TRANSLUMINAL CORONARY ANGIOPLASTY:
an investigational tool and a non operative treatment
of acute myocardial ischemia

CORONAIR ANGIOPLASTIEK:

een onderzoeksmethode en een niet operatieve behandeling van acute myocard ischemie

P.W. SERRUYS

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To my father, John, who advised me to take a 'subsidiary' course in medicine, when I started to study philosophy...
To my wife, Danielle, who since then has tolerated my growing passion for cardiology ...

Contents

Acknowledgements

First of all, I am grateful to Paul Hugenholtz, whose friendship, communicative enthusiasm and intellectual 'clairvoyance' have stimulated me for all these years.

The Thoraxcenter is an scientific melting pot in which new ideas and diverging opinions are always ebullient; I have always viewed the Cath. Lab. as an unique place where I could 'cool' down in the friendly atmosphere in the company of the nurses and the technicians. In the darkness of an angioroom, during a complex and stressfull procedure, there is a complicity in the work which cannot be easily described, but is deeply appreciated.

When I left the University of Leuven (UCL) after 12 years of outstanding scientific education and clinical training (Prof. Brasseur, Chaland, Kremer and Lavenne), I took with me a few basic, clinical and physiological, principles which have helped me to survive the scientific turmoil of the Thoraxcenter.

In 1976 on my arrival in the Thoraxcenter, Geert Meester put me on the right track by introducing me into the Cath. Lab. Since then I have been using a computer system for real time analysis of cardiac catheterisation data of which he is the auctor intellectualis. This thesis would not have been possible without the continuing support from Marcel van den Brand; in September 1980 when we started to perform transluminal coronary angioplasty and intracoronary thrombolysis in our Cath. Lab, we shared the anguish, the excitement and the joy of exploring new possibilities of treatment and a new field of investigation in cardiology. Now in 1986 we still feel the same.

The full support of Jan Nauta, Egbert Bos and their surgical team has been and still is of crucial importance for the further development of the interventional cardiology. I hope the teamwork will flourish further.

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Most grateful I am to my wife, who for many years has tolerated my growing passion for cardiology. Finally I want to thank my family and my children, who as a consequence of this work have had less attention than they deserved.

Introduction and overview of this thesis

Since the introduction of coronary angioplasty in 1977, this procedure has gained increasing importance in the treatment of coronary artery obstruction. From the available evidence it can be estimated that this therapeutic tool will gain even more momentum from the tens of thousands of patients who will be treated in the next few years. Information about the indications, benefits and risks of the coronary angioplasty is accumulating rapidly, in addition to publications about refinements of the technique itself.

Recently, a number of investigators have realised that coronary angioplasty, is not only a therapeutic tool, but can, during the procedure. be used as a source of diagnostic information. When the catheter is placed across a coronary artery obstruction, inflation of the balloon produces transient myocardial ischemia. Before, during and after this period of severe ischemia studies of the performance of the myocardium at risk can be carried out.

The fact that therapeutic coronary angioplasty is carried out in a cardiac catheterization laboratory, which is by definition optimally equipped for the measurements of hemodynamic parameters, has probably also contributed to the execution of these investigations. The combination of hemodynamic and biochemical parameters with morphological information from the coronary angiogram can be utilized for the quantification of myocardial involvement and the success of coronary artery dilatation with angioplasty. Studies of interactions with pharmacological substances are also feasible and informative.

Coronary angioplasty has a most promising future as an unique means to gather insight in the intricacies of myocardial oxygen supply and demand in patients with coronary artery disease.

The first part of this thesis comprises five chapters, in which the sequence of events during transient ischemia induced by Percutaneous Transluminal Coronary Angioplasty (PTCA) is described. In the first four chapters details are provided of the changes in ejection, filling and diastasis. In the fifth chapter, changes in regional blood flow and myocardial metabolism are analyzed during reactive hyperemia after repeated occlusion of the left anterior descending coronary artery. These different studies were undertaken to determine whether in man the effects of ischemia after repeated occlusions were reversible. It is

concluded that repeated complete coronary occlusions of the left anterior descending coronary artery in conscious humans are associated with regional alteration in diastolic function, which persists well after restoration of myocardial blood flow, hypoxanthine and lactate metabolism have returned to normal systolic function. It is suggested that further studies are needed to document the time course of the recovery to a normal regional diastolic function, and to address the responsible derangements of sub-cellular metabolism because the mechanisms of the observed abnormalities are not yet fully understood.

The second part of this thesis deals with the change in the coronary anatomy produced by the angioplasty procedure and discuss its physiological significance. To date, selective coronary cineangiography has remained the only technique available for the visualization of the coronary arterial system with such image contrast and resolution, that the presence and severity of coronary stenosis can be determined with sufficient accuracy. However, of prime concern has been the relationship between the severity of the stenosis and the flow reduction in the stenosed artery. Conventional visual evaluation of the severity of coronary obstructions from the 35 mm cinefilm has been hampered by considerable inter- and intraobserver variations. From the above, it is clear that an objective and reproducible technique of quantitating cross-sectional area stenosis and normal luminal area both in absolute terms and in relative percentage change is needed, if one is to evaluate the efficacy of transluminal coronary angioplasty in a quantitative sense. Cineangiograms of 138 patients, who underwent percutaneous transluminal coronary angioplasty were analyzed with our coronary angiography analysis system and the result before and after dilatation are presented in the chapter VI. The relative merits of the diameter versus densitometric area measurement are discussed and it is suggested that the morphological changes induced by the angioplastic procedures are eccentric in nature.

The term 'critical lesion' is commonly used but poorly defined in human disease. It may be defined from a physiological or clinical standpoint. These two approaches are discussed in chapter VII and VIII. From a physiological perspective, a coronary stenosis is defined as critical, when it prevents an increase in flow over resting value in response to increased myocardial oxygen demands. From the clinical perspective, the critical stenosis may be defined as one resulting in ischemic symptoms at rest.

Non-invasive myocardial imaging with thallium-201 during exercise has been shown to be useful for assessing non-invasively , the regional flow reserve and the physiologic significance of moderate coronary stenosis. In order to evaluate during cardiac catheterization what constitutes a physiologically significant obstruction to blood flow in the human coronary system, quantitative analysis of coronary angiogram was performed in 31 patients with isolated proximal left anterior descending coronary artery disease. The angiographic severity of the stenoses was compared with the transstenotic pressure gradient measured with the dilatation catheter during angioplasty and the result of exercise thallium

scintigraphy (chapter VII). In this chapter it is concluded that the functional significance of coronary stenosis can be evaluated at rest by quantitative analysis of coronary dimensions and transstenotic pressure gradient measurement. In patients with single left anterior descending coronary artery disease, this allows identification at rest of those lesions responsible for thallium perfusion defect induced by exercise.

Restenosis after primary successful percutaneous transluminal coronary angioplasty remains 'the Achilles heel' of this therapeutic procedure.

In chapter VIII the value of exercise testing and thallium scintigraphy in predicting recurrence of angina pectoris and restenosis after primary successful transluminal coronary angioplasty is prospectively evaluated. The findings reported in this chapter demonstrate that early assessment of myocardial perfusion by exercise thallium scintigraphy has a high predictive value for restenosis and recurrence of angina in patients who underwent a technically satisfactory PTCA. In addition the results suggest that restenosis has already occurred to some extent at four weeks in most patients in whom it is documented later. This observation raises many speculations about the underlying mechanism of restenosis after dilatation.

The three chapters of the third part of this thesis review our experience with emergency coronary angioplasty in patients with unstable angina pectoris or acute myocardial infarction. The following specific issues are addressed: Can coronary angioplasty relieve ischemic symptoms and prevent progression to myocardial infarction or death in patients with unstable angina, not responding to intensive pharmacologic therapy lasting for at least 24 hours? Is, in order to prevent reocclusion after initial successful recanalization transluminal angioplasty a mandatory procedure? What is the additional value of immediate transluminal angioplasty following intracoronary thrombolysis in preserving left ventricular function and limiting infarct size and mortality?

On these three questions, tentative answers are formulated in chapter IX, X and XI. The data presented in chapter IX supports our opinion that percutaneous transluminal coronary angioplasty, as an emergency procedure in selected patients with unstable angina refractory to medical treatment, is very efficacious. In addition, the favourable early and late (12 months) clinical results indicate that angioplasty of the ischemia related vessel in patients with multivessel disease and refractory unstable angina pectoris is an attractive alternative to bypass surgery, at least for the short term.

In chapter X, it is shown that intracoronary streptokinase infusion and percutaneous transluminal coronary angioplasty can be carried out safely in the same session in an effort to enhance reperfusion.

Although the current results (chapter XI) might be biased by the selection of those patients whose lesions were suitable for angioplasty and who were hemodynamically stable after thrombolysis, the findings are in agreement with earlier observations that the recovery of regional function is greatest in patients with the

lowest residual stenosis after the intervention. The high survival rate, the lower incidence of reinfarction as well as the preserved regional and global left ventricular function in the subgroup successfully treated with thrombolysis and coronary angioplasty suggests that this combination may be the optimal mode of therapy for selected patients.

As further randomized trials are necessary to show the ultimate benefit of thrombolysis in acute myocardial infarction it is recommended that during these trials the additional value of immediate PTCA should be investigated.

Thus, the ten chapters of this thesis provide a multifaceted view of a novel therapeutic intervention – the Percutaneous Transluminal Coronary Angioplasty, which also has a most promising future as an investigational tool.

Part one:
Intentional coronary artery obstruction by balloon, a controlled model for ischemia.

Chapter I

Early changes in wall thickness and epicardial wall motion during percutaneous transluminal coronary angioplasty in man. Similarities between in vitro and in vivo model

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Introduction

Previously, our laboratory has reported the dynamic endocardial wall motion and myocardial wall thickness changes accompanying acute coronary occlusion in patients undergoing transluminal angioplasty (PTCA) [1, 2]. In these studies, the motion of the region of ischemic myocardium was characterized by the early appearance of a late systolic outward expansion followed by an early diastolic inward contraction. We refer to this biphasic motion as the 'W' phenomenon due to its morphologic characteristics, transient duration, and frequency of appearance in studies of endocardial and wall thickness motion during regional ischemia. Similar types of wall motion abnormalities have been described with acute ischemia in animals [3, 4] and in chronic ischemia in man [5–7]. Since phasic wall motion can, in general, be encountered whenever spatial or temporal nonuniformities in regional contraction or relaxation in the left ventricle exist, the specific etiology of this pattern during acute ischemia is uncertain.

Recently, we had the opportunity to extend these observations by evaluating the changes in wall thickness (M-mode echocardiogram) and epicardial length-pressure changes accompanying acute coronary vascular occlusion in a patient undergoing PTCA of a coronary artery bypass graft in whom pairs of metal markers had been placed, at the time of his original cardiac surgery, on the epicardial wall.

Echocardiographic changes in wall thickness

A continuous M-mode echocardiogram at the chordal level of the left ventricle was obtained immediately before, during, and after balloon occlusion of the

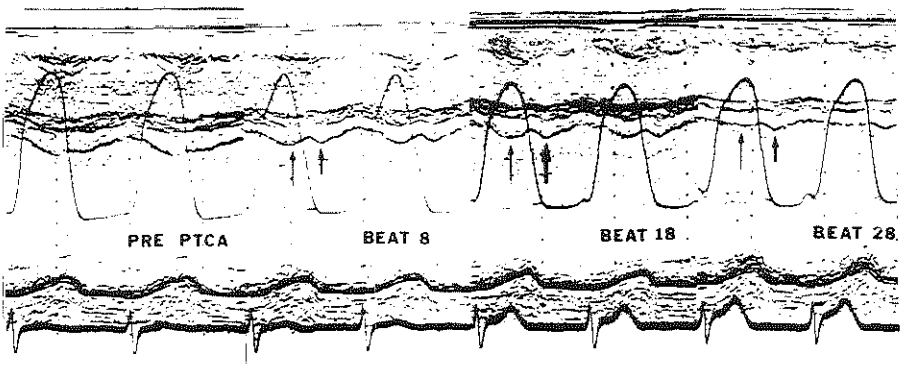

Fig. 1. M-mode echocardiographic and left ventricular pressure pulse patterns before (PRE PTCA) and after (POST PTCA) percutaneous transluminal coronary angioplasty of left anterior descending coronary artery. Normal systolic wall thickening becoming less prominent (long arrow) with early diastolic notch (thick arrow) becoming more prominent during PTCA, and disappearing after PTCA.

stenosis. A total of five separate dilatations of the stenosis were carried out. The echocardiogram during the fifth dilatation is shown (fig. 1). Continuous ECG, high-fidelity tip manometer, left ventricular pressure and its derative (dp/dt), V_{max}, time constant during early (Tau $_1$) and late (Tau $_2$) relaxation were recorded and computed [8, 9]. Coronary sinus-great cardiac vein flow measurements before, during occlusion, and after release of balloon inflation were carried out in a manner similar to our earlier experience [1]. Coronary lactate measurements from great cardiac vein and aorta were also made during these periods (table 1).

With balloon occlusion of the anterior descending coronary artery at the site of stenosis, there was decrease in systolic thickening in the septum with appearance of a prominent notch in early diastole associated with increase in left ventricular end-diastolic and end-systolic dimensions after the seventh beat following occlusion. At the 28th beat, systolic motion in the septum was absent. The only motion in the septum occurred early in diastole. There was pronounced decrease in the end-diastolic thickness of the septum at beat 28. The LV pressure decreased noticeably after beat 15 associated with the appearance of an a wave. The simultaneously recorded ECG showed ischemic changes beginning at beat 16, which became progressively more pronounced until release of the occlusion. No arrhythmias were noted during occlusion or after release of balloon inflation. The earliest hemodynamic alteration was a prolongation in early relaxation, which became apparent after the 6th beat. Following release of balloon inflation at beat 45, the echocardiographic parameter returned to baseline at beat 79, while LV pressure returned to baseline at beat 74.

Table 1. Hemodynamic measurements before and at 8th, 18th and 28th heartbeat during transluminal occlusion.

	Before occlusion	During occlusion		
		beat 8	beat 18	beat 28
RR interval ms	764	776	792	792
LVP mmHg	138	130	126	128
LVEDP mmHg	5	8	14	20
dP/dt mmHg	1364	1038	1003	1085
V_{max}	46.3	40.4	35.9	32.4
dP/dt mmHg	1935	1011	1207	1309
Tau_1 ms	39	66	54	58
Tau_2 ms	25	27	36	44
GCVF ml/min	87	56	52 109[a]	57
Lactate (A-GCV) mmol/l	+ 0.06	–	− 1.32[a]	

Abbreviations; LVP = peak left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; + dP/dt = peak positive rate of change of LVP; V_{max} = theoretical maximum velocity of the contractile element; −dP/dt = peak negative rate of change of LVP during isovolumic relaxation; Tau_1 = time constant of relaxation during the early phase (40 msec) of relaxation; Tau_2 = time constant of relaxation during late phase (40 msec–80 msec after aortic valve closure); GCVF = great cardiac vein flow; A-GCV = aorta great cardiac vein lactate difference.
(a) Measurement taken during reactive hyperemia.

Changes in epicardial wall motion

The patient described in this report is a 47 year old male who presented with severe symptoms of exertional chest pain in 1975. Angiographic evaluation showed significant stenoses of the left main, left anterior descending, and right coronary arteries and he underwent cardiac surgery with three single bypass grafts placed to the left anterior descending, obtuse marginal, and posterior descending vessels. At the time of surgery, the patient was entered into a prospective study assessing the use of epicardial wall markers for longterm assessment of graft patency and left ventricular function as previously described. [9] Recurrent symptoms in January, 1984 led to angiography which revealed the presence of a severe distal stenosis of the left anterior descending bypass graft, occlusion of the obtuse marginal bypass graft, and a high grade stenosis of the distal circumflex, in addition to the lesions previously identified (Figure 2). The right coronary artery was filled by a patent bypass graft and gave collaterals to the left anterior descending. Right anterior oblique left ventricular angiography showed a mildly enlarged left ventricle (end-diastolic volume index, 116 ml/ml^2) with anteroapical and inferior hypokinesis and a global ejection fraction of 0.50.

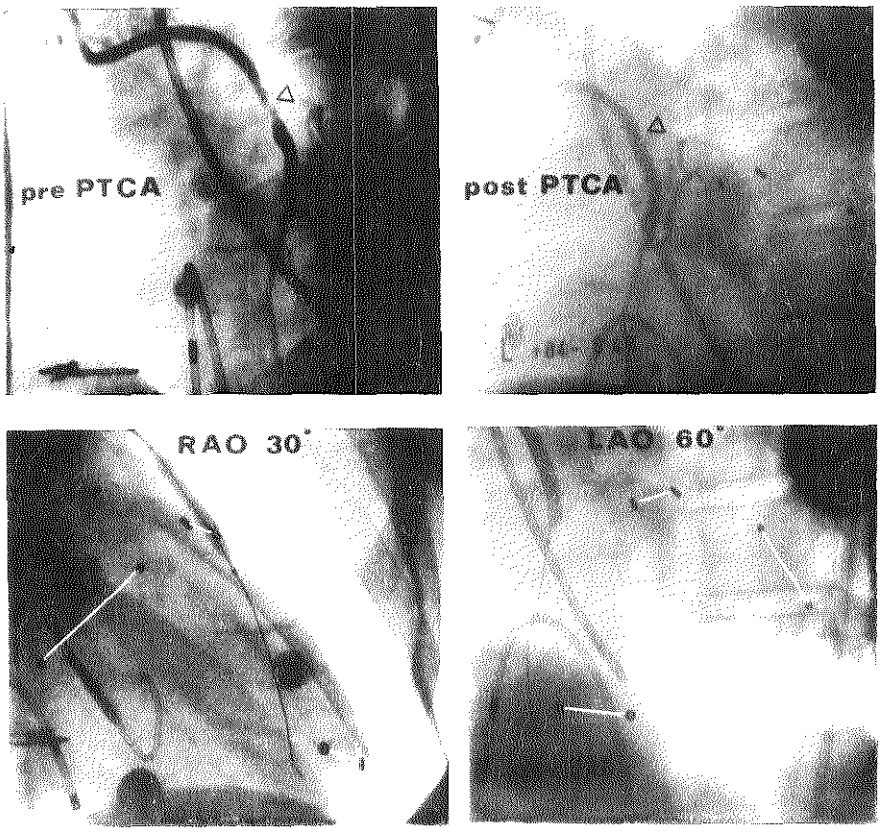

Fig. 2. Angiograms of left anterior descending bypass graft stenosis and markers before and after dilatation.
a. Before dilatation the angiogram shows severe stenosis of the distal bypass graft. The ring markers are located in the vascular territory of the bypass graft. Bead and bar marker pairs are also present.
b. After dilatation, angiogram shows total elimination of bypass graft stenosis.

The patient gave informed consent to the investigational part of the angioplasty of the left anterior descending bypass graft stenosis procedure. The patient's oral medications of beta blockers and calcium antagonists were not discontinued before the procedure.

An 8F tip manometer pigtail catheter (Millar Instruments; Houston) was advanced into the left ventricle. PTCA was performed with a 4.2 mm balloon through an 9F Judkins guiding catheter (Schneider, Zurich) with up to 12 atm. of pressure applied. Following three dilatations with a total occlusion time of 105 seconds, the stenotic pressure gradient decreased from 46 to 9 mmHg and a complete resolution of the angiographic narrowing was achieved (Fig. 2). Then, biplane cameras were positioned for a final investigational occlusion (additional

occlusion time of 50 seconds). Distal perfusion pressure during the investigational occlusion was 26 mmHg.

Regional Marker Motion

Absolute marker separation was determined from radiopaque markers implanted during surgery on the epicardium in each bypassed region as previously described [9]. Markers were placed in pairs 2 cm apart and located from 0–3 cm distal to each coronary anastomosis transverse to the long axis of the heart (Fig. 2). Synchronized biplane cine-films (50 frames/s) at 30° right anterior oblique and 60° left anterior oblique were performed before the placement of the angioplasty catheter (control), during the first 8 seconds of the investigational occlusion (5 minutes following the preceding dilatation), 40 seconds after the onset of occlusion, and 3 minutes post-occlusion. Absolute distances between markers for each marker pair were determined on all frames using a calibration grid. Correction for x-ray and optical distortion was performed to give true anatomic dimension. In order to reduce high frequency spatial noise, raw marker length data was filtered with a digital nearest neighbor averaging algorithm. Lmax and Lmin were defined as the maximal and minimal marker separation. The shortening fraction calculated between these two points (SF max, %) was calculated as (Lmax-Lmin)/Lmax.

Analysis of pressure-derived indexes during systole and diastole

Left ventricular pressure was digitized at 250 samples/s. Left ventricular peak systolic and end-diastolic pressure, peak negative dP/dt, peak positive dP/dt, and the relationship between dP/dt/pressure and pressure linearly extrapolated to pressure = 0 (V_{max}, the maximal velocity of the contractile element), were computed for each measured beat as previously described [10]. Relaxation parameters were also computed for each beat from peak negative dP/dt to the previous left ventricular end-diastolic pressure using the semilogarithmic model $P(t) = P_o e^{-t/T}$ with P_o the pressure at peak negative dP/dt when a true exponential decay is present and T the time constant of relaxation or the time for the best fit pressure curve to fall from P_o to $0.37 \times P_o$ [9]. In addition, to assess asynchronous relaxation, a bi-exponential fit for isovolumic relaxation was determined characterized by two exponential time constants [8]: the fit for the first 40 ms (n = 8 samples), T_1; and the fit after the first 40 ms (n = 4 samples), T_2. When data was fitted to single time constant derivative or nonlinear best fit exponential models with pressure offsets, derived fits differed significantly from actual data points. So only the semilogarithmic analyses were used.

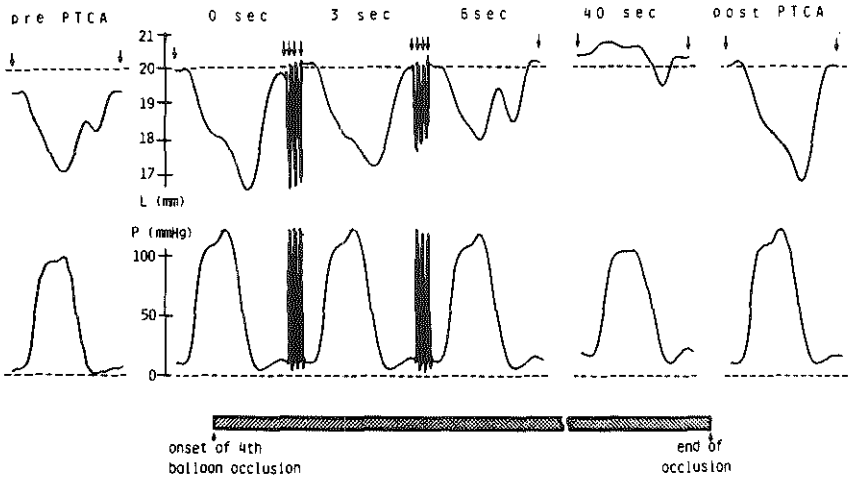

Fig. 3. Changes in epicardial marker pair shortening in region of bypass graft and left ventricular pressure with graft occlusion. Preceding PTCA, marker pair showed abnormal late systolic lengthening and early diastolic lengthening. Similar changes were evident in beats 6–8 after occlusion (see text) (the 'W' phenomenon).

Results

Each pair of markers was located on a characteristically different part of the ventricle. The markers in the left anterior descending artery distribution (rings) were in the post-stenotic territory and showed the most dynamic changes with occlusion (figs. 3 and 4). The second marker pair (beads), distal to the occluded bypass graft on the obtuse marginal, was located in a region that showed initial paradoxical motion (similar to the late occlusion motion in the post-stenotic territory) and was unaffected by the occlusion. The final pair of markers (bars), located in the left circumflex artery distribution, exhibited an initially abnormal and complex motion that became paradoxical during coronary occlusion. The marker pair of interest in the post-stenotic territory was further analyzed and so only data from this region is presented.

Changes in regional epicardial wall motion

In this transiently ischemic zone, epicardial wall motion before the PTCA procedure showed a biphasic systolic shortening pattern (figs 2 and 3) similar to what we refer to as the 'W' phenomenon. At the time of onset of the investigational occlusion, epicardial wall motion had significantly changed with loss of this biphasic 'W' pattern. With coronary occlusion, the earliest change in shortening

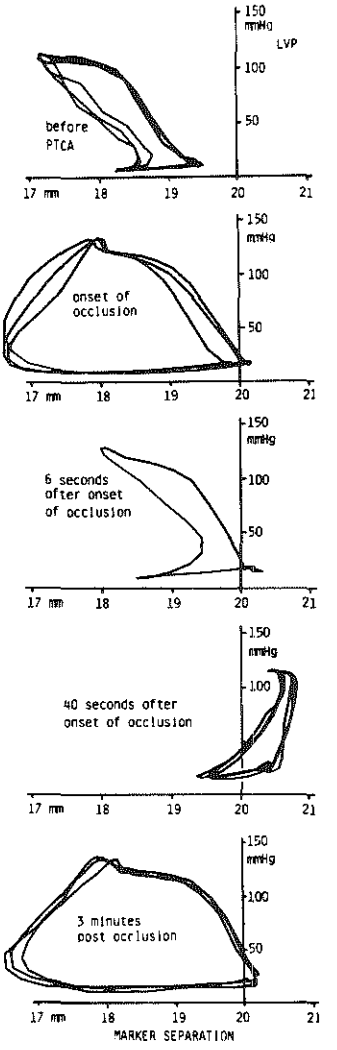

Fig. 4. Changes in epicardial pressure length relationships with graft occlusion. Pressure epicardial marker pair distance relationships are shown for the preceding PTCA, the onset of occlusion, six seconds of occlusion, 40 seconds of occlusion, and post-occlusion; 3 consecutive beats are shown for all except the 1 beat at 6 seconds of occlusion. Early changes in epicardial pressure length relations are exemplified by the curves after 6 seconds of occlusion. Paradoxical systolic expansion is evident after 40 seconds of occlusion. Post occlusion curve returns to that immediately preceding occlusion.

occurred at beat 4 after the onset of occlusion, manifest as a decrease in the shortening fraction from 17.2% to 16.8%. Beats 6 through 8, again manifest the late systolic to early diastolic 'W' pattern as before PTCA, however at a higher initial segment length. Fractional shortening decreased further to 11.9% second-

ary to a decrease in Lmin. During these first seconds of ischemia, the extent of shortening, but not the early systolic velocity of shortening, dL/dt, was affected (fig. 5). Initial segment shortening persisted beyond peak negative dP/dt and thus occurred during isovolumic relaxation. With early ischemia, early diastolic shortening following late systolic lengthening occurred after the onset of peak negative dP/dt and during isovolumic relaxation up to the minimal diastolic pressure. During late occlusion (40 seconds after onset), the ischemic zone showed a

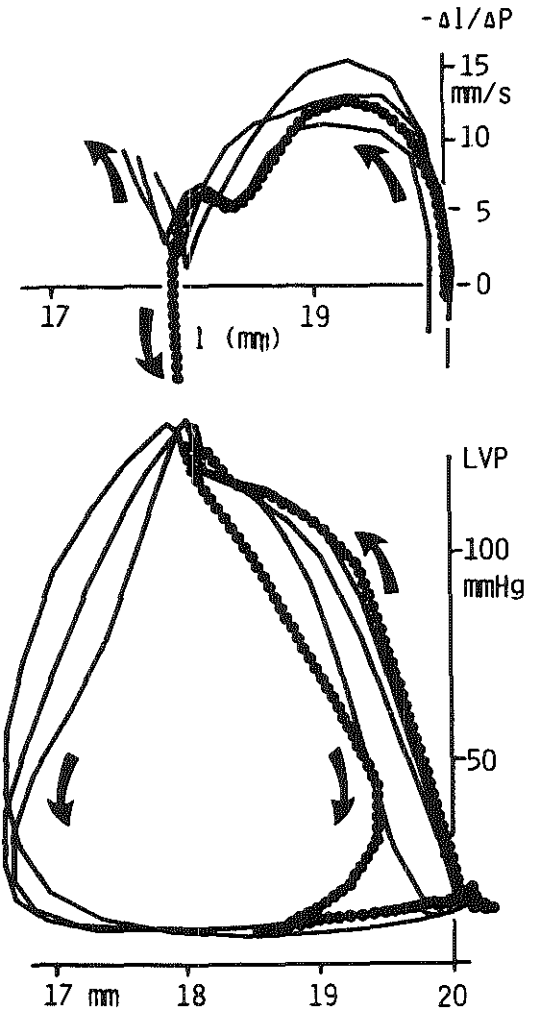

Fig. 5. Early changes in pressure velocity and pressure length relationships with graft occlusion. The early change in epicardial shortening is characterized by a decrease in the extent of shortening with a preservation in the velocity of shortening. Onset of occlusion beats in solid lines, 6 seconds after occlusion beat in dots.

paradoxical lengthening throughout systole beyond the point of initial end-diastolic length followed by an early diastolic shortening below the level of end-diastolic length. Post-PTCA ischemic zone wall motion returned to its onset morphology with a fractional shortening of 17.8% (figs. 3 and 4). The diastolic pressure curve was shifted upward and to the right during occlusion.

Changes in global left ventricular function

Figure 6 shows the time course of change in left ventricular parameters of hemodynamic function. Heart rate did not change during the occlusion. Peak +dP/dt and peak systolic pressure gradually decreased accompanied by a rise in left ventricular minimum and end diastolic pressure. Peak −dP/dt also decreased during the occlusion accompanied by a change in its isovolumic pressure fall such that it was better characterized by a bi-exponential model of relaxation (Table II).

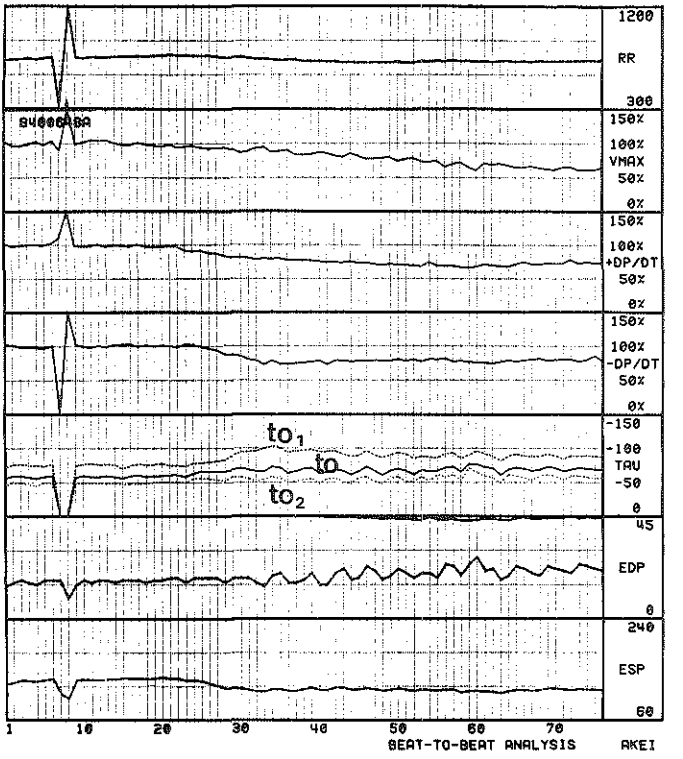

Fig. 6. Time course of changes in parameters of left ventricular function with bypass graft occlusion. From top to bottom. R-R interval (ms), maximal velocity of the contractile elements (V_{max}), peak negative and positive dP/dt expressed as percentages of control values; the time constants of relaxation to_1 (dashed line), to (solid line), and to_2 (dotted line) (scale 50 ms); end-diastolic pressure (EDP, scale 15 mmHg); and peak systolic pressure (ESP, scale 60 mmHg, with 60 mmHg offset). The break in the data at beat 8 corresponds to inflation of the PTCA balloon.

Table 2. Global left ventricular function during transluminal angioplasty.

	Beat	Preceding R-R interval (ms)	LV Sys mmHg	LV EDP mmHg	+dP/dt mmHg/s	V_{max} s^{-1}	−dP/dt mmHg/s	T ms	T_1 ms	T_2 ms
Onset of	− 2	760.0	133.0	17.0	1293.0	39.1	− 1162.	− 56.	− 70.	− 47.
occlusion	− 1	760.0	133.0	17.0	1269.0	39.1	− 1154.	− 60.	− 75.	− 49.
	0	764.0	133.0	17.0	1305.0	40.1	− 1114.	− 61.	− 77.	− 48.
	1	764.0	132.0	16.0	1276.0	39.3	− 1141.	− 59.	− 76.	− 49.
	2	768.0	133.0	17.0	1258.0	38.6	− 1120.	− 60.	− 76.	− 50.
	3	772.0	134.0	17.0	1268.0	38.1	− 1133.	− 60.	− 78.	− 51.
	4	780.0	133.0	18.0	1275.0	39.1	− 1127.	− 61.	− 75.	− 51.
	5	772.0	133.0	18.0	1275.0	37.7	− 1106.	− 62.	− 75.	− 52.
	6	772.0	129.0	16.0	1190.0	38.2	− 1160.	− 59.	− 74.	− 50.
	7	768.0	129.0	18.0	1177.0	38.4	− 1139.	− 64.	− 78.	− 56.
	8	768.0	128.0	18.0	1197.0	37.3	− 1109.	− 66.	− 79.	− 56.
	9	768.0	124.0	18.0	1148.0	37.0	− 1087.	− 66.	− 80.	− 56.
	10	760.0	120.0	18.0	1147.0	37.1	− 1058.	− 66.	− 81.	− 54.
	11	752.0	115.0	16.0	1096.0	37.6	− 990.	− 66.	− 84.	− 53.
	12	752.0	117.0	18.0	1063.0	36.5	− 982.	− 69.	− 90.	− 58.
	13	760.0	116.0	18.0	1065.0	34.5	− 960.	− 71.	− 95.	− 58.
	14	748.0	114.0	18.0	1051.0	35.5	− 902.	− 69.	− 95.	− 56.
	15	744.0	111.0	16.0	1021.0	37.2	− 891.	− 66.	− 96.	− 52
40 seconds of occlusion		724.0	115.0	24.0	940.0	24.4	− 867.	− 71.	− 89.	− 60.
		724.0	114.0	23.0	977.0	24.3	− 894.	− 70.	− 89.	− 58.
Post occlusion		756.0	134.0	20.0	1295.0	41.4	− 1087.	− 64.	− 80.	− 55.
		752.0	132.0	20.0	1297.0	39.4	− 1110.	− 61.	− 77.	− 50.

Abbreviations: LV sys: left ventricular systolic pressure; LVEDP left ventricular enddiastolic pressure; ±dP/dt: peak positive or negative left ventricular dP/dt;T,T_1,T_2: time constants of relaxations for mono- and bi-exponential models. V_{max}; velocity of the contractile element extrapolated to 0 pressure.

Discussion

The time course and magnitude of changes in global parameters of left ventricular function following coronary occlusion in this patient are similar to those previously reported in patients undergoing PTCA of an isolated stenosis of a native coronary artery [1]. Progressive and gradual decreases in parameters of systolic function accompanied very early changes in the rate of left ventricular pressure decay.

The bi-exponential approximation of the isovolumic pressure fall is consistent with an asynchrony of regional myocardial contraction or relaxation [8]. Changes in parameters of isovolumic pressure fall were most pronounced during the first half of occlusion and slightly less at the end of occlusion. In this case, the earliest change in epicardial wall motion was a decrease in the extent of shortening while velocity of early shortening was maintained. These results are similar to the earliest changes of motion of left ventricular mid-wall ultrasonic crystals during ischemia in conscious dogs as reported by Pagani et al [3]. In contrast, Forrester et al observed isovolumic systolic lengthening of mercury-in-silastic epicardial length gauges accompanying the onset of decreases in the extent of shortening in anesthetized dogs [11]. Our findings, in a conscious patient are similar to those reported by Pagani and not Forrester.

After 40 seconds of ischemia, despite paradoxic lengthening throughout systole, early diastolic shortening was still observed consistent with a markedly diminished yet persistent tension becoming manifest only after a decline in the load imposed upon the region by the remainder of the effectively contracting ventricle. Post-occlusion regional function returned to the appearance of wall motion at the onset of occlusion.

Early wall motion changes during acute ischemia

Frist et al [12] demonstrated that the decline of tension is prolonged during hypoxia in euthermic cat papillary muscle preparations. Tyberg et al [13] simulated the effects of asynchronous contraction and relaxation by analyzing a pair of hypoxic and normal papillary muscles in series. Phasic changes in individual tension length relations in both muscles were observed.

Weigner et al [14] extended these observations by simulating normal papillary muscle with a computer-controlled tension generator in series with a hypoxic papillary muscle. A biphasic pattern of motion of the hypoxic muscle was observed analogous to the 'W' phenomenon in the regionally ischemic zone in the intact left ventricle (fig 7). The early lengthening phase of the hypoxic muscle was attributed to a premature onset of force decline and the second late shortening phase was ascribed to either a persisting contractile force of the muscle or a manifestation of stored force from elastic recoil of previously stretched passive

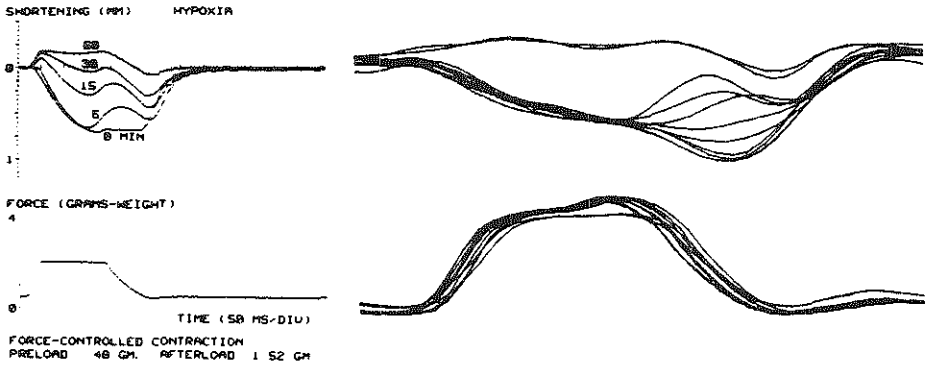

Fig. 7. a: Left hand sided panel: Interaction between a muscle subjected to hypoxia for 60 minutes (length record in upper panel) and a 'normal' muscle (force record in lower panel). The earliest change is a premature onset of lengthening (5 minutes) and as hypoxia progress, there is less total shortening; by 60 minutes the hypoxia muscle demonstrates 'systolic' lengthening which coincides with the period of force development in the normal muscle. During the period of force decline, the hypoxic muscle manifests late systolic shortening. b: right hand sided panel: Beat by beat changes in epicardial marker pair shortening in region of bypass graft and left ventricular pressure with graft occlusion. Within 6–8 beats after occlusion, marker pair showed abnormal late systolic lengthening and early diastolic shortening. Paradoxical systolic expansion is evident after 40 seconds of occlusion.

muscle elements. During graded acute myocardial ischemia in dogs, Smalling et al [15] observed a biphasic expansion and contraction in both endocardial wall motion and myocardial wall thickening. These changes were attributed to both a loss of the early diastolic distending force of coronary pressure (the 'erectile' effect) and to a persistent contraction of the ischemic zone during early diastole.

In summary, the late systolic lengthening and early diastolic shortening in epicardial wall motion following acute coronary occlusion is most likely secondary to the early onset of tension decline in the ischemic region, however, with tension persisting secondary to a decreased rate of decline. Early diastolic contraction may be secondary to passive elastic rebound forces with or without the contribution of persistent active tension. The absence of the 'erectile' properties of coronary blood flow may allow more pronounced early diastolic shortening. The relationship of these mechanical events to the intracellular biochemical events of activation and relaxation is unknown.

Wall motion abnormalities in chronic ischemia

A possible relationship between the resting wall motion abnormalities with chronic ischemia and those transiently observed during acute ischemia is suggested by the similarity in the regional pressure length relationships preceding

PTCA to beats 7–9 following occlusion. Regional epicardial wall motion in this ischemic zone was certainly improved following the first three dilatations although this immediate effect should not be equated to the sustained improvement in systolic and diastolic function following PTCA reported by others [5, 6]. Sasayama et al [7] recently demonstrated an inward motion of left ventricular ischemic segments accompanied by an outward motion of normal segments during isovolumic relaxation in patients with chronic angina. This motion was attributed to both a persisting contractile activity and elastic recoil of passive elements within the ischemic muscle. In these patients, however, a late systolic expansion of ischemic segments preceding early diastolic contraction was not observed.

Whether a relationship exists between abnormal left ventricular relaxation and left ventricular rapid diastolic filling is uncertain. In patients with coronary artery disease, a prolongation of the mono-exponential time constant of relaxation has been shown to correlate with an increase in minimal left ventricular pressure and inversely correlate with early diastolic ventricular inflow rate and inflow volume [16, 17]. Increases in the time constant of isovolumic relaxation have also been associated with increases in the left ventricular diastolic constant of elastic chamber stiffness during both acute coronary occlusion [18] and exercise induced angina [19].

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Chapter II

Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty

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Summary

The response of left ventricular function, coronary blood flow, and myocardial lactate metabolism during percutaneous transluminal coronary angioplasty (PTCA) was studied in a series of patients undergoing the procedure. From four to six balloon inflation procedures per patient were performed with an average duration per occlusion of 51 ± 12 s (mean $\pm$ s.d.) and a total occlusion time of 252 ± 140 s. Analysis of left ventricular hemodynamics in 19 patients showed that the relaxation parameters, peak negative rate of change in pressure, and early time constants of relaxation, responded earliest to short-term coronary occlusion (peak effect at 17 ± 7 s), while other parameters, such as peak pressure, left ventricular end-diastolic pressure, and peak positive rate of change in pressure, responded more gradually, suggesting a progressive depression of myocardial mechanics throughout the procedure. Left ventricular angiograms, available from 14 patients, indicated an early onset of asynchronous relaxation concurrent with the early response in peak negative dP/dt and the time constant of early relaxation. All hemodynamic functions fully recovered within minutes after the end of PTCA. Mean blood flow in the great cardiac vein and proximal coronary sinus and the hyperemic response were measured in 20 patients. Before PTCA mean flow in the great cardiac vein was 69 ± 17 ml/min and in the coronary sinus it was 129 ± 34 ml/min. Reactive hyperemia (great cardiac vein) was 55% after the first PTCA and 91% after the third. A more pronounced reaction was observed when the residual functional coronary stenosis was reduced in subsequent dilatations. Arteriovenous lactate difference appeared constant during the first two occlusions (control + 0.11 mmol/l, first PTCA −0.87 mmol/l, and second PTCA −0.82 mmol/l) and did not increase during subsequent occlusions. Within minutes after the procedure lactate balance was again positive, demonstrating the reversibility of the metabolic disturbances after repeated ischemia. The results of

this study indicate that there is no permanent dysfunction of global or regional myocardial mechanics, myocardial blood flow, or lactate metabolism after PTCA with four to six coronary occlusions of 40 to 60 seconds.

Introduction

Until recently the measurement in man of left ventricular geometry and hemodynamics early after an abrupt occlusion of a major coronary artery has not been feasible. Percutaneous transluminal coronary angioplasty (PTCA), however, now provides a unique opportunity to study the time course of changes during the transient interruption of coronary flow by the balloon occlusion sequence in patients with single-vessel disease and without angiographically demonstrable collateral circulation [1, 2]. We report the dynamic changes in left ventricular hemodynamics in 19 patients and the concurrent left ventricular geometric changes assessed by angiography in another group of 14 patients during PTCA. In a third group of patients regional blood flow and lactate metabolism were analyzed during reactive hyperemia after repeated occlusions of the left anterior descending coronary artery. These different studies were undertaken to investigate the sequence of events during transient ischemia induced by PTCA and to determine whether or not the effects of ischemia after repeated occlusions were reversible.

Materials and methods

Study population and protocol

After a feasibility study of the effect of nonionic contrast media on left ventricular function, permission from the Thoraxcenter Ethics Committee was granted to obtain left ventricular angiograms during transluminal occlusions. All patients in this study gave their informed consent and there were no complications directly related to the research procedure.

For the first part of the study data were collected from 19 adult patients undergoing temporary coronary occlusion of a diseased left coronary artery during PTCA. Four of these patients had had a previous myocardial infarction. Records were analyzed during the first successful PTCA procedure for each patient.

For the second part of the study, 14 patients were selected from 356 consecutive patients in whom angioplasty was attempted. These patients met the inclusion criteria by having isolated obstructive lesions of one coronary vessel (left anterior descending artery in 10 patients, right coronary in four, left circumflex in one) and normal resting left ventricular function and wall motion. Four patients had mild

essential hypertension and elevated left ventricular filling pressures (end-diastolic pressure ≥25 mmHg). During the PTCA procedure the number of transluminal occlusions performed per patient was 4.9 ± 2.2 (mean ± s.d.). The average duration of each occlusion was 51 ± 12 s (mean ± s.d.) and the total occlusion time during the whole procedure was 252 ± 140 s (mean ± s.d.). With a tipmanometer on a No. 8F pigtail catheter, pressures were recorded and derived indices were calculated off-line by a computer system [3, 4]. Three to four ventriculograms (30 degrees right anterior oblique at 50 frames/s) were obtained by injection of 0.75 ml/kg of a nonionic contrast medium (metrizamide, Amipaque). The hemodynamic and angiographic investigations were performed before the PTCA procedure was begun, after 20 sec of occlusion during the second dilatation, after 50 sec of occlusion during the fourth dilatation, and again 5 minutes after completion of the PTCA procedure. These sequential left ventricular angiograms were made only after the values for left ventricular end-diastolic pressure and the various isovolumetric parameters had returned to those recorded before the initial angiogram. In all cases the interval between two angiograms was at least 10 minutes. Care was taken to maintain the patient's position unchanged in relation to the X-ray equipment during the consecutive angiograms. Diaphragm movement was kept to a minimum by instructing patients to keep inspiration shallow and to avoid the Valsalva manoeuvre.

For the third part of the study, data were collected from 20 other patients with proximal lesions in the left anterior descending artery. Coronary sinus and great cardiac vein blood flow were measured by the continuous thermodilution method with a Baim catheter [5, 6]. The main objective of this measurement was to detect changes in the global and regional blood flows, as well as in the regional lactate metabolism, during the reactive hyperemia after consecutive episodes of transluminal occlusion. In the beginning of the investigation the position of the distal thermistor in the great cardiac vein was determined by injection of 3 ml of contrast medium. After each balloon deflation coronary sinus and great cardiac vein flows were measured for 10 sec. The continuous infusion for thermodilution was then interrupted to allow blood withdrawal from the great cardiac vein. Lactate was assayed enzymatically according to Apstein et al. [7] with the AutoAnalyzer II (Technicon, Tarrytown, NY). Blood (4 ml) for lactate measurements was rapidly deproteinized with an equal volume of cold 8% perchloric acid ($HClO_4$) and centrifuged. The supernatant was analyzed on the AutoAnalyzer and compared with standard curves made with lithium lactate in 4% $HClO_4$.

Analysis of pressure-derived indexes during systole and diastole

Left ventricular pressure was measured with a Millar micromanometer catheter and digitized at 250 samples/s. Combined analog and digital filtering resulted in an effective time constant of less than 10 ms. We used an updated version of the

beat-to-beat program described previously [3, 4] that also incorporates the capability of acquiring a calibrated pressure signal and storing it on disk or tape for subsequent off-line analysis. The latter procedure was followed for all PTCA procedures. For off-line analysis of pressure relaxation the following definitions were used: (1) pressure at the beginning of isovolumic relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximum negative dP/dt), and (2) pressure at end of isovolumetric relaxation (P_e) is the pressure less than or equal to the previous end-diastolic pressure, but not less than 1 mmHg.

Although it is possible that the latter definition may result in P_e being measured just after mitral valve opening, estimation of the time constants using more stringent criteria, such as end-diastolic pressure + 10 mmHg, did not result in a significantly better estimation, and on the contrary failed to measure the time constants during high heart rates.

Peak left ventricular pressure, left ventricular end-diastolic pressure, peak negative dP/dt, peak positive dP/dt, and the relationship between dP/dt/pressure and pressure linearly extrapolated to pressure = 0 (V_{max}), where V_{max} is maximal velocity, were computed on-line after a data acquisition of 20 seconds.

Determination of relaxation parameters

Three techniques have been implemented for the off-line beat-to-beat calculation of the relaxation parameters [8–10]. All require a minimum of eight samples (over 32 ms) between P_b and P_e.

Semilogarithmic model

The semilogarithmic model used was: $P(t) = P_o e^{-t/T}$, where P is pressure; t is time; P_o is equivalent to P_b when a true exponential decay is present starting from the time of peak negative dP/dt; the fit for the first 40 ms ($n \geq 8$), T_1, is bi-exponential [10]; the fit after 40 ms ($n \geq 3$), T_2, is bi-exponential [10]; and the fit for all points ($n \geq 8$), T, is mono-exponential. The P_o and T parameters are estimated from a linear least squares fit of $\ln P = -t/T + \ln P_o$.

Exponential model

The exponential model used was: $P(t) = P_o e^{-t/T} + P_1$, with nonlinear least squares fit of P, for P_o, P_1, and T. P_1 represents the offset pressure the system relaxes to for $t \geq T$. The isovolumetric relaxation period is modeled only mono-exponentially.

Derivative model

The derivative model used was: $P(t) = P_o e^{-t/T} + P_1$ or $dP/dt = -1/T \cdot (P(t) - P_1)$, with linear least squares fit of dP/dt vs P for T and P, starting at 16 ms after P_b until P_e.

Analysis of global and regional left ventricular function during systole and diastole

A complete cardiac cycle was analyzed frame-by-frame with the Contouromat for all cineangiograms. End-diastolic pressure was defined as that point on the pressure trace at which the derivative of the pressure first exceeded 200 mmHg/s and in all cases coincided with the maximal measured left ventricular volume [3]. End systole was defined, with reference to the pressure tracing, at the occurrence of the dicrotic notch of the central aortic pressure. To analyze the regional left ventricular function, the computer generated a system of coordinates along which the left ventricular displacement was determined frame-by-frame in 20 segments (figure 1) [11]

Segmental wall velocity was computed as the first-derivative of the instantaneous displacement function. Mean ejection phase wall velocity for each segment was calculated from end diastole to end systole (figure 1). Segmental volume was computed from the local radius (R) and the height of each segment (1/10 of left ventricular long-axis length L) according to the formula $\pi R^2 L/20$. When normalized for end-diastolic volume, the systolic segmental volume change can be considered as a parameter of regional pump function (figure 2). During systole this parameter expresses quantitatively the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction [11]. The sum of the values for all 20 segments equals the global ejection fraction. Diastolic function was analyzed in terms of volume stiffness. Pressure-volume relationships were determined from the lowest diastolic pressure to the beginning of the 'a' wave. The natural logarithm of pressure was used in a linear regression analysis of pressure and volume from which a slope (K) was derived. Changes in K were taken as changes in volume stiffness [12].

Results

Analysis of pressure-derived indices during systole and diastole

Hemodynamic parameter values for a control beat just before occlusion, at peak effect in terms of the change in negative dP/dt and T_1 (occurring, on average, at 17 ± 7 s), and at the end of the occlusion (occurring, on average, at 53 ± 12 s) are summarized in Table 1. No attempt was made to average consecutive beats or to select beats with respect to the respiratory cycle. An example of a continuous recording of V_{max} positive and negative dP/dt, T_1, T_2, T, end-diastolic pressure and peak pressure is illustrated in figure 3.

There was no important change in heart rate during the PTCA procedure. The pattern of change in peak left ventricular pressure, left ventricular end-diastolic pressure, peak positive dP/dt, and V_{max}, however, suggest a progressive depression in myocardial mechanics without any indication of an early peak. The

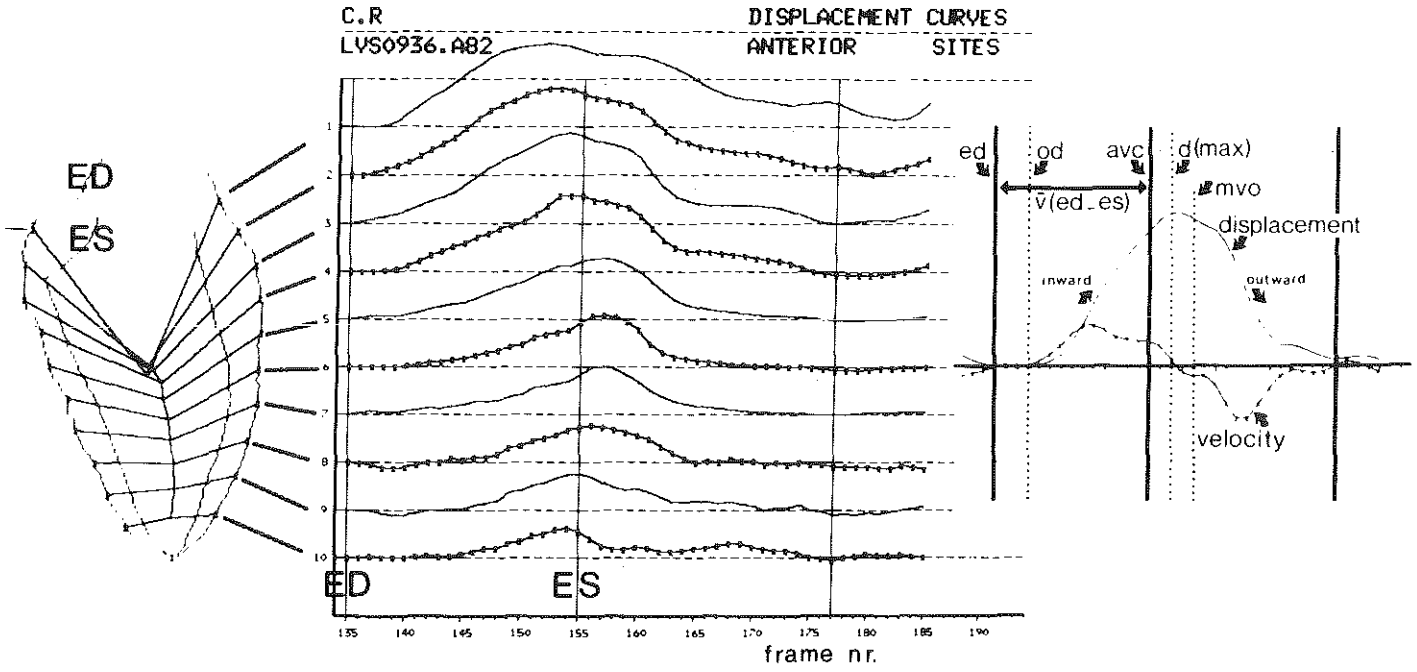

Fig 1. End-diastolic and end-systolic left ventricular contours, as detected by the automated analysis system. Superimposed on these silhouettes is a system of coordinates along which segmental left ventricular wall displacement is detected. Left ventricular wall velocity, the first derivative of wall displacement, is derived from these data. ed = end diastole; es = end systole; od = onset of displacement; v(ed-es) = mean ejection phase wall velocity; d(max) = maximal inward wall displacement; mvo = mitral valve opening.

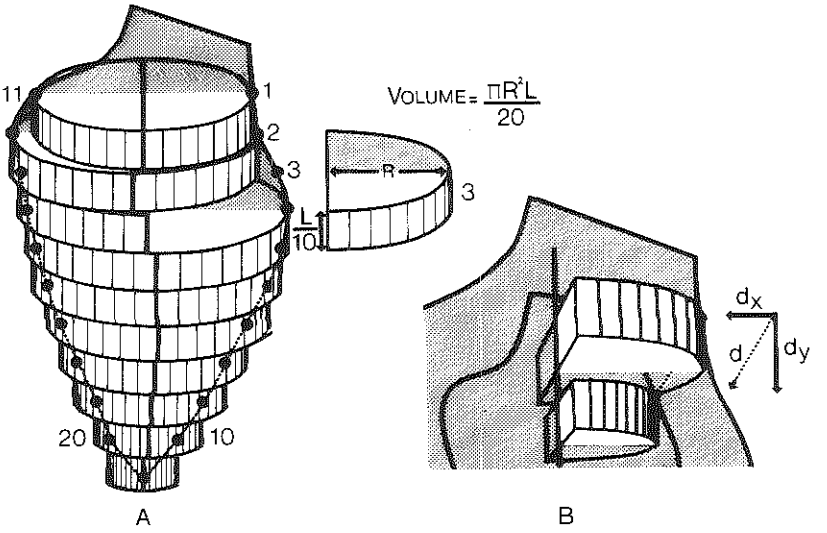

Fig. 2. Method for computing regional contribution to ejection fraction (CREF): The volume of each segment (slice volume) is computed according to the formula shown in the figure. The change in systolic volume is derived from the regional displacement and is mainly a consequence of the decrease in radius (R) of a half slice, which is expressed by the x-component (dx) of the displacement vector (d). L = left ventricular long-axis length extending from base to apex.

$$\text{CREF } (\%) = \frac{\text{(ED-ES) slice volume}}{\text{Global ED volume}} \times 100.$$

pressure at which the isovolumetric relaxation phase was considered to begin (P_b) was not altered appreciably during PTCA in spite of the drop in peak left ventricular pressure and peak negative dP/dt.

Within 4 or 5 beats after occlusion, a deformation appeared in the ascending limb of the negative dP/dt curve (figure 4) and in the next 10 seconds this deformation gradually increased so that the irregularity in the curve reached the same height as peak negative dP/dt, which had progressively decreased to its nadir. In the next 20 to 50 s, peak negative dP/dt began to return towards control level with a resolution of the irregularity in the ascending limb of its curve. At 50 s, this parameter recovered to 77% of the preocclusion value and the deformity was no longer present.

This deformation of the negative dP/dt signal at the early phase of the occlusion indicates that the time course of left ventricular pressure decay deviates substantially from the mono-exponential model usually proposed and also that asynchronous contraction or relaxation may be involved at the very beginning of the transluminal occlusion. Therefore, bi-exponential fitting of the pressure curve was computed during the isovolumetric relaxation, primarily because the pressure curve, when plotted on semilogarithmic paper, was observed to follow two straight lines rather than the one predicted by the mono-exponential mode.

Table 1. Hemodynamic parameter values at control before PTCA, at peak effect with respect to T_1, and peak negative dP/dt (17 ± 7 s), and at the end of the occlusion (52 ± 12 s).

Variables	Control (mean ± s.d.)	Peak effect		End PTCA	
		Mean ± s.d.	p-value	Mean ± s.d.	p-value
Heart rate (bpm)	67 ± 12	66 ± 11	n.s.	69 ± 12	n.s.
Peak LVP (mmHg)	137 ± 21	133 ± 20	n.s.	124 ± 19	<.0003
LVEDP (mmHg)	16.4 ± 6.4	19.3 ± 7.4	<.0003	23.7 ± 5.0	<.0001
Peak + dP/dt (mmHg/s)	1490 ± 330	1300 ± 200	<.0001	1260 ± 250	<.0001
P_h (mmHg)	86 ± 14	90 ± 15	<.04	84 ± 13	n.s.
Peak − dP/dt (mmHg/s)	1710 ± 320	1240 ± 260	$<10^{-6}$	1320 ± 380	$<10^{-5}$
T (model A)	46.4 ± 8.1	58.4 ± 10.8	$<10^{-6}$	59.4 ± 10.2	<.0001
T_1 (model B)	53.0 ± 7.6	81.7 ± 15.3	$<10^{-6}$	66.2 ± 13.0	<.0001
T_2 (model B)	41.3 ± 8.8	48.0 ± 8.7	<.001	55.1 ± 10.8	<.0001
T_2/T_1 (model B)	0.77 ± 0.10	0.60 ± 0.11	<.0001	0.83 ± 0.09	<.002
T (model C)	72.6 ± 18.5	178 ± 96	<.0001	85.5 ± 26.4	<.04
T (model D)	63.2 ± 11.8	120 ± 57	<.0001	76.3 ± 24.3	<.01

All time constant values are in milliseconds. LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure. Computation models: A = single constant without offset; B = double time constant without offset; C = time constant from dP/dt; D = single time constant with offset P_f.

The second half of Table 1 summarizes the results with the different techniques for computing the relaxation parameters. While major differences are apparent in the magnitude of the time constants, however computed, they all showed a highly significant slowing of relaxation early during PTCA and recovery and return to near-control levels by the end of the procedure. The behavior of the two time constants (T_1, T_2) during PTCA is illustrated in figure 3.

Generally the time constants computed from the logarithm of pressure were smaller and showed less variation than those computed from the other two models. The major discrepancies are apparent at the peak effect of PTCA. This is also reflected in the p (significance)-value. The ratio T_2/T_1, an index of asynchrony [10], showed a drop of 0.17 from 0.77 (control) to 0.60 (peak effect), but within 53 s not only returned to the control level but exceeded it slightly. After 53 s of occlusion, the region perfused by the occluded coronary artery could no longer be considered to be asynchronous, but was probably akinetic and not actively contributing to either contraction or relaxation.

Global left ventricular function during systole and diastole

The left ventricular pressures and volumes measured before, during, and after angioplasty are listed in Table 2. During the four sequential cine-angiographic

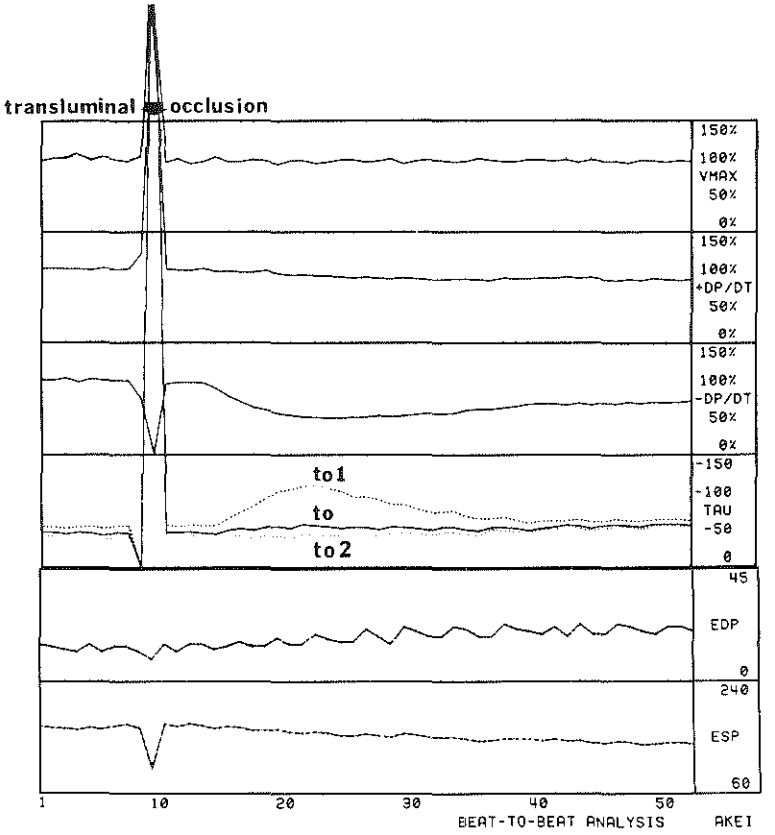

Fig. 3. Hemodynamic measurements in a patient during PTCA. From top to bottom, maximal velocity of the contractile elements (V_{max}), peak negative and positive dP/dt expressed as percentages of control values; the time constants of relaxation to_1 (dashed line), to (solid line), and to_2 (dotted line) (scale 50 ms); end-diastolic pressure (EDP, scale 15 mmHg); and peak systolic pressure (ESP, scale 60 mmHg, with 60 mmHg offset). The break in the data at beat 10 corresponds to inflation of the PTCA balloon.

investigations the heart rates were almost identical, whereas the isovolumetric indices of contraction and relaxation recorded during the second (20 s occlusion) or the third (50 s occlusion) left ventricular angiograms showed changes very similar to those described in the first group of results (Table 1). Occlusion of a major coronary artery for only 20 s resulted in a significant ($p<0.005$) increase in end-systolic volume (from 31 ± 9 to 37 ± 9 ml/m^2), while the end-diastolic volume remained unchanged after 20 s and even after 50 s of transluminal occlusion. At 50 s the ejection fraction decreased from 62% to 48% ($p<0.005$) and this decrease was essentially due to an increase in end-systolic volume from 29 ± 7 to 41 ± 9 ml/m^2 ($p<0.005$).

An example of the relationship between left ventricular diastolic pressure and

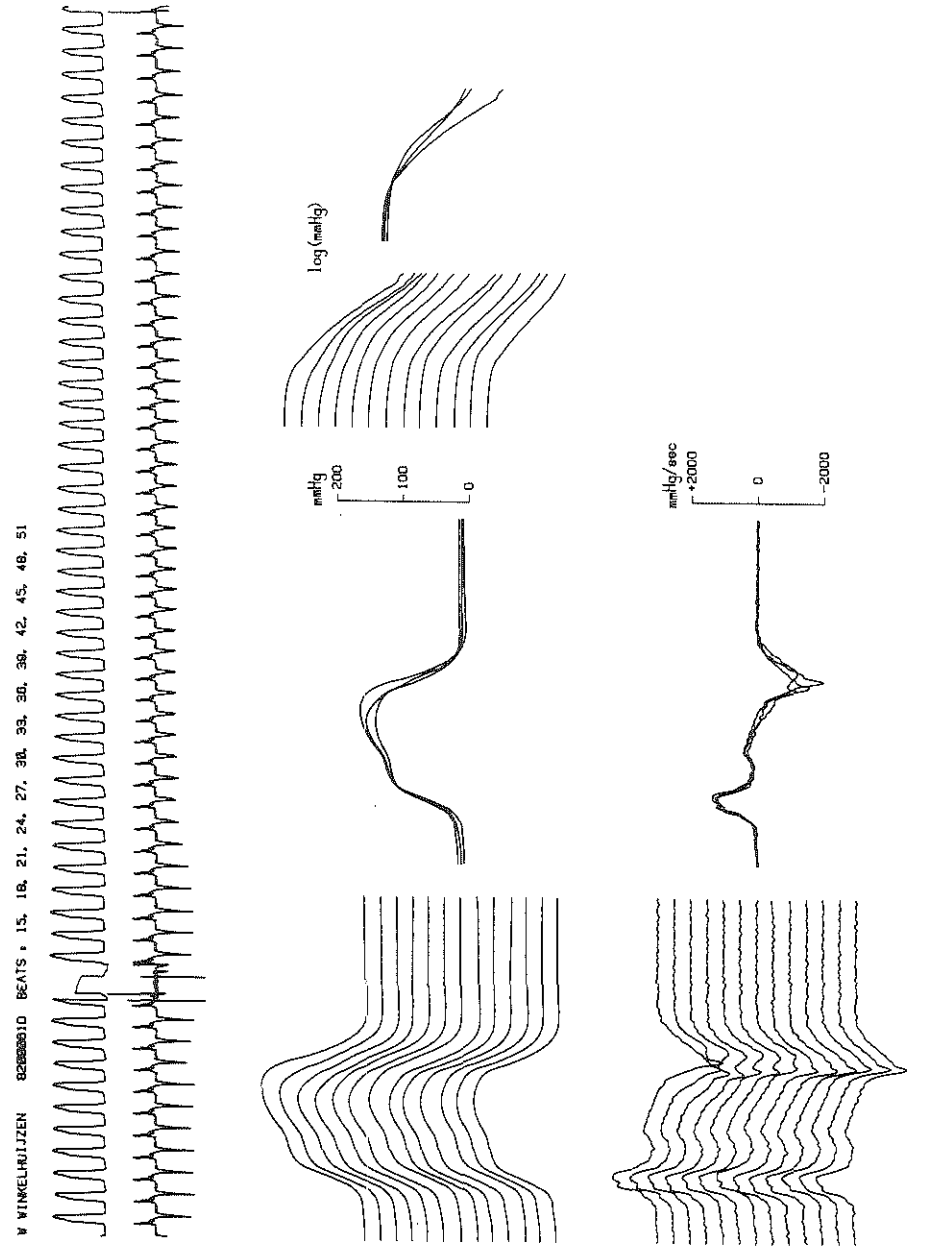

Fig. 4. Effects of coronary artery occlusion on left ventricular pressure (mmHg) and positive and negative dP/dt (mmHg/s). The break in the recording at beat 15 corresponds with the inflation of the balloon. On the left are displayed the left ventricular pressures and positive and negative dP/dt's of individual beats (15, 18, 21, and so forth) while the natural logarithm of the pressure is shown on the right. The decrease in negative dP/dt is associated with an irregularity in the upstroke of the negative dP/dt curve. After 30 s (beat 42) peak negative dP/dt starts to return toward a more normal shape of the signal.

Table 2. Hemodynamic parameter values before PTCA, at 20 and 50 s after occlusion, and after the PTCA procedure.

Variables	Before PTCA		20 seconds occlusion (total group; N = 14)	50 seconds occlusion (subgroup; N = 9)	After PTCA	
	Total group (N = 14)	Subgroup (N = 9)			Subgroup (N = 9)	Total group (N = 14)
HR (bpm)	62 ± 16	59 ± 18	61 ± 13	62 ± 14	63 ± 11	64 ± 11
EDV (ml/m²)	81 ± 15	79 ± 14	81 ± 15	81 ± 16	78 ± 11	77 ± 11
SV (ml/m²)	31 ± 9	29 ± 7	37 ± 9*	41 ± 9*	26 ± 15	27 ± 7*
SV (ml/m²)	50 ± 11	49 ± 11	44 ± 12*	39 ± 14*	52 ± 10	50 ± 9
EF (%)	61 ± 8	62 ± 6	54 ± 8*	48 ± 12*	66 ± 6	64 ± 7
Peak LVP (mmHg)	154 ± 30	151 ± 35	142 ± 29	145 ± 37	148 ± 25	147 ± 21
Peak + dP/dt (mmHg.s⁻¹)	1403 ± 304	1356 ± 257	1312 ± 320	1278 ± 317	1442 ± 384	1412 ± 333
V_{max} (s⁻¹)	39 ± 9	40 ± 8	39 ± 9	34 ± 10*	43 ± 12	42 ± 11
ESP (mmHg)	95 ± 18	92 ± 22	90 ± 19	98 ± 24	91 ± 15	90 ± 14
Peak − dP/dt (mmHg.s⁻¹)	1727 ± 322	1614 ± 267	1268 ± 355*	1404 ± 370*	1665 ± 296	1664 ± 243
T_1 (ms)	55 ± 8	55 ± 6	79 ± 17*	68 ± 16*	56 ± 7.5	54 ± 7
T_2 (ms)	44 ± 7	43 ± 7	51 ± 8*	59 ± 8*	45 ± 8	45 ± 9
Pmin (mmHg)	10 ± 5	8 ± 3	11 ± 4	16 ± 6*	8 ± 5	8 ± 4
EDP (mmHg)	22 ± 8	18 ± 6	22 ± 7	29 ± 5*	21 ± 5	20 ± 6
K ln P/V (ml⁻¹)	0.0244 ± 0.009	0.0239 ± 0.008	0.0314 ± 0.016	0.0431 ± 0.018	0.0349 ± 0.016	0.0339 ± 0.013

HR = heart rate; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EDV, ESV and SV have been normalized for body surface area; EF = ejection fraction; LVP = left ventricular pressure; ESP = end-systolic pressure; Pmin = left ventricular minimal diastolic pressure; EDP = left ventricular end-diastolic pressure; K ln P/V = natural logarithmic slope of diastolic pressure-volume relationship. * $p<.05$ compared with before PTCA, paired Student t test; $p<.005$, compared with before PTCA, paired Student t test.

volume during transluminal occlusion is illustrated in figure 5. It is evident that the entire diastolic pressure-volume relationship during transluminal occlusion was gradually shifted upward and to the right so that at any given volume, the diastolic pressures were higher. This effect was consistently observed after 50 s of occlusion. Furthermore, the K constant, considered to be an index of volume stiffness, was significantly increased after 50 s of transluminal occlusion (Table 2). Nevertheless, the hemodynamic and cineangiographic investigations performed after completion of the PTCA procedure demonstrated the perfect reversibility of these changes in volume as well as the normalization of the different pressure-derived indices.

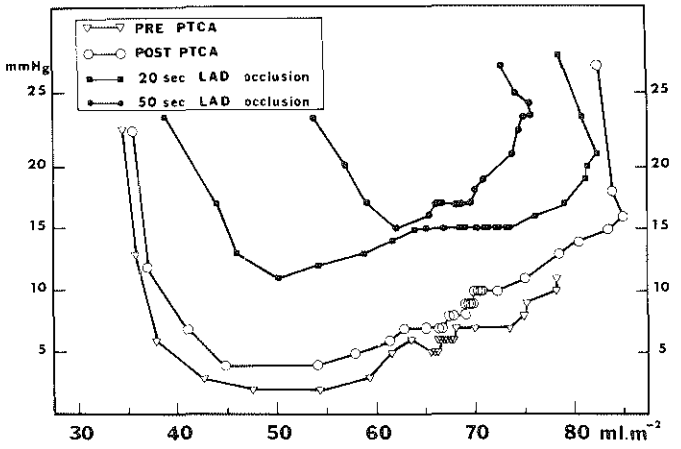

Fig. 5. Diastolic pressure-volume relationships during PTCA. During occlusion there is a gradual shift upward and to the right in the diastolic pressure-volume relationship. LAD = left anterior descending artery.

Regional left ventricular function

The profound effect of a 20 s occlusion of the left anterior descending artery on left ventricular wall motion and its time sequence is shown in figure 6. The delay in onset of displacement with respect to end-diastole as well as the time relationship between the aortic valve closure and the occurrence of the maximal wall displacement is illustrated in figure 7. The onset of displacement of the anterior and inferior walls was not significantly affected after 20 s occlusion of the left anterior descending artery. On the contrary, the moment of maximal wall displacement for the anterior wall shifted from end systole to early diastole. The antero-lateral segment (Nos. 6 and 7 on figure 7), the apical segment (Nos. 9 and 10) of the anterior wall, and the apical segment (Nos. 20 and 19) of the inferior wall appeared to be most affected.

The measurement of mean ejection phase velocity after 20 and 50 s occlusion of the left anterior descending artery showed a decrease which was again more pronounced in the anterior wall segments (figure 8). The regional wall motion and wall velocity (figure 8) showed a similar response to occlusion of this coronary artery. These data clearly demonstrate a progressive myocardial depression that affected specifically the antero-lateral and apical segments (Table 3).

It must be emphasized that all these ischemic changes were transient and perfectly reversible, as demonstrated by the regional analysis of the last cineangiogram performed after completion of the whole procedure.

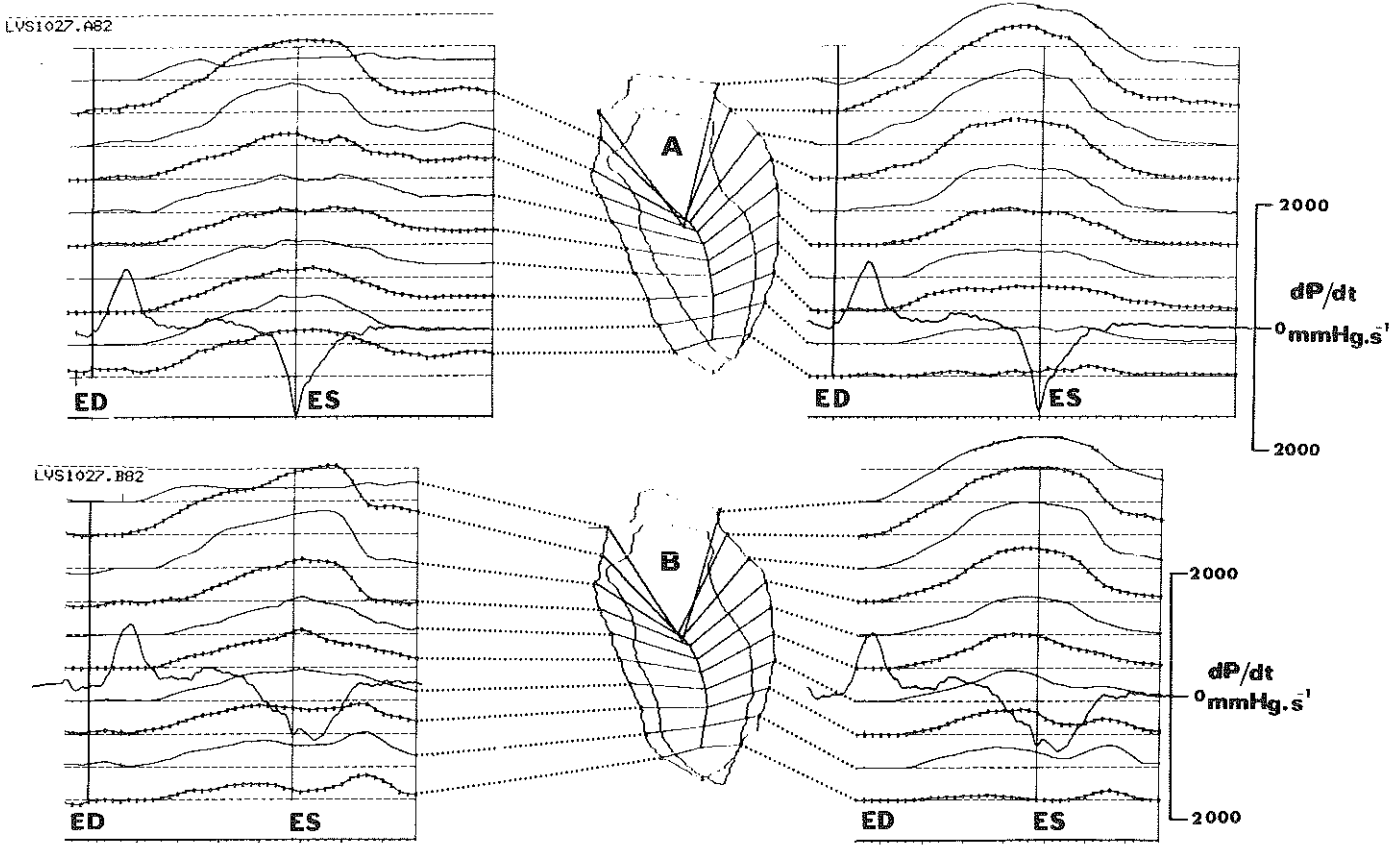

Fig. 6. Left ventricular wall displacement studied in 20 separate segments, 10 in the anterior (right) and 10 in the infero-posterior (left) wall. A typical example of the relationship between segmental wall displacement and dP/dt curve is observed before PTCA (A) and after 20 s (B) of occlusion of the left anterior descending artery. After 20 s of occlusion, the notch in the dP/dt curve corresponds to a second wave of inward wall displacement in the antero-apical and infero-apical segments.

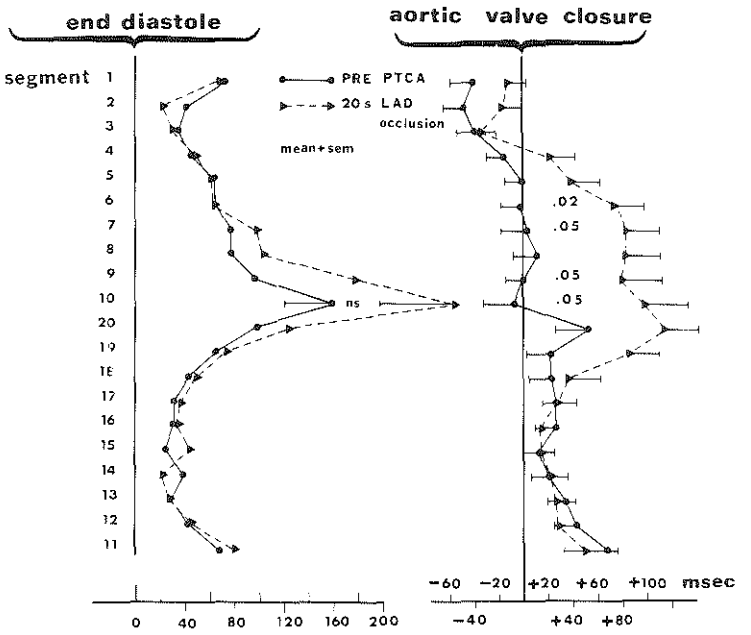

Fig. 7. Delay (ms) in onset of displacement for the 20 individual wall segments with respect to end diastole (time zero) before and after 20 s of occlusion of the left anterior descending artery. Time relationship between aortic valve closure (time zero) and the occurrence of maximal wall displacement before and after 20 s of occlusion of the left anterior descending artery.

Coronary blood flow and lactate metabolism

During the initial dilatation, the mean duration of angioplasty balloon inflation was 41 ± 13 s and during the subsequent dilatations the duration of inflation was gradually increased up to 54 ± 12 s in a subset of four patients who underwent six consecutive dilatations (Table XVIII.4).

The mean blood flow in the great cardiac vein in 20 patients before the first inflation was 69 ± 17 ml/min, falling to 49 ± 23 ml/min ($p<10^{-5}$) during the first inflation and rising to 107 ± 31 ml/min ($p<10^{-5}$) after the first balloon deflation.

The mean hyperemic increase in great cardiac vein flow was 38 ml/min above the control flow value after the first inflation compared with 63 ml after the third inflation ($p<.01$; figure 9).

Proximal coronary sinus blood flow before the first dilation was 129 ± 34 ml/min, falling to 92 ± 27 ml/min ($p<10^{-5}$) during transluminal occlusion and rising to 152 ± 44 ml/min ($p<10^{-4}$) after the first balloon deflation.

During the peak reactive hyperemia that followed the third dilatation, the coronary sinus blood flow was 161 ± 31 ml/min. There was no difference in resting pre-PTCA and post-PTCA levels of great cardiac vein or coronary sinus blood flow.

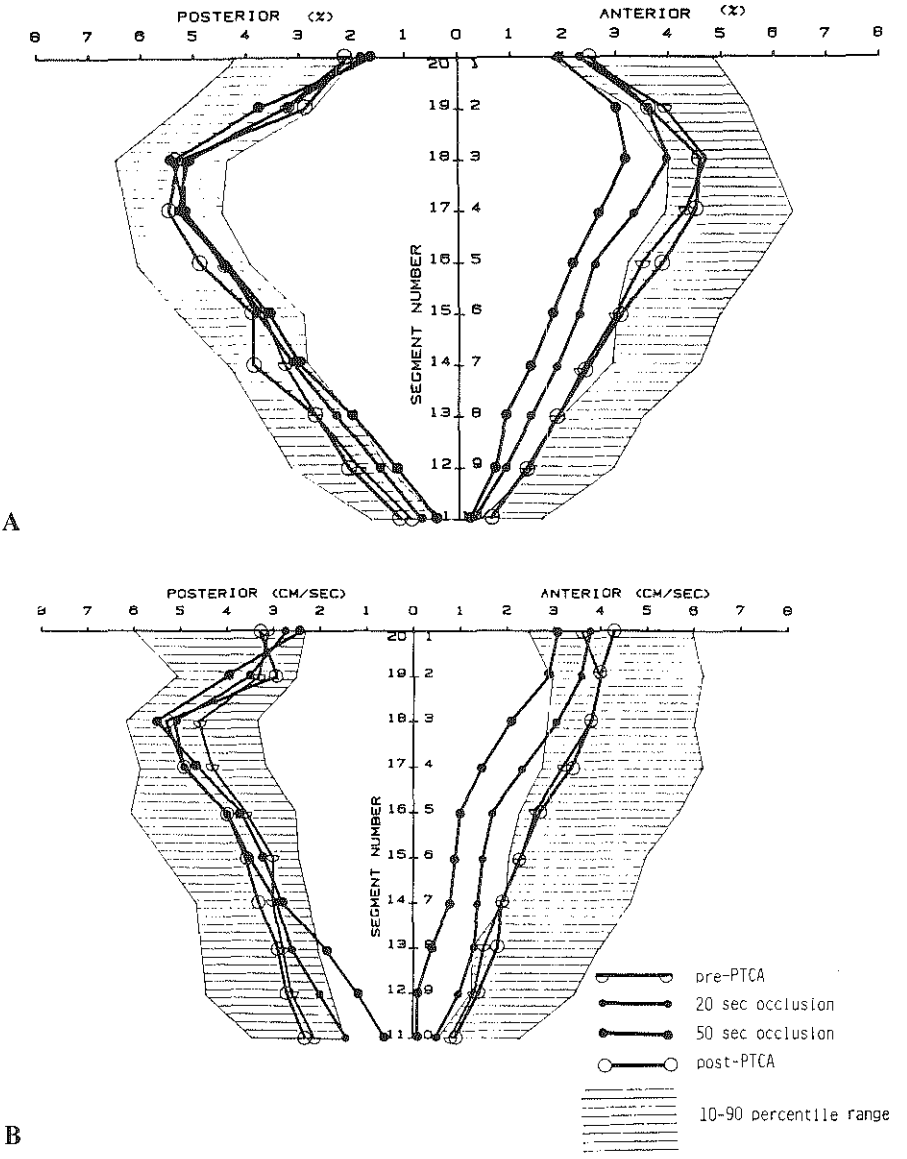

Fig. 8. (A) Display of the computed CREF's (regional contributions to ejection fraction) after a 20 or 50 s occlusion of the left anterior descending artery. On the x-axis the CREF's of the anterior and infero-posterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1 to 10) and of the infero-posterior wall (11 to 20) are depicted. The shaded zones represent the 10th to 90th percentile area of CREF's in normal individuals. (B) Mean ejection phase velocity before PTCA and after 20 and 50 s occlusions of the left anterior descending artery. On the x-axis the velocity values of the anterior and infero-posterior wall areas are displayed (cm/s), while on the y-axis the segment numbers of the anterior wall (1–10) and of the infero-posterior wall (11–20) are depicted. The shaded zones represent the 10th to 90th percentile areas in normal individuals.

Table 3. Ejection phase velocity and regional contribution to ejection fraction (CREF).

	Mean ejection phase velocity (cm/s)				CREF (%)			
Segment No.	Before PTCA (N = 10)	15 s occl. (N = 10)	45 s occl. (N = 7)	After PTCA (N = 10)	Before PTCA (N = 10)	15 s occl. (N = 10)	45 s occl. (N = 7)	After PTCA (N = 10)
1	3.6 ± 1.0	3.8 ± 1.5	3.1 ± 1.5	4.3 ± 1.5*	2.3 ± 0.4	2.3 ± 0.5	1.9 ± 0.7	2.5 ± 0.5°
2	4.0 ± 1.3	3.6 ± 1.2*	2.9 ± 1.5°	4.0 ± 1.8	3.9 ± 0.9	3.6 ± 0.8	3.0 ± 1.0*	3.6 ± 0.8
3	3.8 ± 1.2	3.1 ± 1.3*	2.1 ± 1.4-	3.8 ± 1.6	4.7 ± 0.9	4.0 ± 0.8-	3.2 ± 1.0-	4.6 ± 0.8
4	3.2 ± 1.0	2.4 ± 1.3*	1.5 ± 1.5-	3.4 ± 1.4	4.3 ± 1.0	3.4 ± 1.0°	2.7 ± 1.4-	4.5 ± 0.7
5	2.6 ± 0.9	1.7 ± 1.1*	1.0 ± 1.4+	2.7 ± 1.1	3.5 ± 1.0	2.6 ± 1.0°	2.2 ± 1.6+	3.9 ± 0.6
6	2.3 ± 0.8	1.5 ± 0.9°	0.9 ± 1.3+	2.3 ± 0.8	3.0 ± 0.8	2.3 ± 0.9°	1.8 ± 1.5°	3.1 ± 0.4
7	1.9 ± 0.8	1.4 ± 1.0	0.8 ± 1.3*	1.9 ± 0.7	2.4 ± 0.7	1.9 ± 0.1*	1.4 ± 1.2°	2.5 ± 0.5
8	1.5 ± 0.6	1.3 ± 0.9	0.4 ± 1.2*	1.8 ± 1.0	1.9 ± 0.5	1.4 ± 0.7*	0.9 ± 0.8+	1.9 ± 0.7
9	1.3 ± 0.5	1.0 ± 1.0	0.1 ± 1.0	1.4 ± 0.9	1.3 ± 0.4	0.9 ± 0.6*	0.7 ± 0.8*	1.3 ± 0.6
10	0.8 ± 0.7	0.5 ± 1.3	0.1 ± 0.9	0.9 ± 0.9	0.6 ± 0.3	0.3 ± 0.5	0.2 ± 0.6	0.6 ± 0.5
11	3.1 ± 1.0	2.7 ± 0.7	2.4 ± 0.7*	3.3 ± 0.9	2.1 ± 0.4	1.8 ± 0.3	1.6 ± 0.3-	2.1 ± 0.4
12	3.3 ± 2.0	3.5 ± 2.1	4.0 ± 2.3	2.9 ± 1.5	3.3 ± 1.2	3.3 ± 1.4	3.8 ± 1.5	2.9 ± 1.3
13	4.6 ± 1.3	5.1 ± 1.0	5.5 ± 1.2*	5.3 ± 1.7	5.2 ± 0.7	5.1 ± 0.7	5.4 ± 1.0	5.3 ± 1.1
14	4.3 ± 1.0	4.9 ± 0.8*	4.6 ± 1.0	4.9 ± 1.4	5.2 ± 0.5	5.3 ± 0.3	5.2 ± 0.4	5.5 ± 0.8
15	3.6 ± 0.6	4.0 ± 0.7*	3.7 ± 1.0	4.0 ± 1.1	4.5 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.9 ± 0.6*
16	3.0 ± 0.5	3.5 ± 0.9	3.2 ± 1.1	3.6 ± 1.3	3.7 ± 0.4	3.8 ± 0.4	3.6 ± 0.3	3.9 ± 0.5
17	3.0 ± 0.6	2.9 ± 1.0	2.8 ± 1.2	3.3 ± 1.3	3.3 ± 0.5	3.1 ± 0.5	3.0 ± 0.7	3.9 ± 0.5
18	2.8 ± 0.7	2.6 ± 0.9	1.9 ± 1.1-	2.9 ± 1.2	2.7 ± 0.5	2.3 ± 0.3*	2.0 ± 0.5-	2.7 ± 0.5
19	2.6 ± 0.5	2.0 ± 0.7*	1.2 ± 1.0-	2.7 ± 1.1	1.9 ± 0.5	1.5 ± 0.3*	1.2 ± 0.4-	2.1 ± 0.5
20	2.1 ± 0.9	1.4 ± 1.1	0.6 ± 1.0-	2.3 ± 1.2	0.9 ± 0.4	0.7 ± 0.3	0.4 ± 0.5+	1.1 ± 0.4

Values are mean ± s.d. * $p<0.05$; ° $p<0.01$; + $p<0.005$ vs before PTCA

The arteriovenous lactate measurements are also listed in Table XVIII.4. The control measurements showed a difference of $+0.11 \pm 0.2$ mmol/l, which decreased to -0.87 ± 0.70 and -0.82 ± 0.57 mmol/l after the first and the second dilatations, respectively. After the third dilatation the lactate difference was -0.44 ± 0.34 mmol/l, which was not significantly different from the values recorded after the first and the second dilatation; after the fourth, the fifth and the sixth dilatations the number of measurements was too small to demonstrate a significant increase or decrease in lactate production.

Discussion

Global and regional left ventricular performance

The earliest (1 to 15 s after occlusion) and most sensitive hemodynamic indicator of regional perfusion deficit proved to be an impairment in early relaxation, with

Table 4. Reactive hyperemia and arteriovenous lactate difference after sequential transluminal occlusions.

	Before PTCA (range)	First occl. (range)	Second occl. (range)	Third occl. (range)	Fourth occl. (range)	Fifth occl. (range)	Sixth occl. (range)	After PTCA (range)
No. of patients	20	20	20	19	9	7	4	20
Average duration of transluminal occlusion per patient (sec)	–	41 ± 13* (10,60)	44 ± 14 (20,70)	51 ± 15 (25,90)	52 ± 11 (30,70)	54 ± 11 (30,65)	54 ± 12 (40,75)	–
p-value (vs first occlusion)			<.005	<.005	<.02	<.02	n.s.	
Coronary sinus blood flow (ml/min)	129 ± 34 (101,152)	152 ± 44 (97,203)	155 ± 37 (101,203)	161 ± 31 (110,210)	167 ± 40 (116,200)	161 ± 44 (95,187)	–	144 ± 35 (110,189)
p-value (vs before PTCA)		<.001	<.001	<.0005	<.01	<.01		n.s.
GCV flow (ml/min)	69 ± 17 (40,99)	107 ± 31 (66,152)	127 ± 39 (81,210)	132 ± 22 (109,167)	112 ± 33 (66,160)	109 ± 33 (67,167)	110 ± 33 (99,152)	82 ± 9 (63,87)
p-value (vs before PTCA)		<.001	<.0005	<.0005	<.002	<.02	n.s.	n.s.
Aorto-GCV difference in lactate (mmol/l)	+0.11 ± 0.2 (−0.45,0.4)	−0.87 ± 0.70 (−2.10,0.17)	−0.82 ± 0.57 (−2.10,0.02)	−0.44 ± 0.34 (−0.89,0.0)	−0.62 ± 0.42 (−1.50,0.18)	−0.64 ± 0.37 (−1.30,0.13)	–	+0.18 ± 0.09 (0.06,0.31)
p-value (vs before PTCA)		$<10^{-4}$	$<10^{-6}$	$<10^{-4}$	$<10^{-5}$	<.01		n.s.

GCV = great cardiac vein.

* Mean ± s.d.

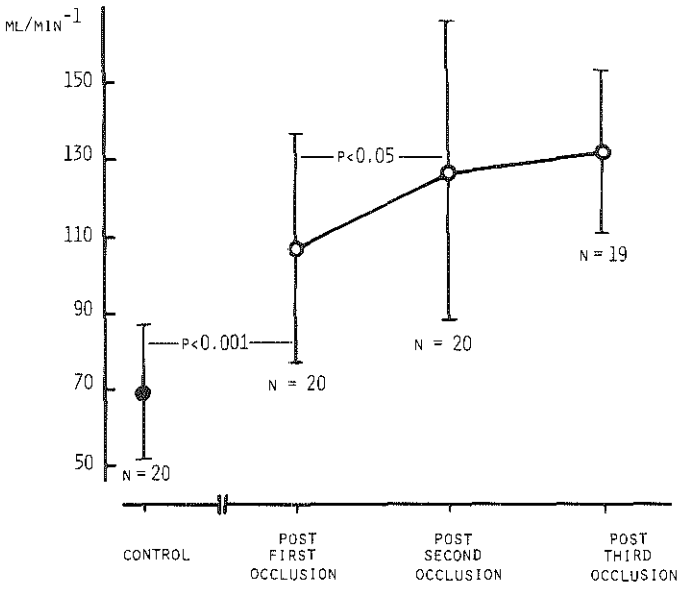

Fig. 9. Great cardiac vein flow during control measurements and after three sequential episodes of reactive hyperemia.

extreme prolongation of T_1, the time constant of the early relaxation phase. If the premise of the two time constant models previously described [10] is correct, then the early change in T_1 with constant T_2 represents an exacerbation in the asynchrony of relaxation. This is illustrated by the change in negative dP/dt and wall displacement induced by a 20 s coronary occlusion (figure 6, B). Within 4 or 5 beats after occlusion, a distinct deformation appears in the ascending limb of the negative part of the dP/dt curve and in the next 10 seconds this deformation reaches the same level as peak negative dP/dt, which in the meantime has progressively decreased to its nadir. Accompanying this change in negative dP/dt, the ischemic segments exhibit a biphasic inward-outward wall displacement that occurs after valve closure and peak negative dP/dt. During the remainder of relaxation and rapid filling the ischemic segments display a second wave of inward wall displacement. The beginning of this second wave of wall displacement in early diastole corresponds closely in time to the irregularity in dP/dt. In the same way, the peak inward displacement of the control segment is consistently observed near the notching in the dP/dt. Shortly after this point, the pressure ceases to have a relaxation time constant T_1 and abruptly switches to T_2. On the other hand, after 50 s of occlusion the majority of the ischemic segments are akinetic and exhibit an increased regional stiffness, whereas T_1 tends to return toward less abnormal values. In our study, at 50 s the deformity in negative dP/dt was no longer present.

The connection between transient asynergy, myocardial ischemia, and alteration in the time course of relaxation was pointed out as early as 1969 by Tyberg et al., [13] who designed an experimental preparation consisting of two papillary muscles in series. They demonstrated that when one muscle of the pair is hypoxic, but still contracting it disturbs the time course of the total fall in tension generated by the two muscles much more than when one of the muscles in series is not contracting at all and infinitely stiff [13]. More recent studies in conscious animals after experimental coronary occlusion have indicated that ventricular dyssynchrony due to late systolic contraction and relaxation in different regions can produce marked effects on the linearity and maximal rate of fall in pressure in the left ventricle [14–16].

Our results suggest that a similar phenomenon may occur in the intact human heart during acute ischemia. At 20 s the late systolic outward displacement of the ischemic segment is probably passive and due to a simultaneously increased and active inward displacement of the nonischemic segments. Conversely, the early diastolic inward displacement of the ischemic segments must correspond to an accelerated outward displacement of the normal segment. Ultimately after 20 s of ischemia the ischemic zone acts as an additional elastic element in series with the actively contracting and relaxing nonischemic segment. This mechanism is consistent with the model of left ventricular pressure relaxation recently proposed by our group [10] in which it is assumed that the observed time constant T_1 results from the combined action of that fraction of the myocardium in the process of relaxing and the remaining fraction in which relaxation has not yet been initiated.

Coronary hemodynamics

The mean great cardiac vein flow of 69 ml/min reported here is well within the range previously reported [5, 6, 17]. This is in agreement with Rothman et al., [18] who reported a flow of 76 ml/min before angioplasty. In their study the mean hyperemic increase in great cardiac vein flow was 29.9% above control flow after the first inflation, compared with 59.3% above control after the final inflation.

In our patients the mean hyperemic increase in great cardiac vein flow was 55% after the first dilatation and 91% after the third dilatation (figure 9). In a subset of nine patients who needed more than three dilatations to satisfactorily reduce the transstenotic gradient, the values of reactive hyperemia were less elevated, ranging between 58% and 63%. As observed by Rothman et al., [18] more pronounced reactive hyperemia developed when the residual functional coronary stenosis associated with the deflated PTCA balloon was reduced by subsequent dilatations.

In general, our values for reactive hyperemia are higher than those found by Rothman et al. [18]. This difference might be explained by the difference in the mean duration of balloon inflation which was 9.8 ± 3.7 s in their patients com-

pared to 41 ± 13 s in our patients. These prolonged occlusion times (41 to 54 s) are due to the fact that we kept the balloon inflated as long as the patient did not manifest any clinical signs of ischemia. In fact, we have noticed that the duration of balloon inflation could be gradually prolonged during subsequent dilatations, as if the anginal threshold had increased following these repeated occlusions.

Metabolic disturbances

Recently, coronary sinus K^+ concentration was measured continuously in two patients undergoing angioplasty of significant stenoses of their left anterior descending coronary arteries [19]. The recordings obtained from these patients show that, although coronary sinus K^+ levels did not change significantly during coronary occlusion, a transient rise occurred when the occlusion was removed. After reducing pressure in the balloon, the coronary sinus K^+ levels began to rise within 8 sec. This fits exactly with the timing of peak reactive hyperemia observed in our study and by Rothman et al. [18]. In our patients, blood samples were obtained 10 to 15 seconds after the start of deflation. Since we could not record the great cardiac vein flow during the sampling period, we did not express our results in terms of lactate efflux. The less elevated concentration (−0.44 mmol/l, A-V difference) in the great cardiac vein after the third sequential occlusion does not necessarily reflect a reduction in lactate production since the reactive hyperemia measured before the sampling was significantly ($p<.05$) greater (132 ml/min) than that measured during the first and second occlusions.

As a first approximation, the amount of lactate lost from the ischemic tissue during the first two occlusions seems to be constant and at least does not increase with subsequent occlusions. The crucial conclusion to be drawn from the observation that a few minutes after termination of this procedure the lactate balance again becomes positive is that the metabolic disturbances induced by repeated ischemia are reversible.

Clinical implications

Experimental data on atherosclerotic vessel segments have shown that volume reduction of atherosclerotic tissue is related to the duration of pressure application. These findings have led many clinicians to use longer inflation durations (30 to 60 s) during PTCA [20–21]. On the other hand, Braunwald and Kloner [22] have recently addressed the question of whether the myocardium can become chronically, even permanently, 'stunned' as a consequence of repeated episodes of myocardial ischemia. Although most episodes of transient ischemia produced in our patients during PTCA were not as severe as those produced in animal studies [14, 15, 23], the total duration of episodes during PTCA has increased

considerably since our initial experience; the median is now 4 min and in a few cases it has exceeded ten minutes in our laboratory [2]. This total occlusion time of 4 min might be excessive since it has been demonstrated in conscious dogs that the return of myocardial function is delayed after periods of coronary occlusion as brief as 100 s. In this case, however, hyperemia that occurs normally during reperfusion is prevented by a residual subtotal occlusion [24] and there is no such occlusion after successful PTCA. In this respect, the results of the present study seem to be reassuring since there is no evidence of global or regional myocardial dysfunction even after four to six coronary occlusions of 40 to 60 s each.

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Chapter III

Asynchrony in regional filling dynamics as a consequence of uncoordinated segmental contraction during coronary transluminal occlusion

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Summary

The effects of brief periods of a major coronary artery occlusion on the global and regional peak filling rates were studied during angioplasty in 14 patients. None had had a previous myocardial infarction. High-fidelity left ventricular pressure and volume (by angiography) were obtained before, 20 and 50 seconds after the onset of transluminal coronary occlusion and shortly after the last balloon inflation. Segmental wall motion was analyzed frame-by-frame along 20 hemiaxes. Global peak filling rate decreased significantly both after 20 (−25%; $p<.05$) and 50 seconds (−24%; $p<.05$) from the onset of the occlusion. The term $\sum \Delta t_1$ was defined as the sum of the absolute values of the time differences between the occurrence of global peak filling rate and the segmental peak filling rate, in 20 segments. This parameter increased significantly during both periods of transluminal occlusion (by 64%; $p<.005$ and by 54%; $p<.005$, respectively) thus indicating an asynchrony in the occurrence of regional peak filling rate. Simultaneously, the sum of time intervals between the aortic valve closure (end systole) and the occurrence of peak segmental shortening, $\sum \Delta t_2$, measured in the 20 segments, increased to a similar extent, thus demonstrating an asynchrony in segmental contraction. A significant, negative correlation was found between the global peak filling rate and both $\sum \Delta t_1$ and $\sum \Delta t_2$ ($r = -.68$; $p<.0001$ and $r = -.73$; $p<.0001$, respectively). Our findings suggest that during coronary transluminal occlusion an early asynchrony in regional peak filling rate occurs which is strictly related to a delayed and asynchronous peak segmental shortening.

Introduction

It is well known, that in patients with coronary artery disease, abnormalities may occur in left ventricular filling dynamics, even in the presence of normal systolic

function [1–4]. Recently, the relationship between the regional and global filling has been investigated in patients with one vessel disease using radionuclide angiography; an asynchrony in diastolic filling of the ischemic regions in the absence of regional systolic dyshomogeneity was reported [5, 6].

We previously observed that transient ischemia induced by luminal occlusion of a major coronary artery during percutaneous transluminal angioplasty (PTCA) caused a shift in timing of the peak inward wall displacement of the ischemic segments from end systole to early diastole [7]. In order to investigate the relationship, if any, between such temporal nonuniformity of contraction and abnormalities in filling dynamics during ischemia, we studied regional wall displacement in systole and diastole during transient ischemia induced by balloon inflation at PTCA.

Materials and methods

Study population

After a preliminary study to confirm the absence of effects of nonionic contrast media (metrizamide-Amipaque®) on left ventricular function, permission was obtained from the Thoraxcenter Ethics Committee to perform left ventricular angiography during balloon inflation at PTCA. All patients involved in the study gave informed consent and no complications related to the research procedure occurred. Fourteen patients with coronary artery disease undergoing PTCA, with the following selection criteria, were studied:

(1) isolated, obstructive lesion in one coronary artery (in ten patients in the left anterior descending artery, in three patients in the right coronary artery and in one patient in the left circumflex artery), without angiographically demonstrable collateral circulation.
(2) normal left ventricular wall motion at rest, as determined from prior diagnostic catheterization.
(3) no intraventricular conduction abnormalities on the resting ECG.

Four patients had mild essential hypertension and an elevated left ventricular end-diastolic pressure ($\geq$25 mmHg). Standard anti-anginal therapy was allowed until the day of the study. An evaluation of the systolic function in the same series of patients had been reported previously [7].

Study protocol

Left ventricular pressure was recorded during ventriculography (30° right anterior oblique view at 50 frames/s) carried out before balloon dilatation, at a mean occlusion time of 20 s during the second dilatation, at a mean occlusion time of 48

s during the fourth dilatation and at a mean of 12 minutes after the last dilatation. Angiography during the fourth dilatation was performed in only 9 patients. A total of 3 to 10 occlusions were performed and the duration of balloon inflation ranged from 15 to 75 s. Each consecutive balloon inflation was made only when end-diastolic pressure and left ventricular pressure-derived isovolumic parameters of contractility and relaxation, which were available on line during the procedure [8, 9], had returned to basal values. Care was taken to maintain the patient's position relative to the X-ray equipment during sequential angiograms which were performed with the patient helding his/her breath in shallow inspiration.

Analysis of pressure and pressure-derived indices

Left ventricular pressure was measured with a tipmanometer on an 8 F pigtail catheter and digitized at 250 samples/s, allowing a beat-to-beat analysis. End-diastolic pressure was defined as that point on the pressure trace at which the derivative of the pressure first exceeded 200 mmHg/s; end systole or aortic valve closure was assumed to occur simultaneously with the dicrotic notch on the central aortic pressure. Details regarding the off-line analysis of pressure – derived indices of relaxation used in our laboratory have been published previously [7]. The isovolumic relaxation period was defined as the time interval between the aortic valve closure and the mitral valve opening. This latter was defined during left ventriculography, as occurring in the last frame preceding the entry of nonopacified blood into the left ventricle from the left atrium. The left ventricular pressure corresponding to this frame was considered to reflect left atrial pressure [10].

Analysis of regional and global left ventricular function

A complete cardiac cycle was analyzed frame-by-frame from each angiogram with the Contouromat. Over a full cardiac cycle, beginning at end diastole, segmental wall displacement was determined in the 20 segments, 10 in the anterior and 10 in the infero-posterior wall. Peak segmental inward and outward velocity was computed as the first-derivative relative to time of the segmental wall displacement after a 3-points smoothing had been applied to the data (figure 1). Peak ejection rate was taken as the peak negative dV/dt value after end diastole; peak global filling rate as the peak dV/dt value after mitral valve opening, and the time to peak filling rate was the time interval between the aortic valve closure and the moment of peak dV/dt. The time interval was measured between the occurrence of the global peak filling rate and the peak velocity of segmental outward displacement (figure 2). We defined $\sum \triangle t_1$ as the sum of the absolute values of the

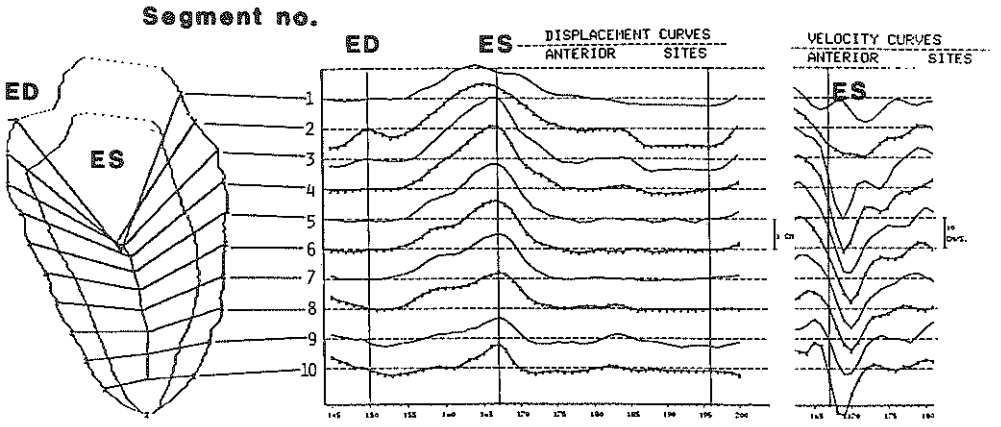


Fig. 1. Example of computer output showing the end-diastolic and end-systolic contours of the 30° RAO left ventriculography. Left ventricular segmental wall displacement is determined along a system of coordinates derived from endocardial landmark trajectories in normal individuals and is studied in 20 separate segments, 10 in the anterior and 10 in the infero-posterior wall. Left ventricular wall velocity, the first-derivative of wall displacement, is derived from these data.

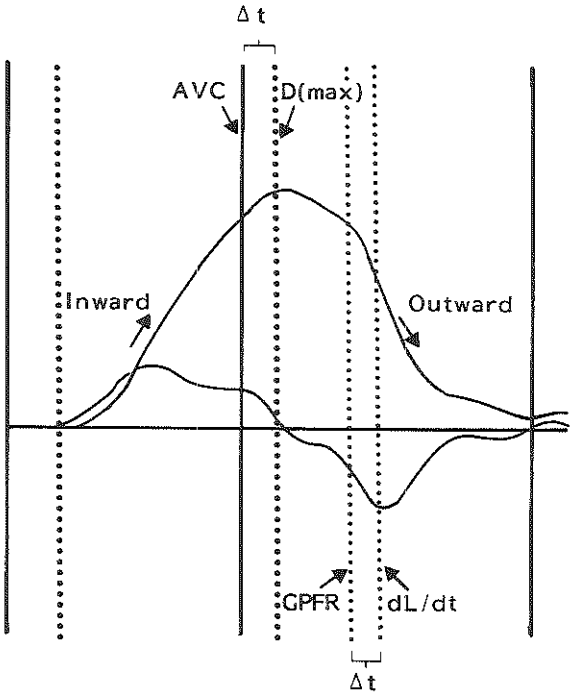


Fig. 2. Segmental wall displacement and its first-derivative are superimposed to show the temporal relationship between inward and outward phases with the moment of aortic valve closure (AVC). The time intervals (Δt) between AVC and the maximal inward wall displacement (Dmax), and between the occurrence of global peak filling rate (GPFR) and the peak velocity of outward displacement (dL/dt) were measured in every segment.

time differences between global peak filling rate and peak velocity of segmental outward displacement; $\sum \Delta t_1/Dt$ was $\sum \Delta t_1$ normalized for diastolic time. We defined $\sum \Delta t_2$ as the sum of the absolute values of the time differences between aortic valve closure and peak segmental inward displacement (figure 2); $\sum \Delta t_2/ET$ was $\sum \Delta t_2$ normalized for ejection time. The terms $\sum \Delta t_1$, $\sum \Delta t_1/Dt$, $\sum \Delta t_2$, $\sum \Delta t_2/ET$ are thus indices reflecting variations in the synchrony of ventricular filling and contraction, respectively.

Statistical analysis

The data are presented as mean ± standard deviation; statistical analysis was performed using the t-test for paired data. The relationships between peak filling rate and the regional indices reflecting asynchrony of contraction and filling were analyzed by regression analysis.

Results

Global indices of left ventricular ejection and filling

An example of the frame-to-frame analysis of left ventricular volume and its derivative (dV/dt) before and during ischemia induced by balloon inflation is shown in figure 3. Volumes, pressures and derived parameters measured before,

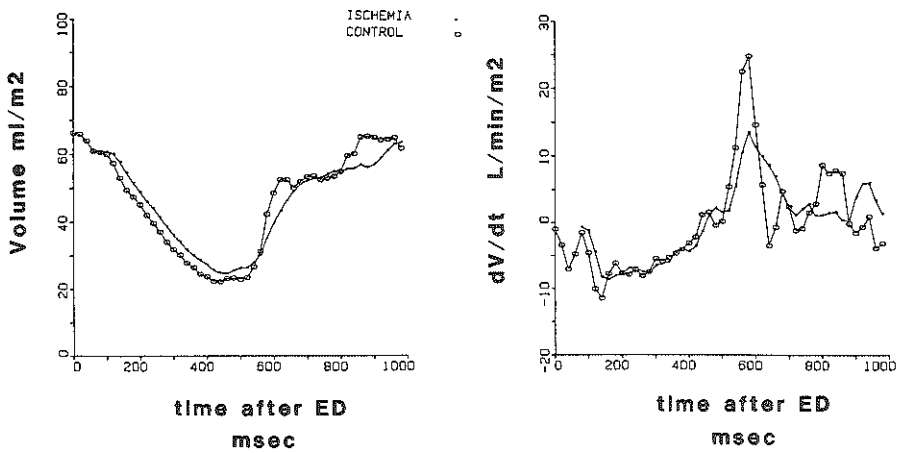


Fig. 3. Left: Left ventricular volume curves for the same patient, derived from angiographic cineframes 20 msec apart analyzed over a complete cardiac cycle, before and during transluminal occlusion. *Right:* Instantaneous left ventricular volume derivative (dV/dt) curves for the same patient, measured every 20 ms throughout a complete cardiac cycle, before and during transluminal occlusion. During ischemia a decrease in peak dV/dt was observed. ED = end diastole.

Table 1A. Global systolic function before PTCA, 20 and 50 s after the onset of occlusion and after PTCA.

Variables	Before PTCA		20 s occlusion (total group; N = 14)	50 s occlusion (subgroup; N = 9)	After PTCA	
	Total group (N = 14)	Subgroup (N = 9)			Subgroup (N = 9)	Total group (N = 14)
Ejection fraction (%)	61 ± 8	62 ± 6	54 ± 8*	48 ± 12*	66 ± 6	64 ± 7
Stroke volume (ml/m²)	50 ± 11	49 ± 11	44 ± 12°	39 ± 14°	52 ± 10	50 ± 9
Mean systolic ejection rate (ml/s)	129 ± 24	127 ± 24	125 ± 32	116 ± 67	165 ± 48	147 ± 27
Peak ejection rate (ml/s)	251 ± 97	255 ± 106	222 ± 69	185 ± 61°	248 ± 77	240 ± 68
Time to peak ejection rate (ms)	172 ± 44	175 ± 50	172 ± 56	153 ± 34	170 ± 88	166 ± 76
Peak ejection rate 1*** (s^{-1})	5 ± 1	5.4 ± 1	5 ± 0.7	5 ± 0.9	5 ± 0.6	4.7 ± 0.6
Peak ejection rate 2*** (s^{-1})	3 ± 0.8	3.3 ± 0.9	2.7 ± 0.5	2.3 ± 0.5*	3.2 ± 0.5	3 ± 0.5
End-systolic pressure (mmHg)	95 ± 18	92 ± 22	90 ± 19	98 ± 24	91 ± 15	90 ± 14
End-systolic volume (ml/m²)	31 ± 9	29 ± 7	37 ± 9*	41 ± 9*	26 ± 15	27 ± 7

° $p<.05$;

* $p<.005$ (compared with before PTCA, paired Student t-test);

** normalized by stroke volume;

*** normalized by end-diastolic volume.

Table 1B. Global diastolic function before PTCA, 20 and 50 s after the onset of occlusion and after PTCA.

Variables	Before PTCA		20 s occlusion (total group; N = 14)	50 s occlusion (subgroup; N = 9)	After PTCA	
	Total group (N = 14)	Subgroup (N = 9)			Subgroup (N = 9)	Total group (N = 14)
tau_1 (ms) [7]	55 ± 8	55 ± 6	79 ± 17*	68 ± 16*	56 ± 7	54 ± 7
tau_2 (ms) [7]	44 ± 7	43 ± 7	51 ± 8°	59 ± 8*	45 ± 8	45 ± 9
IRP (ms)	71 ± 18	77 ± 18	85 ± 16°	80 ± 17	77 ± 16	71 ± 15
MVO pressure (mmHg)	19 ± 5	18 ± 3	23 ± 8	25 ± 6°	19 ± 5	21 ± 6
MVO volume (ml/m²)	37 ± 9	35 ± 7	41 ± 9°	45 ± 10*	30 ± 6	31 ± 8
Peak filling rate (ml/s)	311 ± 83	296 ± 84	234 ± 82°	225 ± 93°	297 ± 117	277 ± 109
Time to peak filling rate (ms)	128 ± 20	133 ± 22	145 ± 38	151 ± 26	130 ± 18	126 ± 23
Peak filling rate (SV/s)	6.5 ± 1	6 ± 0.9	5.9 ± 1	6 ± 2	5.8 ± 0.8	5.7 ± 1
Peak filling rate (EDV/s)	4 ± 1	3.7 ± 0.8	3 ± 8°	2.8 ± 0.7*	3.8 ± 0.9	3.6 ± 1
Pmin (mmHg)	10 ± 5	8 ± 3	11 ± 4	16 ± 6*	8 ± 5	8 ± 4
Volume at Pmin (ml/m²)	51 ± 13	48 ± 11	53 ± 10	55 ± 10	45 ± 11	45 ± 9
MRVI (ml/s)	179 ± 82	198 ± 78	98 ± 78*	104 ± 69*	161 ± 131	138 ± 113

tau_1 and tau_2 = time constant of relaxation (biexponential fitting), tau_1 fit of first 40 ms, tau_2 fit after 40 ms; IRP = isovolumic relaxation period; MVO = mitral valve opening; Pmin = minimal left ventricular diastolic pressure; MRVI = mean rate of volume inflow during the time interval between MVO and Pmin. ° $p<.05$; * $p<.005$ (compared with before PTCA, paired Student t-test).

during and after transluminal occlusion are listed in Tables 1a and 1b. The global indices of the ejection phase decreased during the two periods of coronary occlusion; the ejection fraction fell from 61% to 54% over 20 s ($p<.005$) and from 62% to 48% ($p<.005$) over 50 s, this reduction being mainly due to the increase in end-systolic volume over 20 s (from 31 ± 9 ml/m^2 to 37 ± 9; $p<.005$) and 50 s (from 29 ± 7 ml/m^2 to 41 ± 9; $p<.005$). Consequently, the stroke volume was significantly decreased from 50 ± 11 ml/m^2 to 44 ± 12 ($p<.05$) during the first period of occlusion and from 49 ± 11 ml/m^2 to 39 ± 14 ($p<.05$) during the second. A slight but not significant reduction in peak ejection rate was observed over 20 s, but after 50 seconds it had decreased from 255 ± 106 ml/m^2 to 185 ± 61 ($p<.05$) (figure 4). Normalization for end-diastolic volume and stroke volume did not render the change in peak ejection rate at 20 seconds significant. The relaxation parameters tau_1 and tau_2 [7] significantly increased (Table 1b) during both periods of occlusion and returned to basal values at the end of the PTCA procedure. The isovolumic relaxation period increased from 71 ± 18 msec to 85 ± 16 ($p<.05$) over 20 s and from 77 ± 18 msec to 80 ± 17 (n.s.) over 50 s. The left ventricular pressure at the time of mitral valve opening increased from 19 ± 5 mmHg to 23 ± 8 (n.s.) over 20 s and from 18 ± 3 mmHg to 25 ± 6 ($p<.05$) over 50 s. Peak filling rate was reduced from 311 ± 85 ml/s to 234 ± 82 ($p<.05$) after 20 s of ischemia (figure 4) and from 296 ± 84 ml/s to 225 ± 93 ($p<.05$) after 50 s. When normalized for stroke volume, peak filling rate was unchanged after 20 and 50 s of occlusion, whereas after normalization for end-diastolic volume it was signifi-

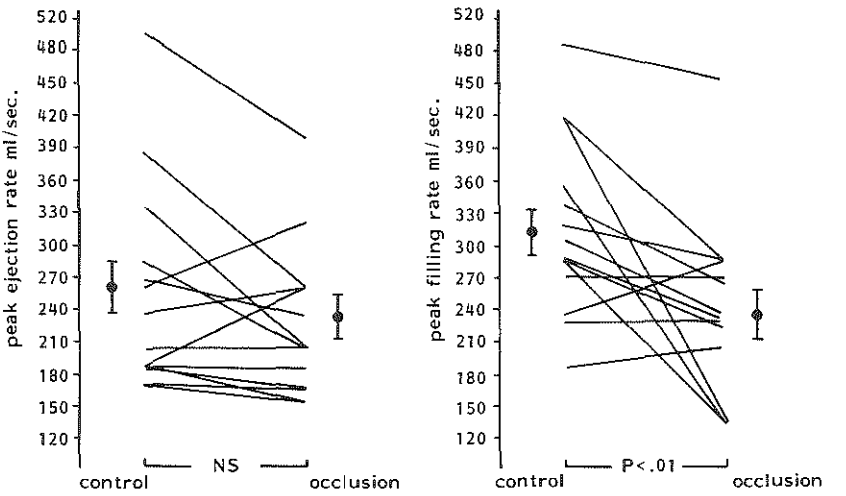


Fig. 4. Individual and mean changes (± SEM) in peak ejection rate and peak filling rate during transluminal occlusion (20 ms). Only the peak filling rate showed a significant decrease during the early phase of coronary occlusion.

cantly decreased after 20 (from 4 ± 1 EDV/s to 3 ± 0.8; $p<.05$) and 50 s (from 3.7 ± 0.8 EDV/s to 2.8 ± 0.7; $p<.005$). The mean rate of volume inflow, measured during the early filling period between the mitral valve opening and the occurrence of minimal diastolic pressure, declined significantly both at 20 (from 179 ± 82 ml/s to 98 ± 78; $p<.005$) and 50 s (from 198 ± 94 ml/s to 104 ± 69; $p<.005$) from the onset of occlusion.

Regional indexes of left ventricular ejection and filling

As previously demonstrated [7], during occlusion of the left anterior descending artery the time of maximal inward wall displacement of the anterior wall shifts from end systole to early diastole (figure 5). In the present study a delay was observed in the occurrence of peak velocity of outward displacement (dL/dt) with respect to aortic valve closure after 20 s of ischemia, particularly in the apical region (segments 10 and 20 in figure 5) and the absolute value of the dL/dt was reduced in the ischemic segments (figure 6). In the nonischemic segments a compensatory increase in dL/dt was observed. In order to test whether this decrease in the absolute value of dL/dt was in fact intrinsically related to a

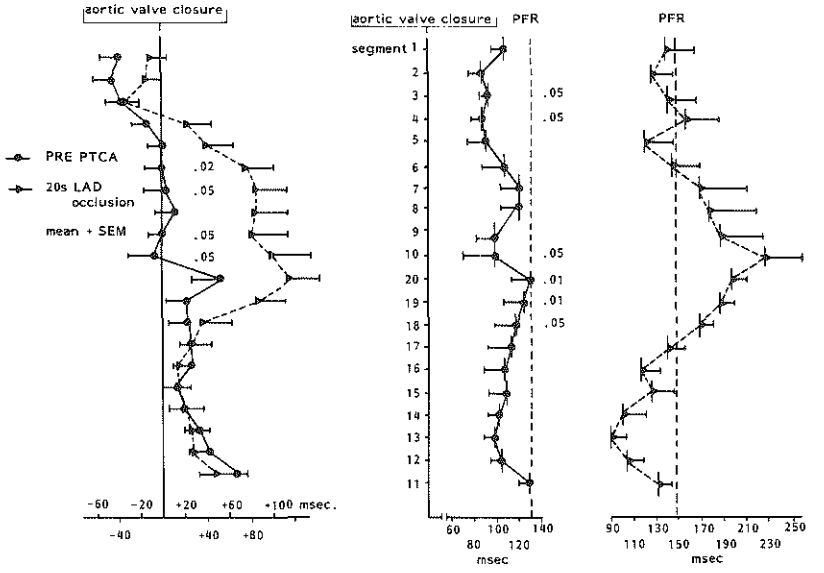


Fig. 5. Left panel: Time relationship between aortic valve closure and the occurrence of maximal inward wall displacement before and after 20 ms of occlusion of the left anterior descending artery. *Center and right panel:* Time relationship between aortic valve closure and the occurrence of peak velocity of segmental outward displacement before (center panel) and after 20 s of occlusion (right panel) of the left anterior descending artery. PFR = global peak filling rate.

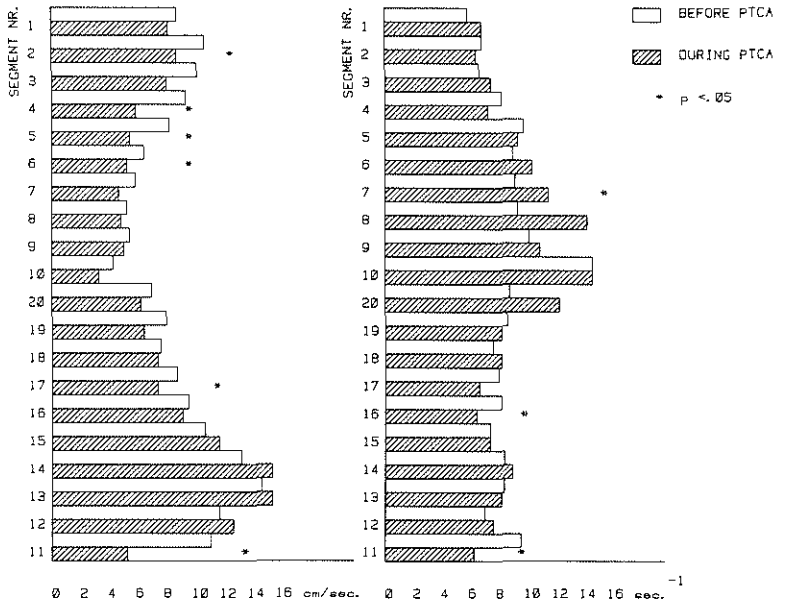


Fig. 6. Left panel: Mean changes in peak velocity of segmental outward displacement (dL/dt) in 10 anterior and 10 posterior segments before and during occlusion of the left anterior descending artery. *Right panel:* Mean changes in the ratio dL/dt/ maximal outward displacement in 10 anterior and 10 posterior segments before and during occlusion of the left anterior descending artery.

reduction in the amplitude of the peak outward displacement, we normalized segmental dL/dt for the corresponding value of maximal outward displacement. After normalization we observed an increase in the ischemic segments, while no major changes were apparent in the nonischemic segments (figure 6). Therefore, a relationship between the asynchrony of segmental dL/dt and the reduction of global peak filling rate was sought by measuring the sum of the absolute values of the time differences from global peak filling rate to the occurrence of peak dL/dt in each of the 20 segments ($\sum \triangle t_i$). This sum increased significantly during both the first (from 572 ± 194 ms to 940 ± 264 ms; $p<.005$) and the second occlusion (from 546 ± 198 ms to 842 ± 224 ms; $p<.005$); increases were also found for $\sum \triangle t_i/Dt$, thus indicating an asynchrony in filling (Table 2). To elucidate whether the decrease in global peak filling rate was related to the asynchrony in regional peak filling rate rather than to other causes, we correlated global peak filling rate with $\sum \triangle t_i$ and found a significant negative correlation ($r = -.68$; $p<.001$), demonstrating that a greater degree of asynchrony was associated with a reduction in peak filling rate (figure 7). To determine whether the asynchrony in regional filling was an isolated phenomenon or the effect of a temporal nonuniformity in inward wall displacement, we quantified this systolic nonuniformity be measuring the time relationship between end systole and the occurrence of the

Table 2. Measurement of regional asynchrony in inward and outward wall displacement before PTCA, 20 and 50 s after the onset of occlusion and after PTCA.

Variables	Before PTCA		20 s occlusion (total group; N = 14)	50 s occlusion (subgroup; N = 9)	After PTCA	
	Total group (N = 14)	Subgroup (N = 9)			Subgroup (N = 9)	Total group (N = 14)
$\sum \triangle t_1$ (ms)	572 ± 194	546 ± 198	940 ± 264*	842 ± 224*	495 ± 179	645 ± 355
$\sum \triangle t_2$ (ms)	965 ± 348	948 ± 415	1442 ± 314*	1472 ± 370°	985 ± 171	978 ± 281
$\sum \triangle t_1$/diastolic time	1.1 ± 0.7	1.3 ± 0.8	1.8 ± 0.8*	1.9 ± 1*	1.3 ± 0.7	1.2 ± 0.6
$\sum \triangle t_2$/ejection time	2.6 ± 0.9	2.8 ± 0.7	4.2 ± 0.9*	4.5 ± 0.9°	3 ± 0.9	2.8 ± 0.8

° $p<.05$; * $p<.005$ (compared with before PTCA, paired Student t-test). $\sum \triangle t_1$ = sum of the time intervals between global peak filling rate and peak velocity of segmental outward displacement (dL/dt). $\sum \triangle t_2$ = sum of the time intervals between aortic valve closure and segmental peak inward displacement.

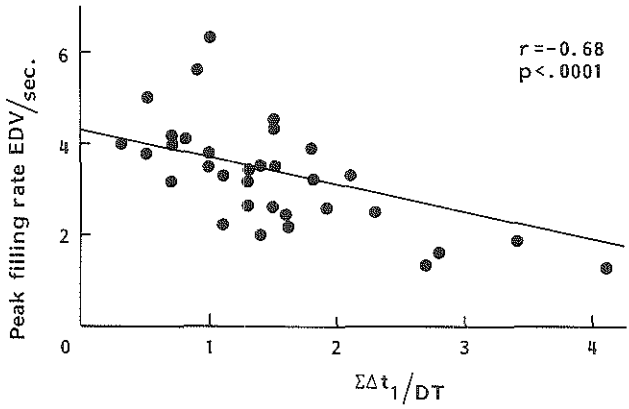


Fig. 7. The negative correlation between the global normalized peak filling rate and the $\sum \Delta t_1$/diastolic time as an index of segmental asynchrony in filling, in patients with left anterior descending artery disease.

segmental peak inward displacement. The sum of the absolute time differences between aortic valve closure and the peak regional inward wall displacement ($\sum \Delta t_2$) was used as an index of systolic asynchrony, and during coronary occlusion both $\sum \Delta t_2$ and $\sum \Delta t_2$/ET increased in the same fashion as $\sum \Delta t_1$ and $\sum \Delta t_1$/Dt (Table 2). In addition, we found a significant correlation ($r = .66$; $p<.001$) between $\sum \Delta t_2$ and $\sum \Delta t_1$ (figure 8), suggesting an interdependance between the asynchrony of contraction and the abnormalities of filling dynamics. This temporal interdependance between inward and outward wall displacement is illustrated in figure 5. Further supportive evidence for the interrelationship between

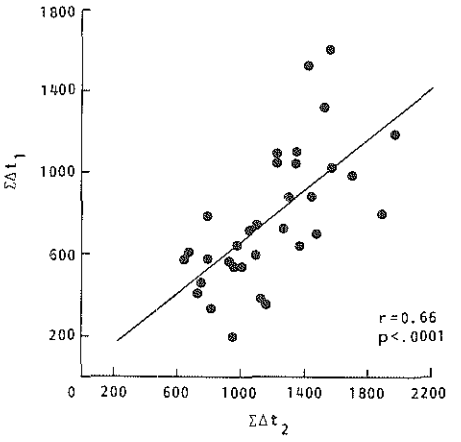


Fig. 8. The correlation between the $\sum \Delta t_1$ as an index of segmental asynchrony in filling and the $\sum \Delta t_2$ as an index of segmental asynchrony in contraction.

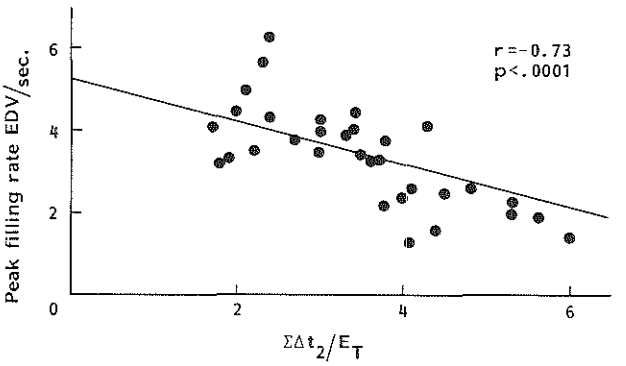


Fig. 9. The negative correlation between the global normalized peak filling rate and the $\sum \Delta t_2$/ejection time as an index of segmental asynchrony in contraction, in patients with left anterior descending artery disease.

contraction and filling was given by the significant negative correlation between the global peak filling rate and $\sum \Delta t_2$ ($r = -.73$; $p<.001$) (figure 9). Thus the greater the asynchrony in the pattern of contraction, the greater the decrease in peak filling rate. All these data indicate that the asynchrony in the occurrence of the regional filling with subsequent decreases in peak filling rate, reflects non-uniformity of left ventricular contraction and occurs within 20 s of the onset of ischemia. To further elucidate the dynamic interplay between asynchrony in contraction and abnormalities in early diastolic phase we correlated $\sum \Delta t_2$ with parameters of the relaxation phase and these latter parameters with the peak filling rate. A significant correlation was observed between $\sum \Delta t_2$ and tau_1 ($r = .75$, $p<.0001$) and between tau_1 and the duration of isovolumic relaxation period ($r = .58$; $p<.0001$). On the other hand, no correlation or only weak correlations were observed between parameters of the relaxation phase and peak filling rate (Table 3).

Table 3. Correlation between parameters of left ventricular relaxation and filling.

Comparison	Correlation coefficient	p-value
tau_1 – PFR	−0.33	0.06
tau_2 – PFR	−0.152	0.37
IRP – PFR	−0.53	0.009
MVO* – PFR	−0.23	0.2

* = pressure. For legends see Table 1B.

Discussion

Variability in the temporal sequence of regional left ventricular contraction in normal subjects has been previously observed and attributed to variations in the sequence of electrical activation or to other factors playing an important role in determining ventricular geometry such as ventricular volume and fiber orientation [11, 12]. In patients with coronary artery disease the completion of ejection was found to be delayed, whereas the onset of ejection was not and the severity of coronary artery disease was positively correlated with the persistence of these contraction abnormalities into early diastole [13]. During spontaneous angina, a significant prolongation of left ventricular ejection time with an accompanying shortening of diastole has also been observed [14]. All these observations dictate that relaxation and filling in early diastole should be correlated with the pattern of contraction. Further insight into this relationship was given by the study of Smalling in the canine model [15]. A biphasic expansion and contraction in both endocardial wall motion and myocardial wall thickening was observed during acute and graded ischemia. This combined biphasic wall motion effect was attributed to a loss of the early diastolic distending forces of coronary pressure (the 'erectile' effect) or to a persistent contraction of the ischemic zone during early diastole. On the basis of these previous studies, we investigated the relationship between the ejection phase and early diastolic filling.

Methodological considerations

Contrast angiography was used rather than radionuclide angiography, because the acquisition time required for radionuclide angiography precludes the detection of acute changes in left ventricular performance [16], although reliable information on segmental wall motion can be derived from changes in regional counts [6, 17]. Recently, the nonimaging nuclear probe has been proved useful in a study of ventricular filling phase during PTCA [18], permitting a beat-to-beat noninvasive assessment of cardiac function 10 seconds after radionuclide injection. However, this technique has two important limitations: (1) the inability to measure absolute volume changes; and (2) the inability to measure regional volume-derived parameters. On the other hand, contrast angiography does not allow a continuous beat-to-beat assessment of the changes in left ventricular function during the early phase of ischemia, but only provides a snapshot of this rapidly evolving situation.

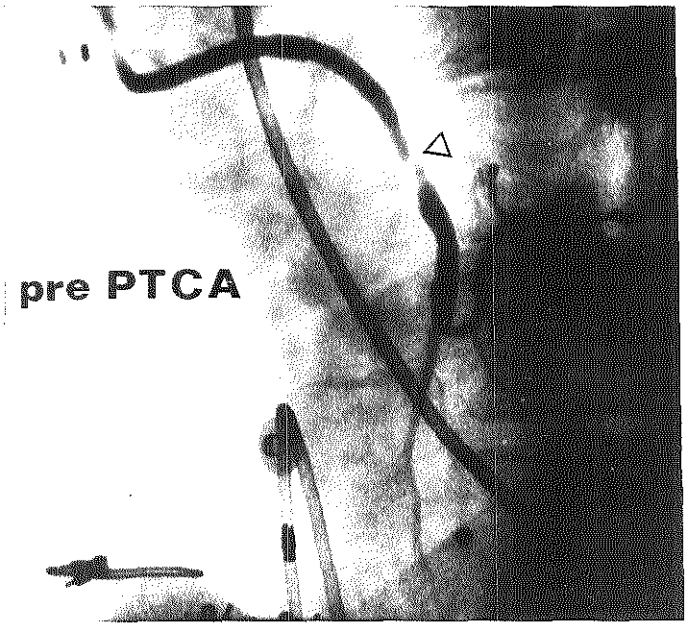
Analysis of the left ventricular angiograms was performed by an automated, high resolution, frame-to-frame edge detection system allowing fast and reliable acquisition of single left ventricular contours over a complete cardiac cycle. Many wall motion models have been proposed to approximate actual endocardial motion, which reflects the problems investigators have had to establish a geo-

metric framework upon which to determine whether the motion of the endocardial contour is normal or abnormal [19, 20]. All these methods assess wall motion in terms of extent of shortening at specific points on an axis reference system and it is highly unlikely that a particular endocardial site will coincide with one of these points during an entire cardiac cycle. The wall motion analysis system we used is based on the motion pattern of small irregularities at the left ventricular endocardial border (endocardial landmarks) which can be detected in the contrast cineangiogram with the automated endocardial outlining system. Such endocardial landmark pathway has been tested previously in 23 normal human left ventricles and validated in pigs with metal endocardial markers inserted via a percutaneous, retrograde, transvascular approach [21]. The major advantage of this wall motion analysis is that it is unaffected by the translation and rotation of the heart, thus permitting an accurate study of segmental wall motion and derived parameters.

Determinants of filling dynamics

It has been suggested that the peak filling rate is dependent on the rate of left ventricular relaxation and on the left atrial pressure [22]. Under normal conditions the relaxing left ventricle produces a rapid change in the atrio-ventricular pressure gradient, which is the driving force for the inflow [23]. Thus, a prolonged relaxation phase as observed during acute ischemia, causes a delay in the development of the atrio-ventricular pressure gradient, and consequently, a greater left atrial pressure is required to open the mitral valve. In fact, we observed a consistent delay in the relaxation occurring 20 s after the onset of ischemia and concomitantly both the isovolumic relaxation period and the left atrial pressure required for mitral valve opening increased. The significant relationship existing between $\sum \triangle t_2$ and tau_1, and between this latter parameter and the duration of the isovolumic relaxation period, suggests that during acute ischemia the atrio-ventricular dynamic interplay occurring during early diastole is affected by the asynchronous left ventricular contraction. Yellin et al. [22], demonstrated in the dog that under conditions of similar left atrial pressure at valve opening, the prolongation of the time constant of relaxation decreases the rate and extent of filling, whereas under conditions of similar left ventricular pressure during relaxation an increase of left atrial pressure increases the extent of early filling. Thus the lack of correlation between peak filling rate and any single parameter of the relaxation phase, such as time constants of relaxation, isovolumic relaxation period or mitral valve opening pressure was expected since these latter parameters are changing in opposite direction during acute ischemia.

A decrease in peak filling rate has been extensively reported in patients with coronary artery disease with or without previous myocardial infarction. Until recently no data were available in the literature regarding the relationship be-



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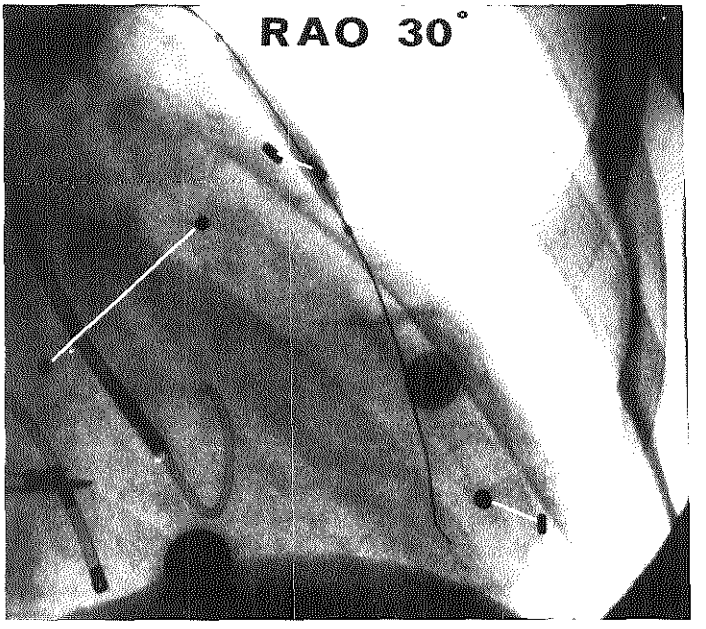

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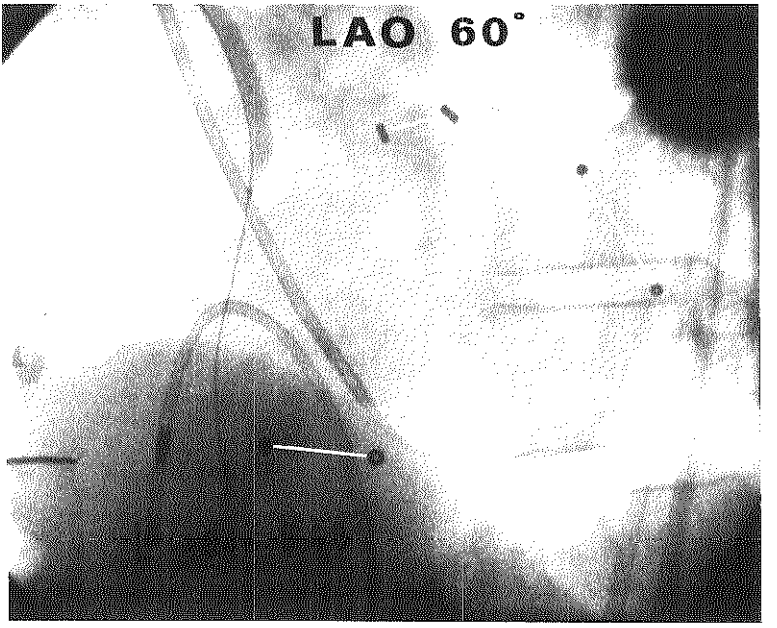

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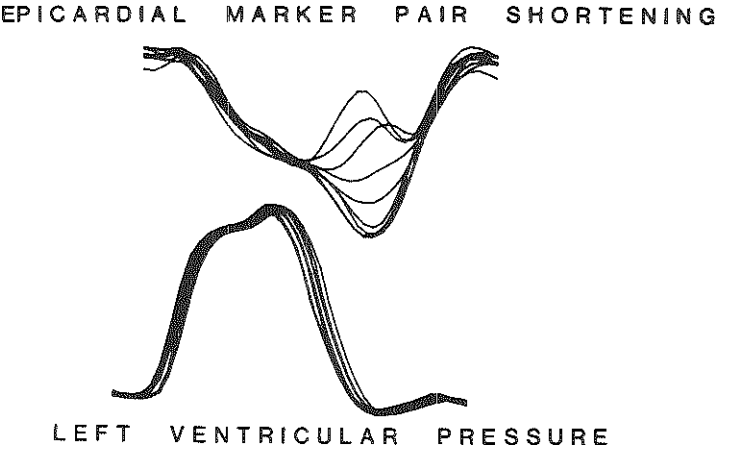
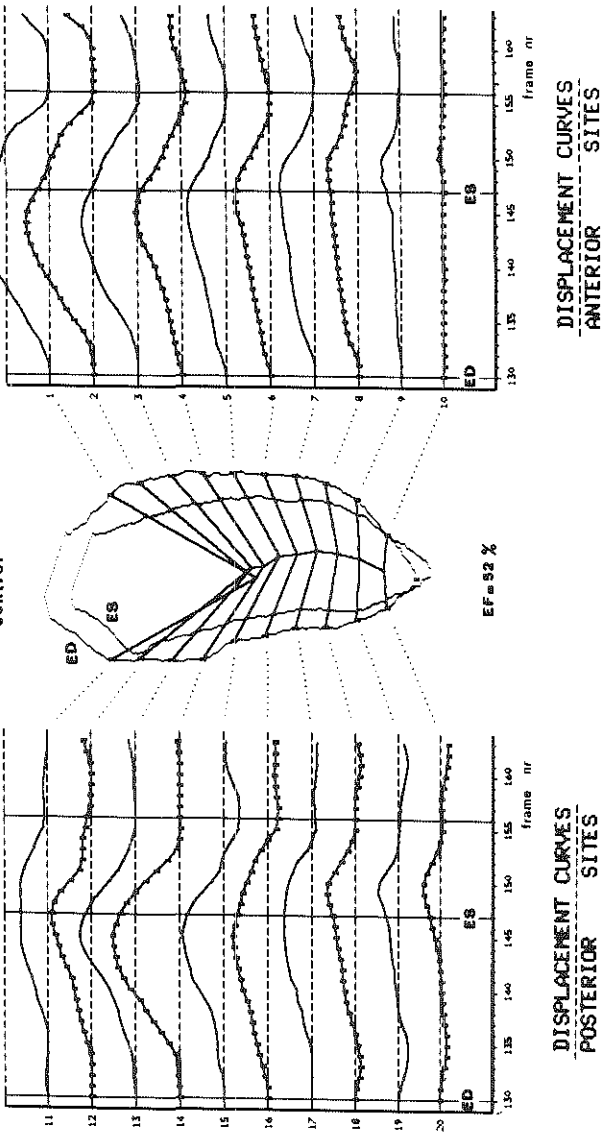


D

Fig. 10. Angiogram of left anterior descending bypass graft stenosis and markers before PTCA (Fig. A). Figures B and C show the inflated angioplasty catheter in place, in RAO 30° and LAO 60° respectively. In Fig. D changes in epicardial marker pair shortening in region of bypass graft and left ventricular pressure during graft occlusion. The W phenomenon (see text) is evident.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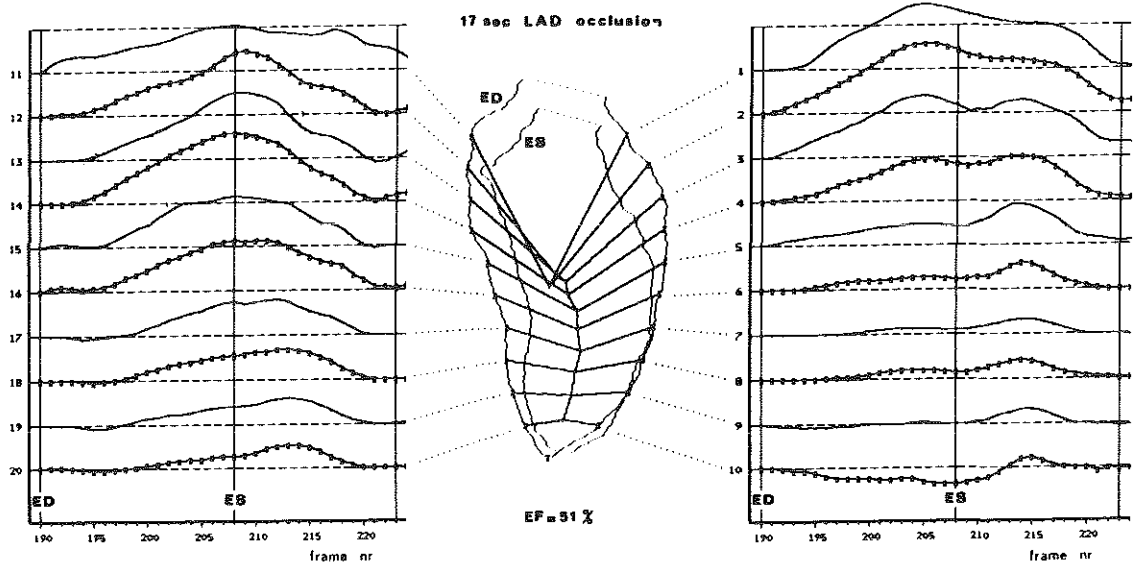

Fig. 11. Left ventricular wall displacement in 10 anterior (right) and 10 infero-posterior (left) segments in the control state (upper figures) and after 17 s of occlusion of the left anterior descending (LAD) artery (lower figures). After 17 s of occlusion of the LAD. A biphasic pattern of contraction is observed in the anterior segments, while the apical segments (anterior and inferoposterior) show a late inward wall displacement occurring in the early diastole. In the nonischemic segments an accelerated outward displacement is observed.

tween global and regional left ventricular filling. Yamagishi et al. [5] investigated this relationship using radionuclide angiography in normal subjects and in patients with left anterior descending coronary artery disease without previous myocardial infarction and found differences in peak filling rate differentiating normals from those with coronary artery disease. To explain this difference they analyzed regional filling dynamics and identified that asynchrony in regional filling was a major determinant of decrease in peak filling rate. The sum of the absolute time differences between the global and regional peak filling rate was inversely correlated to the global peak filling rate and proposed as an index of asynchrony in diastolic filling. More recently Bonow et al. [6] studied with radionuclide angiography the relationship between regional left ventricular diastolic asynchrony and global diastolic filling, before and after PTCA in patients with single vessel coronary artery disease. Before PTCA, impaired global diastolic filling was found and was related to regional variations in the timing of left ventricular relaxation and filling determined by variations in phase among sectors and by regional quadrant analysis. In addition, they demonstrated a negative correlation between the magnitude of global peak filling rate and the extent of regional asynchrony. Reevaluation one day to one month after PTCA showed an improvement of the above mentioned changes in diastolic global and regional function.

Role of the asynchronous contraction

In the present study, we demonstrated that ischemia occurring early during coronary occlusion severely alters filling dynamics and that the major determinant of this change is asynchrony in regional filling. This diastolic asynchrony was secondary to a nonuniformity of inward wall displacement, but the crucial question remains whether this diastolic asynchrony was a direct, intrinsic manifestation of altered relaxation properties of the myocardium (inactivation) or a consequence of dysfunction of the contractile properties of the myocardium (activation) [24, 25].

Recently we evaluated the beat-to-beat myocardial shortening changes accompanying acute coronary occlusion in one patient undergoing PTCA of a coronary artery bypass graft, in whom pairs of epicardial wall markers had been placed at the time of his original cardiac surgery [26]. Their motion reflecting epicardial transverse shortening was characterized, in ischemic myocardium, by the early appearance of a late systolic lengthening followed by an early diastolic shortening (figure 10). We referred to this biphasic motion as the 'W' phenomenon due to its morphologic characteristics, transient duration, and frequency of appearance in studies of endocardial wall thickness motion during regional ischemia. This polyphasic wall motion pattern appears to be similar to that described by Wiegner et al. [27], who studied the interaction of normal and

hypoxic myocardial muscles in series. They identified a biphasic pattern of motion of the hypoxic muscle analogous to that observed in the ischemic region of the intact left ventricle. The early lengthening phase of the hypoxic muscle was attributed to a premature onset of force decline and the second late shortening phase was ascribed to either a persisting contractile force of the muscle or a manifestation of stored force from elastic recoil of previously stretched passive muscle elements. Furthermore, they indicated the possible negative role of late shortening on filling dynamics. Similar types of wall motion abnormalities have been described in animals [28–31] and during chronic ischemia in man [32, 33]. In our angiographic study, the frame-by-frame analysis of the anterior wall displacement during brief occlusion of the left anterior descending artery also showed a variety of biphasic wall motion patterns. As shown in figure 11, after 17 s of occlusion, some of the segments adjacent to the ischemic area exhibited the 'W' phenomenon, while the segment located in the core of the ischemic area exhibited a late inward wall displacement in early diastole. This phenomenon was mirrored by an accelerated outward displacement of the normal segment. Ultimately, the interaction between ischemic and nonischemic segments results in segmental asynchrony in the occurrence of peak velocity of outward displacement. Since this parameter reflects the segmental peak filling rate, an asynchrony in segmental outward displacement corresponds to the asynchrony in the filling phase with consequent changes in the global peak filling rate.

In summary, our study demonstrates that short periods of ischemia, induced by balloon inflation, cause an early disruption of the normal sequence of inward-outward segmental displacement in the ischemic segments. This phenomenon is characterized by an early lengthening occurring during late systole with late shortening occurring during early diastole. These data in part confirm an 'asynchronous contraction' occurring during brief periods of ischemia [34] and, in particular, demonstrate the close relationship existing between uncoordinated contraction and the impairment of filling dynamics. Further investigations are needed to correlate this sequence of mechanical events to the intracellular biochemical events of activation and inactivation.

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Chapter IV

Effect of coronary occlusion during percutaneous transluminal angioplasty in man on left ventricular chamber stiffness and regional diastolic pressure-radius relations.

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Summary

The effect of repeated (3 to 10) and transient (15 to 75 s) abrupt coronary occlusions on the global and regional chamber stiffness was studied in 9 patients undergoing angioplasty (PTCA) of a single proximal left anterior descending coronary artery stenosis. The left ventricular high fidelity pressure and volume relation was obtained prior to and after the procedure, as well as during coronary occlusion, after 20 seconds (N = 9) and after 50 seconds (N = 5). During ischemia, there was an upward shift of the pressure-volume relation. The nonlinear simple elastic constant of chamber stiffness increased from 0.0273 ± 0.017 (mean ± s.d.) pre-PTCA to 0.0621 ± 0.026 after 20 s of occlusion ($p<0.05$) and to 0.0605 ± 0.015 after 50 s of occlusion ($p<0.01$). In 6 patients, the post-PTCA value remained higher than the control value, but at the group level the mean value (0.0529 ± 0.037) was not statistically different. The regional stiffness was determined from the changes in the length of 6 segmental radii during diastole, from the lowest diastolic to the end-diastolic pressure. The regional constant of elastic stiffness was unaffected in the nonischemic zone. In the adjacent and ischemic zones, the regional stiffness was increased during occlusion ($p<0.05$). These regional abnormalities in diastolic function persisted at the time of post-PTCA measurements, 12 minutes after the end of the procedure. This suggests that recovery of a normal diastolic function after repeated ischemic injuries is delayed after restoration of a normal blood flow and systolic function.

Introduction

An increase in left ventricular diastolic pressure relative to volume has been described in patients during pacing and exercise-induced ischemia [1, 2] as well as

during spontaneous angina at rest [3]. The observed upward shift of the entire pressure-volume relation reflects an increased chamber stiffness. From these data it could not be inferred that the intrinsic diastolic properties of the myocardium were altered, since many other factors, such as delayed and incomplete left ventricular relaxation or extrinsic compression by the right ventricle and the pericardium, may be involved [4, 5].

Studies in man [6] using a combined echocardiographic and hemodynamic technique during pacing-induced ischemia related the shift in the left ventricular pressure-volume relation to a regional increase in myocardial stiffness of the ischemic zone. Similar data were obtained in open-chest anesthetized dogs during high demand ischemia induced by pacing tachycardia in an angina physiology model [7]. When low flow ischemia was induced by acute coronary occlusion in closed-chest anesthetized [8] and conscious [9] dogs, an increase in myocardial wall stiffness with upward shift of the diastolic pressure-volume curve was observed as well. The latter was prevented by inferior vena cava occlusion evidencing the modulating role of the right ventricular loading conditions. In patients with coronary disease, interruption of blood flow induced by transient balloon inflation during percutaneous transluminal coronary angioplasty (PTCA) is a situation which mimicks the experimental abrupt coronary occlusion in the animal laboratory. This provides a unique opportunity to study the mechanical and metabolic effects of low flow ischemia in man. Earlier, we reported the dynamic changes in the left ventricular hemodynamics and geometry during PTCA [10 and Chap I, II, III] and demonstrated the perfect reversibility after the procedure of the abnormalities in global and regional systolic functions induced by repeated transluminal occlusions.

The aim of the present study was to analyze the changes in diastolic function induced by coronary occlusion. We determined whether an upward shift in the diastolic pressure-volume relation was actually observed, whether this increase in chamber stiffness, if any, was reversible and could be ascribed to an increased regional stiffness of the ischemic zone.

Patients and methods

Patients

The present study includes 9 patients (1 female and 8 males) with normal resting left ventricular function and wall motion who underwent a percutaneous transluminal coronary angioplasty of a proximal and isolated left anterior descending (LAD) coronary artery stenosis. No patient had had previous infarction. The distal vessel was not filled by collaterals, as shown by diagnostic angiography. One of the 10 previously reported [10] patients was excluded because the small number of available data points due to a higher heart rate precluded valid analysis

of the diastolic function. All patients gave their informed consent and there were no complications related to the research procedure. Medications (beta-blocker, calcium antagonist and long acting nitrates) were not discontinued on the day of the PTCA procedure, but no particular premedication was administered to the patient prior to the angioplasty procedure.

Prior to the approval of the protocol by the Thoraxcenter ethics committee, a feasibility study was performed including an analysis of the effect of non-ionic contrast media on the left ventricular function. Details regarding the angioplasty procedure used in our laboratory have been published elsewhere [11].

Study protocol

Simultaneous left ventricular pressure and volume were obtained by contrast ventriculography before the angioplasty procedure was started (N = 9), after a median occlusion period of 20 seconds (range 15–27) during the second dilatation (N = 9), after a median occlusion period of 48 seconds (range 46–59) during the fourth dilatation (N = 5) and a median time of 12 minutes after the end of the angioplasty procedure (N = 9). A total of 3 to 10 occlusions were performed; the duration of each balloon inflation ranged from 15 to 75 seconds. According to the recommendation by the ethics committee, no investigational occlusions were carried out after completion of a technically successful dilatation. In four patients, this result was achieved after three dilatations so that angiographic data after 48 seconds (fourth occlusion) are only available in 5 out of 9 patients.

These sequential angiograms were made only after the return to baseline of the end-diastolic pressure and of the left ventricular pressure-derived isovolumic parameters of contractility and relaxation, which were available on line during the procedure. The interval between two angiograms was at least 10 minutes. Care was taken to maintain the patient's position unchanged with respect to the X-ray equipment and to reduce diaphragm movement by shallow inspiration. The left ventricular pressure was measured with a Millar micro-manometer on an 8F pigtail catheter. The contrast ventriculograms (30 degrees right anterior oblique at 50 frames/second) were obtained by injection of 0.75 ml/kg of a non-ionic contrast medium (Metrizamide, Amipaque®).

Data analysis

Frame-by-frame left ventricular volumes and the corresponding pressures were simultaneously obtained from a complete cardiac cycle as previously described [12]. The ventricular contours were automatically detected with the Contouromat and the volumes calculated according to Simpson's rule. The end-diastolic pressure was defined at that point on the pressure trace at which the derivative of the

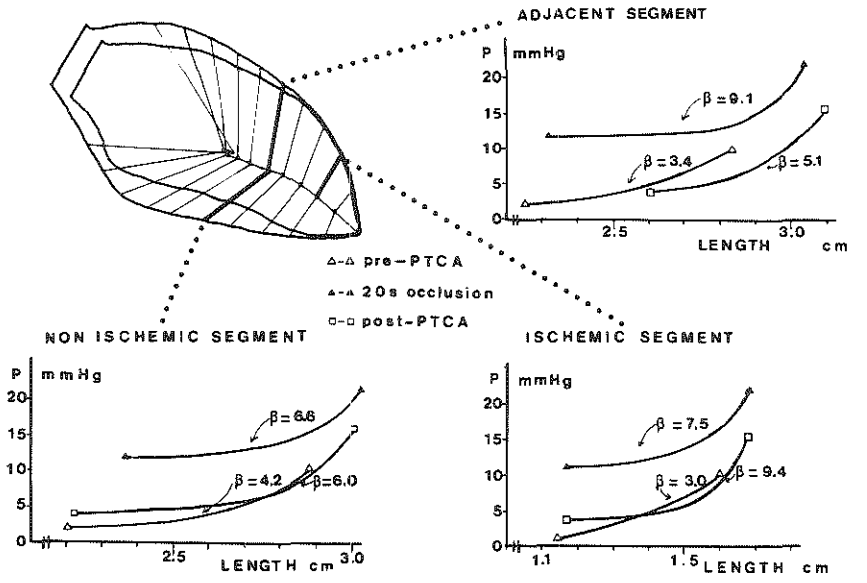

Fig. 1. Pressure-length relation in the core of the ischemic zone (antero-apical segment), in the nonischemic zone (postero-basal segment) and in the segment immediately adjacent to the ischemic zone.

pressure first exceeded 200 mmHg/s [12] and in all cases coincided with the largest left ventricular volume. End systole was defined with reference to the pressure tracing, at the occurrence of the dicrotic notch of the central aortic pressure. The left ventricular pressure decay during the isovolumic relaxation was quantified as previously described [10] using a bi-exponential model, where tau 1 represents the time constant of early relaxation (during the first 40 ms after the peak negative dP/dt).

In the present study, the length of the 20 segmental radii defined by the endocardial landmark model was measured frame-by-frame. Among these, we selected 3 pairs of segments located in the core of the ischemic zone (antero-lateral and apical segments), in the non-ischemic zone (antero-basal and postero-basal segments) and immediately adjacent to the ischemic zone (inferior and anterior segments), as shown in figure 1. The linear correlation coefficients between repeated measurements in 20 patients ranged from 0.96 to 0.99 (SEE = 0.4 to 1.4%) for the same operator and from 0.91 to 0.99 (SEE = 0.4 to 2.3%) for two different operators.

Calculations

For the evaluation of the global chamber stiffness, the left ventricular pressure

(P) and volume (V) data obtained every 20 ms starting at the lowest diastolic pressure and ending at the end-diastolic pressure were fitted by a simple elastic model: $P = \alpha e^{\beta V} + C$, where α = intercept (mmHg), β = constant of elastic chamber stiffness and C = baseline pressure (mmHg). The three constants of this equation (α, β, C) were determined using an iteration procedure until the best non-linear curve fit was obtained [13].

For the evaluation of the regional chamber stiffness, the left ventricular pressure and the segment radius length (L) data were fitted in a similar way for each of the six (1, 2, ... n) analyzed segmental radii: $P = \alpha_1 \cdot e^{\beta_1 \cdot L} + C_1$, where β_1 represents the regional elastic stiffness constant for a given segment 1. The same approach was applied previously by others to pressure-length relations obtained by ultrasonic subendocardial crystals [14], as well as to pressure- circumference relations obtained by contrast ventriculography [8].

Statistical analysis

Results are given for all patients (N = 9) and the subgroup analyzed after 50 s of occlusion (N = 5), either as mean ± standard deviation or as median values using analysis of variance for repeated measurements. Comparisons between pre-PTCA, post-PTCA and 20 s occlusion conditions were performed in 9 patients. The pre-, post-PTCA and 50 s occlusion data were compared in the subgroup of 5 patients. When overall significance was found, multiple comparisons were used to delineate which paired comparisons were significantly different at the $p<0.05$ level.

Results

The left ventricular volumes at the lowest diastolic pressure as well as at end-diastole did not change significantly during and after angioplasty, while the end-systolic volume and tau 1, the time constant of early relaxation, increased markedly ($p<0.01$) already after 20 seconds of occlusion (Table 1). The lowest diastolic ($p<0.05$) and the end-diastolic ($p<0.01$) pressures were significantly increased in the subgroup of patients studied after 50 seconds of LAD occlusion.

After completion of the procedure, all the parameters returned towards control values. This increase in pressure relative to volume during transluminal occlusion resulted in an upward shift of the entire pressure-volume relation as shown for a representative patient in figure 2. The calculated parameters of global chamber stiffness showed a similarly increased constant of elastic stiffness (β) after 20 seconds as well as after 50 seconds of LAD occlusion. The baseline pressure increased significantly ($p<0.01$) only after 50 seconds of coronary occlusion.

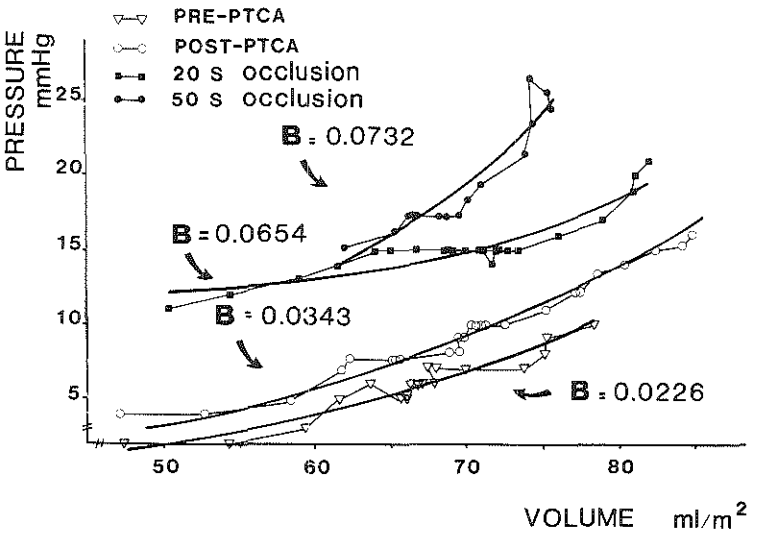

Fig. 2. Diastolic pressure-volume relation in a respresentative patient, showing an increased constant of elastic chamber stiffness after 20 seconds, as well as after 50 seconds of LAD occlusion.

No change in the intercept (α) was observed (Table 2). All but one patients showed an increase in chamber stiffness during coronary occlusion which, after the procedure, returned to values not significantly different from the pre-PTCA value. However, in 6 patients, the post-PTCA value remained higher than the control value. The changes in the constant of regional chamber stiffness (β_1) showed a marked and persistent increased stiffness in the ischemic zone as well as

Table 1. Hemodynamic variables before PTCA, at 20 and 50 s after LAD occlusion and after the PTCA procedure.

	pre-PTCA		20 s occl	50 s occl	post-PTCA	
	all (N=9)	subgroup (N=5)	all (N=9)	subgroup (N=5)	all (N=9)	subgroup (N=5)
Pmin [mmHG]	8	8	12	15*	8	6
V at Pmin [ml/m²]	50	50	55	59	53	53
EDP [mmHg]	20	16	22	30°	19	18
EDV [ml/m²]	78	78	82	87	84	86
ESV [ml/m²]	28	28	36°	44″	27	27
Tau 1 [msec]	58	56	77″	74*	56	57

Abbreviations: PTCA = percutaneous transluminal coronary angioplasty; P = pressure, V = volume; ED = end-diastolic; ES = end-systolic; tau 1 = time constant of early relaxation; median values are shown; p versus pre- and post-PTCA: * = $p<0.05$; ° = $p<0.01$; ″ = $p<0.001$.

Table 2. Global left ventricular chamber stiffness.

	Intercept (mmHg)	Constant of elastic stiffness	Baseline pressure (mmHg) C
All Patients (N=9)	n.s.	*	n.s.
Pre-PTCA	4.6 ± 4.9	0.0273 ± 0.017	−1.4 ± 9.5
20 s occlusion	1.2 ± 3.3	0.0621 ± 0.026*	5.2 ± 8.3
Post-PTCA	1.2 ± 1.5	0.0529 ± 0.037	2.8 ± 4.7
Subgroup (N=5)	n.s.	°	°
Pre-PTCA	5.3 ± 5.9	0.0214 ± 0.007	−5.8 ± 7.4
50 s occlusion	0.2 ± 0.3	0.0605 ± 0.015*	9.4 ± 2.7°
Post-PTCA	1.9 ± 1.8	0.0396 ± 0.027	0.8 ± 5.6

Values are mean ± s.d.; * = $p<0.05$; ° = $p<0.01$; n.s. = nonsignificant; abbreviations as previously; overall and paired (versus pre-PTCA) significance values are given.

in the adjacent inferior segment (Table 3 and figure 1). The regional stiffness in the non-ischemic zone and in the adjacent anterior segment was not affected by the coronary occlusions. No significant changes in the non-linear elastic constant (α_1) were observed for the regional pressure-radius relations. Similar shifts in the baseline pressure as for the global diastolic function were measured, since the same left ventricular pressure data were used for both calculations of global and regional stiffness.

Table 3. Regional left ventricular chamber stiffness β_1 = constant of regional elastic stiffness.

Zone	Non-ischemic	Adjacent	Ischemic		Adjacent	Non-ischemic
Segment	antero-basal	anterior	antero-lateral	apical	inferior	postero-basal
All patients (N=9)	n.s.	n.s.	*	n.s.	n.s.	n.s.
Pre-PTCA	1.59	3.92	3.11	2.93	2.76	4.03
20 s occl.	3.03	4.03	5.63	4.97	6.59	5.01
Post-PTCA	2.73	2.59	6.45*	7.16	5.98	3.64
Subgroup (N=5)	n.s.	n.s.	0.05+	0.05+	°	n.s.
Pre-PTCA	1.59	3.45	2.81	1.09	1.52	2.59
50 s occl.	4.13	4.81	5.39	6.16	7.56*	5.54
Post-PTCA	1.98	3.71	5.59	7.16	6.93	4.35

Given are median values; + the statistical significance was borderline at the 0.05 level; * = $p<0.05$; ° = $p<0.01$; overall and paired (versus pre-PTCA) significance values are given; abbreviations as previously.

Discussion

The major finding of the present study was that ischemia induced by complete occlusion of the left anterior descending coronary artery increased the regional chamber stiffness of the ischemic anterior wall, even during an occlusion as short as 20 seconds. Parallel to this increase in regional stiffness, the global stiffness of the left ventricle increased significantly (Table 2). In experimental studies [8, 9], an increase in global chamber stiffness was only seen when the area rendered ischemic was large, such as during acute occlusion of the left anterior descending coronary artery.

The baseline pressure (constant C) increased slightly from −1.4 to 5.2 mmHg 20 s and from −5.8 to 9.4 mmHg 50 s after acute coronary occlusion (Table 2). This increase in baseline pressure reflects the upward shift of the diastolic pressure-volume relation during coronary occlusion, which was 6.6 mmHg after 20 s and 15.2 mmHg after 50 s.

Twelve minutes after the end of the procedure including repeated (3 to 10) and brief (15 to 75 s) occlusions, angiocardiography was repeated. The parameters of global and regional systolic function were back to normal, as shown from the indices of isovolumic contraction, relaxation and segmental wall motion [10]. In contrast, the parameters of regional diastolic function were still abnormal (Table 3), while the constant of global chamber stiffness and the baseline pressure remained slightly elevated. How can these persisting diastolic abnormalities be explained, when complete recovery of systolic function and relaxation has occurred?

The significance of the upward shift in the pressure-volume and pressure-radius relations is still the subject of controversy. In most studies, this was attributed to changes in diastolic myocardial stiffness, delayed left ventricular relaxation and/or loss of elastic recoil due to left ventricular asynergy [5–9]. Ventricular interaction with changes in right ventricular loading conditions were also considered to be responsible for the upward shift of the diastolic pressure-volume curve during acute myocardial ischemia [9, 15].

However, the upward shift was observed with and without pericardium [16], suggesting no constrictive effect of the pericardium on the diastolic filling of the left ventricle. A limitation of the present study is that diastolic function was assessed from pressure-volume and pressure-radius relations using the slope of these relations, fitted by a simple elastic model, as a measure of global and regional chamber stiffness. Using these measurements, it cannot be inferred that the intrinsic diastolic properties of the myocardium are affected by acute coronary occlusion, since this requires analysis of left ventricular wall stress and strain [4]. Heretofore, regional wall thickness measurements are needed which cannot be obtained accurately at 20 ms intervals from the left ventricular angiocardiograms. The strain data should be normalized for a reference unloaded muscle length, i.e. at a transmural pressure of 0 mmHg, and this cannot be obtained

easily during cardiac catheterization in man. Thus, at least theoretically, coronary and other extrinsic factors such as the right ventricular loading conditions [4, 5] may have contributed to the apparent increase in chamber stiffness. The coronary perfusion, or the so-called 'erectile effect' [4] is not likely to account for the increased stiffness in the core of the ischemic zone.

During coronary occlusion, inflation of the dilatation balloon results on average in a 44% decrease in regional blood flow [17], hereby reducing the myocardial wall blood volume. Likewise, the post-PTCA measurements were obtained at a time where an increased myocardial turgor due to reactive hyperemia is no more expected. The increase in regional stiffness observed in the adjacent inferior segment could, however, be related to an increased turgor as the collateral flow to that area might increase during left anterior descending occlusion [18].

The role of the ventricular loading conditions is controversial. In an angina physiology model [7], where ischemia was induced by pacing in the presence of high-grade coronary stenoses, upward shifts in the pressure-volume and pressure-length relations were found, even when the influence of right ventricular distension was removed by vena caval occlusion. However, such high demand, high flow situation does not necessarily compare to the low flow ischemia induced during PTCA. This situation rather mimicks the experimental coronary occlusion in the animal laboratory. In such a model, Hess et al. [9] showed that the 'myocardial wall stiffness is increased during complete coronary occlusion when there is systolic thinning of the ischemic wall'. In these conscious chronically instrumented dogs with opened pericardium, this alteration in the intrinsic diastolic properties of the muscle resulted in the expected upward shift of the pressure-volume curve. However, this upward shift was prevented by inferior vena cava obstruction, emphasizing that the right ventricular loading conditions and the ventricular interaction have a modulating role and can offset the increase in pressure. Thus, despite the limitations of the present study, the observed changes in global and regional diastolic chamber stiffness are in accordance with previous experimental work [8, 9, 14], showing an increase in the myocardial stiffness during coronary occlusion.The mechanism by which ischemia increases the myocardial stiffness remains speculative and may depend on the pathophysiology of a given ischemic condition. In the acute coronary occlusion model [8, 9], systolic overstretch of the ischemic muscle fibers was thought to be responsible for the diastolic thinning of the ischemic wall and the increase in resting muscle length. This 'creep' effect causes the ischemic myocardium to operate at a higher point on the sarcomere pressure-length relation, and thus at an increased stiffness level. Although no significant change in end-diastolic volume was observed throughout the procedure, it cannot be excluded that 'creep' actually occurred. Echocardiographic studies from our and other laboratories [20] have shown evidence of wall thinning during balloon occlusion of the proximal left anterior descending coronary artery and during attacks of variant angina.

Another possible mechanism refers to the concept of residual diastolic myosin-

actin interaction [21], which may lead to increased stiffness of the ischemic wall as well. Interestingly, we found similar increases in the constant of elastic chamber stiffness after 20 and after 50 seconds of occlusion, while left ventricular asynchrony and late shortening of the ischemic wall were observed only at 20 seconds [10]. This increased chamber stiffness observed at 20 seconds may only be apparent and related more to an increase in viscous resistance than to early filling.

Although experimental data [22] showed that viscous forces are negligible in the intact ventricle at low filling velocity and in the absence of hypertrophy, this probably does not hold during ischemia. Asynchrony and late shortening affect the stiffness of rat heart trabeculae [23] and it was shown recently in humans, that early diastolic filling can be kept normal during ischemia despite delayed relaxation and loss of elastic recoil (increase in end-systolic volume) by increasing the left atrial driving pressure [24]. It is well known that diastolic properties are better characterized by a viscoelastic rather than a simple elastic stress-strain relation [25]. However, the present angiocardiographic data did not allow to quantitate properly strain rates which are essential for determining diastolic viscous effects. Due to the use of the simple elastic model, the stiffness constant that we calculated includes both elastic and viscous forces. Finally, the abnormalities of the regional diastolic function were still present 12 minutes after the procedure, despite normalization of the rate of relaxation. The latter does not exclude the presence of abnormal myocardial 'tone'. As recently emphasized [7], such failure of complete myofilament inactivation implies a reduced extent of relaxation, which is not necessarily synonymous to a reduced rate of relaxation as measured from the time constant of isovolumic left ventricular pressure decay.

In summary, we can conclude that complete coronary occlusion of the left anterior descending coronary artery in man is associated with profound alterations in diastolic chamber stiffness, which persist well after restoration of myocardial blood flow and of a normal systolic function. The analysis of diastolic function may prove a sensitive tool in assessing the possibly deleterious effects of repeated coronary occlusions during PTCA. The need to detect any persisting dysfunction becomes an even greater concern as the number of dilated vessels and the duration of balloon inflation tend to increase, hereby enhancing both the extent and the severity of ischemia. Further work is needed to document the time course of the recovery of a normal regional diastolic function, and to address the responsible derangements of subcellular metabolism, as the mechanisms of the observed abnormalities are not yet fully understood.

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Chapter V

Myocardial release of hypoxanthine and lactate during percutaneous transluminal coronary angioplasty: a quickly reversible phenomenon, but for how long?

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(Abbreviated version is accepted by Circulation).

Summary

The response of myocardial lactate and hypoxanthine metabolism during percutaneous transluminal coronary angioplasty (PTCA) was studied in a series of patients undergoing this procedure. A minimum of four balloon inflations was performed per patient with an average duration per occlusion of 49 ± 11 s (mean $\pm$ SD) for a total occlusion time of 192 ± 40 s.

Thermodilution coronary venous blood flow in the proximal coronary sinus or in the great cardiac vein was measured in 28 patients. Proximal coronary blood flow, measured in 13 patients was 149 ± 12 (mean $\pm$ SEM) ml/min in the basal condition, falling to 108 ± 15 ml/min ($p<0.05$) during the last occlusion.

Flow measured in the great cardiac vein (15 patients) decreased from control values of 72 ± 4 ml/min (mean $\pm$ SEM) to 47 ± 10 ml/min with the fourth coronary occlusion ($p<0.005$). Lactate and hypoxanthine showed peak arteriovenous differences during the reactive hyperemia following the first two occlusions which did not increase after subsequent occlusions. Within minutes after the procedure, lactate and hypoxanthine efflux was no longer seen, demonstrating the reversibility of the metabolic disturbances after repeated ischemia.

The results of this study indicate that there is no permanent alteration in lactate or hypoxanthine metabolism after PTCA with four coronary occlusions of 40 to 60 s, with a total occlusion time of 192 ± 40 s.

Introduction

Until recently the assessment of alteration in myocardial metabolism in man early after an abrupt occlusion of a major coronary artery has not been feasible.

Percutaneous transluminal coronary angioplasty (PTCA), however, now provides a unique opportunity to study the time course of these metabolic changes during the transient interruption of coronary flow by the balloon occlusion sequence in patients with single-vessel disease and without angiographically demonstrable collateral circulation [1, 2]. The need to detect any persisting metabolic or mechanical dysfunction becomes of even greater concern as the number of dilated vessels and the duration of balloon inflation tend to increase, thereby enhancing both the extent and the severity of ischemia. The risk exists that the damage induced by the intervention may exceed its benefit.

During and after ischemia, there is in the heart, as well as in other muscles, excessive ATP breakdown. This degradation of ATP causes an efflux of breakdown products, which are able to pass through the cell membrane into the blood before significant amounts of myocardial enzymes appear. The purine derivatives adenosine, inosine and hypoxanthine are therefore thought to be early markers for ischemia [3]. Because of high activities of adenosine deaminase and nucleoside phosphorylase and low amounts of xanthine oxidase in the heart and blood, hypoxanthine seems most promising as early marker for myocardial ischemia [4].

Recently high pressure liquid chromatography (HPLC) came into use for the determination of nucleosides and purine bases in the whole blood [5, 6], facilitating the determination of purine derivatives, in particular hypoxanthine. This new technical development prompted us to investigate the myocardial release of hypoxanthine during coronary angioplasty.

In a group of 28 patients blood flow, lactate and hypoxanthine metabolism were analyzed during reactive hyperemia after repeated occlusions of the left anterior descending coronary artery. The effects of ischemia proved quickly reversible, but were indicative of impending cellular dysfunction.

Patient material

All patients met the following criteria: a brief history of angina pectoris (less than one year), an isolated obstructive lesion in one coronary vessel (the left anterior descending) and an accessible stenosis of less than 1 cm in length. All patients were candidates for coronary artery bypass graft surgery because of disabling angina, but were selected for angioplasty rather than surgery because of their anatomy.

Twenty-eight patients were studied: 21 men, 7 women, aged from 38 to 74 years. Of these 16 were in NYHA class II, 8 in class III, and 4 in class IV. In all the ejection fraction was greater than 50%. These 28 patients were selected from 58 patients in whom thermodilution coronary sinus blood flow was measured during angioplasty for various indications. They were chosen since they required at least four transluminal dilatations. These four dilations were performed with a total duration of occlusion of 192 ± 40 s (mean $\pm$ SD).

All patients in this study gave their informed consent and there were no complications directly related to the research procedure.

PTCA technique

Percutaneous transluminal coronary angioplasty (PTCA) was performed by the same technique in all patients. Via a 9F, 16 cm introducing sheath, a guiding catheter was directed into the stenotic area under fluoroscopic and pressure control. PTCA was performed according to the technique of Gruentzig, with the equipment of Schneider, via the femoral route. In all cases the pressure gradient across the obstructive lesion was recorded before, during and after balloon inflation. The dilatation catheters were either the 20–30 or 20–37 models. The inflation pressure ranged from 2–12 atm, while individual dilatations ranged from 40 to 60 s. Attempts to dilate the lesion were repeated as long as the gradient persisted. Coronary angiography with non-ionic contrast medium (metrizamide) was performed immediately before and after PTCA. Lateral, anteroposterior, oblique and hemi-axial angiographic views were obtained in virtually all patients.

Premedication consisted of aspirin, nifedipine and/or isosorbide dinitrate. All patients received either 3 mg of isosorbide dinitrate or 0.2 mg nifedipine selectively into the left main coronary artery during control coronary arteriography, but the coronary flow measurements we report were not carried out within the periods of the drug's effect on the coronary circulation. Beta-blockers were not discontinued. During the procedure, heparin and low molecular weight dextran were administered intravenously.

Lactate measurements

Blood (1.5 ml) for lactate measurements was rapidly deproteinized with an equal volume of cold 8% perchloric acid ($HCLO_4$) and centrifuged. After centrifugation, the supernatant fluids were stored at −20° C. Lactate in the supernatant was analyzed enzymatically according to Apstein et al [7] with the AutoAnalyzer.* Standard curves were made with lithium lactate in 4% $HCLO_4$.

Hypoxanthine determination

An isocratic high pressure liquid chromatographic system was used for the estimation of purine nucleosides and oxypurines in blood [6]. Use was made of a reversed-phase column. Since nucleotides derived from erythrocytes affected the

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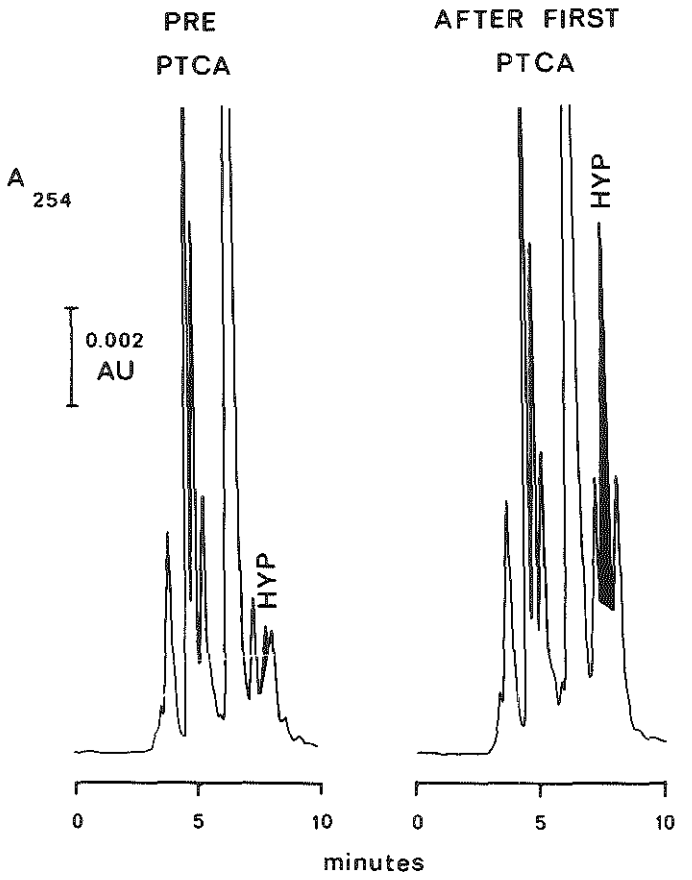

Fig. 1. Isocratic high pressure liquid chromatographic separation of nucleosides and purine bases from a patient before and after a single transluminal occlusion. Abbreviations: hyp = hypoxanthine. Au = absorption unit.

separation, these compounds had to be removed. We used the method of Chatterjee et al [8], with some minor differences. We applied 1.5 ml of the deproteinized, neutralized blood sample onto a pre-washed column of Al_2O_3 (0.6 g) in a Pasteur pipette, and eluted it with 5.0 ml 10 mmol/l Tris/HCl, pH 7.4. For faster elution, a vacuum was applied to a sampling manifold. Twelve samples were treated at the same time.

A Waters M 6000 high pressure liquid chromatograph* was employed with a WISP 710 B autosampler* a Model 440 UV-detector fixed at 254 nm wavelength connected to a BD 41 recorder* *. A 4 mm I.D. × 30 cm prepacked μ Bondapak/

* Millipore Waters, Bedford, MA, U.S.A

C_{18} column*, particle size 102 μm was used in these studies. Chromatographic conditions were adapted from earlier work [9]: 200 μl samples were eluted from this column with 10 mmol/l $NH_4H_2PO_4/CH_3OH$ (10:1, v/v), pH 5.50. The flow rate was 60 ml/h (figure 1).

Blood samples were obtained at six consecutive measurement periods: before the PTCA procedure, 5–10 s after each transluminal occlusion, 5 minutes after termination of the PTCA procedure. Five minutes were allowed between each dilatation for recovery.

Flow measurements

A thermodilution coronary sinus blood flow catheter (Webster) was introduced into the coronary sinus by way of a right brachial vein. In 15 cases, the catheter tip was placed in the great cardiac vein. Coronary sinus blood flow (13 patients, group I) or great cardiac vein blood flow (15 patients, group II) was measured by the continuous thermodilution method before and after the PTCA procedure as well as during each transluminal occlusion. In the beginning of the investigation the location of the external thermistor, in the coronary sinus or in the great cardiac vein, was verified by injection of 3 ml contrast material. Each recording of blood flow during coronary angioplasty began before balloon inflation and was interrupted at the moment of balloon deflation.

Coronary vascular resistance (CVR) was calculated for great cardiac vein (GCV) or coronary sinus (CS) [10] using the mean arterial pressure (MAP) and blood flow in the great cardiac vein (Flow (GCV)) and coronary sinus (Flow (CS)), respectively:

$$CVR\ (GCV) = MAP/Flow(GCV)\ (mmHg.min/ml)$$
$$CVR\ (CS) = MAP/(Flow(CS)\ (mmHg.min/ml)$$

Statistical analysis

Results are expressed as mean ± standard error of the mean. Comparison between pre-PTCA, post-PTCA and occlusion conditions were evaluated using analysis of variance for repeated measurements. When overall significance was found, multiple comparisons were significantly different at the $p<0.05$ level.

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Results

Coronary hemodynamic measurements

The results of the coronary hemodynamic observations are summarized in figure 2 and Table 1 and 2. During the initial dilatation the mean duration of balloon inflation was 47 ± 4 s in group I and 44 ± 4 s in group II. During the subsequent dilatations the duration of inflation was slightly increased up to 53 ± 6 s and 49 ± 6 s. Occlusion pressure did not change throughout these occlusion times of 40 to 60 seconds and there was a high degree of reproducibility of the occlusion pressure during these successive occlusions (Table 1 and 2). Coronary sinus blood flow before the first dilatation was 149 ± 12 ml/min, falling to 96 ± 8 ml/min ($p<.005$) during the third transluminal occlusions and rising to 174 ± 15 ml/min (NS) 5 minutes after the last balloon deflation (Table 1). Consequently, total coronary resistance increased from 0.75 ± 0.06 to 1.2 ± 0.3 mmHg.min/ml ($p<0.05$) by the end of the fourth dilatation (Table 1).

The mean blood flow in the great cardiac vein in group II before the first inflation was 72 ± 4 ml/min, falling to 47 ± 10 ml/min ($p<0.003$) during the fourth inflation and rising slightly to 93 ± 8 ml/min ($p<0.03$) after completion of the PTCA procedure (Table 2) while the differences in resting pre and post coronary angioplasty levels of coronary sinus blood flow did not reach a statistically significant level. Great cardiac vein coronary vascular resistance was 1.42 ± 0.18 mmHg.min/ml before balloon inflation, 2.3 ± 0.6 by the end of the fourth inflation ($p<0.005$) and 1.02 ± 0.11 after completion of the PTCA procedure (Table 2).

Lactate and hypoxanthine metabolism

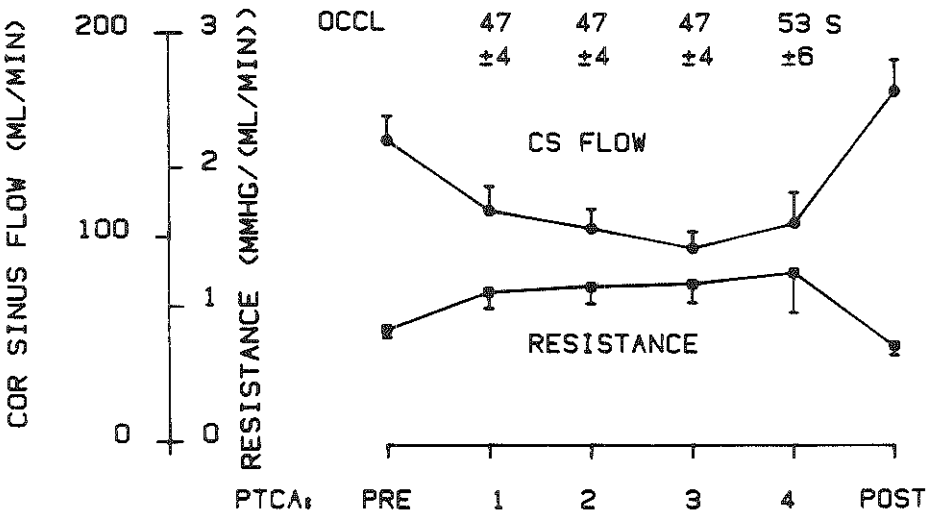
The arteriovenous lactate measurements are listed in table 1 and 2 and shown in figure 3. In group II the control measurements showed a difference of +0.18 mM, which decreased to −1.1 and −0.91 mM, after the first and the second dilatations, respectively. After the third dilatation the lactate difference was −0.60 mM, which was not significantly different from the values recorded after the first and the second dilatation. As a first approximation, the amount of lactate lost from the ischemic tissue during the four consecutive occlusion seems to be more or less constant and at least did not increase with the time. As expected, the pooled A-V lactate difference obtained during PTCA in group II (great cardiac vein sampling, -0.8 ± 0.3 mM) was higher than that in group I (coronary sinus sampling, -0.35 ± 0.12 mM, ($p<.01$). During the four consecutive transluminal occlusions, an average rise in the great cardiac vein hypoxanthine from 3.4 ± 0.7 to $5.6 \pm 1.1 \mu$M, ($p<0.01$) and in coronary sinus hypoxanthine from $2.2 \pm 0.6 \mu$M to $3.6 \pm 0.8 \mu$M, ($p<0.05$) was observed, which fell off after completion of the PTCA procedure. The arterial levels of these compounds remained constant

Table 1. Coronary hemodynamics and metabolic disturbances during sequential transluminal occlusion in group I (13 patients).

	before PTCA	first occlusion	second occlusion	third occlusion	fourth occlusion	after PTCA
Duration of occlusion (s)	–	47 ± 4*	47 ± 4	47 ± 4	53 ± 6	–
Occlusion pressure (mmHg)	–	31 ± 5	28 ± 5	29 ± 3	30 ± 5	–
CS flow (ml/min)	149 ± 12	115 ± 12[b]	106 ± 9[b]	96 ± 8[b]	108 ± 15[a]	174 ± 15
Resistance (mmHg.min/ml)	0.75 ± 0.06	1.03 ± 0.12[a]	1.07 ± 0.13[a]	1.09 ± 0.14[a]	1.2 ± 0.3[a]	0.64 ± 0.07
Arterial lactate (mM)	0.43 ± 0.09	0.46 ± 0.08	0.47 ± 0.09	0.43 ± 0.06	0.42 ± 0.06	0.42 ± 0.12
CS venous lactate (mM)	0.47 ± 0.10	0.81 ± 0.16[a]	0.88 ± 0.19[b]	0.75 ± 0.14[b]	0.79 ± 0.14[a]	0.46 ± 0.07
Art-CS lactate (mM)	0.04 ± 0.04	−0.39 ± 0.14[a]	−0.41 ± 0.14[a]	−0.32 ± 0.08[b]	−0.37 ± 0.10[b]	0.01 ± 0.07
Arterial hypoxanthine (μM)	1.81 ± 0.5	2.5 ± 1.1	1.9 ± 0.6	1.3 ± 0.4	1.6 ± 0.5	1.6 ± 0.5
CS venous hypoxanthine (μM)	2.2 ± 0.6	4.6 ± 1.4[a]	3.0 ± 0.3	2.9 ± 0.9	2.5 ± 0.5	1.9 ± 0.3
Art -CS hypoxanthine (μM)	0.4 ± 0.2	−2.04 ± 1.3	−0.9 ± 0.5	−1.7 ± 1.0	−0.9 ± 0.6	0.1 ± 0.4

CS = coronary sinus; Art = arterial.

* Mean ± SEM [a] $p<.05$ [b] $p<.005$ versus before PTCA.



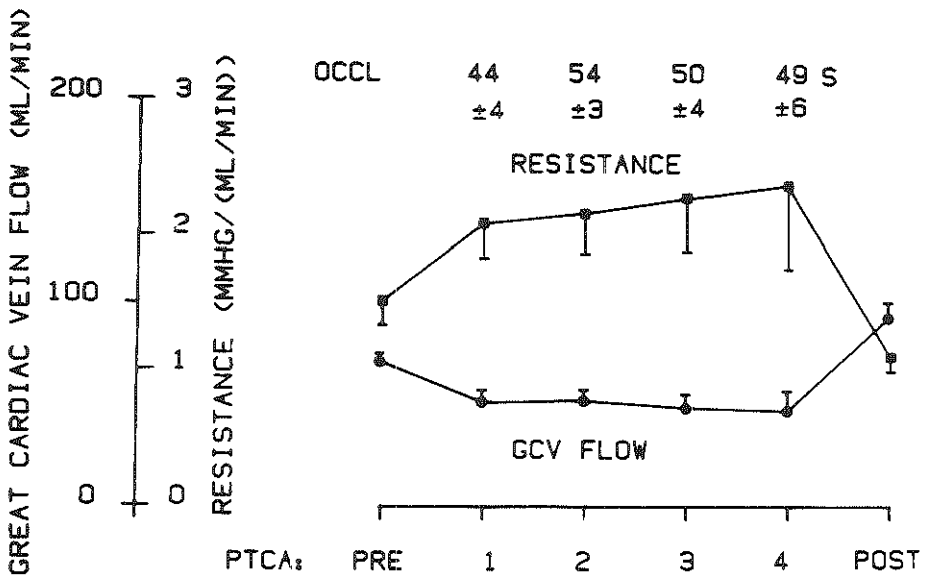


Fig. 2a. Changes in coronary sinus blood flow and resistance during four episodes of occlusion. Abbreviation: CS = coronary sinus; pre: pre angioplasty; post: post angioplasty.
Fig. 2b. Changes in great cardiac vein flow (ml/min) and resistance (mmHg.min/ml) during four transluminal occlusions. Abbreviations: occl = occlusion time (s). GCV = great cardiac vein.

Table 2. Coronary hemodynamics and metabolic disturbances during sequential transluminal occlusion in group II (15 patients).

	before PTCA	first occlusion	second occlusion	third occlusion	fourth occlusion	after PTCA
Duration of occlusion (s)	–	44 ± 4*	54 ± 3	50 ± 4	49 ± 6	–
Occlusion pressure (mmHg)	–	24 ± 4	23 ± 3	21 ± 2	25 ± 5	–
GCV flow (ml/min)	72 ± 4	51 ± 6[a]	52 ± 6[a]	48 ± 7[b]	47 ± 10[b]	93 ± [a]
Resistance (mmHg.min/ml)	1.42 ± 0.18	2.0 ± 0.3[a]	2.1 ± 0.3[a]	2.2 ± 0.4[b]	2.3 ± 0.6[b]	1.02 ± 0.11
Arterial lactate (mM)	0.59 ± 0.12	0.67 ± 0.16	0.65 ± 0.12	0.71 ± 0.14	0.9 ± 0.3	0.58 ± 0.13
GCV lactate (mM)	0.75 ± 0.15	1.8 ± 0.4[b]	1.6 ± 0.3[c]	1.3 ± 0.3[b]	1.8 ± 0.6[a]	0.64 ± 0.12
Art GCV lactate (mM)	0.18 ± 0.06	−1.1 ± 0.3[a]	−0.91 ± 0.18[c]	−0.60 ± 0.17[b]	−0.8 ± 0.4[b]	0.07 ± 0.03
Arterial hypoxanthine(μM)	3.0 ± 0.6	3.0 ± 0.7	3.3 ± 0.6	2.9 ± 0.8	3.0 ± 1.4	3.7 ± 0.7
GCV hypoxanthine (μM)	3.4 ± 0.7	5.2 ± 0.8[c]	7.8 ± 1.4[b]	4.2 ± 1.06	4.4 ± 1.2[a]	3.8 ± 0.7
Art -GCV hypoxanthine (μM)	0.3 ± 0.3	−2.2 ± 0.7[a]	−4.52 ± 1.4[b]	−1.4 ± 0.7	−1.5 ± 0.4	0.2 ± 0.44

GCV = great cardiac vein; Art = arterial.

* Mean ± SEM [a] $p<.05$; [b] $p<.005$; [c] $p<.001$ versus before PTCA.

during transluminal occlusion. The myocardial arterial – GCV difference of hypoxanthine changed from $+0.3 \pm 0.3$ μM before angioplasty at rest to -2.4 ± 1.2 μM ($p<0.01$) during sequential transluminal occlusions and was significantly larger than the changes observed in the myocardial arterial-CS difference (Table 1). Significant production of hypoxanthine, calculated either as arterial-venous difference or extraction, only took place during transluminal occlusion while hypoxanthine release was absent 5 minutes after completion of the PTCA procedure.

The crucial conclusion to be drawn from the observation that a few minutes after termination of the procedure no significant amounts of lactate and hypoxanthine are produced is that metabolic disturbances induced by repeated ischemia are quickly reversible.

Discussion

Use of purine release as a marker for ischemia during transluminal occlusion in man.

Ischemia can be defined as a situation, where coronary blood flow (and hence oxygen and substrate supply, and carbon dioxide and metabolite removal) cannot meet the tissue demand [11]. As a consequence of this O_2 deficiency, mitochondrial function is restricted [12] and the balance between ATP production and usage is disturbed, creatine phosphate (CrP) levels fall, followed by a decline in ATP [3, 13]. Creatine (Cr), ADP, phosphate and H^+ levels increase [14–16], glycolysis rate is enhanced [17, 18] and lactate levels rise. Shortly thereafter K^+, H^+ and lactate are released into the coronary venous blood.

The anaerobic ATP production, however, is insufficient to meet the amount of ATP needed for contraction [15]. This is directly responsible for the decrease in local segmental wall function [19, 20] which is in turn reflected by a loss of systolic wall thickening [20] and shortening [21].

If sufficiently widespread, global hemodynamic measurements will demonstrate a decrease in contractility as reflected by a decrease in LV ejection fraction, and in the maximal velocity of the contractile element (Vmax) as well as an increase in regional myocardial stiffness with a reduction in LV distensibility, which manifests itself by an increase in end-diastolic pressure [1, 22]. This series of events was repeatedly observed in our patients during transluminal angioplasty.

Whether the fall in contractility is caused by a fall in ATP [15], an increase of H^+ [18, 23, 24] or a decrease in the phosphate potential ($= (ATP)/(ADP)(P_i)$ (25) is unknown at the moment. One of the problems hampering this type of investigation relates to the compartmentalization of ATP and the interdependence of several parameters. For example, a fall in ATP or CrP would cause a decrease in

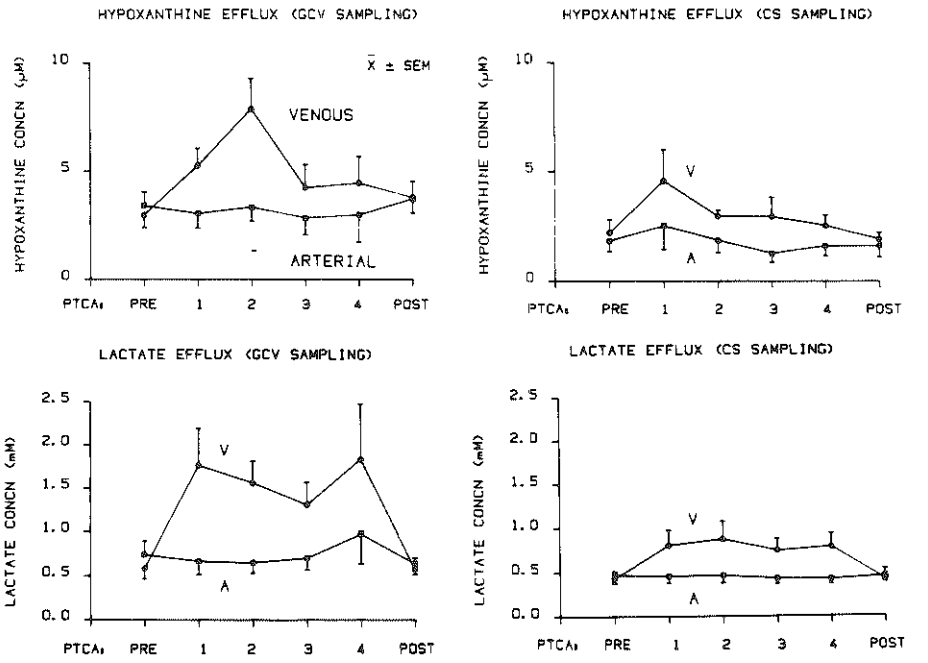


Fig. 3. Changes in arterial and venous concentration of hypoxanthine and lactate during transluminal occlusion. Abbreviations: GCV = great cardiac vein. CS = coronary sinus. pre = pre angioplasty. post = post angioplasty.

phosphate potential and an increase of H^+, therefore rendering the interpretation difficult.

When ATP levels decrease, cellular ADP levels increase. ATP is converted to ADP and AMP, by the action of adenylate kinase. AMP is deaminated to IMP, or dephosphorylated to adenosine, which is further catabolized to inosine and hypoxanthine (figure 4). These components pass the cell membrane (19, 26–28) where adenosine acts as a vasodilator [28, 29]. A slight decrease in ATP is associated with an immediate rise in AMP-catabolites. This release can be used to monitor myocardial ATP-breakdown.

We felt therefore that measuring myocardial arterio-venous differences of blood hypoxanthine levels could give insight into the metabolic state of the heart; the method used makes it possible to measure a number of purine metabolites in blood. In fact, since the 1960's, several studies have discussed the release of purine components during ischemia or anoxia (Table 3). A close correlation has been found between purine- and lactate release from animal and human hearts [6, 30–37]. Lactate as a marker of ischemia, however, has several disadvantages. During normoxia, lactate is preferentially taken up by the heart [38]. In fact, lactate released from a local ischemic area can be metabolized by the surrounding

normoxic tissue [17]. The formation and removal of lactate is also influenced by increased or decreased blood fatty acid levels, acidosis and by a hyperglycemia [39], all metabolic conditions likely to be present during angioplasty. In addition, observations on the patients undergoing an atrial pacing stress test indicate that hypoxanthine is a more sensitive parameter for myocardial ischemia than adenosine, inosine, xanthine or lactate, because hypoxanthine release is more pronounced and of a longer duration than that of the other compounds [6].

In our patients, blood samples were obtained 5 to 10 s after the start of deflation. Coronary sinus K^+ concentration has been measured continuously in patients undergoing angioplasty of significant stenoses of their left anterior descending coronary arteries [40]. The recordings obtained from these patients showed that, although coronary sinus K^+ levels did not change significantly during coronary occlusion, a transient rise occurred when the occlusion was removed. After reducing pressure in the balloon, the coronary sinus K^+ levels began to rise within 8 s. This fits exactly with the timing of peak reactive hyperemia observed by ourselves and by Rothman et al [41] and corresponds with the timing of blood withdrawal in this study. Since we could not record the great cardiac vein or coronary sinus flow during the sampling period, we did not express our results in terms of lactate or hypoxanthine efflux. The less elevated concentrations of lactate and hypoxanthine in the great cardiac vein after the third sequential occlusion donot necessarily reflect a reduction in lactate or hypoxanthine production since the reactive hyperemia measured after the third occlusion might have been significantly greater than that measured after the first and second occlusions [1, 41].

As observed by Rothman et al [41] and ourselves [1], more pronounced reactive hyperemia developed when the residual functional coronary stenosis associated with the deflated PTCA balloon was reduced by subsequent dilatation. In a previous study we demonstrated that the mean hyperemic increase in great cardiac vein flow was 55% after the first dilatation and 91% after the third dilatation [1]. Therefore and as a first approximation, the amount of lactate and hypoxanthine lost from the ischemic tissue during the first two occlusions seems to be more or less constant and at least does not increase with sequential occlusions.

Previous work [42, 43] indicates that repetitive episodes of brief ischemia donot produce a cumulative depletion of high energy phosphate compounds. The content of nucleotide pools at any point in time is determined by the rate of synthesis versus demand. The failure to demonstrate a progressive decrease in nucleotide pools during subsequent ischemic episodes following an initial ischemic episode might be explained by a decreased degradation of nucleotides during the subsequent ischemic episodes. Decreased degradation without increased synthesis is supported by the finding of the current study that the efflux of nucleotide catabolite (such as hypoxanthine) during reperfusion after the third or the fourth occlusion was less or at least not significantly different from the values obtained after the first or the second coronary occlusion.

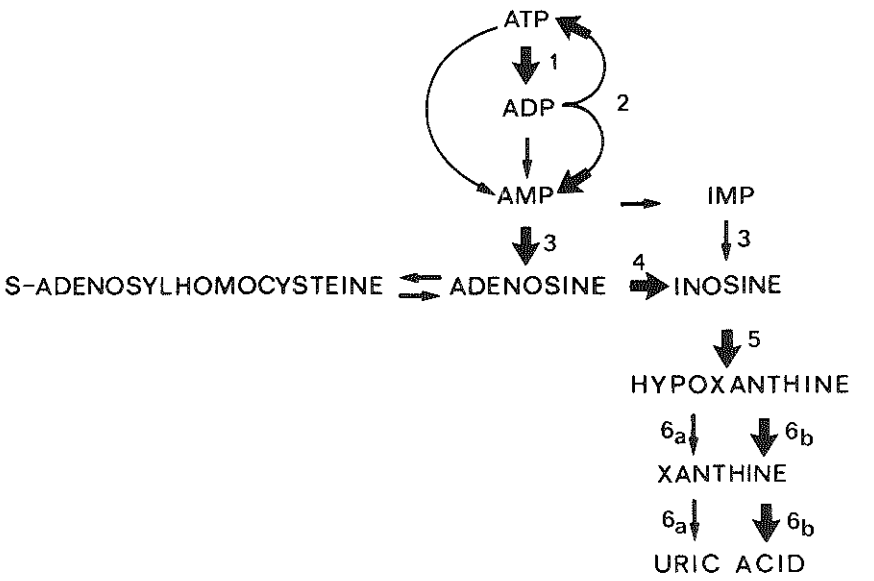


Fig. 4. Myocardial ATP catabolism. The main pathways are: 1) ATPase; 2) adenylate kinase; 3) 5′-nucleotidase; 4) adenosine deaminase; 5) nucleoside phosphorylase; 6) xanthine oxidase (a)/ dehydrogenase (b).

Table 3. AMP-catabolites in blood as marker fOR myocardial ischemia in patients.

Purine	Body fluid	Clinical situation	Ref.
Adenosine	A-CS plasma	APST	30
Adenosine Inosine Hypoxanthine	A-CS plasma	CABS	30
Hypoxanthine	A-CS blood	APST	4,6
Inosine Hypoxanthine	A-CS plasma	APST	31, 32, 33
Adenosine Inosine Hypoxanthine Xanthine	A blood	CABS	34
Hypoxanthine	A-CS blood	2 × APST	35
Adenosine Hypoxanthine	A-CS blood	APST	36
Hypoxanthine	A blood	AS	37

A = arterial; CS = coronary sinus; APST = atrial pacing stress test; CABS = coronary-aorta bypass surgery; AS = aortic surgery.

The mechanism for the putative decrease in coronary nucleotide degradation during subsequent episodes of ischemia is unclear, but several explanations can be proposed to account for this finding. There is growing evidence for compartmentation of myocardial nucleotide pools [44, 45]. The different compartments in the cell may have different susceptibilities to depletion during myocardial ischemia. Susceptible pools may be depleted during the first ischemic episode, with more resistant pools remaining intact during subsequent ischemic episodes of the same duration. Another factor which may have contributed to the reduction in nucleotide degradation during the second and third occlusion is the greater than normal creatine phosphate content of myocardium following a brief ischemic episode [46, 47].

Whatever the mechanism, the increased creatine phosphate stores presumably present at the onset of the second and third coronary occlusion may provide high energy phosphate which serve to protect ATP pools from further depletion. A third potential explanation for decreased nucleotide degradation during the ischemic period is decreased energy consumption from decreased contractile function. However, from our previous hemodynamic studies, it seems unlikely that more rapid contractile failure may account for the preservation of nucleotide pools observed during the third and fourth occlusion. Other hemodynamic factors have to be considered.

Rentrop et al [48] have demonstrated during balloon inflation the angiographic appearance of a previously absent coronary collateral circulation. This apparent recruitment of collaterals might play a major role in the modulation of the ischemic and metabolic phenomenon related to the angioplasty procedure, although its functional significance is not yet well defined. It has been shown that the occlusion pressure measured distally to the stenosis, during balloon inflation, correlates well with the existence of a collateral circulation angiographically demonstrable before or during angioplasty [49, 50]. However, Probst et al [49], Meier and Luethy [50] and ourselves did not observe any change in the coronary occlusion pressure during serial occlusions. In fact, our results confirm their observations. The absence of any increase in coronary sinus and great cardiac vein flow during serial occlusions precludes the gradual recruitment of collateral circulation during repeated occlusions which might have explained a progressive decrease in lactate and hypoxanthine efflux.

Metabolism during reperfusion

The crucial conclusion to be drawn from our observations is that metabolic disturbances induced by repeated ischemia are quickly reversible, provided they are of a short (<90 s) duration.

During reperfusion, cells are re-oxygenated and waste products are removed. After ischemia, for a short period of time, reperfusion induces an enhanced Ca^{2+}

influx, mitochondria are reactivated and ATP and CrP are again produced [51, 52]. The latter compound is transported to the myofibrils. Because of ionogenic disturbances in the cell, contraction is still decreased at this stage, probably due to disturbed Ca^{2+} concentrations in the cell [53]. This can be demonstrated by an increased ventricular wall tension [54, 55], indicating an increased Ca^{2+} level, and increased CrP even to levels higher than the normal range [56–58]. This indicates that ATP consumption by contraction is at this state below ATP production. After activation of the ionic pumps, cellular homeostasis is restored and the cell starts beating again. However, ATP levels will remain subnormal for some time, and these low ATP levels cause an extra risk in as much as a critically low ATP level will be reached earlier during the next ischemic attack [59, 60]. Recently we have demonstrated that complete coronary occlusion of the left anterior descending coronary artery in man is associated with profound alterations in diastolic chamber stiffness which persist well after restoration of myocardial blood flow and of a normal systolic function [61]. In isolated working rat hearts, it has also been demonstrated that the early restoration of oxidative metabolism during reperfusion, determines functional recovery of the reperfused ischemic myocardium despite the presence of low ATP levels [62]. Thus it seems that integrity of the pathways of oxidative metabolism rather than steady state ATP levels, plays a major role in the myocardial functional recovery after acute ischemia. Even so, the decline of high energy phosphate stores heralds the beginning of 'no return'.

Therefore, further work is needed to document the time course of the recovery of a normal regional diastolic function, and address the responsible derangements of subcellular metabolism as the mechanisms of the observed abnormalities are not yet fully understood. Although recovery in terms of lactate and hypoxanthine metabolism is demonstrated the question remains to what extent transport mechanisms and enzymatic reactions have been transiently altered.

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Part two:
Changes in coronary anatomy and its physiological significance

Chapter VI

Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: diameter versus densitometric area measurements

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Summary

Cineangiograms of 138 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) were analyzed quantitatively. In a first study group (120 patients) the severity of the obstructive lesions derived from the automatically detected contours was evaluated in absolute terms as well as in percentage diameter reduction. In a second group of patients, 18 coronary lesions were selected for their extreme severity and symmetric aspect prior to angioplasty as assessed from multiple views. In the second group, the densitometric percentage area stenosis was used to assess the changes in cross-sectional area after PTCA and compared to the circular percentage area stenosis computed from the diameter measurements. Before PTCA, there existed a good agreement between the densitometric percentage area stenosis and the circular percentage area stenosis measurements. After PTCA, important discrepancies between these two types of measurements were observed. It is suggested that these discrepancies in results after PTCA can be accounted for by asymmetric morphological changes in luminal cross section, which cannot be assessed accurately from diameter measurements in a single plane view.

Introduction

When comparing percentage luminal narrowing of obstructions in coronary angiograms only the discrete dimensions at the site of the obstruction and at the so-called normal caliber of the vessel are incorporated. However, the prestenotic and poststenotic segments of a coronary vessel consist of subtle combinations of stenotic and ectatic areas and this fact alone creates a major problem in the quantification of the degree of luminal narrowing [1].

Previous studies on the hemodynamic effects of a stenosis in an artery have demonstrated that the most critical determinant of the severity is the minimal luminal cross-sectional area [2–5]. Assessment of the percentage area reduction in a stenotic area from diameter measurements obtained from a single projection assumes a symmetrical circular cross section, an assumption which will not always be true. In fact, Freudenberg and Lichtlen estimate that 70% of coronary artery stenoses are eccentric rather than concentric [6]. Even a technique of quantitating area stenosis from two orthogonal measurements and computing the area based on an elliptical model would fail to describe an asymmetrical lesion accurately [7]. However, some clue to the presence of this asymmetry will exist, since the observed density is markedly reduced in that area, even though the caliber of the vessel seems normal. It has been demonstrated that the true luminal cross sections of a contrast-filled coronary artery can be computed from a single X-ray projection by densitometric analysis [8].

From the above, it is clear that an objective and reproducible technique of quantitating cross-sectional area stenosis and normal luminal area both in absolute terms and in relative percentage changes is needed, if one is to evaluate the efficacy of transluminal coronary angioplasty in a quantitative sense.

Cineangiograms of 138 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) were analyzed with the Coronary Angiography Analysis System (CAAS) and the results before and after dilation are presented. In a first study group (120 patients), the severity of the obstructive lesions derived from the automatically detected contours was evaluated in absolute terms as well as in percentage diameter reduction. In the second group (18 patients), the severity of the lesion was derived from the densitometric measurements and expressed in percentage area stenosis.

Methods

Quantitative analysis of coronary obstructions

The quantitative analysis of selected coronary segments was carried out with the CAAS. The reference diameters and the percentages diameter reduction of the obstructions were computed according to the interpolated technique. The densitometric analysis was carried out according to the technique described in Chapter VII. The densitometric percentage area reduction of an obstruction was obtained by comparing the minimal area value at the obstruction with the reference area value computed following an interpolative approach similar to the method for diameter measurements [8].

An illustrative example of the results of this technique applied to an aortacoronary bypass graft, successfully dilated and filmed in two orthogonal views, is presented in figure 1. The percentage diameter stenosis from the LAO-view is

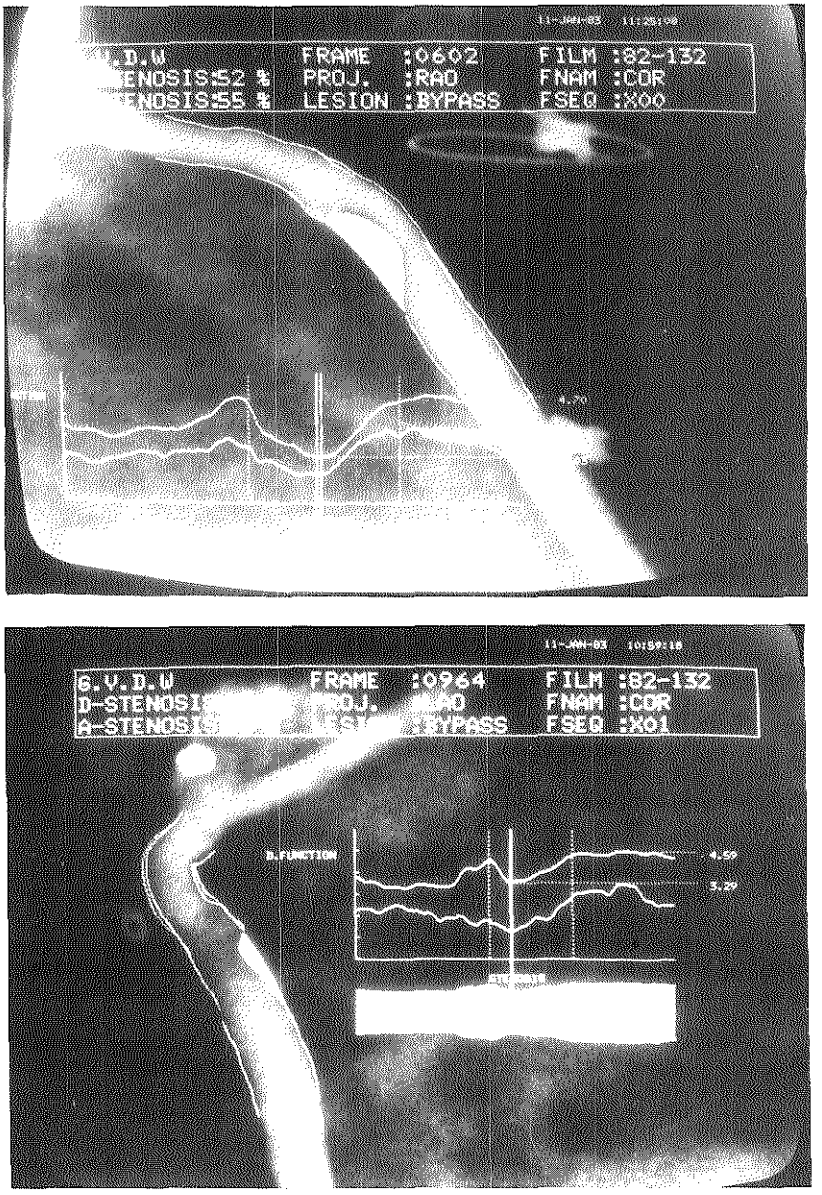

Fig. 1. Contours and densitometric analyses of the severity of an obstruction in the same aortacoronary bypass graft, filmed in right (RAO, upper photograph) and left (LAO, lower photograph) anterior oblique projections. In each illustration, the diagnostic diameter function (upper curve) and the densitometric area function (lower curve) are displayed on the video image. The white areas are a measure for the 'atherosclerotic' plaque and are defined by the difference between the actual luminal contours, detected by the computer and the reconstructed (original) reference contours. The densitometric area stenosis (A-STENOSIS) measured in the orthogonal projections were found to be 53% and 55%, respectively, whereas the diameter stenosis (D-STENOSIS) based on the detected contours was equal to 19% in the LAO-projection and 52% in the RAO-projection.

only 19%; if circular cross sections were assumed, this would result in a circular percentage area stenosis of 34%. However, the image shows a much greater decrease in density level at the obstruction than one would expect from the apparent decrease in diameter, suggesting the presence of an eccentric lesion. Indeed, the densitometric analysis provides a 53% densitometric area stenosis.

The RAO-view gives a 52% diameter stenosis. If only this RAO-view was available without densitometric analysis, then a circular cross-sectional area stenosis of 77% would be our best approximation of cross-sectional narrowing, thus overestimating the severity of the disease; in this view a 55% densitometric area stenosis was measured, which is very consistent with the 53% densitometric area stenosis from the LAO-view.

If only the diameter measurements from the two views were available, then by elliptical approximation a percentage area stenosis of 61% would be found, being an overestimation of the 'true' densitometric area stenosis.

Study population

The first study group consisted of 120 patients who underwent a successful PTCA between September 1981 and December 1982; within 6 months after the procedure 50 of these patients agreed to undergo repeat cardiac catheterization.

The second study group consisted of 18 patients in whom the densitometric percentage area stenosis technique was used to assess the changes in percentage cross-sectional area before and after PTCA. All data were obtained from single projections. The lesions were selected for their extreme severity and symmetric aspect before angioplasty as assessed from multiple views. PTCA was performed according to the technique of Grüntzig, using the equipment of Schneider (20–3.0 or 20–3.7 mm balloon), via a femoral route. In all cases, the pressure difference across the obstructive lesion was recorded before and after dilatation. The inflation pressure ranged from 4 to 10 atm, while the duration of the inflation was usually 30 to 60 seconds. Attempts at dilating the stenotic lesion were repeated as long as the gradient across the lesion persisted (4 to 10 times). Before the procedure all patients received aspirin and nifedipine; β-blocking drugs were not discontinued. During the procedure heparin and low-molecular-weight dextran were administered intravenously; direct intracoronary injection of nifedipine and isosorbide dinitrate was performed before the dilatation. To visualize the effect of the procedure, coronary angiography was performed immediately before and after transluminal angioplasty. Lateral, antero-posterior, oblique, and hemiaxial views were usually obtained.

Results

In the first study group the quantitative analysis was limited to computation of the diameter values, derived from the detected contours. The severity of the obstructive lesion was expressed in relative percentage narrowing and in absolute values (mm). For statistical analysis the average value of the measurements obtained in multiple angiographic projections (2 to 6 views) were determined for each individual. The results for the 138 lesions of the first study group are summarized in Table 1. On the average, the interpolated reference diameter remained unchanged after PTCA; the obstruction diameter increased from 1.28 ± 0.40 mm (mean $\pm$ s.d.) to 2.24 ± 0.57 mm ($p<0.001$); the interpolated percentage diameter stenosis was thus reduced from $62 \pm 12\%$ to $34 \pm 15\%$ ($p<0.001$).

Three groups of individual data are shown in figure 2 according to the severity of the interpolated percentage diameter stenosis before PTCA. Prior to PTCA, 26% of the lesions had a percentage diameter stenosis ranging from 71 to 100%, while 58% of the lesions ranged between 51 and 70%. In the remaining 16% of the lesions that were dilated, the percentage diameter stenosis was less then 51%. In 4 of these patients, PTCA was performed immediately after intracoronary fibrinolysis; in 18 other instances, we felt justified to dilate a second, less critical lesion during the same session.

The quantitative angiographic follow-up of the minimal obstruction diameters in 50 successfully dilated lesions is shown in figure 3. A change superior to the total measurement variability of repeated coronary cineangiography and quantitative analysis (0.44 mm for obstruction diameter, i.e. 2 standard deviations (s.d.) of the difference of duplicate measurements) was considered as significant [9].

In 22 of these lesions, the residual obstruction diameter, measured immediately after PTCA, remained unchanged over a period of 6 months. In 16 other patients, some degree of restenosis occurred, while late further improvement was observed in the remaining twelve.

In the second group, the densitometric percentage area stenosis was used to assess the changes in cross-sectional area after PTCA and compared with the circular percentage area stenosis computed from the diameter measurements. The comparative data are shown in Table 2 and figure 4. Before PTCA, there

Table 1. Effect of PTCA on 138 obstructive lesions in the first study group.

	Before PTCA	After PTCA	p-value
Reference diameter (mm)	3.40 ± 0.68	3.34 ± 0.70	n.s.
Obstruction diameter (mm)	1.28 ± 0.40	2.24 ± 0.57	0.001
Diameter stenosis (%)	62 ± 12	34 ± 15	0.001

n.s. = not significant; PTCA = percutaneous transluminal coronary angioplasty

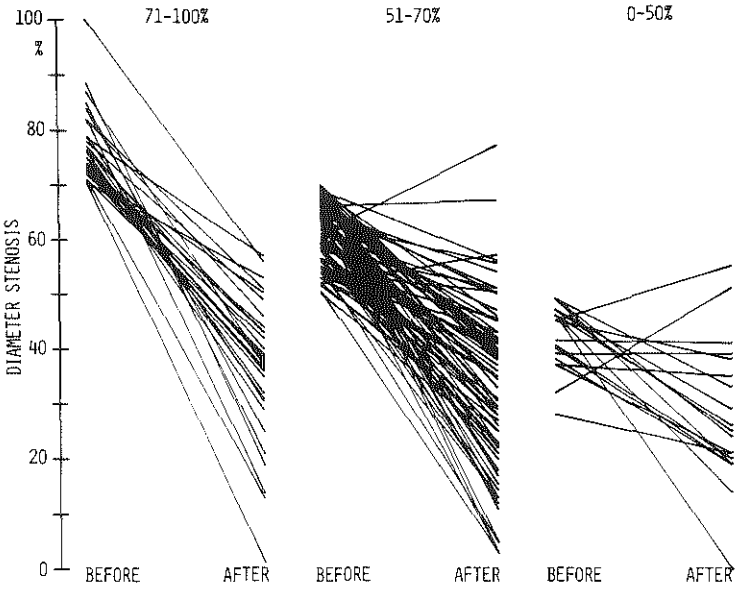

Fig. 2. Individual data of change in percentage diameter stenosis for three subsets of coronary stenoses according to the initial severity. In the group with a stenosis ≥71%, the diameter stenosis decreased on the average from 76% ± 7 to 33% ± 15. In the intermediate group (51–70%), the diameter stenosis decreased from 63% ± 6 to 33% ± 15, while in the last group (0–50%) it decreased from 42% ± 6 to 25% ± 6.

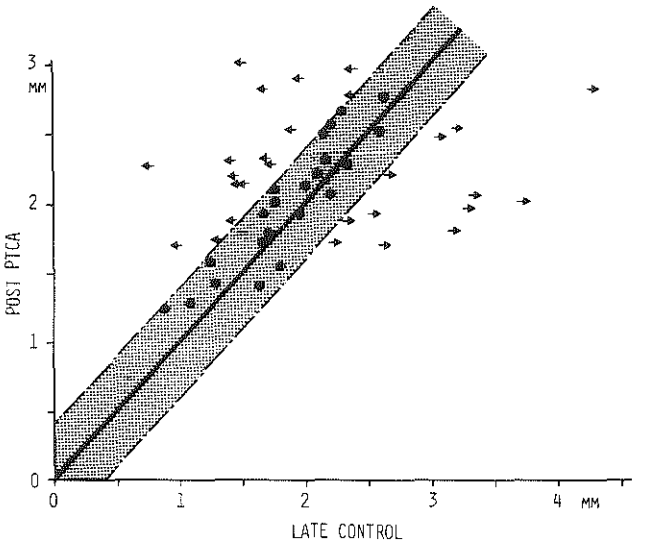

Fig. 3. Quantitative angiographic follow-up after 6 months (late control) of the minimal obstruction diameter (mm) in 50 successfully dilated lesions with comparison to the same parameter immediately after the dilatation. The shaded area represents the total measurement variability (±2 standard deviations) of repeated coronary cineangiography and quantitative analysis. Symbols: ← = late deterioration of the initial angiographic results; ● = unchanged minimal obstruction diameter; → = late improvement.

exists a good agreement between the densitometric percentage area stenosis and the circular percentage area stenosis (standard deviation of the difference = 5.0 %-area stenosis). After PTCA, important discrepancies between these two types of measurements are observed (s.d. of the difference = 18% area stenosis). It is suggested that these discrepancies in results after PTCA can be accounted for by asymmetric morphological changes in luminal cross section, which cannot be assessed accurately from diameter measurements in a single-plane view.

Discussion

Whenever a lesion appears to be of different severity when viewed from multiple projections, asymmetry should be suspected. In this study, asymmetry is considered present when the percentage diameter stenosis measured in one angiographic view exceeded that measured in another view by more than 2 standard

Table 2. Percentage area stenosis derived from detected contours versus densitometric area measurement, before and after angioplasty (PTCA).

	Before PTCA			After PTCA		
Pt. No.	% Circular A-sten	% Densito-metric A-sten	Difference	% Circular A-sten	% Densito-metric A-sten	Difference
1	69	69	0	24	9	− 15
2	93	93	0	57	71	14
3	94	97	4	33	44	11
4	73	85	12	36	64	28
5	85	89	4	73	75	2
6	88	92	4	42	47	5
7	85	90	5	19	44	25
8	70	71	1	21	36	15
9	85	90	5	52	35	− 17
10	93	93	0	23	47	24
11	57	61	4	54	58	4
12	96	99	3	46	17	− 29
13	95	94	− 1	83	82	− 1
14	84	82	− 2	60	46	− 14
15	89	93	4	66	71	5
16	84	89	5	51	66	15
17	88	94	6	28	36	12
18	90	77	− 13	44	10	− 34
mean	84%	87%	2.3%	45%	48%	2.8%
Corr Coeff:	0.89		s.d. 5%	0.62		s.d. 18%

A-sten = area stenosis; Corr Coeff = correlation coefficient; PTCA = percutaneous transluminal coronary angioplasty; s.d. = standard deviation.

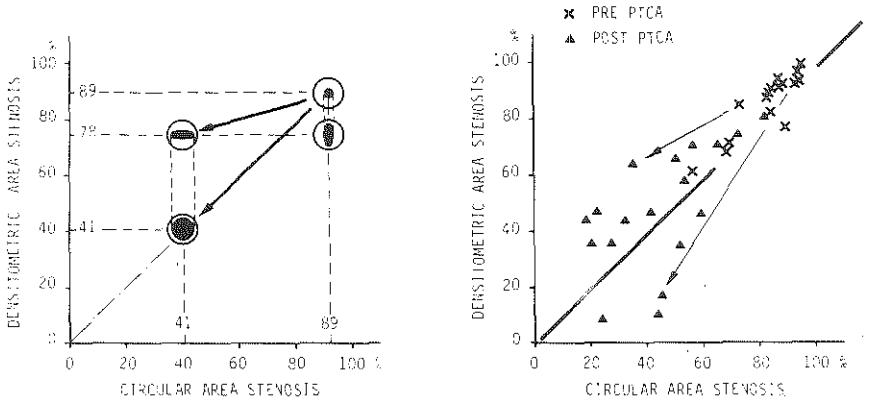

Fig. 4. Left, schematic representation of the potential asymmetric morphologic changes in luminal cross section during angioplasty. Let us assume before PTCA a circular cross section (area stenosis: 89%) at the site of the stenosis. After angioplasty, three hypothetical situations are observed: (1) an elliptical cross section with the long axis perpendicular to the image intensifier; (2) an elliptical cross section with the long axis parallel to the image intensifier; and (3) an enlarged cross section. From the figure, it is clear that for the 2 asymmetric dilatations, the %-area stenosis (41% and 89%) derived from diameter measurements assuming a circular cross-sectional model differs from the densitometric %-area stenosis (78%). Right, before and after (PRE and POST) PTCA comparison between densitometric area stenosis and area stenosis derived from the diameter measurements.

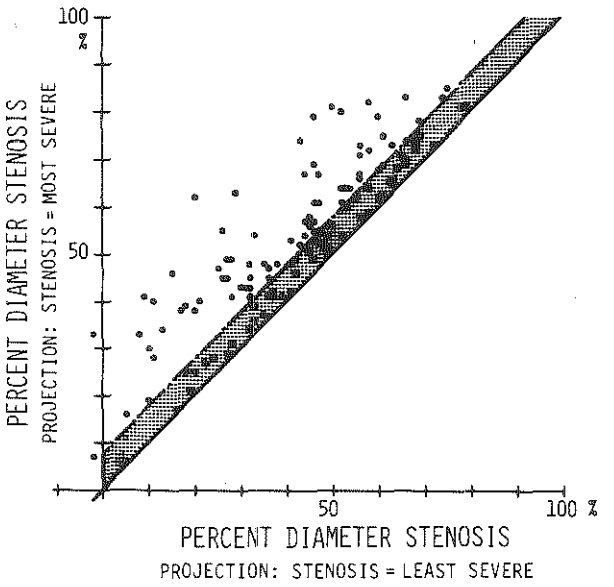

Fig. 5. Asymmetry of 120 obstructive lesions analyzed in more than one projection. On the horizontal axis, percentage diameter stenosis measured in the less severe angiographic projection; on the vertical axis, percentage diameter stenosis of the same lesion measured in the most severe projection.

deviations of the method used. The total measurement variability of repeated coronary cineangiography and quantitative analysis was 7.2% for the interpolated percentage diameter stenosis. In a study reported previously [10], when 120 lesions were analyzed in several orthogonal projections, asymmetric lesions were seen in more than half of the cases (figure 5). This shows that an atheromatous lesion may not always involve the entire circumference of the vessel but frequently results in an asymmetric or eccentric lesion. From postmortem data, it has been proven that a diseased vessel often looks like an exaggerated ellipse in which, ultimately, a slit-like lumen with a crescent shape represents the 'artery' [11]. It has been argued that this latter aspect is a product of postmortem arterial fixation with sectioning in the unpressurized state [12, 13]; yet the present data indicate that this is not an artifact. The corollary of these considerations is that the severity of the lesion to be dilated should be quantitated in as many angiographic views as possible when its efficacy is to be assessed by diameter measurements.

For the entire group the mean diameter stenosis before PTCA was 62%, as an average of multiple views. For the subset of lesions exceeding 50%, it was 69%. This value is almost 10% lower than that commonly reported when values are based on subjective reading of angiograms [14–16]. Such visual interpretation of diameter reductions is subject to systematic overestimation of the severity of the stenosis, as has been shown by several investigators [17, 18]. Luminal reductions greater than 90% with minimal obstruction diameter of 0.35 mm are unlikely to be crossed even by a low-profile deflated balloon catheter, which has a mean diameter of 0.8 mm. One must further keep in mind that a value of 80% of mean diameter stenosis commonly reported before PTCA corresponds to a 96% reduction of the luminal area. Again, this is unlikely to occur in patients with chronic stable angina because this would have limited the resting coronary blood flow at rest to a minimum. In fact, such restrictions are incompatible with adequate blood supply, unless collaterals are present [19].

On the other hand, a diameter stenosis of 69% measured in a single projection could be consistent with a cross-sectional area stenosis between 80 and 97% as shown in figure 6. The latter also illustrates the varying results in percentage area stenosis, assessed from diameter measurements in a single view, depending on whether a circular or an elliptical model is applied.

The results of cross-sectional area measurements obtained in the second study group suggest the creation of asymmetric lesions after angioplasty. As demonstrated elegantly by Block et al. in rabbit arteries after experimentally induced atherosclerotic lesions, transluminal angioplasty leads to the breaking of the intimal surface of the atherosclerotic lesion [20]. This split may extend to the internal elastic membrane. Angiography performed after such procedures in the rabbit frequently shows an irregular column of contrast in this area. As suggested by the investigators, these irregularities must certainly represent contrast material within the remains of the atherosclerotic plaque. Recently, human coronary arteries that had undergone angioplasty were analyzed. They have shown

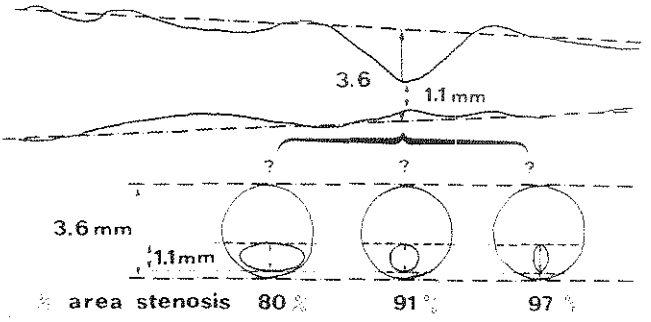

Fig. 6. Schematic representation of a coronary obstruction with an interpolated diameter stenosis of 69% measured in a single projection. The percentage area stenosis, computed from diameter measurements, varied between 80% and 97% depending on the circular or elliptical model applied for the computation.

changes identical to those seen in animal models [21–23]. Such a disruption of the medial layer creating a slit-like appendix to the original lumen is shown in figure 7. Because this tear in the wall is filled by fibrocellular tissue, it must be inferred that the asymmetric morphological aspect is not a postmortem artefact.

In conclusion, our angiographic study suggests that changes in the luminal area of an artery, produced by the mechanical disruption of its internal wall, cannot be assessed accurately from the detected contours of the vessel from a single plane angiographic view. Therefore, the diagnostic value of this type of measurement is restricted by the fact that the angioplastic changes are eccentric in nature. To obviate this limitation, the use of densitometry to compute cross-sectional areas from single views is advocated.

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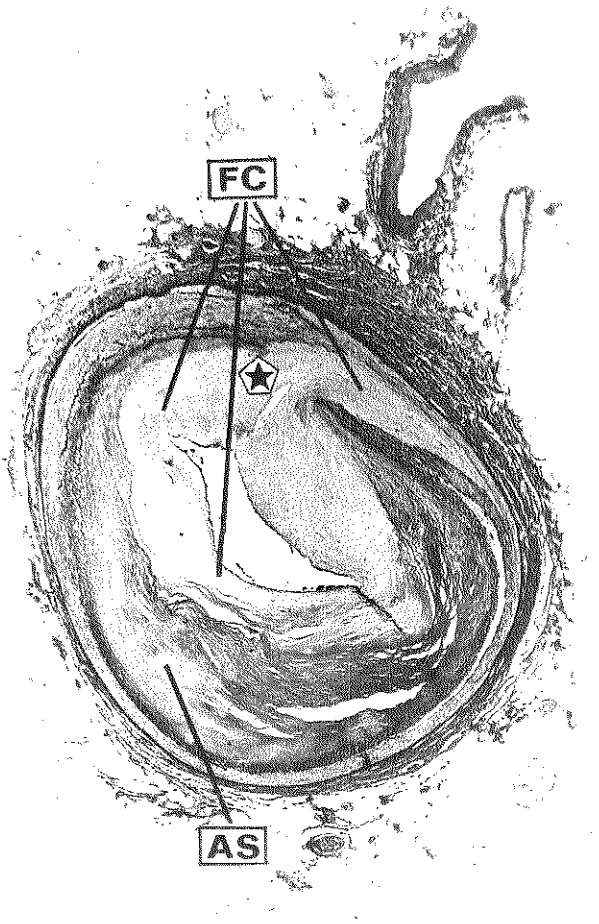

Fig. 7. Histologic section through a stenotic lesion successfully dilated five months before the death of the patient. A disruption of the medial layer (star) is present, which had led to medial dissection. The false channel and the major part of the lumen are filled with fibrocellular tissue (FC). The pre-existent atherosclerotic plaque (AS) is readily identified.

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Chapter VII

Transstenotic pressure drop, exercise thallium 201 scintigraphy, quantitative coronary cineangiography: in what sense are these measurements related?

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Introduction

During cardiac catheterization, the pressure-flow relationship across a coronary stenosis cannot be determined, although the feasibility of transluminal measurements of coronary blood flow velocity has been reported recently [1]. On the other hand, the pressure distal to a coronary stenosis is measured routinely during the PTCA-procedure. The physiologic value of these measurements, even those obtained with the smallest catheters, must be questioned since the catheter impedes flow through the obstruction. In addition, it is well known that the mean pressure gradient is affected by phasic changes in flow velocity. In spite of these limitations, Vogel and his group have shown that the mean pressure gradient measured across the stenosis during angioplasty accurately predicts the coronary blood flow reserve measured by digital angiography [2].

In the present study, we attempted to assess the relationship between the transstenotic pressure drop measured during angioplasty, the angiographic severity of stenosis and the inducibility of regional perfusion defects during exercise Thallium-scintigraphy. As a first step, we decided to investigate the values and limitations of the transstenotic pressure difference measured during PTCA by comparing the transstenotic pressure drop with the theoretical pressure drop calculated from fluid-mechanic equations; the accuracy of the absolute value of the transstenotic pressure difference measured during PTCA must be questioned as the presence of the dilatation catheter further reduces the luminal area. Leiboff et al. [3] have shown in canine femoral arteries that the pressure drop measured transtenotically overestimated the 'true' pressure difference across the stenosis in a predictable manner, which is dependent on the ratio of the diameter of the angioplasty catheter to the stenosis diameter. In order to further characterize this relation in the coronary artery bed of humans, we compared the transstenotic pressure difference with the theoreti-

cal pressure drop calculated from fluid mechanic equations for steady flow of an incompressible fluid in rigid tubes. Therefore, the stenosis geometry was analyzed by quantitative coronary cineangiography and the mean myocardial blood flow was measured by the thermodilution technique in a selected group of patients with proximal left anterior descending coronary artery disease.

Part I: Values and limitations of transstenotic pressure differences measured during percutaneous coronary angioplasty

Patients and methods

Thirteen patients with exertional angina pectoris were studied; all were candidates for PTCA of an isolated proximal left anterior descending stenosis. The distal part of the vessel was not filled by collaterals, as judged from angiography.

The subjects gave informed consent and no complication resulted from the study. Details regarding the PTCA technique used in our laboratory have been described previously [4]. The mean transstenotic pressure difference was measured with the dilatation catheter and calculated on line after a data acquisition period of 20 seconds [5]. The regional coronary blood flow measurement in the great cardiac vein, which must be known for the calculation of the theoretical pressure drop (see below), was obtained with a Baim catheter using the thermodilution technique [6]. The position of the catheter was confirmed by dye injection before and after PTCA. Measurements were included only if selective sampling from the anterior vein was possible. Such selective great cardiac vein flows were available before PTCA in 3 patients, after PTCA in 3 patients, and before and after in 7 patients. Thus, 20 data points were available for comparison.

Quantitative coronary angiography

The quantitative analysis of selected coronary segments was carried out with the help of a computer-based Cardiovascular Angiography Analysis System (CAAS), which has been described elsewhere [7–11]. In short, the boundaries of a selected coronary segment were detected automatically from optically magnified and video digitized portions of a cineframe. Calibration of the diameter data of the vessels in absolute values (mm) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the computed mean diameter in pixels with the known size in mm. Strictly speaking, this calibration factor is only applicable for coronary segments in the plane of the analyzed catheter segment parallel to the image intensifier input screen. The change in magnification for two objects located at different points along the X-ray beam axis is about 1.5% for each centimeter that separates the objects axially, with the commonly used focus-

image intensifier distances. In the present study, the axial distance between catheter and stenosis is short; hence the possible changes in the calibration factor would be negligible and no further corrections were used. In order to correct the contour positions of the arterial and catheter segments for the pincushion distortion, a correction vector was computed for each contour position based on a computer processed cineframe of a cm-grid placed against the input screen of the image intensifier [8].

The contour detection procedure requires the user to indicate a number of center positions with the writing tablet proximal and distal to the lesion such that the straight line segments connecting these points remain within the artery. The first centerline position was selected beyond the take-off of large daughter branches. The contours of the vessel are detected on the basis of the weighted sum of first and second difference functions applied to the digitized brightness information using minimal cost criteria.

From the detected contours, the diameter function, in absolute mm, is determined. From the minimal value of the diameter function determined by the computer and the mean diameter value at the reference position, the percentage area reduction, assuming circular cross-sections, is computed as:

$$\%\text{-A stenosis} = \{1 - (\text{minimal diameter/reference diameter})^2\} \times 100\%.$$

A representative analysis with the detected contours and the diameter function superimposed on the original video image is shown in figure 1a. In arteries with a focal obstructive lesion and a clearly normal proximal arterial segment, the choice of the reference region is straightforward and simple. In cases where the proximal or distal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may be very difficult. Since the functional significance of a stenosis is related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we have implemented two methods to define the reference: one is dependent on the user (user-defined reference), while the other technique is based on the computer estimation of the original arterial dimensions at the site of the obstruction (interpolated reference) [10, 11]. For the latter method, the computed reference diameter function allows the vessel to taper. The resulting reference contours are shown in figure 1b. The interpolated percentage diameter stenosis is then computed by comparing the minimal diameter value at the obstruction with the corresponding value of the reference diameter function at this position; as described earlier, the percentage area stenosis can be calculated as well.

The length of the stenotic segment was determined from the diameter function on the basis of curvature analysis of the D-function and expressed in mm.

The same angiographic projection was used before and after PTCA, except for 2 post-PTCA lesions where the mean value from two orthogonal projections was used. From an extensive validation study of the analysis procedure it has been shown that the variability (standard deviation of the differences) of repeated

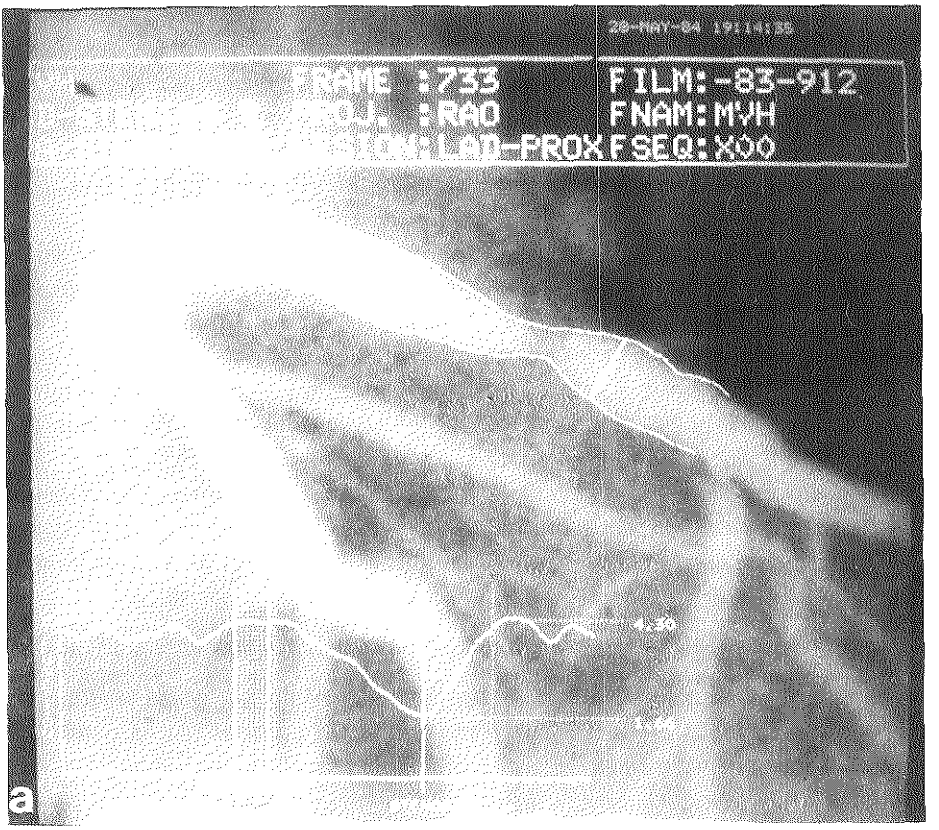
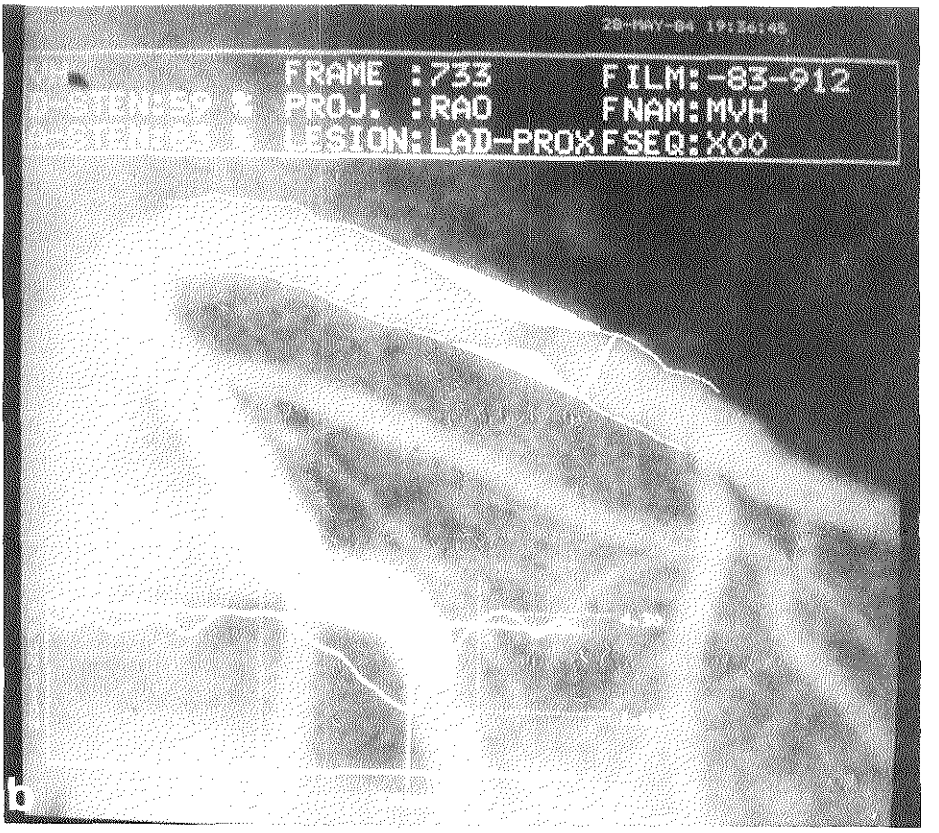


Fig. 1. Detected contours superimposed on the original video image for a representative left anterior descending coronary artery stenosis. The diameter function is shown at the bottom. The calibrated diameter values in mm are plotted along the ordinate and the positions along the analyzed segment from the proximal to the distal part along the abscissa. 1a. The reference diameter (or area) was selected proximal to the stenosis. A percentage area stenosis of 84% resulted. 1b. The normal size of the artery over the obstruction has been estimated by the interpolated method. The resulting reference contours are shown and the difference in area between this boundary and the detected contours is a measure of the atherosclerotic plaque (shaded area). A percentage area stenosis of 83% resulted. 1c. Schematic representation of the coronary artery with the guiding catheter in the ostium (top left), the thermodilution catheter in the coronary sinus (bottom left) measuring the great cardiac vein flow (GCVF). The inset (top right) shows how the transstenotic pressure gradient was measured (between the white dots). The theoretical pressure drop was calculated from: 1) the reference diameter (or area) shown proximal to the stenosis for the sake of clarity; 2) the obstruction diameter (or area) and 3) the length of the stenosis.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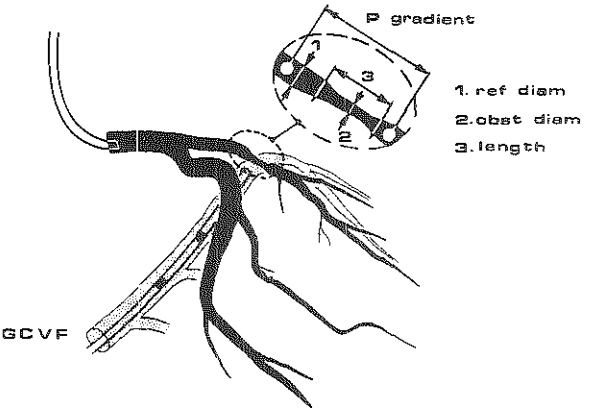
P gradient
1. ref diam
2. obst diam
3. length
GCVF

coronary acquisition and computer analysis is less than 0.22 mm for absolute arterial dimensions in a well-controlled study [11].

Theoretical pressure gradient

The theoretical pressure gradient was calculated according to the well-known formules described in the literature [12, 13]

$$\triangle P = Q \cdot (Rp + Q \cdot Rt),$$

where $\triangle P$ is the theoretical pressure drop (mmHg) over the stenosis, Q the mean coronary blood flow (ml/sec), Rp the Poisseuille resistance and Rt the turbulent resistance. These resistances have been defined as follows:

$$Rp = Cl \cdot \frac{(\text{length obstruction})}{(\text{obstruction area})^2} \left[\frac{\text{mmHg} \cdot \text{sec}}{\text{ml}}\right],$$

where $Cl = 8 \cdot \pi \cdot$ (blood viscosity) with blood viscosity = 0.03 [g/cm · sec]

$$Rt = C2 \cdot \left(\frac{1}{\text{obstruction area}} - \frac{1}{\text{normal distal area}}\right)^2 \left[\frac{\text{mmHg} \cdot \text{sec}^2}{\text{ml}^2}\right],$$

where $C2 = \frac{\text{blood density}}{0.266}$ with blood density ≈ 1.0 [g/cm^3]

In the formules given above the obstruction area calculated from the coronary cineangiograms must be corrected for by the cross-sectional area of the dilatation catheter; for this catheter area the value of 0.64 mm^2 was used.

Statistics

Comparisons between pre- and post-PTCA measurements were performed with the Student t-test for paired data.

Multiple regressions were performed between the obstruction area and either the measured or the theoretical gradient until the best fit was obtained. The individual data are tabulated in Table 1.

Results

The median values and the ranges for the obstruction area, the measured transstenotic pressure difference and the theoretical pressure drop before and after angioplasty are shown in Table 2. A fourfold increase in the luminal area was associated with a fourfold decrease in the measured transstenotic pressure difference; however, the

absolute values for the transstenotic pressure difference were consistently larger than the theoretical pressure drop. No changes in the reference area or the length of the stenosis were observed. The resting blood flow increased sligthly but not significantly from 1.3 to 1.6 ml/s. The relation between the occlusion area and the theoretical pressure drop (figure 2) was best fitted by the equation: $\triangle P = a \cdot (\text{occlusion area})^b$, where $\triangle P$ = theoretical pressure difference, $a = 15$ and $b = -2$ ($r = 0.87$). As expected from the laws of fluid dynamics, this relation is curvilinear and shows a steep

Table 1. Measured versus calculated gradient.

No	Patient name		Angio view	Occlusion area	GCV flow	Sten length	△P calculated	(△P-CA)	△P measured
				mm²	ml/s	mm	mmHg	mmHg	mmHg
1	PO	b	RIO	0.96	2.13	7.0	18.9	–	80 occl
		b	LSO	0.79		9.9	52.2	–	
2	VY	b	RAO	1.19	1.20	12.0	13.5	39.5	59
		a	CRA	2.43	1.52	7.3	1.9	3.9	5
		a	RAO	4.26		11.9	0.8	1.2	
3	MA	b	RIO	1.52	1.40	7.9	5.5	18	59
		a	RIO	3.84	1.62	6.8	0.8	1.3	12
4	BO	b	LSO	1.47	1.02	7.5	3.5	12.3	69
5	ME	b	RAO	0.34	1.42	10.0	107.2	–	62 occl
6	BE	a	LSO	1.87	1.50	6.4	3.2	8.3	4
7	HE	b	CRA	0.48	1.27	8.8	8.2	–	71 occl
8	BA	b	RAO	0.57	1.23	14.3	55.6	–	56 occl
		b	RIO	0.53	1.23	10.8	51.9	–	52 occl
		a	RIO	2.97	1.50	11.3	1.0	2.8	11
9	GR	a	RIO	1.63	1.45	12.0	8.5	19.6	13
10	MA	b	RAO	2.38	1.68	6.9	2.3	5	48
		a	AP	3.41	1.85	10.5	0.9	2.1	17
11	PI	a	RIO	2.06	1.63	8.9	4.2	7.9	23
		a	LAO	3.08		4.1	0.8	1.4	
12	EC	a	RAO	2.88	1.33	13.1	1.5	3.2	13
13	VE	b	RAO	0.32	1.23	8.5	122.5	–	41 occl
		a	RAO	2.04	1.67	6.6	3.3	3.8	5

Abbreviations: b: before angioplasty; a: after angioplasty; angio: angiographic; GCV: great cardiac vein; RIO: right inferior oblique; LSO: Left superior oblique; CRA: cranio-caudal; RAO: right anterior oblique; AP: antero posterior; LAO: left anterior oblique; △P calculated: pressure difference derived from quantitative coronary angiography; (△P-CA): pressure difference derived from quantitative coronary angiography, when the cross sectional area of the angioplasty catheter (CA) is subtracted from the obstruction area; △P measured: measured transstenotic pressure difference; occl: when CA is greater than the luminal obstruction area, the vessel is considered to be completely occluded (occl).

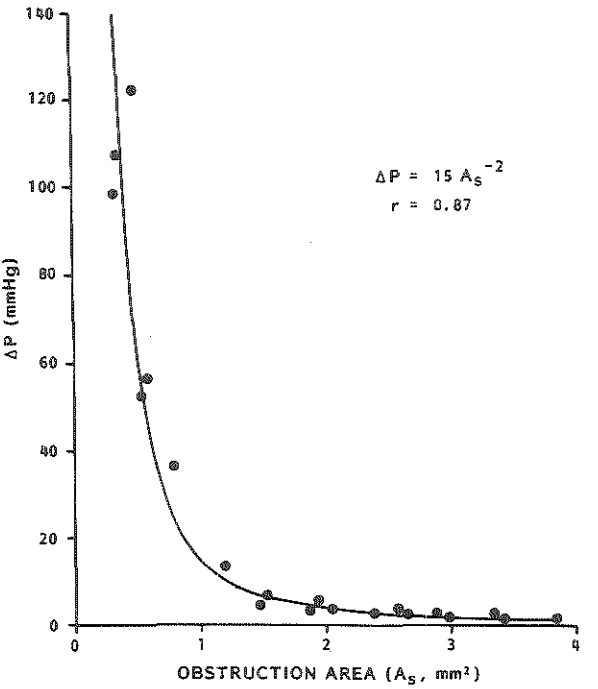

Fig. 2. Curvelinear relationship between the obstruction area (A) and the theoretical pressure drop across the stenosis (△P). The relation is best fitted (r = 0.87) by the equation: $\triangle P = 15.\ A_S^{-2}$.

increase in pressure drop once the critical value of 1 mm² for the occlusion area is reached. Figure 3 shows the relation between the occlusion area and the measured transstenotic pressure difference, which was best fitted by the linear equation: △P = a − b. (occlusion area), where △P is the measured pressure difference, a = 69 and b = 17 (r = 0.76). According to this relation, the average pressure difference measured after PTCA, i.e. 13 mmHg, would correspond to a luminal area of 3.3 mm². The theoretical relation would predict with this area value, a pressure drop of

Table 2. Hemodynamic and angiographic measurements before and after PTCA.

	GCVQ ml/s	Obstruction area (mm²)	△P calculated mmHg	△P measured mmHg
Before	1.3 (1.0–2.1)	0.7 (0.3–2.4) *	44 (2–122) *	59 (41–80) *
After	1.6 (1.3–2.1)	2.8 (1.9–3.8)	2 (1–5)	13 (4–28)

The median value and the range are given; GCVQ = great cardiac vein flow; △P = calculated pressure drop or measured transstenotic pressure difference; * $p<0.005$.

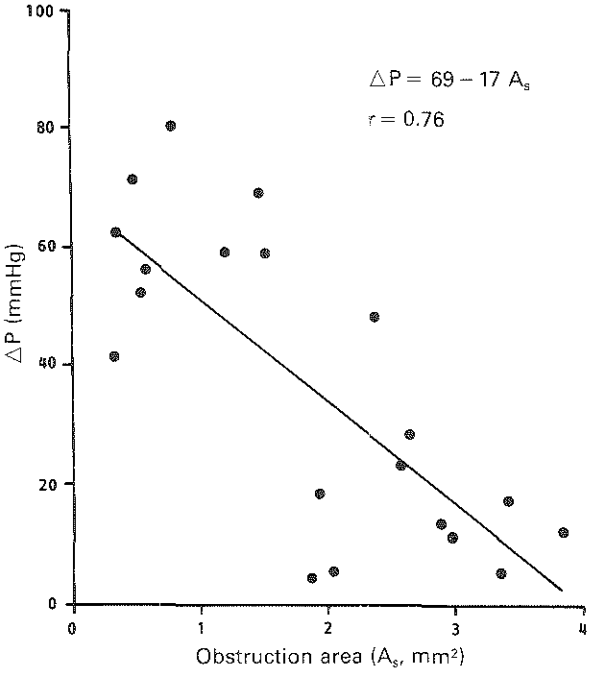

Fig. 3. Linear relation between the obstruction area (A_s) and the transstenotically measured pressure difference ΔP. $\Delta P = 69–17.\ A_s$ ($r = 0.76$).

1.4 mmHg, at least within the observed range of flow. Thus, even when the lumen of the vessel is large as compared to the diameter of the angioplasty catheter, its presence leads to an overestimation of the 'true' pressure drop. In other words, these data show that the absolute value of the transstenotic pressure difference obtained during angioplasty donot reflect accurately the flow resistances. As suggested by others [3, 14], this is related to the presence of the angioplasty catheter across the stenosis, further reducing its minimal luminal area. These findings are not surprising, but were until recently [15] never demonstrated in human coronary arteries. The data also show that calculation of theoretical pressure drop on the basis of an hypothetical coronary blood flow could result in inaccurate numbers as the range of flows that we measured was rather large, even at rest (from 1.02 to 2.13 ml/s.).

However, we were still convinced that useful information could be derived from the transstenotic pressure determination, at least in the setting of angioplasty. And it is this concept that we tried to test in the second part of the study. In a second group of patients, we tried to evaluate during cardiac catherization what degree of narrowing of a major epicardial coronary artery will consistently lead to a definite transstenotic pressure difference at rest and to myocardial ischemia during exercise.

Part II: Quantitative angiography of the left anterior descending coronary artery: correlations with pressure difference and results of exercise thallium scintigraphy

Patients and methods

Thirty-one consecutive patients with stable exertional angina pectoris were studied; all were candidates for percutaneous transluminal angioplasty of an isolated proximal left anterior descending stenosis. All subjects gave informed consent and no complications resulted from the study.

Quantitative coronary angiography

In this study, the coronary angiograms were obtained within five minutes after intracoronary injection of nifedipine (0.1 to 0.2 mg) in order to obtain a vasodilatation of the epicardial vessels and relief of a possible spasm [16, 17]. Since the luminal cross section at the site of the coronary obstruction is frequently irregular in shape especially after angioplasty [18, 19], the average obstruction area and percent area stenosis obtained from multiple views were used (mean of 1.7 views per segment). Since the presence of the dilatation catheter within the stenotic lumen further reduces lumen area, the difference between the luminal area measured from the coronary angiograms and the area of the balloon catheter (0.64 mm^2) was used as an approach to the actual residual lumen and related to the pressure gradient measurements. The mean pressure gradient across the stenotic lesion was measured with the dilatation catheter (mean diameter of 0.9 mm, Schneider 20–30 or 20–37) before and after angioplasty and calculated on line after a data acquisition period of 20 seconds [5].

Noninvasive testing

Exercise thallium-201 myocardial scintigraphy was performed before angioplasty in 7 patients, after angioplasty in 13 patients and before and after in 11 patients. Sequential imaging was performed according to a standard protocol immediately after a symptom-limited exercise test and again 4 hours later. Scintigraphy was performed in the week before angiography (n = 18) and in the three weeks after successful angioplasty (n = 24). No patient had recurrence of angina pectoris during this time interval. During exercise, three orthogonal leads (X, Y, Z) were monitored and analyzed as previously described [20]. The scintigraphic images were processed on a DEC gamma-11 system [21]. Basically, circumferential profiles were computed in three projections (anterior, LAO 45, LAO 65) within the automatically detected contour of the left ventricle following interpolated background subtraction [22]. The circumferential profiles, the processed images

and the analog polaroid images were interpreted by three independent observers, who were unaware of the angiographic data. The myocardial uptake of thallium was scored in a total of 13 segments both for early and late exercise scintigrams in the following manner: 0 = no thallium uptake; 1 = severely abnormal; 2 = definitely abnormal; 3 = doubtfully abnormal; 4 = normal. These scores were summed per patient and the difference between late and early post-exercise sums was taken as a measure of the amount of redistribution. Using this approach, ischemia was considered to be present if at least two observers found that the redistribution score was two or more points higher than the early post-exercise one. Since only patients with single vessel disease were included, the left anterior descending artery stenosis was taken responsible for the regional defects observed in the anteroseptal, anterior, anterolateral as well as apical segments [23].

Statistical analysis

Simple regressions were used to attempt the best fit relation between the pressure gradient and the obstruction area. The Student test for paired data and linear least-squares regressions were used to compare the interpolated and user-defined percent area stenosis measurements. One-way analysis of variance followed by multiple comparisons was used to compare the angiographic measurements between three sub-groups of patients. Data are expressed as mean ± standard deviation.

Results

The absolute dimensions of the minimal obstruction areas are given in Table 3, ranked from the minimal obstruction area value of 0.15 mm^2 to the maximal value of 17.9 mm^2. The interpolated and user-defined percent area stenosis values are shown as well. The user-defined reference was taken proximal to the stenosis in all but 10 cases where it was taken distally due to the take-off of the left circumflex artery just before the stenosis. There was no significant difference between the interpolated and user-defined percent area stenosis: the difference between paired data was 1.7 ± 10 and the correlation coefficient was 0.91 (interpolated % Area st. = 0.95. (user % Area st.) + 4.8; SEE = 10). When the mean pressure difference across the stenosis, normalized for the mean aortic pressure, was compared to the residual obstruction area after subtracting the balloon area (figure 4), a nonlinear relation was found which can be described by the equation:

$$\Delta P/AoP = a + b \cdot \log (\text{obstruction area}),$$

where $a = 0.35$ and $b = -0.12$ ($r = 0.74$).

Table 3. Individual data for quantitative angiography and exercise test results.

Patient		Obstr. area	D st. %	Area st. %		Measured ΔP		Theor. ΔP		Exercise test		
				inter	user	ΔP/AoP	ΔP	1	2	AP	ECG	TL201
1	HD b	0.15	87	98	96	0.75	81	34	126	–	–	+
2	FA b	0.30	85	98	94	0.49	39	16	42	+	+	–
3	HO b	0.36	82	97	97	0.87	54	46	171	+	+	+
4	PL b	0.45	79	96	84	0.46	38	12	32	+	+	+
5	EN b	0.58	81	96	94	0.54	51	17	44	–	–	+
6	KS b	0.58	71	92	91	0.55	51	13	46	–	–	–
7	BO b	0.65	74	93	90	0.74	85	9	33	–	+	+
8	VD b	0.80	69	90	(–)	0.38	27	4	16	–	BB	–
9	HN b	0.88	68	89	89	0.63	65	6	17	–	+	+
10	EL b	0.92	68	90	75	0.73	68	3	10	+	–	+
11	MS b	0.98	54	80	85	0.67	63	5	19	–	–	+
12	HO a	1.23	46	70	75	0.29	31	0	1	–	–	–
13	EM a	1.58	47	72	55	0.16	20	1	2	–	+	–
14	KT b	1.65	66	89	84	0.43	36	1	2	–	+	+
15	HE b	1.74	70	91	89	0.65	73	1	3	+	+	+
16	SK b	1.77	67	89	(–)	0.60	61	(–)	(–)	+	–	+
17	GI b	2.06	66	88	90	0.39	35	4	12	+	BB	+
18	SR b	2.09	65	88	87	0.72	72	4	15	–	+	+
19	DA b	2.38	38	62	69	0.39	26	0	1	–	BB	+
20	RS a	2.75	50	75	72	0.10	10	1	2	+	BB	–
21	MS a	2.83	21	38	65	0.13	13	0	0	–	–	–
22	DA a	2.95	19	34	50	0.18	15	0	2	+	–	–
23	HP a	3.00	33	55	65	0.10	9	0	1	–	–	–
24	FN a	3.11	31	54	64	0.13	13	0	0	–	+	–
25	HD a	3.14	37	60	(–)	0.09	10	0	0	–	–	–
26	BE a	3.14	10	44	32	0.06	4	0	0	–	–	–
27	WI a	3.17	42	66	65	0.28	25	1	2	–	–	–
28	KL b	3.33	41	65	65	0.15	13	4	9	–	–	+
29	MO a	3.70	33	56	54	0.34	31	0	1	–	–	+
30	NS a	3.94	38	61	30	0.16	13	0	0	–	–	–
31	BV a	4.12	48	48	39	0.11	13	0	0	–	–	–
32	HT a	4.16	41	66	48	0.16	14	0	0	–	+	–
33	FA a	4.26	21	37	45	0.21	16	2	8	–	+	–
34	HN a	4.34	40	65	56	0.04	5	0	0	–	–	–
35	KL a	4.95	21	37	52	0.00	0	0	0	–	–	–
36	OW a	5.68	25	44	43	0.16	15	0	0	–	–	–
37	SK a	6.20	38	62	67	0.18	20	(–)	(–)	–	–	–
38	HE a	7.07	40	64	53	0.21	24	0	0	–	–	+
39	SE a	7.50	36	60	57	0.10	8	0	0	–	–	–
40	KN a	8.29	3	6	14	0.21	26	0	0	–	+	–
41	KT a	9.90	17	30	21	0.07	6	0	0	–	–	–
42	GI a	17.87	3	6	6	0.06	5	0	0	–	–	–

Abbreviations: b = before angioplasty (PTCA); a = after PTCA; Obstr. Area = obstruction area in mm^2; Area st. = percent area stenosis; inter = interpolated and user-defined reference; the measured mean pressure difference is shown in absolute values (mmHg) as well as normalized for mean aortic pressure (AoP); theoretical pressure difference were calculated assuming constant coronary flows of 1 and 2 ml/s, according to the formula described by B.G. Brown et al. (12); (–) = missing data; AP = angina pectoris; ECG = ST depression ≥0.1 mV; TL201 = redistribution from exercise to rest scintigram; + = present; – = absent; BB = bundle branch block.

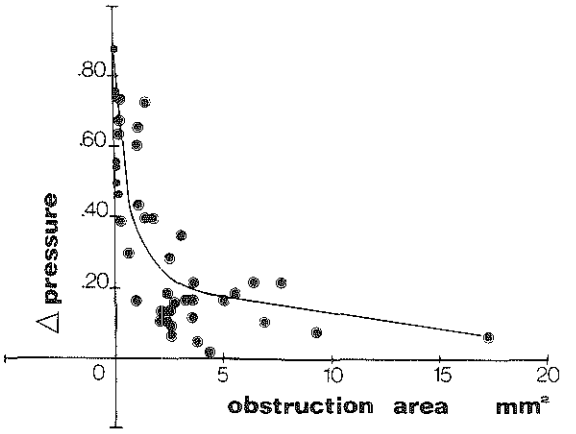

Fig. 4. The relation between the mean transstenotic pressure difference normalized for the mean aortic pressure and the residual obstruction area in mm^2 (after subtraction of the area of the angioplasty catheter) is nonlinear; the best fit is obtained by the logarithmic function ($r = 0.74$). Filled symbols represent stenoses in which the angioplasty catheter totally obstructed the vessel.

It is shown that there is a steep increase in pressure difference across the stenosis once a critical value of 1.5 mm^2 of the stenotic segment is reached. In seven cases, the angioplasty catheter almost totally obstructed the vessel. The computed cross-sectional area reduction is also related to the pressure drop across the stenosis (figure 5). Here, the steep increase in pressure difference is observed once the critical reduction of 80% in cross-sectional area is reached.

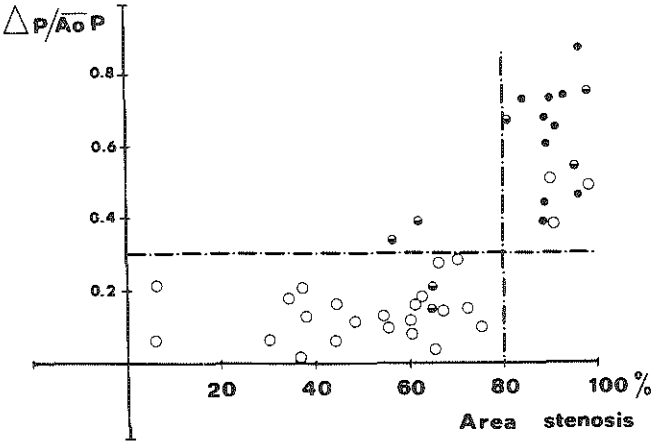

Fig. 5. The relation between mean normalized pressure difference across the stenosis, percentage area stenosis and the results of thallium scintigraphy is shown. Open circles represent patients with a normal scintigram (group I, n = 25), while half-filled circles represent patients with an abnormal thallium but normal exercise test (group II, n = 7). Filled circles represent patients with both abnormal thallium and exercise tests (group III, n = 10).

During the exercise test, the maximal workload averaged 85 ± 17% of the predicted value. According to the results of the thallium scintigraphy, three types of responses are observed. In group I (n = 25), the scintigram is normal, with either normal or abnormal exercise ECG. In group II (n = 7), thallium scintigraphy is abnormal while the exercise test results are normal. In group III (n = 10), both thallium scintigraphy and exercise test results (angina and/or ST-segment changes) are abnormal. The percent area stenosis was 55 ± 23 in group I, 74 ± 17 in group II and 90 ± 4 in group III. The mean pressure difference was: 0.18 ± 0.13 in group I, 0.44 ± 0.23 in group II and 0.62 ± 0.15 in group III. The pressure drop measurements discriminated better between the groups than the area stenosis measurements (table IV). When combining both parameters, two groups of datapoints are delineated as shown in figure 5. Using cut-off values of 0.30 for the pressure difference and 80% for the cross-sectional area reduction, the result of the exercise thallium scintigram was correctly predicted from the angiographic data in 83% of the patients. An abnormal scintigraphy was observed in 13 of the 16 patients with a pressure drop of at least 0.30 and a percent area stenosis equal to or greater than 80% (sensitivity of 81%). Two out of three patients with a normal thallium uptake and exercise test had important collaterals shown by angiography. Conversely, the thallium uptake is normal in 22 of the 24 patients with a pressure difference less than 0.30 together with an area stenosis less than 80% (specificity 92%). Similar figures were found when the user-defined percent area was used instead of the interpolated method (sensitivity 85%, specificity 87%).

Discussion

In this study, we selected the simplest human model available to assess the relationship between the angiographic stenosis severity and the inducibility of regional perfusion defects during exercise thallium scintigraphy. Attempts to correlate closely the anatomy of a coronary stenosis and its physiologic signifi-

Table 4. Noninvasive test results and angiographic estimates of stenosis severity.

		n	% Area stenosis	Mean pressure difference
Group I	(Tl−)	25	55 ± 23 (n.s.)	0.18 ± 0.13 (**)
Group II	(Tl+/ET−)	7	* 74 ± 17 (n.s.)	* 0.44 ± 0.23 (n.s.)
Group III	(Tl+/ET+)	10	90 ± 4	0.62 ± 0.15

Abbreviations as previously; n = number of patients; ET = exercise test result; + = abnormal; − = normal; n.s. = nonsignificant; symbols refer to p-values: * $p<0.001$; ** $p<0.005$

cance are usually hampered by the large intra- and inter-observer variabilities [24, 25] due to subjective visual scoring of coronary angiograms and to the inconstant vasomotor tone. To circumvent these limitations, the coronary angiograms were performed after intracoronary injection of nifedipine and the cinefilms were quantitated with a computerized edge detection technique [10, 11]. Since part of the results are expressed in terms of percent area (or diameter) stenosis, a critical point is the choice by the user of an appropriate reference area (or diameter). When a large vessel gives rise to a major daughter branch, the cross-sectional area of the main vessel distal to the branch point is significanty less than its area proximal to the branch point; hence, the choice of a proximal reference would not be appropriate. Conversely, the choice of an appropriate distal reference is often hampered by the presence of poststenotic ectasia and by anatomical tapering. Therefore, an alternative method was developed, similar to that used by Crawford et al. [26], which is based on the computer estimation of the 'original contour of the pre-atherosclerotic lumen', allowing the vessel to taper. The difference in area between the original lumen and the contours of the obstruction is a measure for the atherosclerotic plaque. Crawford et al. have demonstrated that such angiographic assessment of the atherosclerotic plaque by computer densitometry correlated with the cholesterol content of the corresponding human arterial specimen. Their approach includes both density and edge measurements; among these, the computer detected lumen with taper yielded the best correlation with the pathologic data [26]. The data of Crawford et al. pertain to nonbranching segments of femoral arteries; they have not been confirmed for coronary arteries in which changes in lumen caliber occur predictably at branching points and not by taper [27]. In the present as well as in earlier studies [18, 28], the user-defined and interpolated measurements were closely correlated. However, for the analysis of repeated angiograms [29, 30], the knowledge of the exact location of the reference, either proximal or distal to the stenosis, is not required when the interpolated method is used. For these theoretical and practical reasons, we favor the use of an automated definition of the reference area (or diameter) with the interpolated technique [19, 31].

From these data, obtained in a clinical setting, a curvilinear relation was found between the pressure drop across the stenosis and the minimal obstruction area as well as the percent cross-sectional area reduction. Both relations are similar to those calculated on theoretical grounds by Brown et al. [32], as well as to those experimentally derived from isolated human arteries [33] or dog experiments [34].

Such curvilinear relation is expected from the general equation of fluid dynamics showing that the pressure drop across a stenosis is influenced mainly by viscous losses in the stenotic segment and separation losses at the exit of the stenosis. For a given level of flow, the single most important determinant of stenosis resistance is its minimal cross-sectional area which appears as a second order term in both viscous and separation losses equations. In the animal laboratory, a coronary

stenosis can be characterized precisely by simultaneous measurements of flow and stenosis gradient and related to the quantitative assessment of stenosis geometry. In such experimental setting, blood flow velocity and pressure drop across the stenosis are related in an exponential fashion [35]. Recently, coronary blood flow velocity measurements were obtained in patients during heart surgery and related to the computer-based analysis of their coronary angiograms [36, 37]. It was shown that the minimal cross-sectional area was the best predictor of the physiological significance of a coronary stenosis. During cardiac catheterization, the pressure-flow relation across a coronary stenosis cannot be determined, although the feasibility of transluminal measurements of coronary blood flow velocity has been reported recently [1]. However, the pressure distal to a coronary stenosis is measured routinely during the transluminal angioplasty procedure. This has stimulated the development of very small catheters for the in vivo investigation of the functional significance of pressure drop measurements [38]. The physiological value of these measurements, even those obtained with the smallest catheters, must be questioned since the catheter impedes flow through the obstruction. Experimental data obtained in dog femoral arteries suggest that the pressure difference over the lesion is overestimated in a predictable manner dependent on the ratio of the catheter diameter over the stenosis diameter [3]. In addition, the mean pressure gradient is affected by phasic changes in flow velocity [35]. The distal coronary pressure may be affected by collaterals and is entirely determined by collateral flow when the angioplasty catheter totally obstructs the vessel. In spite of these limitations, Vogel et al. [2] have shown that the mean pressure difference measured across the stenosis during angioplasty predicted accurately the coronary flow reserve measured as the ratio of hyperemic over control myocardial contrast appearance times by digital angiography. In the present study, the pressure drop was related in a curvilinear way with the actual luminal area obtained by subtracting the area of the deflated balloon catheter from the minimal obstruction area as assessed by quantitative angiography. The major finding of this study is that the combination of pressure drop measurements across the stenosis with quantitative assessment of the luminal narrowing predicted the occurrence of exercise thallium perfusion abnormalities better than the measurements of the stenosis alone. Using the cut-off values of 0.30 for the pressure drop and 80% for the percent cross-sectional area reduction, the result of the exercise thallium scintigram was correctly predicted from the angiographic data in all but six patients. In four of them, thallium perfusion abnormalities occurred without signs of ischemia in the presence of a noncritical cross-sectional area stenosis of about 60%. These discrepancies are not surprising since many other factors such as blood density, viscosity, stenosis length and divergence angle were not accounted for [32, 33]. Two patients had normal scintigrams and exercise tests while ischemia was expected from the angiographics measurements. This can be due to the presence of coronary collaterals as shown by angiography, since previous work suggests that

these could prevent the occurrence of thallium perfusion defects during exercise [39, 40].

In summary, the functional significance of a coronary stenosis can be evaluated at rest by quantitative analysis of coronary dimensions and transstenotic pressure drop measurements. In patients with single left anterior descending coronary artery disease this allowed identification, at rest, of those lesions responsible or not for thallium perfusion defects induced by exercise.

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Chapter VIII

Early detection of restenosis after successful percutaneous transluminal coronary angioplasty by exercise-redistribution thallium scintigraphy

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Summary

The ability of exercise testing and thallium scintigraphy to predict recurrence of angina pectoris and restenosis after a primary successful transluminal coronary angioplasty (PTCA) was prospectively evaluated. In 89 patients, a symptom-limited exercise ECG and thallium scintigraphy were performed 4 weeks after they had undergone a successful PTCA. Thereafter, the patients were followed during 6.4 ± 2.5 months (mean ± s.d.) or until recurrence of angina. They all had a repeat coronary angiography either at 6 months or earlier if symptoms reoccurred.

The PTCA was considered successful if the patients had become symptom free and if the stenosis was reduced to less than 50% of the luminal diameter. Restenosis was defined as an increase of the stenosis to more than 50% luminal diameter. The ability of the thallium scintigram (presence of a reversible defect) to predict recurrence of angina was 66% versus 38% for the exercise ECG (ST segment depression and/or angina peak workload). Restenosis was predicted in 74% of patients by thallium scintigraphy but only in 50% of patients by exercise ECG.

Thus, thallium scintigraphy was highly predictive but the exercise ECG was not ($p<0.005$). These results suggest that restenosis had occurred to some extent already at 4 weeks after the PTCA in the majority of patients in whom it was going to occur.

Introduction

Restenosis after primary successful percutaneous transluminal coronary angioplasty (PTCA) occurs in 19 to 36% of cases within the first 6 months after the procedure [1–5]. This restenosis may manifest itself by changes in the patient's

clinical status and may be detected by non-invasive diagnostic tests or by the coronary angiography. Scholl et al [2] as well as Hirzel [6] have shown that an abnormal exercise ECG response and a myocardial perfusion defect on thallium scintigraphy is associated with an angiographically documented restenosis of the dilated vessel or is a sign of the presence of additional disease. The present study was performed to determine the value of early nonivasive testing in the prediction of restenosis and recurrence of symptoms. The included patients had undergone a technically successful PTCA, which resulted in a 'complete' anatomical correction. They were all free of angina pectoris up to the time of the exercise ECG and thallium scintigraphy, which were performed a median of 4 weeks after PTCA. Follow-up data regarding subsequent recurrence of symptoms and a repeat coronary angiography obtained a median of 6 months after the procedure were compared in a prospective manner with the nonivasive test results obtained at 4 weeks.

Methods

Between September 1980 and September 1983, 296 consecutive first PTCA procedures for stable or unstable angina pectoris were attempted at the Thoraxcenter; 221 were primary successes. The 162 patients from our own institution were asked to cooperate with a follow-up protocol which included an exercise ECG and thallium scintigraphy 4 to 6 weeks after the procedure, a visit to the outpatient clinic at 2 month intervals and a repeat angiography at 6–8 months. The 59 patients referred from institutions in other cities were excluded. Hundred twenty patients met the inclusion criteria for the present study: (1) 'complete' anatomical correction, i.e. no significant residual coronary obstructions after PTCA; (2) absence of anginal symptoms until the time of exercise testing; (3) ability to complete the exercise test. Thirty one patients refused the repeat coronary angiography. This report is thus based on the prospective evaluations of 89 patients, 74 males and 15 females. A single stenosis was dilated in 85 cases and two vessels in 4. The dilated vessel was the left anterior descending artery in 59 cases, the left circumflex in 9, the right coronary artery in 24 and the distal anastomotic site of a saphenous vein bypass graft on the left anterior descending coronary artery in 1 patient. PTCA was performed according to the technique of Gruentzig [1], with Schneider equipment via a femoral route. Details regarding the procedure used in our laboratory have been previously described [7, 8]. The PTCA was considered successful when the residual stenosis was less than 50% in diameter with a good run-off and filling of the distal vessel at angiography. In the 91 stenoses with satisfactory recordings, the residual pressure drop (normalized for the mean aortic pressure) was less than 0.20 in 63 cases and less than 0.40 in 25 cases.

In an attempt to reduce the restenosis rate [3, 5], all patients received nifedi-

pine, 10 mg every 2 hours for the first 8 hours following the procedure and were maintained on acetosalicylic acid 500 mg a day and nifedipine 10 mg 3–6 times a day until repeat angiography was performed. Beta adrenergic agents were stopped unless hypertension was present. The repeat angiography was performed 7.0 ± 2.3 months (mean ± s.d.) after PTCA in the patients who remained asymptomatic and 4.9 ± 2.3 months (mean ± s.d.) after PTCA in patients who had recurring angina during follow-up. The coronary angiograms were obtained in multiple views (including hemiaxial views for the left coronary artery) and were interpreted visually without knowledge of the initial noninvasive test results. The clinical definition of restenosis was an increase of the diameter stenosis of the dilated lesion above the 50% level.

In addition, quantitative analysis of the dilated stenosis was obtained in the same angiographic projection for each angiogram by means of our computer based coronary angiographic analysis system [9]. Based on these accurate and more objective measurements of stenosis severity [10], the definition of restenosis used by the NHLBI registry [4] was applied as well, i.e. an increase in stenosis ≥30% (in absolute term) from the immediate post PTCA result and/or the loss of at least half the initial gain in diameter.

The exercise studies were performed 4.7 ± 1.9 weeks (mean ± s.d.) after the PTCA. The subjects performed a symptom limited exercise on the bicycle ergometer with stepwise increments of 20 Watt every minute. The three orthogonal leads XYZ of the Frank lead system were recorded and analyzed as previously described. The reported sensitivity and specificity for the diagnosis of significant coronary disease were 85% and 90%, respectively. A 0.1 mV or greater horizontal ST depression and/or typical angina during exercise were considered as an abnormal (or positive) response. One minute prior to peak exercise, thallium (1.5 mCi) was injected intravenously. Imaging was started 5 minutes later in three views: anterior, left anterior oblique 45 and 65°. Static planar images (500 kcounts full field, zoom 2×) were obtained post-exercise and 4 hours later with a Searle Phogamma V camera. The scintigraphic images were processed on a DEC gamma-11 system with a quantification procedure developed at our institution [12]. The late image was corrected for acquisition time differences with respect to the early image. The exercise and redistribution images were registered on the basis of the detected positions of point sources taped to the patient's chest. After automated left ventricular contour detection [13] and interpolative background correction [14], circumferential profiles were computed at 6° intervals. The profiles of the early and late images were normalized for the maximum value in the early image (100%) excluding the outflow tract of the left ventricle. The analog Polaroid images from the gamma camera, the processed images and the circumferential profiles were analysed prospectively on a routine basis by three experienced observers without knowledge of the angiographic data. The thallium uptake in a total of eleven segments was scored both in the post-exercise and late images on a 5 point scale in the following manner: 0 = no

thallium uptake; 1 = severely abnormal; 2 = definitely abnormal; 3 = doubtfully abnormal; 4 = normal. The following segments were defined: postero septal, inferior, apical and antero-lateral in the anterior view; antero-septal, apical and postero-lateral in the LAO 45° view; anterior, apical, inferior and posterior in the LAO 65° view. The scores of all segments were summed per patient and the difference between late and early post-exercise sum was taken as a measure of the amount of redistribution. An increase in thallium uptake score of 2 points or more between post exercise and late images was taken as the cutoff between normal (absence of exercise-induced ischemia) and abnormal (presence of exercise-induced ischemia) scintigrams. Persistent defects without redistribution were considered to represent scars without exercise-induced ischemia. With this analysis, the previously reported sensitivity and specificity for the diagnosis of significant coronary artery obstructions were 80 and 88%, respectively [12].

The patients followed up in the outpatient clinic until occurrence of typical angina pectoris and/or a new myocardial infarction. The follow-up duration was 6.4 ± 2.5 months (mean ± s.d.). No patient died during this period.

Results are presented as mean ± standard deviation. The t test for paired or unpaired data was used whenever appropriate. The positive predictive value for restenosis (or recurrent angina) was calculated as the frequency of restenosis (or recurrent angina) in those with abnormal test results. The negative predictive value for the absence of restenosis (or recurrent angina) was calculated as the frequency of long term success in those with normal test results. Differences between correct and incorrect classifications by exercise ECG versus thallium were evaluated by the McNemar test.

Results

The characteristics of the PTCA procedure and of the exercise test are shown in Table I for the following 2 groups: (1) patients with restenosis of the dilated vessel, i.e. diameter stenosis at repeat angiography 50% (n = 35); (2) patients with longterm success (n = 54). There was no significant difference between these 2 groups in the pressure drop across the stenosis either before or after the PTCA. The exercise testing results and the recurrence of symptoms during the follow-up are summarized for both groups in Table 2. The time of exercise testing after the PTCA and the maximal workload and heart rate achieved were similar. Ninety two percent of the patients reached 80% of their predicted maximal workload. An abnormal exercise ECG was observed in 26 cases: 21 had ST segment depression, 4 had angina at peak workload and 1 patient had both.

Exercise-induced ischemia as assessed by the thallium redistribution was observed in 35 cases. During the follow-up, angina recurred in 29 cases. No patient had a new myocardial infarction in the territory of the dilated vessel. The positive and negative predictive values of each single test are shown in Table 3. Thallium

was superior to the exercise ECG both for the prediction of recurrent stenosis ($p<0.005$) and recurrent angina ($p<0.005$). In figure 1, the predictive value for recurrent stenosis of the 4 combinations of test result is shown. An abnormal scintigram was associated with a high incidence of restenosis which was not influenced by the exercise ECG result: 71% of restenosis when both tests were abnormal versus 76% when tests were discordant. Conversely, a normal scintigram was associated with a low incidence of restenosis which was also not

Table 1. Characteristics of the PTCA procedure.

		Group 1 restenosis * n = 35 pts	Group 2 longterm success n = 54 pts
PTCA procedure			
dilated vessel	LAD	25	34
(n = 93)	LCX	6	3
	RCA	5	19
	bypass	1	–
% diameter	pre-	66 ± 15 ns	62 ± 11
stenosis	post-	33 ± 12 ns	31 ± 13
	late	62 ± 14	31 ± 13
pressure drop	before	0.64 ± 0.16 (33) ns	0.61 ± 0.13 (55)
	after	0.19 ± 0.11 (35) ns	0.16 ± 0.10 (55)

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; The translesional pressure drop is normalized for the mean aortic pressure, numbers under parentheses refer to the number of available measurements; pts = patients; P values for comparison between group 1 and 2; ns = non significant; * = stenosis >50% luminal diameter at repeat angiography.

Table 2 Exercise tests results and recurrence of symptoms during follow-up.

n patients	Group 1 restenosis 35	Group 2 longterm success 54
weeks after PTCA (range)	4.7 ± 2.3 (2–11) ns	4.7 ± 1.7 (2–8)
maximal workload (% of predicted)	96 ± 13 ns	90 ± 16
maximal heartrate	140 ± 28 ns	149 ± 22
Abnormal exercise ECG	13	13
angina during test	1	3
ST depression 0.1 mV	11	10
both	1	–
Abnormal scintigram	26	9
Recurrent angina	23	6
New myocardial infarction	–	–

Abbreviations and definitions as previously.

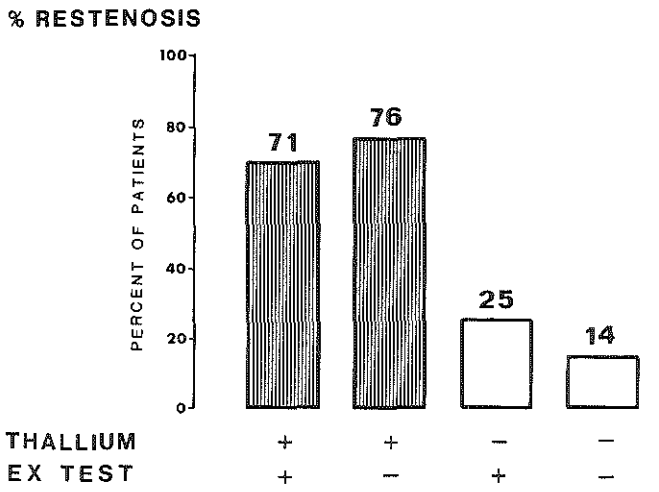

Fig. 1. The predictive value for angiographic restenosis is shown for the various possible combinations of non-invasive test results: (+) = abnormal test and (−) = normal test; EX TEST = exercise ECG. The columns shaded with vertical bars represent the patients with abnormal scintigraphy. Both tests were abnormal in 14 and normal in 42 patients; only thallium was abnormal in 21 and only exercise ECG in 12 patients.

Table 3 Positive and negative predictive values of the noninvasive tests.

	Restenosis				Recurrent angina	
	50% diameter		NHLBI criteria*			
	present (35)	absent (54)	present (37)	absent (32)	present (29)	absent (60)
Predictive value	+	−	+	−	+	−
Exercise ECG						
ST Segment	55 (12/22)	66 (44/67)	55 (12/22)	63 (42/67)	32 (7/22)	67 (45/67)
ST and/or AP	50 (13/26)	65 (41/63)	54 (14/26)	63 (40/63)	38 (10/26)	70 (44/63)
Thallium scintigraphy	74 (26/35)	83 (45/54)	74 (26/35)	80 (43/54)	66 (23/35)	89 (48/54)

Positive (+) and negative (−) predictive values of respectively abnormal and normal tests are in %; number of patients under parentheses; AP = angina during exercise; * = an increase in stenosis ≥30% from the immediate post-PTCA result and/or the loss of at least half the initial gain in diameter.

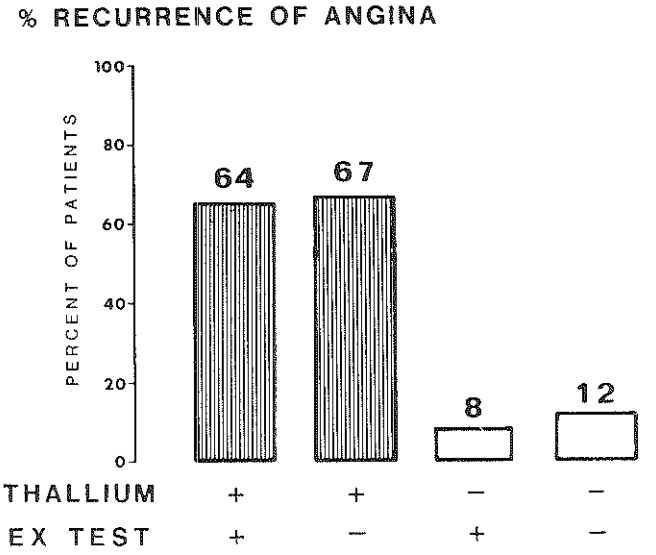

Fig. 2. The predictive value of the non-invasive tests is shown for the clinical end-point (recurrent angina); others as previously.

influenced by the exercise ECG result: 14% of restenosis when both tests were normal versus 25% when tests were discordant.

The value of combined noninvasive tests results for the prediction of recurrent angina is shown in figure 2. Angina recurred in 64% of patients with both tests abnormal and in 67% of patients with only thallium abnormal. In the presence of a normal thallium, the % recurrent angina was low, around 10%, regardless of the result of the exercise ECG.

By the NHLBI definition of restenosis based on the quantitative analysis of the angiograms, only 6 patients were categorized in another group; 37 having restenosis by these criteria. The predictive value of the noninvasive tests was not significantly different: 54% restenosis when the exercise ECG was abnormal versus 74% restenosis when the scintigram was abnormal (Table 3).

Discussion

The present report demonstrates that early assessment of myocardial perfusion by exercise thallium scintigraphy has a high predictive value for restenosis and recurrence of angina in patients who underwent a technically satisfactory PTCA. Previous studies [2, 6, 15–17] assessing the results of PTCA by noninvasive tests have focussed on the reversibility of the ischemic changes after a successful procedure and on their induction at the time of recurrence. However, more

recently, DePuey et al [18] reported that failure to increase ejection fraction or the development of a new regional wall motion abnormality during exercise radionuclide ventriculography early post-PTCA predicted restenosis at 4–12 months in 73% out of 41 patients. Their findings as well as the present study suggest that restenosis had occurred to some extent already at 4 weeks in the majority of patients in whom it was documented later. This observation raises speculations about the underlying mechanism of restenosis after dilatation. Fibrocellular proliferations as a reparative response to coronary wall laceration has been described in necropsy studies [19] and may represent the pathological substrate of early restenosis. In analogy with aortic dissection, exposure of vascular smooth muscle cells to blood may trigger an exuberant tissue reaction leading to obliteration of the false channel and eventually of the functional lumen. Preliminary data [20] from experimental angioplasty in pigs suggest that balloon dilatation is a potent stimulus to early platelet deposition and subsequent intimal hyperplasia. In this model, the reparative process was observed as early as two weeks after the procedure. If present in patients, such ongoing processes may have induced the observed perfusion abnormalities. Since only successful cases were included and the decrease in stenosis severity and in the transstenotic pressure gradient were comparable in patients with restenosis and long term success, there is no evidence that recurrence occurred predominantly in patients in whom the dilatation was incomplete. In this study, the high predictive value of the perfusion scintigram contrasts with the poor predictive value of the exercise ECG response, especially for the prediction of restenosis.

This could be explained by a lower sensitivity of the exercise ECG in the detection of moderate coronary artery narrowing, as compared to thallium scintigraphy. The combination of a normal exercise ECG with a reversible thallium perfusion abnormality could be an early indicator of the presence of a non-critical stenosis, still insufficient to induce ST segment depression during exercise [21]. Indeed, 66% of the patients with an initially abnormal scintigram became symptomatic at some time distant during the follow-up period. The problem of defining restenosis is not a trivial one. Applying the stringent criteria of the NHLBI registry to eyeball estimations of stenosis severity has major limitations, due to the large intra- and interobserver differences in interpretation, especially for stenoses between 20 and 80% [22]. Therefore, the stenoses were analysed by computerized edge detection. Although this method may not be optimal after angioplasty [9], it provides an objective and quantitative measurement, hereby avoiding unintentional bias in reading the angiograms. This complex definition of restenosis resulted, however, in similar findings as the usual clinical approach based in the presence or the absence of a hemodynamically significant stenosis (>50% luminal diameter). By this clinical definition, restenosis of the dilated artery was observed in 39% and recurrent angina pectoris in 33% of the patients.

The true incidence of recurrence is probably lower since the majority of the

patients who refused to undergo a repeat angiography were asymptomatic. The patient population is thus biased in favor of those with recurrent stenosis. The clinical implication of these findings for the routine management of PTCA patients remains to be established. Certainly we share with DePuey et al [18] the conclusion that noninvasive test early after PTCA in an asymptomatic patient is an indication for close clinical monitoring in view of the high chance of recurrence of symptoms. Currently, we feel that decisions to perform a repeat angiogram, followed by a redilatation when restenosis is found, should primarily be based on the severity of the anginal symptoms rather than on the results of the testing procedure by itself. This is analogous to the issue of bypass surgery for documented coronary artery disease in asymptomatic patients, particularly since no benefit of surgical intervention over pharmacological treatment was shown in mildly or nonsymptomatic patients [23]. As long as the outcome of prophylactic PTCA has not been studied, the procedural complications and incomplete success rates, would militate against carrying out PTCA when diagnostic testing reveals restenosis in the absence of symptoms.

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Part three:
Coronary angioplasty, a non operative treatment of acute ischemic syndromes

Chapter IX

Emergency coronary angioplasty in refractory unstable angina: immediate and follow-up results

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Summary

Percutaneous transluminal coronary angioplasty (PTCA) was performed as an emergency in 60 patients with unstable angina pectoris (UAP), refractory to treatment with maximally tolerated doses of beta-blockers, Ca-antagonists and intravenous nitroglycerine. The initial PTCA success rate was 93% (56/60). There were no deaths related to the procedure, although total occlusion occurred in four patients. Despite emergency bypass grafting all four sustained a myocardial infarction (MI).

All patients were followed for at least 6 months. Late cardiac death occurred in 2% (1/60) while 13% (8/60) had recurrent angina pectoris. There was no progression to MI. The restenosis rate was 28%, (13/46) in the patients with an initial successful PTCA, who had repeat angiography. Improved cardiac functional status after sustained successful PTCA was demonstrated by an almost normal capacity on bicycle exercise testing and absence of ischemia on Thallium isotope studies in 80%.

It is concluded that in selected patients emergency PTCA has a major place in the therapeutic options, when maximal pharmacological efforts fail.

Introduction

The clinical syndrome of unstable angina causes great concern to clinicians because of the perceived high risk of progression to myocardial infarction or cardiac death [1–6]. Given the heterogeneous coronary pathoanatomy, the variations in time and severity of clinical presentation of patients with unstable angina and the uncertainty of the extent of threatened or already necrotic myocardium, it is unlikely that any one therapeutic approach will be appropriate for all such individuals. The various options among pharmacological treatment and surgery have led to one consensus [3–6]. It is now common practice to initially stabilize

the acute ischemic symptoms with intensive medical treatment first and to reserve bypass surgery for those refractory to medical treatment [3–6]. Since PTCA has gained acceptance as an alternative form of revascularization [7] patients with unstable angina pectoris, although initially not thought suitable as candidates, because of their instability, have successfully undergone this procedure [8, 10]. Now that investigator experience has grown and as significant advances have been made in catheter technology, it was considered timely to present our experience with emergency PTCA, with a steerable dilatation catheter, as an alternative to CABG. The following specific issues were addressed: 1) can PTCA relieve ischemic symptoms and prevent progression to myocardial infarction or death in patients not responding to 24 hours of intense pharmacological therapy, 2) what is the incidence of major complications of the procedure, 3) what is the rate of recurrence of symptoms or occurrence of major cardiac events during at least 6 months follow-up.

Patients and methods

During the period January 1983 to April 1984 a total number of 1283 patients was admitted to our coronary care unit. Unstable angina pectoris was diagnosed in 217 patients (Table 1). The extent of coronary artery disease in these patients is shown in Table 1. Refractory to intensification of treatment were 109 patients. Of these, 60 patients with unstable angina pectoris satisfied all of the following criteria:

1. chest pain at rest of at least 15 minutes accompanied by reversible electrocardiographic ST-T changes without signs of cardiac necrosis such as CPK enzyme rise to twice normal, or development of Q waves.

Table 1. Selection of patients with unstable angina pectoris for emergency PTCA from 1283 patients admitted to the CCU during January 1983 to April 1984.

Total no pt.	Extent coronary artery disease					
	0V	1V	2V	3V	L.M.	
unstable angina pectoris	217	7	75	40	71	24
refractory to pharmacological treatment	109					
emergency PTCA	60	–	44	12	4	–
emergency CABG	49	–	3	7	24	15
initially stabilised with pharmacological treatment	108					
elective PTCA	33	–	25	6	2	–
elective CABG	40	–	1	7	28	4
pharmacological treatment	35	7	2	8	13	5

2. hospitalization of at least 24 hours in an intensive care unit, with continuous ECG and hemodynamic monitoring.
3. optimal medical therapy including adequate administration of beta-adrenergic blockade to a resting pulse of 60 beats/min., nifedipine and i.v. nitroglycerine to optimize preload (PCW <14 mmHg) and afterload (systolic aortic pressure 110 mmHg) in an effort to increase coronary blood supply to the jeopardized myocardium.
4. continuation of ischemic attacks, despite such therapy.
5. adequacy of the lesion for surgical intervention and/or coronary artery lesion suitable for PTCA. Suitable for PTCA were considered patients with localised disease in 1 vessel and in case of multivessel disease only if the vessel selected for attempted dilatation did not give off collaterals and absence of left main stem disease.
6. normal or slightly abnormal left ventricular function.

Sixty patients fulfilled these criteria. Their clinical characteristics are presented in table 2. The procedure was attempted in 39 patients with a lesion of the left anterior descending artery (LAD), in 10 with a lesion of the right coronary artery (RCA), in 10 with a lesion of the circumflex artery (CX) and in 1 with a lesion of a graft. In 5 patients the lesion, thought to be technically suitable for angioplasty, was found to be totally occluded at the time of PTCA; in 2 patients the lesion was already totally occluded at the time of the diagnostic angiogram. The time from admission to angiography was 2.7 ± 3.6 days and from angiography to PTCA 3.6 ± 5.6 days. PTCA was performed in 32 (53%) patients during normal working hours and in 28 (47%) at night or during the weekend.

The PTCA was performed according to the technique of Grüntzig [7] with a steerable balloon catheter either manufactured by Schneider* or by Meditech*, via a femoral route. Before the procedure 250 mg acetylsalicylic acid dissolved in 5 ml normal saline and 100 mg heparin i.v. were given; during the procedure a continuous drip of rheomacrodex was given. A Zucker pacing electrode was positioned in the right ventricle. To prevent coronary artery spasm, nifedipine 0.2 mg or nitroglycerin (disosorbide dinitrate 1–3 mg) was given into the coronary artery and this was repeated when necessary [11]. Only the ischemia-related

Table 2. Clinical characteristics of 60 patients with unstable angina pectoris and emergency PTCA.

males:	51 (85%)
age (years): mean	59 (range 36–73)
previous coronary artery bypass grafting	5 (8%)
previous myocardial infarction	23 (38%)
new onset angina pectoris at rest	29 (48%)
worsening of pre-existing stable angina	20 (33%)
post myocardial infarction angina:	11 (18%)
left ventricular ejection fraction:	0.60 ± 0.09

coronary lesion was dilated in cases where multivessel disease was present. The ischemia related lesion was determined by the localisation of the recorded electrocardiographic changes.

Electrocardiographic changes in leads V_1–V_5 were associated with lesions of the LAD; changes in I, AVL and V_6 with the marginal branch of the CX or diagonal branch of the LAD; changes in inferior leads with either the RCA or the CX. The transstenotic pressure gradient was measured before and after each dilatation. The inflation pressure varied from 2–12 atm for a period of 10–60 seconds; on the average the pressure applied ws 9.8 ± 1.8 atm for a total period per dilatation of 218 ± 111 seconds.

A PTCA procedure was considered successful when clinical relief of acute ischemic symptoms with a reduction in the severity of the lesion to less than 50% of the luminal diameter or a reduction of the transstenotic pressure drop to less than 0.30 (the pressure drop normalized for mean aorta pressure) [12].

After the procedure all patients were monitored for 24 hours in the CCU where electrocardiograms and enzyme levels were measured. The patients were usually discharged 3 days after the procedure. They were kept on treatment with nifedipine 40–60 mg daily and acetylsalicylic acid 500 mg daily during a period of 6 months with the aim to prevent spasm or platelet aggregation. During the procedure a surgical team provided standby. A peri-operative myocardial infarction was diagnosed when a new Q wave developed in the 12-lead electrocardiogram. Clinical follow-up information was obtained at 3, 6 and 12 months. Either from a visit to the outpatient clinic or by information obtained from the referring physician. Cardiac death, occurrence of myocardial infarction and recurrence of angina pectoris were tabulated. The majority of patients underwent an exercise test with thallium scintigraphy and repeat angiography. The patients performed symptom limited exercise on the bicycle with stepwise increments in load of 20 W every minute. The 3 orthogonal leads X, Y, Z of the Frank lead system were recorded and analyzed. A 0.1 mV or greater horizontal ST depression during exercise was considered a positive response.

Exercise Thallium scintigraphic imaging was performed in the anterior, left anterior oblique 45 and 65° views, immediately after injection of 1.5 mCi of Thallium 201 at peak stress. The redistribution images were obtained 4 hours later. Images were obtained using a gamma camera (Searle Phogamma V camera)* and processed with a computer interface as previously described [13]. Defects with redistribution were considered to represent exercise-induced ischemia. Persistent defects without redistribution were considered as scars. Repeat angiograms were obtained in multiple views including hemiaxial angulation and were interpreted by observers without knowledge of the patient's clinical status. Restenosis was defined as an increase of the luminal diameter narrowing of the dilated lesion to beyond 50%. The severity of the stenosis before and after PTCA and at control was calculated with the help of a computer-based coronary angiography analysis system [14]. Data are expressed as mean ± SD.

Results

The PTCA procedure was initially successful in 93% (56/60 patients). The initial success rate in patients with a totally occluded vessel was 86% (6/7). The mean pressure difference across the stenosis before PTCA was 61 ± 13 mmHg and after PTCA 18 ± 12 mmHg. The diameter stenosis before PTCA was 69 ± 13% and after successful PTCA 28 ± 10%. The success rate for the LAD was 95% (37/39), for the RCA 90% (9/10), for the LCX 90% (9/10) and for the bypass 100% (1/1). In 7% (4/60) the procedure was complicated by total occlusion of the vessel; all 4 patients sustained a myocardial infarction (3 developed pathologic Q waves and 1 had a significant enzyme rise) despite urgent CABG. There were no deaths related to the procedure.

All patients were followed for at least 6 months after successful PTCA; half of these for 12 months (table 3). One patient died due to myocardial infarction. Seven patients had recurrent angina, all within 6 months after PTCA; six were treated either by repeat PTCA or by CABG. The 4 patients with unsuccessful PTCA and urgent CABG were all followed for 12 months; one had recurrence of angina pectoris.

Table 3. Late results after initial successful PTCA in 56 patients with refractory unstable angina.

Follow-up period in months	3	6	12
Number patients	56	55	27
Death	1	0	0
Non-fatal MI	0	0	0
Recurrence AP	5	2	0
re-PTCA	1	1	0
CABG	3	1	0
medical treatment	1	0	0

Table 4. Exercise ECG testing and Thallium scintigraphy after successful PTCA and uneventful follow-up (49 patients).

Extent CAD	No pts	Exercise capacity % achieved of normal value	ST-segment depression 1mm	Thallium* reversible perfusion defect
1 vessel disease	34	99 ± 17	2 (6%)	6/30 (20%)
multi-vessel disease°	13	93 ± 15	2 (15%)	2/12 (17%)
Total	47	97 ± 16	4 (8%)	8/42 (19%)

* only 42 patients with Thallium scintigraphy available.

° pt with MV-disease in whom only the ischemia-related vessel was dilated.

Table 5. Relation of repeat angiographic findings and recurrence angina pectoris after successful PTCA in 46 patients.

	angina pectoris no pts	no angina pectoris no pts
Re-stenosis	6	7
No re-stenosis	0	33

The exercise test data are presented for patients with successful PTCA and an uneventful course during follow-up (49 patients) (table 4). ECG exercise tests were available in 96% (47/49) and Thallium scintigraphy in 86% (42/49). The stress tests were performed 2.1 ± 1.7 months after the procedure. The exercise capacity was virtually normal in all. Although symptom-free 8% (4/47) showed ischemic ST-depression and 19% (8/42) reversible perfusion defects. There were no differences between single vessel or multivessel disease patients. A repeat angiogram was available in 9 of the 10 patients with a positive stress test (either ST-segment depression and/or reversible perfusion defect). The restenosis rate in these asymptomatic patients was 33% (3/9 patients), whereas 2 other patients later became symptomatic and then showed restenosis.

Repeat angiograms were available in 84% (46/56) of the patients with an initially successful PTCA. In 10 patients angiography was not repeated; one patient had recurrent angina, eight were symptom free and one had sustained a fatal myocardial infarction. The angiograms were performed 2.3 ± 1.8 months after PTCA.

Restenosis occurred in 13 patients (28%) of which 7 were symptom free (table 5). All 6 patients with recurrent angina pectoris had restenosis.

At repeat angiography the diameter stenosis in asymptomatic patients was $34 \pm 18\%$; in the symptomatic patients this was $68 \pm 8\%$.

Discussion

Management in patients with unstable angina pectoris is firstly directed towards relief of acute ischemic symptoms and secondly to the prevention of progression to myocardial infarction [4–6]. This syndrome of unstable angina is nearly always associated with high grade fixed coronary narrowing [15–17], leading to restricted antegrade flow. Other factors, such as generalized increased vasomotor tonus, severe localized spasm of the healthy wall in eccentric lesions or platelet deposition up to complete thrombosis also play a role [18–22]. Pharmacological treatment therefore aims either to decrease the myocardial oxygen demand by reduction in heart rate (bedrest, β-adrenergic blockers), by adjusting pre and afterload pressures (nitrates, Ca-antagonists) and by cardioprotection of the stunned myocardium (Ca-antagonists with β-adrenergic blockers) or more directly to increase

oxygen supply by coronary vasodilation (Ca-antagonists, nitrates) or by inhibition of platelet deposition and thrombus formation (acetylsalicylic acid). While, with optimal medical treatment, consisting of hospitalization and a combination of β-adrenergic blockade , Ca-antagonists and i.v. nitroglycerine [18, 23–26] adjusted during continuous ecg and hemodynamic monitoring and administered in maximally tolerated doses the majority will stabilise, a subgroup of patients will continue to have pain and presumably ischemia. Previous studies have indicated that high mortality and cardiac event rates occur in this subset of patients [3, 4] [23–26]. CABG has been suggested as the treatment of choice.

PTCA has been shown to improve coronary blood flow by reducing the severity of the obstruction in selected patients with stable angina pectoris [7]. Therefore the rationale of PTCA in patients refractory to medical treatment lies in its potential to provide the revascularisation of the jeopardized myocardium, without the need for CABG with its attendant risks of perioperative myocardial infarction or death [27]. However, PTCA often causes vasospasm in patients with stable angina and if vasospasm or other dysregulations are a frequent and significant factor in unstable angina, then intracoronary instrumentation may be unduly hazardous. The study of Williams et al [8] and more recently of Meyer et al [9] and Faxon et al [10] showed that PTCA could be performed safely and successfully in unstable angina.

The patients who underwent emergency PTCA in our study constitute a small subgroup of the large spectrum of patients with unstable angina. Our selection process implied that the patients had to be refractory to intensive medical therapy after at least 24 hours of hospitalization and had coronary lesions technically suitable for bypass surgery. From this group were ultimately selected for emergency PTCA those who had a lesion of the ischemia-related vessel suitable for PTCA, no left main stem disease and a normal or only slightly abnormal left ventricular function.

In our study PTCA was successful in 93% of the patients in whom the procedure was attempted. This success rate is higher than the 61–76% reported by the three above cited studies, but is comparable to the 85–90% reported in series of stable angina pectoris [28–30]. It should be emphasized here that the procedure in our study was performed with a steerable dilatation catheter system, which has been shown to increase the initial success rate to 10% above that achieved with a non-steerable dilatation catheter, as was used in the other studies. The NHLBI PTCA Registry [30] reported that acute coronary events associated with PTCA occurred more frequently in patients with unstable angina.

In our study the procedure resulted in progression to coronary artery occlusion in 7% (4/60). In 2 patients the vessel occluded during the attempts to cross the lesion apparently due to damage of the vessel by the guide wire at the site of the lesion. In 2 patients the dilatation resulted in dissection with total occlusion. These patients were promptly revascularised with CABG yet all developed a myocardial infarction. Although the prognosis of such patients without CABG is

uncertain, we feel that these cases show again that immediate surgical standby remains a requirement to assure patient safety. In actual fact there were no deaths related to the PTCA procedure. These results compare favorably with the complication rates of hospital mortality and myocardial infarction of 0.9% and 9%, reported by the NHLBI PTCA Registry [10].

During a follow-up of at least 6 months after successful PTCA there was clinical progression of disease in 15% (8/56) with fatal myocardial infarction in 2% (1/56) and recurrence of angina pectoris in 13% (7/56) The patient who died was symptomfree during 1 week after the procedure and died after recurrent infarction. At autopsy the initially successful dilated lesion was totally occluded by a fresh thrombus. This recurrence of symptoms after dilatation was corroborated by an angiographically determined restenosis in all symptomatic patients. The angiographic restenosis rate was 28% (including 10% who were asymptomatic). This rate is similar to that reported in stable angina pectoris (20–30%) [7] and unstable angina pectoris (22%) [9].

The results of ECG exercise testing and Thallium scintigraphy indicated that in asymptomatic patients after PTCA, the exercise capacity was virtually normalised, although there was a 8% incidence of an abnormal electrocardiographic response and a 19% incidence of reversible perfusion defects. These abnormal responses occurred to the same extent in patients with one-vessel disease as in patients with multivessel disease, in whom only the ischemia related vessel was dilated. These results support our opinion that PTCA of the ischemia-related vessel in patients with multivessel disease with refractory unstable angina pectoris is an attractive approach at least for the shortterm.

Thus, at an acceptable risk, and with a high initial success rate, PTCA can restore coronary blood flow in refractory unstable angina, these results must compete with those of emergency CABG.

A recent, non-randomised study [10], compared the myocardial infarction and death rates in a comparable group of patients with 1-vessel disease and unstable angina pectoris who underwent either CABG or PTCA. From these data it appears that PTCA compares favorably with CABG. The procedure is associated with similar mortality and morbidity rates, but a more marked improvement in symptoms can be expected after PTCA. Unfortunately, the data available from that study do not contain information about patients with refractory unstable angina, but support our opinion that PTCA, as an emergency procedure, in selected patients with unstable angina refractory to medical treatment, is very efficacious.

* Schneider-Grüntzig
Steerable balloon dilatation system
Zürich/Switzerland

* Meditech
Coronary Balloon Dilatation Catheter System
Watertown M.A.
U.S.A.

* Searle Radiographics Inc.
Des Plaines Illinois 60018
U.S.A.

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Chapter X

Is transluminal coronary angioplasty mandatory after successful thrombolysis? A quantitative coronary angiographic study

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Summary

Percutaneous transluminal coronary angioplasty has been advocated as a mandatory procedure to prevent reocclusion after successful thrombolysis in acute myocardial infarction. This study describes our experience with both procedures over a 12 month period. Out of 105 patients catheterized in the acute phase of myocardial infarction, 64 were recanalized with 250.000 units of streptokinase, while in 25 patients recanalization could not be achieved. In the remaining sixteen, the infarct-related vessel was patent at the time of the procedure. Eighteen of the 78 patients who had a patent infarct-related vessel at the end of the recanalization procedure underwent transluminal angioplasty immediately afterwards.

Postlysis angiograms were analyzed quantitatively with a computerized measurement system. The contours of the relevant arterial segments were detected automatically. Reference diameter, minimal obstruction diameter, length of the lesions, and percentage diameter stenosis were averaged from multiple views. In 31% of our patients a diameter stenosis of less than 50% was found, whereas one of 70% or more was seen only in 19% of the patients. Eleven stenotic lesions, recanalized at the acute stage, reoccluded in the short term, and in the long term eight other patients sustained a reinfarction in the same myocardial territory. Seventeen of these 19 recanalized lesions had a diameter stenosis of 58% or more.

In view of these results, we felt justified in combining recanalization and angioplasty in 18 patients selected from the most recent admissions. In these patients, the mean diameter stenosis decreased from 59% to 30% and mean pressure gradient from 41 to 8 mmHg. Late follow-up showed reocclusion in one case.

Although percutaneous transluminal coronary angioplasty does not seem to be mandatory at the acute stage in the majority of patients, it is feasible to undertake

in one sitting and seems to prevent reocclusion in patients selected on the basis of quantitative angiographic criteria.

Introduction

Salvage of ischemic but still viable myocardium around areas of myocardial infarction is currently a topic of much clinical interest. The removal of obstruction of the nutrient artery by intracoronary thrombolysis in the first hours after the onset of myocardial infarction [1–3] has provided a new approach which is undergoing randomized trials in our own and other institutions [4–6]. Since there is often residual stenosis, additional transluminal angioplasty and/or coronary artery bypass grafting have been advocated as a mandatory procedure after successful recanalization. It has been argued that a severe residual stenosis in the area of the previous occlusion might cause reocclusion over the ensuing days [7–11]. In order to elucidate this question, quantitative angiographic analysis was applied to recanalized vessels of 78 patients who had an open infarct related vessel at the end of the procedure. Tentative answers were formulated on three questions: How severe are the residual lesions after 'successful' thrombolysis? Is it possible to identify those lesions that are liable to re-occlude in the short term? In order to prevent re-occlusion after initial successful recanalization, is transluminal angioplasty a mandatory procedure?

Patients and methods

Between September 1980 and December 1982, coronary recanalization was attempted in 105 patients. Different procedures were used since our first experience with intracoronary thrombolysis in September 1980. They have been described elsewhere [4]. In the current randomized trial, patients below 65 years of age were selected, without a history of haemorrhagic diathesis of previous cerebrovascular accident. On admission all patients suffered from chest pain lasting less than four hours. The electrocardiogram showed typical myocardial infarction with ST elevation. The combination of hypotension (systolic pressure below 90 mmHg) and sinus tachycardia (heart rate over 100 beats/minute) led to temporary exclusion, but if the hemodynamic condition of the patient returned to normal quickly, he could still be included in the study. Informed consent was obtained from all patients assigned to thrombolytic treatment. Immediately after admission, an infusion of glyceryl trinitrate was started and as soon as possible the patient was transferred to the catheterization laboratory. Prophylactic lidocaine was given intravenously in a dose of 2 mg/min.

Technique of intracoronary thrombolysis

After puncturing the femoral vein and artery a pacemaker catheter was positioned in the right ventricle. Heparin 50 mg, was administered intravenously as well as 250 mg acetosalicylic acid and 100 mg diadresone F®. A nonionic contrast agent (Amipaque®) was used as a contrast medium for coronary angiography of the artery suspected to be thrombosed; subsequently 0.2 mg nifedipine was injected into the occluded artery over a period of three minutes, while the aortic pressure was monitored.

Coronary angiography was then repeated to evaluate the spasmolytic effect on the coronary occlusion. Intracoronary perfusion with streptokinase was carried out at a rate of 4000 units per minute to a maximum of 250.000 units of streptokinase, diluted in 500 ml physiological solution at a flow rate of 8 ml per minute. Coronary angiograms were repeated every 15 minutes until the chest pain disappeared. The appearance of ventricular extrasystoles or any conduction disturbance was an additional reason to revisualize the artery. If there were no signs of recanalization, an attempt was made to administer streptokinase locally in a higher concentration by passing a thin catheter (French 2 or 3) with a radiopaque tip through the Judkins catheter (French 8). After the procedure, selective coronary angiography in multiple projections was performed with an ionic contrast medium (Urografin® 76%).

All arteriograms were recorded on Kodak 35 mm cinefilm at the rate of 25 frames/s. The stenotic areas were filmed in two different projections in stenoses of the right coronary artery and of the left circumflex coronary artery, and in at least three projections, including one cranio-caudal, in stenoses of the left anterior descending artery.

Technique of percutaneous transluminal coronary angioplasty

In 18 patients an attempt was made to dilate the residual stenosis. In 16 patients, PTCA was performed in the same session, 20 to 60 min after the end of streptokinase infusion. In two other patients, PTCA was performed in a second session, respectively 8 hours and 12 days later. Via a 9 F, 16 cm long introducing sheath, a guiding catheter was directed into the stenotic area under fluoroscopic and pressure control. In four of the 18 successfully treated cases, we used a balloon catheter with an outer diameter of 3.7 mm, in the 14 other patients its outer diameter was 3 mm. The mean pressure gradient across the stenotic lesion was computed on line after 20 seconds of data acquisition. Two to 9 (mean 4.5; s.d. 2.3) balloon inflations were performed for a period of 10 to 70 s (mean 49; s.d. 12) at a pressure of 4 to 8 bar (mean 6; s.d. 1). After the dilatation procedure the sheath was left in place for the next 24 hours, while the patients were monitored in the coronary care unit.

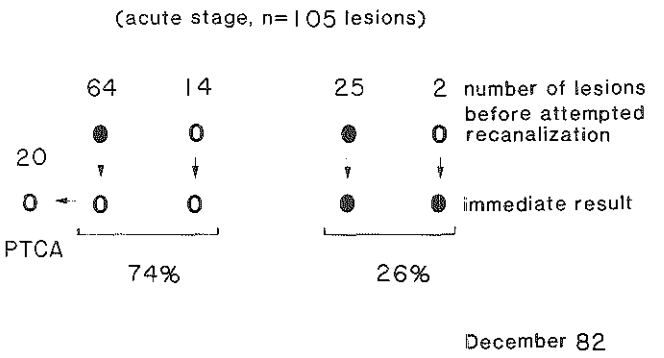

Fig. 1. Results of attempts at intracoronary thrombolysis in 105 patients. The upper line represents the initial angiographic findings, the lower line the state of the infarct related vessel at the end of the procedure. ● = occluded vessel; ○ = patent vessel.

All patients received heparin (20.000 U/24 h) followed by oral coumarin until discharge from the hospital. Anticoagulants were continued after discharge in patients with left ventricular aneurysm or recognized mural thrombus in the left ventricle. In addition, nifedipine was given, 10 mg every four hours, for two days in patients treated with streptokinase [12].

Quantitative angiographic analysis

The quantitative analysis of selected coronary segments was carried out with the Cardiovascular Angiography Analysis System (CAAS). The severity of a coronary obstruction was determined in terms of the interpolated percentage diameter stenosis measurement.

Results

Patency of the infarct-related vessel, acute and chronic stage

The angiographic findings at the beginning and at the end of the recanalization procedure are given in figure 1. In 64 patients, thrombolysis was successful and after recanalization, transluminal angioplasty was performed in 20 of these 64 patients. In 16 other patients the infarct related vessel was found to be patent at the first coronary angiogram. In two of the 16 cases, occlusion of an initially patent artery occurred during the procedure. Thus, 78 infarct related vessels were patent at the end of the catheterization procedure. In 25 patients we did not succeed in recanalizing the thrombosed arteries.

Fifty-seven patients, excluding those who had undergone PTCA in the acute

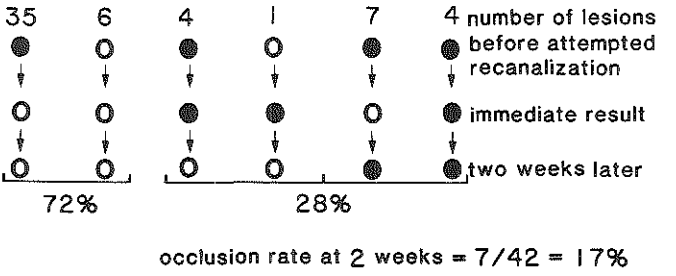

Fig. 2. Infarct related vessel patency at the chronic stage (two weeks after attempted thrombolysis) in 57 patients. ● = occluded vessel; ○ = patent vessel.

phase, agreed to be restudied angiographically two weeks later (figure 2). In forty-one patients, the infarct related vessel was still patent at the chronic stage. Five lesions, which had remained occluded at the acute stage, were found recanalized at this point; in seven other patients the coronary arteries which had been successfully recanalized at the acute stage were now found to be reoccluded. This observation suggests a reocclusion rate of 17% two weeks after recanalization.

Moreover, in the long term follow-up (mean 8.3 months) eight other patients sustained a re-infarction in the same myocardial territory, which was documented with the electrocardiogram and cardiac enzymes: two of them were restudied angiographically and in one patient the infarct related vessel had reoccluded. Finally, four lesions which had remained occluded at the acute stage were still occluded at the chronic stage.

Quantitative angiographic analysis

The individual data of the quantitative analysis of 75 stenotic lesions are given in figure 3. Three lesions could not be analyzed because of the poor quality of the angiograms. Each depicted value represents the average value of measurements obtained in different angiographic projections. The median value for the reference diameter is 2.98 mm, whereas the 10th and 90th percentiles are 2.22 mm and 4.20 mm, respectively; the median value for the minimal obstruction diameter is 1.32 mm, and the values of the 10th and 90th percentiles are 0.78 mm and 1.88 mm, respectively. As for the length of the lesion, the median value is 9 mm, while values of the 10th and 90th percentiles are 5 and 16 mm, respectively. Figure 4 is a histogram of the percentage diameter stenosis measured on 75 stenotic lesions after the successful thrombolysis. At the acute stage, the median value for the percentage diameter stenosis is 58% in this group of 75 patients; the values of the 10th and 90th percentiles are 37% and 74%, respectively. A percentage diameter stenosis less than 50% is measured in 31% of the patients, whereas a diameter

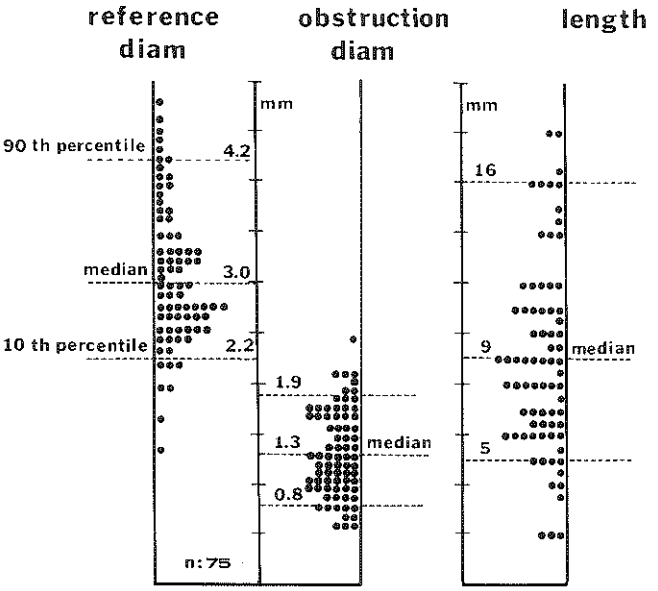

Fig. 3. Individual data for the reference and obstruction diameters as well as the length of the obstructions of 75 lesions. The dotted lines represent the 10th and 90th percentiles and the median values.

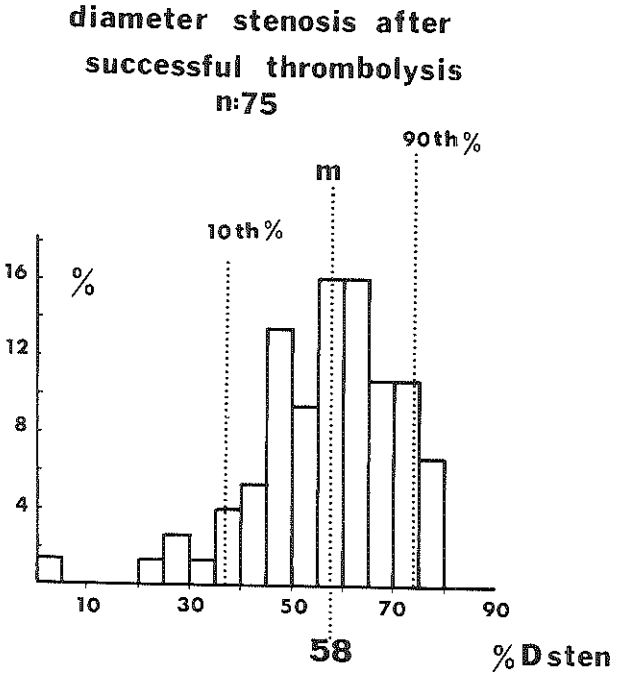

Fig. 4. Histogram (in percentage distribution) of the percentage diameter stenosis measured on 75 lesions after successful thrombolysis. The median value and the 10th and 90th percentiles are given.

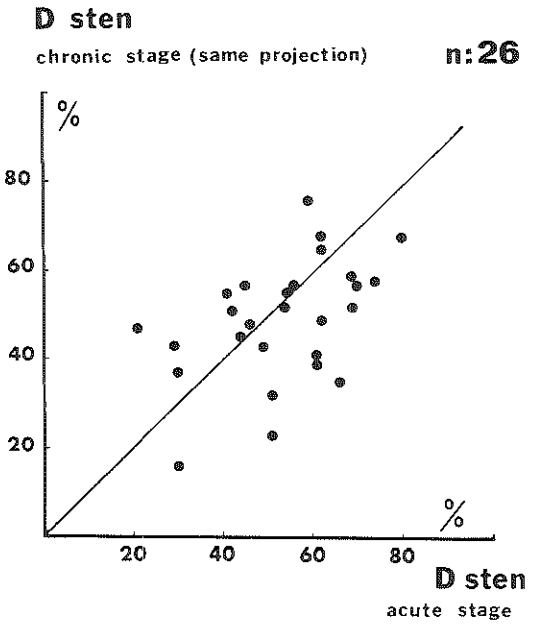

Fig. 5. Percentage diameter stenosis of 26 stenotic lesions analyzed in the same projection at the acute and chronic stage.

stenosis greater or equal to 70% is seen only in 19%. When comparing the percentage diameter stenosis in a subgroup of 26 individual lesions, analyzed in identical projections in the acute and chronic stage, no significant improvement or deterioration of the recanalized lesions at the chronic stage could be demonstrated (figure 5).

There are, of course spectacular individual changes in diameter stenosis, but for the whole group the percentage diameter stenosis does not change significantly: $54 \pm 16\%$ at the acute stage versus $48 \pm 14\%$ at the chronic stage.

The percentage diameter stenosis of eight recanalized lesions in patients who initially underwent a successful recanalization and subsequently sustained a reinfarction in the same myocardial territory is shown in figure 6. Six of eight stenotic lesions had a percentage diameter stenosis greater or equal to 58% (the median value) immediately after thrombolysis. The second column represents 11 stenotic lesions which reoccluded at the acute stage ($N = 4$) or at the chronic stage ($N = 7$) after they had been recanalized. All of them had a percentage diameter stenosis greater than or equal to 58%. The diameter stenoses of 14 stenotic lesions found to be patent at the first coronary angiogram during the acute phase of their myocardial infarction are also given. Nine of them had a diameter stenosis less than 58% (median value).

From these data it appeared that reocclusion and recurrent myocardial infarc-

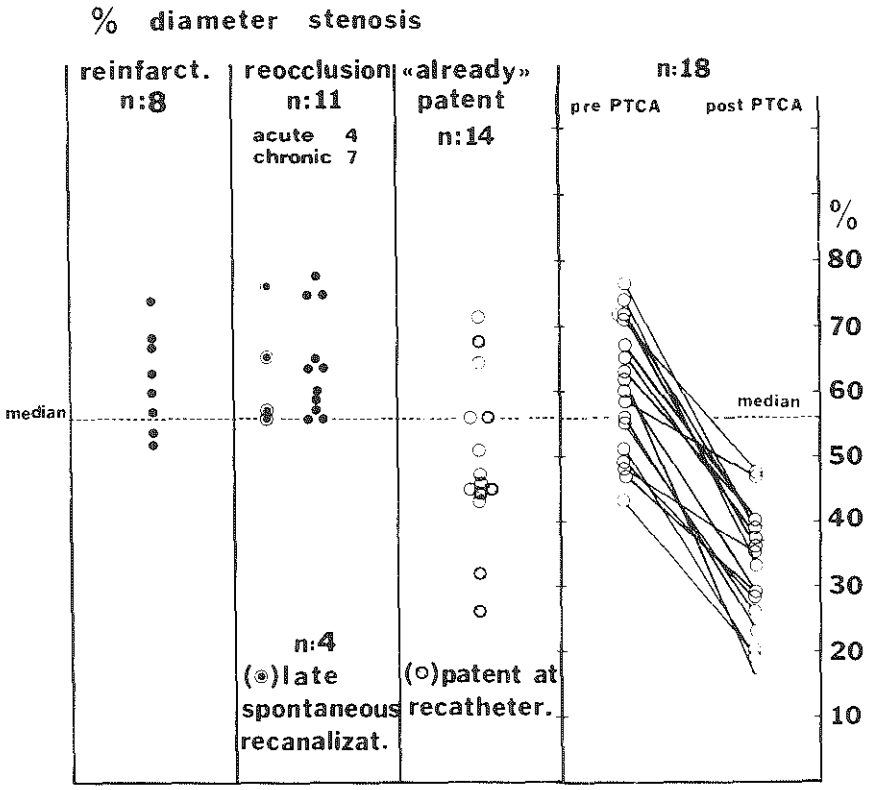

Fig. 6. Percentage diameter stenosis of coronary lesions in a subset of patients with reinfarction, reocclusion, late 'spontaneous recanalization' or with 'already' patent infarct related vessels. In the last column the changes in percentage diameter stenosis after PTCA are given.

tion were more frequent in patients with greater than 58% diameter stenosis after recanalization. The angiographic results of the combined procedure performed in 18 patients are also shown. Although the selection and decision to perform angioplasty had been based on a visual evaluation of the severity of the lesion at the time of the procedure, it appears retrospectively that 13 of the 18 lesions had a diameter stenosis greater than 58% after thrombolysis. In these 18 patients angioplasty decreased the average percentage diameter stenosis from 59% (s.d.: 9.9%) to 30% (s.d.: 9.9%) and the minimal obstruction diameter increased from 1.3 mm (s.d.: 0.4 mm) to 2.2 mm (s.d.: 0.3 mm). This reduction in diameter stenosis was highly significant ($p<0.0001$) and was associated with a significant decrease in mean pressure gradient from 41 mmHg (s.d.: 17 mmHg) to 8 mmHg (s.d.: 5 mmHg) (Figure 7). On the basis of the changes in pressure gradient, dilatation had not been necessary in two of these patients.

Fifteen out of the 18 patients who underwent PTCA were restudied angiographically after a mean follow-up of four months (range from 10 days to 11

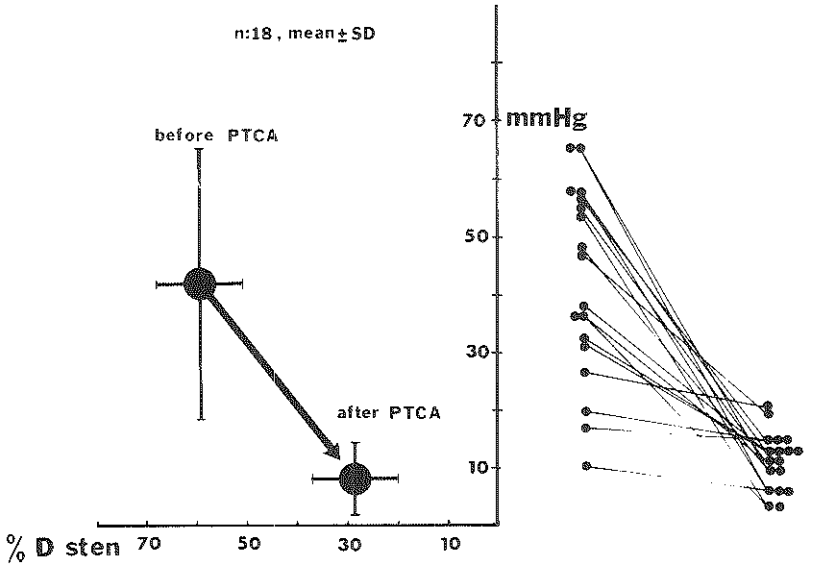

Fig. 7. Relation between the percentage diameter stenosis and the mean pressure gradient before and after PTCA.

months). In all but one, the dilated vessel was patent. One patient developed exertional angina three months later. A restenosis at the site of the previous occlusion was successfully dilated a second time.

Discussion

In this chapter it is shown that intracoronary streptokinase infusion and percutaneous transluminal coronary angioplasty can be carried out in the same session in an effort to enhance reperfusion. The issue, however, is not whether these combined interventions can be performed safely in the setting of acute infarction, but rather whether one is justified in doing so. The present work is a tentative answer to this question and its conclusions are based on the results of quantitative angiographic analysis of recanalized vessels.

Since at the end of the procedure, 31% of our patients had a recanalized vessel with a percentage diameter stenosis below 50%, whereas a diameter stenosis greater than 50% was seen in the remainder, we had no evidence of a major residual thrombus at the site of the stenosis. No retention of contrast medium or staining of a distal thrombus was seen, so residual clot, reported by others [13–15] appears unlikely as well. Furthermore, it has been the custom to continue the streptokinase treatment for about 30 minutes after patency has already been established.

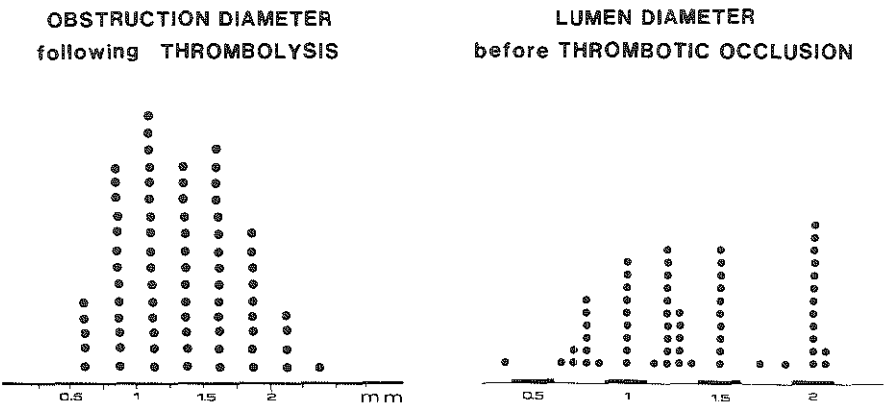

Fig. 8. Lumen diameter 'before thrombotic occlusion' in 63 patients with fatal infarct (modified with permission from Fulton [22]) compared with our *in vivo* angiographic measurement of obstruction diameter after thrombolysis.

On the other hand, severe residual stenosis of the recanalized vessel has been reported by other groups [10,16]. Their reports are based on visual and therefore subjective interpretation of the stenotic lesions. Overestimation and excessive variations by intra- or interobserver error have been reported [17, 18]. These discrepancies led us to evaluate the exact condition of the stenotic lesions after successful lysis by an objective, computer aided, interpretation.

In 14 cases with clear clinical, electrocardiographic, and enzymatic signs of an acute infarction, the diseased vessel was patent at the time of coronary angiography. In these patients long lasting vasospasm superimposed on organic lesions may have led to transient occlusion and myocardial infarction [19, 20]. Another possibility is that the clot had already lysed in the meantime. In nine out of these 14 patients, the infarct related vessel had a mild stenotic lesion, a factor that might have facilitated the reopening of the vessel. This is the more likely as these patients were started on an intravenous perfusion of glyceryl trinitrate before intracoronary lysis was attempted. In patients with transmural acute myocardial infarction and coronary arterial thrombi, histologic sections of coronary arteries have been shown to be narrowed by the atherosclerotic plaque alone to 33 to 98% (mean 81%), at the site of the thrombus [21]. When histological cross-sectional areas are compared to cross-sectional areas derived from diameter measurements, our quantitative angiographic results *in vivo* are consistent with the histologic findings. Furthermore, it is remarkable how closely the obstruction diameters after successful thrombolysis correspond with the postmortem findings reported by Fulton [22] as shown in figure 8.

In one third of our patients the myocardial infarction had occurred when the relevant artery showed a stenosis of less than 50%. Gertz et al. have shown experimentally that endothelial damage and thrombus formation may occur at

the site of focal arterial constriction even when the reduction in luminal diameter by itself is insufficient to alter significantly the rate of flow [23].

As shown by Fulton in his elegant study on the morphology of coronary thrombotic occlusions, atherosclerotic lesions are usually of a complex nature [22]. In two thirds of his cases, a break or a tear in the luminal lining exposed blood flowing to the material composing the underlying lesion. He postulated that this was the probable cause of platelet aggregation and fibrin deposition [24, 25]. In half of his cases, a haemorrhagic dissection was found which resulted in an apparent reduction of the lumen. Successful thrombolysis could again expose the material of the atheromatous lesion to flowing blood.

Whether the thrombogenic activity of this material would be as active as it was in the first instance remains speculative, but secondary thrombotic occlusion may occur. Accordingly, there are strong theoretical reasons for adopting antithrombotic measures after successful thrombolysis. On the other hand, instrumental dilatation of the coronary artery stenosis underlying the occlusive thrombus might produce desquamation of endothelium and shearing of the superficial portion of endothelial plaque, possibly altering its thrombogenic propensity. Subsequent fibrosis and healing appear to cause further enlargement of the lumen and thereby may improve the local rheological conditions [26]. Thus, arguably, it might be advisable to perform angioplasty even in patients with a stenosis of less than 50%.

Reported rates of reocclusion vary between less than 10% [27] to 25% [28]. In this study two weeks after thrombolysis, the reocclusion rate was 17%. Moreover, during follow-up, eight patients sustained reinfarction in the same myocardial region, so that reocclusion and/or reinfarction might affect 25% of our patients who had undergone a successful recanalization. Thus it seems rational at the acute stage to dilate recanalized arteries with a residual stenosis greater than 58% since these stenotic lesions are liable to early reocclusion. This concept was supported by our observations that during streptokinase infusion, reocclusion occurred in four patients (figure 6) despite intravenous or intracoronary administration of glyceryl trinitrate or nifedipine. Here PTCA might have been the only way to restore blood flow adequately and to prevent immediate reocclusion. As emphasized by Meyer et al., the advantages of the combined procedure are savings in time and money [11]. The same introducing sheath can be used, the catheterization laboratory equipment and the personnel have to be used only once, and it appears to be less strenuous for the patient. To date no reocclusions have occurred during such immediate dilation of the critical stenosis. Fifteen out of the 18 patients who underwent PTCA were restudied angiographically after a median follow-up of four months (range from 10 days to 11 months). In all but one patient, the dilated vessel has remained patent. All 17 patients have been followed at the outpatient clinic at three months intervals. The mean period of follow-up has been seven months and the longest one year. None of these patients has sustained a reinfarction thus far.

These observations indicate that PTCA immediately after thrombolysis is a safe and reasonable procedure when after lysis of the obstruction a 58% stenosis is still present. This combined approach seems to result in a lower rate of reocclusion or reinfarction than thrombolysis alone. As further randomized trials are necessary to show the ultimate benefit of thrombolysis in acute myocardial infarction, it is recommended that during them the additional value of immediate PTCA is investigated.

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Chapter XI

Additional value of immediate coronary angioplasty following intracoronary thrombolysis in acute myocardial infarction

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(Material contained in this chapter has been published in part in JACC 1986, vol 7, pp 718-728 and pp 729-742).

Summary

A total of 533 patients with acute myocardial infarction of less than 4 hours duration was enrolled in the multicenter randomized trial of intracoronary thrombolysis compared to conventional treatment. In two of the 5 participating centers, an additional coronary angioplasty immediately after thrombolysis was attempted in 46 patients.

According to the treatment allocation and early and late patency of the infarct-related vessel, patients were subdivided into 5 groups: conventionally treated (group A); successful coronary angioplasty following thrombolysis with persistent patent infarct-related vessel (group B); late patency of the infarct-related vessel after thrombolytic therapy without angioplasty (group C); persistent occlusion despite attempted recanalization (group D); and initially successful recanalization with late re-occlusion (group E). The highest global ejection fractions were observed in group B ($54 \pm 10\%$) and in group C ($55 \pm 13\%$), while the lowest ejection fractions were found in group A ($47 \pm 14\%$) and in group D ($45 \pm 16\%$). The sequential changes in global ejection fraction from the acute to the chronic stage was $+4\%$ ($p = 0.05$) in group B and -4% ($p = 0.05$) in group E, while no significant changes could be demonstrated in the other subsets of patients. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to 3 months after the intervention. This was supported by analysis of regional myocardial function of the infarct zone ($+16\%$ improvement, $p = 0.01$). The longterm clinical follow-up (median 24 months) of the patients successfully

treated by combined procedure of thrombolysis and angioplasty (group B) was most favourable with a survival rate of 97%.

These results suggest that reperfusion may need to be supplemented by additional revascularization procedures such as angioplasty in order to optimize the chances of obtaining full functional recovery and so to improve the prognosis.

Introduction

Since the first study by Rentrop et al [1], we and many others have demonstrated that rapid recanalization can be achieved by intracoronary infusion of streptokinase in approximately 80% of patients with an acute myocardial infarction [2–5]. The large multicenter trial conducted by the Interuniversity Cardiology Institute in the Netherlands has documented that early recanalization is associated with a limitation of infarct size, preservation of left ventricular function, and improved survival [6–8]. However, a frequent finding after recanalization is a severe recurring or residual coronary stenosis which may limit antegrade flow and restrict the recovery of regional left ventricular function. Therefore, additional interventions, such as coronary angioplasty and coronary artery bypass surgery have been advocated in this setting to improve this incomplete restoration of flow and maximize myocardial salvage [4, 9–22].

The aim of this study was to investigate whether immediate angioplasty after thrombolysis indeed provided additional benefit in the preservation ofregional myocardial function in the infarct zone by retrospectively reviewing the results of the Netherlands multicenter trial of thrombolytic therapy [6–8] in which selected patients underwent angioplasty.

Patients and methods

In June 1981 a multicenter randomized trial of intracoronary thrombolysis compared to conventional treatment was initiated at the Thoraxcenter and later supported by the Interuniversity Cardiology Institute in the Netherlands. The study was completed in March 1985. Five hundred and thirty-three patients with an acute myocardial infarction of less than 4 hours duration were enrolled in the trial. Two hundred and sixty-four patients were allocated to conventional and 269 to thrombolytic therapy. The protocol and some initial results were published in 1982 [23–26]. The initial protocol was modified in two ways: the first resulted from data which suggested that reocclusion of the coronary artery occurred predominantely in patients with severe residual stenosis [4, 12, 15, 16]. It was therefore decided to proceed to immediate coronary angioplasty in such patients at two of the 5 participating centers (predominantely the Thoraxcenter, Rotterdam). The second change (January 1984) was to introduce intravenous streptokinase

(500.000 U) at the time of admission to hospital. This was initiated when published data showed that streptokinase given within 1–3 hours intravenously was effective [27–29], and that a brief interval between onset of myocardial infarction and reperfusion was essential in the preservation of myocardium at risk. Intravenous streptokinase upon admission meant that thrombolytic therapy could begin approximately one hour earlier.

During the study period consecutive patients up to the age of 70 years with chest pain and ECG signs of typical myocardial infarction, who arrived within four hours of the onset of symptoms, were admitted to the trial. The exclusion criteria for thrombolytic therapy were applied as described in previous reports [6–8, 23–26, 30–33]. After inclusion, patients were registered by a central telephone answering service which also provided treatment allocation. Informed consent was only obtained from patients allocated to thrombolytic therapy as proposed by Zelen [34]. Patients who refused acute angiography were treated according to the same guidelines as the control group [6, 7]. All patients received heparin followed by acenocoumarol (SintromR8) until hospital discharge. After discharge anticoagulants were continued only in patients with ventricular aneurysm, intraventricular thrombus, mitral incompetence or large ventricles with a poor contraction pattern. Metoprolol 100 mg twice daily, was prescribed in the majority of patients unless contra-indications were present.

In all patients from both the control and thrombolysis-treated group who agreed to late catheterization, coronary and left ventricular angiography were performed either before discharge or 4-8 weeks after the acute phase.

Patients were subdivided into 5 groups based on treatment allocation and early and late patency of the infarct related vessel:

group A: patients allocated to conventional treatment (n = 264)

group B: patients who were recanalized by coronary angioplasty following thrombolysis with persistent patency of the infarct related vessel at follow-up angiography (n = 31)

group C: patients treated by thrombolytic therapy without angioplasty with subsequent late patency of the infarct related vessel (n = 102)

group D: patients with persistent occlusion in spite of attempted recanalization procedures (n = 36)

group E: patients with initial patency after recanalization in whom the infarct related vessel was found reoccluded at follow-up angiography (n = 25)

The necessary angiographic data was unobtainable in the remaining 75 patients; the recanalization procedure could not be performed in spite of allocation to thrombolysis (n = 35), or the late patency of the infarct related vessel could not be evaluated (n = 40).

Measurement of serum alpha-hydroxybutyrate dehydrogenase (HBDH)

Serum alpha-hydroxybutyrate dehydrogenase levels were determined on admission, every 12 hours for the first two days and then every 24 hours until 5 days after admission. Cumulative release of alpha-hydroxy- butyrate dehydrogenase (HBDH) in the first 72 hours was calculated from these data as described earlier [33, 35]. In two of the 5 participating hospitals total lactate dehydrogenase was measured instead and converted to alpha-hydroxybutyrate dehydrogenase by exchange of standards.

Radionuclide angiography

Radionuclide angiography was carried out at the bedside on the first or second day after admission and repeated before hospital discharge and at three months. Gated images were obtained with 20 frames in each heart cycle after in vivo labelling with 15 mCi Tc99m. Data were analyzed by a fully automated computer program on a DEC-gamma 11 or an ADAC system [36], or with a MDS or a Philips data analysis system.

Technique of intracoronary thrombolysis and transluminal angioplasty

After puncturing the femoral vein and artery, a pacemaker catheter was positioned in the right ventricle or atrium and 5000 units of heparin and 250 mg of acetosalicylic acid was given intravenously. In order to reduce the potential antigenic effects of streptokinase, 100 mg of diadreson F^{R}, a corticosteroid, was also given. A non-ionic contrast agent (Amipaque^{R}) was employed as contrast medium for angiography of the artery suspected to be thrombosed. Intracoronary perfusion with streptokinase was carried out at a rate of 4000 units per minute to a maximum of 250,000 units. Coronary angiograms were repeated every 15 minutes until the vessel was patent or the chest pain disappeared. Coronary angioplasty was attempted in 46 patients in whom it was judged to be technically and organisationally feasible. It was carried out when the residual stenosis was 60% or more after thrombolysis. Since February 1983 we have used low profile balloons with steerable guide wires to cross the stenotic lesions. The mean pressure drop across the stenotic lesion was computed on-line after 20 seconds of data acquisition. A total of 2 to 9 balloon inflations were performed of 10 to 70 seconds duration. If the clinical condition was stable with left ventricular end-diastolic pressure below 35 mmHg, left ventriculography in the right anterior oblique projection was performed at the end of the catheterization. From the patients who agreed to follow-up catheterization, coronary and left ventricular angiography were obtained both in the control group and the thrombolysis-treated group, either before discharge or 4–8 weeks after the acute phase.

Analysis of global and regional left ventricular function

Global and regional left ventricular function was studied from the 30° right anterior oblique view using an automated hardwired endocardial contour detector linked to a mini-computer [37]. For each analyzed cineframe left ventricular volume was computed according to Simpson's rule. After the end-diastolic and end-systolic frames were identified, stroke volume, global ejection fraction and total cardiac index were computed. In figure 1A, examples of the end-diastolic (ED) and end-systolic (ES) contours of the left ventriculogram, as displayed by the analysis system, are shown. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals [38] and generalized as a mathematical expression amenable to automatic data processing [39, 40]. For each segment, segmental volume was computed from the local radius (R) and the height of each segment (1/10 of left ventricular long axis length (L) according to the formula: $1/20\,\pi\,R^2L$). When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function (fig 1B,C). During systole this parameter expresses quantitatively the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction or CREF [39]. It follows that the sum for all segments equals the global ejection fraction. The cross-hatched zones in figure 1D represent the segmental CREF values between the 10th and 90th percentile, as determined from 20 normal individuals. The segmental CREF-values in the anterobasal (segments 1–5), anterolateral (segments 5–9), apical (segments 9–12), inferior (segments 12–16) and posterobasal (segments 16–20) wall regions were analyzed in all subsets of patients.

Clinical follow-up

All patients were followed at the outpatient clinic for at least one year after admission and survival status was assessed for all patients at six month intervals. Recurrent myocardial infarction, angina pectoris, cardiac failure, bypass surgery and percutaneous transluminal coronary angioplasty as well as prescribed medication were recorded.

Statistical analysis

Data are expressed as mean SD. Paired or unpaired Student t tests were applied to the hemodynamic data whenever appropriate. Differences in baseline characteristics between groups were tested with Fisher's exact test.

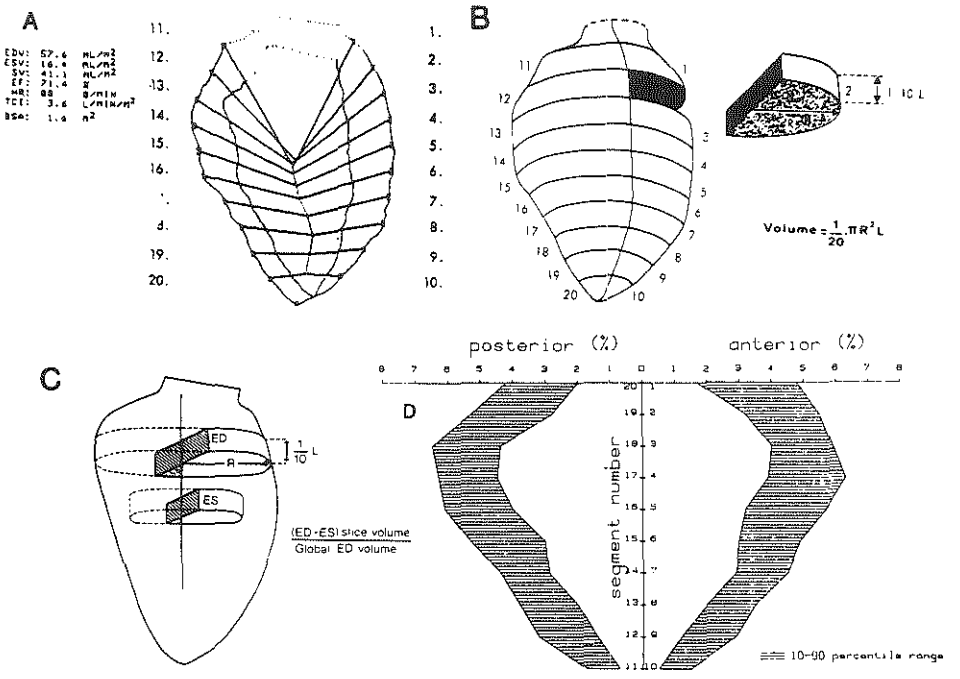

Fig. 1. A. Example of the computer output showing the end-diastolic and end-systolic contours of the 30° RAO left ventriculogram and the system of coordinates along which left ventricular segmental wall displacement is determined. B. The left ventricular end-diastolic cavity is divided into twenty half slices. The volume of each half slice is computed according to the given formula. R is radius and L is left ventricular long axis length. C. The regional contribution to global ejection fraction (CREF) is determined from the systolic decrease of volume of the half slice which corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half slice. D. The shaded zones represent the 10th-90th percentiles area of CREF values in normal individuals. On the X-axis the CREF values of the anterior and infero-posterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1-10) and of the infero-posterior wall (11-20) are depicted.

Results

Early and late angiographic findings

A total of 533 patients was admitted to the trial in five participating hospitals; 264 patients were allocated to conventional therapy and 269 patients to thrombolysis. The results of early and late angiography have been reported [8] and are detailed in table I. Briefly, in spite of allocation to thrombolysis angiography could not be performed in 35 patients. Out of 234 patients who underwent acute angiography, 65 had a patent infarct related artery and in 169 this artery was occluded.

Table 1. Results of acute and late angiography.

Acute angiography	Late angiography missing				Late angiography			
	patient refusal	death	CABG	inadequate quality of LV angio	other	adequate LV angio	coronary patency	
							○	●
264 controls	19	27	4	31	9	174	106	99
269 thrombolysis → 35 no angiography	5	4	2	8	2	14	13	9
269 thrombolysis → 65 ○ → 65 ○	1	1	9	13	5	36	46	3
269 thrombolysis → 169 ● → 133 ○	11	4	4	18	5	91	87	22
269 thrombolysis → 169 ● → 36 ●	5	6	5	2	1	17	11	8
533 patients	41	42	24	72	22	332	263	140

Results of acute and late angiography. Patent vessels are indicated (○) and occluded vessels are marked (●); death = patients who died before late angiography was performed; CABG = patients without late angiography due to bypass surgery; other = other missing data e.g. due to transfer to another hospital.

Recanalization was achieved by intracoronary streptokinase or mechanical perforation (5 patients) in 133 patients. Ultimately the infarct-related artery remained occluded in 36 out of 234 patients who underwent angiography and at least one attempt at recanalization (15%) while the artery was open at time of study or became recanalized in 198 patients (85%). Transluminal coronary angioplasty was attempted in 46 patients and was successful in 44 patients. The median time between onset of symptoms and angiographic documentation of a patent infarct-related vessel for the entire thrombolysis group was 200 minutes, ranging from 55 to 375 minutes. Late coronary angiograms were available in 199 patients allocated to thrombolytic therapy and in 205 patients allocated to conventional treatment (table I), while left ventricular angiograms of quality sufficient to allow automated contour analysis were obtained in 158 and 174 patients respectively. The patency rates in the control group and thrombolysis group were respectively 52% (106/205) and 79% (157/199) ($p = 0.0001$). The reocclusion rate in patients recanalized by intracoronary streptokinase was 20% (22 out of 109 patients), while late occlusion in the patients with a patent infarct related vessel at first angiogram was 6% (3 out of 49 patients).

Baseline data

Patients were subdivided into 5 groups based on treatment allocation and early and late patency of the infarct related vessel (see patients and methods). Baseline characteristics in these 5 subsets of patients are shown in table 2. The median time delay for hospital admission was longer in patients in which recanalization was unsuccessful (group D) when compared to other subsets of patients. All other baseline data were distributed evenly, including a history of previous myocardial infarction and previous bypass surgery.

Global and regional left ventricular function

Acute angiography (at admission) was performed only in patients allocated to thrombolysis, while late angiography (before discharge or at 4 to 8 weeks) was performed in the thrombolysis as well as in the control group (table 1). The global left ventricular volume data determined from contrast angiography are presented in table 3.

At the chronic stage, the highest global ejection fractions were observed in patients with persistent patent infarct related vessel after thrombolysis either with (group B, $54 \pm 10\%$) or without (group C, $55 \pm 13\%$) angioplasty, while the lowest ejection fractions were found in the control group (group A, $47 \pm 14\%$) and in the patients in whom recanalization failed (group D, $45 \pm 16\%$).

In table 3, the sequential changes in global ejection fraction from the acute to

Table 2. Baseline characteristics.

	Controls (group A)	TR + PTCA (group B)	TR alone (group C)	Unsucc recanalization (group D)	Reocclusion (group E)
N	264	31	102	36	25
Female	41 (16%)	4 (13%)	18 (18%)	9 (25%)	6 (24%)
Age yrs (mean ± SD)	55 ± 8	57 ± 8	55 ± 10	58 ± 8	53 ± 9
Previous infarction	60 (23%)	8 (26%)	12 (12%)	11 (31%)	5 (20%)
Previous CABG	8 (3%)	0	1 (1%)	1 (3%)	1 (4%)
Time to admission (median, min)	90	95	90	120	90
Sum of ST-elevation (median, mm)	12	14	12	10	11

Baseline characteristics of the 5 subdivided groups; TR + PTCA = recanalization with angioplasty following thrombolysis with late patency; TR alone = recanalization following thrombolysis alone with late patency; unsucc recanalization = persistent occlusion in spite of attempted recanalization procedures; Reocclusion = re-occlusion of the infarct related vessel at late angiography after initially successful recanalization procedure; CABG = coronary bypass surgery.

Table 3. Left ventricular hemodynamics.

	Controls (A)	TR + PTCA (B)	TR alone (C)	Unsucc recanalization (D)	Reocclusion (E)
EDV 2 ml/m²	95 ± 37 (n = 180)	80 ± 21§§ (n = 29)	82 ± 32§§ (n = 86)	96 ± 46 (n = 18)	82 ± 23§ (n = 23)
Δ EDV ml/m²	–	−0.4 ± 19 (n = 24)	9 ± 23* (n = 43)	19 ± 25 (n = 7)	18 ± 19** (n = 19)
ESV 2 ml/m²	53 ± 31 (n = 177)	38 ± 14§§§ (n = 27)	39 ± 24§§§ (n = 80)	58 ± 46 (n = 17)	38 ± 18§§§ (n = 22)
Δ ESV ml/m²	–	−3.4 ± 14 (n = 23)	5 ± 13* (n = 40)	21 ± 14* (n = 5)	13 ± 13** (n = 15)
EF 2 %	47 ± 14 (n = 174)	54 ± 10§§§ (n = 27)	55 ± 13§§§ (n = 79)	45 ± 16 (n = 17)	55 ± 10§§§ (n = 21)
Δ EF %	–	4.2 ± 9* (n = 23)	−0.5 ± 8 (n = 40)	−3 ± 7 (n = 5)	−4 ± 7* (n = 15)

Abbreviations: EDV, ESV, EF = enddiastolic volume, endsystolic volume (ml/m²), ejection fraction % at chronic (2) stage; Δ EDV, Δ ESV, Δ EF = sequential change in enddiastolic volume, endsystolic volume and ejection fraction from acute to chronic stage when both were available; See also table 2. Values are expressed as mean ± SD; Student t test for unpaired and paired (Δ) data. §p = .05 and §§p = .005 versus controls; $p = .05 versus unsucc recanalization; *p = .05 and **p = .005 acute versus chronic.

chronic stage are also shown. In the angioplasty group (group B), the global ejection fraction improved significantly by 4.2% ($p = 0.05$), while the global ejection fraction decreased significantly by 4% ($p = 0.05$) in the patients with late reocclusion of the infarct related vessel (group E). No significant changes in global ejection fraction could be demonstrated in the other subsets of patients.

Similar trends were observed in the regional myocardial function of the infarct zone (table 4).

Figure 2 and 3 show the sequential changes in regional myocardial function from the acute to the chronic stage of the 4 subsets of patients (group B,C,D,E), in whom the left ventriculogram was performed at the acute as well as at a follow-up catheterization. In the angioplasty group (group B), the significant improvement in global ejection fraction was primarily due to a 16% increase in regional contribution to ejection fraction of the infarct zone as shown in fig. 2 and 3. In the group of patients with persistent patent infarct related vessel after thrombolysis without angioplasty (group C) and in the patients in whom the recanalization failed (group D), the regional contribution to ejection fraction of the infarct zone remained unchanged. Conversely, in the patients with late reocclusion of the infarct related vessel after recanalization (group E), regional contribution to ejection fraction of the infarct zone was significantly decreased (-17%, $p = 0.05$).

Radionuclide angiography

Left ventricular ejection fraction as determined by radionuclide angiography at the acute stage (day 1–3, $n = 418$), before discharge (day 10–20, $n = 361$) and at 3 months ($n = 307$) in all subsets of patients are presented in table 5. Paired analysis of the sequential changes in global radionuclide ejection fraction from day 1–3 to day 10–20 and from day 1–3 to 3 months, respectively, showed a significant improvement only in the patients with persistent patent infarct related vessel after recanalization (group B and C) and this was most marked when intracoronary thrombolysis was followed by angioplasty (group B). No significant changes in global radionuclide ejection fraction could be detected in the other subsets of patients. These data are in agreement with the contrast angiographic findings.

Enzymatic infarct size

Enzymatic infarct size was estimated by cumulative HBDH release in the first 72 hours after onset of symptoms. As shown in fig. 4, the median cumulative HBDH release in the control group (1136 U/L) and in the group in which recanalization failed (1097 U/L) was significantly higher than in the 3 other groups.

Table 4. Regional myocardial function of the infarct zone.

CREF-IZ		Controls (group A)	TR + PTCA (group B)	TR alone (group C)	Unsucc recanalization (group D)	Reocclusion (group E)
Anterior infarction	n =	69	20	40	7	4
Antero-basal	%	12.2	15.7	13.7	13.1	14.3
Antero-apical	%	4.4	6.0	5.8	5.1	3.6
Apex	%	1.1	1.8	1.9	1.1	0.8
Inferior infarction	n =	105	7	39	10	17
Apex	%	2.6	3.0	3.6	2.3	3.7
Infero-apical	%	6.9	10.7	10.8	7.6	8.4
Infero-basal	%	10.8	14.4	13.5	10.9	11.4

Regional contribution to global ejection fraction (%) of the infarct zone (CREF-IZ) at follow-up angiography. Antero-basal = segment 1–5; Antero-apical = segment 5–9; Apex = segment 9–12; Infero-apical = segment 12–16; Infero-basal = segment 16–20. See also table 2 and figure 2.

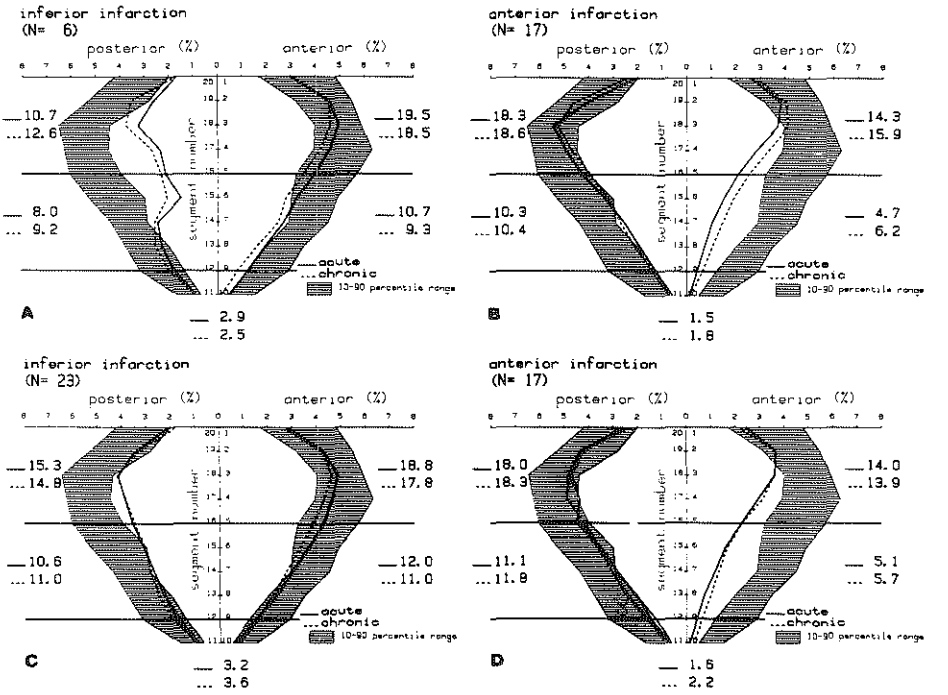

Fig. 2. Sequential changes in regional contribution to global ejection 9fraction from the acute (at admission, solid line) to the chronic (before discharge, dotted line) stage in patients with inferior (left sided) and anterior (right sided) infarction treated by a combined procedure of thrombolysis and angioplasty (A and B) as well as treated by thrombolysis alone (C and D). The improvement in global ejection fraction of patients treated by angioplasty following thrombolysis was due to significant improvement of the regional myocardial function of the infarct zone even after the disappearance of compensatory actions of the initially enhanced function of the non-infarct zone.

Clinical follow-up

Median clinical follow-up of 24 months after admission in all subsets of patients are presented in table 6. The survival rate was 97% in the patients treated by a combined procedure of thrombolysis andangioplasty (group B) and 98% in patients treated by thrombolysis alone (group C), while the highest mortality rate was observed either in the patients treated conventionally (group A, 17%) or in the patients in whom recanalization failed (group D, 25%). Apparently, late reocclusion (group E) did not affect the lonterm survival (96%).

The longterm clinical follow-up of the patients treated by thrombolysis and angioplasty (group B) was most favourable when the patency of the infarct related vessel could be demonstrated prior to discharge.

These patients had a low reinfarction rate (6%); late coronary bypass surgery

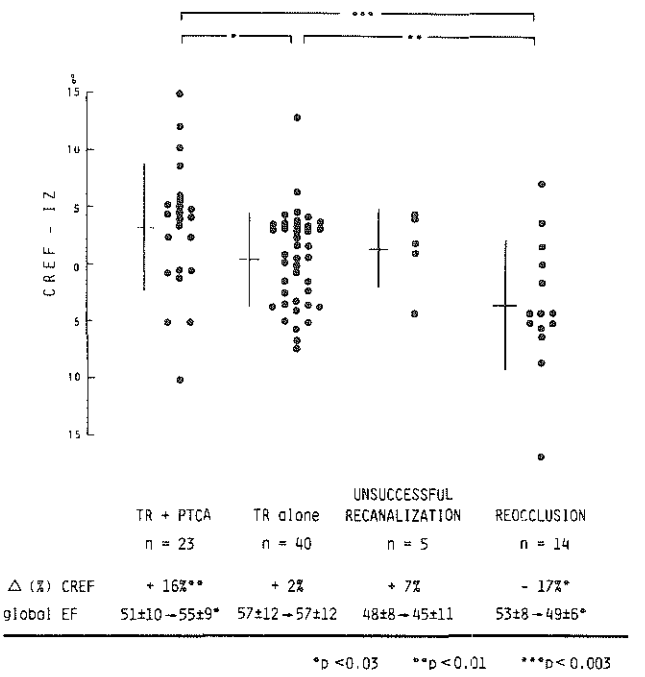

Fig. 3. Sequential changes (%) in regional contribution to global 9ejection fraction (CREF) of the infarct zone (anterior = segment 1 to 10; inferior = segment 11 to 20) from acute to chronic stage in patients receiving thrombolytic therapy in whom both angiograms were available. TR + PTCA = recanalization with angioplasty following thrombolyis with late patency; TR alone = recanalization following thrombolysis alone with late patency; unsucc recanalization = persistent occlusion in spite of attempted recanalization procedures; re-occlusion = re-occlusion of the infarct related vessel at late angiography after initially successful recanalization procedure (see also table 2).

(13%) and/or (re)-PTCA (3%) was performed less frequently than in the other groups.

Conversely, the incidence of late reinfarction was 21% in the group treated by thrombolysis alone.

Discussion

There have been many clinical trials of the efficacy of thrombolytic therapy in achieving reperfusion, salvaging myocardial function and reducing mortality. However, the efficacy of thrombolysis in randomized trials has varied widely in several studies [41–48]. This may be due to varying success in achieving reperfusion due to differences in the dose, timing or route of administration of the drugs, to differences in patient selection or to differences in standard clinical care procedures. Our data from the multicenter randomized trial on intracoronary

Table 5. Radionuclide angiography.

	Controls (A)	TR + PTCA (B)	TR alone (C)	Unsucc recanalization (D)	Re-occlusion (E)
RNAEF 1 %	43 ± 14 (n = 200)	40 ± 15 (n = 26)	47 ± 14[$] (n = 90)	39 ± 13 (n = 31)	48 ± 9[$] (n = 21)
RNAEF 2 %	44 ± 15 (n = 172)	49 ± 16 (n = 23)	51 ± 15[$] (n = 85)	42 ± 13 (n = 20)	48 ± 14 (n = 21)
RNAEF 3 %	45 ± 15 (n = 144)	56 ± 14[$] (n = 17)	52 ± 15[$] (n = 78)	41 ± 14 (n = 18)	51 ± 9[$] (n = 20)
△ EF 2 − 1 %	0.9 ± 11 (n = 141)	10 ± 7* (n = 18)	4 ± 9* (n = 76)	4 ± 9* (n = 19)	2 ± 9* (n = 18)
△ EF 3 − 1 %	1.7 ± 13 (n = 115)	9 ± 14* (n = 14)	3 ± 12* (n = 68)	3 ± 12 (n = 18)	4 ± 10 (n = 18)

RNAEF = Radionuclide ejection fraction (%) at day 1–3 (1), day 10–20 (2) and at 3 months (3); △ EF = sequential change in radionuclide ejection fraction. [$]p = .05 and [$$]p = .005 versus controls; [$]p = .05 and [$$]p = .005 versus unsucc recanalization; [£]p = .05 versus TR + PTCA; *p = .05 and **p = .005 acute versus chronic. See also table 2 and 3.

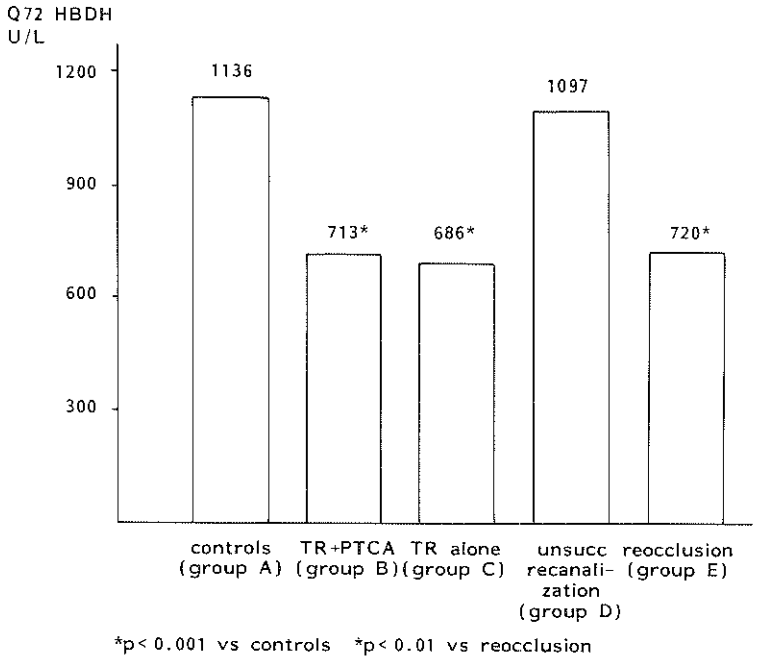

Fig. 4. Median cumulative serum alpha-hydroxybutyrate dehydrogenase 9release in the first 72 hours after onset of symptoms (Q72 HBDH).

thrombolysis recently showed the beneficial effects of early thrombolysis in acute myocardial infarction compared to conventional treatment [6–8].

The present study based on data from the same trial emphasizes the additional value of immediate angioplasty following thrombolysis in preserving global and regional left ventricular function and in reducing infarct size.

Preservation of left ventricular function and need for regional assessment

Global left ventricular ejection fraction was measured by contrast and radionuclide angiography (table 3 and 5). Both methods showed higher ejection fractions at the follow-up study when recanalization had been successful either with (group B) or without (group C) additional angioplasty. This finding is supported by analysis of regional wall motion and enzymatic infarct size measurement. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to 3 months after the intervention.

In most studies published thus far, the assessment of global ejection fraction has prevailed since it is relatively easily obtainable. In fact, measurement of the

Table 6. Longterm clinical follow-up (median 24 months).

	Controls (A) n = 264	TR + PTCA (B) n = 31	TR alone (C) n = 102	Unsucc recanalization (D) n = 36	Re-occlusion (E) n = 25
Re-infarction	17 (6%)	2 (6%)	21 (21%)	3 (8%)	6 (24%)
CABG	33 (13%)	4 (13%)	14 (14%)	6 (17%)	5 (20%)
(Re)-PTCA	13 (5%)	1 (3%)	14 (14%)	1 (3%)	3 (12%)
Death	46 (17%)	1 (3%)	2 (2%)	9 (25%)	1 (4%)

See table 2.

global ejection fraction is a rather crude method which may not detect improvement of regional left ventricular function. Therefore, analysis of left ventricular wall motion in the area at risk which potentially should benefit most from reperfusion, must be carried out in order to detect any real benefit of reperfusion [49–52]. In fact, increased motion of the non-infarcted regions of the heart, often kept the global ejection fraction within normal limits despite severe regional hypokinesia in the infarction area. Contractile performance of the non-infarcted area may be enhanced by the Frank-Starling mechanism and by increased levels of circulating catecholamines during the first hours. After subsidence of compensatory augmented motion in the non-infarcted regions of the heart, which may have masked a significant deterioration in regional wall motion, the initially maintained global left ventricular function declined. Here again, regional wall motion must be measured to adequately assess this effect. In this study, the regional contribution to global ejection fraction of the infarct zone was most improved in the subgroup of patients successfully treated by thrombolysis followed by angioplasty. In this subset of patients, global ejection fraction increased significantly ($p = 0.03$) from 51% to 55% from the acute to the chronic stage, an improvement primarily due to a 16% increase in the regional contribution to ejection fraction of the infarct zone (fig. 2 and 3).

These results suggest that reperfusion may need to be supplemented by additional revascularization procedures such as angioplasty in order to optimize the chances of obtaining full functional recovery. The additional value of immediate angioplasty in preserving left ventricular function and limiting infarct size might help to explain the observed reduction in one year mortality and other major cardiac events.

Major factors influencing functional recovery

Even when regional function was measured, Khaja et al [41] failed to demonstrate any significant benefit in reperfused patients. There must be other factors besides achievement of reperfusion which control or affect the extent to which left ventricular function recovers following reperfusion. The time delay from onset of symptoms to reperfusion [8, 53], the severity of residual stenosis after recanalization [49, 50], and/or the extent of regional and global left ventricular dysfunction at the acute stage [48, 54] may all be the major factors influencing the functional recovery. Besides providing an adequate flow, reperfusion must be achieved early to salvage myocardial function, in order to reduce the mortality. Function is unlikely to improve if the residual stenosis is severe or if the time from onset of symptoms to angiographic reperfusion exceeds 3 hours [31, 50, 53]. The need for early reperfusion agrees with earlier studies in experimental animals showing that the amount of myocardium salvaged by reperfusion decreases with progressively longer occlusion times [55–57], and may result in abnormal metabolism, acceler-

ated necrosis, local hemorrhage and decreased function [58, 59]. However, as it is now generally accepted that the functional characteristics of the coronary circulation in animals differ significantly from those of man, no animal model can completely mimick the human situation. Nevertheless, all these data support the concept that reperfusion must be established soon after occlusion, and no major beneficial effects in the human can be expected beyond 3-4 hours after the onset of ischemia. Recent clinical studies have confirmed this temporal relationship [8, 31, 42, 53, 60].

Rentrop et al [13] has found that while the extent of salvage is less when therapy is started beyond the 4th hour after onset of symptoms, late recanalization may still result in some improvement, particular in those patients in whom collaterals are demonstrable by acute angiography. It is likely that in these patients, the evolution of myocardial necrosis, 'stuttering necrosis', is slowed when collateral flow is enhanced early on.

Current concept of reperfusion strategy

Our own data have shown that the best improvement in cardiac function, the smallest infarct size and the lowest mortality was present in the subset of patients in whom intracoronary lysis was preceded by intravenous streptokinase [7, 8]. In these patients lysis was begun a median of 2 hours after onset of symptoms. However, angiography in these patients before the start of subsequent intracoronary streptokinase showed a patent coronary artery in less than half of the cases. This finding supports the notion that lytic therapy can work, not only through recanalization of the main infarct-related vessel, but also via improved rheology and reduced viscosity in the collateral bed. In keeping with this is the fact that enzyme washout was highest in those patients who were treated earliest but was also higher in those in whom the infarct-related vessel remained occluded when compared to the control group [33]. The GISSI data [61] which demonstrated a significant mortality reduction when intravenous administration was begun within 3 hours of symptoms, together with the drastic reduction in mortality in the group initially treated by intravenous but followed by the intracoronary route in the Netherlands trial [6–8] have confirmed for the first time, the thesis proposed by Verstraete [62] that intravenous administration is 'the only way'. However the very efficacy of this initial treatment has created a new problem: How to manage the patients with residual atheromatous lesions whose ischemic symptoms persist after thrombolysis, and who may constitute up to half of the patients treated. In order to maintain the initial benefit achieved by thrombolysis it is necessary to deal with the underlying obstruction. Percutaneous transluminal coronary angioplasty or surgery may play a valuable role in attaining these goals.

The present study shows that intracoronary streptokinase combined with coronary angioplasty can be safely used to provide reperfusion in the setting of

acute myocardial infarction. This approach seems rational if an isolated occlusion is only minimally open with streptokinase, since it is these residual high-grade stenoses that are the most likely to reocclude [4, 12, 15, 16]. Although the current results might be biased by the selection of those patients whose lesions were suitable for angioplasty and who were hemodynamically stable after thrombolysis, the findings are in agreement with earlier observations that the recovery of regional function is greatest in patients with the lowest residual stenosis after the intervention [49, 50].

The high survival rate, the lower incidence of reinfarction as well as the preserved regional and global left ventricular function in the subgroup successfully treated with thrombolysis and coronary angioplasty suggests that this combination may be the optimal mode of therapy for selected patients.

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Samenvatting

Sedert de introductie van coronair angioplastiek in 1977, is deze methode steeds belangrijker geworden voor de behandeling van kransvat stenose. Vanuit de ons ter beschikking staande gegevens kan worden berekend dat deze behandelings methode van onschatbare waarde zal worden voor tienduizenden patiënten in de eerst komende jaren.

Meerdere gegevens zullen in versneld tempo tot onze beschikking komen over de indicatie, de voordelen en de risico's van angioplastiek van vernauwingen van kransvaten en ook over verdere verfijning van de techniek.

Recentelijk hebben een aantal onderzoekers aangetoond dat coronair angioplastiek niet alleen geschikt is voor de behandeling van de stenose maar tevens een belangrijke bron is voor het verkrijgen van diagnostische informatie. Indien de catheter, die gepositioneerd is ter hoogte van de kransvatvernauwing, wordt opgeblazen, ontstaat er een tijdelijke ischemie van de hartspier. Vlak voor, gedurende en na deze periode van tijdelijke ischemie kan de hartspier werking worden bestudeerd, welke in gevaar gebracht is, door de tijdelijke ischemie. Het feit dat een therapeutische coronair angioplastiek wordt uitgevoerd in een hartcatheterisatie laboratorium, welke per definitie optimaal is uitgerust voor het meten van hemodynamische parameters, heeft er waarschijnlijk toe bijgedragen dat deze onderzoekingen ook werden geëffectueerd. De conbinatie van hemodynamische en biochemische parameters tesamen met morfologische informatie verkregen van het coronair angiogram, kan worden gebruikt voor het kwantificeren van de uitgebreidheid van de hartspierafwijking en het succes van de dilatatie van het kransvat. Studies over de interacties van farmacologische stoffen zijn uitvoerbaar en zullen veel informatie opleveren.

Coronair angioplastiek heeft een veelbelovende toekomst omdat het een unieke manier is om ons diepgaande informatie te verschaffen in de ingewikkelde interacties tussen zuurstof vraag en aanbod bij patiënten die lijden aan ziekten van de kransvaten.

Het eerste deel van dit proefschift bevat 4 hoofdstukken, waarin de volgorde van de gevolgen wordt beschreven welke plaats vinden gedurende het tijdelijk introduceren van ischemie door angioplastiek.

In de eerste 4 hoofdstukken worden de veranderingen in de ejectie, de vulling

en de diastase beschreven. In het vijfde hoofdstuk worden de veranderingen beschreven van de regionale doorbloeding en het hartspier metabolisme gedurende de reactieve hyperemie na herhaalde occlussies van de ramus descenders anterior. (RDA).

Het doel van deze studies was om aan te tonen dat het effect van ischemie na herhaalde occlusies reversibel was. Geconcludeerd kan worden dat herhaalde totale afsluiting van de RDA bij mensen bij volledig bewustzijn, gepaard gaat met een regionale verandering van de diastolische functie van de hartspier, welke nog steeds aanwezig is nadat de hartspierdoorbloeding, het hypoxanthine en lactaat metabolisme hersteld zijn en al een normale systolische functie is. De suggestie wordt gewekt dat meerdere studies nodig zijn om het tijdsverloop van de herstelfase tot een normale diastolische functie vast te leggen. Bovendien moet, omdat het mechanisme wat ten grondslag ligt aan deze waargenomen afwijkingen niet geheel duidelijk is, meer aandacht geschonken worden aan mogelijk verantwoordelijke afwijkingen van het subcellulaire metabolisme.

Het tweede deel van dit proefschrift behandelt de veranderingen van de coronaire anatomie welke worden geproduceerd door de angioplastiek en vervolgens wordt besproken welke fysiologische betekenis dit heeft. Heden ten dage is selectieve coronair angiografie de enige beschikbare techniek die in staat is het kransvatsysteem in beeld te brengen met een dusdanig beeld contrast en resolutie dat de aanwezigheid en de ernst van een kransvatvernauwing bepaald kan worden met voldoende accuratesse. Echter, de relatie tussen de ernst van de stenose en de bloedstroom belemmering in de vernauwde arterie is uiterst belangrijk. Conventionele visuele beoordeling van de ernst van kransvatvernauwingen vanaf een 35 mm cinefilm wordt belemmerd door aanzienlijke inter- en intra waarnemer variaties. Uit het bovenstaande volgt dan ook dat we een objectieve en reproducerende techniek nodig hebben om kwantitatief de dwars doorsnede (oppervlakte) van een vernauwing en de dwars doorsnede van een normaalvat in absolute diameter en in relatieve diameter te kunnen berekenen, indien we het nuttig effect van percutane transluminale coronaire angioplastiek in kwantitatieve termen willen evalueren. Daartoe werden 138 angiogrammen geanalyseerd van patiënten, die een angioplastiek ondergingen, met ons coronair angioplastiek analyse systeem (CAAS). De resultaten voor en na dilatatie worden getoond in hoofdstuk 6. Besproken wordt de relatieve voordelen van de diameter versus de densitometric doorsnede meting. Gesuggereerd wordt dat de morfologische veranderingen welke geïntroduceerd door de angioplastiek 'eccentrisch' zijn.

De uitdrukking 'kritische vernauwing' wordt vaak gebezigd maar is slecht gedefinieerd bij mensen met kransvatafwijkingen. De definitie kan vastgesteld worden vanuit twee achtergronden: een fysiologische en een klinisch. Deze twee benaderingen worden besproken in de volgende 2 hoofdstukken (hoofdstuk 7 en 8). Een kransvat stenose, bekeken vanuit de fysiologische hoek, is kritisch indien de stenose een toename in de bloedstroom t.o.v. een rustwaarde voorkomt als

antwoord op een toename van de hartspier zuurstof vraag. Indien bekeken met een klinische achtergrond kan men een klinische stenose definiëren als een stenose welke aanleiding geeft tot klachten optredend in rust.

Het is aangetoond dat niet invasieve beeldvorming met Thallium-201 gedurende inspanning van belang is voor het niet invasief vaststellen van de regionale bloedstroom reserve en daardoor van de fysiologische betekenis van een matig ernstige coronair stenose. Teneinde gedurende hartcatherisatie te kunnen vaststellen wanneer een stenose een fysiologisch significante belemmering van de bloedstroom veroorzaakt, werd een met de computer gestuurde quantitatieve analyse van de coronair angiogrammen uitgevoerd bij 31 patiënten met een geïsoleerde vernauwing in het proximale deel van de RDA.

De angiografisch bepaalde ernst van de stenose werd vergeleken met de transstenotische druk gradiënt welke wordt gemeten met de dilatatiecatheter gedurende de angioplastiek en eveneens vergeleken met de uitkomsten van de inspannings Thallium scintigrafie: (hoofdstuk 7). In dit hoofdstuk wordt de conclusie getrokken dat de functionele betekenis van een kransvatvernauwing in rust geëvalueerd kan worden door een kwantitatieve analyse voor de afmetingen van het kransvat en de meting van de transstenotische drukgradiënt. Zo is het mogelijk om bij patiënten met een enkelvoudige stenose in de RDA die vernauwingen te identificeren welke in rust verantwoordelijk zijn voor het Thalliumperfusiedefect dat wordt geïnduceerd door inspanning. Restenose na een initiële geslaagde PTCA blijft de 'Achilles hiel' van deze therapeutische procedure.

In hoofdstuk 8 wordt de waarde van de inspanningsproef en Thalliumscintigrafie voor het voorspellen van het terugkeren van angina pectoris prospectief geëvalueerd. De bevindingen, beschreven in dit hoofdstuk, tonen aan dat de vroege vaststelling van onvoldoende hartspierperfusie met inspannings Thalliumscintigrafie een predictieve waarde heeft voor het voorspellen van restenose en terugkeren van klachten bij een overigens technisch goed geslaagde PTCA procedure. Bovendien suggereren de resultaten dat restenose al in zekere mate had plaats gevonden vier weken na de procedure in het merendeel van de patiënten bij wie dit ook later definitief kon worden vastgesteld. Deze waarneming geeft aanleiding tot speculaties omtrent het mechanisme wat schuilt achter restenose na dilatatie.

De drie hoofdstukken van deel 3 van deze thesis geven een overzicht van onze ervaring met spoed coronair angioplastiek bij patiënten met onstabiele angina pectoris of acuut myocard infarct. De volgende specifieke vragen worden aan de orde gesteld. Kan coronair angioplastiek de ischemische klachten wegnemen en voorkomen dat er een myocard infarct op hartdood ontstaat bij patiënten met onstabiele angina pectoris, die niet reageren op intensieve farmacologische behandeling die langer dan 24 uur werd geprobeerd?

Teneinde reconclusie te voorkomen na een aanvankelijk geslaagde recanalisatie kan men zich afvragen of angioplastiek een noodzakelijke procedure is. Bovendien, wat is de additionele waarde van angioplastiek onmiddellijk na intra

coronaire thrombolyse om de linker kamerfunctie te preserveren, en de infarctgrootte te beperken en de mortaliteit te reduceren.

De voorlopige antwoorden op deze 3 vragen worden in hoofdstuk 9, 10 en 11 geformuleerd.

De gegevens, die gepresenteerd worden in hoofdstuk 9, steunen onze mening dat PTCA een zeer effectieve methode is voor de spoedbehandeling van geselecteerde patiënten met onstabiele angina pectoris, welke refractair is tegen de ingestelde pharmacologische behandeling. Bovendien geven de gunstige vroege en late (12 maanden) klinische resultaten aan, dat angioplastiek alleen van het vat dat verantwoordelijk gesteld kan worden voor de ischemie in patiënten met meertaks afwijkingen en refractaire onstabiele angina pectoris een aantrekkelijk alternatief is voor bypass chirurgie, tenminste indien beschouwd voor de korte termijnsresultaten.

In hoofdstuk 10 wordt aangetoond dat intracoronaire streptokinase infusie en PTCA veilig kan worden uitgevoerd in dezelfde zitting in een poging om de reperfusie te verbeteren.

Alhoewel de huidige resultaten (hoofdstuk 11) sterk worden beinvloed door de selektie van patiënten met afwijkingen welke geschikt zijn voor angioplastiek, en door de selektie van patiënten die hemodynamisch stabiel zijn na thrombolyse, geven de uitkomsten aan dat er een overeenstemming bestaat met de vroegere observaties dat het herstel van de regionale functie het grootst is bij patiënten met de kleinste overblijvende vernauwing na de interventie. Het hoogste overleveringspercentage, het laagste voorkomen van reinfarcering en de best bewaarde regionale en globale linker kamerfunctie in de subgroep die met succes behandeld is met thrombolyse en coronair angioplastiek, suggereren dat deze combinatie de beste manier kan zijn om geselecteerde patiënten te behandelen.

Aanbevolen wordt dat, daar verdere gerandomiseerde studies nodig zullen zijn om een uiteindelijk gunstig resultaat aan te tonen van thrombolyse in het acute hartinfarct, gedurende deze studies de additionele waarde van onmiddellijk uitgevoerde PTCA zou moeten worden bestudeerd

Concluderend wordt in de 10 hoofdstukken van dit proefschrift een veelzijdige kijk gegeven op een nieuwe therapeutische interventie – de percutane transluminale coronair angioplastiek.

Curriculum vitae

Patrick Washington Serruys was born on the 27 of April 1947 in Brussels. He received his medical degree summa cum laude from the University of Leuven, Belgium in 1972 and his certificate as Cardiologist in Belgium and the Netherlands in July 1977. He is married and has 3 children.

In 1978 he became 'Wetenschappelijk hoofdassistent' and in 1979 followed his appointment to 'Hoofdgeneeskundige'.

From 1977 until 1980 he was co-Director of the Catheterization Laboratory and since then he has been the Director of the Clinical Research Program of the Catheterization Laboratory and the Clinical Imaging Laboratory for Angiography. This year he was appointed to 'Chef de Clinique'.

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