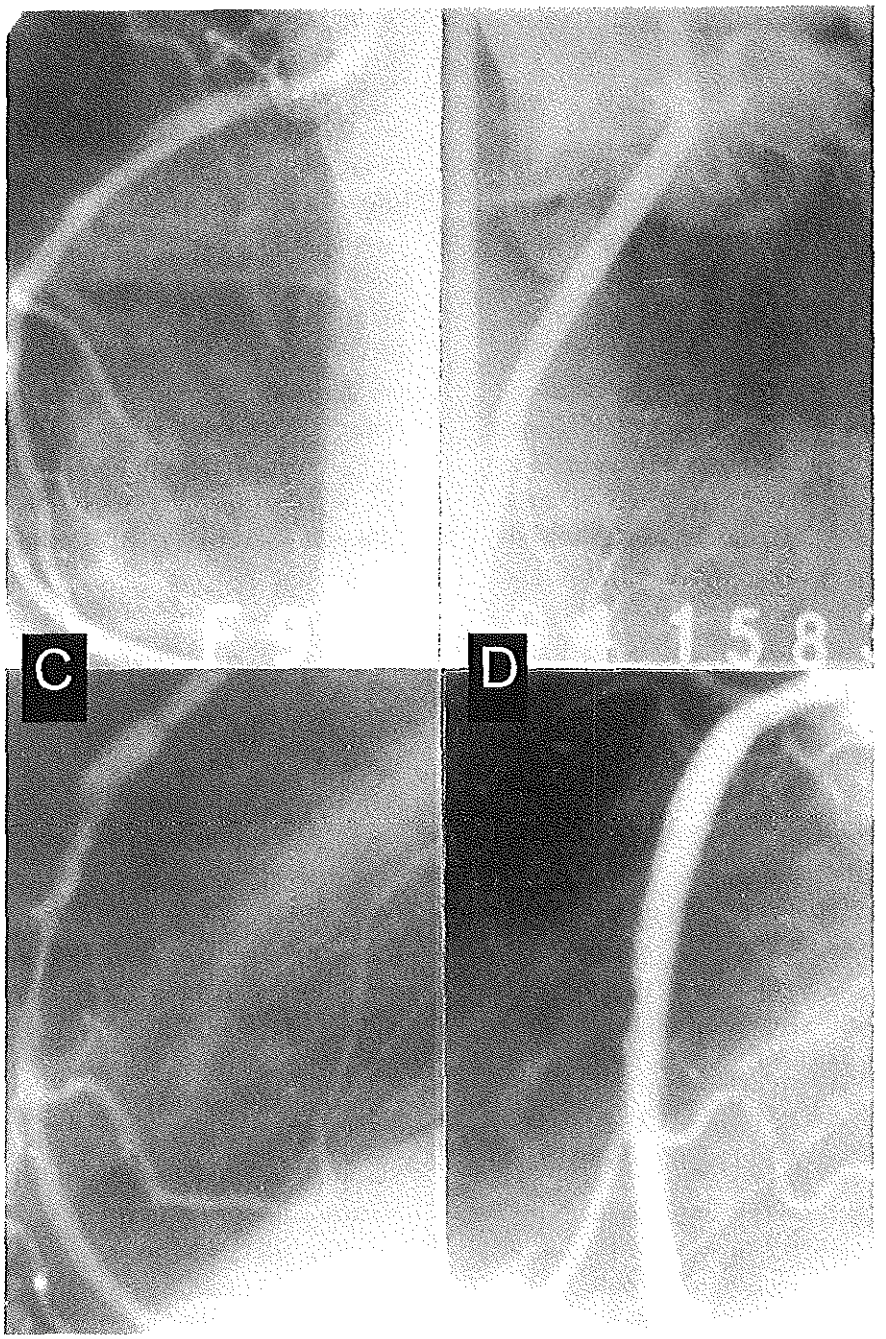


Figure 6 *(Upper panels: left anterior oblique view; bottom panels: left lateral view) A, Proximal occlusion of the right coronary artery. B, Alignment of the laser guidewire with the distal target segment. C, Results after a single pass with a 1.7 mm laser catheter. D, Final result after placement of multiple stents.*

small number of patients were included in this pilot study.

Finally, the large difference in success rates with the laser guide wire compared with mechanical guide wires (with additional backup support from a balloon catheter) cannot be ascribed solely to potentially superior mechanical qualities of the laser guide wire. This pilot study was not conducted in double-blind fashion; thus, a potential bias cannot be fully excluded. In this context it has been suggested that a "double-deaf " study-where the laser makes the usual sound during activation with or without producing the


C
D

actual laser light beam-might resolve this issue.

CLINICAL IMPLICATIONS

With the successful development of new technologies for percutaneous interventions, total coronary occlusion is no longer the exclusive domain of the cardiac surgeon. In the light of a recent report[14] on the high success rate of treating total occlusion with mechanical guide wires, the potential of the laser guide wire should be investigated in a randomized trial. The ongoing randomized TOTAL trial, with serial clinical and angiographic documentation, is expected to evaluate the place of percutaneous recanalization in general and the true value of the laser guide wire compared with the best available mechanical guide wires in particular.

CONCLUSIONS

Despite the aforementioned limitations, we conclude that use of the laser guide wire for recanalization of chronic total coronary occlusions refractory to treatment with mechanical guide wires is feasible, relatively safe and successful in 59% of attempted cases.

REFERENCES

1. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am Heart J* 1993;126:561–564.
2. Stone GW, Rutherford BD, McConahay DR, et al. Procedural outcome of angioplasty for total coronary artery occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15:849–865.
3. Serruys PW, Umans V, Heyndrickx GR, et al. Elective PTCA of totally occluded coronary arteries not associated with acute myocardial infarction; short-term and long-term results. *Eur Heart J* 1985;6:2–12.
4. DiScascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total coronary occlusion. *Am Heart J* 1986;111:833–839.
5. Holmes DR, Vlietstra RE, Reeder GS, et al. Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 1984;3:845–849.
6. Meyer B, Gruentzig AR. Learning curve for percutaneous transluminal coronary angioplasty: skill, technology or patient selection. *Am J Cardiol* 1984;53:65C–66C.
7. Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB. Angioplasty in total coronary artery occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985;6:526–533.

8. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase 1 findings. *N Engl J Med* 1985;31:932– 936.
9. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264–1269.
10. Ruygrok PN, De Jaegere PPT, Verploegh J, van Domburg, De Feyter PJ. Immediate outcome following coronary angioplasty: a contemporary single center audit. *Eur Heart J* 1995;16(Suppl):24–29.
11. Cherrier F, Monassier JP, Hanssen M, Danchin N, Coulbois PM, Juilliere Y. Rotacs: un système utilisable dans les désobstructions arterielles coronaires et périphériques. *Arch Mal Coeur* 1991;84:87–88.
12. Meier B. Total coronary occlusion: a different animal? *J Am Coll Cardiol* 1991;17(Suppl B):50B–57B.
13. Hamburger J, Seabra-Gomes R, Simon R, et al. for the TOTAL Investigators. Recanalization of chronic total coronary occlusions using a laser guidewire: the European TOTAL multicenter surveillance study [abstract]. *J Am Coll Cardiol* 1997; 29(Suppl A):69A.
14. Kinoshita I, Katoh O, Nariyama J, et al. Coronary angioplasty of chronic total occlusions with bridging collateral vessels: immediate and follow-up outcome from a large single-center experience. *J Am Coll Cardiol* 1995;26:409–415.
15. den Boer A, de Feyter PJ, Hummel WA, Keane D, Roelandt JRTC. Reduction of radiation exposure while maintaining high-quality fluoroscopic images during *Interventional Cardiology* using novel x-ray tube technology with extra beam filtering. *Circulation* 1994;89:2710–2714.
16. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radio contrast agents. *N Engl J Med* 1994;331 :1416–1420.
17. Ivanhoe RJ, Weintraub WS, Douglas JS Jr, et al. Percutaneous transluminal coronary angioplasty of chronic total occlusions: primary success, restenosis and long-term clinical follow-up. *Circulation* 1992;85:106–115.
18. Finci L, Meyer B, Favre J, Righetti A, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary artery occlusion. *Am J Cardiol* 1990;66:660–662.
19. Violaris AG, Melkert R, Serruys

PW. Long term luminal renarrowing after successful elective coronary angioplasty of total occlusions: a quantitative angiographic analysis. *Circulation* 1995;91:2140–2150.

20. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995;91:1676–1688.
21. Goldberg SL, Colombo A, Maiello L, Borrione M, Finci L, Almagor Y. Intracoronary stent insertion after balloon angioplasty of chronic total occlusions. *J Am Coll Cardiol* 1995;26:713–719.
22. Sirnes PA, Golf S, Myreng Y, et al. Stenting in chronic coronary occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;28:1444–1451.

CHAPTER 9

Recanalization of total coronary occlusions using a laser guide wire: The European TOTAL Surveillance Study

Jaap N. Hamburger, Patrick W. Serruys, Ricardo Seabra-Gomes, Rudiger Simon, Jacques J. Koolen, Eckhardt Fleck, Detlef Mathey, Horst Sievert, Wolfgang Rutsch, Andreas Buchwald, Jean Marco, Said Al Kasab, Luciano Pizzuli, Christian W. Hamm, Thierry Corcos, Nicolaus Reifart, Peter Hanrath, Yves Taeymans

Am J Cardiol 1997;80:1419-1423

RECANALIZATION OF TOTAL CORONARY OCCLUSIONS USING A LASER GUIDEWIRE: THE EUROPEAN TOTAL SURVEILLANCE STUDY

ABSTRACT

The success rates of coronary angioplasty for the treatment of chronic total occlusions are less favorable than for coronary stenosis. Therefore, a new laser guidewire (LW) was designed to facilitate the crossing of chronic total occlusions. We report on the results of a European multicenter surveillance study, evaluating the laser guidewire performance. Between May 1994 and July 1996, 345 patients (age 59 ± 10 years, 291 men) with chronic total occlusions were enrolled in 28 European centers. The median age of occlusion was 29 weeks (range 2 to 884), the occlusion length 19 ± 10 mm. LW recanalization was successful in 205 patients (59%). LW perforation occurred in 73 patients (21%), with hemodynamic consequences in 4 (1%). There were no deaths, emergency coronary artery bypass surgery, or Q-wave myocardial infarctions. In a multivariate regression analysis an occlusion age of <40 weeks (p=0.001, RR=1.34) and an occlusion length <30 mm (p=0.01, RR=1.59) were independent predictors of success. Results indicate that the LW is an effective and safe tool in the treatment of chronic total occlusion refractory to conventional guidewires.

Chronic total occlusions remain the "enfant terrible" of coronary angioplasty, as the success rates still lag behind those of angioplasty for coronary stenosis.[1-6] Because total occlusion is estimated to be present in one third of the angioplasty population[7,8] an attempt was made to improve on the procedural success rates in this specific patient category. Thus, a steerable guidewire with forward debulking properties, the laser wire (LW), was developed. Following a single center pilot-study[9] in May 1994, a multicenter surveillance study evaluating the performance of the Spectranetics Prima Total Occlusion System (Spectranetics, Colorado Springs, Colorado) was initiated. In this report we discuss the final outcome of the European Multicenter TOTAL Surveillance Study, which served as a preamble for the currently ongoing multicenter randomized trial, the "TOTAL trial".

METHODS

THE LASER WIRE

The LW and the technique of the LW procedure have been described elsewhere.[10-12] In short, the Prima Total

Occlusion System consists of an 0.018-inch guidewire containing 12 silica fibers with a 45-μm diameter and a support catheter providing additional coaxial back-up support. Since its introduction in 1993, the LW has been subject to a number of technical improvements. It changed from a nonsteerable straight wire to a steerable guidewire, designed to function as an exchange wire (Model 018-003, Generation 2B), which is the currently used model.

THE LASER

The laser was the Spectranetics CVX 300 XeCl excimer laser. The fluence typically used during a LW procedure was 60 mJ/mm^2, with a pulse repetition rate of 25 Hz. If any resistance prohibited sufficient wire progression, the pulse repetition rate was increased to 40 Hz, thus increasing the LW ablation rate. During pulse trains with a maximum of 5 seconds the wire was gently advanced at a rate of up to 1 mm/s.

PATIENT POPULATION

Data of patients with a total occlusion (Thrombolysis In Myocardial Infarction [TIMI] trial 0 and I flow)[13] existing for >2 weeks who underwent a procedure using the LW were prospectively collected. A written informed consent was obtained from all patients, according to local medical ethics committee recommendations. Lesions typically unfavorable for an attempt at recanalization, such as bridging collaterals or a major side branch originating from the occlusion stump, were deliberately not excluded. However, a visible entry point and visualization of the distal vessel through collateral flow were mandatory. The study protocol did not provide restrictions to whether or not an attempt with a mechanical guidewire should be made before the LW attempt. All data regarding clinical history, preprocedural angiographic assessment, angioplasty procedure, and eventual serious adverse effects were recorded in a standard case report form. The reference diameter of the occluded segment and the length of occlusion were determined by visual assessment.

DEFINITIONS

LW success was defined as angiographic evidence of reaching the true lumen of any branch distal to the occlusion. This was subdivided in "total success," meaning the LW reached the true distal lumen, and "partial success," referring to patients in whom a combination of LW and mechanical guidewire was used to achieve reconstitution with the parent neolumen. Procedural success was defined as an average diameter stenosis of <50% in 2 orthogonal views at completion of the procedure. Clinical success was defined as procedural success without death, myocardial infarction, emergency coronary artery bypass graft

surgery, or repeat percutaneous transluminal coronary angioplasty during the hospital stay.

ADJUNCTIVE ANGIOPLASTY

After successful crossing of a guidewire, the nature of the ensuing angioplasty was at the discretion of the investigator. For excimer laser coronary angioplasty (ELCA), the 1.4-, 1.7-, or 2.0-mm Vitesse (Spectranetics) rapid exchange coronary catheters were available. For ELCA procedures it was advised to use a saline flush. The removal of contrast medium and blood before and during laser activation diminishes vascular wall damage resulting from fast expanding water vapor bubble formation with subsequent shock wave formation[14,15] and thereby reduces the incidence of coronary dissection.[16]

STATISTICAL ANALYSIS

A multivariate regression analysis using SAS statistical software was performed to identify independent predictors of success. Incidents with a p value <0.05 were considered significant.

RESULTS

Between May 1994 and July 1996, in 28 centers, 345 patients (age 59 ± 10 years, 291 men, previous myocardial infarction 217 [63%] with a TIMI 0 flow [n = 284] or TIMI I flow [n = 61] coronary occlusion) who were treated with the LW entered the study. In 16% of cases (n = 54), a previous failed attempt at recanalization using mechanical wires was reported. The median angiographic age of occlusion was 12 weeks (range 2 to 728) or 29 weeks (range 2 to 894) according to clinical history (Fig 1). The occlusion length was 19 ± 10 mm (Table I). The enrollment per center was ≤10 patients in 13 centers, 11 to 20 patients in 14 centers and 66 patients in 1 center.

WIRE SUCCESS

None of the primary mechanical wire attempts (n=182, median duration 15 minutes, range 1 to 135) were successful (Figure 2). In all patients, a second attempt was performed using the LW, which was successful in 105 (58%). In patients in whom the LW was the primary guidewire (n = 163, median duration 25 min, range 1 to 180), the attempt was successful in 100 cases (61%). From the 205 cases successfully performed with the LW, 169 cases were a "total success," whereas in 36 cases (17.5%) a combination of techniques was used ("partial success"). As a result, the overall LW success rate was 59% (205 of 345 cases).

STATISTICAL ANALYSIS

The following parameters were entered in a multiple univariate analysis: the age of occlusion, the occlusion length, the reference diameter, the presence of a side branch originating from the occlusion

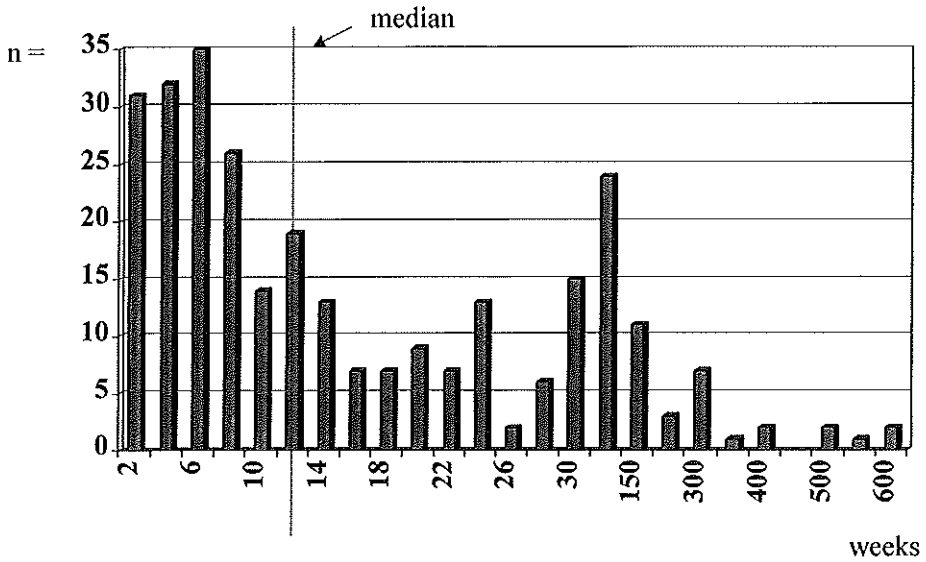


Figure 1 Distribution of the angiographically documented age of occlusion. As the distribution is "nonnormal", the median (at 12 weeks), rather than the mean age of occlusion is given.

stump, the presence of bridging collaterals, the funnel shape (central vs eccentric funnel, or a blunt stump) and the location of the occlusion (left anterior descending vs no left anterior descending). A logarithmic transformation of the age of occlusion was performed to compensate for skew due to a nonnormal distribution of parameters. A multivariate regression analysis of these variables indicated that the independent predictors of success were clinical age of occlusion ($p = 0.004$) and the occlusion length ($p = 0.0004$). When the analysis was repeated for only patients with a TIMI 0 flow coronary occlusion, again the clinical age of occlusion ($p = 0.005$) and the occlusion length ($p = 0.002$) were independent predictors of success. The respective cutoff lines of success were reached at the clinical age of occlusion of 40 weeks (crossing success 63% for age <40 weeks vs. 47% for age ≥40 weeks, $p=0.012$, RR=1.34) and

Table 1 Baseline Lesion Characteristics

	n	(%)
Left Anterior Descending artery	125	(36)
Circumflex Artery	51	(15)
Right Coronary Artery	168	(49)
TIMI Flow		
0	284	(82)
1	61	(18)
Stump morphology		
Central funnel	125	(36)
Eccentric funnel	95	(28)
Blunt stump	125	(36)
Major side branch	126	(37)
Micro capillary refill	36	(10)
Age of occlusion (wk)	Median	(range)
Angiographic age (n=161)	12	(2 - 728)
Clinical age (n=174)	29	(2 - 894)
Lesion measurements (mm) (mean ± SD)		
Length of occlusion (n=198)	19 ± 10*	
Reference diameter (n=184)	2.84 ± 0.55	

* Range: 2 to 50 mm. TIMI=Thrombolysis In Myocardial Infarction trial

an occlusion length of 30 mm (crossing success 62% for length <30 mm vs 39% for length ≥30 mm, p=0.0013, RR=1.59).

ADJUNCTIVE ANGIOPLASTY

An adjunctive angioplasty was performed after successful crossing of the total occlusion in all 205 patients. Of these, 194 were successful (procedural success rate of 95%). Only a minority of patients were treated with balloon angioplasty alone (23%). The remaining patients were treated with ELCA and adjunctive balloon angioplasty (n = 78, 38%), whereas in another 78 patients, angioplasty was completed by implantation of ≥1 intracoronary stent (Table II). The overall procedure duration was 105 minutes (range 20 to 330).

PROCEDURE RELATED COMPLICATIONS

Noteworthy is the relatively high number of LW perforations (n = 73, Table III) that were originally perceived as a reason to terminate the procedure (n = 56). In 4 patients (1.2%), the wire position was mistakenly thought to be intraluminal. In these cases, the advancement of a device over the LW caused extravasation of contrast medium leading to tamponade, which in all patients could be treated by means of nonsurgical drainage. However, because no clinical sequelae were reported resulting from LW perforation per se, LW perforation emerged to be a more or less benign event, thus allowing for a continuation of the procedure after withdrawal of the wire into the proximal part of the coronary artery.

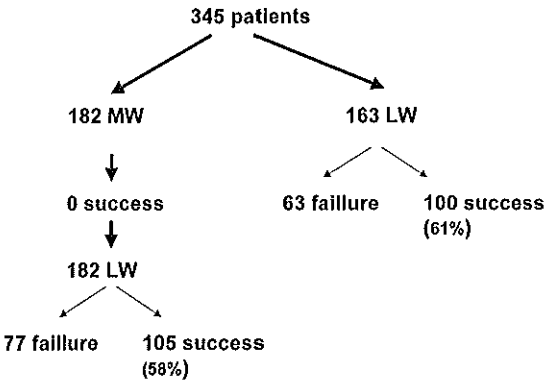


Figure 2 Breakdown of the results. MW = initial attempt at recanalization using a mechanical guidewire; LW=attempt at recanalization using a LW.

SERIOUS ADVERSE EVENTS

Serious adverse events were reported in twelve patients (3.5%): 3 non-Q wave myocardial infarctions, 4 repeat percutaneous transluminal coronary angioplasties, 4 tamponades, and 1 LW malfunction. Of interest is the overall benign character of these events, in the absence of Q-wave myocardial infarction, emergency coronary artery bypass surgery and death. As a result of these adverse events, clinical success was obtained in 54% of the original patient cohort.

DISCUSSION

Since the early days of angioplasty, despite the introduction of various new

Table 2 Procedural Success of Adjunctive Angioplasty

Procedure	No.	Success (%)
LaLa	2	0 (0)
LaBa	47	40 (85)
LaLaBa	78	78 (100)
LaBaSt	40	39 (98)
LaLaBaSt	38	37 (97)
Total	205	194 (95)

LaLa = LW assisted laser angioplasty, LaBa = LW assisted balloon angioplasty, LaLaBa = LW assisted laser- and balloon angioplasty, LaBaSt = LW assisted balloon angioplasty with stenting, LaLaBaS t= LW assisted laser- and balloon angioplasty with stenting. (LW = laser wire).

mechanical devices,[17-19] we have not witnessed a substantial improvement in the success rates of recanalization of chronic total occluded coronary arteries. The only exception to this experience could be the results described by Kinoshita et al,[20] which were achieved with the Japanese "Athlete" guidewire.

Although the baseline characteristics of our study population indicated that the patient group was representative of current coronary angioplasty practice, the number of patients with a previous myocardial infarction was relatively high. As reported, 16% of the patients had a previously failed mechanical attempt at recanalization. In addition, in the study there was a 100% failure of primary mechanical attempts. Obviously, by the very nature of this device registry, cases in which a mechanical guidewire attempt was successful were not reported because in these cases the LW was not used. However, we feel that an average 59% success rate with the LW after a failed attempt with any type of mechanical guidewire is an encouraging development. Furthermore, it is conceivable that in a number of cases a failed primary attempt with a mechanical wire, causing dissection, might have negatively influenced the success rate of the LW during a subsequent attempt.

Table 3 Reason for Failure Laser Wire Crossing (n=144)

	No. (%)
Misalignment	44 (31)
Wire stuck	27 (19)
Wire perforation	56 (39)
Wire fracture	1 (0.7)
Other	12 (9)

In 4 patients a LW exit resulted in tamponade. In all 4 this was due to the advancement of a catheter into the free pericardial space. Therefore, it is strongly recommended not to advance any device over the LW before the intraluminal position of the wire tip has been confirmed by angiography.

In this registry there was a marked absence of serious adverse events. No LW-related deaths, Q-wave myocardial infarction, or emergency coronary artery bypass graft surgery have been reported, suggesting that recanalization of total occlusions by using a LW is a relatively safe procedure.

Notwithstanding the initially positive results with this new technology in a notoriously difficult subset of patients, there are some limitations to this study. Given the protocol design, there was freedom in initial guidewire selection (mechanical wire, LW), without recording of the intention to treat. Completion of a screening log was not required. As a result, it could not be determined what percentage of patients with chronic total occlusions were enrolled in this study. Earlier, we demonstrated the influence of a "learning curve," showing an increase in success rates of 50% to 85% in a single center experience.[9] Therefore, the inclusion of learning curve data (13 of the 28 participating centers enrolled ≤10 patients) and the implementation of technical changes in the LW during the study may possibly interfere with the results and their just interpretation. Finally, the limited collection of in-hospital events, in the absence of an angiographic and/or electrocardiographic corelab, precludes the possibility of determining the mid- and long-term condition and prognosis of these patients. Therefore, a randomized trial with intention to treat recorded by a central telephone allocation center was initiated in 1995. This trial, with extensive and prospective collection of clinical and angiographic data, will be conducted by an independent coordinating center with corelab facilities.

APPENDIX

List of participating investigators, in order of the number of patients recruited for the European Multicenter Laser Guidewire Surveillance Study.

1. Thoraxceneter, University Hospital Rotterdam, The Netherlands. J.N. Hamburger, P.W. Serruys
2. Santa Cruz Hospital, Lisbon, Portugal. R. Seabra-Gomes
3. Christian Albrechts Universität Kiel, Germany. R. Simon
4. Catherina Hospital, Eindhoven, The Netherlands. J.J. Koolen, H. Bonnier
5. Deutsches Herzzentrum Berlin, Germany. E. Fleck
6. Kardiologisches Gemeinschafts-praxis Hamburg, Germany. D. Mathey, J. Schofer
7. Bethanièn Krankenhaus, Frankfurt am Main, Germany. H. Sievert
8. Rudolf Virchow, Charité, Berlin, Germany. W. Rutsch
9. Universitätsklinik Goettingen, Germany. A.B. Buchwald
10. Clinique Pasteur, Toulouse, France. J. Marco, J. Fajadet
11. Armed Forces Cardiac Center, Riadh, Saudi Arabia. S. Al Kasab
12. Medizinisches Universitätsklinik Bonn, Germany. L. Pizzulli
13. Universitätskrankenhaus Eppendorf Hamburg, Germany. C. Hamm
14. CMC Parly Grand Chesnay, Paris, France. Th. Corcos

15. Rotes Kreuz Krankenhaus Frankfurt, N. Reifart
16. RWTH Aachen, Germany. P. Hanrath
17. R.U. Gent, Belgium. Y. Taeymans
18. Harefield Hospital, London, United Kingdom. Ch. Ilsley
19. Hospital "Gregorio Maranon", Madrid, Spain. E. Garcia
20. Sahlgrenska University Hospital Götenborg, Sweden. H. Emmanualson
21. St. Anthonius Ziekenhuis, Nieuwegein, The Netherlands. J. Ernst, H. Plokker
22. Universitätsklinik Essen, Germany. M. Haude
23. Universitätsklinik Inselspital, Bern, Switserland. B. Meier
24. Centro Cuore Columbus, Milano, Italy. A. Colombo
25. St. Thomas, London, United Kingdom. M. Webb-Peploe
26. UH Gasthuisberg, Leuven, Belgium. F. van der Werf
27. Clairval Hospital, Marseille, France. H. Escojido
28. Franz Volhard Klinik, Berlin, Germany. Dr. Waigand

REFERENCES

1. Stone GW, Rutherford BD, McConahay DR, Johnson Jr WL, Giorgi LV, Ligon RW, Hartzler GO. Procedural outcome of angioplasty for total coronary artery occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15: 849-65
2. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W, Jaski B, Hugenholtz PG. Elective PTCA of totally occluded coronary arteries not associated with acute myocardial infarction; short-term and long-term results. *Eur Heart J* 1985;6:2-12
3. DiScascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for sub acute and chronic total coronary occlusion. *Am Heart J* 1986;111: 833-839
4. Holmes DR, Vlietstra RE, Reeder GS, Bresnahan JF, Smith HC, Bove AA, Schaff HV. Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 1984;3:845-849
5. Meyer B, Gruentzig AR. Learning curve for percutaneous transluminal coronary angioplasty: skill, technology or patient selection. *Am J Cardiol* 1984;53:65C-66C
6. Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB. Angioplasty in total coronary artery occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985;6:526-533
7. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am*

Heart J 1993;126:561-564

8. Ruygrok PN, De Jaegere PPT, Verploegh J, van Domburg, De Feyter PJ. Immediate outcome following coronary angioplasty: a contemporary single center audit. *Europ Heart J* 1995;16 (Supp. L):24-29
9. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol*, 1997;30:649-56
10. Hamburger JN, Aiirian S, Gijsbers GHM, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a single institution experience with the initial one-hundred cases. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, (Philadelphia: Current Medicine 1996); 63-69
11. Hamburger JN, Serruys PW. Recanalization of chronic total occlusions using a laser guidewire. In: U Sigwart, M Bertrand and PW Serruys (eds) *Handbook of Cardiovascular Interventions*, (WB Saunders, London 1996); 493-500.
12. Hamburger JN, Serruys PW. Laser guidewire for Recanalization of Chronic Total Occlusions. In: R Beyar, G Keren, M Leon and PW Serruys (eds) Frontiers in *Interventional Cardiology*, (Martin Dunitz, London 1997); 47-53.
13. The TIMI Study group. The Thrombolysis In Myocardial Infarction Group (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985;31: 932-936.
14. Leeuwen van TG, Meertens JH, Velema E, Post MJ, Borst C. Intraluminal vapor bubble induced by excimer laser pulse causes microsecond arterial dilation and invagination leading to extensive wall damage in the rabbit. *Circulation* 1993; 87:1285-1263
15. Hamburger JN, Gijsbers GHM, Verhoofstad GGAM, van Marle J, van den Broecke D, Hanekamp CEE, Serruys PW, van Gemert MJC. Excimer laser coronary angioplasty: A physical perspective to clinical results. In: Topol E, Serruys PW (eds), *Current Review of Interventional Cardiology*, 2nd edn (Philadelphia: Current Medicine, 1995); 159-172.
16. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264-9
17. Pande AK, Meier B, Urban P, de la Serna F, Villavicencio R, Dorsaz PA, Favre J. Magnum/Magnarail versus conventional systems for recanaliza-

tion of chronic total coronary occlusions: A randomized comparison. *Am Heart J* 1992;123: 1182-86

18. Cherrier F, Monassier JP, Hanssen M, Danchin N, Coulbois PM, Juilliere Y. Rotacs: un système utilisable dans les désobstructions arterielles coronaires et périphériques. *Archives des Maladies du Coeur et des Vaisseaux* 1991;84(1):87-8
19. Rees MR, Michalis LK. Activated-guidewire technique for treating chronic coronary artery occlusion. *Lancet* 1995;346:943-44
20. Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T, Shibata N, Ishihara T. Ohsawa N. Coronary Angioplasty of Chronic Total Occlusions With Bridging Collateral Vessels: Immediate and Follow-Up Outcome From a Large Single-Center Experience. *J Am Coll Cardiol* 1995;26:409-15

CHAPTER 10

Laser wire for crossing chronic total occlusions - "learning phase" results from the U.S. TOTAL Trial

Stephen N. Oesterle, John A. Bittl, Martin B. Leon,

Jaap N. Hamburger, James E. Tcheng, Frank Litvack,

James Margolis, Paul Gilmore, Ronald Madsen, David Holmes,

Jeffrey Moses, Howard Cohen, Spencer King, Jeffrey Brinker,

Terence Hale, Dean J. Geraci, William J. Kerker, Jeffrey Popma

For the U.S. TOTAL Investigators

Cathet Cardiovasc Diagn1998; 44:235-243

LASER WIRE FOR CROSSING CHRONIC TOTAL OCCLUSIONS- "LEARNING PHASE" RESULTS FROM THE U.S. TOTAL TRIAL

ABSTRACT

The Prima® laser guidewire system (Spectranetics Corp., Colorado Springs, CO) consists of an 0.018" hypotube containing a bundle of 45-μm optical fibers coupled to a pulsed excimer laser operating at a tip fluence of 60 mJ/mm^2 and a repetition rate ranging from 25-40 Hz. This laser guidewire was specifically designed to cross total occlusions refractory to passage with conventional wires. The Prima wire was evaluated in a feasibility study at 14 U.S. centers. Following failure to cross a total occlusion with approved guidewires, the Prima wire was utilized in 179 patients. Average age of subjects was 61 yr. Lesion locations included left anterior descending (36%), right (45%) and circumflex (19%) coronary arteries. Mean angiographic age of total occlusions was 70 wk (range, 2-1,020 wk, median, 14 wk). The use of the Prima wire either solely or in combination with conventional guidewires resulted in successful crossing in 61% of these previously impenetrable occlusions. Failure of the device was commonly related to length of the occlusion and tortuosity along the occluded pathway. Major complications included myocardial infarction in 7 patients (3.9%), tamponade in 3 (1.7%), and death in 2 (1.1%). This "learning phase" pilot study confirmed the feasibility of a laser guidewire in chronic total occlusions that are resistant to passage of conventional guidewires. An extended registry at these investigative sites is planned.

Chronic total occlusion of a major epicardial coronary artery presents a major obstacle to complete coronary revascularization by percutaneous techniques. The presence of a chronic total occlusion is often a primary factor in choosing surgical revascularization over a percutaneous approach. The inability to cross a coronary occlusion with a conventional guidewire precludes the use of any device (balloon, atherectomy, or stent), as all require delivery over a guidewire. Despite two decades of technological advances, angioplasty success rates rarely exceed 60%.

The most important determinants of failure to cross chronic total occlusions include age and length of the obstruc-

The original Figure 2 was omitted for technical reasons.

tion. The inability to cross totally occluded coronary segments with conventional guidewires is usually related to an inability to generate sufficient force to pass through the plaque and the propensity of mechanical guidewires to seek a "false" or subintimal passage.

To address these limitations, a steerable laser guidewire (Prima® wire, Spectranectics Corporation, Colorado Springs, CO) was developed and tested in this study. The Prima wire is an 0.018" guidewire capable of delivering high-density laser energy, at its tip, through an optical fiber bundle. From January 1995-November 1996, 14 centers in the United States enrolled patients in a feasibility and "learning phase" study of this laser guidewire as a prelude to a controlled trial (TOTAL, for Total Occlusion Trial with Angioplasty by using a Laser Wire). Results of this United States Phase I learning phase registry are summarized in this report.

METHODS

PATIENT SELECTION

The primary objective of this feasibility study was to characterize the safety and efficacy of the Prima laser guidewire while allowing investigators to familiarize themselves with the operational characteristics of the system and master the nuances of laser guidewire manipulation. The learning phase of the U. S. TOTAL trial was approved by the United States Food and Drug Administration. Institutional review board approval was obtained at each site. All patients gave informed consent before participation in the study.

The study group comprised patients with angina or objective evidence of ischemia (by stress echo or nuclear scintigraphy) and a documented total occlusion, demonstrated by previous angiographic or clinical indicators. By protocol, the minimum age of occlusion was greater than 2 wk by clinical symptoms. Patients with an acute myocardial infarction within 2 wk of the planned procedure were excluded.

Patients were entered into the study at the discretion of the principal investigator at each site. Angiographically unfavorable lesions (e.g., bridging collaterals, side branch emanating from occlusive funnel, heavy calcification, curved occlusive segments and ultra-long occlusions) were included; however, total occlusions that had distal segments poorly visualized by collaterals (less than Rentrop grade 2) were excluded.

DEVICE DESCRIPTION

The Prima coronary total occlusion system was designed to couple the mechanical attributes of a conventional coronary guidewire with the ablative

energy of a laser to facilitate crossing of total occlusions, especially when mechanical force proves insufficient.

The proximal end of the laser guidewire is connected to the excimer laser (Spectranecties CVX- 300® excimer

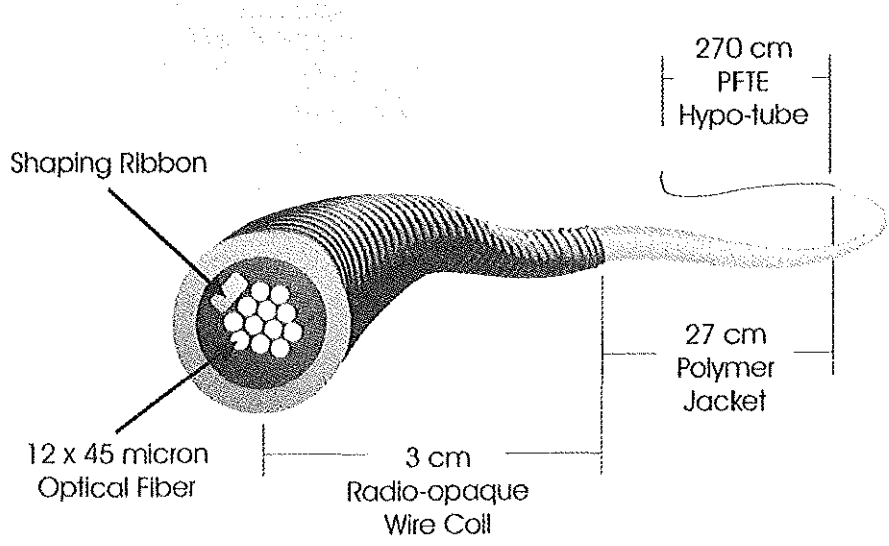


Figure 1 Schematic diagram of the Prima laser guidewire.

The laser guidewire consists of a concentric array of 12 optical fibers (45-µm diameter) enclosed in an 0.018" diameter hypotube (Fig 1). The working length is 175 cm, which can be converted to an exchange length of 300 cm by removing the proximal coupler and tail-tubing. The leading 30 cm of the laser guidewire is covered with a lubricious coating to reduce friction. The tip is a 3-cm shapeable coil that is easily visualized by fluoroscopy. The laser guidewire can be steered like a conventional guidewire with a torque device, mounted on the proximal shaft.

laser console) with a proprietary "plug-in" coupler. The laser guidewire is externally calibrated at the laser console and is designed to operate at a maximum tip fluence of 60 mJ/mm^2 and a repetition rate of 25-40 Hz (pulses per sec).

The Prima coronary total occlusion system includes a support catheter used to position the laser guidewire at the site of total occlusion and to facilitate guidewire exchange. The support catheter is 135 cm long and has a single lumen for insertion of an 0.018" or smaller diameter guidewire. The sup-

port catheter has a 1-mm radiopaque marker band mounted 1 mm back from the leading tip. The shaft of the catheter is tapered from 3.5 French proximally to 2.4 French at its distal tip. The leading 35 cm of catheter are coated with lubricious material. The support catheter is introduced through a hemostatic Y-adapter into any conventional 8 French coronary guiding catheter.

The Prima laser guidewire has been extensively used in Europe, where a randomized trial was recently completed. It is limited to use in the United States under an Investigational Device Exemption from the U.S. Food and Drug Administration.

LASER GUIDEWIRE PROCEDURE

A general description of the technique is as follows. Procedures were performed using standard techniques of percutaneous coronary intervention. After failure to cross an occlusion with conventional guidewires, the laser guidewire was positioned at the proximal stump of the total occlusion before activating the laser. Although the laser guidewire could usually be advanced to the site of occlusion without use of the support catheter, the tip of the wire is relatively stiff and its rapid and safe delivery to the segment of total occlusion could often be facilitated by prior delivery of the support catheter. The support catheter was easily advanced to the proximal occlusion over conventional coronary guidewires. The mechanical wire was then exchanged for the laser guidewire.

The segment of coronary artery with the targeted total occlusion had to be clearly visualized in orthogonal views. The proximal vessel and the distal reentry site had to be visible by angiography. Adequate visualization of the coronary artery distal to the occlusion was a prerequisite for enrollment. The absence of collaterals to the coronary segment distal to the occlusion was felt to be a relative contraindication to the use of the laser guidewire.

Simultaneous contrast injections of the ipsilateral and contralateral coronary artery were frequently required to delineate the extent and trajectory of the total occlusion.

The operator-shaped laser guidewire tip was torqued and advanced to the proximal aspect of the total occlusion. The excimer laser is an obligate contact laser; hence, the tip of the wire had to be firmly applied to the plaque. Firm guiding catheter support was needed. The support catheter also provided substantial "backup" support for advancement of the wire.

Appropriate guidewire trajectory was confirmed by multiplane angiography, the laser was activated by a foot switch, and the laser guidewire was slowly advanced (the laser automatically

defaults to an inactive mode after 5 sec of operation). Procedures were performed at a fluence of 60 mJ/mm^2 and a pulse repetition rate of 25-40 Hz. The laser guidewire was generally advanced no more than 1-2 mm with each 3-5-sec laser burst. The laser guidewire trajectory was reconfirmed by biplane angiography; adjustment in tip direction, if necessary, was made and the laser reactivated. The support catheter was frequently advanced over the laser guidewire to provide continued support for advancement. The laser guidewire was occasionally exchanged for a conventional wire, allowing the support catheter to be redirected; the laser guidewire was then re-introduced.

Laser guidewire entry through the distal aspect of the total occlusion and into the distal vessel was characterized by unconstrained advancement within the distal coronary segment without laser activation. With the laser guidewire positioned in the distal artery, the very proximal segment of the wire was cut, converting the device to a 300-cm exchange-length 0.018" wire. Further debulking of the total occlusion was usually carried out with a 1.4-, 1.7-, or 2.0-mm concentric laser catheter (Spectranectics). The laser guidewire was then exchanged, if necessary, over the support catheter for a conventional 0.014" guidewire, and the residual stenosis was further treated with adjunct balloon angioplasty, atherectomy and/or stenting.

DEFINITIONS

Primary laser success was defined as reaching the true lumen of any branch distal to the total occlusion, solely with the laser guidewire, without major complication (myocardial infarction, tamponade, emergency surgery or death). Success was documented by angiographic demonstration of the wire moving freely in the true lumen of the distal coronary segment.

Facilitated laser success was defined as reaching the true lumen of any branch distal to the total occlusion with the combined use of the Prima laser wire and any approved conventional guidewire, without major complication.

Procedure success was defined as device success and final residual stenosis < 50% on visual assessment, following adjunctive angioplasty, atherectomy, and/or stenting, with absence of major complications in hospital (myocardial infarction, need for revascularization of target occlusion during concurrent admission, tamponade, emergency coronary bypass, or cardiac related death).

RESULTS

BASELINE CHARACTERISTICS

A total of 179 patients were enrolled at 14 centers from January 1995-November 1996 (Table I). The mean age was 61 years (range, 38-96 yr). Men comprised 82% of the study group. Previous target

Table I Clinical Characteristics

Number of Patients	179
Age	61 yr (range, 37-96 yr)
Male	147 (82%)
Previous Q wave infarction	87 (49%)
Previous revascularization of target	54 (30%)
CABG	30 (17%)
PTCA	21 (12%)
Stent	2 (1%)
Laser	2 (1%)

lesion revascularization had been attempted in 30%. Nearly half (49%) had had previous transmural myocardial infarction, with 69% of these in the distribution of the target lesion.

LESION CHARACTERISTICS AND LOCATION

The mean angiographic age of total occlusions attempted was 70 wk (± 142 wk) with a clinical estimate of 89 wk (± 159 wk). The range of angiographically demonstrated total occlusions was 2-1,020 wk (Table II). The median angiographic age of occlusion was 14 wk.

The proximal stump morphology (Fig 2) was central in 30%, eccentric in 18%, and blunt in 49%. Major side branches emanated from the proximal stump in 27% of cases.

Nearly half of the total occlusions attempted were in the right coronary artery (44%), a third were in the left anterior descending (35%) and 19% were in the left circumflex coronary artery. The mean reference diameter of treated vessels was 3.0 ± 2.2 mm. The mean length of total occlusion was 18.6 ± 10.4 mm. The origin of collaterals was ipsilateral in 41%, contralateral in 51%, bridging in 23%, and micro-capillary in 4%.

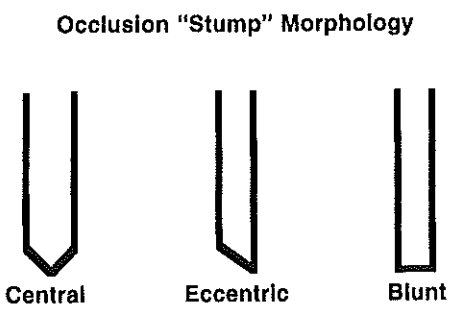


Fig. 2. Proximal "stump" morphology. A:Central. B:Eccentric. C:Blunt

PROCEDURAL RESULTS

Each patient in this study had a total occlusion that could not be crossed after a concerted attempt with conventional mechanical coronary guidewires. The combined use of the Prima laser guidewire and mechanical guidewires resulted in successful crossing of 109 of 179 occlusions (61%) (Table III). Success was greatest in the left anterior descending artery (70%), intermediate in the circumflex artery (62%), and lowest in the right coronary artery (54%). Procedural success appeared to be independent of age of occlusion. Mean age of occlusion in successful cases was

Table II Target Lesion Characteristics (N=176)

Location	
LAD	63 (36%)
RCA	79 (45%)
LCX	34 (19%)
Proximal morphology	
Blunt	87 (50%)
Central	53 (31%)
Eccentric	33 (19%)
Mean age of occlusion (wk)	
Angiographic	70 ± 141 (median 14)
Clinical	89 ± 159 (median 28)
Origin of collaterals	
Ipsilateral	73 (41%)
Contralateral	92 (51%)
Bridging	41 (23%)
Microcapillary	8 (4%)
Proximal Reference Diameter	3.01 mm (± 2.21)

65 wk, as compared to 85 wk in unsuccessful cases (p =NS). The length of the occlusion was clearly related to procedural success. The mean length was 8.6 mm for successful vs. 22.3 mm for failed cases (p = 0.003).

The laser guidewire was used alone in 48 of the 109 successful crossings (44%). A combination of laser guidewire and mechanical guidewires was used to successfully perform the procedure in the remaining cases.

The common causes for failure to cross with the laser guidewire are delineated in Table IV. Misalignment of the wire tip frequently led to recurrent wire exits and the development of multiple false channels. These wire exits, however, did not result directly in clinical sequelae.

Table III Results With Laser Guidewire N=179

Laser wire success	86 (48%)
Facilitated success	23 (13%)
Overall success	109 (61%)
Procedure success	101/109 (93%)
Mean duration of attempt	25 min (range 1-176)
Total procedure time	122 min (range 3-360)

The mean time for laser guidewire application was 25 minutes (range, 1-176 min). The mean procedure time was 122 min (range, 3-360 min).

ADJUNCTIVE TREATMENT

Following successful crossing with the laser guidewire, occlusions were usually further debulked with an excimer laser catheter (1.4-, 1.7-, or 2.0-mm), followed by balloon angioplasty and stenting (Table V). Procedural success was accomplished in 101 of the 109 (93%) occlusions crossed with the laser guidewire. TIMI 3 flow was achieved in 91% of these successful procedures. The mean residual stenosis was 26% (± 34%).

Table IV Common modes of failure to cross with laser guidewire

Misalignment	19%
False route	17%
Wire fracture	1%
Wire stuck	19%
Perforation	27%

COMPLICATIONS

The laser guidewire caused several local complications (Table VI).

Table V Adjunctive percutaneous procedures following laserwire crossing

La (laser guidewire (GW) alone)	3(3%)
LaLa (laser GW, laser angioplasty)	1(1%)
LaBa (laser GW, balloon angioplasty)	18(19%)
LaLaBa (laser GW, laser angioplasty, balloon angioplasty)	15(16%)
LaLaSt (laser GW, laser angioplasty, stent)	3(3%)
LaBaSt (laser GW, balloon angioplasty, stent)	5(16%)
LaLaBaSt (laser GW, laser angioplasty, balloon, stent)	40(42%)
LaRaBa (laser GW, rotational atherectomy, balloon angioplasty)	1(1%)

Coronary spasm was the most commonly encountered local complication. Major dissections were rare (2%). Cardiac rhythm disturbances were not encountered.

Serious adverse events (Table VII) included death in 2 patients (1.1%), and myocardial infarction in 7 patients (3.9%). Cardiac tamponade occurred in 3 patients (1.7%) who were stabilized by catheter drainage of their hemorrhagic effusions.

The two deaths were both related to the procedure. The first occurred in an 85-year-old man. An attempt to open the left anterior descending artery with a laser wire was unsuccessful. During the attempt he developed mild congestive heart failure, which was treated with diuretics. The right coronary artery was then dilated and stented during the same procedure. The combined procedure time was long (2 hr, 49 min) and the patient left the laboratory with early evidence of pulmonary edema. He subsequently deteriorated with renal insufficiency and pulmonary edema. The family requested no intubation or dialysis and he died 5 days after the procedure.

Table VI Minor Complications

Spasm	
Conventional wire	30 (17%)
Laser wire	31 (17%)
Dysrhythmia	
Conventional wire	1 (1%)
Laser wire	0
Minor dissection	
Conventional wire	2 (1%)
Laser wire	6 (3%)
PTCA	4 (2%)
Other	6 (3%)
Major dissection	
Conventional wire	2 (1%)
Laser wire	3 (2%)
PTCA	2 (1%)
Perforation	
Conventional wire	0
Laser wire	24 (13%)
PTCA	1 (1%)

Table VII Major Adverse Events (10 cases- 6%)

Myocardial Infarction	7 (3.9%)
Tamponade	3 (1.7%)
Death	2 (1.1%)

The other death occurred in an 86-year-old man who had successful recanalization of a totally occluded proximal right coronary artery with placement of four 3.5x15 mm Palmaz-Schatz® coronary stents. Subacute stent thrombosis occurred the following day. He was

returned to the laboratory where he received heparin (30,000 units IV), ticlopidine (500 mg), ReoPro® and 60 mg of rTPA. Balloon angioplasty restored flow to TIMI 3. Three hours following the procedure a massive intracranial hemorrhage occurred, leading to coma and death.

DISCUSSION

When introduced 20 years ago, percutaneous transluminal coronary angioplasty (PTCA) was largely limited to concentric noncalcified stenoses in proximal coronary arteries. Although angioplasty of acute total occlusions in the setting of a myocardial infarction was soon promoted by many operators, chronic total occlusions were usually beyond the reach of the initial fixed wire dilatation devices. The advent of independently movable guidewires[1] with the evolution of steerability and variable tip stiffness allowed experienced operators to explore the potential of treating chronic total occlusions with PTCA.

Following improvements in guidewire manufacturing in the early 1980s, numerous single-center reports of total occlusion angioplasty were published.[2-11] Procedural success rates in these reports varied from 40 - 70%. Patient selection and operator experience had a clear impact on the ultimate success of the procedure. Age and length of the occlusion were the most important lesion determinants of procedural success.

Finci et al.[12] clarified the clinical significance of successful transluminal recanalization of totally occluded arteries. At long-term follow-up, successfully treated patients had greater relief of symptoms and performed better on a treadmill workload. There was a lower incidence of surgical revascularization and myocardial infarction in the group with successful PTCA. Melchior et al.[13] have also documented improvement in left ventricular function following successful angioplasty of total occlusions.

The common causes of failure of conventional balloon angioplasty include vessel wall dissection leading to abrupt closure, inability to dilate the lesion, failure to cross with a guidewire, and long-term restenosis. The broad application of intracoronary stents has led to substantial lowering of restenosis rates.[14,15] Stents have, for the most part, obviated the need for emergency surgery by their ability to stabilize dissections. High speed rotational atherectomy (Rotablator®)[16] and excimer laser angioplasty[17] have facilitated treatment of inelastic stenoses resistant to balloon angioplasty. The inability to cross a total occlusion with a guidewire remains one of the few primary modes for angioplasty failure and a common indication for surgical revascularize-

tion.

Mechanical modifications to conventional guidewires have had variable influence on the treatment of chronic total occlusions. Meier et al.[18] and Alleman et al.[19] reported a substantial experience with a blunt-tip, stiff guidewire (Magnum® wire, Schneider Medintag, Zürich, Switzerland). Although apparently useful in the hands of a few operators, the Magnum wire has not been widely adopted. The development of lubricious guidewires with hydrophilic coatings has allowed some operators to cross occlusions that were impassable with non-coated guidewires.[20-24] The general use of these wires has been limited by their propensity to seek subintimal routes and the inability to generate sufficient force in some resistant occlusions.

The potential for use of a laser guidewire in chronic total occlusions was recognized early in the development of lasers for angioplasty. Excimer laser energy is commonly utilized to "debulk" long segments of total occlusions, after successful passage of a mechanical guidewire.[25,26] The delivery of laser catheters, as well as balloon dilatation catheters, stents, and atherectomy devices, is predicated on the successful delivery of the guidewire within the true lumen, distal to the site of total occlusion. It was anticipated that in cases where a guidewire could not pass, a laser guidewire could be used to gain access to the distal vessel and then serve as a "rail" to track these angioplasty devices.

The Prima laser guidewire is the first laser wire prototype to be used for recanalization of refractory total coronary occlusions. The wire is a 0.018" hypotube containing a bundle of flexible optical fibers that transmit laser energy. The laser wire tip can be readily shaped. The hypotube is relatively stiff but retains reasonable torque response. Operating at relatively high fluence (60 mJ/mm^2), the Prima laser guidewire can ablate while traveling through all but the most heavily calcified occlusions.

This "learning phase" study demonstrates the potential of the Prima laser guidewire to successfully cross total occlusions resistant to passage of a conventional guidewire. Over half (61%) of lesions that had been uncrossable with a mechanical wire were retrieved with the adjunctive or stand-alone use of the Prima wire. These results are nearly identical to those from a concurrent European registry of Prima wire use.[27]

The subset of patients with total occlusions of the left anterior descending artery experienced the greatest success with the laser guidewire (70%); this is likely explained by the relatively straight course of the anterior descending artery in the interventricular groove.

Patients with occlusions of the right and circumflex coronary arteries had lower success rates, perhaps related to the curvilinear course of these vessels in the atrioventricular groove.

The age of the occlusion had no significant influence on the success of the laser wire. Excessive length of the occlusion was clearly an impediment, particularly in the atrioventricular groove.

Despite the potential of the laser guidewire to "exit" the native vessel, these wire perforations were almost always benign, without contrast extravasation, pain, or hemodynamic compromise. When "wire exits" were encountered, the laser guidewire was customarily retracted, realigned, and laser advancement continued. The laser wire procedure was most frequently aborted due to an inability to enter into the true distal lumen.

Successful laser wire crossing was followed by adjunctive laser angioplasty, balloon angioplasty, and stenting in the majority of cases. Debulking of the chronic total occlusion with a 1.4-, 1.7-, or 2.0-mm laser catheter was used by most investigators to facilitate balloon angioplasty and stenting. The incidence of restenosis in this study cohort was not determined. Simple balloon angioplasty of chronic total occlusions is followed by a high incidence of restenosis; hence, adjunct stenting was used in virtually all of these patients.

This "learning phase" study confirms the efficacy and safety of a laser guidewire for crossing chronic total occlusions that have been uncrossable with conventional guidewires. The laser guidewire has the potential to convert to success over half the cases of chronic total occlusions that could not be crossed with prevailing wires, including the new generation of hydrophilic coated devices. We emphasize that this aggressive approach to chronic total occlusions does have the potential for serious complication and should be reserved for those patients with compelling indications. Many chronic total occlusions are clinically benign and do not warrant intervention. The economic value of the procedure and durability of the successful results clearly await definition in the context of a controlled clinical trial comparing the laser guidewire with mechanical guidewires.

APPENDIX

Collaborative centers and principal investigators

1. Brigham and Women's Hospital, Harvard Medical School- John Bittl
2. Duke University- James Tcheng
3. Cedars-Sinai Medical Center, Los Angeles-Frank Litvak, Neal Eigler
4. Columbia-Miami Heart Institute- James Margolis, Sameer Mehta, Jorge Bejarano
5. Emory University-Spencer King,

John Douglas, Neal Scott, Ziyad Ghazzal, Douglas Morris

6. Jewish Hospital, Louisville, Kentucky- Ronald Madsen
7. Johns Hopkins Hospital-Jeffrey Brinker, John Resar
8. Lenox Hill Hospital-Jeffrey Moses, Antonio Colombo
9. The Mayo Clinic-David Holmes, Kirk Garratt, Guy Reeder, Peter Berger, Malcom Bell
10. Presbyterian Medical Centerl University of Pittsburgh-Howard Cohen, Conrad Smith, John Power
11. Providence Hospital, Mobile Alabama-Terence Hale,Charles Parrott
12. Stanford University- Stephen Oesterle, Alan Yeung, Simon Stertzer, David Clark
13. University Medical Center, Jacksonville, Florida-Paul Gilmore, Ted Bass
14. Washington Hospital Center, Washington D.C.- Martin Leon, Kenneth Kent, Lowell Satler, Augusto Pichard, Jeffrey Popma
15. Core Angiographic Laboratory Washington Hospital Center, Washington D.C.- Jeffrey Popma, M.D.

REFERENCES

1. Simpson JB, Baim DS, Robert EW, Harrison DC: A new catheter system forcoronary angioplasty. *Am J Cardiol* 1982; 49: 1216
2. Dervan JP, Baim DS, Cherniles J, Grossman W. Transluminal angioplasty of occluded coronary arteries: use of a movable guide wire system. *Circulation* 1983; 68: 776-784
3. Holmes DR, Vlietstra RE, Reeder GS, Bresnahan JF, Smith HC, Bove AA, Schaff HV: Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 31 984; 845-849
4. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W: Elective PTCA of totally occluded coronary arteries not associated with acute myocardial infarction: short-term and long-term results. *Eur Heart J* 1985; 6: 2-12
5. Kereiakes DJ, Selmon MR, McAuley Bj, McAuley DB, Sheehan DJ, Simpson JB: Angioplasty in total coronary occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985; 6: 526-533
6. DiSciascio G, Vetrovec GW, Cowley Mj, Wolgang TC: Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total occlusions. *Am Heart J* 1986; 111: 833-839
7. Melchior JP, Meier B, Urban P, Finci L, Steffenino G,Noble J, Rutishauser W: Percutaneous transluminal coronary angioplasty for chronic total coronary arterial occlusion. *Am J Cardiol* 1987; 59: 535-538

8. Safian RD, McCabe CH, Sipperly ME, McKay RG, Baim DS: Irtitial success and long-term follow-up of percutaneous transluminal coronary angioplasty in chronic total occlusions versus conventional stenoses. *Am J Cardiol* 1988: 23G28G
9. Ruocco NA, Ring ME, Holubkov R, Jacobs AK, Detre KM, Faxon DP. Results of coronary angioplasty of chronic total occlusions (The National Heart Lung and Blood Institute, 1985-1986 Percutaneous Transluminal Angioplasty Registry) *Am J Cardiol* 1992; 69: 69-76
10. Ivanhoe Rj, Weintraub WS,Douglas JS, Lembo NJ, Furman M, Gershony G, Cohen CL, King SB Ill: Percutaneous transluminal coronary angioplasty of chronic total occlusions: primary success, restenosis, and long-term clinical follow-up. *Circulation* 1992; 85: 106-115,
11. Stone GW, Rutherford BD, McConahay DR, johnson WL, Giorgi LV, Ligon RW, Hartzler GO. Procedural outcome of angioplasty for total coronary occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15: 849-65
12. Finci L, Meier B, Favre J, Righetti A, Rutishauser W. Long-term results of successful and failed angioplasty for chronic coronary artery occlusion. *Am J Cardiol* 1990; 66: 660-62
13. Melchior JP, Doriot PA, Chatelain P, Meier B, Urban P, Finci L, Rutishauser W. Improvement of left ventricular contraction and relaxation synchronism after recanalization of chronic total coronary occlusion by angioplasty. *J Am Coll Cardiol* 1987; 4: 763- 768
14. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331; 496-501
15. Serruys PW, De Jaegere P, Kiemenij F, et al. A comparison of balloon expendable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331: 489-95
16. Maclsaac AI, Bass TA, Buchbinder M, Cowley Mj, Leon MB, Warth DC, Whitlow PL. High speed rotational atherectomy: Outcome in calcified and noncalcified coronary artery lesions. *J Am Coll Cardiol* 1995; 26(3): 73-76
17. Ahmed WA, AI-Anazi MM, Bittl JA. Excimer Laser facilitated angioplasty for undilatable coronary narrowings. *Am J Cardiol* 1996; 78: 1045-1047
18. Meier B, Carlier M, Finci L, Nukta E, Urban P, Niederhauser W, Favre J. Magnum wire for balloon recanalization of chrordc total coronary

occlusions. *Am J Cardiol* 1989;64: 148-154

19. Allemann Y, Kaufmann UP, Meyer Bj, Gunnes P, Urban P, Miilhuaser B, Dorsaz PA, Meier B. Magnum wire for percutaneous coronary balloon angioplasty in 800 total chronic occlusions. *Am J Cardiol*, 1997; 80(5)634-637
20. Hosny A, Lai D, Mancherje C, Lee G: Successful recanalization using a hydrophilic-coated guidewire in total coronary occlusions after unsuccessful PTCA attempts with standard steerable guidewires. *J Intervent Cardiol* 1990;3:225-230
21. Gray DF, Sivanantha UM, Verma SP, Michalis LK, Rees MR: Balloon angioplasty of totally and subtotally occluded coronary arteries: results using the hydrophilic Terumo RadiofocusTm Guidewire (GlidewireTM). *Cathet Cardiovasc Diagn* 1993;30:293-299
22. Freed M, Boatman JE, Siegel N, Safian RD, Grines CK, O'Neill W: Glidewire treatment of resistant coronary occlusions. *Cathet Cardiovasc Diagn* 1993;30:201-204,
23. Zimaraino M, Rasetti G, Vernarucci V, Pagliacci M: Terumo Glidewire: The wire of choice for chronic total occlusion (letter to editor). *Cathet Cardiovasc Diagn* 1995;3:186-188,
24. Corcos T, Favereau X, Funck F, Toussaint M, Guerin Y,Durand P, Bouharaoua T: Coronary angioplasty of chronic total occlusions using a new 0.014" nitinol Glidewire with platinum coil. *J Invas Cardiol* 1997; 9:278-282
25. Bittl JA, Sanborn TA, Tcheng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser coronary angioplasty. *Am J Cardiol* 1992;70: 1533-1539
26. Holmes DR jr, Forrester JS, Litvack F, Reeder GS, Leon MB, Rothbaum DA, Cummins FE, Goldenberg T, Bresnahan JF. Chronic total obstruction and short-term outcome: The excimer laser angioplasty registry experience. *Mayo Clin Proc* 1993; 68:5-10
27. Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E, Mathey D, Sievert H, Rutsch W, Buchwald A, Marco J, Al-Kasab SM, Pizulli L, Hamm C, Corcos T, Reifart N, Hanrath P, Taeymans Y on behalf of the European TOTAL investigators. Recanalization of total coronary occlusions using a laser guidewire (The European TOTAL Surveil-lance Study). *Am J Cardiol* 1997;80:1419-1423

CHAPTER 11

Total occlusion trial with angioplasty by using laser guidewire: the TOTAL Trial

Patrick W. Serruys, Jaap N. Hamburger, Jacques J. Koolen, Jean Fajadet, Michael Haude, Heinrich Klues, Ricardo Seabra-Gomes, Thierry Corcos, Christian Hamm, Luciano Pizzuli, Rudiger Simon, Bernhard Meier, Detlef Mathey, Eckhard Fleck, Patrick Kay, Yves Taeymans, Luc Verhees, Rein Melkert, Yvonne Teunissen

submitted for publication

TOTAL OCCLUSION TRIAL WITH ANGIOPLASTY BY USING LASER GUIDEWIRE: THE TOTAL TRIAL

ABSTRACT

Background-Despite continuous improvement of conventional guidewires for coronary angioplasty, chronic total occlusions remain a true challenge. A novel laser wire (Spectranectics Inc. Colorado Springs, CO) combines mechanical attributes with the ablative energy of the CVX-300 excimer laser to facilitate recanalization of chronic total occlusions. Therefore, a multicenter, randomized trial was performed to assess its safety and efficacy.

Methods and Results-In 18 European centers, 303 patients (age 58.7 ± 9.9 years) with an angiographically documented TIMI 0 flow coronary occlusion (≥ 1 month) were randomized to treatment with either the laser wire (LW, n=144) or conventional guidewires (MW, n=159). The median angiographic age of occlusion was 9 weeks (range 0 – 668). The occlusion length (LW vs. MW) was 18 ± 11 vs. 16 ± 10 mm. The primary end-point of the study was treatment success, defined as reaching the true lumen distal to the occlusion by the allocated wire within 30 minutes of fluoroscopic time: LW vs. MW; 52.8% (n=76) vs. 47.2% (n=75), p = 0.33. The average cumulative success (including crossover to a non-allocated guidewire) was 64.7% (n=196, C.I. 59.3-70.1%). Serious adverse events (death, MI, emergency CABG, tamponade) following the initial guidewire attempt were 0% (LW) and 0.6% (MW) respectively. Angioplasty was successful in 179 patients (91%, LW n=79, MW n=100), followed by stent implantation in 149 (79%). Routine angiographic follow-up was completed in 147 cases (82.1%). Although the absolute loss in MLD at 6 month was larger in the LW group (LW vs. MW; 1.11 ± 0.92 mm vs. 0.80 ± 0.89 mm, p=0.04), the difference in binary restenosis rate (LW vs. MW; 45.5% vs. 38.3 %, p=0.72) or reocclusion rate (25.8% vs. 16.1%, p=0.15) did not reach statistical significance. The one-year clinical follow-up was completed in all patients. At 1, 6 and 12 month, the angina and MACE-free survival was 69%, 35% and 24% (LW) vs. 74%, 40% and 31% (MW).

Conclusions-Although LW technology was safe, the increase in crossing success did not reach statistical significance. Despite a liberal use of stenting, long term results of successful recanalization are still plagued by a high incidence of restenosis and re-occlusion.

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA), recanalization of chronically occluded coronary arteries has been recognized as a true challenge. Consecutive series of patients treated with various guidewire technologies have been reported by a large number of investigators. Typically, the success rates in most reports were less than favorable, the most common reason for failure being the inability to pass a guidewire through the occlusion into the distal true lumen.[1,2] As several reports have demonstrated the clinical relevance of successful recanalization of occluded coronary arteries,[3-8] further exploration and improvement of percutaneous techniques seemed justifiable. As a result, a laser wire (LW), the Spectranetics Prima Coronary Total Occlusion System Model 018-003 (Spectranetics, Colorado Springs, CO) was developed. Following a single center pilot-study,[9] and the European- and US multicenter registries,[10,11] a multicenter randomized controlled clinical trial was performed. Here we report on the final results of the randomized trial.

METHODS

PATIENT SELECTION

From May 1995 until June 1997, a multicenter randomized controlled clinical trial was conducted in 18 European centers. A total of 303 patients with angina and/or objective evidence of ischemia and a TIMI 0 flow[12] occlusion, older than 4 weeks, as proven with prior coronary angiography, were included in the study. Angiographic exclusion criteria consisted of: less than Rentrop Classification[13] Grade 2 visualization of the distal lumen via collaterals; an occluded ostium of the right coronary artery or the main stem of the left coronary artery; a non-visible entry point of the target lesion; more than one anatomical curve expected within the missing segment of the vessel; or angiographic evidence of thrombus in the target occlusion. The study had the approval of the local Ethical Review Committees. Written informed consent was obtained from all patients enrolled in the study.

STUDY DESIGN AND ENDPOINTS

The primary objective of the study was to evaluate the safety and efficacy of crossing a chronic coronary total occlusion using the laser wire as compared to "conventional" mechanical guidewires. The primary endpoint was treatment success, defined as reaching the true lumen of any branch distal to the occlusion within 30 minutes of fluoroscopic time. This had to be angiographically documented by an antegrade or retrograde filling of the distal segment showing the tip of the wire in the true lumen. In case of failure, the study protocol

allowed for a crossover to the non-allocated guidewire for a second attempt. The duration of the additional attempt was also restricted to 30 minutes of fluoroscopic time. Finally, the protocol allowed for a third attempt, re-using the allocated guidewire. Clinical follow-up was performed at 1, 6 and 12 months. Routine angiographic follow-up of those patients who underwent successful angioplasty was carried out at the 6-month visit. Diagnostic angiography before the procedure, after the procedure and at the 6-month follow-up was performed according to standard angiographic acquisition procedures for quantitative analysis.[14]

SECONDARY OBJECTIVES

Secondary objectives were to establish the safety and efficacy of the laser wire compared to mechanical guidewires within 1, 6 and 12 months after the initial crossing and adjunctive angioplasty; to investigate the efficacy and safety of crossover treatment after initial unsuccessful attempt with the allocated guidewire; to investigate within 6 months after treatment the event-free survival rate, the anginal status, the target vessel patency and restenosis of the recanalized target vessel; to investigate within 12 months after treatment the event-free survival rate and anginal status; and to explore resource utilization of the procedure, which consisted of procedure time, procedure related materials (catheters, angioplasty devices and contrast medium used) and length of hospital stay.

DEFINITIONS

Procedural success was defined as an average diameter stenosis of less than 50% in 2 orthogonal views. Clinical success was defined as procedural success without death, myocardial infarction, coronary bypass surgery, tamponade or repeat angioplasty during the index hospital stay. Safety was evaluated on the occurrence of perforation of the vessel wall, defined as leakage of contrast dye into the pericardial space, or tamponade necessitating either medical treatment, pericardiocentesis with drainage or thoracotomy. MACE-free survival was defined as freedom from cardiac death, myocardial infarction, or revascularization of the target vessel (PTCA and/or CABG). All deaths were considered cardiac unless otherwise documented. All myocardial infarctions were counted as events, whether or not they occurred in association with angioplasty or CABG. A positive diagnosis of myocardial infarction was made if one of the following ECG or enzyme criteria was met: development of new abnormal Q-waves not present on the patient's baseline ECG (i.e. before randomization), enzyme changes defined by more than twice the upper limit of normal of

creatine kinase and the presence of creatine kinase MB (i.e. greater than the upper normal limit for the appropriate laboratory). A non Q-wave myocardial infarction was defined as enzyme changes defined by more than twice the upper limit of normal of creatine kinase and the presence of creatine kinase MB (i.e. greater than the upper normal limit for the appropriate laboratory) without the development of new abnormal Q-waves. Elective repeat angioplasty or CABG during follow-up was preceded by an exercise tolerance test showing anginal complaints and/or objective evidence of ischemia. In addition, coronary angiography was performed to indicate a diameter stenosis of greater than 50% (visual assessment).

TREATMENTS

The laser wire consisted of a 0.018" shapeable guidewire containing 12 silica fibers with a 45-micron diameter. The supplied support catheter had a 2.5 French tapered tip providing additional coaxial back-up support. The guidewire was designed to function as an exchange guidewire. The laser was the Spectranetics CVX 300 XeCl excimer laser. The fluence typically used during a laser wire procedure was 60 mJ/mm^2, with a pulse repetition rate of 25 Hz. On encountering resistance with the guidewire, the laser was activated in pulse trains for a maximum of 5 seconds. During laser activation, the laser wire was advanced at a rate of approximately 1-mm per second, usually during a simultaneous injection of contrast medium in the contra lateral coronary artery, if applicable. Simultaneous biplane right and left coronary angiography was recommended to assess the alignment of the laser wire with the segment to be crossed. Whenever the laser wire encountered intraluminal resistance during laser activation (for instance in more calcified lesions) the pulse repetition rate was increased to 40 Hz thus increasing the ablation rate. The choice of mechanical guidewire was left to the discretion of the investigators with the following exceptions: rotational mechanical devices (e.g. Rotacs) or fixed wire-balloon systems (e.g. Omniflex, which did not allow for a stepwise debulking). The type of adjunctive angioplasty was also left up to the discretion of the investigator.

DATA MANAGEMENT AND TRIAL ORGANIZATION

Cardialysis, based at Rotterdam, the Netherlands, was the Data Coordinating Center. The randomization procedure was pre-defined and the balance between treatments within the centers was obtained by randomizing in blocks. Patients were randomized through a Central Telephone Allocation Service, which was provided with a complete randomization list before recruitment of

the first patient. An independent Angiographic Core Laboratory, based at Cardialysis, was responsible for confirming all angiographic components of the primary and secondary endpoints and for the quantitative analysis of the post-procedure and 6 month follow-up angiograms. Compliance with the angiographic criteria was assessed by the Angiographic Core Laboratory and adjudicated by an Angiographic Committee that was not blinded for the treatment assignment. Protocol violations were documented as such.

POWER CALCULATIONS AND STATISTICAL ANALYSIS

The power calculations were based on a success rate of 60% in the mechanical wire treated patients and a type I error level of 0.05 (two-sided). With 320 patients, the trial had a power of 91% to detect an increase in success rate to 77.5% in the laser wire treated group, and a power of 79% to detect an increase to 75%. The Data Safety Monitoring Committee (DSMC) reviewed the efficacy and safety data after one hundred and sixty patients had been enrolled in the study. Two types of statistical analysis were prespecified according to the protocol and study design. The first analysis included all randomized patients (intention to treat analysis). The second analysis included only those patients who actually fulfilled the angiographic inclusion and exclusion criteria of the study (per protocol analysis). Continuous variables were tested with the Student's t-test. For categorical variables the chi-square test (without continuity correction) was used. Event-free survival distributions were estimated according to the Kaplan-Meier method and tested with the Log-Rank test. As there was only one primary endpoint, no correction for multiple comparisons was made.

RESULTS

Between March 1995 and June 1997 a total number of 303 patients were randomized in 18 European centers. The enrolment per center was ≤10 patients in 7 centers, 11-20 patients in 6 centers and 20-50 patients in 5 centers. The baseline demographic and lesion characteristics are shown in Table 1. The majority of patients had stable angina (73%), while 56% had suffered from a previous myocardial infarction. The median angiographic age of occlusion was 9 weeks in both study arms (Fig 1). According to the clinical history the median occlusion age was 30 weeks for the laser wire and 20 weeks for the mechanical guidewire arm. The occlusion length as determined by QCA was 18 ± 11 mm in the laser wire group (range 5-58 mm) and 16 ± 10 mm (range 4-63 mm) in the mechanical guidewire group. During the first attempt, a large

TABLE 1 - PATIENT DEMOGRAPHICS AND LESION CHARACTERISTICS

	LASER (n = 144)	MECHANICAL (n = 159)
Male	122 (84.7%)	126 (79.2%)
Mean age	58.6 ± 9.3 years	58.7 ± 10.4 years
Prior MI	84 (58.3%)	86 (54.1%)
Prior CABG	14 (9.7%)	8 (5.0%)
Prior PTCA	34 (23.6%)	38 (23.9%)
Hypertension	61 (42.4%)	57 (35.8%)
Diabetes	22 (15.3%)	21 (13.2%)
Multivessel Disease	71 (49.3%)	65 (40.9%)
Smoking		
Never	49 (34.0%)	54 (34.0%)
Previously	62 (43.1%)	70 (44.0%)
Still smoking	33 (22.9%)	35 (22.0%)
Family history of CAD	48 (33.8%)	54 (34.2%)
Anginal status		
No angina	21 (14.6%)	25 (15.7%)
Unstable	17 (11.8%)	19 (11.9%)
Stable	106 (73.6%)	115 (72.3%)
CCS Class 1	7 (4.9%)	10 (6.3%)
Class 2	58 (40.3%)	50 (31.4%)
Class 3	50 (34.7%)	65 (40.9%)
Class 4	8 (5.6%)	9 (5.7%)
Distribution vessel		
RCA	72 (50.0%)	77 (48.4%)
LAD	58 (40.3%)	59 (37.1%)
LCX	14 (9.7%)	23 (14.5%)
Stump morphology		
Blunt stump	64 (44.4%)	65 (40.9%)
Central funnel	45 (31.3%)	59 (37.1%)
Eccentric	35 (24.3%)	35 (22.0%)
Major side branch from stump	79 (54.9%)	61 (38.4%)
Micro Capillary Refill	22 (15.3%)	29 (18.2%)
Occl. Length (Vis. Assess.)		
< 10 mm	17 (11.9%)	25 (15.8%)
10 - 20 mm	73 (51.6%)	67 42.4%)
21 - 30 mm	31 (21.5%)	48 (30.4%)
31 - 40 mm	14 (9.8%)	12 (7.6%)
> 40 mm	8 (5.6%)	6 (3.8%)

variety of wires with different mechanical properties were used. They were grouped in 3 categories of stiffness: soft (42%), intermediate (29%) and stiff (29%). For both study arms the total amount of contrast (LW vs. MW: 517 ± 244 ml vs. 492 ± 262 ml, p=0.28), the total fluoroscopic time (42 ± 26 min vs. 41 ± 26 min, p=0.84) and the overall procedural time (172 ± 87 min vs. 164 ± 102 min, p=0.25) were comparable. The duration of hospital stay was shorter in the mechanical guidewire group (LW vs. MW: 4.6 ± 3.7 days vs. 4.0 ± 4.9 days, p=0.03).

In Table 2, the crossing success in the laser wire group and the mechanical guidewire group are listed according to an intention to treat analysis. The difference in primary success rate between the laser wire and the mechanical wire (treatment success) did not reach statistical significance (53% vs. 47%, p = 0.33). The procedure was discontinued after a failed initial attempt in 17% (LW) and 11% (MW) of cases. The reasons for failure with the allocated wire are listed in Table 3. The most frequent reason for failure observed in the laser group was misalignment (10.8%) and false route tracking (15.1%), whereas in the mechanical group the most common reason for failure was non-progression of the wire (29.6%). Guidewire perforation was seen in a similar proportion of cases in both study arms (7.2% for LW vs. 8.8% for MW). The rate of perforation in the entire patient cohort (successful and unsuccessful) was 14% (LW) and 10% (MW). A second attempt using the non-allocated guidewire was performed in 31% (LW) and 42% (MW). The success

rate of an additional attempt after crossover to the laser wire was 45% (30 out of 66), while in the initially laser-treated group the success rate after crossover to a mechanical guidewire was 27% (12 out of 44, p = 0.054). A third attempt using the initially allocated guidewire was performed in 3% (LW) and 5% (MW). The overall success rate after the third attempt was 63% in the laser group and 66% in the mechanical group (p=0.61). The average cumulative success rate combining the sequential use of LW and MW was thus 65% (198/303, C.I. 59.3-70.1%), compared to 47% (75/159, C.I. 39.4-54.9%) with the use of mechanical guidewires

TABLE 2 - TREATMENT SUCCESS

	ITT				
	LW		MW		
	n	%	N	%	P
1st attempt	144	100	159	100	
Success	76	53	75	47	0.33
Failure	68	47	84	53	
No 2nd attempt	24	17	18	11	
2nd Attempt	44	31	66	42	
Success	12	8	30	19	0.05
Failure	32	22	36	23	
No 3rd attempt	27	19	28	18	
3rd attempt	5	3	8	5	
Success	3	2	0	0	0.04
Failure	2	1	8	5	
Success 1,2,3	91	63	105	66	0.61
Failure 1,2,3	53	37	54	34	

TABLE 3 - REASONS FOR FAILURE OF 1ST ATTEMPT AS ASSESSED BY THE INVESTIGATOR

	LASER (n = 144)	MECHANICAL (n = 159)	P
Misalignment (Incongruence of wire axis and target vessel axis)	14 (9.7%)	1 (0.6%)	<0.001
Wire Stuck (No progression of wire despite mechanical manipulation)	9 (6.3%)	47 (29.6%)	<0.001
False Route (subintimal tracking)	21 (14.6%)	14 (8.8%)	0.12
Perforation (extravasation of contrast)	10 (6.9%)	14 (8.8%)	0.55
Insufficient support Guiding Catheter	0 (0.0)	1 (0.6%)	1.00
Other	10 (6.9%)	6 (3.8%)	0.22
Unknown	4 (5.9%)	1 (1.2%)	0.17

only. In the laser wire group, following successful recanalization in 91 patients, angioplasty was successful in 79. In the mechanical guidewire group, angioplasty was successful in 100 out of 105 patients following successful guidewire crossing. As a result, clinical success was achieved in 51% (LW) and 60% (MW) respectively (p=0.12).

LONG TERM CLINICAL FOLLOW-UP ACCORDING TO RANDOMIZATION

The composite end-point and the itemized events at 400 days (LW vs. MW) are given in Table 4a. The angina- and MACE free survival as shown by the Kaplan-Meier curves in Figure 2 show no significant difference in clinical outcome between the two groups (Log-Rank test: p=0.11, chi-square test: p=0.17).

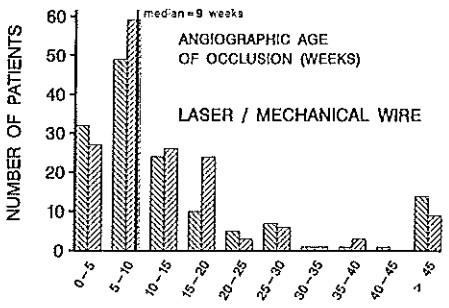


Figure 1 - Distribution of the angiographically documented age of occlusion. The vertical line indicates the median age.

LONG TERM CLINICAL FOLLOW-UP ACCORDING TO SUCCESS OF RECANALIZATION

Table 4b outlines the MACE and anginal status at 12-month follow-up for the patients with successful PTCA vs. unsuccessful PTCA. The angina and MACE free survival as shown by the Kaplan-Meier curves in Figure 2 show that patients with successful angioplasty (n=179) had an angina and MACE free survival rate of 35.2%, while in patients with failed recanalization (n=124) this rate was 17.7% (Log-Rank test: p<0.001, chi-square test: p< 0.001). This significant difference is mainly ascribed to a 33% incidence of surgery in the failed recanalization group. In addition, in the successfully treated group 45.8% of patients were angina free vs. 25% in the failed recanalization group.

ANGIOGRAPHIC ENDPOINTS

Following successful recanalization in 179 patients, routine 6-month angiographic follow-up was performed in 147 (82%). Table 5 describes the result of quantitative angiography measurements. Immediately post-procedure, the MLD in the laser wire group was slightly larger than in the mechanical guidewire group (LW vs. MW: 2.43 ± 0.47 mm vs. 2.34 ± 0.52 mm). However, at follow-up the MLD in the mechanical guidewire group was larger (MW vs. LW: 1.52 ± 0.87 mm vs. 1.30 ± 0.90 mm)

due to a significantly larger loss in the laser wire group (LW vs. MW: 1.11 ± 0.92 mm vs. 0.80 ± 0.89 mm, p=0.04). Consequently the restenosis rate in the laser wire group (45.5%) was slightly, but not significantly higher than in the MW group (38.3%, p=0.38). The re-occlusion rates were 25.8% (LW) and 16.1% (MW, p=0.15), despite a liberal use of stenting in both groups (90% vs. 78%, respectively).

DISCUSSION

STUDY DESIGN AND RELATED ISSUES

The design of this trial was a complex issue and involved consultation with the investigators, the Food and Drug Administration and the sponsor. The reason for the relatively long gestation of the protocol is that the European investigators did not want to conduct a major clinical trial with conventional, clinical end-points without having prior

FIGURE 2 – KAPLAN MEIER CURVES OF EVENT-FREE SURVIVAL

Comparison of groups with Log Rank test:

		LW/MW	S/U
Death/MI/CABG/Re-PTCA	:	0.027	0.17
Death/MI/CABG/Re-PTCA/Angina	:	0.19	<0.001

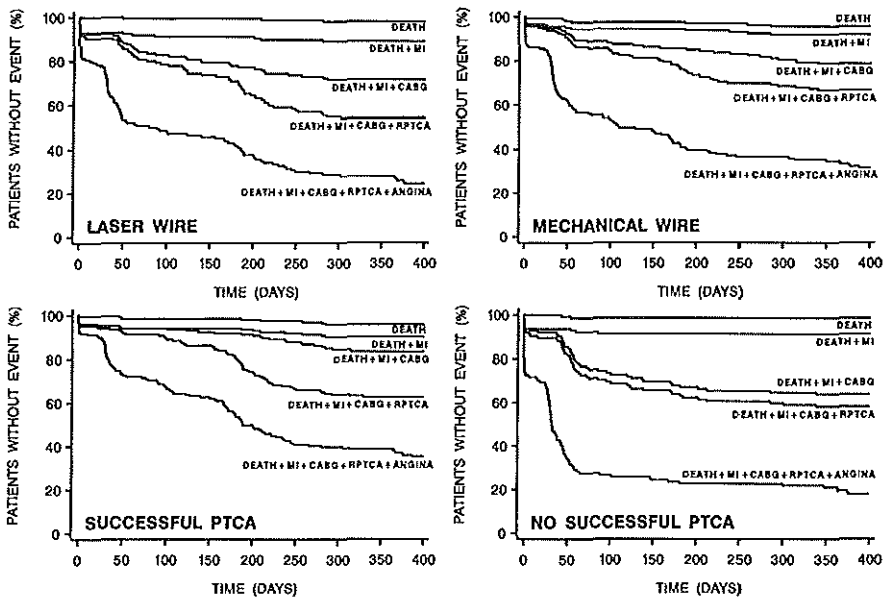


TABLE 4a – EVENTS (NR. OF PATIENTS WITH EVENTS)

	LASER		MECHANICAL		p
	N	%	N	%	
400 days					
Death	3	2.1	7	4.4	0.26
MI	13	9.0	8	5.0	0.17
- Q-wave	1	0.7	5	3.1	0.22
- non Q-wave	12	8.3	3	1.9	0.0098
CABG	30	20.8	23	14.5	0.15
RePTCA	34	23.6	27	17.0	0.15
No MACE	78	54.2	106	66.7	0.026
Angina	91	63.2	99	62.3	0.87
Angina + Event free	35	24.3	50	31.4	0.17

TABLE 4b – EVENTS (NR. OF PATIENTS WITH EVENTS)

	PTCA success		PTCA failure		P
	N	%	N	%	
400 days					
Death	8	4.5	2	1.6	0.17
MI	11	6.1	10	8.1	0.52
- Q	3	1.7	3	2.4	0.69
- non Q	8	4.5	7	5.6	0.64
CABG	12	6.7	41	33.1	<0.001
RePTCA	51	28.5	10	8.1	<0.001
No MACE	112	62.6	72	58.1	0.43
Angina	97	54.2	93	75.0	<0.001
Angina + Event free	63	35.2	22	17.7	<0.001

evidence of the technical superiority of the new laser wire. Therefore, a technical, device related primary end-point was chosen. Secondly, the investigators did not want to see their patients denied the potential benefit of a cross-over design allowing the use of a laser wire in case of a failure with a mechanical guidewire, or vice versa. As a consequence of a cross-over design, the short, medium, and long-term outcome would not reflect the initial intention to treat with an allocated guidewire, but would reflect the clinical outcome of a recanalization procedure obtained either with a laser wire, a mechanical wire or a combination of both. A intention to treat analysis was only applied during the first 30 minutes of fluoroscopic time. From a strict point of view, the trial was inconclusive, as the difference in primary treatment success did not reach statistical significance. A per protocol analysis (excluding specific angiographic violation criteria) prospectively described in the trial design also failed to show a significant difference (p=0.10). However, we must acknowledge, that a catheter laboratory without "laser capabilities" would have only achieved a crossing success rate of 47%, while a laboratory having at its disposal a laser wire would have a cumulative success rate of 65%. Since the ultimate success rate in both arms was similar, an additional attempt with the laser wire only after a failed attempt with conventional wires would be more cost–effective than a primary attempt with the laser wire. It should be emphasized that in terms of clinical outcome a composite end-point of death, MI, CABG and re-PTCA may not reflect the true clinical benefit of a successful versus a failed attempt at recanalization. The outcome of a failed recanalization may be accepted and may not result in an event (e.g. revascularization) although the patient remains symptomatic; conversely a failed recanalization may be followed by a surgical revascularization (event) with as a consequence

TABLE 5 – Quantitative Coronary Angiography

	LASER (n=79/66)	MECHANICAL (n=100/81)	P
Ref. Diameter (mm):			
Post	3.06 ± 0.45	3.01 ± 0.50	0.50
FUP	2.88 ± 0.50	2.97 ± 0.56	0.41
MLD (mm):			
Post	2.43 ± 0.47	2.34 ± 0.52	0.19
FUP	1.30 ± 0.90	1.52 ± 0.87	0.13
Absolute loss (mm):	1.11 ± 0.92	0.80 ± 0.89	0.04
Diameter stenosis (mm):			
Post	20.5 ± 8.1	22.5 ± 10.1	0.15
FUP	54.8 ± 29.6	48.8 ± 26.3	0.20
Restenosis ≥50 %, <100%	13 (19.7%)	18 (22.2%)	0.71
Re-occlusions FUP	17 (25.8%)	13 (16.1%)	0.15
Restenosis / re-occlusion	30 (45.5%)	31 (38.3%)	0.38

alleviation of angina pectoris. An initially successful recanalization may result in the medium-term in a restenotic lesion with resurgence of angina necessitating a reintervention. Therefore, the angina and event-free survival rate was considered as a secondary end-point.

SAFETY ISSUES

Despite sometimes multiple attempts at recanalization, there was no incidence of death, emergency CABG or tamponade. However, extravasation of contrast dye was seen in 13.8% of the laser wire group and 10.1% in the mechanical group. The most frequent reasons for laser wire failure were false route tracking (15.1%) and misalignment (10.8%), while the most common reason for failure in the mechanical wire group was absence of wire progression despite mechanical manipulation (LW vs. MW, 6.5% vs. 29.6%. p=<0.001). This difference is presumably related to the ablative properties of the laser wire. Post-procedure, the incidence of cardiac enzyme leak was not significantly different for both groups (CK>2 x upper limit of normal LW vs. MW 7.8% vs. 3.6%, p=0.14). Thus, the additional ability to recanalize a chronic total occlusion with a laser wire was not at the cost of an increased risk of complications.

ANGIOGRAPHIC FOLLOW-UP

Despite a liberal use of stents (79%), the reocclusion rate for the entire study population was 20.7%. The restenosis and reocclusion rates were comparable in both study arms. The main reason for not stenting a recanalized lesion was ascribed to a combination of small vessel size (PTCA vs. stent, reference diameter post procedure 2.65 mm vs. 3.13 mm, $p<0.01$) and a low post-balloon angioplasty residual diameter stenosis (27%). Indeed, from previous studies we have learned that "stent-like balloon angioplasty" results in a 6-month angiographic outcome comparable to post-stenting.[15-18] The percentage of reocclusion was comparable to reocclusion rates for chronic total occlusions as previously reported in the literature.[19,20] As it has been suggested that reocclusion occurs early in the course of follow-up, this could potentially be prevented by an aggressive policy of anticoagulant and antiplatelet treatment.[21]

LONG TERM FOLLOW-UP AND CLINICAL BENEFIT

LASER WIRE VS. MECHANICAL WIRE

This study was not designed and powered to detect differences in clinical outcome at 6 or 12 months. However, a sub-analysis of the follow-up results could be helpful in understanding the specific clinical problems related to the pathology of chronic total coronary occlusions. The freedom-from-MACE curves (Fig 2) indicated that the laser wire arm had a significantly lower MACE free survival at one year ($p=0.026$). This difference resulted from a higher incidence in the LW group of MI, CABG and re-PTCA without an increase in the incidence of mortality (LW vs. MW, 2.1% vs. 4.4%, $p=0.26$). However, the freedom from MACE and angina at 1 year was similar for both groups (LW vs. MW, 24.3% vs. 31.4%, $p=0.17$).

SUCCESS VS. FAILURE

The freedom from MACE at one-year (Fig 2) did not differ for either successful or failed recanalization. This seemingly lack of treatment efficacy was explained by an increased incidence of early CABG in the failed group (success vs. failure, 12/179 (6.7%) vs. 41/124 (33%), $p<0.001$) and a higher incidence of late re-PTCA in the successful group (success vs. failure, 51/179 (28.5%) vs. 10/124 (8.1%), $p<0.001$). As a result of vessel patency at one year (79.6%) the incidence of combined CABG and re-PTCA was lower in the successful PTCA group (success vs. failure, 56/179 (31.3%) vs. 49/124 (39.5%, $p=0.14$). The difference in freedom from MACE and angina until 1 year was statistically significant (success vs. failure, 35.2% vs. 17.7%, $p<0.001$). Also, the percent-

age of angina-free patients at 12 months was higher in the successful group (success vs. failure, 65% vs. 53%, p=0.02). With regard to CCS classification, those patients following successful recanalization fared better (Wilcoxon RS: p=0.023, chi-square test: p=0.04, Table 6). Following failed recanalization, the incidence of angina at 12 months in those patients undergoing surgery was 23.1%. In contrast, 58.2% of patients

TABLE 6 – Anginal status at 12 months, successful vs. unsuccessful PTCA

	PTCA SUCCESS	PTCA FAILURE
Angina free	111 (65.3%)	63 (53.4%)
Angina CCS Class I	23 (13.5%)	18 (15.3%)
II	27 (15.9%)	23 (19.5%)
III	9 (5.3%)	13 (11.0%)
IV	0	1 (0.9%)

p=0.02 Wilcoxon RS. Angina y/n p=0.04 X²

not referred to CABG were symptomatic (CABG vs. no CABG, 9/39 vs. 46/79, p<0.001). This would favor a policy of consequent referral for elective CABG following a failed percutaneous attempt at recanalization.

CONCLUSIONS

Although laser wire technology was safe, the increase in crossing success did not reach statistical significance. However, as the protocol allowed for crossover, the combined use of both laser wire and mechanical guidewire technology increased the success rate from 47.2% (C.I. 39.4-54.9%, MW only) to 64.7% (C.I. 59.3-70.1%, LW + MW). At 1 year, the clinical outcome (MACE-free) was approximately 60%, which is inferior to long term outcome of PTCA of patent stenotic lesions of similar length. Successful recanalization resulted in an event-free survival of 63% with an incidence of 7% CABG and with 46 % of patients remaining asymptomatic, whereas failed recanalization had a 58% event-free survival with an incidence of 33% of CABG and with 25% of the patients remaining asymptomatic. Long-term results of successful recanalization are still plagued by a high restenosis (20.5% excluding re-occlusions) and reocclusion rate (20.4%) despite a liberal use of intracoronary stents. Taking in to account a rapid progress of mechanical guidewire technology, further improvement in laser wire technology (steerability, lubricity, diameter reduction and guidance system) is warranted in order to render this technology more efficacious.

REFERENCES

1. Hamburger JN, de Feyter PJ, Serruys PW.The laser wire experience: "crossing the Rubicon". In: Seminars in *Interventional Cardiology*; 1996;1/2:163-171
2. Puma JA, Sketch MH Jr, Tcheng JE, Harrington RA, Philips HR, Stack RS, Califf RM. Percutaneous revascularization of chronic coronary occlusion: an overview. *J Am Coll Cardiol* 1995;26(1):1-11

3. Holmes DR, Vlietstra RE, Reeder GS, Bresnahan JF, Smith HC, Bove AA, Schaff HV. Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 1984;3:845-849
4. Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB. Angioplasty in total coronary artery occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985;6:526-533
5. DiScascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for sub acute and chronic total coronary occlusion. *Am Heart J* 1986;111: 833-839
6. Finci L, Meyer B, Favre J, Righetti, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary artery occlusion. *Am J Cardiol* 1990;66: 660-2
7. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W, Jaski B, Hugenholtz PG. Elective P.T.C.A. of totally occluded coronary arteries not associated with acute myocardial infarction; short-term and long-term results. *Eur Heart J* 1985;6:2-12
8. Stone GW, Rutherford BD, McConahay DR, Johnson Jr. WL, Giorgi LV, Ligon RW, Hartzler GO. Procedural outcome of angioplasty for total coronary artery occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15: 849-65
9. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser wire: a pilot-study. *J Am Coll Cardiol*, 1997;30:649-56
10. Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E, Mathey D, Sievert H, Rutsch W, Buchwald A, Marco J, Al Kasab S, Pizzuli L, Hamm C, Corcos Th, Reifart N, Hanrath P, Taeymans Y. Recanalization Of Total Coronary Occlusions Using a Laser Guide Wire: The European TOTAL Surveillance Study. *Am J Cardiol* 1997;80:1419-1423
11. Oesterle SN, Bittl JA, Leon MB, Hamburger J et. al. for the U.S. TOTAL investigators. Laser wire for crossing total occlusions-"learning phase" results from the U.S. TOTAL Trial. *Cathet Cardiovasc Diagn* 1998; 44:235-243
12. The TIMI Study group. The Thrombolysis in Myocardial Infarction Group (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985; 31:932-936.
13. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden con-

trolled coronary artery occlusion in human subjects: a prospective study. *Circulation* 1986;74(3):469-76

14. Reiber JHC, Serruys PW (Eds). *Advances in quantitative coronary arteriography*, 1993, Kluwer Academic Publishers.
15. Serruys PW, Di Mario C, Piek JJ, Schroeder E, Vrints C, Probst P, de Bruyne B, Hanet C, Fleck E, Haude M, Verna E, Voudris V, Geschwind H, Emanuelson H, Muhlberger V, Danzi G, Peels HO, Ford AJ Jr, Boersma E. Prognostic value of intra coronary flow velocity and diameter stenosis in assessing short- and long-term outcomes of coronary balloon angioplasty: the DEBATE study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation* 1997;96(10):3369-77
16. Haase KK, Athanasiadis A, Mahrholdt H et al. Acute and one year follow-up results after vessel size adapted PTCA using coronary ultrasound. *Eur Heart J* 1998; 19(2): 263-72.
17. Narins CR, Holmes DR Jr, Topol EJ. A call for provisional stenting: the balloon is back. *Circulation* 1998;97(13):1298-305
18. Foley DP, Serruys PW. Provisional stenting - stent like balloon angioplasty: evidence to define the continuing role of balloon angioplasty in percutaneous revascularization. *Semin Interv Cardiol* 1996;1(4):269-73
19. Sirnes PA, Gol S, Myreng Y, Molstad P, Emanuelson H, Albertsson P, Brekke M, Mangschau A, Endressen K, Kjekshus J. Sten-ting in Chronic Coronary Occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;28 (6):1444-51
20. Hancock J, Thomas MR, Holmberg S, Wainwright RJ, Jewitt DE. Randomised trial of elective stenting after successful percutaneous transluminal coronary angioplasty of occluded coronary arteries. *Heart 1997;* 79(1):18-23
21. The EPISTENT Investigators. Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998; 352: 87-92

LIST OF INVESTIGATORS

1. Dr. J.Ernst, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands
2. Dr. J.N. Hamburger, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands
3. Prof. P.W. Serruys, Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam, The Netherlands

4. Dr. H.W.M. Plokker, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands
5. Dr. J.J. Koolen, Catharina Ziekenhuis, Eindhoven, The Netherlands
6. Dr. Y. Taeymans, Universitair Ziekenhuis Gent, Gent, Belgium
7. Dr. Th. Corcos, C.M.C. Parly Grand Chesnay, Le Chesnay, France
8. Dr. J. Fajadet, Clinique Pasteur, Toulouse, France
9. Prof. R. Erbel, Universitätsklinikum für Innere Medizin, Essen, Germany
10. Prof. dr. E. Fleck, Deutsches Herzzentrum Berlin, Berlin, Germany
11. Prof. C.W. Hamm, University Hospital Eppendorf, Hamburg, Germany
12. Prof. P. Hanrath, Medizin. Einrichtungen der RWTH Aachen, Aachen, Germany
13. Dr. M. Haude, Universitätsklinikum für Innere Medizin, Essen, Germany
14. Prof. dr. D. Mathey, Prof. J. Schofer & Partner, Hamburg, Germany
15. Dr. L. Pizzulli, Medizinische Universitätsklinik, Bonn, Germany
16. Prof. Dr. W. Rutsch, Univ. Klin. Charité der Humboldt Univ., Berlin, Germany
17. Prof. R. Simon, Christian Albrechts Universitätsklinik, Kiel, Germany
18. Prof. R. Seabra-Gomes, Hospital de la Santa Cruz, Linda-a-Velha, Portugal
19. Prof. B. Meier, Medizinische Universitätsklinik, Bern, Switzerland
20. Dr. Ch. Ilsley, Harefield Hospital, Uxbridge, United Kingdom

MEMBERS OF THE STEERING COMMITTEE

Prof. dr. P.W. Serruys, Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam, The Netherlands
Prof. dr. E. Fleck, Deutsches Herzzentrum Berlin, Berlin, Germany
Dr. J.J. Koolen, Catharina Ziekenhuis, Eindhoven, The Netherlands

CHAPTER 12

Recanalization of chronic total coronary occlusions using a laser guidewire: long-term follow-up

Jaap N. Hamburger, David P. Foley, Pim J. de Feyter,

Alexander J. Wardeh, Patrick W. Serruys

Accepted for publication, Journal of the
American College of Cardiology

RECANALIZATION OF CHRONIC TOTAL CORONARY OCCLUSIONS USING A LASER GUIDEWIRE: LONG-TERM FOLLOW-UP

ABSTRACT

Objectives-In this study, we report the long-term follow-up of patients with a laser guidewire attempt at recanalization of a chronic total coronary occlusion (CTO).

Methods-All patients with a CTO eligible for coronary artery bypass surgery (CABG) and a laser guidewire attempt at recanalization were prospectively evaluated. Routine follow-up angiography was performed at six months. Patients were seen at 30 days, six months and one year. Subsequently, patients were contacted by telephone annually for recording of irreversible adverse events (death, cerebro-vascular stroke, myocardial infarction (MI)), revascularization events (CABG, re-PTCA), anginal status and current medication.

Results-The study population comprised 101 patients with 103 occlusions of median 30 weeks duration (range 6 – 884 weeks) who completed ≥one year of clinical follow-up. The occlusion length was 22 ± 13 mm (mean ± SD). Laser guidewire crossing was successful in 61 patients (63 occlusions, 61.2%). Procedural success was achieved in 55 patients (57 occlusions). Sub-acute reocclusion <24 hours occurred in 3 patients, re-PTCA was successful in two. Following a failed attempt at recanalization (n=46), elective CABG was performed in fourteen patients. During follow-up, one patient died of carcinoma. Angiographic follow-up was completed in 51 of 53 eligible patients (96.2%) showing reocclusion in ten, and significant restenosis (>50% DS) in an additional seven patients (combined recurrence rate of 33.3%). During the remainder of the study, clinical recurrence occurred in six additional cases. Patients with recurrence of symptoms (n=23) had either re-PTCA (n=8), CABG (n=10), or were treated medically (n=5). As a result, revascularization was performed in 62 patients (PTCA, n=38 or CABG, n=24, group A), while medical therapy was the preferred regimen in the remaining 38 (group B). Referral for CABG was influenced by pre-procedural vessel size (reference diameter, mean ± SD; CABG vs. no CABG, 2.94 ± 0.52 mm vs. 2.68 ± 0.48 mm, p=0.05) and LAD location (CABG vs. no CABG, 13/24 vs. 6/38, p=0.001, RR 2.67 (95%CI: 1.48-4.85). Clinical follow-up of ≥12 months was completed in all patients, with a median duration of 31.5

months (12 – 54 months). Revascularization resulted in a decrease in irreversible adverse events (A vs. B, 2/62 vs. 7/38, p=0.025, RR 5.71 (95% CI 1.25 – 26.08)), angina classification (CCS classification, A vs. B: 1.26 ± 0.65 vs. 2.13 ± 0.74, p<0.0001) and the need for cardiac medication (number of prescriptions, A vs. B, 2.6 ± 1.3 vs. 3.8 ± 1.2, p<0.0001). Overall, the event free survival of irreversible adverse events following revascularization, was 100% (at 6 months), 100% (at one year) and 97% (at 32.2 ± 12.4 months) respectively.

Conclusion-A combined strategy of percutaneous recanalization and surgical revascularization is superior to medical treatment in the treatment of patients with chronic total coronary occlusion.

Percutaneous transluminal coronary angioplasty (PTCA) for recanalization of chronically occluded coronary arteries has been associated with lower procedural success rates and higher recurrence rates in comparison with PTCA of non-occlusive stenoses.[1-4] However, some reports have indicated clinical benefit from successful recanalization, while more recent studies have stressed the advantage of intra coronary stenting with regard to increased vessel patency and/or reducing restenosis rates.[5-17] Despite a steady progress in new device technology for coronary angioplasty, passage of a guidewire through a chronic total occlusion to the distal coronary bed remains a true technical challenge. Therefore, at the clinical introduction of the Spectranetics laser guidewire (Prima Total Occlusion System, Spectranetics, CO, USA) we prospectively evaluated its additional value within this context. As the initial results of the laser guidewire procedure have been reported previously,[18-23] the emphasis of the current study was on the long-term outcome of laser guidewire facilitated recanalization of chronic total coronary occlusions.

METHODS

STUDY POPULATION

Between August 1993 and July 1998 we prospectively collected the procedural and follow-up data of all patients who underwent a laser guidewire facilitated attempt at recanalization of a chronic total coronary occlusion at the Rotterdam Thoraxcenter. The study protocol had the approval of the University Hospital of Rotterdam Medical Ethics Committee. Written informed consent was obtained from all patients. Patients with acute myocardial infarction (MI) within two weeks prior to the intervention were excluded from this study. Angiographic exclusion criteria were the presence of thrombus, a non-visible entry point of the target lesion (including a flush occlusion of the aorto-coro-

nary ostium) or a less than Rentrop Classification Grade 2 visualization of the distal target lumen. Saphenous vein bypass grafts were excluded as target vessel. Otherwise, lesions which are typically considered to be unfavorable for a mechanical attempt at recanalization (i.e., bridging collaterals, a major side branch originating from the stump of the occlusion, or eccentric stump morphology) were intentionally not excluded. The age of occlusion was assessed by a combination of angiographic data and data from clinical history.

PROCEDURES

The stump morphology was evaluated from the pre-procedural angiogram. Routinely the distal vessel lumen was visualized by a contrast medium injection in the contra lateral coronary artery. The length of occlusion was measured by quantitative coronary angiography (QCA) after visualization of both the occluded stump and the distal lumen by means of a simultaneous bilateral coronary injection at the commencement of the procedure.

LASER EQUIPMENT

The laser guidewire and the technique of the laser guidewire procedure have been described in detail elsewhere.[24,25] In short, the Prima Total Occlusion System consists of a 0.018" guide wire containing 12 silica fibers with a 45-micron diameter and a support catheter providing additional coaxial back-up support. Since its introduction in 1993, the laser guidewire has been subject to a number of technical improvements. It changed from a non-steerable straight wire to a steerable guide wire, designed to function as an exchange wire. The laser was the Spectranetics CVX 300 XeCl excimer laser. The fluence typically used during a laser guidewire procedure was 60 mJ/mm^2, with a pulse repetition rate of 25 Hz. If resistance prohibited laser guidewire progression, the pulse repetition rate was increased to 40 Hz, thus increasing its ablation rate. During pulse trains with a maximum of 5 seconds the wire was gently advanced at a rate of up to 1 mm per second.

ADJUNCTIVE ANGIOPLASTY

Once the intraluminal position of the wire in the distal lumen was confirmed by means of a contrast injection, an adjunctive angioplasty was performed. Typically, this would be a combination of balloon angioplasty and excimer laser coronary angioplasty (ELCA), with or without additional intra coronary stent implantation. Balloon angioplasty was performed using semi-compliant balloons matched 1:1 to the interpolated reference diameter, as measured by on-line QCA. For ELCA, catheter advancement speeds of 0.5 mm/sec

were used, and all cases were performed using the saline flush method.[26] Following stent implantation, high pressure post dilatation (with balloon inflations at >14 atmospheres, using a 1.1:1 balloon artery ratio) was performed to ensure adequate stent deployment, aiming at a <20% residual stenosis. According to treatment protocol, after a successful procedure patients were maintained on a heparin drip for 24 hours, keeping the activated prothrombin time between 60 and 90 seconds. Following stent implantation, patients were treated with Aspirin and Warfarin for six months. As of 1995, Warfarin was replaced by Ticlopidine 250 mg. twice daily for four weeks.

DEFINITIONS

Chronic total occlusion was defined as absence of antegrade flow {Thrombolysis In Myocardial Infarction 0 flow}[27] as visualized by diagnostic angiography and a minimum of two weeks delay between the diagnostic angiogram and the recanalization procedure. Laser guidewire success was defined as angiographic evidence of reaching the true lumen of any branch distal to the occlusion. Procedural success was defined as restoration of TIMI 3 flow and an average diameter stenosis of less than 50% in two orthogonal views by on - line QCA at the end of the procedure. Clinical success was defined as procedural success without death, cerebrovascular stroke, myocardial infarction, coronary bypass surgery, or repeat angioplasty during the index hospital stay. Myocardial infarction was defined as more than twice the upper limit of the serum creatinin, with formation of new Q-waves on the electrocardiogram. Non Q-wave myocardial infarction was defined as more than twice the upper limit of the serum creatinin, in the absence of new Q-waves on the electrocardiogram.

At the time of the six-month follow-up angiography, vessel patency was defined as maintenance of antegrade blood flow in the target vessel. Restenosis was defined as a >50% diameter stenosis, reocclusion as an absence of antegrade flow in a previously successfully recanalized target vessel. The absolute loss in MLD at follow-up (in mm) was defined as post-procedure MLD minus MLD at follow-up. The loss index is the relation of late loss to acute gain and was defined as post-procedure MLD minus MLD at follow-up divided by post-PTCA MLD minus pre-procedure MLD.

For purpose of analysis we divided the study population in two subgroups.

At 1 year following the initial attempt at recanalization patients were in Group A in case of either

- a successful percutaneous recanalization and vessel patency at the 6

month angiographic follow-up, or
- a succesful percutaneous recanalization, target vessel failure at 6 months followed by coronary artery bypass surgery, or
- a failed percutaneous attempt at recanalization followed by coronary artery bypass surgery.

Patients were in group B in case of a failed percutaneous attempt at recanalization, or target vessel failure at 6 month angiographic follow-up without additional coronary artery bypass surgery, who were kept on cardiac medication.

MEASUREMENTS

Serial QCA measurements were made before and after the recanalization procedure and at 6 month follow-up, using an automated edge detection algorithm (CAAS II system, PIE Medical, Maastricht, The Netherlands). The non-contrast filled guiding catheter was used as the calibration standard.[28] The interpolated reference diameter, MLD and percent diameter stenosis (DS%) were calculated in multiple views and are given as the resultant average. The occlusion length was measured in the view with the least amount of foreshortening. Fluoroscopic time, total procedure time and the amount of contrast medium used were recorded. Blood samples for CPK analysis were taken 6 and 12 hours post - procedure.

FOLLOW-UP

A routine follow-up angiography was performed six months after the initial procedure. The decision to perform repeat PTCA was clinically driven. Clinical evaluation included an interview, complete physical examination and electrocardiogram and was performed before hospital discharge, at 30 days, 6 months (two weeks prior to follow-up angiography) and one year after the recanalization procedure. Following the first year, patients were contacted by telephone annually for recording of irreversible adverse events (death, stroke, MI), clinical events (CABG, re-PTCA), anginal status and current cardiac medication. The recorded cardiac medication included, but was not confined to anti-anginal medication. Adverse events were recorded in a ranking order of clinical severity (death, stroke, Q-wave MI, CABG, repeat PTCA or angina). As the purpose of this study was the long-term evaluation following a laser guidewire procedure, only those patients who completed a clinical follow-up of one year or more were included in the current analysis.

STATISTICAL ANALYSIS

Categorical data were presented as frequencies. Continuous data were presented as mean ± SD, or in case of a non normal distribution of values as median with range. Comparisons of continuous

variables were performed using unpaired two-tailed t tests, while comparison of categorical variables was performed using Chi-square or Fisher's exact test, whichever was appropriate. Comparison of medians was performed using a Mann-Whitney test. A multivariate logistic regression analysis using SAS statistical software was performed to identify independent predictors of procedural success and vessel patency at follow-up angiography. Incidents with a p value <0.05 were considered significant.

RESULTS

PROCEDURAL DATA

The data of 101 consecutive patients (103 TIMI 0 flow chronic total coronary occlusions) with a laser guidewire attempt at recanalization were analyzed. The baseline clinical characteristics are given in Table 1. These data confirm that, with the exception of a relatively high percentage of previous myocardial infarction (63.4%), the patient group was representative of current clinical practice with percutaneous angioplasty. In 66 patients (65.4%), an initial attempt at recanalization by using conventional guidewires was per-

TABLE 1. Patient Demographics

		Procedural outcome		Group	
	Total	Success	Failure	A	B
No. of patients	101	55	46	62	38
No. of vessels	103	57	46	64	38
Male	88	46 (84)	42 (91)	53 (86)	34 (90)
Age, y	57 ± 9	57 ± 10	57 ± 8	57 ± 9	56 ± 9
Angina class* (n, %)					
I/II	16	10 (18)	6 (13)	11 (18)	5 (13)
III/IV	85	45 (82)	40 (87)	51 (82)	33 (87)
Risk Factors (n,%)					
Previous MI	66	36 (66)	30 (65)	39 (63)	26 (68)
Prior PTCA†	28	13 (24)	15 (33)	17 (27)	10 (26)
Hypertension	30	18 (33)	12 (26)	16 (26)	14 (37)
Diabetes	14	10 (18)	4 (9)	10 (16)	4 (11)
Hypercholesterol	39	20 (36)	19 (41)	24 (39)	16 (42)
Current smoker	33	20 (36)	13 (28)	21 (34)	12 (32)
Family HX	24	17 (31)	7 (15)	20 (32)	5 (13)**

Group A: patients with successful revascularization; Group B: patients on medical therapy.
* According to Canadian Cardiovascular Society; MI, myocardial infarction; † = prior attempt at recanalization by using conventional guidewires; HX, history; **p=0.035

formed prior to a laser guidewire attempt. The baseline angiographic data for the entire patient cohort are given in Table 2.

Laser guidewire crossing was successful in 61 patients (63 occlusions, 61.2%) and increased from 46% in 1994/95 to 78% in 1996/97 (Fig 1). Due to severe dissection precluding additional angioplasty (n=3), TIMI 2 flow following stent implantation (n=2) and a 55% residual diameter stenosis in one patient, procedural success was achieved in 55 patients (57 occlusions). Balloon angioplasty was the sole treatment in 6 patients, ELCA+PTCA was performed in 15 cases (26.8%), while intra coronary stenting (with or without ELCA) was performed in 34 patients (61.8%, 2.1 stents/patient, median stent length 50 mm (15-130 mm, Table 3). The final MLD was 2.36 ± 0.63 mm with a residual DS of 20.5 ± 9%. In a univariate analysis, which was performed for all items listed in Tables 1 and 2, the occlusion length (mean ± SD) was significantly longer in the procedure failure group (success vs. failure 19.2 ± 10.4 mm vs. 25.6 ± 15 mm, p=0.005), while the presence of a central funnel in the occlusion stump was associated with a successful outcome

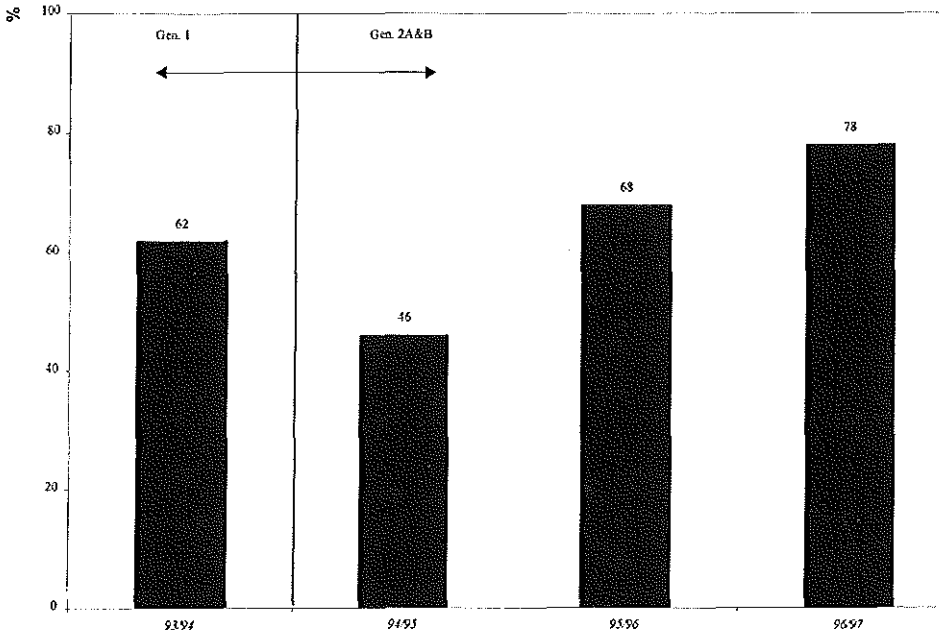


Figure 1 Laser guidewire success rate per year of experience (1993-1997 time frame). Gen.1= first generation laser guidewire. Gen. 2A & B= second and third generation laser guidewire

(p=0.05). A Multiple linear regression analysis identified occlusion length as the only independent predictor of procedural outcome (p=0.012).

In-hospital events were sub-acute reocclusion of the target vessel in three patients. A repeat PTCA was successful in two. As a result, 54 patients had target vessel patency upon hospital discharge (Fig 2). There were no deaths, Q-wave myocardial infarctions or emergency CABG's during the index hospital stay.

Following a failed attempt at recanalization (n=46), fourteen patients had bypass surgery. Consequently, during the index hospital stay, 68 patients (68.3%) had successfully undergone either percutaneous or surgical revascularization of a chronic total coronary occlusion ("group A"), while 32 patients remained on medical treatment ("group B").

ANGIOGRAPHIC FOLLOW-UP

As one patient died of pancreatic carcinoma seven months after successful recanalization (angiography performed at three months, had shown a patent vessel without signs of restenosis), 53 patients were eligible for six month angiographic follow-up, which was completed in 51 (96.2%). Ten coronary arteries had reoccluded, while in the remaining 41 patients, an additional 7 patients had significant restenosis (a combined restenosis/reocclusion rate of 33.3%). In a univariate analysis, longer occlusion length (occlusion length, patency vs. reocclusion 17.8 ± 9.8 mm vs. 25.2 ± 12.1 mm, p=0.045) and a positive family history for cardiovascular disease (p=0.045) had a significant bearing on vessel patency. A post-procedure larger MLD was also associated with vessel patency (patency vs. reocclusion, MLD-post: 2.42 ± 0.60 mm vs. 2.06 ± 0.59 mm, p=0.09, Table 4). However, in a multivariate regression model, no independent predictors of vessel patency at six months were identified. In the sub population of patients with intracoronary stents, a longer stented segment was associated with a less favorable outcome (patency vs. reocclusion, stent length (median-range): 39 mm (15-130), n=27, vs. 96 mm (66-120), n=5, p=0.008). In patients with vessel patency at follow-up, the absolute loss in MLD was 0.47 mm,with a loss index of 0.19 (Table 5).

CLINICAL FOLLOW-UP

Clinical follow-up of ≥12 months was completed in all patients, median 31.5 months, range 12 - 54 months). Recurrence of symptoms associated with restenosis at six months (n=17), resulted in CABG in seven patients, re-PTCA in five, while the remaining 5 patients were treated by continuation of medical treatment. During the 6-12

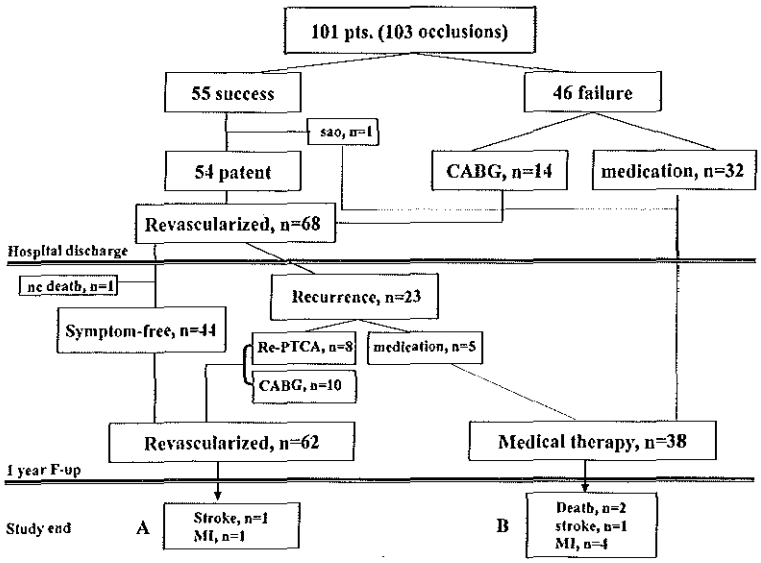


Figure 2 Patient flow chart. Pts = patients, sao = sub acute occlusion, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting, nc death = non-cardiac death, MI = myocardial infarction

months follow-up period, recurrence of angina in six more patients resulted in additional CABG (n=3) and re-PTCA (n=3). As a result, continued revascularization (PTCA and/or CABG) at one year follow-up was achieved in of 62 patients (61.4%, Fig 2).

During the entire follow-up period, in the successfully revascularized patient cohort (group A) there were no deaths, one stroke and one myocardial infarction. In contrast, in the non-revascularized patient group (group B) there were two deaths, one stroke and four myocardial infarctions (combined end-point, A vs. B, n=2/62 vs. n=7/38, p=0.025, RR 5.71 (95% CI 1.25 – 26.08), Figures 3A,B).

Referral for CABG was influenced by pre-procedural vessel size (reference diameter, CABG vs. B, 2.94 ± 0.52 mm vs. 2.68 ± 0.48 mm, p=0.05) and strongly influenced by whether or not the LAD was the target vessel (LAD, CABG vs. no CABG, 13/24 vs. 6/38, p=0.001, RR 2.67 (95%CI: 1.48-4.85). At the end of the study period, significantly more patients in group A were symptom-free (A vs. B, n=50/62 vs. n=8/38, p<0.0001; mean CCS classification, A vs. B, 1.26 ± 0.65 vs. 2.13 ± 0.74, p<0.0001). Likewise, the need of cardiac medication was significantly reduced in these patients (number of prescriptions, A vs. B, 2.55 ± 1.3 vs. 3.81 ± 1.2, p<0.0001).

DISCUSSION

TECHNICAL CONSIDERATIONS

Since the first reports in the early 1980s on percutaneous recanalization of chronic total coronary occlusions, various aspects of this sub-topic have been addressed. A number of the early studies stressed the feasibility of a percutaneous approach.[1-4] Typically, the emphasis was put on proper case selection, describing various predictors of procedural failure. However, more recent studies, as well as our findings suggest that some of the "classic predictors of procedural failure", such as the presence of bridging collaterals or the age of the occlusion are of less importance with currently available technology.[19,29]

During the course of this study, it emerged that with the introduction of new dedicated guidewires, such as the laser guidewire, the Crosswire and Stiffwire (Terumo, Tokyo, Japan), the Choice PT wire (Scimed, MN, USA), or the Miracle guidewires (Asahi Intecc, Tokyo, Japan), the key to success was more in using a combination of different guidewires with different technical specifications rather than the use of one single type of guidewire. Also, the consequent use of biplane fluoroscopy (or multiple views, when using single plane) and the technique of double cannulation of both coronary arteries, using the collateral circulation to visualize the distal target lumen, have been instrumental in the improvement of procedural success rates. Nevertheless, it should be stressed that the introduction of the laser guidewire in 1993 has positively stimulated many of these technical developments.

THE LASER GUIDEWIRE LEARNING CURVE

The overall success rate of the laser guidewire was 61.2%. It is likely that at least three different factors contributed to this result. First, the laser guidewire experience was actually the laser *guidewires* experience, as the technology of this device evolved during the time frame of this study. As the first version was not steerable, the earlier cases might have been somewhat less challenging than the long tortuous segments attempted with the steerable second generation laser guidewire. This phenomenon could explain for the initially "reversed" learning curve (Fig 1). Second, in the current era of cost constraint, we deliberately pushed the performance of this new device to the limit by intentionally applying a liberal case selection policy. This is maybe reflected by the fact that typically those patients were referred for a laser guidewire attempt after initial attempts by using conventional guidewires had failed (66 patients with at least one recorded, failed attempt, comprising 65.4% of the

TABLE 2. Lesion Characteristics

		Procedural outcome		Group	
	Total	Success	Failure	A	B
Age of occlusion *					
Clinical	30 (6-884)	28 (6-728)	32 (6-884)	30 (6-728)	25 (6-884)
Angiographic	13 (2-728)	10 (2-728)	14 (3-156)	13 (2-728)	13 (4-156)
Vessel, n					
RCA	56	28	28	28	28 †
LAD	37	24	13	31	6 ††
LCX	10	5	5	5	4
Stump, n					
Central	51	35 **	16	37	13 †††
Blunt	35	20	15	20	15
Eccentric	17	2	15 ***	7	10
Major SB	45	22	22	25	19
Bridging Coll.	28	17	11	16	12

* in weeks, median (range); RCA, right coronary artery, LAD, left anterior descending artery, LCX, left circumflex artery; Stump, occlusion stump morphology; SB, side branch; Bridging Coll, bridging collaterals; **p=0.009;***p<0.0001; †p=0.007; ††p=0.0006; ††† p=0.023

reported patient population). Finally, the steady increase in success rate from 46% in 1994 to 78% in 1996/'97 compares well with similar chronic total occlusion learning curves as reported by other groups.[4,29]

CLINICAL AND FUNCTIONAL ASPECTS

A successful percutaneous recanalization converts a patient not at risk into a patient at risk for restenosis, reocclusion and/or additional revascularization procedures. As this study was not designed to evaluate a difference in long-term outcome between percutaneous recanalization and surgical revascularization, we chose to evaluate the effect of revascularization (percutaneous and/or surgical) on a combined end-point of irreversible adverse events, death, stroke and myocardial infarction. In addition, we analyzed the influence of revascularization on freedom of angina and the need for cardiac medication. In concordance with earlier reports,[7-10,17] we found a significant reduction in the combined end-point of death, stroke or MI (p=0.025) following successful revascularization. In addition, the majority of these patients were free of angina, with a marked reduction in the need for cardiac medication.

Another rationale for the efforts to reconstruct chronically occluded coronary arteries can be found in studies on the

TABLE 3. Procedural Characteristics

MW attempts, n (%)	66	(65.4)
LW time*	33.5	(28.7)
Procedure time	174.6	(60.6)
Fluoroscopy time	88	(45.8)
Contrast medium, ml	618.2	(247.9)
PTCA, n (%)	6	(10.9)
PTCA+ELCA	15	(27.3)
PTCA+Stent	12	(21.8)
PTCA+ELCA+Stent	22	(40)

MW, mechanical guidewires; LW, laser guidewire;
* time in minutes; (mean ± SD); PTCA, percutaneous transluminal coronary angioplasty; ELCA, excimer laser coronary angioplasty; Stent, coronary stent implantation;
ml, milliliters.

effect of recanalization on left ventricular performance.[10,30-33] In a previous study, using dobutamine stress echocardiography, significant improvement in wall motion score was detectable within 48 hours following successful recanalization.[11]

RECURRENCE RATES

In this study, the combined angiographic recurrence rate at six months was 33.3%. At the time of the six-month follow-up angiography, the MLD in the cohort without reocclusion was 1.95 ± 0.66 mm,

TABLE 4. QCA, Procedural Data

	Procedural outcome			Vessel patency at F-up		
	Success	Failure	*p*	Yes	No	*p*
	n=55	n=46		n=41	n=10	
RD pre	2.80 ± 0.49	2.78 ± 0.49	ns	2.81 ± 0.52	2.72 ± 0.46	ns
RD post	2.95 ± 0.49	2.73 ± 0.44	*0.02*	3.01 ± 0.45	2.74 ± 0.53	ns
MLD post	2.36 ± 0.63	0		2.42 ± 0.60	2.06 ± 0.59	*0.09*
DS	20.5 ± 9.1	100		19.9 ± 9.0	24.8 ± 8.4	ns
Occ. L.	19.2 ± 10.4	25.6 ± 15	*0.013*	17.8 ± 9.8	25.2 ± 12.1	*0.045*

RD, reference diameter (mm, mean ± SD); pre/post, pre/post procedure; MLD, minimum lumen diameter, (mm, mean ± SD); DS, diameter stenosis (%, mean ± SD); Occ. L., length of occlusion (mm, median+range);

TABLE 5. QCA, Follow-up Data

	All	Reocclusion at follow-up	No reocclusion at follow-up
	n=51	n=10	n=41
Reference diameter (mm)			
Pre	2.79 ± 0.51	2.72 ± 0.46	2.81 ± 0.52
Post	2.94 ± 0.47	2.74 ± 0.53	3.0 ± 0.45
Follow-up	2.98 ± 0.61	2.77 ± 0.60	3.02 ± 0.59
MLD (mm)			
Post	2.35 ± 0.61	2.06 ± 0.59	2.42 ± 0.60
Follow-up	1.56 ± 0.99	0	1.95 ± 0.66
Absolute loss	0.79	2.06	0.47
Loss index	0.34	1	0.19
Recurrence rate (%)	33.3%	19.6%	13.7%
DS (%)			
Post	20.9 ± 9.0	24.8 ± 8.4	19.9 ± 9.0
Follow-up	48.2 ± 28.9	100	35.3 ± 14.1

while the loss index was no more than 0.19 (Table 5). This confirmed an earlier finding that as compared to dilatation of non-occlusive disease the recurrence rate following recanalization of chronic occlusions is primarily related to reocclusion rather than to restenosis.[34] As it has been suggested that reocclusion is likely to be an early phenomenon, a more liberal use of new, powerful antiplatelet drugs, such as abciximab and clopidogrel, could prove to be instrumental in maintaining initially achieved results.

The increasing number of studies on the effect of intra coronary stenting on vessel patency at 6 month have suggested that stenting may be mandatory for the maintained optimization of recanalization procedures.[12-17] In our series, stent implantation was performed in 61.8% of vessels (2.1 stents/patient, median stent length 50 mm (15-130 mm). In this sub-group, the 6-month reocclusion rate was 14.7% with an additional restenosis rate of 10.3%. Especially when the length of the stented segment is taken in to consideration, these results compare favorably with the literature.

IRREVERSIBLE ADVERSE EVENTS

The occurrence of myocardial infarction and cardiac death in patients with chronically occluded coronary arteries can not be explained by progression of disease in the occluded vessel. However, it is not unlikely that the absence of the potential for collateral flow from the occluded vessel could prove to be fatal in case of progression

of disease in the non-occluded vessels. Routinely, the indication for PTCA or CABG is based on the assumed influence of revascularization on life expectancy as related to the diseased artery. In contrast, in patients with chronic total occlusion the indication for revascularization should take into account not just the immediate, target vessel related reduction of myocardial ischemia, but also the potential future importance of the now occluded vessel in case of a life-threatening coronary incident in the contralateral artery. Consequently, the decision to refer a patient with single vessel occlusive disease for coronary revascularization should involve a non-target vessel related risk strategy.

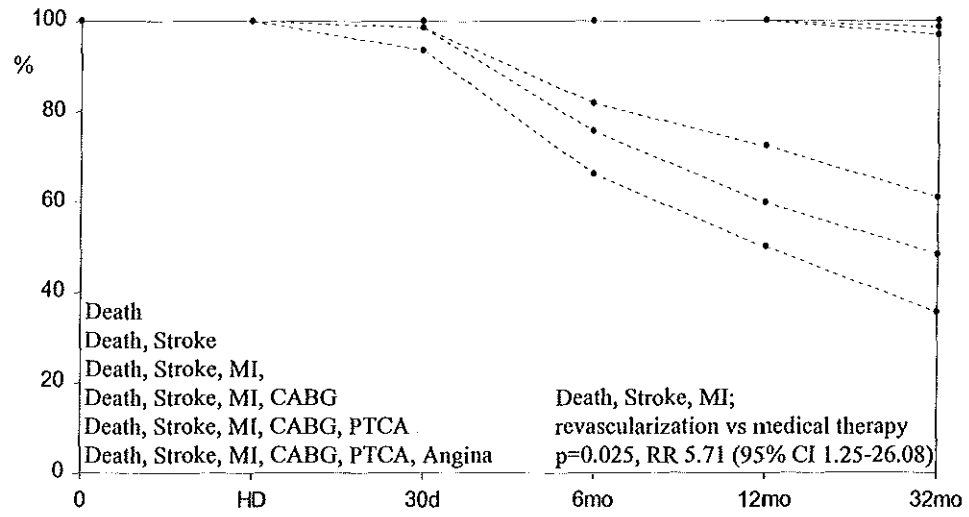
In conclusion, percutaneous reconstruction of previously occluded coronary segments is technically feasible and safe. In this patient cohort, successful recanalization reduced the incidence of irreversible adverse events, the need for coronary bypass surgery, the angina classification and the need for cardiac medication. Although chronic occlusion is still considered as a less rewarding indication for PTCA, the incidence of chronic total occlusion could be as high as 20 - 30 percent.[19,35] In order to make "reconstructive angioplasty" a reasonable option for general practice, continuous efforts should be made to improve the technology aimed at making the primary procedure easier and more predictable in its outcome. Whether new, (3D)-imaging modalities will prove to have a function in this setting is an up coming challenge. Whether additional treatments, such as intra coronary brachytherapy should be applied to further reduce recurrence rates was beyond the scope of this study.

STUDY LIMITATIONS

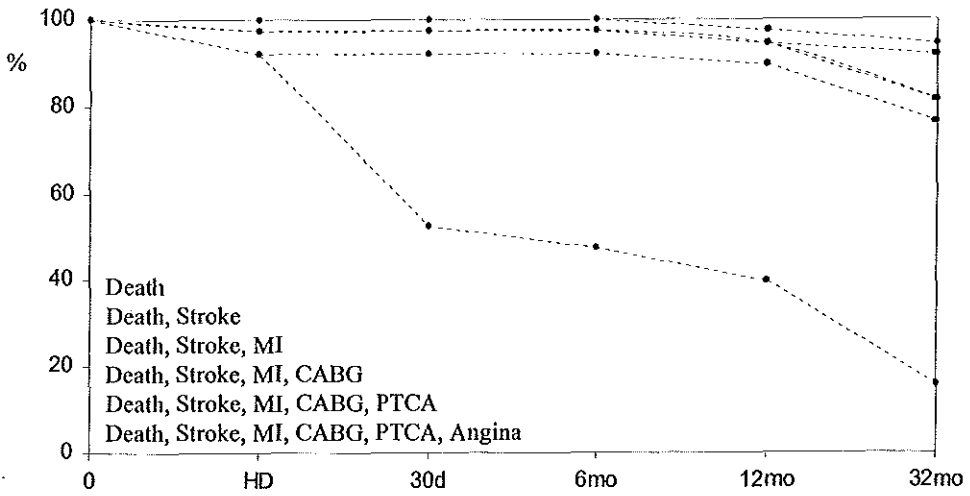
Although this study comprised the world's largest single-center experience with the laser guidewire, the total number of patients treated was relatively small. Second, although data were collected prospectively, the study was not designed as a randomized trial. Therefore, some of the study results could be a mere reflection of evolving clinical experience and decision making. Of importance is that a bias, influencing the pattern of patient referral for CABG can not be ruled out. Finally, the laser guidewire technology evolved during the study period, potentially interfering with a uniform analysis of this technology.

CONCLUSION

The success rate of laser guidewire facilitated recanalization procedures increased from 46% in 1994 to 78% in 1997. A combined strategy of percutaneous techniques with CABG for those



A



B

Figure 3 A. Survival curves following successful revascularization. B. Survival curves for patients on medical therapy, following a failed attempt at recanalization. HD= hospital discharge, d=days, mo= months, MI=myocardial infarction, CABG= coronary artery bypass grafting, PTCA= percutaneous transluminal coronary angioplasty, angina=angina pectoris

patients not successfully recanalized resulted in a significant reduction in the combined end-point of death, stroke and MI, the angina classification and the need for cardiac medication. As a result, this strategy seems superior to medical therapy in the treatment of patients with chronic total coronary occlusions.

REFERENCES

1. Holmes DR, Vlietstra RE, Reeder GS, Bresnahan JF, Smith HC, Bove AA, Schaff HV. Angioplasty in total coronary artery occlusion. *J Am Coll Cardiol* 1984;3:845-849
2. Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB. Angioplasty in total coronary artery occlusion: experience in 76 consecutive patients. *J Am Coll Cardiol* 1985;6:526-533
3. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W, Jaski B, Hugenholtz PG. Elective P.T.C.A. of totally occluded coronary arteries not associated with acute myocardial infarction; short-term and long-term results. *Eur Heart J* 1985;6:2-12
4. Stone GW, Rutherford BD, McConahay DR, Johnson Jr. WL, Giorgi LV, Ligon RW, Hartzler GO. Procedural outcome of angioplasty for total coronary artery occlusion: an analysis of 971 lesions in 905 patients. *J Am Coll Cardiol* 1990;15: 849-65
5. DiScascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for sub acute and chronic total coronary occlusion. *Am Heart J* 1986;111: 833-839
6. Finci L., Meyer B, Favre J, Righetti, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary artery occlusion. *Am J Cardiol* 1990;66: 660-2
7. Warren RJ, Black AJ, Valentine PA, Manolas EG, Hunt D. Coronary angioplasty for chronic total occlusion reduces the need for subsequent coronary bypass surgery. *Am Heart J* 1990;120:270
8. Ivanhoe RJ, Weintraub WS, Douglas Jr. JS, Lembo NJ, Furman M, Gershhony G, Cohen CL., King III SB. Percutaneous transluminal coronary angioplasty of chronic total occlusions: primary success, restenosis and long-term clinical follow-up. *Circulation* 1992;85:106-115
9. Bell MR, Berger PB, Bresnahan JF, Reeder GS, Bailey KR, Holmes DR. Initial and long-term outcome of 354 patients after coronary balloon angioplasty of total coronary balloon angioplasty of total coronary

artery occlusions. *Circulation.* 1992;85:1003-1011

10. Stewart JT, Denne L, Bowker TJ, Mulcahy DA, Williams MG, Buller NP, Sigwart U, Rickards AF. Percutaneous coronary angioplasty in chronic total coronary artery occlusion. *J Am Coll Cardiol* 1993;21:1371-6
11. Rambaldi R, Hamburger JN, Geleijnse ML, Kimman GJ, Aiazian AA, Fioretti PM, Ten Cate FJ, Roelandt JRTC, Serruys PW. Early recovery of wall motion abnormalities after recanalization of chronic totally occluded coronary arteries: a Dobutamine-Atropine Stress Echocardiographic prospective single center experience. *Am Heart J* 1998;136:831-836
12. Carozza JP, Kuntz RE, Levine MJ, Pomerantz RM, Fishman RF, Mansour M, Gibson MC, Senerchia CC, Diver DJ, Safian RD, Baim DS. Angiographic and clinical outcome of intracoronary stenting: immediate and long-term results from a large single center experience. *J Am Coll Cardiol* 1992;20:328-37
13. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G , Gaglione A, Goldberg SL., Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995; 91(6): 1676-88
14. Goldberg SL, Colombo A, Maiello L, Borrione M, Finci L, Almagor Y. Intracoronary Stent Insertion After Balloon Angioplasty of Chronic Total Occlusions. *J Am Coll Cardiol* 1995;26:713-9
15. Ozaki Y, Violaris A, Hamburger JN, Melkert R, Foley D, Keane D, de Feyter PJ, Serruys PW. Short- and Long-Term Clinical And Quan-titative Angiographic Results With The New, Less Shortening Wallstent for Vessel Reconstruction in Chronic Total Occlusion: A Quantitative Angiographic Study. *J Am Coll Cardiol* 1996;28:354-60
16. Sirnes PA, Golf S, Myreng Y, Mølstad P, Emanuelsson H, Albertsson P, Brekke M, Mangschau A, Endresen K, Kjekshus J. Stenting in Chronic Coronary Occlusion (SICCO): A Randomized, Controlled Trial of Adding Stent Implantation After Successful Angioplasty. *J Am Coll Cardiol* 1996;28:1444-51
17. Anzuini A, Rosanio S, Legrand V, Tocchi M, Coppi R, Bonnier H, Sheiban I, Kulbertus HI, Chierchia S. Wiktor stent for treatment of total coronary artery occlusions: short- and long-term clinical and angiographic results from a large multicenter experience. *J Am Coll Cardiol* 1998;31:281-8
18. Hamburger JN, Aiirian S, Gijsbers GHM, de Feyter PJ, Serruys PW.

Recanalization of chronic total coronary occlusions using a laser guidewire: a single institution experience with the initial one-hundred cases. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, 1996, (Philadelphia: Current Medicine 1996);

19. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol* 1997;30:649-56
20. Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E, Mathey D, Sievert H, Rutsch W, Buchwald A, Marco J, Al Kasab S, Pizzuli L, Hamm C, Corcos Th, Reifart N, Hanrath P, Taeymans Y. Recanalization Of Total Coronary Occlusions Using a Laser Guide Wire: The European TOTAL Surveillance Study. *Am J Cardiol* 1997;80:1419-1423
21. Hamburger JN, de Feyter PJ, Serruys PW.The laser guidewire experience: "crossing the Rubicon". In: Seminars in *Interventional Cardiology* 1996;1/2:163-171
22. Oesterle SN, Bittl JA, Leon MB, Hamburger JN, Tchengs JE, Litvack F, Margolis J, Gilmore P, Madsen R, Holmes DR, Moses J, Cohen H, King S, Brinker J, Hale T, Geraci DJ, Kerker WJ, Popma J. for the U.S. TOTAL investigators. Laser Wire for Crossing Chronic Total Occlusions-"Leaming phase" results from the U.S. TOTAL Trial. *Catheter Cardiovasc Diagn* 1998;44:235-243
23. Schofer J, Rau Th, Schlüter M, Mathey D. Short-term results and intermediate-term follow-up of laser wire recanalization of chronic coronary artery occlusions: a single-center experience. *J Am Coll Cardiol* 1997;30:1722-8
24. Hamburger JN, Serruys PW. Recanalization of chronic total occlusions using a laser guide wire. In: *Handbook of Cardiovascular Interventions* (U. Sigwart, M. Bertrand and PW Serruys Ed.) 1996, WB Saunders, London.
25. Hamburger JN, Serruys PW. Laser guidewire for Recanalization of Chronic Total Occlusions. In: Frontiers in *Interventional Cardiology*, (Beyar, Keren,Leon and Serruys Ed.) 1997, Martin Dunitz, London.
26. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264-9
27. The TIMI Study group. The Thrombolysis In Myocardial

Infarction Group (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985;31: 932-936

28. Di Mario C, Haase J, den Boer A, Reiber JH, Serruys PW. Edge detection versus video densitometry in the quantitative assessment of stenosis phantoms: an in vivo comparison in porcine coronary arteries. *Am Heart J* 1992;124:1181-1189
29. Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T, Shibata N, Ishihara T. Ohsawa N. Coronary Angioplasty of Chronic Total Occlusions With Bridging Collateral Vessels: Immediate and Follow-Up Outcome From a Large Single-Center Experience. *J Am Coll Cardiol* 1995;26:409-15
30. Hancock J, Thomas MR, Holmberg S, Wainwright RJ, Jewitt DE. Randomised trial of elective stenting after successful percutaneous transluminal coronary angioplasty of occluded coronary arteries. *Heart* 1998;79(1):18-23
31. Melchior JP, Doriot PA, Chatelain P, Meier B, Urban P, Finci L, Rutishauser W. Improvement of left ventricular contraction and relaxation synchronism after recanalization of chronic total coronary occlusion by angioplasty. *J Am Coll Cardiol* 1987;9(4):763-8
32. Danchin N, Angioi M, Cador R, Trioche O, Dibon O, Juilliere Y, Guillierre M, Cherrier F. Effect of late angioplastic recanalization of total coronary artery occlusion on left ventricular remeoddeling, ejection fraction and regional wall motion. *Am J Cardiol* 1996;78(7): 729-35
33. Mori M, Kurogane H, Hayashi T, Yasaka Y, Ohta S, Kajiya Y, Takarada A, Yoshida A, Matsuda Y, Nakagawa K, Murata T, Yoshida Y, Yokoyama M. Comparison of results of intracoronary implantation of the Palmaz-Schatz stent with conventional balloon angioplasty in chronic total coronary arterial occlusion. *Am J Cardiol* 1996;78(9): 985-9
34. Violaris AG, Melkert R, Serruys PW. Long term luminal renarrowing after successful elective coronary angioplasty of total occlusions: a quantitative angiographic analysis. *Circulation* 1995; 91:2140-2150
35. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am Heart J* 1993;126:561-564

CHAPTER 13

Six-month outcome after excimer laser coronary angioplasty for diffuse in-stent restenosis: a single center experience

Jaap N. Hamburger, David P. Foley, Alexander J. Wardeh,

Pim J. de Feyter, Patrick W. Serruys

Accepted for publication, American Heart Journal

SIX-MONTH OUTCOME AFTER EXCIMER LASER CORONARY ANGIOPLASTY FOR DIFFUSE IN-STENT RESTENOSIS: A SINGLE CENTER EXPERIENCE

ABSTRACT

Objective-This study evaluated the intermediate-term follow-up after excimer laser coronary angioplasty (ELCA) and adjunctive percutaneous transluminal coronary angioplasty (PTCA) in patients with diffuse in-stent restenosis.

Background-Coronary stenting is now the preferred mode of percutaneous revascularization in more than fifty percent of patients undergoing PTCA. In-stent restenosis requiring re-PTCA occurs in up to 20% of cases, but increased incidence may occur with the use of longer stents or stenting of small vessels. Following its capacity to ablate soft coronary plaque, we used ELCA to treat patients with diffuse in-stent restenosis of long stented coronary segments.

Methods-Patients with diffuse restenotic lesions (> 10 mm) in previously stented segments were treated with slow-pass ELCA+PTCA. Clinical- and angiographic follow-up was performed at 6 months. Quantitative coronary angiography (QCA) performed at three stages - during stent implantation, pre- and post ELCA+PTCA, and at follow-up - included measurements of the minimum lumen diameter (MLD) and percent diameter stenosis (DS).

Results-Seventeen consecutive patients were included. The (median+range) stent length was 37 mm (15-105 mm), with a restenotic lesion length of 32 mm (10-90 mm). Following ELCA+PTCA, the MLD increased from 0.61 ± 0.40 mm to 2.33 ± 0.51 mm, while the DS decreased from 75.3 ± 15.5% to 22.5 ± 8.2%. Despite adjunctive high pressure PTCA (balloon-artery ratio of 1.32 ± 0.29), the MLD post ELCA+PTCA remained smaller than the MLD post initial stent implantation, (2.33 ± 0.51 mm vs. 2.69 ± 0.32 mm, $p<0.019$). Adverse events included four ELCA related acute occlusions, necessitating additional stenting. This included left main stenting in one patient, who was referred for elective coronary artery bypass grafting. One patient having received abciximab suffered from an intracerebral haematoma and died during the index hospital stay. Despite recurrence of angina in all, two patients refused follow-up angiography. Therefore, angiographic follow-up was completed in 14 patients (82.4%) showing a reocclusion in 6 (42.9%), a >50% DS in 7 (MLD 0.89 ± 0.55 mm, DS 69 ± 17%) and a distal de novo lesion in one.

Conclusion-Although it was possible to achieve satisfactory acute angiographic results, the recurrence of significant restenosis in all patients suggests that ELCA+PTCA is not a suitable stand-alone therapy for diffuse in-stent restenosis of long stented segments.

An improved clinical outcome after coronary stenting -as compared to balloon angioplasty alone- has been proven for the treatment of short lesions in large coronary arteries.[1-4] Improved techniques for stent deployment[5] and the introduction of many new stent designs have made intracoronary stenting a procedure with a relatively predictable, high procedural success rate. As a consequence of the increasing rates of coronary stenting in the last five years (including in patients with lesions potentially less favorable for stenting) a new iatrogenic disease "in-stent restenosis" has been generated. Initial studies on the intermediate-term results of balloon angioplasty as a treatment for in-stent restenosis have reported recurrence rates ranging from 20%[6,7] to as high as 85%.[8] It has been shown that in-stent restenosis is primarily based on intimal hyperplasia rather than stent recoil.[9,10] Also, it has been demonstrated that extruded restenotic material recoiled towards the lumen within minutes following balloon dilatation.[11] Therefore, atheroablation of neointima rather than mere re-dilatation seems a reasonable therapeutic approach. Excimer laser coronary angioplasty (ELCA), given its capacity to ablate soft coronary plaque, is potentially an adequate technique to treat in-stent restenosis.[12-14] As the type of restenosis appears to have a bearing on the late outcome after repeat percutaneous treatment, it has been suggested that in-stent restenosis should be subclassified as focal- (<10 mm), marginal- (on the proximal and/or distal rim of the stent), or diffuse restenosis (>10 mm in-stent lesion or stent occlusion).[9,14-17] Thus far, no experience has been reported on catheter based treatment of patients with in-stent restenosis in long stented segments. Therefore, the purpose of this study was to evaluate the place of ELCA in the treatment of this patient sub-set.

METHODS

PATIENT AND LESION POPULATION

Between November 1995 and November 1997, seventeen consecutive patients (11 male, age 58.8 ± 12.9 years) with diffuse in-stent restenosis (stented lesion length >10 mm) following initial stent implantation were treated with ELCA+adjunctive PTCA. Written informed consent was obtained from all patients. The indication for initial stent placement was a sub optimal balloon result (n=7), recanalization of a chronic

total occlusion (n=5), elective (n=4) or acute myocardial infarction (n=1). Vessels treated were the right coronary artery (RCA, n=8), left anterior descending (LAD, n=7), left circumflex artery (LCX, n=1) and saphenous vein bypass graft (SVG, n=1). Fourteen patients had been treated with a single stent, three patients with two stents. The stents used and their specific lenghts are shown in Table 1. Risk factors for coronary artery disease included diabetes in 3 patients (18%), a positive family history in 15 (88%), hypercholesterolaemia in 10 (59%), hypertension in 7 (41%), and cigarette smoking in 4 (24%). The initial stent implantation was performed in a standard procedure, using high-pressure post dilatation (≥14 Atm) and a balloon-artery ratio of 1.1 ± 0.10 as determined by on-line QCA. Procedures were performed under iv heparin and aspirin, and all patients were post treated with Ticlopidine 250-mg twice daily for four weeks.

ELCA+PTCA PROTOCOL

A repeat angioplasty was performed in case of recurrence of angina and/or objective signs of ischemia in patients with a >50% diameter stenosis on diagnostic angiography. Patients were treated with ELCA only, if the in-stent stenosed segment had a minimum length of 10 mm as assessed by on-line QCA. The laser was a CVX 300 XeCl excimer laser (Spectranetics, Colorado Springs, CO). The fluence used ranged

Table 1. Stents Used

Patient	Stent-Type	Stent Length	Manufacturer	Coronary artery
#1	Wallstent	1x32mm	Schneider	LAD
#2	Wallstent	1x60mm	Schneider	SVG
#3	NIR	3x32mm	Medinol	RCA
#4	Wallstent	1x35mm	Schneider	RCA
#5	Wallstent	1x35mm	Schneider	LCX
#6	NIR	1x32, 1x16mm	Medinol	LAD
#7	NIR	2x32mm	Medinol	RCA
#8	Freedom	1x24mm	Global	LAD
	Palmaz-Schatz	1x20mm	JJIS	
#9	NIR	2x32, 2x16, 1x9mm	Medinol	RCA
#10	NIR	2x32, 2x16	Medinol	LAD
#11	Palmaz-Schatz	1x15mm	JJIS	LAD
#12	NIR	2x16mm	Medinol	RCA
#13	beStent	1x35mm	Medtronic	RCA
#14	Multilink	1x15mm	ACS	LAD
#15	Palmaz-Schatz	1x20mm	JJIS	RCA
	Microstent II	1x18mm	AVE	
#16	Wallstent	1x22mm	Schneider	RCA
	Palmaz-Schatz	1x15mm	JJIS	
#17	Wallstent	1x20mm	Schneider	LAD
	NIR	3x16, 1x9mm	Medinol	

from 45 to 60 mJ/mm^2 (mean 50.6 ± 7 mJ/mm^2) with a pulse repetition rate of 25 to 40 Hz (mean 29.7 ± 7 Hz). To ensure maximum debulking, we consequently used the largest diameter catheter available. At the onset of this study, this would be the 1.7 mm concentric catheter (n=2). However, during the study, the 2.0 concentric (n=8), the 1.7 mm eccentric (n=3), and the 2.0 mm eccentric laser catheter (n=4) became available. During activation of the laser, the laser catheter was moved forward at a speed of approximately 0.5 mm/sec. To optimize the procedure, a saline flush was used as described elsewhere.[18] The median number of pulses applied was 2407 (range 725-16,000) in 3.1 ± 1.9 passes. High-pressure post dilatation was performed in all cases (maximum balloon pressure of 15.7 ± 3.7 atmosphere), to achieve an optimal acute result (<20% DS). The nominal balloon diameter size ranged from 2.5 to 4.5 mm (mean 3.4 ± 0.5 mm, balloon-artery ratio of 1.3 ± 0.3), with a balloon length of 30.6 ± 9.6 mm. Procedural success was defined as an average diameter stenosis of less than 50% in two orthogonal views by on - line QCA. Clinical success was defined as procedural success without death, Q-wave myocardial infarction, coronary bypass surgery, or repeat angioplasty during the index hospital stay. A non Q-wave myocardial infarction was defined as a post procedure maximum CPK of more than 200 U/L in the absence of new Q-wave formation on the ECG.

QCA ANALYSIS

Serial off-line QCA measurements were made of the stent implantation, before and after the treatment of in-stent restenosis and at intermediate-term follow-up, using an automated edge detection algorithm (CAAS II system, PIE Medical, Maastricht, The Netherlands). The non-contrast filled guiding catheter was used as the calibration standard.[19] The reference diameter (RD), MLD and percent DS were calculated in multiple views and are given as the resultant average (Table 2). The lesion length was measured in the view with the least amount of foreshortening.

PATIENT FOLLOW-UP

All patients had a 30 day- and six month clinical follow-up. Angiographic follow-up was scheduled at 6-month post ELCA, or performed earlier if clinically indicated.

STATISTICAL ANALYSIS

Categorical data were presented as frequencies. Continuous data were presented as mean ± SD, or in case of a non normal distribution of values as median with range. Comparisons of continuous variables were performed using unpaired t tests. A p value of <0.05 was considered statistically significant.

RESULTS

PROCEDURAL RESULTS

ELCA+PTCA was performed in seventeen patients with diffuse in-stent restenosis 6.6 ± 2.6 months after the initial stent implantation. The median stent length was 37.5 mm (range 15-105 mm), with a restenotic lesion length of 33.5-mm (range 10-90 mm). Due to in-stent restenosis, the MLD had decreased from 2.72 ± 0.30 mm (post stenting) to 0.58 ± 0.39 mm (absolute loss 2.14 ± 0.53 mm, p<0.0001). In four patients the stent was totally occluded. Following ELCA+PTCA the MLD increased to 2.33 ± 0.53 mm (absolute gain 1.76 ± 0.69 mm, p<0.0001), while the DS was reduced from 76.3 ± 15.4% to 22.1 ± 8.3%. Despite this improvement, the MLD post ELCA+PTCA remained significantly smaller than the original MLD post stenting (2.33 ± 0.53 vs. 2.72 ± 0.30, p<0.013, Fig 1).

PROCEDURAL COMPLICATIONS

In four cases (24%), the ELCA procedure was complicated by intracoronary thrombus formation. After i.v. administration of abciximab and additional stenting, normal flow was restored. As this involved left main stenting in one, this patient was referred for elective CABG during the same hospital stay. High-pressure post dilatation induced edge dissections, required additional stenting in two patients. In two patients, the ELCA procedure was complicated by side branch occlusion, which resulted in a non Q-wave myocardial infarction in one. Post pro-

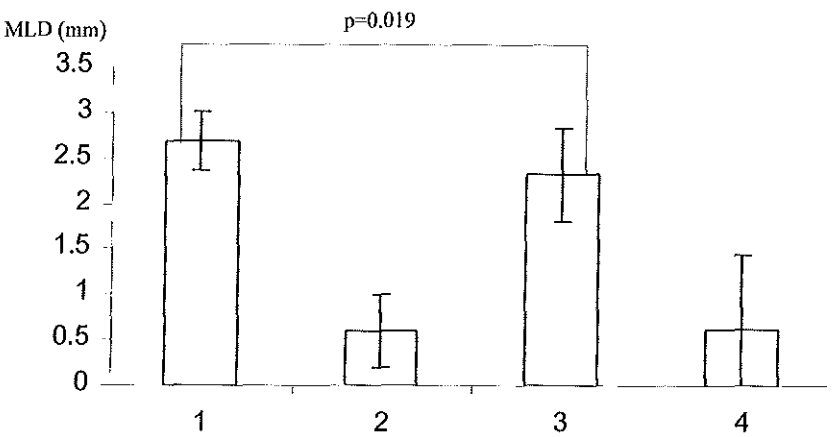


Figure 1 QCA results of MLD measurements. 1 = post stent implantation, 2 = pre-ELCA, 3 = post ELCA+PTCA, 4 = 6 month angiographic follow-up. QCA= quantitative coronary angiography, MLD= minimal lumen diameter, ELCA= excimer laser coronary angioplasty, PTCA= percutaneous transluminal coronary angioplasty. Values are given as mean ± SD.

Table 2. Serial QCA measurements

I	Reference diameter	3.29 ± 0.39	
	MLD	2.69 ± 0.32	
	DS%	15.7 ± 6.2	n=17
II	Reference diameter	2.68 ± 0.44	
	MLD	0.61 ± 0.40	
	DS%	75.3 ± 15.5	
	absolute loss	2.08 ± 0.58	
	relative loss	0.79 ± 0.27	n=17
III	Reference diameter	3.05 ± 0.55	
	MLD	2.33 ± 0.51	
	DS%	22.5 ± 8.2	
	absolute gain	1.71 ± 0.66	
	relative gain	0.57 ± 0.19	n=17
IV	Reference diameter	2.91 ± 0.42	
	MLD	0.63 ± 0.81	
	DS%	79.8 ± 23.6	
	absolute loss	1.74 ± 0.92	
	relative loss	0.59 ± 0.36	
	loss index	0.99 ± 0.58	n=14

Serial QCA measurements. I= post stent deployment, II= pre-ELCA, III=post ELCA+PTCA, IV= 6 month follow-up. Reference diameter, in mm, MLD= minimum lumen diameter, in mm, DS= diameter percent stenosis. All values are given as mean ± SD

cedural CK values were elevated in 7 patients (Table 3). Finally, in one patient, the ELCA catheter did not cross the lesion, due to an (initial) under deployment of the stent ("pseudo in-stent restenosis"). This could be confirmed with intravascular ultrasound, after which the stent was re-dilated (Fig 2). Unfortunately, post-procedure this 68-year-old female patient developed an intra-cerebral bleeding possibly related to the combined use of heparin, aspirin and abciximab. Despite adequate neurosurgical drainage, her condition deteriorated and she died post operatively from pulmonary complications. As a result, procedural success was achieved in all cases but clinical success in 15 patients only (88%).

CLINICAL- AND ANGIOGRAPHIC FOLLOW-UP

After an interval of 7.1 ± 4.4 months, clinical follow-up was completed in all 16 remaining patients. All patients had a recurrence of angina (CCS classification): class II in 6, class III in 7 and class IV in 3 patients. Two symptomatic patients refused a repeat coronary angiography. Therefore, repeat coronary angiography

Table 3. CK values* (n=14)

Patient	CK	CK-MB
#1	889	
#2	219	22
#3	397	28
#5	105	12
#6	182	28
#7	249	20
#8	82	13
#9	64	16
#10	99	17
#11	164	18
#12	117	9
#14	69	9
#15	36	8
#16	221	25

*Normal values: CK 110 U/L, CKMB 14 U/L

was performed in 14 patients (82%). Of these, 6 segments were totally occluded while 7 segments showed a significant recurrence of in-stent restenosis (MLD 0.89 ± 0.55 mm, absolute loss 1.74 ± 0.92, loss index 0.99). In those patients with stent reocclusion, the initial indication for stent implantation had been recanalization of a chronic total occlusion in two, and optimization of a sub-optimal balloon angioplasty result in four. The recurrence of angina in the patient electively referred to CABG was explained by a combination of reocclusion in the ELCA treated segment and a de novo stenosis at the site of the anastomosis of the left internal mammary artery with the LAD. In one patient, a de novo lesion just distal to the segment previously treated with ELCA was held responsible for the recurrence of ischemia and subsequently treated with additional stenting.

DISCUSSION

THE PROBLEM

Although the advantage of stenting has been confirmed for certain lesion subgroups, such as relatively short lesions in large vessels[1-4] or chronic total occlusions,[20-23] the long-term advantage of stenting for a number of other indications remains to be proven. Maybe, that in the current era with "optimal" operator techniques for stent deployment (high-pressure post dilatation, IVUS guidance, Aspirin/Ticlopidine co-medication, etc.) stent implantation as a primary approach for coronary revascularization, has become a more safe and predictable therapy. However, being technically capable of treating long lesions, small vessels or complex bifurcations, it could be that the trade-of for these achievements is a sometimes seriously therapy resistant complication. Nevertheless, in the past few years the number of coronary stent procedures has steadily increased. As a result, the group of patients with in-stent restenosis is an uncomfortably growing cohort.

THE MECHANISTIC APPROACH

In-stent restenosis is typically the result of neo-intima formation within a stent.[9,10] The mechanism of lumen enlargement after PTCA is probably a combination of tissue extrusion out of the stent and additional stent expansion.[24] A repeat balloon angioplasty is a

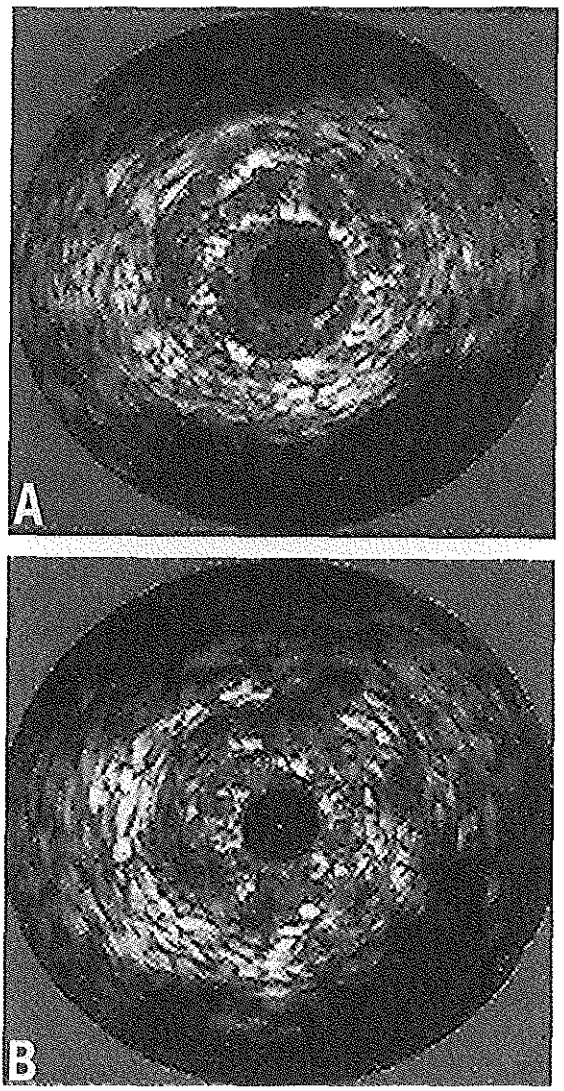


Figure 2 Intravascular ultrasound image of "pseudo in-stent restenosis" due to stent collapse. A=-in the stent, proximal to the stenosis, B=in the stent, at the site of the stenosis.

relatively safe and effective therapy for focal in-stent restenosis.[6,7] Nevertheless, given the possibility of tissue recoil in to the stent following initial dilatation,[11] a combined use of an atheroablative technique and balloon angioplasty seems a more logic approach. However, recently it emerged that the extent of in-stent restenosis (diffuse, or stent occlusion as opposed to focal intima hyperplasia) had a direct bearing on the recurrence rate, regardless of the type of ablative technology used.[25,26] Given the median stented segment length (37.5 mm, range 15-105) and lesion length (33.5 mm, range 15-90) as reported in this study, these patients could very well represent a "worst case scenario": despite aggressive laser debulking and high pressure post dilatation with relatively oversized balloons, no more than 85% of the original MLD post stenting could be regained. Moreover, the number of procedural complications and the high percentage of target vessel failure at 6 month follow-up (43% reocclusion, 50% re-restenosis and 7% de novo distal disease) would suggest that ELCA+ PTCA -at least using the current methodology- may not be a suitable treatment for diffuse in-stent restenosis. Indeed, the use of multiple- and long stents have seriously broadened the scope of percutaneous revascularization and multivessel disease is no longer the exclusive domain of the cardiac surgeon.[27] However, if proven to be associated with an increased risk of diffuse in-stent restenosis, the initial use of

long stents, especially in the LAD, maybe should be reconsidered. An alternative concept of "spot-stenting" has been suggested within this context.[28]

THE ALTERNATIVES

Intra coronary brachytherapy with gamma irradiation has been shown to be potentially beneficial in the treatment of in-stent restenosis in a small patient cohort.[29] Whether this finding will borne out for beta irradiation in longer stents and in longer lesions, remains to be seen. In order to preserve the acute improvement achieved with debulking, brachytherapy could be usefully combined with ELCA as a potential treatment for diffuse in-stent restenosis. The combination of aggressive laser debulking followed by beta irradiation and balloon dilatation is currently under investigation in our department. Thus far, fourteen patients with iterative in-stent restenosis have thus been treated and follow-up is pending. Meanwhile, in patients with particularly diffuse in-stent restenosis, coronary artery bypass surgery must be considered as an alternative to the "intraluminal mechanistic approach."[30]

STUDY LIMITATIONS

The limitations of this study are 1). evolving catheter technology during the study: catheter diameters ranged from 1,7 concentric to 2.0 eccentric. Therefore, the ablation therapy efficacy might not have been uniform throughout the study. 2). the number of patients in this single-center study is small.

CONCLUSION

This study evaluated the intermediate-term efficacy of ELCA+PTCA in seventeen consecutive patients with diffuse in-stent restenosis [stent length (median/range) 37.5 mm (15-105), lesion length 33.5 mm (15-90), initial reference diameter post stenting 3.34 ± 0.38 mm]. ELCA+PTCA resulted in a significant acute angiographic improvement (MLD pre vs. post: 0.61 ± 0.4 vs. 2.33 ± 0.51, $p<0.0001$). However, in-hospital adverse events included one death and one CABG, while at 6-month follow-up all patients had recurrence of angina and target vessel failure was angiographically confirmed in 14 (82%). Thus, ELCA+PTCA alone may not result in favorable intermediate-term results in patients with diffuse in-stent restenosis.

REFERENCES

1. Serruys PW, de Jaegere P, Kiemeney F, Macaya C, Rutsch W, Heyndrikx G, Emanuelson H, Morco J, Legrand V, Materne P, Belardi MA, for the BENESTENT Study Group. A comparison of balloon expandable-stent implantation with balloon angioplasty in

patients with coronary artery disease: Benestent Study Group. *N Engl Med J* 1994;331:489-95

2. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Deter K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shacknovich A, Hirschfeld J, Bailey S, Ellis S, Rake R, Goldberg S, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease: Stent Restenosis Study Investiga-tors. *N Engl Med J* 1994;331:496-501
3. Serruys PW, Sousa E, Belardi J, Nobuyoshi M, Probst P, Gulba DC, Brachmann J, Almagor Y, Bos HS, van den Heuvel P. BENESTENT-II trial: subgroup analysis of patients assigned either to angiographic or clinical follow-up or clinical follow-up alone. *Circulation* 1997;96 (Suppl I): I-653
4. Versaci F, Gaspardone A, Tomai F, Crea F, Chiarello L, Gioffrè P. A comparison of coronary artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *New Engl J Med* 1997;336: 817-22
5. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G , Gaglione A, Goldberg SL., Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995; 91(6): 1676-88
6. Reimers B, Moussa I, Akiyama T, Tucci G, Ferraro M, Martini G, Blengino S, Di Mario C, Colombo A. Long-term clinical follow-up after successful repeat percutaneous intervention for stent restenosis. *J Am Coll Cardiol* 1997;30:186-92
7. Bauters Ch, Banos JL, van Belle E, McFadden EP, Lablanche JM, Bertrand ME. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. *Circulation* 1998; 97:318-321
8. Yokoi H, Kimura T, Nakagawa Y, Nosaka H, Nobuyoshi M. Long-term clinical and angiographic follow-up after the Palmaz- Schatz restenosis. *J Am Coll Cardiol* 1996;27:224(A)
9. Hoffmann R, Mintz G, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Grifin J, Leon MB. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. *Circulation* 1996;94:1247-1254
10. Mudra H, Regar E, Klauss V, Werner F, Henneke K-H, Sbarouni E, Theised K. Serial follow-up after optimized ultrasound- guided deployment of Palmaz-Schatz stents. In-stent neointimal proliferation without significant reference segment response. *Circulation* 1997;95:363-370

11. Shiran A, Mintz GS, Waksman R, Mehran R, Abizaid A, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Early lumen loss after treatment of in-stent restenosis. An intravascular ultrasound study. *Circulation* 1998;98:200-203
12. Hamburger JN, Verhoofstad GGAM, van Marle J, van den Broecke D, Hanekamp CEE, Serruys PW, van Gemert MJC. Excimer laser coronary angioplasty: A physical perspective to clinical results. In: Topol E, Serruys PW (eds), *Current Review of Interventional Cardiology*, 2nd edn (Philadelphia: Current Medicine, 1995); 159-172.
13. Appelman YEA, Piek JJ, de Feyter PJ, Tijssen JGP, Strikwerda S, David GK, Serruys PW, Margolis JR, Koelemay MJ, van Swijndregt E, Koolen JJ. Excimer laser coronary angioplasty versus balloon angioplasty in the treatment of obstructive coronary artery disease: a randomized clinical trial. *Lancet* 1996; 347:79-84
14. Mehran R, Mintz GS, Satler LF, Pichard AD, Kent KM, Bucher TA, Popma JJ, Leon MB. Treatment of in-stent restenosis with excimer laser coronary angioplasty. Mechanisms and results compared with PTCA alone. *Circulation*; 1997;96: 2183-2189
15. Mintz G, Hoffmann R, Mehran R, Pichard AD, Kent KM, Satler LF, Popma JJ, Leon MB. In-stent Restenosis: The Washington Hospital Center Experience. *Am J Cardiol* 1998;81 (7A):7E-13E
16. vom Dahl J, Klues HG, Radke P, Haager P, Kastrau F, Reffelmann T, Janssens U, Hanrath P. Angiogra-phic long-term results of coronary rotational atherectomy for treatment of diffuse in-stent restenosis are dependent on the length of the initial in-stent restenosis *Eur Heart J* 1998;19:757(A)
17. Köster R, Hamm CW, Terres W, Reimers J, Koshyk DH, Kähler J, Meinertz T. Long-term results of laser angioplasty for in-stent restenosis. *Eur Heart J* 1998;19: 756(A)
18. Deckelbaum LI, Strauss BH, Bittl JA, Rohlfs K, Scott J. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 1995;26:1264-9
19. Di Mario C, Haase J, den Boer A, Reiber JH, Serruys PW. Edge detection versus video densitometry in the quantitative assessment of stenosis phantoms: an in vivo comparison in porcine coronary arteries. *Am Heart J* 1992;124:1181-1189
20. Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol* 1997;30: 649-56

21. Ozaki Y, Violaris A, Hamburger JN, Melkert R, Foley D, Keane D, de Feyter PJ, Serruys PW. Short- and long-term clinical and quantitative angiographic results with the new, less shortening Wallstent for vessel reconstruction in chronic total occlusion: a quantitative angiographic study. *J Am Coll Cardiol* 1996; 28:354-60
22. Sirnes PA, Golf S, Myreng Y, Møl-stad P, Emanuelsson H, Albertsson P, Brekke M, Mangschau A, Endre-sen K, Kjekshus J. Stenting in Chronic Coronary Occlusion (SICCO): A randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;28:1444-51
23. Hancock J, Thomas MR, Holmberg S, Wainwright RJ, Jewitt DE. Randomised trial of elective stenting after successful percutaneous transluminal coronary angioplasty of occluded coronary arteries. *Heart* 1998;79(1):18-23
24. Mehran R, Mintz GS, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J, Leon MB. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. *Am J Cardiol*, 1996;78:618-622
25. Mehran R, Abizaid AS, Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Patterns of in-stent restenosis: classification and impact on subsequent target lesion revascularization. *J Am Coll Cardiol* 1998;31:1060-85(A)
26. Büttner HJ, Müller C, Hodgson JMcB, Frey AW, Jander N, Bestehorn HP, Petersen J, Roskamm H. Rotational ablation with adjunctive low-pressure balloon dilatation in diffuse in-stent restenosis: immediate and follow-up results. *J Am Coll Cardiol* 1998;31: 1060-88(A)
27. Moussa I, Reimers B, Moses J, Di Mario C, Di Francesco L, Ferraro M, Colombo A. Long-term angiographic and clinical outcome of patients undergoing multivessel coronary stenting. *Circulation*. 1997;96:3873-3879
28. DeGregorio J, Kobayashi Y, Reimers B, Albiero R, Di Mario C, Colombo A. Intravascular ultrasound guided PTCA with spot stenting. *J Am Coll Cardiol* 1998; 31:387A:896-3.
29. Teirstein PS, Massulo V, Jani S, Popma JJ, Mintz GS, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Morris NB, Leon MB, Tripuraneni P. Catheter-based radiotherapy to inhibit stenosis after coronary stenting. *N Engl J Med* 1997;336:1697-1703
30. Bergsma TM, Grandjean JG, Voors AA, Boonstra PW, den Heyer P, Ebels T. Low recurrence of angina pectoris after coronary artery bypass graft surgery with bilateral internal thoracic and right gastroepiploic arteries.

CHAPTER 14

Conclusions

CONCLUSIONS

The hypotheses in this thesis, as presented in the introduction section, were

1. Damaging side-effects during excimer laser coronary angioplasty (ELCA) are related to intrinsic mechanisms of excimer laser tissue ablation
2. Optimization of ELCA can be achieved by elimination of UV-absorbing media, reduction of catheter advancement speeds and by reduction of the non-light emitting area at the tip of a laser catheter
3. Percutaneous recanalization of chronic total coronary occlusions by using laser guidewire is feasible and safe
4. Revascularization therapy is superior to medical therapy in patients with chronic total coronary artery occlusions

HYPOTHESIS 1

Side effects of ELCA can be summarized into three categories

- ELCA related mechanisms that interfere with the anatomic integrity of the coronary arterial vessel wall
- ELCA related mechanisms that interfere with the functional integrity of the coronary artery
- ELCA related mechanisms that interfere with the mid-long-term healing response

Excimer laser tissue ablation (as described in Part I) is based on heat production and accumulation (resulting in water vaporization) and photochemical dissociation. These mechanisms predominantly occur in tissue lipids (e.g. cell membranes). A direct consequence of water evaporation and lipid dissociation is volume expansion. Therefore, it is likely that the mechanism of excimer laser tissue removal is a combination of forceful tissue disruption due to volume expansion, water evaporation and photochemical dissociation. This combined mechanism is reflected in the histology of tissue samples (Chapter 2), with the occurrence of lobes (incomplete tissue removal), tissue splits and vacuoles. If the results of the experiments as described in Part I of this thesis are representative of the phenomena during ELCA, it is conceivable that angiographic complications such as dissection, acute vessel closure and/or perforation are related to these physical phenomena.
With regard to the functional integrity

of the coronary artery, the production of significant volumes of insoluble gas could result in coronary flow disturbances. The volumes of insoluble gas that were measured (Chapters 3 – 5) were often in excess of those as described in the literature as being responsible for ischemic changes in myocardial function. It is of importance, to note that optimal ablation was achieved using those parameters which also resulted in lower insoluble gas yields even in the presence of relatively large water vapor bubbles (see Chapters 4 and 5). A major microscopic feature related to lower gas yields was a reduction in the extent of mechanical tissue damage, or more specifically a reduction in the presence of tissue vacuoles.

The clinical introduction of ELCA in 1988 was accompanied by high expectations with regard to its efficacy and a possible reduction of angioplasty related restenosis rates. A few randomized studies powered to evaluate a difference in the angiographic restenosis rates at six months have been performed (e.g. the AMRO and ERBAC trials). Unfortunately, these studies failed to demonstrate a difference in favor of ELCA. It should be noted that these trials were performed with first generation ELCA catheters and without the use of saline infusion. Also, ELCA procedures were performed with a manually controlled forward movement of the laser catheters, typically at speeds of more than one millimeter per second. The poor results of tissue ablation at catheter speeds of >0.5 mm/s were discussed in Chapter 3. Therefore, it is possible that the angiographic restenosis propensity of ELCA in these studies is merely the reflection of such technical and/or procedural shortcomings. Whether the mid-long-term results of ELCA can be improved by using optimally designed catheters [e.g. the 2.0 High-Density catheter (see Chapter 4) or the recently introduced O(ptimal) S(pacing) catheter (Spectranetics Inc., CO. USA)], a saline infusion technique and significantly reduced catheter advancement speeds, should be evaluated in a prospective, randomized trial in which these new developments are incorporated.

HYPOTHESIS 2

Ablation in ELCA is the result of an interaction of photons with a wavelength of 308 nm with tissue. Therefore, any substance capable of photon absorption, which is located between the source of photons (the catheter tip) and the tissue would cause a reduction of the ablation efficacy. The absorption of, and interaction with 308 nm photons by hemoglobin and angiographic contrast media was demonstrated (Introduction, chapter 1), while the

clinical benefit of a saline flush during ELCA (to wash out contrast medium and blood as much as possible), was confirmed by Decklebaum et al.

The efficacy of tissue ablation is reduced if the speed of catheter advancement exceeds the capacity of the laser system to ablate tissue. The currently advised catheter advancement speed for ELCA procedures is 0.5-1 mm/s. In ablation experiments, using 1.7 mm ELCA catheters and laser parameters typical for ELCA, optimal ablation was achieved for catheter advancement speeds of 0.06 mm/s (Chapter 3). As such low advancement speeds are difficult (if not impossible) to control manually, it is likely that currently performed ELCA procedures are sub-optimal and could be improved by introducing an automated catheter advancement device (Chapter 3, Appendix 1). Furthermore, it is of practical relevance that the use of the new 2.0 High-Density catheter and higher pulse repetition rates (40 Hz instead of 25 Hz) allowed for higher catheter advancement speeds (up to 0.1 mm/s). This adjustment of the pulse repetition rate improved the *in vitro* ablation efficacy without increasing the collateral tissue damage (Chapter 4). However, in case of a clinical introduction of improved catheter technology and an automated catheter advancement device, there are two major concerns. Secondary to an increase in tissue removal, we measured a significant increase in the volume of non-soluble gas. Consequently, it is conceivable that a volume of non-soluble gas in excess of a certain critical value could result in a no-reflow phenomenon due to obstruction of the capillary bed. Second, the maximum temperature increase above ambient as measured during slow advancement speed experiments was 22 ± 3 °C. In a coronary artery, a temperature increase of 22 °C above ambient (± 37 °C) would lead to a vessel wall temperature of approximately 60 °C. Thermal damage following porcine *in vivo* studies been reported. Therefore, prior to a clinical introduction with slow catheter advancement speeds and/or higher pulse repetition rates, ELCA induced thermal necrosis of the vessel wall cannot be ruled out.

The use of multifiber technology and more specifically, the absence of overlap between light beams coming from individual fibers, results in the presence of a certain amount of "dead space" at the catheter tip-tissue interface. The relative dimensions of the active area and total area at the catheter tip determine the efficacy of a multifiber catheter. Subsequently, reducing the amount of dead space increases the ablation efficacy. This can be achieved by

increasing the number of fibers in a catheter (e.g. the High-Density catheter, Chapter 4), or by diffusing the emitted light prior to incidence into the tissue (Homogeneous Light Distribution, Chapters 1, 5 and Appendix 2). A direct comparison of the standard 2.0 mm ELCA catheter with the new 2.0 mm High-Density catheter (with an increased number of fibers) demonstrated the superior ablation characteristics of the latter (Chapter 4). Diffusion of a certain amount of laser energy over a larger light emitting area results in a relatively lower energy density, which is an additional - and maybe more significant - advantage of eliminating dead space at the catheter-tip. Based on the results of consecutive measurements we found a relationship between energy density, gas yields and the dimension of water vapor bubbles: an increase in energy density led to an increase in gas yield and an increase in the diameter of the fast expanding vapor bubbles. Of importance was that the increase in gas yield was linear up to an energy density of approximately 35 mJ/mm^2. Further, relatively minor increments in energy density resulted in an exponential increase in gas yields, suggesting a "second threshold" for insoluble gas formation. Following an increase in gas yields and bubble diameters we found an increase in collateral tissue damage. Therefore, a reduction of the amount of dead space at the catheter-tip allowed for ablation at lower energy densities, which in turn resulted in a reduction of ablation related mechanical tissue damage.

HYPOTHESIS 3

The safety and efficacy of the laser guidewire for recanalization of chronic total coronary occlusions, especially those refractory for recanalization with conventional guidewires, was established in a number of studies, conducted both in Europe and the United States of America (Chapters 6-12). In recent years we have seen the introduction of improved, conventional guidewire technology. As a result, the outcome of the TOTAL trial, a randomized trial in which the safety and efficacy of the laser wire was prospectively evaluated as compared to mechanical guidewires, showed no significant difference between both study arms (Chapter 11). Nevertheless, the 1993 introduction of the laser guidewire added significantly to the development of percutaneous techniques for recanalization of chronic total occlusions. With the expected development of improved technologies for guidance of interventional procedures, such as intravascular ultrasound forward imaging, it is conceivable that the future of percutaneous recanalization techniques remains within the domain of "active guidewire technology".

HYPOTHESIS 4

Percutaneous transluminal coronary angioplasty (PTCA) for recanalization of chronically occluded coronary arteries has been associated with lower procedural success rates and higher recurrence rates in comparison with PTCA of non-occlusive stenoses. As a result, it has been a less favorable indication for PTCA. Therefore, it is not uncommon that these patients (especially when the occlusion is situated in the right coronary artery) remain on medical therapy. However, in a single center study, percutaneous or surgical revascularization resulted in significantly less irreversible events (death, cerebrovascular stroke and myocardial infarction, Chapter 12). This more favorable outcome following revascularization could be the result of a reduction in myocardial ischemia of the target area, but it could also be the result of a restoration of the capacity to supply collaterals in case of progression of disease in the contra-lateral coronary arteries. Therefore, it seems justifiable to state that the decision to refer a patient with single vessel occlusive disease for coronary revascularization should involve a non-target vessel related risk strategy.

In the last chapter of this thesis we reported the medium long-term outcome of excimer laser coronary angioplasty for the treatment of in-stent restenosis. In a small series of seventeen patients with diffuse in-stent restenosis it was demonstrated that with a combination of laser debulking and adjunctive balloon angioplasty approximately 85% of the original lumen after initial stent implantation could be regained. However, with a late loss index of 0.99 at the six-month follow-up angiography the initial benefit was not maintained. Thus far, no catheter based interventional modality has been proven effective in the treatment of this iatrogenic disease. As there are accumulating data on the long-term efficacy of intra-coronary brachytherapy, a combined strategy of in-stent tissue debulking, followed by intravascular radiation therapy might prove to be the best possible treatment for this patient category. This combined therapeutic approach is currently under investigation in our department.

The studies described in this thesis are a reflection of ten years of applied research activities. During this period the authors tried to evaluate the working mechanism and effectiveness of light as a therapeutic modality for the treatment of coronary artery disease. As could be expected, we must conclude, that we found more questions than answers. In referring to the Gospel of Thomas: "Let him who seeks, continue seeking until he finds. When he finds,

he will become troubled. When he becomes troubled, he will be astonished, and he will rule over the all", we did not reach beyond the first half of the third sentence: we are still astonished, indeed. Maybe we should go even further back, to the beginning of time when it was said: ...and darkness was upon the face of the deep and the spirit of G'd hovered over the face of the waters. And G'd said: "Let there be light" and there was light. And G'd saw the light that it was good and G'd divided the light from the darkness". One could argue, that (long before the days of Andreas Grüntzig), the creation of light was the very first intervention in the history of man, surely with far stretching consequences. In summary, the outcome of the experimental work and the increasing clinical experience with ELCA helped us to get a better understanding of the mechanisms involved in excimer laser induced tissue removal. These new insights, hopefully, will prove their value in the ongoing development of this exciting technology and the further refinement of percutaneous tools for ablative coronary angioplasty.

APPENDIX 1

Spectranetics
Catheter Advancement Device
a device description

SPECTRANETICS CATHETER ADVANCEMENT DEVICE

DEVICE DESCRIPTION

The Spectranetics motorized advancement device is designed to advance a laser catheter through a coronary lesion at a predetermined, constant rate of speed.

The device is a hand-held, battery operated unit housed in an anodized aluminum case. The external drive mechanism is a 2.5 cm stainless wheel containing 2 elastomeric o-rings mounted on the circumference. The drive wheel is designed to accept and provide friction to the proximal catheter shaft. A spring-loaded housing surrounds the external portion of the drive wheel and contains two stainless steel pinch rollers, which provide a bearing surface for the catheter when loaded into the advancement device. The spring-loaded housing can be positioned to load the catheter and then repositioned to contain the catheter between the pinch rollers and the drive wheel. A speed adjustment knob is located on the exterior of the CAD housing and permits catheter drive speeds of approximately 0.3 to 0.9 mm per second. A toggle switch is located on the exterior of the CAD housing and activates the drive wheel when moved to the ON position.

COMPATIBILITY

The motorized advancement device is compatible with all Spectranetics Vitesse fast exchange laser catheters. The motorized advancement device

SPECIFICATIONS

Model Number	518-015
Height	6 cm
Width	3 cm
Length	16 cm
Weight	400 grams
Power Source	Two 3-volt Lithium batteries
Battery Life	Approximately 90 minutes
Speed Range	0.3 to 0.9 mm/second
Sterilization Method	Autoclave
Multiple or Single Use	Multiple Use

does not currently interface directly with the Spectranetics CVX 300 laser system so there are no software changes associated with the use of this device.

SUMMARY OF TESTING

STERILIZATION & LIFETIME

- In-house testing demonstrated the safety of exposing the device to autoclave conditions.
- A testing laboratory performed preliminary testing to demonstrate the device would become sterile when exposed to a standard autoclave cycle.
- Batteries have demonstrated ability to operate in a continuous condition for more than 24 hours. Start-stop operation and exposure to multiple autoclave cycles will shorten battery life.

SPEED

- Bench-top testing showed actual speed to range from approximately 0.3 mm/second to 0.9 mm/second.

HEARTMODEL & USE

- It is possible to deliver approximately 0.8 lb. of linear force within the catheter shaft prior to slippage occurring between the catheter shaft and the advancement device drive wheel. This is 3 times the value expected with clinical use.
- A delayed response is experienced at the distal tip of the catheter if it is not placed in a compressed state prior to activating the CAD.
- Movement of the catheter distal tip is approximately 77% of the movement of the proximal shaft at the location of the advancement device.

SET-UP AND RECOMMENDED USE

SET-UP

It is recommended to secure the guide catheter to the patient approximately 3.5-6.0 cm distal of the hemostatic connector by sterile tape, a hemostatic clamp, etc. The catheter should be secured to the CAD approximately 5.0-7.5 cm proximal of the hemostatic Y-valve connector following the "Loading Catheter" instructions outlined below. The CAD can be held in hand or against the patient with slight pressure. This set-up allows for the CAD to be held static during lasing while providing the physician the opportunity to retract or advance the catheter with the CAD should it be necessary.

Prior to lasing, select the desired advancement rate using the speed control knob. The speed control knob allows the user to select one of ten discreet speeds. The units of the labeled speeds are microns per second.

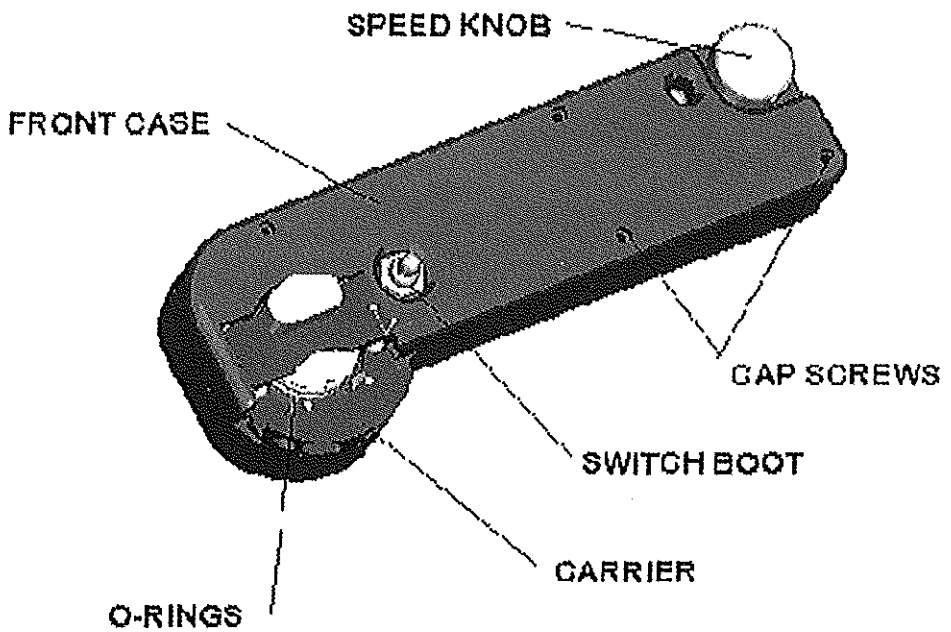


Figure 1. Catheter advancement device (CAD)

USE

LOADING CATHETER

After the catheter has been advanced to a point just proximal of the lesion, the catheter advancement device may be placed on the proximal catheter shaft. Depress the knob on the spring-loaded carrier in the direction of the arrow. Position the catheter in the center of the drive wheel and idler wheels and release the carrier knob to secure the catheter in the advancement device. Slide the catheter advancement device and catheter forward in unison until the catheter engages the lesion. This places the catheter under slight compression in the guide catheter. It is important that the catheter be under compression, not tension, prior to starting the catheter advancement device during lasing.

ACTIVATION OF ADVANCEMENT DEVICE

The advancement device shall be turned on simultaneously with the activation of the laser foot switch and turned off when the lasing train is terminated either by the user or by the laser software. An indicator light, located next to the speed control knob, will illuminate when the switch is moved to the on position.

OPTIONAL

UTILIZING THE CLAMPING MECHANISM

First clip or slide the guiding catheter clamp onto the hub of the hemostatic Y-valve that attaches to the guide catheter. Slide the catheter advancement device proximal so the clamp is on the proximal half of the hub. Be sure to use a hemo-valve that insures hemostasis while allowing uninhibited catheter movement. If the CAD and catheter are withdrawn or advanced by hand while utilizing this set-up, be careful to remove the hemostatic valve from the CAD clamp.

OPTIONAL

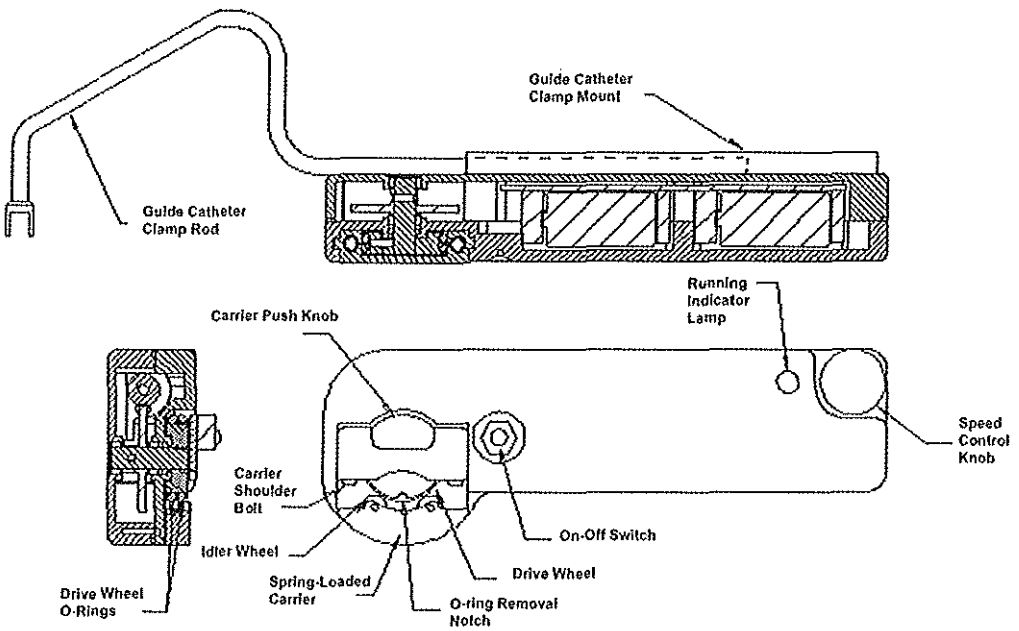
ATTACHING SAFETY LINE

The safety line attaches to the CAD and the catheterization table to prevent the device from falling to the floor should it be dropped.

To install the safety line, insert a washer onto the thumbscrew. Pass the thumbscrew through the eyelet of the safety line and screw into the threaded hole on the backside of the CAD. Use the threaded hole farthest from the drive wheel portion of the CAD. The safety line is attached to the catheterization table by looping the line around the bar on the table and adjusting the safety line for the proper length. Clamp the safety line back onto itself at the location for proper length adjustment.

CLEANING

After completion of the procedure, the spring-loaded carrier, drive wheel o-rings, and guide catheter clamp assembly may be removed for cleaning if necessary. If the unit does not become soiled during the procedure, disassembly of the unit is not required. Use the screwdriver to remove the two bolts securing the carrier to the advancement device. Use the pick to remove the o-rings from the drive wheel. This is most easily accomplished by inserting the pick into the notch on the drive wheel and underneath the top o-ring. Next, pry the o-ring upward and pull to one side to remove from the drive wheel. Repeat with the second o-ring. The guide catheter clamp rod may be pulled out of its mounting hardware, and the mounting hardware can be removed by removing the two screws securing it to the catheter advancement device case. The carrier, shoulder bolts, compression springs, o-rings, and guide catheter clamp assembly should be immersed in a aqueous high-level disinfectant (phenolic or quartenary ammonium) according to established hospital procedures. Prolonged immersion or soaking of the motorized portion of the advancement device must be avoided. The motorized portion may be dipped briefly in the previously mentioned aqueous solution to wet the exterior for further cleaning.



Spectranetics

The Spectranetics Corporation

Figure 2 Catheter advancement device, blueprint

To clean the motorized portion of the advancement device, use routine hospital or clinical procedures for aqueous washes. Use cleaning brushes to remove contamination from irregular surfaces such as the guides for the spring loaded carrier, the surface of the drive wheel, holes in the heads of the housing screws and surfaces of the immersed components. After cleaning, rinse the drive unit and disassembled hardware with purified water and allow to air dry.

STERILIZATION

Reassemble the parts of the catheter advancement device that were removed during cleaning prior to sterilization. Wrap or containerize the advancement device for steam sterilization according to practices at the hospital or clinic where the device is being used. Expose the catheter advancement device to a standard hospital autoclave cycle. Remove the catheter advancement device as soon as possible after comple-

tion of the autoclave cycle. Document exposure, and transfer into use as a sterile item, again according to the routine procedures in place at the respective hospital or clinic.

APPENDIX 2

Methode voor het verkrijgen van een homogene lichtdistributie (HLD) bij intravasculaire bestraling met laserlicht, alsmede daarbij te gebruiken lasercatheter, en werkwijze voor het vervaardigen daarvan

Jaap N. Hamburger, Geert H.M. Gijsbers

Dutch patent application no. 9300064 concerning
the concept of homogeneous light distribution

METHODE VOOR HET VERKRIJGEN VAN EEN HOMOGENE LICHTDISTRIBUTIE (HLD) BIJ INTRAVASCULAIRE BESTRALING MET LASERLICHT, ALSMEDE DAARBIJ TE GEBRUIKEN LASERCATHETER, EN WERKWIJZE VOOR HET VERVAARDIGEN DAARVAN

De uitvinding heeft betrekking op een methode voor het verkrijgen van een homogene lichtdistributie (HLD) bij intravasculaire bestraling met laserlicht, waarbij via een lasercatheter, die een bundel flexibele, lichtgeleidende vezels bevat, het licht van een excinierlaser wordt ingestraald in een bloedvat voor topische weefselablatie bij vaatvernauwingen.

Vaatvernauwing als gevolg van arteriosclerose en in het bijzonder atherosclerose vormt een ernstige bedreiging voor de gezondheid van de mens.

Ischaemische hartziekte, waaronder het acute myocardinfarct, is kwantitatief gezien de belangrijkste sterfte oorzaak in de westerse wereld. Het proces dat doorgaans aan deze ziekte ten grondslag ligt, is de atherosclerose, welke leidt tot vernauwing, c.q. afsluiting van de kransslagaderen. Tegen het eind van de zeventiger jaren werd een techniek geïntroduceerd, de zogenaamde Percutane Transluminale Coronair Angioplastiek (PTCA), welke het mogelijk maakte om via de bloedbaan, met behulp van een mechanische kracht (te weten het opblazen van een klein ballonnetje) dergelijke vernauwingen in kransslagaderen op te heffen. Inmiddels blijkt PTCA een betrouwbare en veilige behandelingsmethode te zijn, met een initieel hoog behandelingssuccespercentage. De belangrijkste tekortkoming van deze techniek wordt gevormd door het hoge restenoseringspercentage. Hiermee wordt bedoeld de kans dat na een succesvolle behandeling op de behandelde plaats in de kransslagader opnieuw een zodanige vernauwing ontstaat, dat deze aanleiding geeft tot hernieuwde klachten en/of klinische verschijnselen van myocardiale ischaemie. Uit literatuurgegevens blijkt dat de kans op restenosering het grootst is in de eerste zes maanden volgend op behandeling en in de orde van grootte ligt van 30 tot 40 % van de initieel succesvol behandelde afwijkingen. De oorzaak van dit restenoseringsproces is nog niet geheel verklaard, doch lijkt wel gerelateerd te zijn aan de invloed van mechanische kracht op de vaatwand.

Met het streven dit restenoseringspercentage te verlagen werden in de afgelopen jaren diverse nieuwe technieken ontwikkeld ter vervanging van

PTCA. Een voorbeeld hiervan is de introductie van Excimer Laser Coronair Angioplastiek (ELCA), een techniek welke gebruik maakt van laserlicht.
In de afgelopen jaren is de ontwikkeling van nieuwe typen lasercatheters er onder meer op gericht geweest, om gebruik te maken van meer vezels van een kleinere diameter, teneinde de flexibiliteit van de catheter te vergroten, Voor alle op dit moment commercieel verkrijgbare lasercatheters voor ELCA geldt, dat er door de gebruikte catheterconfiguratie, ondanks een geringe divergentie van de uittredende lichtbundeltjes, geen sprake is van overlapping van het uittredende licht op het weefseloppervlak. Er vindt zodoende laserweefselinteractie plaats op het niveau van elke individuele vezel, met rondom elke vezel een zogenaamde "dode ruimte".
Echter, door berekeningen met behulp van een mathematisch model welke het gedrag van fotonen beschrijft in weefsel (het zogenaamde Monte Carlo simulatiemodel), werd een direkte relatie gevonden tussen de grootte van de lichtenergie op een willekeurig punt in het weefsel (fluence rate per irradiance) en de diameter van de gebruikte vezel. Dit suggereert dat met eenzelfde laserenergiedichtheid met behulp van een brede vezel meer weefsel per tijdseenheid en oppervlakte-eenheid verwijderd kan worden dan met een smalle vezel. Dit kon inderdaad experimenteel worden bevestigd.
Volgens de uitvinding is nu een systeem ontwikkeld, waarbij enerzijds door gebruikmaking van fijne vezels met een kleine diameter de flexibiliteit van de catheter kan worden gewaarborgd, terwijl anderzijds het uittredende licht zodanig wordt gehomogeniseerd, dat dit als het ware uit een enkele brede vezel lijkt te komen.
Daartoe voorziet de uitvinding in een methode zoals omschreven in de aanhef, met het kenmerk, dat de uit fijne vezels bestaande vezelbundel aan haar lichtuittree-einde is afgesloten door een op de vezeleinden aansluitend, een integraal geheel daarmee vormend, lichtdoorlatend venster waarvan de brekingsindex is aangepast aan die van het vezelmateriaal, en waarvan de dikte zodanig is gekozen, dat lichtconussen, die uittreden uit afzonderlijke vezels, binnen het venster tot overlapping komen.
De uitvinding voorziet verder in een lasercatheter, te gebruiken bij deze methode, bestaande uit een holle kern van flexibel, inert kunststofmateriaal, bijvoorbeeld polytetrafluorethyleen, omgeven door een coaxiale bundel dunne, beklede kwartsvezels, welke bundel is ingevat in een buitenmantel van flexibel, inert materiaal, met het kenmerk, dat de lichtuittree-einden van de kwartsvezels zijn versmolten met

een gemeenschappelijk afsluitend kwartsvenster.

Met deze catheterconfiguratie kon experimenteel opnieuw een verdere toename van de weefselablatie-efficiëntie worden aangetoond.

Het direkte voordeel van deze efficiëntietoename is dat ook met lagere laserenergie weefsel verwijderd kan worden. Aangezien de mate van mechanische beschadiging van de vaatwand - door schokgolfformatie en gasvorming gerelateerd is aan de hoogte van de ingevoerde laserenergie, kan zodoende een aanzienlijke vermindering van randzonebeschadiging bereikt worden. Het werken met lagere laserenergie geeft bovendien het bijkomende voordeel, dat de lasercatheter langer kan worden gebruikt.

De toepassing van een venster om laserlicht van een multivezelcatheter te homogeniseren werd (om andere redenen) reeds eerder toegepast in combinatie met een argon- en een holmiumlaser. Daarbij wordt het venster op mechanische wijze vastgezet tegen de vezeltips. Aangezien het excimerlaserlicht, dat bij de methode volgens de uitvinding gebruikt wordt een aanmerkelijk kortere golflengte heeft dan argon of holmium, is het alleen al om veiligheidsredenen niet mogelijk om voor de excimerlaser gebruik te maken van een apart aan de cathetertip te bevestigen venster. Dit probleem wordt bij de uitvinding ondervangen doordat het venster een integraal geheel vormt met de cathetervezels zelf.

Een doelmatige werkwijze voor het vervaardigen van een lasercatheter volgens de uitvinding kan zijn gekenmerkt door de volgende stappen:

- het vormen van een bundel van parallelle, fijne kwartsvezels,
- het smelten van het ene uiteinde van deze bundel tot een kwartsdruppel.
- het slijpen en polijsten van deze druppel tot een venster van gewenste afmetingen,
- het centraal doorboren van het venster,
- het dompelen van de vezelbundel buiten het venster in een bekledingsbad en drogen van de beklede vezels.
- het aanbrengen van de holle kern door de boring in het venster,
- het invatten van de bundel in een buitenmantel.

Rekening houdende met de geringe warmtegeleidingscapaciteit van glas kan een dusdanig versmelten van de tips van de vezels plaatsvinden, zonder dat daardoor beschadiging in het kwarts ontstaat. Na de verdere bewerkingen. zoals het slijpen en polijsten tot de juiste dimensies voor het venster en het doorboren van het venster waar doorheen het guidewire-kanaal (de

kern) wordt aangebracht, en na versteviging door een kunstharslaag (epoxy) en invatten in een kunststofmantel, wordt een lasercatheter voor ELCA verkregen, met een uitstekende HLD aan het ablerende oppervlak.

Het is ook mogelijk om het venster te vervaardigen vanuit een smeltvormbad, dat gesmolten kwarts in de vorm van het gewenste venster bevat, Daartoe voorziet de uitvinding in een werkwijze voor het vervaardigen van een lasercatheter, gekenmerkt door de volgende stappen:

- het vormen van een bundel van parallelle, fijne kwartsvezels,
- het inbrengen van het ene einde van deze bundel in een venstervormbad van gesmolten kwarts,
- het stollen van het vormbad waardoor een kwartsvenster ontstaat,
- het centraal doorboren van het venster,
- het dompelen van de vezelbundel buiten het venster in het bekledingsbad en drogen van de beklede vezel-s, ~ het aanbrengen van de holle kernen door de boring in het venster, - het invatten van de bundel in een buitenmantel.

De uitvinding wordt thans nader toegelicht aan de hand van de tekening. In de tekening toont:

Fig. 1 een schematisch aanzicht van het laser-cathetersysteem volgens de uitvinding,

Fig. 2 een schematische dwarsdoorsnee van de catheterbuis,

Fig, 3 een schematische dwarsdoorsnee van het distale einde van de catheterbuis, en

Fig. 4 in schematische langsdoorsnee het distale einde van de catheterbuis waar kwartsspiegel en kwartsvezels integraal met elkaar versmolten zijn.

Zoals getoond in de tekening bestaat het feitelijke lasersysteem uit een excimerlaser 1, waarop een lasercatheter 2 is aangesloten, Een excimerlaser (Excited Dimer Laser) is een ultraviolet laser, waarvan het lasermedium gevormd wordt door een XeC1-mengsel. De laser is voorzien van een gebruikelijk reflectie- en focusseringssysteem, bestaande uit lenzen en spiegels (niet getoond) en heeft zijn uitgang aangesloten op de lasercatheter 2.

Zoals te zien is in Figure 2 bestaat de catheterbuis uit en holle kern 3 van flexibel, sterk kunststofmateriaal, bijvoorbeeld een teflonbuis, welke omgeven is door een groot aantal zeer fijne kwartsvezels 4. Deze kwartsvezels met een diameter van 50 mm zijn bekleed met een gebruikelijke cladding, en bevinden zich dicht opeengestapeld rondom de kernbuis 3. De kwartsvezels worden bijeengehouden door een epoxyhars en zijn coaxiaal rondom de kern ingevat in een buitenmantel 5, die

eveneens van soepel teflon kan zijn.
Deze zeer buigzame catheterbuis is bedoeld om ingebracht te worden in een slagader, waarin UV-bestraling ter verwijdering van weefsel moet worden uitgevoerd.
De holle kern vormt een zogenaamd guidewire-kanaal. Bij het inbrengen van een lasercatheter in een slagadersysteem wordt eerst een dunne metalen geleidedraad ingebracht via een vooraf ingebrachte kunststof guiding-catheter, waarna de lasercatheter over de geleidedraad heen naar binnen wordt geschoven.
Aan het distale einde van de catheter, waar het laserlicht uitstraalt, bevindt zich een kwartsvenster 6, dat integraal versmolten is met de kwartsvezels 4. Zoals te zien in fig 4, gaan de kwartsvezels van de catheter continu over in het venster 6, waardoor de doorgelaten energie ongehinderd het kwartsvenster kan bereiken, om aldaar te worden gehomogeniseerd. Rekening houdende met de divergentie van de uit de afzonderlijke kwartsvezels tredende lichtkegels kan de dikte van het kwartsvenster zodanig worden gekozen, dat de afzonderlijke lichtkegels elkaar overlappen binnen het venster. Bij 50 mm vezels is een dikte van 1,25 mm voor het kwartsvenster voldoende. De diameter van het kwartsvenster is afgestemd op de afmeting van de catheterbuis, die in het algemeen een diameter heeft in afhankelijkheid van de beoogde toepassing lopende van 1,3 tot 2,0 mm.
Het kwartsvenster 6 heeft een centrale doorboring 7 met het oog op het doorlaten van de holle teflonkern 3.
Direkt achter het kwartsvenster 6 is een dunne ring bladgoud aangebracht. die dient als markering voor het vaststellen van de juiste lokatie van de cathetertip in een te behandelen bloedvat.
Een bijzonder doelmatige wijze van vervaardigen het integrale venster 6 is om een naakte bundel kwartsvezels aan hun ene einde in vacuum te verhitten tot boven het smeltpunt van kwarts (ca. 1200 °C). Daarbij zullen de vezelpunten met elkaar versmelten tot één kwartsdruppel, die vervolgens door polijsten en slijpen kan worden afgewerkt tot een doelmatige integrale kwartsspiegel. Vervolgens kan daarin een centrale opening wordt geboord, waar doorheen de holle teflonkern 3 kan worden ingebracht en doorgevoerd tussen de bundel holle vezels, nadat deze zijn bekleed met een geschikte cladding. Aldus kan op relatief eenvoudige wijze een bijzonder doelmatige en met hoge efficiëntie werkende catheter worden vervaardigd.
Dankzij de uitvinding is het mogelijk gemaakt, om met zeer fijne en dus zeer soepele kwartsvezels een groot bestralingsrende-ment van homogene straling te bereiken dankzij de voorziening van een integraal met de kwartsvezels gevormd venster. Met de lasercatheter volgens de uitvinding zijn storende randbeschadigin-

gen bij inwendige slagaderbestraling met excimerlicht nagenoeg verdwenen.
Verdere modificaties en variaties van de uitvinding zullen de vakman na kennisname van het bovenstaande duidelijk zijn.

CONCLUSIES

1. Methode voor het verkrijgen van' een homogene lichtdistributie (HLD) bij intravasculaire bestraling met laserlicht, waarbij via een lasercatheter, die een bundel flexibele, lichtgeleidende vezels bevat. het licht van een excimerlaser wordt ingestraald in een bloedvat voor topische weefselablatie bij vaatver nauwingen, m e t h e t k e n m e r k, dat de uit fijne vezels bestaande vezelbundel aan haar lichtuittreeeinde is afgesloten door een op de vezeleinden aansluitend, een integraal geheel daarmee vormend, lichtdoorlatend venster, waarvan de brekingsindex is aangepast aan die van het vezelmateriaal, en waarvan de dikte zodanig is gekozen, dat lichtconussen, die uittreden uit afzonderlijke vezels, binnen het venster tot overlapping komen,

2. Lasercatheter te gebruiken bij de methode volgens conclusie 1, bestaande uit een holle kern van flexibel, inert kunststofmateriaal, bijvoorbeeld polytetrafluorethyleen, omgeven door een coaxiale bundel dunne, beklede kwartsvezels, welke bundel is ingevat in een buitenmantel van flexibel, inert materiaal, m e t h e t k e n n e r k, dat de lichtuittree-einden van de kwartsvezels zijn versmolten met een gemeenschappelijk afsluitend kwartsvenster.

3. Werkwijze voor het vervaardigen van een lasercatheter volgens conclusie 2, g e k e n m e r k t d o o r de volgende stappen:
- het vormen van een bundel van parallelle. fijne kwartsvezels,
- het smelten van het ene uiteinde van deze bundel tot een kwartsdruppel,
- het slijpen en polijsten van deze druppel tot een venster van gewenste afmetingen,
- het centraal doorboren van het venster,
- het dompelen van de vezelbundel buiten het venster in een bekledingsbad en drogen van de beklede vezels.
- het aanbrengen van de holle kern door de boring in het venster.
- het invatten van de bundel in een buitenmantel.

4. Werkwijze voor het vervaardigen van een lasercatheter volgens conclusie 2, g e k e n m e r k t d o o r de

volgende stappen:

- het vormen van een bundel van parallelle. fijne kwartsvezels,
- het inbrengen van het ene einde van deze bundel in een venstervormbad van gesmolten kwarts,
- het stollen van het vormbad, waardoor een kwartsvenster ontstaat,
- het centraal doorboren van het venster,
- het dompelen van de vezelbundel buiten het venster in het bekledingsbad en drogen van de beklede vezels,
- het aanbrengen van de holle kernen door de boring in het venster.
- het invatten van de bundel in een buitenmantel.

UITTREKSEL

Bij Excimer Laser Coronair Angioplastiek (ELCA), een techniek, waarbij het licht van een excimerlaser via een kwartsmultivezelcatheter wordt ingestraald in kransslagaderen op plaatsen waar deze vernauwd zijn, wordt homogene lichtdistributie (HLD) bij intravasculaire bestraling verkregen doordat de lasercatheter, bestaande uit een coaxiale bundel van zeer fijne kwartsvezels aan het lichtuittree-einde van de bundel voorzien is van een afsluitend kwartsvenster dat door versmelting met de eindtips van de vezels een integraal geheel daarmee vormt. De diameter van het venster is aangepast aan de diameter van de vezelbundel, en de dikte van het venster is zodanig gekozen dat uit de afzonderlijke kwartsvezels tredende lichtconussen binnen dit venster tot overlapping komen. Daardoor wordt bereikt, dat aan de uittreezijde van het venster een homogene lichtdistributie ontstaat, vergelijkbaar met die, wanneer het licht zou zijn geleid door één enkele, brede vezel.

Dankzij de grote homogeniteit van het aldus verkregen bestralingslicht zijn de zogenaamde "dode ruimtes" tussen afzonderlijke vezels geëlimineerd, en treden er geen randzone-effekten op.

De nieuwe lasercatheter behoudt het voordeel van het gebruik van een groot aantal fijne vezels, waardoor een soepele catheter kan worden verkregen. maar heeft het nadeel daarvan, namelijk een aanzienlijk aantal dode ruimtes, geëlimineerd.

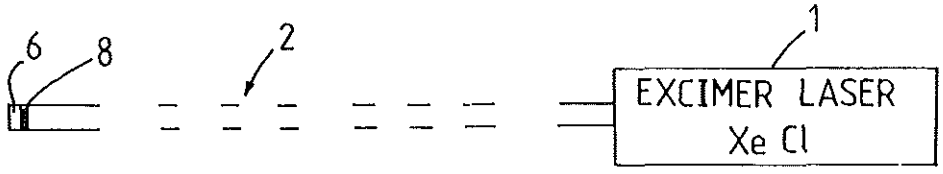


FIG. 1

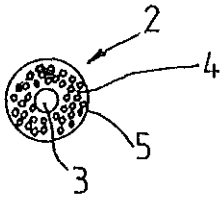


FIG. 2

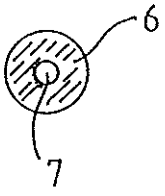


FIG. 3

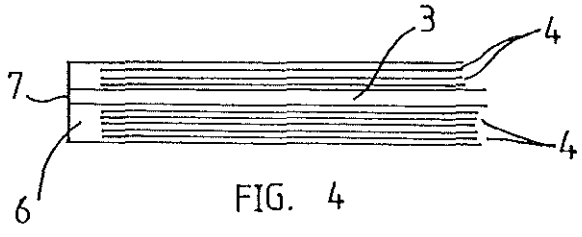


FIG. 4

SAMENVATTING EN CONCLUSIE

SAMENVATTING VAN HET PROEFSCHRIFT "NIEUWE ASPECTEN VAN EXCIMER LASER CORONAIRE ANGIOPLASTIEK FYSISCHE ASPECTEN EN KLINISCHE RESULTATEN"

HET *IN VITRO* ONDERZOEK

In de cardiologie wordt gebruik gemaakt van een zogenaamde excimer laser. De excimer laser genereert laserlicht in het ultraviolette deel van het electro-magnetische spectrum. Het verwijderen, of "ableren" van vaatweefsel met behulp van ultraviolet laserlicht is gebaseerd op twee fysische fenomenen. Enerzijds worden moleculaire verbindingen tussen grote organische moleculen door de energie van de laserlicht deeltjes verbroken. Het resultaat hiervan is dat een deel van de moleculen in het weefsel overgaan in de gasfase. Het op deze wijze ontstane gas is in water (bloed) niet oplosbaar. Dit proces wordt photochemische dissociatie genoemd en is specifiek voor laser-weefsel interactie met ultraviolet laserlicht. Het tweede mechanisme dat een belangrijke rol speelt is de omzetting van laserenergie in warmte. Omdat een deel van de energie die vrijkomt niet resulteert in photo-chemische dissociatie, maar direct wordt omgezet in warmte, zal het bestraalde weefsel in temperatuur stijgen.

De volgende uitkomsten van ons *in vitro* onderzoek waren essentieel voor de wijze waarop wij thans excimer laser-weefsel interactie begrijpen en de toepassing van laser therapie bij de patienten trachten aan te passen.

Ten eerste bleek de productie van het in water niet-oplosbare gas vrij aanzienlijk te zijn. Als voorbeeld: bij het verwijderen van een kransslagadervernauwing met een lengte van 10 mm met behulp van een zogenaamde High-Density laser catheter wordt circa 382 µl niet-oplosbaar gas geproduceerd. Accumulatie van deze hoeveelheid gas in een vloeistof (zoals bijvoorbeeld in bloed) leidt tot de vorming van een gasbel met een doorsnede van circa 9 mm. Aangezien de diameter van een normale kransslagader 2,5 tot 5 mm bedraagt zal een dergelijk grote gasbel schade kunnen veroorzaken door overrekking van de wand van het bloedvat. Tevens zou een dergelijke hoeveelheid niet-oplosbaar gas de normale bloedstroom door de kransslagader kunnen belemmeren.
Ten tweede berekenden wij dat slechts vijf procent van de laserenergie wordt gebruikt voor de vorming van dit niet-

oplosbare gas. Dat betekent, dat (volgens de wet van behoud van energie) het grootste deel van de laserenergie wordt omgezet in warmte. Deze warmte vorming blijkt dusdanig intens, dat aan de tip van de lasercatheter na iedere laserpuls een waterdampbel wordt gevormd. Deze waterdampbellen expanderen in enkele microseconden tot een diameter van circa 3 tot 5 mm. Derhalve zouden ook deze waterdampbellen kunnen bijdragen tot het ontstaan, cq verergeren van vaatwand beschadigingen. Van belang is, dat zowel de hoeveelheid gas, als de grootte van de waterdampbellen een directe relatie bleken te hebben met de energiedichtheid aan de tip van de lasercatheter. Dat wil zeggen: hoe hoger de energie per mm^2 aan de tip van de lasercatheter is, des te meer niet-oplosbaar gas wordt geproduceerd en hoe groter de waterdamp bellen zijn welke worden gevormd. Indien de relatieve grootte van dat deel van de cathetertip dat licht uitstraalt groter wordt, neemt de energie dichtheid (energie per mm^2) aan de tip van de catheter juist af (dat wil zeggen, indien de totale energie afgifte door de laser constant wordt gehouden). Hierdoor nemen de gasproductie en de waterdampbel grootte ook af. Een dergelijke verlaging van de energiedichtheid kan worden bereikt door toepassing van de techniek van "homogene licht distributie". Door toepassing van deze techniek wordt het licht dat uitstraald uit de individuele fibers in een multifiber lasercatheter, voordat het licht de catheter "verlaat", eerst verstrooid in een quartz venster aan de tip van de lasercatheter. Het zelfde effect –in mindere mate – wordt nagestreefd door toepassing van de zogenaamde High-Density techniek. Bij deze techniek wordt het uittredende licht niet eerst verstrooid, maar in de lasercatheter verdeeld over een groter aantal laserlichtgeleidende quartz fibers.

Tenslotte bleek dat de snelheid waarmee een lasercatheter door een vernauwing in een bloedvat wordt opgevoerd van belang te zijn voor de effectiviteit waarmee een lasercatheter vaatweefsel kan verwijderen. Deze snelheid werd aanvankelijk geschat op circa 0.5 mm/s, doch bleek bij nader onderzoek veel lager te zijn. Deze waarneming resulteerde in het ontwerpen van een gemotoriseerde constructie welke een lasercatheter kan voortbewegen met gecontroleerde snelheden tussen de 0.3 en 0.9 mm/s. Dientengevolge is recent de High-Density catheter techniek en het gebruik van de Motorized Advancement Device in de kliniek geïntroduceerd. Het is nu echter nog te vroeg om conclusies te formuleren ten aanzien van de klinische resultaten welke worden bereikt met behulp van deze nieuwe laser toepassingen.

DE KLINISCHE STUDIES

De percutane transluminale coronair angioplastiek (PTCA) ofwel het "Dotteren"van de kransslagaderen werd als klinische therapie geïntroduceerd door Andreas Grüntzig in 1977. Inmiddels zijn – naast de klassieke ballon dilatatie – diverse andere catheter technieken ontwikkeld die ten doel hebben om de door aderverkalking ontstane vernauwingen in de kransslagaders op te rekken, weg te boren, te snijden, danwel weg te branden. Wat al deze catheter technieken met elkaar gemeen hebben, is dat de catheters zelf niet stuurbaar zijn. Dat wil zeggen, om een ballonnetje op de plaats van de vernauwing te krijgen is de catheter net als een trein, afhankelijk van rails om op de juiste plaats te komen. In het geval van een PTCA is de "rails"een dun metalen draadje (0.014-inch) dat door de kransslagader langs de vernauwing wordt gelegd, een zogenaamde gidsdraad. Vervolgens wordt de catheter over dit metalen draadje naar voren geschoven om de te behandelen plaats te bereiken. De Dotter techniek is derhalve primair gericht op het oprekken van vernauwingen. Een technisch geheel andere situatie ontstaat indien de klachten van de patient niet worden veroorzaakt door een vernauwing, maar door een totale afsluiting van een kransslagader. In dat geval moet eerst een gidsdraad door de verstopping tot achter in het bloedvat worden gebracht, alvorens de verstopping met behulp van een balloncatheter kan worden geopend. Echter, de in de literatuur vermelde succes percentages van een dergelijke behandeling waren aanvankelijk niet hoger dan circa 50%, meestal tengevolge van het feit dat het niet lukte om een metalen draadje door een dergelijke verstopping te krijgen. Gebruikmakend van de specifieke eigenschappen van lasertechniek werd in samenwerking met de firma Spectranetics Corporation Inc. (gevestigd in Colorado Springs, Colorado, U.S.A.) een stuurbaar gidsdraadje ontwikkeld waarin enkele laserlicht geleidende fibertjes zijn vervat. Zodoende kon met behulp van laser-energie het passeren van verstoppend materiaal mogelijk worden vereenvoudigd. De vraag of de "laser gidsdraad" techniek veilig en in een hoger percentage dan de conventionele gidsdraden succesvol zou zijn bij de behandeling van patienten met totaal afgesloten kransslagaderen werd bestudeerd in de "TOTAL pilot-studie", de "TOTAL surveillance study", en in de gerandomiseerde "TOTAL trial". Zowel het directe resultaat, alswel het resultaat op midellange termijn werden beoordeeld met behulp van quantitatieve coronair angiografie (QCA). Tevens was voorzien in een poliklinische controle ter beoordeling van eventuele "klinische eindpunten" (sterfte, myocard infarct, coronaire

bypass operatie, re-PTCA of angina pectoris) na 30 dagen, 6 maanden en 1 jaar.

RESULTATEN

De TOTAL pilot-study werd uitgevoerd in het Thoraxcentrum van het Dijkzigt Ziekenhuis. In deze studie werden 51 patienten bij wie een procedure met conventionele gidsdraden had gefaald alsnog met behulp van een laser gidsdraad behandeld. In de europese surveillance study, uitgevoerd in samenwerking met twintig europese klinieken, was de laserprocedure succesvol in 60% van 345 gevallen waarin conventionele draden hadden gefaald. Echter, het succes van de laser gidsdraad studies leidde in de jaren 1997-1998 tot de ontwikkeling van kwalitatief sterk verbeterde conventionele gidsdraden, speciaal ontwikkeld voor het passeren van totale afsluitingen. Met name ten gevolge van de klinische introductie van deze verbeterde mechanische gidsdraden was het voordeel van de lasergidsdraad in de gerandomiseerde TOTAL trial (303 patienten) statistisch niet langer significant. De patient was echter toch de uiteindelijke "winnaar": de belangrijkste klinische winst die werd bereikt door het doen van deze projecten, was een geleidelijke toename in de (internationaal gepu-bliceerde) succespercentages van de behandeling van patienten met een afgesloten kransslagader. Als voorbeeld, in 1998 bleek in onze afdeling - in een tijdsbestek van vier jaar – dit percentage te zijn gestegen van circa 50% tot circa 75%. Tevens kon bij deze patienten met behulp van echocardiografie al binnen 48 uur na een geslaagde behandeling een belangrijke verbetering van de contractiekracht van de linker hartkamer worden aangetoond.

Tenslotte bleek, dat zich minder vaak ernstige complicaties voordeden in de groep van patienten die een geslaagde Dotter behandeling, danwel een succesvolle coronaire bypass operatie hadden ondergaan ter behandeling van een totale afsluiting, dan in de groep van patienten die na een niet geslaagde Dotterbehandeling verder werden behandeld met behulp van medicijnen.

TOEKOMSTVERWACHTING

In het afgelopen jaar werd een aanvang gemaakt met de evaluatie van de waarde van laser behandeling in combinatie met brachytherapie (locale, intravasculaire bestraling met radioactieve ß-stralen) voor de behandeling van patienten met recidiverende littekenweefselvorming na eerdere intracoronaire stentimplantatie. Nochtans zijn veertien patienten succesvol met deze combinatie therapie behandeld. Aangezien het aantal behandelde patienten nog gering is, en het klinisch vervolgonderzoek bij deze patienten nog niet is voltooid, kunnen vooralsnog geen conclusies worden getrokken ten aanzien van de effectiviteit van deze combinatie therapie op de langere termijn.

ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

In the fifth century before common era the Roman army marched for the city of Corioli, defeating the army of the Volscians.[1] Amongst the most distinguished of the young soldiers in the camp at that time was Cnaeus Marcius. It was a brilliant strategic maneuver by Marcius, which had forced the Volscians to surrender, for which he earned the epithet, Coriolanus. Following his achievements on the battlefield, Coriolanus went into politics. In a bitter dispute with the Roman Senate, he denied the recently acquired right of the Plebeians to have their own magistrates. To underscore his arguments, he joined forces with the Volscians, whose defeat he had just masterminded. What followed was a siege of Rome, resulting in a severe famine. As the Romans were not capable of breaking the siege by force, various political and religious leaders were sent to negotiate a political solution. However, Coriolanus refused to compromise and bitterly continued the siege, thus starving Rome's population. As a last resort, the Senate turned to Veturia, the mother of Coriolanus, and Volumnia, his wife. They succeeded in inducing the aged Veturia to go with Volumnia and her two little sons to the enemies' camp. On their arrival a message was sent to Coriolanus that a large body of women were present. He had remained unmoved by the power of the State in the persons of its ambassadors and its priests; he was still more unyielding to the tears of women. Then one of his friends said to him, "Unless my eyes deceive me, your mother and wife and children are here." Coriolanus sprung from his seat to embrace them. It was only when the commander was confronted with his (hungry) beloved ones that he realized the humanitarian consequences of his military actions. He broke down in tears and moved his camp away from the city of Rome.

This story is a classical example of the specific capacity of women to put a man's work into a different perspective. This book on excimer laser coronary angioplasty had not been written without the adamant support of my wife, Iris. She changed my house into a home, allowed me to work on the manuscript during endless nights and weekends, raised and fed our children, and still allowed me the illusion of being a husband and father. In comparison, I realize that my contribution to this book pales into insignificance.

Writing a thesis is a long and humbling process of thoughts, ideas, and work shared with many others. The first person to be acknowledged is Professor dr. Patrick W. Serruys, my promotor. Dear Patrick, I clearly remember the first meeting we had in November 1992, when I came to Rotterdam to show you my initial findings on the topic of homogeneous light distribution. The research projects described in this book could, and would not have been realized if it was not for your scientific curiosity, imagination and inexhaustible drive. Your encyclopedic knowledge of interventional cardiology and your capacity to analyze complex situations make you an unparalleled medical teacher.

Much I owe to Professor dr. Jos R.T.C. Roelandt, who from the very start, strongly supported the efforts to expand the laser research in our department, and gave me the opportunity to further my career at the Thoraxcenter. Dear Jos, I remember when, shortly after the opening of the Laser Laboratory in Septem-ber 1993, you told me: "You are a difficult man, but successful. Continue to be difficult." I hereby apologize for all those moments that I was difficult and less successful.

A special and profound word of gratitude is reserved for two of my teachers who supported me in my efforts to write this thesis, and greatly honored me by making the effort to travel to the Netherlands to participate in the occasion of my PhD defense: Professor dr. Martin Leon, Head Department of Cardiology at the Washington Hospital Center, Washington D.C., U.S.A. and Professor dr. Raphael Beyar, Dean of the Medical Faculty at the Technion, Israel Institute of Technology, Haifa, Israel.

Dear Marti, during my first visit to your unequaled "TCT" course in Washington, in February 1993, I was overwhelmed by your knowledge, and your capacity to integrate and present a vast range of topics within the field of cardiology. As such, you seemed to redefine interventional cardiology during a single course. Since then, I came to realize that with each following edition of "TCT", your personal, "seamless" presentation of each and every aspect of coronary intervention was nothing less than a yearly redefinition of our profession. The value of your detailed, and critical comments during the years that the manuscript of this book came into being, cannot be overestimated. That you call me "your friend" I consider as one of my greatest achievements in life.

Dear Rafi, the combination of your precise, and critical approach to medical science, and your warm, personal friendship have been a continuing stimulus for me. Throughout the past seven years we have had the chance to work

together on various projects, and each time you invited me to the Technion, or the Rambam Hospital, you succeeded in making me feel at home. I continue to look forward to work with you, inside or outside your beautiful cathlab with "a view of the ocean."

The final version of this book was considerably influenced by the involved criticism of Professor dr. ir. N. Bom, and Professor dr. P.D. Verdouw. Dear Klaas, your decisive intervention in the autumn of 1998 resulted in the, much improved, current version of this thesis. Your advice to expand the scope of the book, and not to get carried away with the rushing spirit of the moment, greatly contributed to a further maturation of the manuscript. It clearly demonstrated your position as a man who has seen all PhD students, and seen them twice.

A separate chapter could be devoted to acknowledge the co-promotores of this thesis, Dr. Ir. G.H.M. Gijsbers, and Dr. P.J. de Feijter.
Dear Geert, where can I begin to thank you for your friendship? It was you, who taught me my "first steps in science." It was you, who soberly corrected me with the right, scientific arguments, whenever I allowed myself to get carried away with associations, rather than deductions. When together, we struggled through gazillions of porcine-aortic-tissue samples, our minds shrouded by clouds of insoluble gas, our vision blurred by im-, and exploding vapor bubbles, it was you, who always managed to boost my spirit when, during moments of despair, my soul lost track and failed to see the true value of a parallel, monochromatic light beam. But above all, the fact that you allowed me to persuade you, time and again, to continue the efforts to prove the value of a homogenized light distribution, was to me the strongest, most convincing circumstantial evidence of the basic goodness of mankind. As a friend and colleague, you are second to none.
Dear Pim, you never ceased to amaze me with your creative capacity of reducing a challenging clinical problem to a "simple" situation for which you unfailingly found the most practical solution. In the whirlwind of activities in our department, your office was always "a quiet place, with a cool breeze, where the weary traveler can repose and reflect on the days' turmoil." Your critical analysis of the patient-care-related chapters in this book very much helped to improve the clarity of the clinically relevant message, hidden in the description of the collected data.

Much I owe to the support of my fellow "senior interventionists," Marcel van den Brand, Wim van der Giessen and

David Foley, who allowed me so often to spend time out of the catheterization laboratory to work on this thesis. A very special thanks to my "room-mate" David who embodies the saying "a friend in need, is a friend indeed."

A cathlab is not a cathlab without a large group of nurses and technicians. The stamina these people had in enduring fatigue and hunger in coronary procedures in which I threatened to kill everyone in the room, simply by continuing-for-another-six-hours-in-order-to-open-up-the-occluded-artery, is more than admirable. Their friendship and skilled experience contributed significantly to my training and development.

Jan Tuin, the head of the audio-visual department, and Paula Delfos were responsible for all the artwork in this thesis. Jan, as a true self-made wizard, proved to be a rich, creative source with whom many, long nights were spent, creating numerous photography and video productions.

A seperate thank you to René Sprangers, whose friendship and support during the past (twenty) years stood at the very basis of the work discribed in this thesis.

I would like to acknowledge the efforts of all those people who worked with Geert and me in the laserlaboratory; Clara, Duco, Sandjay, Virgil, Koen, Robin, Wiebe, Thelma, Jeanette, Lionne and Cora.
Critical was the support of Jan Ekas from the Erasmus University Glass Shop, who kelped us to construct HLD catheter prototypes, and Harvey Wong Loi Sing for his technical support with the gasflow measurements.

Further, I would like to acknowledge the large group of clinical fellows and research fellows at the Thoraxcenter for their friendship and support: Benno and Jeroen, Manel, Stephane, Glenn, Peter, Veronique, Marco, Mariano, Pedro, Ken, Madoka and Addy. A special thank you to Patrick Kay, who proofread the manuscript, and to Alex Wardeh, who was always willing to help out on digging-up "lost" data for a continuously expanding database.

One does not survive the day to day activities in a medical department, if not for the structural, ever available support of good secretaries. Laetitia, Monique and Ilse, I must often have caused you to have "nightmares during daytime." However, this never stopped you from helping-out on numerous occasions, and always with a smile and a friendly word. Similar gratitude goes to Anja, Claudia, Pien, Trude, Willeke, Yvonne, Arita, and Els, our manager.

Most definitively, a separate word of gratitude should go to Marianne Eichholtz, President of the Department of PhD Affairs. If it was not for her constant, and terrifying reminders of various deadlines (all of which I crossed, of course), this book would never have been finished.

Acknowledgement goes to the publishers of those Books and Journals, who allowed me to reprint previously published papers. A special 'thank you' to Alan Burgess (Martin Dunitz, Inc.), the man with the right smile over the right beau-tie, for his continuous support.

I would like to emphasize that the second part of this book is based on patient-related research. These studies could never have been conducted without the consent and compliance of many, many patients, who, for obvious reasons, remain anonymous. The openness of most of our patients, and their eagerness to share their sometimes very personal fears and hopes, are among the most impressive, and rich experiences during the past few years.

Nothing of substance is achieved without the structure supplied by a loving family. No single expression is adequate to express the support I had from my parents, Jannie and David, from Hans, Patricia and Gideon, Carrie, Geert-Jan, Aaron, Nico and Joël, and my younger sister, Marty. Where in this section do you express the love for your children, my son Reuben, and my two wickedly beautiful daughters, Melody and Eleane? In the beginning? In the middle, in the end? If it were up to me, all over the place: I must have done something right in my life to deserve such wonderful kids!

Finally, I want to mention one more name, of a friend who more than anyone else I would have liked to have been here with me, to share the joy of the occasion. As cited on the first page of this book, "Remembrance is the secret of redemption": I hope my friend Paul Ulrich (1955-1993) smiles in heaven, wrapped in a long white dress, smoking his usual cigar, looking down on me with a long drawn "Yeah..." in support.

REFERENCE

1. Titus Livius. The History of Rome, Vol. II. Editor: Ernest Rhys, Translator: Reverend Canon Roberts.

CURRICULUM VITAE

CURRICULUM VITAE

1. PERSONALIA

Name	:	Jaap Nico Hamburger
Date and place of birth	:	December 28, 1957 Amsterdam, The Netherlands
Marital status	:	Married
Married to	:	Iris Algom
Children	:	Reuben (20-08-1988), Melody (01-12-1996), and Eleane (08-11-1998)
Address	:	Nieuwe Spiegelstraat 14, 1017 DE Amsterdam,
Telephone/fax	:	31-20-62 67 443

2. EDUCATION

	Institution	Conferring	Year
Schooling (College) Degree	VWO B	Amsterdam	1976
Soloist Degree Piano	Sweelinck Academy	Amsterdam	1984
Medical School	Municipal University	Amsterdam	1986

3. RESEARCH TRAINING AND CLINICAL EXPERIENCE

Institution		Year
Slotervaart Hospital Amsterdam	Fellow Neurology	1986 - 1987
Andreas Hospital Amsterdam	Fellow Medicine	1987 - 1989
Academic Medical Center Amsterdam	Fellow Cardiology	1989 - 1993
	Member Intercollegial Quality Assessment Committee	1992 - 1993
Laser Center, Academic Medical Center Amsterdam,	Training "Lasers in Clinical Medicine",	1991

J.A. Cohen Institute, University of Leiden,	Radiation- and Radiotherapy expertise, Level 4B,	1992
Thoraxcenter, University Hospital Rotterdam,	Director, Laser Laboratory,	1993 - 1996
	Fellow, Interventional Cardiology	1993 - 1996
	Senior Interventional Cardiologist,	1996 - present
Current position	Clinical Co-Director, Dept. of Interventional Cardiology	1998 - present

4. RESEARCH PROJECTS

	Institution	Year
The abnormal knee-jerk reflex in patients with a low lumbar hernia nuclei pulposi	Slotervaart Hospital Amsterdam	1982 - 1987
308 nm laser-tissue interaction: aspects of ablation efficacy and quality	Laser Center, Academic Medical Center Amsterdam	1991 - 1993
Optimization of intracardiac ultrasound imaging using 10 MHz, 10F ultrasound catheters	Thoraxcenter, Rotterdam	1993
Evaluation and optimization of 308 nm excimer laser energy as a therapeutic tool in the treatment of symptomatic coronary artery disease	Laser Laboratory Thoraxcenter	1993 - present

Member of the Scientific Committee of the European Society of Cardiology	1994 -1998
Faculty member of the TCT, Washington	1994 - present
Faculty member of the Int. Conference on Interventional Cardiology, Jerusalem	1995 - present
Faculty member of the CCIC, Japan	1996 - present
Faculty member Live Course, Nat. Heart Centre Singapore	1996 - present
Faculty member NIR School of the Heart	1998 - present
Member of the Organizing Committee of the Thoraxcenter Stent Course	1997 - present
Recipient of the Revolving Fund Award (on: Optimization of excimer laser coronary angioplasty using HLD)	1996
Co-recipient of the Revolving Fund Award (on: Optimization of percutaneous transluminal renal angioplasty)	1997

Clinical (co-) investigator: The TOTAL Pilot-, Surveillance- and Randomized Study
The FINESS I and FINESS II Trial
The Multicenter BeStent Registry
The ROSE Trial
The ITALICS Trial
The EURO-VEGAS Study
The ADVANCE Trial (member steering committee)
The Biosense Noga and DMR Study
The ARTS Trial
Chairman of the Angiographic Committee TOTAL and ADVANCE Trials

LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

ORIGINAL PAPERS (PEER REVIEWED JOURNALS)

1 Prati F, Di Mario C, Hamburger JN, Gil R, von Birgelen C, Serruys PW. Perforation of chronic total occlusion with laser guide wire followed by multiple stent deployment: usefulness of three dimensional intra coronary ultrasound. *Am Heart J*, 1995;130;6:1285-1289

2 Hamburger JN, de Feyter PJ, Serruys PW.The laser guidewire experience: "crossing the Rubicon". In: *Semin Intervent Cardiol* ; 1996;1/2:163-171

3 Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution to reduce vessel trauma during excimer laser angioplasty. *Semin Intervent Cardiol* 1996; 1/2: 143-148

4 Ozaki Y, Violaris A, Hamburger JN, Melkert R,Foley D, Keane D, de Feyter PJ, Serruys PW. Short- and Long-Term Clinical And Quantitative Angiographic Results With The New, Less Shortening Wallstent for Vessel Reconstruction in Chronic Total Occlusion: A Quantitative Angiographic Study. *J Am Coll Cardiol* 1996;28:354-60

5 Beyar R, Roguin A, Hamburger J etal. Multicenter Pilot Study of a Serpentine Balloon-Expandable Stent (beStent): Acute Angiographic and Clinical Results. *J Interven Cardiol* 1997; 10:277-286

6 Hamburger JN, Serruys PW. The early Thoraxcenter experience with the new BeStent: a single-center, observational study. *J Interv Cardiol* 1997; 10;3:1-9

7 Hamburger JN, Gijsbers GHM, Ozaki Y, Ruygrok PN, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a pilot-study. *J Am Coll Cardiol*, 1997;30:649-56

8 Hamburger JN, Serruys PW, Seabra-Gomes R, Simon R, Koolen JJ, Fleck E, Mathey D, Sievert H, Rutsch W, Buchwald A, Marco J, Al Kasab S, Pizzuli L,

Hamm C, Corcos Th, Reifart N, Hanrath P, Taeymans Y. Recanalization Of Total Coronary Occlusions Using a Laser Guide Wire: The European TOTAL Surveillance Study. *Am J Cardiol* 1997;80:1419-1423

9 Hamburger JN and Serruys PW. Treatment of thrombus containing lesions in diseased native coronary arteries and saphenous vein bypass grafts using the AngioJet Rapid Thrombectomy System. *Herz* 1997;22:318-321 (Nr. 6)

10 Rambaldi R, Hamburger JN, Geleijnse ML, Kimman GJ, Aiazian AA, Fioretti PM, Ten Cate FJ, Roelandt JRTC, Serruys PW. Early recovery of wall motion abnormalities after recanalization of chronic totally occluded coronary arteries: a Dobutamine-Atropine Stress Echocardiographic prospective single center experience. *Am Heart J* 1998 Nov;136(5):831-6

11 Carlier SG, Li W, Cespedes I, van der Steen AF, Hamburger JN, Bom N, Serruys PW. Simultaneous Morphological and Functional Assessment of a Renal Artery Stent Intervention with Intravascular Ultrasound. *Circulation* 1998;97(25):2575-6

12 Oesterle SN, Bittl JA, Leon MB, Hamburger J et. al. for the U.S. TOTAL investigators. Laser wire for crossing total occlusions-"learning phase" results from the U.S. TOTAL Trial. *Cathet Cardiovasc Diagn* 1998; 44:235-243

13 Hamburger JN, Foley, DP, de Feyter PJ, Wardeh AJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: long-term follow-up. *J Am Coll Cardiol*, accepted for publication

14 Hamburger JN, Foley, DP, de Feyter PJ, Wardeh AJ, Serruys PW. Six-month Outcome After Excimer Laser Coronary Angioplasty For Diffuse In-Stent Restenosis in Native Coronary Arteries. *Am J Cardiol*, accepted for publication

15 Hamburger JN, Brekke M, di Mario C, Wijns W, Amor M, Marco J, Bertrand M, Erbel R, Serruys PW. The Euro-ART Study: An Analysis of the Initial European Experience with the AngioJet Rapid Thrombectomy Catheter. *J Interven Cardiol*, accepted for publication

16 van Domburg RT, Foley DP, de Jaegere PP, de Feyter PJ, van den Brand M,

van der Giessen W, Hamburger JN, Serruys PW. Long-term outcome after coronary stent implantation: a 10-year single centre experience of 1,000 patients. *Heart*, accepted for publication

17 Gijzel AL, Wardeh AJ, van der Giessen WJ, Coen V, Levendag P, Hamburger JN, Ligthart JN, den Boer A, Serruys PW. Endovasculaire radiotherapie bij rePTCA voor recidiverende in-stent restenosen. *Cardiologie* 1999;6:303-307

ORIGINAL PAPERS (NON-PEER REVIEWED JOURNALS)

18 Hamburger JN, Gijsbers GHM, van den Broecke D, Lansink KWW, Serruys PW, Roelandt JRTC. Coronary Laser Angioplasty 1994: "And where do we go from here?" *Thorax Centre Journal* 1994;6/2:4-8

19 Hamburger JN, Gijsbers GHM, van den Broecke D, Lansink KWW, Roelandt JRTC, Serruys PW. Excimer Laser Coronary Angioplasty: The "Choice Of A New Generation?" *Thorax Centre Journal* 1995;7/3:27-33

20 Hamburger JN and Serruys PW. Laser guidewire technology for percutaneous treatment of chronic total coronary occlusions: light at the beginning of the tunnel. *Thorax centre Journal* 1997;9/4:24-29

ORIGINAL PAPERS (SUBMITTED FOR PUBLICATION)

21 Gijsbers GHM, Hamburger JN, Wonders JHM, Zondervan PE, Serruys PW. Method for the Assessment of Ablation Performance: a Novel Technique for Direct Evaluation of *In-Vitro* Excimer Laser Tissue Ablation. *Submitted for publication.*

22 Gijsbers GHM, Hamburger JN, Serruys PW. Ablation Properties of a New 2.0 mm High Density Excimer Laser Catheter For Coronary Angioplasty. *Submitted for publication.*

23 Hamburger JN, Gijsbers GHM, Wonders JHM, van der Putten R, Ansems V, Witteveen Th, Serruys PW. The Usefulness of Slow-Speed Automated Catheter Advancement for Optimization of Excimer Laser-Tissue Debulking. *Submitted for publication.*

PUBLISHED ABSTRACTS

24 Hamburger JN, Gijsbers GH, Lijmer JG, Oei F, Sprangers RL, van Gemert MJ, Dunning AJ. 308 nm excimer laser tissue interaction, using a modified multifiber catheter. *J Am Coll Cardiol* 1993;21:385A

25 Serruys PW, Hamburger JN, de Feyter PFJ, van den Brand M. Recanalization of chronic total occlusions using a laser guide wire: A preliminary experience. *Circulation* 1994; 90,4:1776

26 Serruys PW, Hamburger J, Fleck E, Koolen JJ, Teunissen Y. Laser Guidewire: a Powerful Tool in Recanalization of Chronic Total Coronary Occlusion. *Circulation* 1995;92,8:0363

27 Hamburger JN, van den Broecke D, Gijsbers G, Serruys PW. An evaluation of multiplexing on the efficiency and quality of excimer laser tissue ablation. *Eur Heart J* 1995; P2792

28 Gijsbers G, Hamburger JN, van den Broecke D, Roelandt JRTC, Serruys PW. The influence of homogeneous light distribution on excimer laser tissue interaction. *J Interv Cardiol*; June, 1995

29 van den Broecke D, Hamburger JN, Gijsbers G, Serruys PW. The influence of CO2 flush on the quality of excimer laser-tissue ablation. *J Interv Cardiol*; June, 1995

30 Hamburger JN, van den Broecke D, Gijsbers G, Serruys PW. The influence of multiplexing on the efficiency and quality of excimer laser tissue ablation. *J Interv Cardiol*; June, 1995

31 Serruys PW, Hamburger JN, de Feyter et al. Recanalization of chronic total coronary occlusions using the Prima 0.018 laser guidewire: The European multicenter surveillance study. *J Interv Cardiol*; June, 1995

32 Ten Cate F, Aiazian A, Hamburger JN, et al. Combined use of Dobutamine stress echocardiography and myocardial contrast echocardiography. *J Am Coll Cardiol* 1995:159A:937-4

33 Ten Cate F, Aiazian A, Hamburger JN, et al. Reconstruction of three dimensional myocardial perfusion maps in humans by myocardial contrast echocardiography. *J Am Coll Cardiol* 1995:247A:971-57

34 Aiazian A, Ataoullakhanova D, Ten Cate F, Hamburger J, Roelandt JRTC. Three dimensional visualization of myocardial perfusion: initial clinical experience with intracoronary contrast echocardiography. *Eur Heart J* 1996; P343

35 Hamburger JN, de Feyter PJ, Foley D, et al. The NIR stent: a single center preliminary experience as a preamble to the FINESS I trial. *Eur Heart J* 1996; P994

36 Hamburger JN, Brekke M, di Mario C. Preliminary experience with the coronary AngioJet Rheolytic Thrombectomy Catheter: a preamble to The Euro-ART Study. *Eur Heart J* 1996; P1001

37 Serruys PW, Hamburger JN, Rutsch W et al. Recanalization of chronic total coronary occlusions using a laser guidewire: The European multicenter surveillance study. *Eur Heart J* 1996; P2856

38 Ozaki Y, Violaris AG, Hamburger JN et al. Six month clinical and angiographic outcome of the new less shortening Wallstent implantation for chronic total occlusion. *Eur Heart J* 1996; P2858

39 Hamburger JN, de Feyter PJ, et al. Recanalization of chronic total occlusions using a laser guidewire: The the first 100 patients in a single-center experience. *Circulation* 1996;

40 Hamburger JN, Brekke M, di Mario C et al. The Euro-ART Study: An Analysis of the Initial European Experience with the AngioJet Rapid Thrombectomy Catheter. *J Am Coll Cardiol* 1997;739-1:186A

41 Beyar R, Hamburger JN, Saaiman A, et al. A multi-center pilot study of a serpentine balloon expandable stent (beStent): acute angiographic and clinical results. *J Am Coll Cardiol* 1996;494A

42 Serruys PW, Leon MB, Hamburger JN, Rutsch W, O'Neill W, et al. Recanalization of chronic total coronary occlusions using a laser guide wire: the global experience. *J Am Coll Cardiol* 1996

43 Rambaldi R, Geleijnse M, Aiazian A, Hamburger J, Ten Cate F, Fioretti P. Improvement of Dobutamine-Induced Wall Motion Abnormalities in Patients with Chronic Total Occluded Coronary Arteries After Recanalization with Laser Guidewire. *J Am Coll Cardiol* 1997;905-24:19A

44 Hamburger JN, Seabra-Gomes R, Simon R et al. Recanalization of chronic total occlusions using a laser guidewire: The European TOTAL Multicenter Surveillance Study. *J Am Coll Cardiol* 1997;29:69A

45 Beyar R, Hanburger J, Saaiman A, Bartorelli AL, DiMario C, Colombo A, Hamm C.W., White C.J., Serruys PW. A Multicenter Pilot Study of a Serpentine Balloon-Expandable Stent (beStent): Acute Angiographic and Clinical Results. *J Am Coll Cardiol* 1997;1080-13:494A

46 Hamburger JN, Koolen JJ, Fajadet J, et al. Randomized comparison of laser guidewire and mechanical guidewires for recanalization of chronic total coronary occlusion: the TOTAL Trial. *Circulation* 1997; 96(8):1495

47 Beyar R, Roguin A, Hanburger J, Saaiman A, Bartorelli AL, DiMario C, Colombo A, Serruys PW. Longer lesion coverage is associated with an increase in six months clinical events: results from a multicentre evaluation of the serpentine balloon-expandable stent (beStent). *Eur Heart J* 1997;18:158(P1012)

48 Kutryk MJB, de Groot MR, van den Brand M, Hamburger JN, van der Giessen WJ, Foley DP, de Feyter PJ, von Birgelen C, Camenzind E, Serruys PW. Feasibility of the local delivery of antisense oligonucleotide against c-myc for the prevention of in-stent restenosis: acute results of the Thoraxcentre ITALICS trial. *Eur Heart J* 1997;18:507(P2918)

49 van Domburg RT, Foley DP, de Feyter PJ, van den Brand M, van der Giessen W, Hamburger JN, Serruys PW. Long-term outcome after coronary stent implantation: a 10-year single centre experience of 1,000 patients *Eur Heart J* 1998;19:21(310)

50 Serruys PW, Hamburger JN, Koolen JJ et al. TOTAL Study: randomized comparison of laser guidewire and mechanical guidewires for recanalization of chronic total coronary occlusions, the 6 month follow-up. *Eur Heart J* 1998;19:471(2675)

51 Kutryk MJB, Serruys PW, Bruining N, Sabate M, Ligthart J, van den Brand M, Hamburger JN, van der Giessen WJ, Foley DP, de Feyter PJ. Randomized trial of antisense oligonucleotide against c-myc for the prevention of restenosis after stenting: results of the Thoraxcentre "ITALICS" trial. *Eur Heart J* 1998;19:569(3264)

52 Serruys PW, Kutryk MJB, Bruining N, Sabate M, Foley D, van den Brand M, Hamburger JN, van der Giessen WJ, Eijgelshoven, de Feyter PJ. Antisense oligonucleotide against c-myc administered with the Transport catheter for the prevention of in-stent restenosis: results of the randomized ITALICS trial. *Circulation* 1998;17,I-363(1909)

53 Hamburger JN, van Langenhove G, Smits P, van der Meer P, Onderwater E, Serruys PW. The Use of Low-Dose Dobutamine Noga™ in the Assessment of Potential Recovery of Hibernating Myocardium. *Int J Cardiovasc Intern* 1999;2(2):10

54 Hamburger JN, Foley DF, Wardeh A, Serruys PW. Six-Month Outcome after Excimer Laser Coronary Angioplasty for Diffuse In-Stent Restenosis: a single-center experience. *Int J Cardiovasc Intern* 1999;2(2):18

55 Hamburger JN, Foley DF, Wardeh A, Serruys PW. Recanalization of Chronic Total Occlusions using the new Terumo Stiff Guidewire: a single-center experience . *Int J Cardiovasc Intern* 1999;2(2):44

56 Hamburger JN, Foley DF, Wardeh A, Serruys PW. Recanalization of Chronic Total Coronary Occlusions: long term follow-up . *Int J Cardiovasc Intern* 1999;2(2):44

CHAPTERS IN BOOKS

57 Hamburger JN, Verhoofstad GGAM, van Marle J, van den Broecke D, Hanekamp CEE, Serruys PW, van Gemert MJC. Excimer laser coronary angioplasty: A physical per-

spective to clinical results. In: Topol E, Serruys PW (eds), *Current Review of Interventional Cardiology*, 2nd edn (Philadelphia: Current Medicine, 1995); 159-172.

58 Hamburger JN, Aiirian S, Gijsbers GHM, de Feyter PJ, Serruys PW. Recanalization of chronic total coronary occlusions using a laser guidewire: a single institution experience with the initial one-hundred cases. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, (Philadelphia: Current Medicine 1996); 63-69

59 Hamburger JN, Serruys PW. Recanalization of chronic total occlusions using a laser guide wire. In: U Sigwart, M Bertrand and PW Serruys (eds) *Handbook of Cardiovascular Interventions*, (WB Saunders, London 1996); 493-500.

60 Gijsbers GHM, Hamburger JN, Serruys PW. Homogeneous light distribution and high-density laser techniques in excimer laser coronary angioplasty. In: Holmes D and Serruys PW (eds) *Current Review of Interventional Cardiology*, 3rd edn, (Philadelphia: Current Medicine 1996); 101-111

61 Hamburger JN, Serruys PW. Laser guidewire for Recanalization of Chronic Total Occlusions. In: R Beyar, G Keren, M Leon and PW Serruys (eds) *Frontiers in Interventional Cardiology*, (Martin Dunitz, London 1997); 47-53.

62 Hamburger JN and Holmes Jr DR . Treatment of Chronic Total Coronary Occlusions. In: Ellis and Holmes (eds) *Practical Guide for Interventional Cardiology* 2nd edn (Lippincot Williams & Wilkins) in press.

INVITED LECTURES

63 48th Scientific Session of the American College of Cardiology in "Meet the Expert session: Treatment of Chronic Total Coronary Occlusions"

64 49th Scientific Session of the American College of Cardiology on "Matching the device with the lesion session: The Chronic Total Coronary Occlusion"