# Ultrasonography of the LIMA graft

Joost M. Hartman

ISBN: 978-90-8559-483-3



Layout: Freddy van der Meijden

Printed by: Optima Grafische Communicatie

Cover design: M.E. van Nierop-Schäfer

The financial support for the publication of this thesis by the following companies is gratefully acknowledged: Baxter BV, Bis Foundation, Edwards Lifesciences BV, Krijnen Medical Innovations BV, MediStim, Medtronic Trading NL BV, Sorin Group Nederland NV, St. Jude Medical Nederland BV.

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Ultrageluidsonderzoek van de LIMA graft

## Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 14 januari 2009 om 9.45 uur

door

Joost Michael Hartman

geboren te Bussum

**Promotiecommissie**

| | |
|---|---|
| Promotor: | Prof.dr. A.J.J.C. Bogers |
| Overige leden: | Prof.dr. D.J.G.M. Duncker |
| | Prof.dr. P.J. de Feyter |
| | Prof.dr.ir. H.A. van Swieten |
| Co-promotor: | Dr. A.P. Kappetein |

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged

**Contents**

*CHAPTER 1*

# GENERAL INTRODUCTION

## 1.1 Coronary artery bypass grafting

Coronary artery bypass grafting (CABG) is a surgical procedure that has been in existence since 1967 [1]. Over the years, the use of the left internal mammary artery (LIMA), has been shown to be the conduit of choice for single or sequential bypass grafting to the anterior wall of the heart because of its long-term patency [2-10]. The LIMA originates from the stem of the concave side of the subclavian artery opposite the vertebral artery. It runs behind the cartilage of the first rib via the pleura to the front wall of the thorax and descends 1-2 cm from the lateral edge of the sternum. This anatomy of the LIMA graft allows easy visualisation by supraclavicular or transthoracic ultrasonography.

Long term follow up has shown not only superior patency of the LIMA graft but also reduced mortality and angina and increased freedom from late cardiac events [5]. The success of the artery as a bypass conduit is partly caused by its dynamic capacity to dilate in response to increased blood flow and the relative resistance to atherothrombotic occlusion. Due to these excellent long term results it has been hypothesized that exclusive arterial (composite) grafts also would result in improved long term patency and is therefore nowadays an preferred method for coronary revascularization [11-14].

## 1.2 Follow up of the IMA graft in CABG

To evaluate the short and long-term patency of grafts, a simple, repeatable and accurate noninvasive functional test without contrast to assess graft patency would be useful for clinical follow up and for the study of coronary and graft physiology and pharmacology.

At present, postoperative angiography is the current gold standard method to assess graft patency, especially at rest, but the invasive nature limits its routine use. Other limitations of invasive (control) arteriography are its costs, the overall complication rate of 4 % in stable and 4.8 % in unstable patients and possible disturbance of baseline haemodynamics by contrast injection [15-17]. Difficulties in interpretation may contain the inability to quantify severe vulnerable plaques, inadequate contrast filling especially into the distal coronary artery parts and small side branches, catheter-

induced spasm of the LIMA, underestimation of eccentric plaques and overprojection of coronary arteries. It should be emphasized that angiography demonstrates anatomy and mechanical function but does not directly establish myocardial ischemia [18].
Over the last years, other promising methods were reported, f.e. multi-slice computed tomography (MSCT) and intravascular, transthoracic and supraclavicular ultrasonography [19-22].
Nowadays, follow up of coronary artery bypass grafts by 16- and 64- MSCT demonstrates high diagnostic accuracy in the assessment of arterial and venous bypass grafts compared with the gold standard of coronary angiography [23-28].
Echo Doppler ultrasonography has become, because of the anatomy of the LIMA and RIMA, an easy method for preoperative internal mammary artery (IMA) screening and postoperative assessment of the in situ IMA graft patency and IMA graft function [29-31].

## 1.3 Blood flow patterns

Blood flow through the heart and vessels can be visualized by Doppler ultrasound. Laminar flow occurs along parallel lines in a vessel so that all the red cells in an area are moving at approximately the seem speed and in the same direction. Flow is always slightly less near the walls of a vessel. With the pulsations of the heart, the red cells generally accelerate and decelerate at approximately the same speed. Flow in the cardiovascular system is mostly laminar and rarely exceeds a maximum velocity of 1.5 m/sec [32].
In contrast, turbulent or disturbed flow is present when there is some obstruction that results in a disruption of the normal laminar pattern. This causes the orderly movement of red blood cells to become disorganized and produces turbulences due to different velocities and directions [32]. Obstruction usually results to increase in blood velocity. Turbulent flow is usually an abnormal finding and is considered indicative of underlying pathology. For example, if the coronary artery blood flow is normal, the flow is laminar. The presence of stenosis will induce a turbulent flow pattern. The resulting flow of blood creates complex flow and velocity characteristics.

### 1.3.1 The Doppler display

All Doppler systems have audio outputs. The changing velocities (frequencies) are converted into audible sounds and emitted from speakers. High pitched sounds result from large Doppler shifts and indicate the presence of high velocities while low pitched sounds result from lesser Doppler shifts. The audio output allows the operator to easily differentiate laminar from turbulent flow. Laminar flow produces a smooth tone because of the uniform velocities. Turbulent flow (different velocities) results in a commonly high pitched raspy sound [32].
Flow velocity toward the transducer is displayed as a positive, or upward, shift in velocities while flow away from the transducer is displayed as a negative, or downward shift in velocities (Fig. 1.1).

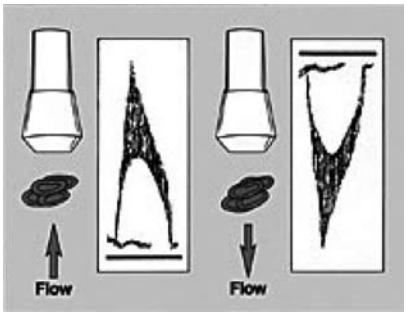


*Figure 1.1. The displayed direction of flow regarded to the transducer. Time is on the horizontal axis.*

When flow is laminar, an envelope of these similar velocities is recorded over time (Fig. 1.2). When flow is turbulent, a spectrum of different velocities results in the spectral broadening of velocities that are low, mid and high and an increase in peak velocity as seen in diseased states (Fig. 1.2).

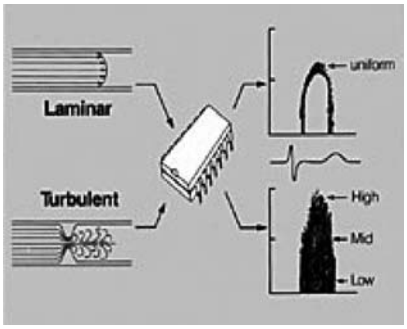


*Figure 1.2. Different blood flow patterns result in different duplex spectra. Time is on the horizontal axis.*

### 1.3.2 Continuous and pulsed wave Doppler

Two types of Doppler echocardiographic systems are in common clinical use today, continuous wave (CW) and pulsed wave (PW) [33].

*Continuous wave Doppler*
CW Doppler involves continuous generation of ultrasound waves coupled with continuous ultrasound reception. A two crystal transducer accomplishes this dual function with one crystal devoted to each function (Fig. 1.3).

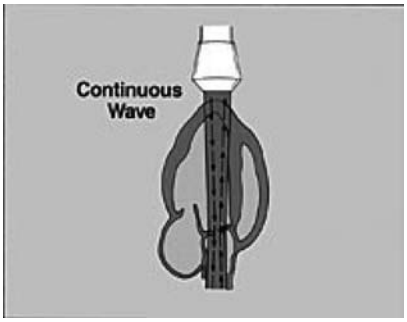


*Figure 1.3. Continuous generation and reception of CW Doppler in the heart.*

The main advantage of CW Doppler is its ability to record the highest velocities in any valvular and congenital heart disease. The main disadvantage of CW Doppler is its lack of selectivity or depth discrimination [32].

*Pulsed wave Doppler*

Pulsed wave (PW) Doppler systems use a transducer that alternates transmission and reception of ultrasound. One main advantage of pulsed Doppler is its ability to provide data selectively from a small segment. An ultrasound pulse is transmitted into the tissues and travels for a given time until it is reflected back by a moving red cell. It then returns to the transducer over the same time interval but at a shifted frequency. It can be calibrated so that as the operator chooses a particular location for the sample volume, the range gate circuit will permit only Doppler shift data from inside that area to be displayed as output. All other returning ultrasound information is essentially "ignored".

The main disadvantage of PW Doppler is its inability to accurately measure blood flow velocities above 1.5 to 2 m/sec.

In general, if a specific area of abnormal flow is to be located pulsed wave Doppler is indicated. If accurate measurement of elevated flow velocity is required, then CW Doppler should be used [32].

Advantages of the ultrasonographic method are:

- it can be performed noninvasively
- there is no harmful radiation
- no specific pre- and post-duplex treatments of the patients are needed
- patients remain conscious
- the method is not painful
- the results are directly visible
- there are relatively low costs of the equipment
- ultrasonography can be performed at rest and during hyperaemic response

### 1.3.3 Preoperative ultrasonography

Preoperative supraclavicular (Fig. 1.4) and transthoracic ultrasound of the LIMA shows predominantly systolic and low diastolic velocity patterns as in peripheral arteries demonstrating the systemic circulation is mainly perfused during the systolic phase [29, 34-35].

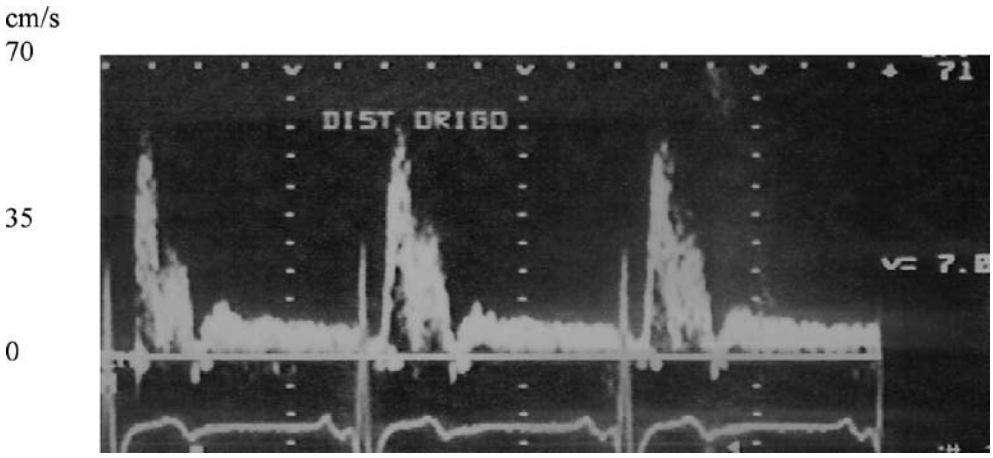


*Figure 1.4. Preoperative supraclavicular ultrasound of the LIMA.*

However, there is a difference in the perfusion pattern between the systemic and coronary circulations. Intramyocardial blood vessels differ from other muscle beds because they exhibit a high resistance, due to high compressive forces of the left ventricle, to blood flow during systole and a low resistance in diastole. Flow in distal epicardial coronary arteries is almost entirely diastolic.
So, after the operation echo Doppler characteristics of the (patent) LIMA bypass graft should show a shift towards diastolic coronary Doppler velocity spectra [34, 36-37].

### 1.3.4 Postoperative ultrasonography

The LIMA graft can be studied by non-invasive ultrasonography from the supraclavicular approach or by transthoracic view. Essentially, the location of either of the examination approaches is not crucial for assessing the patency of the LIMA graft: distal diastolic velocities, as close as possible to the coronary arteries, are higher compared to the proximal diastolic velocities, as far as possible from the coronary arteries but the appearance of a diastolic pattern is considered diagnostic for graft patency as shown in Fig. 1.5 [19, 38-41].

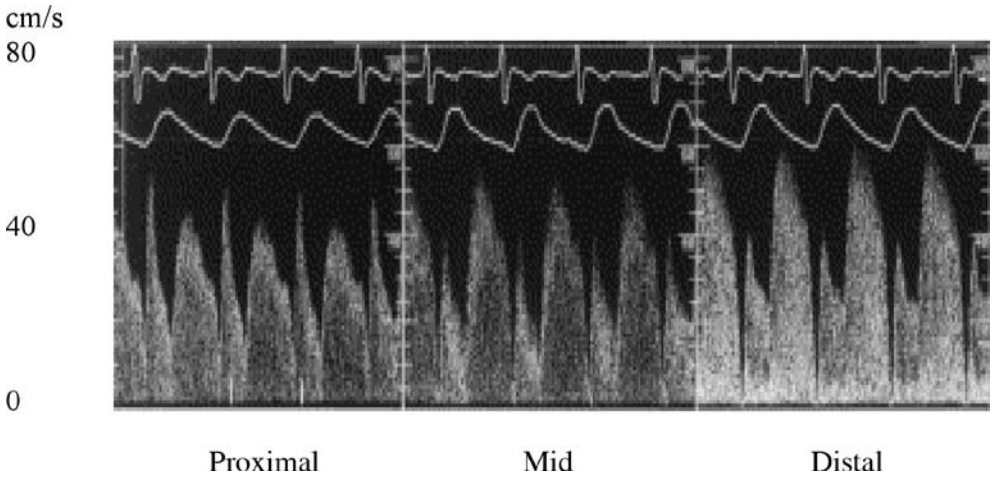


*Figure 1.5. Ultrasound baseline flow recordings in a patent LIMA to the LAD graft.*

However, postoperative diastolic velocity patterns are not always obvious for assessing LIMA graft patency. Therefore, different methods are described for the evaluation of the LIMA graft patency: Takagi et al. [42] stated that a diastolic/systolic peak velocity ratio < 0.6 and a diastolic fraction < 0.5 predict severe LIMA stenosis. Crowley et al. [43] stated that a systolic/diastolic > 1 and a diastolic velocity time integral fraction < 0.5 predict a severe stenosis. In a review report Jones et al. [16] described that the diastolic fraction of less then 0.5 was shown to be the best criteria for prediction of LIMA graft stenosis.

### 1.3.5 String sign of the IMA graft

The luminal diameter of the LIMA graft can become small [44-48]. This “string sign” or “thread phenomenon” is associated with (virtually) no or very low contrast passage at selective angiography. This finding can be crucial for the treatment of a patient especially when a patient has recurrent complaints of angina.
Possible causes for the development of the “string sign” LIMA graft are:

- (chronic) competition induced by a moderate coronary stenosis on the bypassed coronary artery can induce “luminal narrowing or string sign” or even occluded LIMA grafts. However, data are still controversial [34, 49-62].

- operative excessive tension which can cause intimal thickening during the ITA dissection leading to narrowing or obstruction [63-65].
- electrocautery damage during harvesting can cause intimal thickening during the ITA dissection leading to narrowing or obstruction [63-67].
- spasm of the IMA graft [63].
- technical problems [68-69].
- surrounding inflammation as in the postpericardiotomy syndrome [66].
- focal lesions secondary to intimal hyperplasia [70].
- steal phenomenon by large side branches of the IMA graft [71-72].
- regression of the coronary artery stenotic lesion which results in chronic competitive flow [45,73].
- stenosis at the anastomosed site [67].

Follow-up studies reported that the ITA graft increased in diameter as stenosis of the recipient coronary artery advanced and that the ITA graft, which one seemed obstructed, regained patency with progression of the coronary artery lesion [25, 48, 74-75]. These studies of the string sign LIMA graft have demonstrated the late anatomical patency of these (no or low flow) LIMA grafts at (consecutive) angiograms. However, no data are available concerning the use of consecutive noninvasive supraclavicular ultrasonographic performances to analyse velocity spectra in different myocardial conditions in string sign LIMA grafts, documented with angiography at rest. Furthermore, also no quantitative and qualitative analyses are available from string sign and patent LIMA grafts by transthoracic ultrasonography and 64-MSCT scans in a long term follow-up period.

## 1.4 Aim of the study

In this thesis we analyse the value of supraclavicular ultrasonographic velocity spectra in the evaluation of patients with functional and (partial) string sign LIMA grafts to the LAD area at angiography in order to developed criteria to differentiate between functional and (partial) string sign LIMA grafts in the short and mid-term follow-up period. For long-term follow-up transthoracic ultrasonographic LIMA velocity spectra and 64-MSCT scan findings of single LIMA to the LAD and arterial composite T-grafts were analysed to substantiate these data.

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*CHAPTER 2*

# DIFFERENT BEHAVIOR OF SEQUENTIAL VERSUS SINGLE LEFT INTERNAL MAMMARY ARTERY TO LEFT ANTERIOR DESCENDING AREA GRAFTS

JM Hartman
JC Kelder
RGA Ackerstaff
ET Bal
FEE Vermeulen
AJJC Bogers

***Cardiovasc Surg 2001;9:586-594.***

Presented at the 49th International Congress of the European Society for Cardiovascular Surgery, Dresden, Germany, June 24-27, 2000.

## Summary

To study echo Doppler characteristics of sequential versus single left internal mammary artery (LIMA) to left anterior descending (LAD) area grafts transthoracic echo Doppler at the LIMA origin and angiography were performed pre- and postoperatively.

In 17 patients single LIMA to LAD (group I) and in 45 patients sequential LIMA to LAD area (group II) bypass grafting was performed. All patients show an early postoperative shift towards diastolic coronary Doppler velocity spectra. Only group II shows a further significant late increase in diastolic, velocity time integral and some systolic echo Doppler parameters at rest. Diastolic peak and diastolic as well as total mean and velocity time integral maximal values are significantly higher in group II in late postoperative hyperemic response. Preoperative and late control angiography showed no significant differences in overall grading of native LAD stenosis between both groups. The large coronary reserve in LIMA sequential grafts may contribute to an improved long-term patency.

## Introduction

The left internal mammary artery (LIMA) is at present the conduit of choice in myocardial revascularisation of the anterior wall [1-3]. However, there is no consensus whether arterial sequential grafting, when indicated, to the anterior wall is useful.

Over recent years transthoracic echo Doppler of the LIMA at its subclavian origin has been investigated as a noninvasive method to evaluate LIMA grafts postoperatively [4-5]. The LIMA origin is close to the chest wall and can easily be localized in order to study LIMA velocity characteristics. However no study has evaluated echo Doppler at late follow up compared to late angiography.

It is known that postoperative echo Doppler characteristics show a shift towards coronary Doppler velocity spectra [6-8]. We investigated in a prospective study whether the LIMA Doppler characteristics at late follow up as compared with late angiographic follow up were different for single versus sequential LIMA to left anterior descending (LAD) area grafting. Therefore echo Doppler characteristics were analysed late postoperatively at rest, during and after hyperemic response.

## Materials and methods

Sixty-two patients (52 M, 10 F, mean age 62 ± 7.3 years) were prospectively entered in a follow-up study.

The following exclusion criteria were used: age over 75 years, (semi) urgent coronary artery bypass surgery, transmural infarction of the anterior wall, LIMA grafting in previous operation, serious co-morbidity (malignancy, radiation treatment of the chest previously), arterial subclavian stenosis and intended combined cardiac surgery. From all patients informed consent was obtained.

All patients underwent LIMA bypass surgery to the LAD area. In each patient the LIMA was investigated at the origin shortly before the operation and twice postoperatively at 4.8 ± 3.7 months and 1.8 ± 0.9 years. At the late follow-up examination the transthoracic echo Doppler analyses were performed at rest for 1 min, in maximal hyperemic response for 6 min and at rest after hyperemic response for 2 min to obtain a pulsed wave echo Doppler velocity pattern of the LIMA.

Three patients in group I and 10 patients in group II were treated postoperatively with angiotensin converting enzyme-inhibitors until late follow up. Two patients in group II were treated with calcium antagonists until late follow up.

We studied the LIMA from the fossa supraclavicularis and if adequate visualization could not be obtained detection was performed at the first intercostal space to confirm velocity spectra of the LIMA. For the purpose of this study we elected one localization for LIMA detection. All used echo Doppler measurements were obtained from the fossa supraclavicularis.

Postoperative control angiography was performed at 1.5 ± 0.9 years. The angiograms were analysed and quantitatively scored for native disease as well as patency for LIMA grafts and distal anastomoses by two independent observers [9]. In order to evaluate the physiological impact of sequential LIMA grafting two groups with LIMA to LAD area bypass grafting were studied; In 17 patients single LIMA to LAD grafting was performed (group I) and in 45 patients sequential LIMA to LAD area bypass grafting was performed (group II).

In group I 15 LIMA grafts were prepared as pedicle and two were skeletonized. In group II 39 LIMA grafts were prepared as pedicle and six were skeletonized. All but 5 LIMA grafts in group II were treated with intraluminal injection and/or topical application of diluted papaverine solution. No other vasodilating agents were used in preparing the LIMA.

In 11 patients two side to side LIMA anastomoses and 34 patients one side to side LIMA anastomoses were constructed.

*Echo Doppler technique*

Initially we used a model Sonos 2000 ( Hewlett Packard, Andover, MA) and later a Sonos 2500 ( Hewlett Packard, Andover, MA) duplex scanner that both combined B-mode imaging and pulsed Doppler ultrasound to evaluate blood velocity parameters of the LIMA. A 7.5 MHz sector scanner was held at an angle of approximately 60 degrees of the long axis of the LIMA and software with correction for the angle of insonation was used. Blood velocity measurements of the LIMA were recorded during 3-5 cardiac cycles and audiovisually stored. The echo Doppler investigation was performed in supine position of the patients under continuous electrocardiographic control. The acoustic gel was applied to the chest area and the LIMA was localized at

the origin. The data of velocity parameters were analysed off line. The intraobserver variability was tested and less than 2 %.

Patients were allowed to use their usual medication except on the day of late postoperative echo Doppler study because of the hyperemic response test. Before adenosine infusion was started, the LIMA was localized at the origin. After one minute in which LIMA hemodynamic parameters were recorded adenosine infusion (0.14mg/kg/min) started for 6 min [10-11]. Every minute echo Doppler characteristics, electrocardiograms and blood pressures were recorded. When adenosine infusion stopped patients were still monitored continuously for at least 2 min.

The following parameters were analysed: diastolic and systolic peak velocity (DPV and SPV), diastolic, systolic and total mean velocity (DMV, SMV and TMV) and diastolic, systolic and velocity time integral (DVI, SVI and VTI).

The velocity-time integral is the integral of the Doppler spectral instantaneous velocity ($V_i$) over the time interval (T). The integral is approximated by the following sum:

$$VTI = \sum_{i=1}^{n} V_i \times t_i$$

where T is the time interval ( the sum of all $t_i$ time increments).

Total mean velocity is calculated as averaged instantaneous mean of 3-5 cardiac cycles by manual tracing of the phasic velocity spectra.

*Statistical analysis*

Statistical analysis was performed by use of Epi Info 6.04 ( Centers for Disease Control and Prevention, Atlanta, GA) software. All data are expressed as mean ± standard error of the mean. Data within groups were tested by paired and between groups by unpaired *t*-tests. Data was considered statistically significant when the calculated *P*-value was 0.05 or less.

## Results

*Preoperative*

Coronary angiography was performed 3.6 ± 3.0 months before operation and analysed quantitatively.

The degree of LAD stenosis between the two groups was not different: 84.6 ± 12.4 % (group I) versus 82.0 ± 16.7 % (group II), $P = 0.59$.

Transthoracic echo Doppler was studied 2.2 ± 5.2 days before operation. All patients presented in sinus rhythm. In 4 of the 62 patients (6.5 %) prospectively entered in the follow up study, 3 patients in group I and one patient in group II, the LIMA origin could not be identified and in one patient ( 2 %) in group II signals were unreliable. In all of these 5 patients echo Doppler velocity parameters were identified distal of the origin but not used in this study. The mean preoperative values for both groups are shown in Table 1. Hemodynamic values for both groups did not differ: heart rate 61.0 ± 17.5 (group I) versus 59.1 ± 10.4 b/min (group II), $P = 0.62$, systolic blood pressure 148.0 ± 21.8 (group1) versus 141.9 ± 26.2 mmHg (group II), $P = 0.40$ and diastolic blood pressure 80.3 ± 8.2 (group I) versus 80.2 ± 9.4 mmHg (group II), $P = 0.98$. A preoperative sonogram is shown in Fig. 1.

*Early postoperative*

All patients were in sinus rhythm. No patients presented angina and no intercurrent infarction occurred.

Time between surgery and early postoperative transthoracic echo Doppler for the groups was not different: 5.7 ± 3.8 (group I) versus 4.3 ± 3.5 months (group II), $P = 0.22$. In 5 patients (8.1 %), 4 in group I and one in group II echo Doppler detection of the LIMA origin was unsuccessful and in 2 patients (3.2 %), both in group II, echo Doppler signals could not be used. In all of these 7 patients echo Doppler velocity parameters were identified distal of the origin but not used in this study.

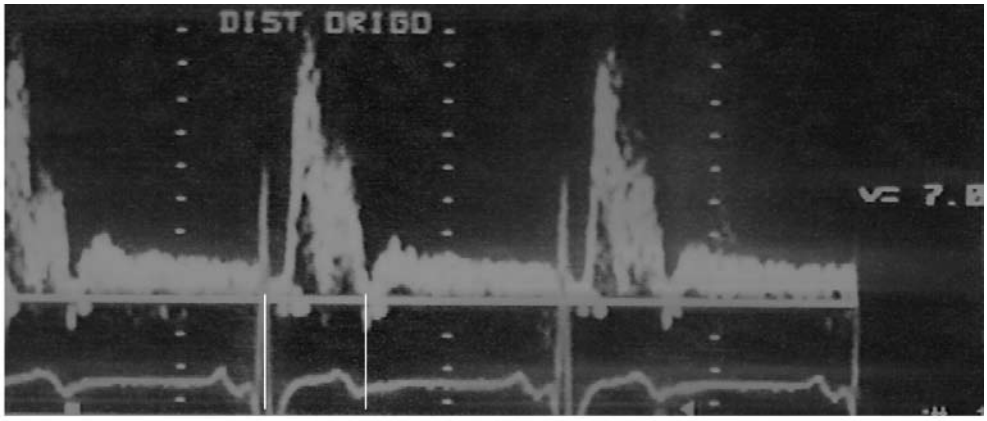
The heart rate increased significantly within groups versus preoperative: 78.2 ± 11.4 b/min (group I), $P < 0.05$ versus 76.0 ± 12.4 b/min (group II), $P < 0.05$. The heart rate between both groups was not different: $P = 0.58$. Systolic blood pressure did not decrease significantly within groups versus preoperative: 134.6 ± 15.6 mmHg (group I), $P = 0.1$ versus 140.9 ± 22.7 mmHg (group II), $P = 0.6$. Systolic blood pressure

between both groups was not different, $P = 0.37$. Diastolic blood pressure did not increase significantly within groups versus preoperative: 79.2 ± 7.9 mmHg (group I), $P = 0.9$ versus 83.8 ± 10.9 mmHg (group II), $P = 0.3$. Diastolic blood pressure between both groups was not different: $P = 0.19$.

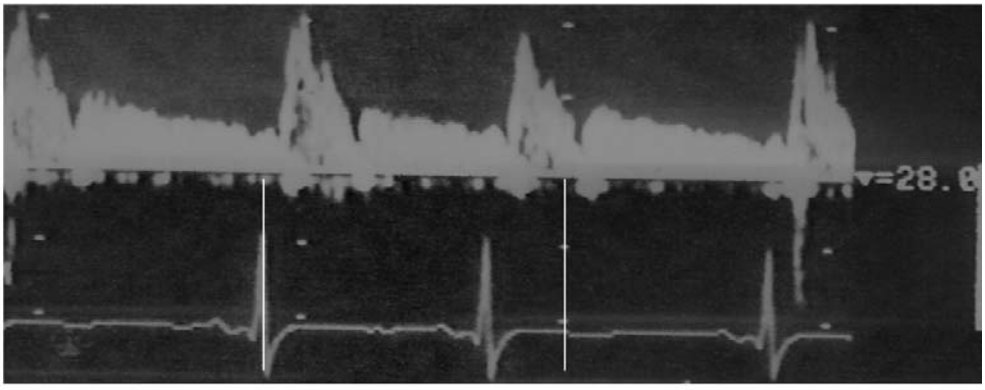
The mean values of early postoperative transthoracic echo Doppler measurements are incorporated in Table 1.

A early postoperative sonogram is shown in Fig. 1.

*Figure 1. (A) Flow velocity pattern of the ungrafted LIMA. (B) Flow velocity pattern of the LIMA 9 months after operation. S = systolic, D = diastolic*




(A) S D




(B) S D

*Table 1. Values of pre- and early postoperative parameters of LIMA echo Doppler*

| | *Preoperative values* | | |
|---|---|---|---|
| | Group I | Group II | |
| DPV (cm/sec) | 13.9 ± 7.6 | 13.6 ± 5.8 | * |
| DVI (cm²) | 5.4 ± 4.1 | 4.5 ± 3.0 | * |
| DMV (cm/sec) | 8.1 ± 7.0 | 6.9 ± 4.7 | * |
| SPV (cm/sec) | 97.4 ± 35.9 | 90.5 ± 26.3 | * |
| SVI (cm²) | 17.1 ± 7.2 | 16.2 ± 5.0 | * |
| SMV (cm/sec) | 49.1 ± 18.5 | 47.0 ± 12.6 | * |
| VTI (cm²) | 22.7 ± 10.3 | 20.6 ± 6.4 | * |
| TMV (cm/sec) | 22.1 ± 10.7 | 20.4 ± 6.3 | * |

| | *Early postoperative values* | | | | |
|---|---|---|---|---|---|
| | Group I | ** | Group II | | ** |
| DPV (cm/sec) | 38.8 ± 18.9 | < 0.01 | 33.0 ± 12.4 | * | < 0.001 |
| DVI (cm²) | 11.3 ± 5.7 | < 0.01 | 11.8 ± 4.9 | * | < 0.001 |
| DMV (cm/sec) | 25.5 ± 13.1 | < 0.01 | 22.8 ± 9.1 | * | < 0.001 |
| SPV (cm/sec) | 62.9 ± 15.6 | < 0.02 | 52.0 ± 16.7 | * | < 0.001 |
| SVI (cm²) | 9.7 ± 2.7 | < 0.02 | 9.1 ± 3.1 | * | < 0.001 |
| SMV (cm/sec) | 35.5 ± 9.1 | < 0.04 | 32.0 ± 10.2 | * | < 0.001 |
| VTI (cm²) | 20.9 ± 7.9 | n.s. | 20.9 ± 7.2 | * | n.s. |
| TMV (cm/sec) | 29.1 ± 11.4 | < 0.05 | 26.1 ± 8.7 | * | < 0.002 |

DPV, diastolic peak velocity; DVI, diastolic velocity integral; DMV, diastolic mean velocity; SPV, systolic peak velocity; SVI, systolic velocity integral; SMV, systolic mean velocity; VTI, velocity time integral; TMV, total mean velocity. * *P* values are not significant for data between both groups preoperative and early postoperative. ** *P* values within groups for early postoperative versus preoperative data. Data are mean ± standard deviation. n.s.: not significant.

*Late postoperative*

Time between surgery and late postoperative transthoracic echo Doppler for the groups was not different: 1.8 ± 0.9 (group I) versus 1.9 ± 0.9 years (group II), $P = 0.84$. All patients were in sinus rhythm. In all patients echo Doppler detection was successful and all echo Doppler signals could be used. The mean values of transthoracic echo Doppler measurements are incorporated in Table 2.

*At rest*

The heart rate did not increase significantly within groups versus early postoperative but did increase significantly versus preoperative: 79.8 ± 12.3 b/min (group I) $P < 0.05$ and 74.5 ± 11.3 b/min (group II), $P < 0.05$. The heart rate between both groups was not different: $P = 0.14$. Systolic blood pressure did not differ within groups versus early postoperative and preoperative. Values versus preoperative: 141.9 ± 25.9 mmHg (group I), $P = 0.56$ and 140.5 ± 22.0 mmHg (group II), $P = 1.0$. Systolic blood pressure between both groups was not different: $P = 0.84$.

Diastolic blood pressure differs within groups versus preoperative in group II but did not in group I: 86.3 ± 10.9 mmHg (group I), $P = 0.07$ and 88.4 ± 11.5 mmHg (group II), $P = 0.0001$. Diastolic blood pressure differs within groups versus early postoperative in group I but did not in group II: $P < 0.04$ (group I) and $P = 0.08$ (group II). Diastolic blood pressure between both groups was not different: $P = 0.53$.

Only one patient presented angina related to the occlusion of the venous graft to the right coronary artery. After the successful PTCA procedure the patient stayed asymptotic until the late postoperative follow-up analyses.

Only in group II all diastolic echo Doppler velocity values increased significantly as compared to the early postoperative values: DPV 37.2 ± 15.1 versus 33.0 ±12.4 cm/s, $P < 0.01$, DVI 13.5 ± 5.1 versus 11.8 ± 4.9 cm², $P < 0.001$, DMV 26.2 ± 10.6 versus 22.8 ± 9.1 cm/s, $P < 0.001$. VTI and TMV also increases significantly : VTI 23.3 ± 8.1 versus 21.0 ± 7.2 cm², $P < 0.001$ and TMV 29.0 ± 10.9 versus 26.1 ± 8.7 cm/s, $P < 0.01$. In group I no significant increases were measured.

Differences between groups were significant for all diastolic, velocity time integral and total mean velocity parameters: DPV 33.2 ± 12.8 (group I) versus 37.2 ± 15.1 cm/s (group II), $P < 0.04$, DVI 10.6 ± 4.3 (group I) versus 13.5 ± 5.1 cm² (group II), $P < 0.04$, DMV 22.2 ± 9.8 (group I) versus 26.2 ± 10.6 cm/s (group II), $P < 0.03$, VTI

19.8 ± 7.1 (group I) versus 23.3 ± 8.1 cm² (group II), $P < 0.05$ and TMV 25.1 ± 9.1 (group I) versus 29.0 ± 10.9 cm/s (group II), $P < 0.04$.

The mean values of late postoperative transthoracic echo Doppler measurements at rest are incorporated in Table 2. A late postoperative sonogram at rest is shown in Fig. 2.

*Figure 2. (A) Flow velocity pattern of the LIMA 2 years after operation. (B) Flow velocity pattern of the LIMA 2 years after operation during adenosine infusion. S = systolic, D = diastolic*

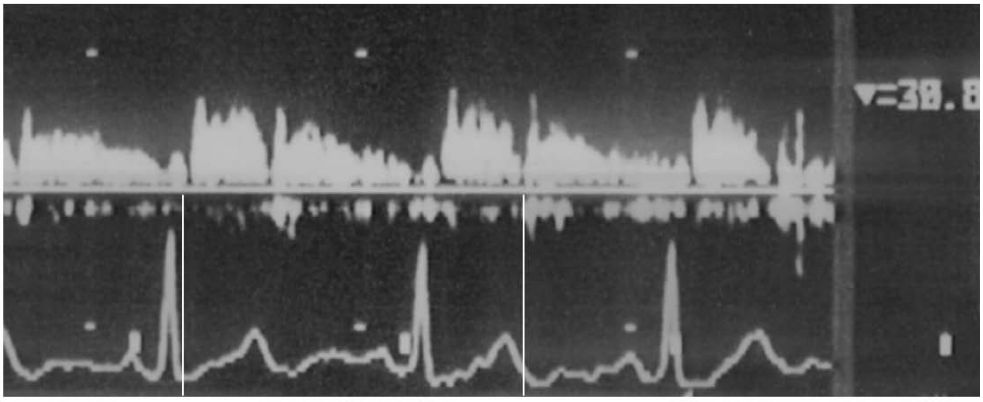


*Table 2. Echo Doppler velocities for late postoperative at rest, maximal hyperaemic values, maximal increase in percentage and maximal hyperemic response values*

| | | *Late postoperative values at rest* | | | | |
|---|---|---|---|---|---|---|
| | | Group I | * | Group II | * | ** |
| DPV | (cm/sec) | 33.2 ± 12.8 | n.s. | 37.2 ± 15.1 | < 0.002 | n.s. |
| DVI | (cm²) | 10.6 ± 4.3 | n.s. | 13.5 ± 5.1 | < 0.001 | n.s. |
| DMV | (cm/sec) | 22.2 ± 9.8 | n.s. | 26.2 ± 10.6 | < 0.001 | n.s. |
| SPV | (cm/sec) | 51.7 ± 19.1 | n.s. | 54.4 ± 20.8 | n.s. | n.s. |
| SVI | (cm²) | 9.1 ± 3.2 | n.s. | 9.9 ± 4.0 | < 0.02 | n.s. |
| SMV | (cm/sec) | 29.9 ± 8.6 | n.s. | 34.0 ± 13.5 | < 0.06 | n.s. |
| VTI | (cm²) | 19.8 ± 7.1 | n.s. | 23.3 ± 8.1 | < 0.001 | n.s. |
| TMV | (cm/sec) | 25.1 ± 9.1 | n.s. | 29.0 ± 10.9 | < 0.003 | n.s. |

| | | *Maximal hyperemic values* | | |
|---|---|---|---|---|
| | | Group I | Group II | ** |
| DPV | (cm/sec) | 86.7 ± 29.9 | 103.7 ± 26.6 | < 0.05 |
| DVI | (cm²) | 24.3 ± 8.4 | 30.7 ± 10.3 | < 0.04 |
| DMV | (cm/sec) | 63.3 ± 22.7 | 76.9 ± 22.1 | < 0.05 |
| SPV | (cm/sec) | 82.4 ± 24.7 | 93.0 ± 24.3 | n.s. |
| SVI | (cm²) | 16.9 ± 4.9 | 18.8 ± 5.4 | n.s. |
| SMV | (cm/sec) | 60.3 ± 18.3 | 69.5 ± 19.9 | n.s. |
| VTI | (cm²) | 40.4 ± 12.1 | 49.0 ± 13.7 | < 0.04 |
| TMV | (cm/sec) | 61.3 ± 20.2 | 73.9 ± 19.9 | < 0.04 |

*Table 2 continued*

| | | *Maximal increase in percentage* | | | | |
|---|---|---|---|---|---|---|
| | | Group I | * | Group II | * | ** |
| DPV | (cm/sec) | 273.0 ± 86.4 | < 0.001 | 306.3 ± 96.9 | < 0.001 | n.s. |
| DVI | (cm²) | 238.0 ± 64.0 | < 0.001 | 245.3 ± 80.0 | < 0.001 | n.s. |
| DMV | (cm/sec) | 307.9 ± 126.7 | < 0.001 | 322.5 ± 108.2 | < 0.001 | n.s. |
| SPV | (cm/sec) | 172.8 ± 64.2 | < 0.001 | 185.9 ± 61.1 | < 0.001 | n.s. |
| SVI | (cm²) | 195.4 ± 54.5 | < 0.001 | 207.9 ± 69.5 | < 0.001 | n.s. |
| SMV | (cm/sec) | 207.9 ± 59.4 | < 0.001 | 220.0 ± 66.5 | < 0.001 | n.s. |
| VTI | (cm²) | 211.4 ± 57.0 | < 0.001 | 224.3 ± 67.3 | < 0.001 | n.s. |
| TMV | (cm/sec) | 256.2 ± 84.7 | < 0.001 | 276.2 ± 87.9 | < 0.001 | n.s. |

| | | *Maximal hyperemic response values* | | | | |
|---|---|---|---|---|---|---|
| | | Group I | * | Group II | * | ** |
| DPV | (cm/sec) | 53.4 ± 24.0 | < 0.001 | 66.5 ± 21.6 | < 0.001 | n.s. |
| DVI | (cm²) | 13.7 ± 6.5 | < 0.001 | 17.2 ± 8.3 | < 0.001 | n.s. |
| DMV | (cm/sec) | 40.9 ± 19.5 | < 0.001 | 50.6 ± 18.3 | < 0.001 | n.s. |
| SPV | (cm/sec) | 30.7 ± 23.3 | < 0.001 | 38.6 ± 18.1 | < 0.001 | n.s. |
| SVI | (cm²) | 7.8 ± 4.3 | < 0.001 | 8.9 ± 4.1 | < 0.001 | n.s. |
| SMV | (cm/sec) | 30.5 ± 15.7 | < 0.001 | 35.4 ± 13.9 | < 0.001 | n.s. |
| VTI | (cm²) | 20.5 ± 10.2 | < 0.001 | 25.7 ± 10.7 | < 0.001 | n.s. |
| TMV | (cm/sec) | 36.3 ± 17.3 | < 0.001 | 44.9 ± 15.8 | < 0.001 | n.s. |

Echo Doppler velocity parameters as described in Table 1. * *P* values for data within groups late postoperative versus early postoperative, maximal increase in percentage and in absolute values for hyperemic response. ** *P* values for data between both groups late postoperative, for absolute maximal values during hyperemic response, for maximal response in percentage and for maximal hyperemic response values. Data are mean ± standard deviation. n.s.: not significant.

*Maximal hyperemic response*

Hemodynamic values for both groups did not differ: heart rate 97.1 ± 14.1 (group I) versus 97.1 ± 12.4 b/min (group II), $P = 1.0$, systolic blood pressure 152.4 ± 25.5 (group I) versus 152.1 ± 22.4 mmHg (group II), $P = 0.96$ and diastolic blood pressure 92.6 ± 10.3 (group I) versus 92.8 ± 11.1 mmHg (group II), $P = 0.96$.

In one patient (group II) adenosine infusion was stopped after 2 min because of shortness of breath. Missing data of this patient were not extrapolated.

All systolic and diastolic echo Doppler velocity parameters increased significantly in absolute values as well as expressed as percentage of the resting values during hyperemic response in both groups.

Between the groups no differences were measured. When analyzing the maximal increase of the hyperemic response minus the values at rest no differences between the groups appeared. However the DPV values for group II were close to significance, $P = 0.052$. Analyzing the maximal values of the hyperemic response, all diastolic, total velocity integral and total mean velocity parameters were significant different between the groups.

The mean values of maximal hyperemic response are incorporated in Table 2. A late postoperative sonogram at hyperemic response is shown in Fig. 2.

*Residual hyperemic response 2 minutes after stopping adenosine infusion*

All hemodynamic and transthoracic echo Doppler data were obtained 2 minutes after stopping adenosine infusion. All hemodynamic values decreased significantly within groups versus maximal hyperemic response. Systolic blood pressure: 125.0 ± 10.5 mmHg (group I), $P < 0.001$ versus 135.5 ± 21.6 mmHg (group II), $P < 0.001$ Systolic blood pressure between both groups was not different: $P = 0.15$. Diastolic blood pressure: 80.5 ± 6.0 mmHg (group I), $P < 0.001$ versus 75.9 ± 9.9 mmHg (group II), $P < 0.001$. Diastolic blood pressure between both groups was different: $P < 0.05$. Heart rate: 87.6 ± 13.9 b/min (group I) $P < 0.001$ versus 83.7 ± 9.6 b/min (group II), $P < 0.001$. Heart rate between both groups was not different: $P = 0.84$.

All diastolic and total mean echo Doppler velocity values decreased significantly but did not decrease to values at rest: DPV 134.2 ± 38.0 % (group I) versus 134.4 ± 47.4 % (group II), DVI 108.5 ± 31.3 % (group I) versus 111.1 ± 38.0 % (group II), DMV 131.4 ± 47.5 % (group I) versus 131.8 ± 50.6 % (group II) and TMV 114.6 ± 37.3 %

(group I) versus 121.0 ± 41.4 % (group II). No differences were measured between both groups.

Velocity time integral and all systolic echo Doppler velocity values decreased significantly to values at rest or less: VTI 99.3 ± 29.6 % (group I) versus 107.4 ± 34.6 % (group II), SPV 97.2 ± 32.8 % (group I) versus 106.6 ± 34.2 % (group II), SVI 89.8 ± 27.8 % (group I) versus 102.3 ± 34.5 % (group II) and SMV 98.2 ± 31.2 % (group I) versus 105.6 ± 32.8 % (group II).

No differences were measured between both groups. Transthoracic mean echo Doppler measurements two minutes after stopping adenosine infusion are incorporated in Table 3.

*Table 3. Echo Doppler of LIMA residual values after adenosine infusion was stopped for two minutes*

| | | *Two minutes after hyperemic response* | | | | |
|---|---|---|---|---|---|---|
| | | Group I | * | Group II | * | ** |
| DPV | (cm/sec) | 43.9 ± 19.0 | < 0.001 | 46.2 ± 17.1 | < 0.001 | n.s. |
| DVI | (cm²) | 11.4 ± 5.0 | < 0.001 | 13.8 ± 4.7 | < 0.001 | n.s. |
| DMV | (cm/sec) | 28.6 ± 15.9 | < 0.001 | 31.6 ± 11.8 | < 0.001 | n.s. |
| SPV | (cm/sec) | 47.9 ± 17.1 | < 0.001 | 55.0 ± 21.3 | < 0.001 | n.s. |
| SVI | (cm²) | 8.0 ± 3.1 | < 0.001 | 9.7 ± 3.9 | < 0.001 | n.s. |
| SMV | (cm/sec) | 29.5 ± 11.7 | < 0.001 | 34.3 ± 13.2 | < 0.001 | n.s. |
| VTI | (cm²) | 19.5 ± 7.9 | < 0.001 | 23.6 ± 7.7 | < 0.001 | n.s. |
| TMV | (cm/sec) | 28.6 ± 13.3 | < 0.001 | 32.8 ± 11.2 | < 0.001 | n.s. |

Echo Doppler velocity parameters as described in Table 1. * *P* values within groups for data of maximal values during hyperemic response minus residual hyperemic values after adenosine infusion was stopped for two minutes. ** *P* values between groups for data of maximal values during hyperemic response minus residual hyperemic values after adenosine infusion was stopped for two minutes. Data are mean ± standard deviation. n.s.: not significant.

*Postoperative control angiography*

Late control angiography was performed 1.5 ± 0.9 years after operation and analysed quantitatively. Differences in time between both groups were not significant: $P$ = 0.08 versus preoperative angiography, $P$ = 0.09 versus date of operation and $P$ = 0.13 versus late postoperative echo Doppler.

In 2 patients (3.2 %), one patient in group I and one patient in group II, late postoperative angiography was not performed. Missing data of these patients were not extrapolated.

All LIMA pedicles were patent. In 2 LIMA grafts end to side anastomoses were arguably obstructed.

Except one LIMA graft all were selectively injected. In one patient in group I LIMA origin detection was not successful but contrast injection in the native coronary system showed competition by the LIMA graft inflow. Data of these three grafts were not excluded because LIMA Doppler characteristics showed postoperatively a shift towards coronary Doppler velocity spectra.

The degree of LAD stenosis between the two groups was not different: 89.9 ± 12.5 % (group I) versus 86.3 ± 18.9 % (group II), $P$ = 0.48. In group II the degree of stenosis in the first diagonal side branch was 80.5 ± 21.2 % versus 72.1 ± 21.6 % preoperatively and in the second diagonal side branch 89.0 ± 14.5 % versus 80.9 ± 19.9 % preoperatively.

## Discussion

As shown by Takagi et al. [12] non-invasive supraclavicular duplex Doppler and invasive Doppler catheter measurements for flow patterns of the LIMA grafts show an excellent correlation.

Several groups investigated transthoracic echo Doppler velocity patterns of the ungrafted and grafted LIMA in different detection locations. Adequate visualization of the LIMA ranges from less then 80 % to nearly 100 % [5, 13-16].

In our investigation the visualization was successful in 91.5 % preoperatively, in 88.7 % early postoperatively and in 100 % late postoperatively.

In our opinion it is debatable to rely on the LIMA diameter as measured transcutaneously. Therefore the velocity data can not be transformed into flow.

We performed in both study groups echo Doppler measurements and late control angiography at the same postoperative time interval hence measurements could be compared easily.

At preoperative investigation transthoracic echo Doppler of the LIMA shows predominantly systolic velocity patterns as can be expected from a systemic artery. Postoperatively LIMA echo Doppler characteristics show a shift towards diastolic coronary Doppler velocity spectra [6-7]. In all patients systolic velocity integral decreases and diastolic velocity integral increases postoperatively versus preoperatively.

Coronary hyperemic response has been investigated by transthoracic echo Doppler by some investigators as a method to discriminate between intact and/or compromised outflow of the LIMA [6, 17]. Detection of distal pedicle or outflow lesions was however not the aim of our study. Hence we included data from the supraclavicular fossa of patients with apparently 'string-sign' LIMA grafts. All of them presented predominant diastolic velocity patterns before adenosine infusion was started.

Adenosine infusion to measure the coronary reserve was chosen as the preferred method in order to obtain reliable supraclavicular repetitive measurements in a relaxed patient in stable supine position during the hyperemic test. In our study late control coronary angiography showed patent LIMA pedicles in all patients and the overall grading of native LAD stenosis between both groups did not differ. All systolic, diastolic and total velocity parameters increased significantly during adenosine infusion compared to baseline within both groups but all diastolic velocity patterns predominated. All velocity parameters within groups increased significantly ($P < 0.001$).

We used values of measurements at rest and in hyperemic response to evaluate if the use of sequential grafting technique could indicate a higher flow as judged from the velocity parameters or a higher flow carrying capacity in sequential versus single grafts. At rest in late postoperative follow up, diastolic, systolic and total velocity parameters did not differ. As mentioned before, during hyperemic response all velocity parameters increased in absolute as well as percentage within both groups. In group II all velocity parameters increased more in absolute as well as percentage during hyperemic response compared to group I. Between the groups, diastolic peak velocity and diastolic mean velocity were close to significance, $P < 0.06$ resp. $P < 0.09$.

We demonstrated that diastolic as well as total velocity parameters increased in time in group II. Absolute values of all velocity parameters measured at rest in the late postoperative follow-up are higher in group II compared to group I. Our study demonstrates progressive diastolic and total velocity characteristic increase in sequential LIMA grafting in time. We also demonstrate that absolute maximal hyperemic values differ significantly between both groups. The large coronary reserve we demonstrated in LIMA sequential grafts may contribute to an improved long-term patency. Considering the results, LIMA to LAD area sequential grafting technique appeared to be a reliable technique in coronary revascularization and appears indicated when diagonal branch stenosis are present in the LAD area.

Our study has some limitations: first, we did not correct differences in individual patients so far. In some patients pre- and postoperatively LAD stenosis did not differ and in others LAD stenosis increased or decreased postoperatively. Corrections for these inter-individual differences were not taken into account. Furthermore, individual patient echo Doppler velocity patterns were not studied closely so far. We know that in some patients residual intercostal branches originated from IMA grafts, so far we did not take this variable into account. Finally, our conclusions regarding sequential arterial grafting are limited to in situ LIMA with one or two side to side anastomoses to the LAD area. Further studies are needed to demonstrate that these findings could also apply to other revascularization areas or to the in situ right internal mammary artery.

## Conclusions

(1) Duplex Doppler echography from the supraclavicular fossa can detect LIMA graft velocities with high sensitivity rate. (2) In all patients LIMA Doppler characteristics show postoperatively a shift towards coronary Doppler velocity spectra. (3) Only sequential LIMA grafts show a further significant late increase in diastolic, velocity time integral and some systolic Doppler parameters. (4) All LIMA grafts show significant hyperemic response; in both groups in absolute as well as percentage increase. However, the diastolic peak and diastolic as well as total mean and integral maximal values are significantly higher in sequential LIMA grafts. (5) LIMA to LAD area sequential grafting technique appeared to be a reliable technique in

coronary revascularization. (6) The large coronary reserve in LIMA sequential grafts may contribute to an improved long-term patency. (7) We confirm the excellent performance of LIMA grafts.

*Acknowledgments*

This study was financed by The Netherlands Heart Foundation Grant 89.258

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*CHAPTER 3*

# DIFFERENCES IN LIMA DOPPLER CHARACTERISTICS FOR DIFFERENT LAD PERFUSION AREAS

JM Hartman
JC Kelder
RGA Ackerstaff
FEE Vermeulen
AJJC Bogers

***Eur J Cardiothorac Surg 2001;20:1135-1141.***

Presented at the 14th Annual Meeting of the European Association for Cardiothoracic Surgery, Frankfurt, Germany, October 7-11, 2000.

## Abstract

Objective: To correlate supraclavicular left internal mammary artery (LIMA) to left anterior descending artery (LAD) area Doppler characteristics with angiographically perfused area.

Methods: Sixty patients (50 M, mean age 62 ± 7.3 years) with LIMA to LAD area grafting were prospectively entered in a follow up study. Supraclavicular echo Doppler of the LIMA was studied at the LIMA origin preoperatively and at 4.8 ± 3.8 months and 1.8 ± 0.9 years postoperatively. The potential area to be revascularized judged from preoperative angiography was called the "target" area. Control angiography (native and LIMA) was done at 1.5 ± 0.9 years. The perfused area % was classified into group I ≤ 17.0 % (n = 16), group II > 17.0 % and < 22.50 % (n = 17) and group III ≥ 22.50 % (n = 18) and related to LIMA Doppler characteristics. Multivariate linear regression analyses (MLRA) was performed to assess the relations between Doppler variables and the perfused area, target area and ratio of perfused/target area.

Results: At MLRA perfused area was significantly related to the natural logarithm of diastolic peak velocity (DPV) ($P$ = 0.013) and diastolic mean velocity ($P$ = 0.048) and the ratio only to the degree of LAD stenosis ($P$ = 0.004). In hyperaemic response maximal DPV (DPV max) showed significant correlation to the perfused area ($P$ = 0.005) as well as to the ratio ($P$ = 0.017). When analyzing the additive power of both investigations, only DPV max ($P$ = 0.005) correlated significantly to the perfused area and for the ratio only the degree of stenosis of the LAD emerged as significant ($P$ = 0.004).

Conclusions: At MLRA the diastolic flow pattern at rest and the maximal DPV in hyperaemic response correlated significantly with the LIMA run off area whereas the last variable is the strongest predictor of the LIMA run off area.

## Introduction

The internal mammary artery (IMA) is the conduit of choice for single or sequential coronary artery revascularisation in view of its long term patency [1-3]. In this regard postoperative control angiography is the gold standard for assessing IMA graft patency. Over the last years transthoracic echo Doppler has become a frequently used non invasive method for postoperative assessment of the IMA graft patency. The IMA origin is close to the chest wall and can be detected at its origin or in the first or second intercostal space in order to evaluate IMA graft patency by Doppler velocity characteristics [4-6].

Differences in postoperative transthoracic echo Doppler velocity spectra caused by different degrees of left anterior descending artery (LAD) stenosis have already been described [7]. We analyzed whether left IMA (LIMA) Doppler velocity characteristics at late follow up at rest and in hyperaemic response correlate with perfusion areas, as determined at late postoperative angiography, in order to assess the reliability of echo Doppler studies as a non-invasive method for functional assessment of IMA grafts.

## Materials and methods

Sixty consecutive patients (50 M, 10 F, mean age 61.8 ± 7.3 years) who planned to undergo LIMA bypass surgery to the LAD area were prospectively entered in a follow- up study. Exclusion criteria included an age of over 75 years, urgent coronary artery bypass surgery, patients with transmural infarction of the LAD perfusion area, previous LIMA grafting, serious co-morbidity (malignancy, previous radiation treatment of the chest), subclavian artery stenosis and other combined cardiac surgery. Informed consent was obtained from all patients. Aiming at total revascularisation of the LAD area, all graftable and significantly stenotic diagonal branches were bypassed as well with the LIMA pedicle.

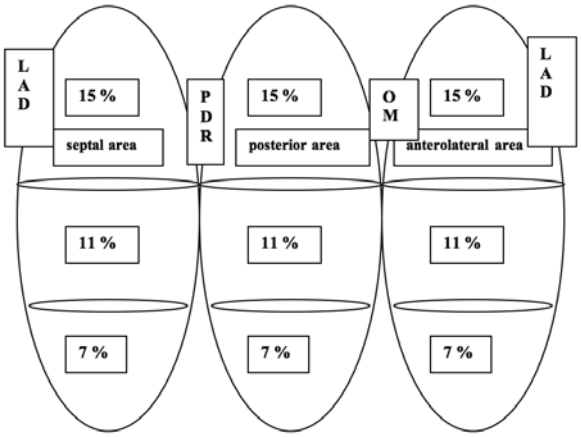
In each patient the LIMA was investigated at its origin shortly before the operation and twice postoperatively at 4.8 ± 3.8 months and 1.8 ± 0.9 years. At late follow up examination the echo Doppler analyses were performed at rest for 1 min and in hyperaemic response for 6 min to obtain a pulsed wave echo Doppler velocity pattern

of the LIMA. For the purpose of this study we analyzed only patients in whom all LIMA velocity patterns were obtained from the supraclavicular approach.

Postoperative control angiography was performed at 1.5 ± 0.9 years. The angiograms were analyzed by two independent observers and assessed for the following aspects: native coronary artery stenosis [8], patency and proximal diameter of the LIMA grafts, percentage stenosis of distal anastomoses and native vessel competitive flow in the LIMA perfusion areas. Diameters of the proximal LIMA at angiography and of the tip of the catheter with a known diameter used for LIMA visualization were determined by callipers.

In order to assess perfusion areas, the perfused areas at angiography were drawn on a graded left ventricular surface map. This map was constructed according to the ventricular-slice method described by Edwards et al. [9]. The proportional importance of the anterolateral, posterolateral and septal area as well as the subdivisions in proximal, middle and distal areas were based on analyses performed in five specimens in the Department of Pathology of the St. Antonius Hospital, Nieuwegein, The Netherlands. The obtained subdivisions of 33, 15, 11 and 7 % were also extensively used and tested in studies on surface estimation for assessment of left ventricular endocardial resection in postinfarction arrhythmia surgery [10] (Fig. 1).

*Figure 1. Classification in the ventricular-slice method for assessing perfusion areas*




(Edwards et al. [9])

LAD, left anterior descending artery; PDR, posterior descending artery; OM, obtuse marginal artery.

As only anteroseptal areas were compared one can assume that between groups systematic deviation would be balanced. The same is true for transformation of areas into muscle mass: between groups no differences were present regarding the presence of hypertension and/or left ventricular hypertrophy; no patients with transmural anteroseptal infarction were included and any systematic under- or overestimation would probably be balanced within the subgroups analyzed. The "target" area was the potential area intended to be revascularized by the LIMA graft as judged from the preoperative coronary angiography.

During late postoperative native and LIMA angiography the "perfused" area was drawn on the surface map and expressed as surface percentage. At both injections competitive flow was visually assessed by two independent observers looking at to and fro movements of contrast. The perfused area was the surface percentage obtained on repetitive estimations by adding two perfusion areas: the one exclusively filled at the LIMA injections counted for 100 % and the competitive area – filled as well at the LAD as at the LIMA injection – was estimated to belong to the LIMA perfusion area for 0-100 % depending on the severity of competition. The investigators grading the perfusion areas were blinded for the results obtained with the Doppler data analysis. Perfused areas served to classify patients into three almost equally sized groups: group I with a perfused area less than or equal to 17 %; group II with a perfused area between 17.0 and 22.5 %; and group III with a perfused area greater than or equal to 22.5 %.

Group I consisted of 16 patients (12 M, 4 F, mean age 66.4 ± 4.5 years) with 6 single LIMA to LAD, 8 LIMA jump grafts to the LAD area and 2 LIMA triple jump grafts to the LAD area. In group II were 17 patients (12 M, 5 F, mean age of 57.8 ± 7.5 years) with 4 single LIMA to LAD, 10 LIMA jump grafts to the LAD area and 3 LIMA triple jump grafts to the LAD area. In group III were 18 patients (17 M, 1 F, mean age 60.3 ± 7.1 years) with 4 single LIMA to LAD, 12 LIMA jump grafts to the LAD area and 2 LIMA triple jump grafts to the LAD area.

Nine patients were excluded from the study; In 6 patients the late postoperative echo Doppler investigation was not performed and in 3 patients technical failures in detecting echo Doppler signals occurred during the hyperaemic study.

*Echo Doppler technique*

Initially we used a model Sonos 2000 ( Hewlett Packard, Andover, MA) and later a Sonos 2500 ( Hewlett Packard, Andover, MA) duplex scanner that both combined B-mode imaging and pulsed Doppler ultrasound to evaluate blood velocity parameters of the LIMA. The echo Doppler investigation was performed with the patients in the supine position under continuous electrocardiographic and blood pressure control after 3 min of resting.

A 7.5 MHz sector scanner was held at an angle of approximately 60 degrees of the long axis of the LIMA at the origin and software with correction for the angle of insonation was used. Only values obtained from the supraclavicalar approach were used for the evaluation. The diameter of the proximal LIMA was also determined only at rest.

Spectral analysis of IMA Doppler velocity recording was performed during three to five cardiac cycles. The data of velocity parameters were analyzed off line. The intraobserver variability was tested and was less than 2 %.

Patients were allowed to use their usual medication except on the day of late postoperative echo Doppler study because of the hyperaemic response test. Before adenosine infusion was started the LIMA was localized at the origin and resting values were determined. After 1 min, adenosine infusion (0.14 mg/kg per min) was started for 6 min. Every minute echo Doppler characteristics and electrocardiograms were recorded. Of all Doppler registrations the following parameters were analyzed: diastolic and systolic peak velocity (DPV and SPV), diastolic, systolic and total mean velocity (DMV, SMV and TMV) and diastolic, systolic and total velocity integral (DVI, SVI and TVI).

The velocity-time integral is the integral of the Doppler spectral instantaneous velocity (Vi) over the time interval (T) [6,11].

DMV, SMV and TMV are calculated as the averaged instantaneous mean of 3-5 cardiac cycles by manual tracing of the appropriate phasic velocity spectra.

*Statistical analysis*

Data entry, descriptive statistics and univariate statistical analyses were performed with the use of Epi Info 6.04c (CDC, Atlanta, GA). Non-parametric tests and multivariate linear regression analyses were performed with the use of SAS 8 (SAS

Institute Inc., Cary, NC). Within groups comparisons were tested with the paired t-test or Wilcoxon test where appropriate; if the data were skewed to the right the logarithmic transformation was used; no formal statistical hypothesis test for normality was used. To assess univariately the qualitative (be it linear or not) and quantitative relation between perfused areas and predictors the perfused areas were subdivided into three ordered groups: low, mid and high.

After estimating the univariate linear relation with perfused areas we performed the multivariate linear regression analyses with forward selection, setting the *P* value for entry at 0.15. When modelling the perfused areas the addition of the percentage stenosis of the proximal LAD appeared to be a significant predictor. We choose not to include this variable in the model because the perfused area already takes the LAD stenosis into account and therefore is not a confounder by definition. The other predictor variable regression parameters did not change notably.

Modelling was also performed for the target area and the ratio of the perfused over target area.

## Results

*Preoperative coronary angiography*

Coronary angiography was performed 3.6 ± 3.0 months before operation. The degrees of native coronary vessel stenosis of the anterior wall are shown in Table 1. The target areas of the three subgroups were larger than the perfused areas as expected and were not statistically different between the three groups.

*Early postoperative echo Doppler*

The time interval between surgery and the early postoperative transthoracic echo Doppler evaluation was not different between the groups ($P = 0.88$) All patients were in sinus rhythm. No patients presented angina and no intercurrent infarction occurred. The mean proximal LIMA diameters were 2.69 ± 0.56 mm and were statistically significant smaller than preoperative ($P = 0.0012$).

All diastolic echo Doppler velocity parameters increased significantly and all systolic parameters decreased significantly compared to the preoperative echo Doppler values while the total velocity integral did not change. These preoperative data are not

included because they were not part of the present analysis. All early postoperative echo Doppler values are incorporated in Table 2.

*Table 1. Degree of native coronary vessel stenoses of the anterior wall*[a]

| | Group I | Group II | Group III | *P* |
|---|---|---|---|---|
| *Preoperative* | | | | |
| LAD stenosis | 76.4 ± 17.1 | 82.7 ± 12.4 | 88.0 ± 15.4 | 0.092 |
| First diagonal branch stenosis | 56.7 ± 28.6 | 77.8 ± 17.5 | 79.0 ±19.7 | 0.039 |
| Second diagonal branch stenosis | 75.0 ± 35.4 | 85.3 ± 12.3 | 77.0 ± 31.1 | 0.889 |
| *Postoperative* | | | | |
| LAD stenosis | 79.8 ± 19.7 | 87.6 ± 14.4 | 93.6 ± 14.4 | 0.055 |
| First diagonal branch stenosis | 70.2 ± 29.2 | 86.2 ± 15.1 | 86.5 ± 18.3 | 0.126 |
| Second diagonal branch stenosis | 90.0 ± 14.1 | 93.3 ± 5.8 | 85.0 ± 21.2 | 0.803 |

[a] Group I, perfused area less than or equal to 17 %; Group II, perfused area between 17.0 and 22.5 %; Group III, perfused area greater than or equal to 22.5 %. *P*: ANOVA *P*- test for differences between groups.

*Postoperative control angiography*

The postoperative control angiography was performed 1.5 ± 0.9, 1.3 ± 0.5 and 1.7 ± 1.2 years after operation in group I, II and III respectively. The time intervals between late control angiography and operation ($P = 0.51$), late postoperative echo Doppler ($P = 0.83$) and preoperative angiography ($P = 0.63$) did not differ significantly between the groups. All LIMA grafts except one were selectively injected. All grafts were patent. The degrees of postoperative native coronary vessel stenoses of the anterior wall are shown in Table 1. The mean proximal LIMA diameter was 3.10 ± 0.64 mm.

*Late postoperative echo Doppler*

In all patients echo Doppler detection at the origin was successful and all signals could be used. The time interval between surgery and late supraclavicular echo Doppler evaluation was 1.8 ± 0.9, 1.8 ± 0.7 and 1.9 ± 1.1 years in group I, II and III, respectively ($P = 0.92$). All patients were in sinus rhythm. The mean proximal LIMA diameter was 2.58 ± 0.75 mm and was significant smaller than the early postoperative echo Doppler diameters ($P = 0.03$). The correlation coefficient of the proximal LIMA diameters between the control angiography and late postoperative echo Doppler was poor; 0.13. Supraclavicular echo Doppler values at rest and at hyperaemic response are incorporated in Tables 2 and 3, respectively.

*Echo Doppler at rest*

At late echo Doppler some values increased significantly but inconsistently. At univariate analysis perfused areas as defined in the three subgroups were related significantly to the DMV, SPV, SMV and TMV (Table 2). Multivariate linear regression analysis showed significant differences for age ($P = 0.048$), smoking history ($P = 0.039$) and hypertension ($P = 0.033$) in group II versus groups I and III. At analysis of the relationship between the individual perfused area and the Doppler characteristics with multivariate linear regression the following factors were entered: natural logarithm of DPV, DVI, DMV, natural logarithm of SPV, SVI, SMV, TVI, TMV, diastolic peak/systolic peak velocity ratio, diastolic/total velocity integral ratio, time between control angiography and echo Doppler examination, gender, age at operation, the presence of LIMA intercostal branches, the degree of the stenosis of the diagonal branches, the presence of small anterior infarction, weight, diabetes, hyperlipidaemia, hypertension and smoking history.

At multivariate analysis the individual perfused areas were related to the natural logarithm of DPV and DMV (Table 4). The regression parameters and *P* values for the other factors we examined were negligible, an indication that these factors hardly affected the perfused areas ($P > 0.15$). At multivariate analysis for the target area the degree of LAD stenosis at control angiography was also included; no factor emerged as significantly related (Table 4). At multivariate analysis for the ratio perfused over target area the degree of LAD stenosis was also included. Only the degree of stenosis of the LAD emerged as significant (Table 4).

*Table 2. Early and late postoperative values of supraclavicular LIMA echo Doppler parameters*[a]

| | | Group I | Group II | Group III | *P* |
|---|---|---|---|---|---|
| *Early postoperative* | | | | | |
| DPV | (cm/s) | 34.5 ± 16.5 | 31.3 ± 9.2 | 34.7 ± 14.0 | NS |
| DVI | (cm²) | 12.1 ± 5.5 | 11.0 ± 4.6 | 10.6 ± 4.7 | NS |
| DMV | (cm/s) | 23.1 ± 11.1 | 22.3 ± 6.9 | 22.3 ± 9.8 | NS |
| SPV | (cm/s) | 54.2 ± 14.7 | 56.2 ± 17.1 | 50.5 ± 21.2 | NS |
| SVI | (cm²) | 9.3 ± 2.1 | 9.3 ± 3.5 | 8.5 ± 3.2 | NS |
| SMV | (cm/s) | 32.8 ± 7.1 | 32.8 ± 11.0 | 30.7 ± 10.9 | NS |
| TVI | (cm²) | 21.5 ± 7.3 | 20.2 ± 7.3 | 19.1 ± 7.2 | NS |
| TMV | (cm/s) | 26.4 ± 9.6 | 26.0 ± 7.5 | 25.5 ± 9.7 | NS |
| *Late postoperative* | | | | | |
| DPV | (cm/s) | 29.8 ± 14.5 | 42.0 ± 16.3 * | 35.7 ± 10.8 | NS |
| DVI | (cm²) | 11.3 ± 6.8 | 13.3 ± 4.8 * | 13.0 ± 3.7 * | NS |
| DMV | (cm/s) | 21.2 ± 11.6 | 29.9 ± 11.1 * | 24.1 ± 7.3 * | 0.049 |
| SPV | (cm/s) | 43.1 ± 18.0 | 64.0 ± 18.3 * | 49.0 ± 15.4 | 0.003 |
| SVI | (cm²) | 9.0 ± 4.3 | 10.9 ± 3.8 * | 8.5 ± 2.5 | NS |
| SMV | (cm/s) | 29.3 ± 11.9 | 38.1 ± 12.3 * | 29.1 ± 8.4 | 0.031 |
| TVI | (cm²) | 20.3 ± 10.5 | 24.1 ± 7.7 * | 21.6 ± 5.3 | NS |
| TMV | (cm/s) | 24.1 ± 11.2 | 33.0 ± 10.8 * | 25.9 ± 7.0 | 0.027 |

[a] Groups I, II and III as described in Table 1. * $P < 0.05$ within groups for late postoperative versus early postoperative values. *P*: ANOVA *P*- test for differences between groups. Data are mean ± standard deviation. NS: not significant.

*Echo Doppler at maximal hyperaemic response*

All diastolic, systolic, total mean and integral echo Doppler values increased significantly within groups in absolute values. Between groups only diastolic peak velocity maximal hyperaemic values (DPV max) differ significantly: 86.0 ± 27.1 (group I) versus 96.8 ± 30.4 (group II) versus 110.6 ± 23.4 cm/s (group III) ($P = 0.036$) (Table 3).

At multivariate linear regression analysis only maximal DPV (cm/s) was related to the perfused area in hyperaemic response. For the target area no single hyperaemic response factor was related. Again for the ratio perfused over target area only the maximal diastolic peak velocity emerged as significant (Table 4).

*Table 3. Maximal hyperaemic values of supraclavicular LIMA echo Doppler parameters*[a]

| | | Group I | Group II | Group III | *P* |
|---|---|---|---|---|---|
| DPV | (cm/s) | 86.0 ± 27.1 | 96.8 ± 30.4 | 110.6 ± 23.4 | 0.036 |
| DVI | (cm²) | 26.0 ± 11.4 | 26.9 ± 8.5 | 32.8 ± 10.1 | NS |
| DMV | (cm/s) | 63.8 ± 24.2 | 71.9 ± 23.0 | 80.9 ± 20.0 | NS |
| SPV | (cm/s) | 83.1 ± 21.2 | 92.2 ± 24.4 | 90.2 ± 22.3 | NS |
| SVI | (cm²) | 17.6 ± 4.8 | 18.2 ± 5.8 | 18.5 ± 5.0 | NS |
| SMV | (cm/s) | 62.2 ± 17.3 | 68.1 ± 21.0 | 67.5 ± 17.2 | NS |
| TVI | (cm²) | 42.9 ± 15.5 | 44.6 ± 13.3 | 50.6 ± 12.7 | NS |
| TMV | (cm/s) | 62.5 ± 20.5 | 70.4 ± 21.4 | 75.6 ± 17.8 | NS |

[a] Groups I, II and III as described in Table 1. *P*: ANOVA *P*- test for differences between groups. Data are mean ± standard deviation. NS: not significant.

*Analyses for combined values at rest and at maximal hyperaemic response*

At multivariate linear regression analyses for parameters at rest and at maximal hyperaemic response only the DPV max (cm/s) was related to the perfused area. For the target area no factor was related. For the ratio perfused over target area only the degree of stenosis of the LAD emerged as significant (Table 4).

*Table 4. Predicting Doppler parameters for different areas at multivariate linear regression analysis*[a]

| | Parameters | Unit | Regression parameter | *P* |
|---|---|---|---|---|
| *At rest* | | | | |
| Perfused area | Natural logarithm of diastolic peak velocity[b] | cm/s | 17.50 | 0.013 |
| | Diastolic mean velocity | cm/s | -0.53 | 0.048 |
| Target area | Diastolic velocity integral | cm | 0.34 | 0.055 |
| Ratio perfused/ target area | Degree of stenosis of the LAD | % | 0.01 | 0.004 |
| | Small anterior wall infarction | | -0.18 | 0.054 |
| *At adenosine hyperaemic response* | | | | |
| Perfused area | Maximal diastolic peak velocity | cm/s | 0.11 | 0.005 |
| Target area | Maximal diastolic velocity integral | cm | 0.16 | 0.080 |
| Ratio perfused/ target area | Maximal diastolic peak velocity | cm/s | 0.01 | 0.017 |
| | Maximal total velocity integral | cm | -0.01 | 0.111 |
| *At rest and adenosine hyperaemic response* | | | | |
| Perfused area | Maximal diastolic peak velocity | cm/s | 0.11 | 0.005 |
| Target area | Diastolic velocity integral | cm | 0.34 | 0.055 |
| Ratio perfused/ target area | Degree of stenosis of the LAD | % | 0.01 | 0.004 |
| | Small anterior wall infarction | | -0.17 | 0.054 |

[a] Univariate parameters with *P* values of > 0.15 were not included. [b] Due to the logarithm the association is multiplicative, i.e. 50 % increase in diastolic peak velocity results in an increase in perfusion area of 7 %.

## Discussion

We confirm that preoperative and postoperative LIMA velocity patterns can be obtained by echo Doppler from the supraclavicular approach in the majority of the patients. This confirms findings by other groups [12,13]. Some investigators determined the LIMA diameter using echo Doppler from the supraclavicular fossa and transformed the velocity measurements into LIMA graft flow [6].

We agree with others [13-15] that it is difficult to reliably measure vessel diameter transcutaneously especially in small calibre vessels. We found a correlation coefficient of 0.13 between the control angiography and late postoperative echo Doppler for proximal LIMA diameter measurements. Therefore we did not transform velocity data into flow and evaluated only the supraclavicular echo Doppler parameters of the LIMA pre- and postoperatively.

As described by other groups [16,17] preoperative transthoracic echo Doppler of the LIMA shows predominantly systolic velocity patterns as can be expected from a systemic artery and postoperatively LIMA echo Doppler characteristics show a shift towards diastolic coronary velocity spectra [4,17]. In all patients in our study systolic velocity parameters decreased and all diastolic velocity parameters increased significantly early postoperatively versus preoperatively. Although no early postoperative coronary angiogram was performed we concluded that all LIMA grafts were patent because all echo Dopplers showed these high diastolic velocity patterns and no patients presented angina [18]. In all patients control angiography was performed and LAD stenosis and perfused areas were analyzed quantitatively [8]. Leta Petracca et al. [19] reported that the presence of competitive flow or predominant native coronary arterial flow may lead to predominantly systolic echo Doppler flow pattern. Evaluating our postoperative control angiograms revealed large competitive coronary flow in some patients. Therefore we graded perfusion areas and analyzed the target as well as the perfused areas in which we visually accounted for the competitive flow. We explored the correlation between echo Doppler velocity parameters with LIMA target areas as well as the perfused areas – corrected for competitive flow – at late postoperative angiographic follow up. To our knowledge this has never been reported previously. We evaluated hyperaemic response, a measure of coronary reserve, and correlated maximal hyperaemic response values to

values at rest and to the perfused areas.

We estimated the predicting parameters at rest as well as at maximal hyperaemic response in order to determine if analysis at hyperaemic response added any additional information to analysis at rest.

All systolic, diastolic and total velocity parameters increased significantly during adenosine infusion compared to baseline values within all groups. The increase in diastolic parameters was more pronounced compared to the other parameters.

We found a significant correlation between two diastolic echo Doppler parameters at rest (natural logarithm of DPV and DMV) and the perfused area indicating that the diastolic flow pattern was correlated with the LIMA run-off area even after correction for competitive flow. The target area was not significantly related with diastolic parameters. Looking at the ratio of perfused over target area the only determinant was the percentage LAD stenosis at late angiography. Hence notwithstanding variable flow competition our data demonstrated that these diastolic Doppler parameters at rest are related to the actual perfusion area.

At the maximal hyperaemic response by adenosine infusion the perfused area correlated significantly with maximal diastolic peak velocity while no factor could significantly predict the target area. However, the ratio of perfused over target area was not further significantly related to the degree of LAD stenosis but showed a correlation with the maximal diastolic hyperaemic velocity.

Looking at the resting as well as the hyperaemic echo Doppler parameters the maximal diastolic peak velocity remained the only significant predictor of the perfused areas. Hence, adenosine testing response reinforces the correlation between diastolic velocity parameters and the perfused area. Even though the competitive flow is determined by the degree of LAD stenosis the diastolic Doppler parameters remain significantly related with the perfused area. This supports the validity of echo Doppler as a tool to investigate and follow patients with LIMA revascularization of the anterior myocardium.

Our study does not allow anatomical remodelling to be determined [20] as only the proximal diameter of the LIMA was investigated and in our findings a further decrease rather than an increase in diameter was found between both Doppler investigations. During adenosine testing we did not study instantaneous changes in proximal LIMA diameter. However, according to our findings in adenosine testing all Doppler velocity

parameters doubled their absolute values with a stronger diastolic hyperaemic response, expressing the instantaneous 'flow' increase, which can be considered the expression of the 'functional' remodelling. At maximal hyperaemic response the ratio of perfused over target area was not further determined by the degree of stenosis of the LAD suggesting that the increased LAD % stenosis at follow up angiography, which was severe in all patients, could be a limiting factor for native flow competition at hyperaemia.
Our study does not allow us to distinguish between instantaneous 'flow' increase related to coronary reserve or increased perfusion area at hyperaemia.

## Conclusions

Pre- and postoperative LIMA velocity patterns can be obtained by echo Doppler from the supraclavicular approach in the majority of the patients. LIMA Doppler characteristics show postoperatively a shift towards coronary Doppler velocity spectra. All echo Doppler parameters increased significantly during adenosine infusion compared to baseline values and the increase of the diastolic parameters was more pronounced.
At multivariate linear regression analyses the diastolic flow pattern at rest and the maximal diastolic peak velocity in hyperaemic response correlated significantly with the LIMA run off area. Maximal diastolic peak velocity in hyperaemic response is the strongest predictor in determining the LIMA run-off area.

*Acknowledgements*
This study was funded by The Netherlands Heart Foundation Grant 89.258.

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*CHAPTER 4*

# POSTOPERATIVE CHANGES OF DUPLEX ULTRASOUND VELOCITY CHARACTERISTICS IN THE NONMOBILIZED RIGHT INTERNAL MAMMARY ARTERY IN PATIENTS WITH LEFT INTERNAL MAMMARY ARTERY BYPASS GRAFTING

JM Hartman
JC Kelder
RGA Ackerstaff
HA van Swieten
FEE Vermeulen
AJJC Bogers

***Ann Vasc Surg 2004;18:207-211.***

Presented at the 25th World Congress of the International Society for Cardiovascular Surgery, Cancun, Mexico, September 9-13, 2001.

## Abstract

Introduction: The internal mammary artery (IMA) is the conduit of choice in coronary revascularisation in view of its long term patency. We analyzed the effect of left internal mammary artery harvesting on sternal perfusion.

Methods: Diameters and velocity parameters of the non-mobilised right internal mammary artery (RIMA) were non-invasively analyzed with duplex ultrasound in 41 patients with LIMA myocardial revascularisation pre- (2.6 ± 5.0 days) and postoperatively (4.9 ± 3.9 months).

Results: Data of 41 patients was analysed; 38 patients underwent all examinations with adequate supraclavicular signals. The proximal RIMA diameter and all velocity parameters increased significantly at follow-up (3.1 ± 0.6 vs. 3.2 ± 0.5 mm, $P = 0.03$; diastolic peak velocity (DPV) 15 ± 7 vs. 27 ± 9 cm/sec, $P < 0.0001$; systolic peak velocity (SPV) 90 ± 24 vs. 105 ± 29 cm/sec, $P < 0.02$. This was more pronounced for the diastolic parameters and for all parameters in the proximal part of the RIMA than in the distal part (DPV 11.9 ± 10.1 vs. 9.5 ± 10.2 cm/sec, $P$ = ns; SPV 14.9 ± 33.9 vs. 7.4 ± 26.0 cm/sec, $P$ = ns). With longer time intervals of follow-up the increase in all diastolic velocity parameters became less pronounced.
As demonstrated in the RIMA velocity parameters, patients with skeletonized LIMA grafts (n = 4), had significantly more flow, suggesting hyperaemic flow, than patients with pedicled LIMA grafts (n = 34). Only in diastolic velocity integral (DVI) and systolic/diastolic velocity ratio (SDVRA) were there significant differences between diabetics (n = 9) and non-diabetics (n = 29) and only in DVI between female, (n = 8) and male (n = 30) patients.

Conclusion: This study indicates that the duplex ultrasound is a useful tool for noninvasive RIMA follow-up in LIMA myocardial revascularisation.

## Introduction

The internal mammary artery (IMA) has been shown to be the conduit of choice in left anterior descending coronary artery bypass grafting (CABG) because of its long term patency [1-2]. The effects of IMA dissection on sternal vascularisation have been reported by several groups [3-5]. The aim of this study was to evaluate postoperative changes of the echo Doppler characteristics in the nonmobilized right internal mammary artery (RIMA) in patients with left internal mammary artery (LIMA) myocardial revascularization.

## Materials and methods

*Patients*

Fourty-one patients (32 M, 9 F, mean age 62.3 ± 7.4 years) scheduled to undergo LIMA bypass grafting with median sternotomy and extracorporeal circulation were prospectively entered in a follow-up study. Exclusion criteria included an age of over 75 years, urgent coronary artery bypass surgery, patients with anterior transmural myocardial infarction, previous sternotomy, chest irradiation, and subclavian or innominate artery stenosis. All patients treated medically for hyperglycaemia were incorporated in the diabetic (DM) group (n = 9).

Forty-one patients underwent supraclavicular, first and third intercostal RIMA duplex ultrasonography pre- (2.6 ± 5.0 days) and postoperatively (4.9 ± 3.9 months). In 15 of these patients, duplex ultrasonography was repeated within 3 months, in 16 patients, between 3 and 6 months, and in 10 patients after 6 months. All operations were done at St. Antonius Hospital, Nieuwegein. In none of the patients was RIMA mobilization performed. No patient developed sternal dehiscence or wound infection.

*Echo Doppler technique*

Initially a Sonos 2000 (Hewlett Packard, Andover, Mas) and later a Sonos 2500 duplex scanner was used that combined both B-mode imaging and pulsed Doppler ultrasound to evaluate blood velocity parameters of the RIMA. All duplex ultrasound investigations and recordings were performed by two trained and experienced technicians. Ultrasound investigation was performed with patients in the supine

position, under continuous electrocardiographic control. A 7.5 MHz sector scanner was positioned in the supraclavicular fossa and velocity spectra were measured and recorded at an angle of approximately 60 degrees of the long axis at the origin of the RIMA. The RIMA diameter was measured. Software with correction for the angle of insonation was used. Spectral analysis of RIMA duplex velocity recordings was performed during 3-5 cardiac cycles and data were analyzed off-line. Diameter and velocity recordings in the first and third intercostal space were obtained as well. All recordings were interpreted by three different experienced physicians. The intraobserver variability was tested by one technician and one physician and was < 2%. The following velocity parameters were analyzed: diastolic and systolic peak velocity (DPV and SPV), diastolic, systolic and total mean velocity (DMV, SMV, and TMV) and diastolic, systolic and total velocity integral (DVI, SVI, and TVI). The systolic peak/diastolic peak velocity ratio (SDVRA) was also calculated.

*Statistical analyses*

Data were tested by paired and unpaired t-tests and analysis of variance (ANOVA) tests. All data are expressed as mean ± standard deviation (SD). Data were considered statistically significant when the calculated *P* value was 0.05 or less.

## Results

In 38 (93%) of the 41 patients, velocity patterns could be identified preoperatively. Preoperative data were missing for two patients because of their obesity and for one patient because no optimal signal could be obtained. All patients underwent control supraclavicular duplex ultrasonography of the origin of the nonmobilized RIMA and velocity patterns were identified in all patients.

In postoperative measurements, diameter of the RIMA at the origin increased significant, in contrast to the diameters of the first and third intercostal space (Table 1).

All supraclavicularly measured velocity parameters increased significantly at follow-up (Table 2). Diastolic velocity parameters increased more than systolic parameters, although the systolic characteristics remained very dominant; this resulted in a marked decrease of the SDVRA (Table 2). With longer time intervals of follow-up, we noticed significantly less pronounced increases in diastolic velocity parameters.

Consequently, the SDVRA increased progressively (Table 3).

With regard to duplex ultrasound characteristics at different levels, all values increased more in the proximal part of the RIMA, although no significant differences could be demonstrated (Table 4).

In 4 patients the LIMA was skeletonized. There were no significant differences between the preoperative velocity values of the pedicled versus skeletonized LIMA grafts, but postoperatively most RIMA velocity values were significantly higher in patients with skeletonized LIMA grafts (Table 5).

*Table 1. Pre- and postoperative RIMA diameters (mm)*

| Area | n | Preoperative (mean ± SD) | Postoperative (mean ± SD) | * *P* |
|---|---|---|---|---|
| Origo | 38 | 3.1 ± 0.6 | 3.2 ± 0.5 | 0.03 |
| First i.c. space | 32 | 3.0 ± 0.6 | 3.1 ± 0.4 | 0.4 |
| Third i.c. space | 31 | 2.6 ± 0.4 | 2.5 ± 0.5 | 0.3 |

i.c.: intercostal, * *P*: values for postoperative versus preoperative diameter.

*Table 2. Pre-and postoperative supraclavicular duplex ultrasound values of RIMA*

| | | Preoperative (mean ± SD) | Postoperative (mean ± SD) | * *P* |
|---|---|---|---|---|
| DPV | (cm/sec) | 15 ± 7 | 27 ± 9 | < 0.0001 |
| DVI | (cm²) | 5 ± 3 | 8 ± 3 | < 0.0003 |
| DMV | (cm/sec) | 8 ± 5 | 18 ± 7 | < 0.0001 |
| SPV | (cm/sec) | 90 ± 24 | 105 ± 29 | < 0.02 |
| SVI | (cm²) | 16 ± 5 | 19 ± 6 | < 0.02 |
| SMV | (cm/sec) | 47 ± 12 | 62 ± 18 | < 0.0001 |
| TVI | (cm²) | 21 ± 7 | 27 ± 9 | < 0.002 |
| TMV | (cm/sec) | 21 ± 7 | 35 ± 11 | < 0.0001 |
| SDVRA | | 10 ± 17 | 4 ± 2 | < 0.005 |

DPV, diastolic peak velocity; DVI, diastolic velocity integral; DMV, diastolic mean velocity; SPV, systolic peak velocity; SVI, systolic velocity integral; SMV, systolic mean velocity; TVI, total velocity integral; TMV, total mean velocity; SDVRA, systolic peak/diastolic peak velocity ratio. * *P*: values for postoperative data versus preoperative data.

*Table 3. Absolute supraclavicular RIMA duplex ultrasound values for different follow-up time intervals*

| | | DU < 3 months n=15, (mean ± SD) | DU 3-6 months n=16, (mean ± SD) | DU > 6 months n=10, (mean ± SD) | * *P* |
|---|---|---|---|---|---|
| DPV | (cm/sec) | 33.7 ± 9.9 | 24.6 ± 5.7 | 20.6 ± 6.1 | 0.0003 |
| DVI | (cm²) | 10.1 ± 3.6 | 7.2 ± 2.6 | 7.1 ± 3.4 | 0.02 |
| DMV | (cm/sec) | 23.1 ± 7.4 | 16.1 ± 5.0 | 13.9 ± 5.4 | <0.002 |
| SPV | (cm/sec) | 109.1 ± 26.3 | 100.2 ± 29.2 | 104.6 ± 32.7 | NS |
| SVI | (cm²) | 19.7 ± 6.1 | 17.4 ± 5.6 | 20.2 ± 7.4 | NS |
| SMV | (cm/sec) | 65.5 ± 19.4 | 58.3 ± 17.1 | 61.3 ± 18.2 | NS |
| TVI | (cm²) | 29.3 ± 10.2 | 24.6 ± 7.1 | 26.1 ± 7.7 | NS |
| TMV | (cm/sec) | 39.6 ± 12.9 | 33.2 ± 8.6 | 31.7 ± 9.8 | NS |
| SDVRA | | 3.3 ± 0.7 | 4.2 ± 1.4 | 5.5 ± 2.6 | 0.009 |

DU; duplex ultrasound, duplex ultrasound parameters as described in Table 2. NS: not significant. * *P*: values for postoperative data between groups.

Except for DVI (*P* = 0.03) and SDVRA (*P* = 0.02) no significant differences were measured in preoperative, postoperative (DPV 24 ± 8 vs. 28 ± 9 cm/sec, *P* = 0.25; SPV 112 ± 31 vs. 102 ± 28 cm/sec, *P* = 0.32), or increasing values of velocity parameters between diabetic (n = 9) and nondiabetic (n = 29) patients. Except for DVI (6 ± 2 vs. 9 ± 4 cm/sec, *P* = 0.03), there were no significant differences in velocity values between female (n = 8) versus male (n = 30) patients, although all velocities appeared to be higher in males postoperatively.

*Tabel 4. Postoperative minus preoperative values of RIMA origin and third intercostal space*

| | | Origin ** | Third i.c. space | * *P* |
|---|---|---|---|---|
| DPV | (cm/sec) | 11.9 ± 10.1 | 9.5 ± 10.2 | NS |
| DVI | (cm²) | 3.1 ± 4 | 2.7 ± 4.4 | NS |
| DMV | (cm/sec) | 10.3 ± 8 | 8.8 ± 7.9 | NS |
| SPV | (cm/sec) | 14.9 ± 33.9 | 7.4 ± 26 | NS |
| SVI | (cm²) | 3.1 ± 7.1 | 1.6 ± 6.3 | NS |
| SMV | (cm/sec) | 13.8 ± 20.8 | 9.9 ± 16.6 | NS |
| TVI | (cm²) | 5.9 ± 10.4 | 4.4 ± 10.8 | NS |
| TMV | (cm/sec) | 13.7 ± 12.9 | 11 ± 11.9 | NS |
| SDVRA | | -6.2 ± 18.8 | -2.5 ± 5.3 | NS |

Duplex ultrasound parameters as described in Table 2. i.c.: intercostal. NS: not significant. ** origin values derived from the data in Table 2. * *P*: values for different increasing values between RIMA origin and third intercostal space.

*Table 5. Pre- and postoperative duplex ultrasound values of the RIMA in patients with pedicled and skeletonized LIMA grafts*

| | Pedicled LIMA | | Skeletonized LIMA | | | |
|---|---|---|---|---|---|---|
| | Preoperative | Postoperative | Preoperative | Postoperative | *P | **P |
| DPV (cm/sec) | 15.6 ± 6.5 | 25.8 ± 8.9 | 11.2 ± 6.3 | 35.3 ± 7.1 | NS | 0.03 |
| DVI (cm²) | 5.2 ± 3.2 | 7.8 ± 3.3 | 4.4 ± 3.3 | 11.6 ± 2.2 | NS | 0.02 |
| DMV (cm/sec) | 8 ± 5 | 17.2 ± 6.9 | 6.3 ± 5.5 | 25 ± 4.9 | NS | 0.02 |
| SPV (cm/sec) | 90.2 ± 23.3 | 101.6 ± 28.6 | 90.9 ± 26 | 125.2 ± 20.8 | NS | 0.08 |
| SVI (cm²) | 15.9 ± 4.6 | 18.3 ± 6.4 | 16.4 ± 3.9 | 23.4 ± 2.9 | NS | 0.09 |
| SMV (cm/sec) | 47.9 ± 12.1 | 59.5 ± 18 | 47 ± 9.3 | 76.7 ± 10.2 | NS | 0.04 |
| TVI (cm²) | 21 ± 6.5 | 25.4 ± 8.4 | 20.6 ± 6 | 35.3 ± 4.1 | NS | 0.01 |
| TMV (cm/sec) | 21.5 ± 6.7 | 33.7 ± 10.6 | 19.1 ± 6.4 | 45.8 ± 6.7 | NS | 0.01 |
| SDVRA | 9 ± 17.5 | 4.3 ± 1.8 | 15 ± 16.7 | 3.6 ± 0.8 | NS | 0.02 |

Duplex ultrasound parameters as described in Table 2. NS: not significant. * *P*: values for preoperative data between groups. ** *P*: values for postoperative data between groups.

## Discussion

Sternal complications after median sternotomy are a major problem in cardiac surgery. From a pathophysiological point of view, LIMA harvesting in coronary artery bypass may decrease sternal vascularization and thereby increase the risk of sternal complications.

The major blood supply to the sternum originates from the IMA and continues to the intercostal, perforating, mediastinal and mainly sternal branches. The sternal branches pass medially and bifurcate anteriorly and posteriorly and form a periosteal plexus with anastomotic vertical arcades [10].

In view of the clinically greater rate of sternal wound complications in DM than in non-DM patients, in bilateral than in single IMA preparation, and in pedicled than in skeletonized IMA mobilization [6-8], many studies on sternal perfusion have been conducted. Most studies have been experimental or perioperative.

Acute experimental data after IMA mobilization demonstrate a tremendous decrease in sternal perfusion immediately after mobilization and it is most marked at the ipsilateral side. Seyfer et al. [3] noted a 90 % decrease in primates. Parish et al. [5] demonstrated that this decrease was more pronounced in the distal sternal flow than in the manubrium and more pronounced in the pedicled than in the skeletonized mobilization technique.

In humans, sternal perfusion studies after IMA mobilization have been performed mostly using scintigraphic techniques and at an early postoperative interval. In both DM and non-DM patients, Carrier et al. [4] noticed limited hypoperfusion of 13 % in LIMA patients and 24 % in bilateral IMA patients at day 7. He studied some of these patients at 30 days and noticed almost complete normalization of the sternal perfusion.

Korbmacher et al. [10] studied 44 non-DM patients with either simple sternotomy or LIMA or bilateral internal mammary artery (BIMA) mobilization preoperatively and at day 12 postoperatively. All patient groups showed an approximately 50 % increase in sternal perfusion, even in BIMA mobilization. However, they noted a slightly larger increase in right sternal half perfusion in LIMA patients. In this study only non-DM patients and pedicled IMA-mobilization was used, and no statistical analyses of the data were performed.

We did not investigate the early phases of the change in postoperative duplex ultrasound velocity characteristics of the unharvested RIMA. The time course of our observations suggests a substantial residual hyperemia in patients measured before the fourth (2.7 ± 0.4) month postoperatively and a progressive decrease subsequently. We can only speculate on the reasons for these observations. The velocity characteristics in the RIMA in the presence of an increased diameter at the origo suggest a compensatory increased sternal perfusion. However, this methodology does not allow the target area of this perfusion to be determined. This mechanism behind the larger diastolic than systolic increase in velocity parameters is unclear. Perhaps a lower vascular resistance area, as in arteriovenous shunting, is related to osseous periostal repair.

Our rather late postoperative data indicate an overall increase in diastolic velocity parameters, with a significantly different diastolic perfusion increase in the skeletonized grafts than that in the pedicled LIMA grafts. This might be related to a lower resistance of the preserved contralateral venous IMA outflow in patients with skeletonized IMA grafts [6]. The number of skeletonized LIMA's, however, was small.

We also studied the proximal versus distal hyperemic values of the RIMA. We noticed increased velocity characteristics, systolic as well as diastolic, in the third intercostal space, but of lesser magnitude than at the origin. In addition, the significantly increased diameters at the origin and not in the third intercostal space suggest a more proximal contribution of the observed increase in velocity parameters of the RIMA. These findings correlate with the early postoperative observations of Parish et al. [5] demonstrating a more proximal than distal hyperaemic response. At the third intercostal level we observed diastolic hyperemic characteristics that may suggest a residual increase of perfusion in the osseous periostal repair. We investigated some specific determinants that could have contributed to differences in the observations. As observed by Carrier et al. [4] we did not find any important differences between DM and non-DM patients. There were also no important differences in velocity parameters between female and male patients.

Limitations of our study are lack of very early postoperative observations and the rather small number of patients in the subgroups (skeletonized LIMA grafts, n = 4; diabetic patients, n = 9; female patients, n = 8) not allowing multivariate analysis.

## Conclusions

Duplex ultrasound from the supraclavicular fossa can detect velocity patterns at the origin of the intact RIMA in almost all patients. All postoperative RIMA duplex velocity parameters increased significantly suggesting a hyperemic response to LIMA harvesting after median sternotomy. This increase was more marked in diastolic parameters and these diastolic parameters apparently decrease at longer follow-up intervals. Duplex findings from the supraclavicular fossa at the origin of the nonmobilized RIMA are a useful tool to investigate changes due to mobilization and the type of mobilization of the LIMA. Skeletonized LIMA grafts apparently induce larger RIMA perfusion.

No significant duplex differences could be demonstrated between DM and non-DM patients, nor between female and male patients.

Our findings do not support longerlasting vascularization impairment to explain sternal problems after median sternotomy for cardiac surgery.

This method is a reliable and simple technique for follow-up of RIMA velocity parameters.

*Acknowledgements*

The Netherlands Heart Foundation Grant 89.258 funded this study.

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*CHAPTER 5*

# CAN LATE SUPRACLAVICULAR ECHO DOPPLER RELIABLY PREDICT ANGIOGRAPHICAL STRING SIGN OF LIMA TO LAD AREA GRAFTS?

JM Hartman
JC Kelder
RGA Ackerstaff
HA Swieten van
FEE Vermeulen
AJJC Bogers

***Echocardiography 2007;24:689-696.***

Presented at the 50th International Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary, June 20-23, 2001.

## Abstract

Objective: To investigate whether supraclavicular ultrasonography of left internal mammary artery (LIMA) to left anterior descending (LAD) area grafts can reliably predict (distal) string sign grafts on arteriography.

Methods: Fifty-five patients (42 M, 61 ± 7 years) with the LIMA to LAD area grafting were prospectively studied. Control arteriography was performed at 1.4 ± 0.8 years postoperatively. Angiography demonstrated in 46 patients (group I) functional grafts, in 4 patients (group II) sequential distal string sign grafts and in 5 patients (group III) total string sign grafts. Ultrasonography was performed at 1.8 ± 0.8 years postoperatively and compared with control angiography. Data were tested by unpaired t- and ANOVA tests. The diagnostic accuracy was assessed by the area under the curve of the Receiver Operator Characteristic. A formula was developed to predict the probability of (distal) string sign phenomena of sequential as well as single LIMA grafts.

Results: Between the groups all duplex parameters showed a highly significant linear relation ($P \leq 0.004$) and all parameters between group I and III are significantly different with high Area Under Curve values. The model for the probability of (distal) string sign grafts fitted best with diastolic and systolic peak velocities as the most discriminative factors for (distal) string sign grafts.

Conclusions: Postoperative supraclavicular duplex as a method to assess the patency of LIMA to LAD area grafts allows discriminating functional grafts from (distal) string sign grafts.

## Introduction

The internal mammary artery (IMA) has been shown to be the conduit of choice in left anterior descending coronary artery bypass grafting (CABG) because of its long-term patency [1-3]. At present, postoperative angiography is still the golden standard to assess IMA graft patency but the invasive nature limits its routine use. Other methods were reported over the last years, including intravascular, transthoracic, and supraclavicular duplex ultrasonography, magnetic resonance imaging and multi-slice computed tomography [4-10]. Nowadays, 64-multislice computed tomography (MSCT) angiography has potential diagnostic performance in the diagnosis of coronary artery disease and in (symptomatic) patients after bypass surgery. The overall accuracy of MSCT is high compared with the gold standard of coronary angiography [11-14].

Duplex ultrasonography in postoperative left internal mammary artery (LIMA) velocity spectra caused by different degrees of left anterior descending artery (LAD) stenosis have been described previously as well [15-16]. It is well known that the luminal diameter of IMA grafts may become very small [17]. This so called "string sign" or "thread phenomenon" is associated with no or virtually no contrast passage into the recipient coronary artery at selective angiography. Follow-up studies have demonstrated the late anatomical patency of these (no flow IMA) grafts at consecutive angiograms. String sign of IMA grafts used as a coronary artery bypass conduit has frequently been described [18-21]. No data are available concerning the use of non-invasive supraclavicular duplex to analyse velocity spectra in string sign grafts, documented with angiography. In the present study, we analyzed the velocity spectra of supraclavicular duplex in patients with functional and (partial) string sign of the LIMA to LAD area at angiography and developed criteria to differentiate between the functional and (partial) string sign LIMA grafts.

## Materials and methods

Fifty-five patients (42 M), mean age of 61 ± 7 years, were scheduled for LIMA bypass grafting to the LAD area and prospectively entered in a follow-up study. Excluded were patients over 75 years of age, urgent coronary artery bypass surgery,

patients with transmural infarction of the LAD perfusion area, previous LIMA grafting, serious co-morbidity (malignancy, previous radiation treatment of the chest), subclavian artery stenosis, and combined revascularisation with other cardiac surgery. Informed consent was obtained from all patients. In each patient the LIMA duplex velocities were analysed by two independent observers at the LIMA origin by the supraclavicular approach during postoperative follow-up at 1.8 ± 0.8 years. The observers were blinded for the angiography results.

Postoperative coronary angiography was performed by the standard femoral approach at 1.4 ± 0.8 years. The angiograms were also analysed by two independent observers and assessed for the following aspects: native coronary artery stenoses [22], possible stenosis of coronary anastomoses, and the patency of LIMA grafts.

To assess the patency and run-off of the LIMA grafts, the LIMA grafts and the native coronary arteries were studied by selective injections. LIMA patency and contrast run-off were classified in 3 categories; group I: patent and functional LIMA grafts; no narrowing of the LIMA graft and high flow of contrast (Fig. 1C). Group II: sequential LIMA distal string sign graft; no narrowing of the LIMA graft and high flow of contrast from the origin to the first anastomosed branch with narrowing and no or very low contrast flow into the distal graft segment (Fig. 2C). Group III: total LIMA string sign graft; narrowing of the LIMA graft and no or very low flow of contrast into the LIMA graft (Fig. 3C). Group I consisted of 46 patients (36 M), mean age 62 ± 8 years, with 12 single LIMA to LAD and 34 LIMA jump grafts to LAD area. In group II were 4 patients (2M), mean age of 66 ± 4 years, all with LIMA jump grafts to LAD area. In group III were 5 patients (4M), mean age of 66 ± 5 years, with 3 single LIMA to LAD and 2 LIMA jump grafts to LAD area.

*Duplex ultrasonography technique*

Initially a Sonos 2000 (Hewlett Packard, Andover, Mass.) and later a Sonos 2500 (Hewlett Packard, Andover, Mass.) duplex scanner was used that combined both B-mode imaging and pulsed Doppler ultrasound [23] to evaluate blood velocity parameters of the LIMA. Duplex ultrasound investigations and recordings were performed by 2 trained and experienced technicians. The ultrasound investigation was performed in supine position of the patients under continuous electrocardiographic control. A 7.5 MHz sector scanner was positioned in the supraclavicular fossa and

duplex velocities were measured and recorded at an angle of approximately 60 degrees just distal to the origin of the LIMA. Software with correction for insonation angle was used. Spectral analysis of IMA duplex velocity recording was performed during 3-5 cardiac cycles and data were analysed off-line and interpreted by 3 experienced physicians. The interobserver variability was tested between them and was 1.9 % for the systolic peak velocity and total mean velocity. The following velocity parameters were analysed: systolic and diastolic peak velocity (SPV and DPV), systolic, diastolic and total mean velocity (SMV, DMV and TMV) and systolic, diastolic and velocity time integral (SVI, DVI and VTI). The velocity-time integral is the integral of the instantaneous velocity (Vi) over the time interval (T) [24-25]. Systolic, diastolic and total mean velocities are calculated as the averaged instantaneous mean of 3-5 cardiac cycles by manual tracing of the appropriate phasic velocity spectra.

*Statistical analysis*

Data entry and univariate statistical analyses were performed with the use of Epi Info 6.04c (CDC, Atlanta, GA). Data within groups were tested by paired t-tests and between groups by unpaired t-tests and ANOVA tests. All data were expressed as mean ± standard deviation. Data were considered statistically significant when the *P* value was 0.05 or less. Linear regression analyses evaluating the velocity parameters between the three groups were computed using SAS v8 (SAS Institute, Cary, NC). To assess the diagnostic accuracy we computed the area under curve (AUC) of the receiver operator characteristic (ROC), which plots the sensitivity versus specificity for all available cut-off points of the variable of interest [26]. A non-informative test yields an AUC of 0.5, whereas a perfect test yields an AUC of 1.0. Computation of AUC was done with SAS v8 (SAS Institute, Cary, NC).

The logistic regression analysis models probability in the form of the logarithm of the odds: $\log(\text{odds}) = \text{constant} + ß_1*X_1 + \ldots . ß_n*X_n$, in which $ß_1$ denotes the first regression parameter for the first predictor $X_1$, etc. The logistic formula can be rewritten to the probability form as follows: $\text{probability} = 1/(1 + \exp(\text{constant} + ß_1*X_1 + \ldots ß_n*X_n))$ [27]. We modelled the probability of string sign dependent on various velocity variables to determine independent predictors. Variables could enter the model when $P < 0.10$. In order not to over-fit the model we restricted the number of variables to 2. Only variables with $P < 0.05$ were retained in the model. We also explicitly selected

variables for the final model which were conceptually independent, e.g. when the most predictive variable was mean systolic velocity and the next best two variables were diastolic peak velocity and systolic velocity integral, we selected the diastolic peak velocity for the final model.

## Results

*Postoperative control angiography*

The postoperative control coronary angiography was performed at 1.4 ± 0.8 years. The mean time intervals between arteriography and operation and between duplex and arteriography did not differ significantly between the groups.

The degrees of native coronary vessel stenoses of the anterior wall at coronary angiography are shown in Table 1. No LIMA graft stenoses or stenoses at the distal anastomoses could be detected either at selective LIMA graft arteriography or native coronary arteriography. Even in the areas of the string sign LIMA native flow angiography allowed perfect assessment. No patient presented with recurrent angina at late control angiography and control duplex; no myocardial infarction of the revascularised anterior wall could be detected at late electrocardiography.

*Table 1. Percentage of native coronary vessel stenosis of the anterior wall at control arteriography*

| | Group I | Group II | Group III | *P* |
|---|---|---|---|---|
| LAD stenosis | 88.2 ± 16.2 | 76.0 ± 30.7 | 82.8 ± 12.7 | 0.356 |
| First diagonal branch stenosis | 83.2 ± 16.4 | 87.5 ± 25.0 | 35.0 ± 49.5 | 0.004 |
| Second diagonal branch stenosis | 91.3 ± 11.3 | – | – | – |

LAD : left anterior descending artery. Group I, patent and functional LIMA grafts; Group II, distal LIMA string sign grafts; Group III, total LIMA string sign grafts. *P*: values for differences between groups. Data are mean ± standard deviation.

*Postoperative duplex ultrasonography*

In all patients duplex detection at the origin of the LIMA was successful and all registrations could be used for analysis. The time interval between surgery and postoperative evaluation was 1.8 ± 0.8 years and did not differ significantly between groups and neither the heart rate nor the systolic or diastolic blood pressure were significantly different between the groups. All patients were in sinus rhythm.

To analyse the differences and relationship of velocity parameters between the groups all velocities were compared and statistically analysed. All velocity values of functional LIMA grafts (Fig. 1A,B) versus LIMA string sign grafts (Fig. 3A,B) differ significantly and correspondingly the AUC-values are very high (Table 2). A clear tendency can be noticed comparing functional grafts versus distal string sign grafts (Fig. 1A,B and Fig. 2A,B). All functional LIMA graft parameters appear to be higher whereas a few differ significantly (Table 2). This is probably due to the small number of patients in group II. Comparing the velocity parameters of LIMA with the distal string sign graft versus total string sign graft only DVI and VTI are significantly different. This can also be related to the small number of patients because all diastolic parameters and TMV show high values in the AUC while DVI and VTI show the maximal discriminative power of 1 in the AUC (Table 2).

The linear relations for all velocity parameters between the 3 groups are shown in Table 2. All parameters appear to be highly significant.

From the multivariate logistic regression analysis the following formula function for the probability of (partial) string sign was derived: $1/1 + \exp (11.1 - 0.2 \times \text{SPV} - 0.16 \times \text{DPV})$, whereas the AUC for this formula yields 0.94. With increasing SPV the probability of string sign decreases ($P = 0.03$), as is with DPV ($P = 0.06$). The probabilities are graphically depicted in Fig. 4.

*Table 2. Postoperative supraclavicular LIMA duplex velocities*

| | | Group I<br>n = 43 | Group II<br>n = 4 | Group III<br>n = 5 | $P^{\S}$ |
|---|---|---|---|---|---|
| DPV | (cm/sec) | 38.3 ± 13.8 | 26.1 ± 7.5 | 19.6 ± 7.9 | 0.002 |
| DVI | ($cm^2$) | 13.4 ± 5.0 | 11.1 ± 2.8 | 5.9 ± 2.0 | 0.001 |
| DMV | (cm/sec) | 26.7 ± 9.9 | 19.8 ± 6.6 | 12.1 ± 5.9 | 0.001 |
| SPV | (cm/sec) | 57.5 ± 18.7 | 36.2 ± 8.0 | 28.8 ± 7.2 | < 0.001 |
| SVI | ($cm^2$) | 10.2 ± 3.8 | 6.9 ± 0.9 | 5.8 ± 1.7 | 0.004 |
| SMV | (cm/sec) | 34.7 ± 11.7 | 22.7 ± 3.3 | 20.9 ± 5.5 | 0.003 |
| VTI | ($cm^2$) | 23.6 ± 7.7 | 18.2 ± 3.2 | 11.7 ± 3.2 | < 0.001 |
| TMV | (cm/sec) | 29.6 ± 9.8 | 20.9 ± 5.0 | 15.0 ± 4.6 | < 0.001 |

| | | *P* | *P*** | *P*** | AUC | AUC* | AUC** | $P^{\S}$ |
|---|---|---|---|---|---|---|---|---|
| DPV | (cm/sec) | 0.091 | 0.005 | 0.253 | 0.797 | 0.921 | 0.850 | 0.002 |
| DVI | ($cm^2$) | 0.382 | 0.002 | 0.013 | 0.616 | 0.967 | 1.0 | 0.001 |
| DMV | (cm/sec) | 0.181 | 0.003 | 0.107 | 0.703 | 0.926 | 0.850 | 0.001 |
| SPV | (cm/sec) | 0.031 | 0.002 | 0.186 | 0.860 | 0.958 | 0.800 | < 0.001 |
| SVI | ($cm^2$) | 0.092 | 0.013 | 0.266 | 0.826 | 0.886 | 0.700 | 0.004 |
| SMV | (cm/sec) | 0.049 | 0.013 | 0.578 | 0.884 | 0.860 | 0.600 | 0.003 |
| VTI | ($cm^2$) | 0.178 | 0.001 | 0.018 | 0.733 | 0.965 | 1.0 | < 0.001 |
| TMV | (cm/sec) | 0.086 | 0.002 | 0.108 | 0.797 | 0.944 | 0.85 | < 0.001 |

DPV, diastolic peak velocity; DVI, diastolic velocity integral; DMV, diastolic mean velocity; SPV, systolic peak velocity; SVI, systolic velocity integral; SMV, systolic mean velocity; VTI, velocity time integral; TMV, total mean velocity. Group I, II and III as described in Table I. *P*: values for differences between group I and II, *P**: values for differences between group I and III, *P***: values for differences between group II and III. $P^{\S}$: values for linear relation between the three groups. AUC: Area under the curve for group I versus II. AUC*: Area under the curve for group I versus III. AUC**: Area under the curve for group II versus III. Data are mean ± standard deviation.

## Discussion

LIMA sequential bypass grafting is a widely accepted method for revascularisation of the LAD area. Short and long-term follow-up of the LIMA graft patency are excellent [28-29]. However, there are some reports of distal LIMA string sign grafts. Tashiro et al. [30] describes that 5 % of the sequential LIMA grafts showed a string sign phenomenon between the proximal, side to side, and distal anastomoses at control angiography. So far, no data are available describing supraclavicularly measured flow or velocity pattern analyses in sequential LIMA bypass grafts to the LAD area with distal LIMA string sign grafts documented at control angiography. Akasaka et al. [4] describe Doppler guide wire measured flow dynamics of angiographically no-flow patent IMA grafts. Phasic flow velocities were recorded in the proximal, mid and distal portion of the LIMA graft. They describe predominantly systolic and lower diastolic peak velocities in the proximal portion of the graft shifting toward predominantly diastolic "coronary" flow in the distal portion of the patent grafts containing to and fro signals with systolic reversal and diastolic antegrade flow. Systolic and diastolic peak velocities as well as the time average of the instantaneous spectral peak velocities at rest were significantly lower in the no-flow patent grafts then in normally functioning LIMA grafts. Nasu et al. [31] also describe similar characteristics of predominantly systolic flow in the proximal portion and systolic reversed flow in the distal portion of the graft to left anterior descending arteries with 50 % stenoses. In contrast to Akasaka et al. and Nasu et al., we used the noninvasive duplex supraclavicular approach and did not transform velocity data into flow because of the low correlation between ultrasound and arteriographically measured diameter of the proximal LIMA graft [32]. However, we also measured significantly higher velocities in functional LIMA grafts when compared with (distal) LIMA string sign grafts and we measured higher velocities in distal string sign grafts when compared with total string sign grafts although these values did not all differ significantly. Analyzing the proximal IMA graft Doppler spectra and speculate on a possible cause of the string sign we have to consider that blood through the IMA flows into the coronary circulation in confluence with native coronary flow. In this regard the high degree of stenoses in the diagonal and LAD branches in group I suggest low or no competitive flow resulting in patent LIMA bypass grafts. Considering the degree

of stenoses in the bypassed branches in group II, we assume that competitive flow into the diagonal branch is small in contrast to the competitive flow into the LAD. Consequently, the LIMA bypass to the diagonal branch remains patent, whereas the moderate stenotic lesion in the LAD induces competitive flow which probably attribute to the development of a LIMA string sign bypass to this area. In group III, a very low degree of stenotic lesion in the proximal side to side anastomotic diagonal branch is present. Blood flow through the LIMA graft passes this region first and competitive flow through this proximal anastomose may influence distal LIMA graft patency. We believe that the string sign appearance is a dynamic state and that the LIMA can adapt to different myocardial conditions.

When using the supraclavicular approach the distal LIMA graft velocity spectra cannot be obtained. Takagi et al. [33] stated that obtaining LIMA graft flow noninvasively with the transthoracic approach is difficult because of its narrow lumen and constant pulsatile movement. Therefore Takagi et al. evaluated the LIMA graft flow with echo Doppler from the supraclavicular approach because the proximal part of the LIMA graft is close to the chest wall and fixed with soft tissue and hence free from pulsatile displacement. Our observations with the supraclavicular approach confirm the reliability of this approach. We also demonstrated that the sonogram of the grafted LIMA has a biphasic pattern of forward flow, consisting of a systolic and diastolic phase as observed by others [34-35]. Takagi et al. also describe the supraclavicular flow pattern which consisted of 2 phases corresponding to systole and diastole and compared these findings with flow patterns obtained by intravascular echo Doppler. His findings show a significant similarity in flow pattern and significant correlations of all velocity parameters between the 2 methods.

Seki et al. [36] indicated that LIMA grafts have flow adaptability and respond to the flow demand of the recipient coronary artery. He concluded that the internal mammary graft was smaller in patients with well preserved flow of the native coronary artery and that LIMA string sign grafts developed mainly as an outcome of the absence of its physiological demand. In his study, 6.1 % of patients and in our study 9.2 % of the patients developed IMA string sign grafts.

The differences of velocities between the groups in our study may be due to the differences of amount of myocardial demand or run off areas. It is to be expected that the run-off area of the patent graft in group I is higher when compared with the run-

off area in group II and III and the run-off area in group II is higher when compared with group III. However, the current study was not designed to define the frequency or the causes of postoperative changes of the LIMA grafts, but to study whether LIMA string sign grafts can be detected by supraclavicular duplex with angiography as the golden standard. In our study we did not observe any graft failure because of stenotic lesions or total or segmental occlusion.

In view of the small number of patients in group II and III we can only speculate that the supraclavicular duplex allows us to indicate those patients in whom the distal part of the LIMA graft or the total LIMA graft is inadequately functioning.

Nasu et al. [31] showed also differences in the LIMA systolic flow with only single LAD anastomoses where the proximal native LAD stenosis was less then 50 % compared to 100 % stenosis.

We developed a model based on duplex characteristics to predict in individual patients the presence or absence of string sign phenomenon. In this model DPV and SPV were intercalated because these characteristics were the independent variables with the highest AUC values.

We do not advocate routine supraclavicular Doppler in all patients so far. It can be performed in a clinical setting when patients experience angina postoperatively, in a follow-up study or in other research settings.

*Limitations*

In view of the high AUC value, theoretically this model allows to select correctly 94 % of the cases when one can choose between a case with a patent versus a (partial) string sign graft. Because of the relatively small number of patients with an observed string sign phenomenon in our study, the clinical applicability of the model is moderately reliable. Testing the model in our study population, as in a clinical situation with unknown arteriographical status of the graft and accepting that the model is adequate if one would be able to correctly allocate the IMA into less than or equal to 10 % or greater or equal to 90 % change of patency, 36 of the 53 patients (68 %) would have been allocated correctly. Two patients with a less or equal to 10 % score presented indeed the string sign and 34 patients with a greater or equal to 90 % score presented patent grafts. Seventeen patients, in whom the predictive values are between 10 and 90 %, were constituted of 3 of the 5 patients with total

LIMA string sign grafts and all, 4 patients as expected, for sequential LIMA distal string sign grafts but also included 10 patients with fully patent grafts. Hence, we should consider the ability of additional hyperemic response testing to provide a more accurate prediction model. The applicability of the model should be confirmed in other data sets. Feasibility for IMA grafts to other areas has to be demonstrated.
Furthermore, there is a delay between the postoperative control examinations. Nevertheless, no patients developed angina and no infarction could be detected at control electrocardiography.

## Conclusions

Using supraclavicular echo Doppler linear regression analyses show a highly significant linear relation between the 3 groups for all LIMA velocity parameters. Assessing the diagnostic accuracy, the area under the curve of the receiver operator characteristic show very high linear discriminative power between all groups.
Supraclavicular duplex ultrasonography demonstrated significant differences between velocities in functional grafts versus string sign LIMA grafts and differences between functional grafts versus distal string sign grafts and distal string sign grafts versus total string sign grafts with high AUC values.
However, the predictive model is not refined enough to determine the condition of all IMA grafts (as in the clinical situation) with high accuracy.

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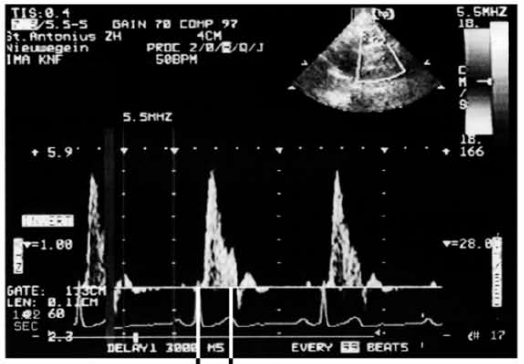
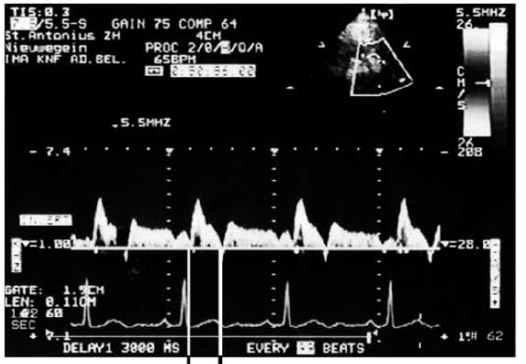
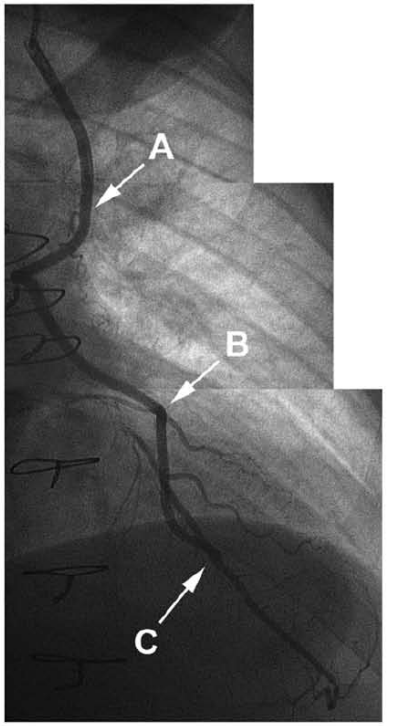
*Figure 1. Pre- (a) and postoperative (b) supraclavicular duplex of the patent LIMA graft at angiography (c) from a patient in group I (patent and functional LIMA grafts) * note the scale*
*(A) LIMA jump graft with anastomosis to the diagonal (B) and left anterior descending artery (C) branch. sy = systolic; di = diastolic*




1a sy di




1b sy di




1c

*Figure 2. Pre- (a) and postoperative (b) supraclavicular duplex of sequential LIMA distal string sign graft at angiography (c) from a patient in group II (sequential LIMA distal string sign grafts) * note the scale*
*(A) LIMA jump graft with anastomosis to the diagonal (B) and left anterior descending artery (C) branch. (D) Distal string sign graft. sy = systolic; di = diastolic*

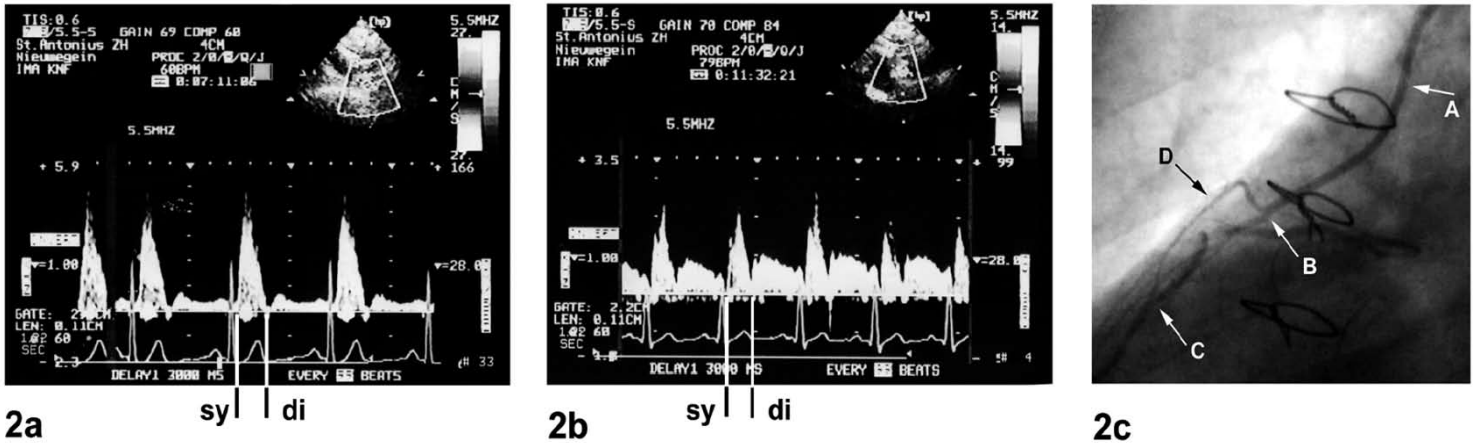
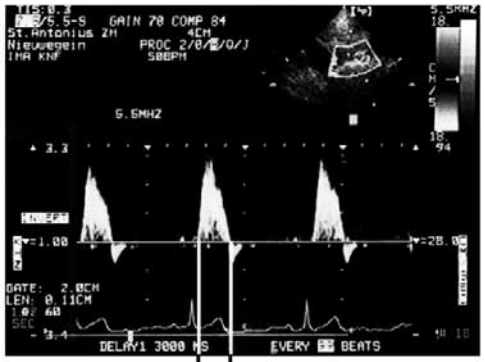
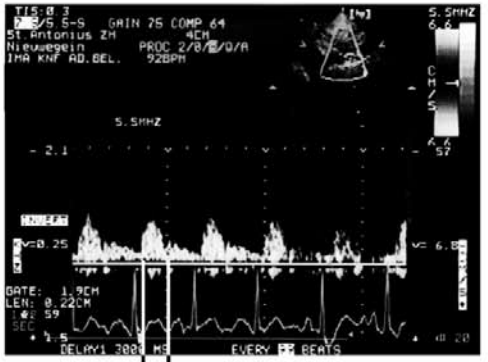


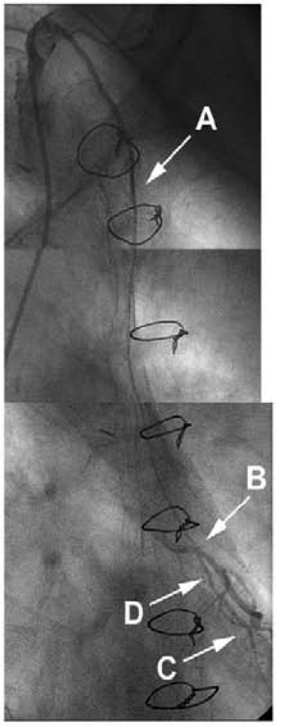
*Figure 3. Pre- (a) and postoperative (b) supraclavicular duplex of a total LIMA string sign (jump) graft at angiography (c) from a patient in group III (total LIMA string sign grafts) * note the scale*
*(A) LIMA string sign graft with anastomosis to the diagonal (B) and left anterior descending artery (C) branch. (D) distal part of the total LIMA string sign graft. sy = systolic; di = diastolic*




3a

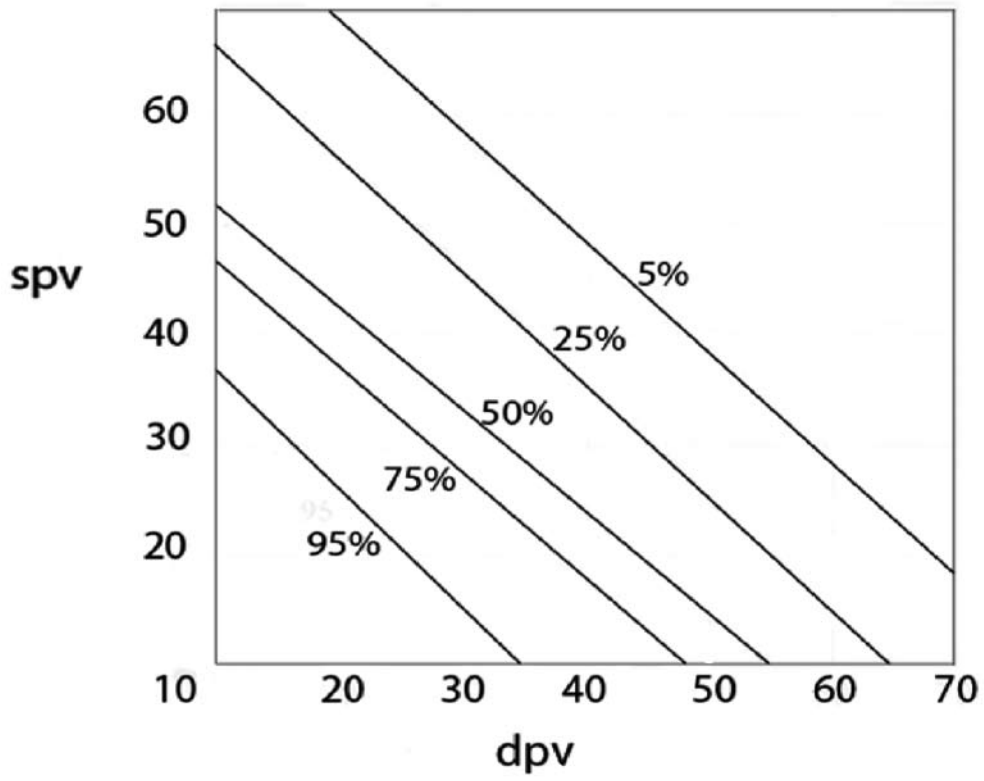



3b




3c

*Figure 4. The probability of (partial) LIMA string sign grafts. SPV = systolic peak velocity (cm/s), DPV = diastolic peak velocity (cm/s). On the diagonals; the probability of (partial) LIMA string sign grafts*



*CHAPTER 6*

# PRESERVED HYPERAEMIC RESPONSE IN SUPRACLAVICULAR ULTRASONOGRAPHY DEMONSTRATES FUNCTION ON DEMAND OF THE LIMA TO LAD STRING SIGN GRAFT AFTER CABG

JM Hartman
JC Kelder
RGA Ackerstaff
HA Swieten van
FEE Vermeulen
AJJC Bogers

***J Cardiovasc Surg 2007;48:59-66.***

Presented at the 11th World Congress of the World Society of Cardio-Thoracic Surgeons, Sao Paulo, Brasil, August 12-15, 2001.
Presented at the meeting of the Dutch Association Thorax-Surgery, Nieuwegein, The Netherlands, Octobre, 2005. (Neth Heart J 2005;13 Suppl III:15)

## Abstract

Background: To correlate supraclavicular ultrasonography with angiographically patent and string sign left internal mammary artery (LIMA) to left anterior descending artery (LAD) grafts.

Methods: Sixteen patients with a single LIMA anastomosis to the LAD were prospectively entered in a follow-up study. The supraclavicular ultrasonography of the LIMA origin was studied preoperatively and at 5.3 ± 3.6 months and 1.7 ± 0.4 years postoperatively. At the late postoperative ultrasonography electrocardiographically controlled hyperemic response was also studied for 6 min. Control angiography was performed at 1.5 ± 0.8 years. Differences within groups were tested with a paired t-test and between groups with an unpaired t-test.

Results: Control angiography showed in 13 patients (group I) a patent LIMA graft and in 3 patients (group II) a string sign LIMA graft. Preoperative blood velocities were not significantly different between groups. Postoperatively, both groups revealed higher diastolic and lower systolic blood velocities compared to preoperative values.
The blood velocities at rest did not change in group I and all velocities decreased in group II in time postoperatively. The blood velocities in maximal hyperemic response increased significantly within the groups and were not significantly different between the groups. No ischemia could be detected electrocardiographically during hyperaemic response and no patient presented angina.

Conclusions: Both groups showed a shift towards coronary type diastolic blood velocities at rest and at hyperaemic response. Significant hyperaemic response was also present in string sign LIMA grafts and demonstrates response capacity to increased myocardial oxygen demand.

## Introduction

Using the left internal mammary artery (LIMA) as a bypass graft to revascularize the left anterior descending artery (LAD) has improved the results of coronary artery bypass grafting [1-2]. The widespread use of the LIMA has led to a number of papers describing the LIMA string sign phenomenon and its aetiology [3]. Using this conduit in mild to moderate stenosis of the LAD is suggested to be the most probable cause of the string sign of the LIMA graft [4-9]. To evaluate the performance of the LIMA graft an accurate non-invasive functional test of the LIMA graft is important. Although several methods have been described to assess LIMA graft patency, at present angiography is the most widely accepted method. This method is superior to other methods especially for patients at rest. However, angiography comes short in assessing the functionality or graft patency when the myocardial oxygen demand rises. This is in particular important in case of string sign LIMA grafts. To assess functionality of the LIMA to LAD graft we performed a hyperaemic myocardial response test using adenosine and measured velocity parameters in the LIMA origin by supraclavicular ultrasonography.

## Materials and methods

Sixteen patients (13 M, 63 ± 8 years) with a single LIMA anastomosis to the LAD were prospectively entered in a follow-up study. Informed consent was obtained from all patients. Exclusion criteria included urgent coronary bypass grafting, redo surgery, serious co-morbidity (malignancy, previous chest irradiation), infarction of the LAD region, combined cardiac surgery and subclavian artery stenosis.

In these 16 patients, supraclavicular ultrasonography of the LIMA origin was studied preoperatively and at 5.3 ± 3.6 months and 1.7 ± 0.4 years postoperatively. Ultrasonography in early follow up was performed at rest and in late follow-up at rest during 1 min and during hyperaemic response using adenosine infusion (0.14 mg/kg per min) during 6 min. After the hyperaemic response ultrasonography was continued for 2 min. Simultaneous electrocardiographic (ECG) monitoring was incorporated for exact systolic-diastolic timing.

Postoperative control angiography was performed at 1.5 ± 0.9 years. The angiograms

were analysed for native coronary artery disease, LIMA graft patency as well as LIMA distal anastomosis patency . In order to assess the patency and run-off of the single LIMA grafts, the LIMA grafts and the native coronary arteries were studied by selective injections. LIMA patency and contrast run off were classified into 2 groups: Group I: patent single LIMA grafts with good contrast run off into the native LAD (n = 12). Group II: String sign (narrowing) single LIMA graft with no or low contrast flow in the graft and no or low contrast run off into the native LAD (n = 3). In one patient in group I no adequate ultrasonography signals could be obtained due to adipositas and this patient was excluded from the study. One patient in group II had diabetis.

*Ultrasonography*

A Sonos 2500 (Hewlett Packard, Andover, Mass.) duplex scanner that combined both B-mode imaging and pulsed Doppler ultrasound was used to evaluate blood velocity parameters in the LIMA. The patients were in supine position and continuously electrocardiographically monitored. A 7.5 MHz sector scanner was positioned in the left supraclavicular region and blood flow velocities were measured and recorded at an angle of approximately 60 degrees just distal to the origin of the LIMA. Software with correction for the angle of insonation was used. No other velocity parameters than those obtained by supraclavicular approach were studied. Ultrasonographic recording was performed for at least 3 to 5 cardiac cycles. All data were analysed by three physicians off-line. At the day of the late ultrasonographic follow up patients were not allowed to take any medication because of the adenosine test. At rest, blood flow velocities, ECG and blood pressure were recorded. After adenosine infusion started (0.14 mg/kg/min), these variables were recorded every minute for a period of 6 minutes (min). After 6 min the infusion was stopped and the patients were continuously monitored for at least 2 min.

The following ultrasonography parameters were analysed: diastolic and systolic peak velocity (DPV, SPV), diastolic and systolic velocity integral (DVI, SVI), peak diastolic/peak systolic velocity ratio (DSVR) and diastolic/total velocity integral ratio (DTVIR).

*Statistical analysis*

Statistical analysis is performed by the use of Epi Info 6.04 (Centers for Disease Control and Prevention, Atlanta, GA) software. Data comparison between groups are tested by unpaired and within groups by paired t-tests. All data are expressed as mean ± SD. A $P$ value of $< 0.05$ is considered significant.

## Results

*Preoperative ultrasonography*

Adequate visualisation and Doppler signals of the LIMA were obtained in all 16 (100 %) patients. Ultrasonography was performed 1.4 ± 1.3 (group I) versus 2.0 ± 1.4 days (group II), $P = 0.6$, before operation. All patients were in sinus rhythm and free of angina at the time of ultrasonography. All signals showed a predominant systolic waveform with no or very little diastolic velocities (Fig. 1a and Fig. 2a) and no significant differences were observed between the groups ($P$ in Table 1).

Preoperative haemodynamic variables did not differ significantly between the groups: heart rate 64 ± 20 (group I) versus 54 ± 2 bpm (group II), $P = 0.48$, systolic blood pressure 147 ± 30 (group I) versus 139 ± 17 mmHg (group II), $P = 0.7$, diastolic blood pressure 76 ± 14 (group I) versus 62 ± 16 mmHg (group II), $P = 0.2$.

*Early postoperative ultrasonography*

At early follow up, no patient presented with angina or had intercurrent infarction (clinically nor electrocardiographically) and all patients remained in sinus rhythm. Early postoperative haemodynamic variables did not differ significantly between the groups except systolic blood pressure: 142 ± 7 (group I) versus 110 ± 14 mmHg (group II), $P = 0.0005$ and diastolic blood pressure 81 ± 7 (group I) versus 73 ± 4 mmHg (group II), $P = 0.17$. Early postoperative ultrasonography was performed at 5.3 ± 3.7 months with no significant differences in the follow-up period between both groups, 5.2 ± 3.9 (group I) versus 5.7 ± 2.6 months (group II), ($P = 0.82$) and between the groups no significant differences appeared in the velocity parameters ($P$* in Table 1).

*Table 1. Pre- and early postoperative ultrasonography velocity parameters of the LIMA*

| | | Preoperative | | |
|---|---|---|---|---|
| | | Group I | Group II | *P* |
| DPV | (cm/sec) | 14 ± 9 | 12 ± 2 | 0.83 |
| DVI | ($cm^2$) | 5 ± 4 | 5 ± 3 | 0.91 |
| SPV | (cm/sec) | 94 ± 39 | 106 ± 17 | 0.68 |
| SVI | ($cm^2$) | 17 ± 7 | 21 ± 4 | 0.52 |
| DSVR | | 0.2 ± 0.1 | 0.1 ± 0.01 | 0.56 |
| DTVIR | | 0.3 ± 0.2 | 0.2 ± 0.1 | 0.61 |

| | | Early postoperative | | | | |
|---|---|---|---|---|---|---|
| | | Group I | Group II | *P** | *P*** | *P**** |
| DPV | (cm/sec) | 33 ± 14 | 42 ± 28 | 0.51 | 0.03 | 0.28 |
| DVI | ($cm^2$) | 11 ± 4 | 10 ± 6 | 0.92 | 0.14 | 0.18 |
| SPV | (cm/sec) | 64 ± 15 | 50 ± 19 | 0.21 | 0.03 | 0.04 |
| SVI | ($cm^2$) | 10 ± 3 | 9 ± 4 | 0.71 | 0.06 | 0.01 |
| DSVR | | 0.4 ± 0.2 | 0.8 ± 0.2 | 0.05 | 0.03 | 0.09 |
| DTVIR | | 1.1 ± 0.4 | 1.1 ± 0.3 | 0.99 | 0.00 | 0.00 |

Group I, patent LIMA-LAD grafts (n = 12); Group II, string sign LIMA-LAD grafts (n = 3). DPV, diastolic peak velocity; DVI, diastolic velocity integral; SPV, systolic peak velocity; SVI, systolic velocity integral; DSVR, diastolic/systolic peak velocity ratio; DTVIR, diastolic/total velocity integral ratio. *P*: values for differences between the groups. *P**: values for differences of postoperative values between the groups. *P***: values for early postoperative versus preoperative values in group I. *P****: values for early postoperative versus preoperative values in group II. Data are mean ± standard deviation.

In all patients of group I and II a higher systolic than diastolic peak velocity was present. Compared to preoperative values in all but one patient in group I there was a lower peak systolic velocity and in all patients of both groups a higher peak diastolic velocity was present. In all patients of both groups the postoperative diastolic velocity integral (diastolic fraction) became more pronounced compared to preoperative values. Except for one patient of group I, the systolic velocity integral (systolic fraction) in both groups became less pronounced compared to the preoperative values. So, the systolic and diastolic waveforms equalized (DSVIR 1.1 ± 0.4 in group I versus 1.1 ± 0.3 in group II, $P = 0.99$) but the peak systolic velocity remained higher than the peak diastolic velocity (Fig. 1b and Fig. 2b). The mean values are incorporated in Table 1.

In group I, the peak systolic velocity decreased significantly and the peak diastolic velocity increased significantly (*P*** in Table 1). In group II, the systolic parameters decreased significantly as well while the diastolic parameters did not. In group II, diastolic values increased but probably due to the small number of patients in this group (n = 3) the increase is not significant (*P**** in Table 1).

*Late postoperative ultrasonography (at rest)*

During follow-up, no patient presented angina, no infarction occurred (clinically or electrocardiographically) and all patients maintained sinus rhythm. Haemodynamic variables did not differ significantly between the groups except systolic blood pressure as in early postoperative follow-up: 150 ± 23 (group I) versus 117 ± 18 mmHg (group II), $P = 0.04$ and diastolic blood pressure 88 ± 11 (group I) versus 77 ± 6 mmHg (group II), $P = 0.11$. Late postoperative ultrasonography was performed at 1.7 ± 0.4 years without significant differences between both groups; 1.6 ± 0.4 (group I) versus 1.7 ± 0.6 years (group II), $P = 0.8$. The ultrasonographic velocities at rest were not different between the groups (*P* in Table 2). However, in group I all systolic and diastolic values remained more or less the same compared to early postoperative values. In group II all systolic and diastolic values decreased compared to the early postoperative values (Table 2).

Comparing the changes between the early and late postoperative values between the two groups, the peak diastolic velocity changed significantly while all systolic values did not (*P** in Table 2). Compared to the preoperative values all velocities were

significantly higher in group I ($P^{\dagger}$ in Table 2) but not in group II ($P^{\S}$ in Table 2). Late postoperative ultrasonography of both groups is shown in Fig. 1c and Fig. 2c.

*Late postoperative ultrasonography (adenosine hyperaemic response test)*

In group I as well as in group II, all diastolic and systolic parameters increased (Table 2). In group I, all parameters increased significantly ($P^{**1}$ in Table 2). In group II, all systolic and diastolic velocity integral parameters increased significantly ($P^{**2}$ in Table 2). Since all diastolic values showed a more then 200 % increase, the small amount of patients in group II is probably the reason that the increase in the diastolic peak velocity is not statistically significant. This assumption is enhanced by the fact that there are no significant differences between the groups for maximal hyperaemic response ($P^{***}$ in Table 2). During the test, no patient had angina and no ischaemia could be detected on the electrocardiogram. Maximal hyperaemic response ultrasonography is shown in Fig. 1d and Fig. 2d. During maximal hyperaemic response haemodynamic variables did not differ significantly between the groups: Systolic blood pressure 159 ± 24 (group I) versus 135 ± 22 mmHg (group II), $P = 0.14$ and diastolic blood pressure 94 ± 12 (group I) versus 89 ± 6 mmHg (group II), $P = 0.47$.

*Table 2. Late postoperative ultrasonography velocity parameters of the LIMA*

| | | At rest | | | | | |
|---|---|---|---|---|---|---|---|
| | | Group I | Group II | *P* | *P** | *P*† | *P*§ |
| DPV | (cm/sec) | 36 ± 14 | 24 ± 7 | 0.18 | 0.03 | 0.00 | 0.20 |
| DVI | ($cm^2$) | 11 ± 4 | 7 ± 1 | 0.13 | 0.21 | 0.00 | 0.27 |
| SPV | (cm/sec) | 54 ± 19 | 34 ± 4 | 0.08 | 0.53 | 0.00 | 0.14 |
| SVI | ($cm^2$) | 10 ± 4 | 7 ± 1 | 0.22 | 0.40 | 0.00 | 0.15 |
| DSVR | | 0.7 ± 0.2 | 0.7 ± 0.3 | 0.75 | 0.10 | 0.00 | 0.24 |
| DTVIR | | 1.2 ± 0.3 | 1.1 ± 0.4 | 0.51 | 0.56 | 0.00 | 0.11 |

| | | Maximal hyperaemic response | | | | |
|---|---|---|---|---|---|---|
| DPV | (cm/sec) | Group I | *P***1 | Group II | *P***2 | *P**** |
| DVI | ($cm^2$) | 90 ± 32 | 0.00 | 75 ± 32 | 0.05 | 0.49 |
| SPV | (cm/sec) | 25 ± 8 | 0.00 | 18 ± 5 | 0.02 | 0.21 |
| SVI | ($cm^2$) | 85 ± 27 | 0.00 | 76 ± 23 | 0.03 | 0.62 |
| DSVR | | 18 ± 5 | 0.00 | 15 ± 4 | 0.03 | 0.35 |
| DTVIR | | 1.2 ± 0.3 | 0.00 | 1.1 ± 0.2 | 0.01 | 0.62 |
| | | 1.8 ± 0.5 | 0.00 | 1.5 ± 0.2 | 0.01 | 0.25 |

Ultrasonography velocity parameters and groups as described in Table 1. *P*: values for differences of late postoperative values between the groups *P**: values for differences of postoperative values in time between the groups. *P*†: values for differences of late operative versus preoperative values within group I. *P*§: values for differences of late operative versus preoperative values within group II. *P***1 and *P***2: values for differences of late postoperative values at rest versus maximal hyperaemic response within the groups. *P****: values for differences of maximal hyperaemic response between groups. Data are mean ± standard deviation.

*After the resting period for 2 minutes after the hyperaemic response test*

Two minutes after the test, no patient had angina and no ischaemia could be detected at the electrocardiogram. All velocity parameters in group I and the DVI in group II decreased significantly (*P** and *P*** in Table 3). Between the groups, no significant differences appeared (*P* in Table 3). The systolic blood pressure did not differ significantly between the groups in contrast to the diastolic blood pressure: systolic blood pressure 133 ± 6 (group I) versus 118 ± 25 mmHg (group II), $P = 0.14$ and diastolic blood pressure 88 ± 3 (group I) versus 80 ± 7 mmHg (group II), $P = 0.03$.

*Table 3. Ultrasonography velocity parameters 2 minutes after hyperaemic response test*

| | | Group I | Group II | *P* | *P** | *P*** |
|---|---|---|---|---|---|---|
| DPV | (cm/sec) | 48 ± 21 | 36 ± 13 | 0.38 | 0.00 | 0.07 |
| DVI | ($cm^2$) | 13 ± 7 | 9 ± 2 | 0.32 | 0.00 | 0.04 |
| SPV | (cm/sec) | 52 ± 20 | 44 ± 8 | 0.55 | 0.00 | 0.07 |
| SVI | ($cm^2$) | 9 ± 3 | 7 ± 2 | 0.54 | 0.00 | 0.08 |
| DSVR | | 1 ± 0.3 | 1 ± 0.2 | 0.42 | 0.00 | 0.04 |
| DTVIR | | 2 ± 0.5 | 1 ± 0.4 | 0.36 | 0.01 | 0.21 |

Ultrasonography velocity parameters and groups as described in Table 1. *P*: values for differences of ultrasonography values 2 min after the hyperaemic response test between groups. *P**: values for differences of maximal hyperaemic response versus 2 min after the hyperaemic response test in group I. *P***: values for differences of maximal hyperaemic response versus 2 min after the hyperaemic response test in group II. Data are mean ± standard deviation.

*Pre- and late postoperative control angiography*

Native coronary angiograms were performed 4.0 ± 2.4 (group I) versus 3.2 ± 2.4 months (group II), $P = 0.6$, preoperatively. The native coronary vessel stenosis of the LAD appeared not significantly different; 84 % ± 11 % in group I versus 75 % ± 9 % in group II, $P = 0.23$. No intercurrent angiograms were performed for ischaemic symptoms. Control angiography (Fig. 1e and Fig. 2e) was performed by the standard femoral artery approach at 1.9 ± 1.2 years with no significant time differences between the groups; 1.8 ± 1.1 (group I) versus 2.1 ± 1.8 years (group II), $P = 0.8$. The postoperative stenosis of the LAD appeared not significantly different; 91 % ± 9 % in group I versus 80 % ± 17 % in group II, $P = 0.21$. All LIMA grafts were selectively injected and all grafts and anastomoses were patent. In one patient in group II a large pectoral branch was identified. In this patient lower velocities were measured during the hyperaemic response test and after the test. However, the ratios did not differ from the other patients. The time interval of the late ultrasonography and control angiography follow up examinations did not differ significantly between the groups; $P = 0.39$.

## Discussion

The supraclavicular approach measures only the blood flow velocities in the proximal part of the LIMA graft. Compared to the preoperative velocities which presents a systemic blood flow profile, in both groups a shift towards a coronary flow profile is present in the postoperative systolic and diastolic blood flow velocities.

The remarkable decrease of all parameters in group II at 1.7 years postoperatively, especially the diastolic parameters, shows that the LIMA graft changed in function and performance towards a string sign graft. However, the postoperative velocity values at rest remain higher compared to the preoperative values. This suggests that the LIMA graft is functioning and the oxygen demand of the heart at rest can be delivered mainly through the native system. This opinion is supported by the fact that no patient had subjective or objective clinical signs and symptoms of ischaemia.

To determine graft patency a hyperaemic response test was performed at 1.7 years. In group I all blood flow velocities increased significantly as expected for patent grafts (Table 2). Remarkably, in group II almost all velocity parameters increased

significantly as well compared to values at rest (Table 2) and these hyperaemic values were much higher than the values in the early postoperative ultrasonography.

Comparing the hyperaemic to the preoperative velocities in both groups, all diastolic values are higher, all systolic values are lower and the DSVR > 1 (Table 2 and 1) which indicates a coronary flow profile and confirms the patency of LIMA grafts in both groups.

All these findings strongly suggest that the string sign LIMA grafts –as investigated by angiography- at rest remains potentially functional and when the myocardial oxygen demand increases they can change and adapt their function and performance to the need of increased oxygen delivery to the myocardium. This statement is supported by the facts that no patient had complaints of angina, no ischaemia could be detected at the electrocardiogram during the hyperaemic test and 2 min after the hyperaemic test all velocities were decreased to almost pre-hyperaemic-test velocities (Table 3). These observations do not support organic lesions and indicates physiological, reversible and 'functional' change of the LIMA graft [10].

Postoperative ultrasonography of the LIMA graft has been performed either by the supraclavicular, transthoracic or the intravascular approach. Preoperative ultrasound of the LIMA shows a high systolic and a low diastolic blood flow velocity as in peripheral arteries demonstrating the systemic circulation is mainly perfused during the systolic phase [11-13]. The coronary arteries are mainly perfused during the diastolic phase [14], resulting in lower systolic and higher diastolic blood flow velocities compared to the systemic circulation.

Takagi et al. [15] compared supraclavicular with proximal intravascular ultrasonography of the LIMA graft postoperatively and demonstrated an overall higher peak systolic than peak diastolic velocity from the supraclavicular and intravascular approach with significant correlations between both methods. However, diastolic fractions were predominant in both approaches as we also observed in both groups at early and late follow up (DTVIR > 1).

Intravascular ultrasonography studies [4, 16-17] show predominantly diastolic fractions in different parts of the patent LIMA graft. Ichikawa et al. [13] performed intravascular measurements in patent LIMA grafts: even after 5 and 10 years the peak diastolic to peak systolic velocity in the proximal LIMA segment was less than 1 and so the systolic peak velocity remains superior. Our and other studies also showed a

higher peak systolic than peak diastolic velocity in supraclavicular ultrasonography of patent LIMA grafts [15, 18-19].

Akasaka et al. [8] studied 12 patients with angiographically no LIMA flow and compared intravascular flow dynamics with patients with patent LIMA grafts. He stated that in the proximal part both in the no-flow LIMA and in the patent LIMA the systolic peak was higher than the diastolic peak velocity with a DSVR < 1 at rest. Our findings were similar.

Many authors discuss the reasons of development of the string sign LIMA graft. Competitive flow can be important in the development of string sign LIMA grafts or diminished patency of the LIMA graft [4-5, 20-21].

Despite all studies investigating the relationship between the degree of stenosis of the LAD and the patency of the LIMA to LAD graft, no consensus can be obtained about the impact of the degree of the LAD stenosis related to the LIMA graft patency [4, 9, 12, 17, 22-24].

Factors like operative excessive tension or thermal injury, inadequate anastomotic techniques, poor distal LAD run-off bed, persistent LIMA side branches, LIMA spasm, regression of the coronary lesion, distal anastomotic stenosis, chest irradiation, media necrosis, subendothelian fibrocellular proliferation, postpericardiotomy syndrome and left subclavian artery stenosis have been all discussed.

In this study, no significant differences in coronary artery stenosis could be demonstrated in time or between the groups although the stenosis in group I remained more severe. So, it is reasonable to assume that many aspects affect the development and persistence of the string sign graft. Besides the importance to study the causes why LIMA grafts become string sign, it is probably more interesting to demonstrate that the LIMA string sign graft has the capacity to adapt and can provide the sufficient amount of blood to the myocardium when the myocardial oxygen demand increases. In this study, the supraclavicular approach allows differentiation between patent and string sign LIMA grafts based on consecutive analysis in the same patients. The resting values can not predict the potential adaptation to increased myocardial demand. We confirm the “functionality of the string sign LIMA graft” by performing the hyperaemic response test with adenosine.

*Limitations*

First, the number of patients of both study groups is small. This hampers statistical analyses although trends remain clear.

Secondly, we did not calculate flow in the bypass graft because –as previously documented [25]- the correlation of the diameter of the LIMA graft measured at angiography and at ultrasonography was only moderate ($P = 0.5$). We agree with Driever et al. [26] that the calculation of the absolute flow values should be regarded with caution due to inaccuracy in the determination of the diameter. Thirdly, in addition no hyperaemic testing during angiography was done. Fourthly, no control group could be included of patients with a non-functional LIMA graft to the LAD for study of the hyperaemic response.

## Conclusions

Supraclavicular ultrasonography allows detecting velocity patterns of the origin of the LIMA graft in the majority of patients. Patients with a patent LIMA graft as well as patients with a string sign LIMA graft showed a shift towards a coronary flow profile at rest and in hyperaemic response postoperatively. Low postoperative ultrasonography velocities of the LIMA graft should be interpreted carefully. The hyperaemic response test revealed the 'functionality' of the string sign LIMA graft demonstrating the adaptability responding to increased myocardial oxygen demand and may eliminate unnecessary catheterisations. Other clinical implications include the potential of a non-invasive mid- and long-term follow up of LIMA grafts although further studies with a higher number of patients with string sign LIMA grafts are necessary to validate our findings.

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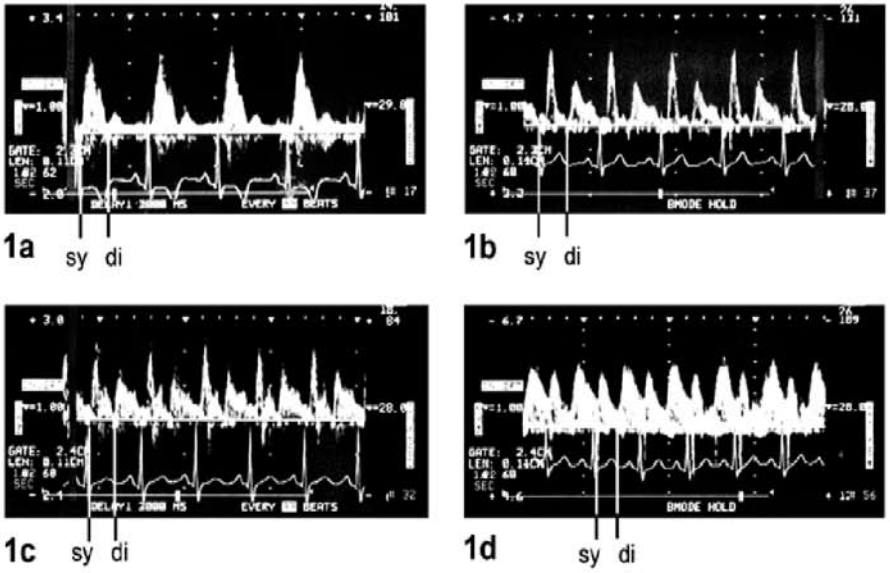
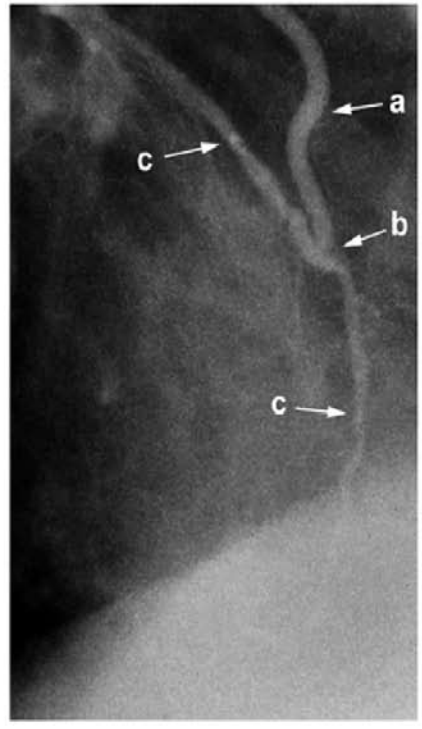
**Figure 1. Supraclavicular ultrasonography of a patent LIMA graft at angiography.**

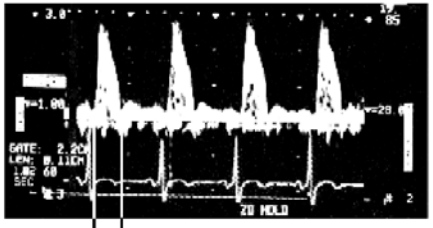


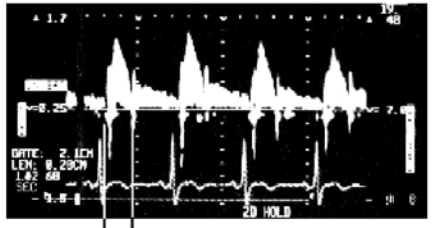



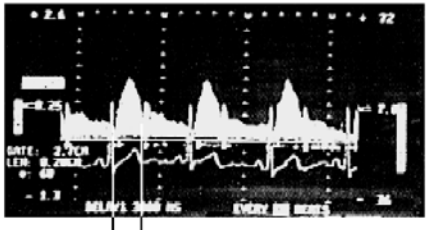

1e

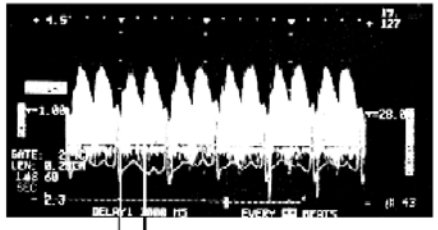
1a.Preoperative ultrasonography of the LIMA origin. 1b. Postoperative ultrasonography of the LIMA origin at 6 months. 1c. Postoperative ultrasonography of the LIMA origin at rest at 1,5 yr. 1d. Postoperative ultrasonography of the LIMA origin during hyperaemic response at 1,5 yr. 1e.Angiographically patent LIMA graft (a) with a single anastomosis (b) to the left anterior descending artery (c) branch at 1,5 yr. sy: systolic di: diastolic

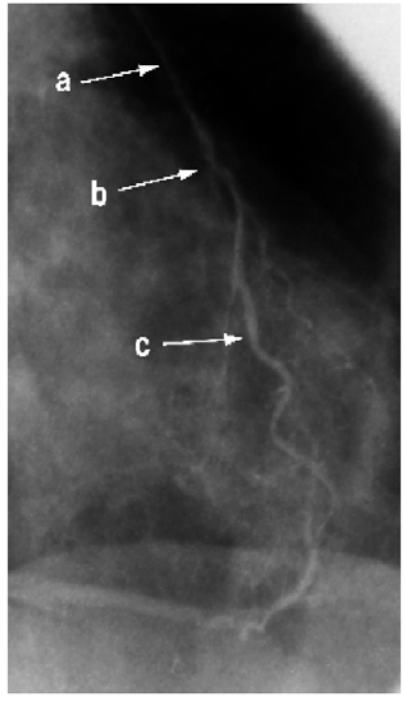
Figure 2. Supraclavicular ultrasonography of a string sign LIMA graft at angiography.




2a. Postoperative ultrasonography of the LIMA origin. 2b. Postoperative ultrasonography of the LIMA origin at 6 months. 2c. Postoperative ultrasonography of the LIMA origin at rest at 1,5 yr. 2d. Postoperative ultrasonography of the LIMA origin during hyperaemic response at 1,5 yr. 2e. Angiographically string sign LIMA graft (a) with a single anastomosis (b) to the left anterior descending artery (c) branch at 1,5 yr. sy=systolic di=diastolic

*CHAPTER 7*

# PRESERVED HYPERAEMIC RESPONSE IN (DISTAL) STRING SIGN LEFT INTERNAL MAMMARY ARTERY GRAFTS

JM Hartman
JC Kelder
RGA Ackerstaff
HA van Swieten
FEE Vermeulen
AJJC Bogers

***Eur J Cardiothorac Surg 2007;31:283-289.***

Presented at the joint 20th annual meeting of the European Association for Cardio-Thoracic Surgery and the 14th annual meeting of the European Society of Thoracic Surgeons, Stockholm, Sweden, September 10-13, 2006.

## Abstract

Objective: To correlate supraclavicular ultrasonography at rest and in hyperaemic response with angiographically patent and (distal) string sign left internal mammary artery (LIMA) to left anterior descending (LAD) area grafts.

Methods: Fifty-three patients with LIMA to LAD area grafting were prospectively entered in a follow up study. Arteriography (native and LIMA) was performed at 1.4 ± 0.8 years postoperatively and ultrasonography was performed at rest, in hyperaemic response and 2 minutes after hyperaemic response at 1.8 ± 0.8 years postoperatively and compared to arteriography. Ultrasonographic parameters analysed: systolic and diastolic peak velocity, systolic and diastolic velocity integral, diastolic/systolic peak velocity ratio and diastolic/total velocity integral ratio.

Results: One patient was excluded because obesity hampered ultrasonography. Arteriography demonstrated functional grafts in 43 patients (group I), sequential distal string sign grafts in 4 patients (group II) and total string sign grafts in 5 patients (group III). Between the groups all ultrasonographic velocities showed a significant linear relation ($P \leq 0.013$) at rest and during maximal hyperaemic response all velocities increased significantly within all groups ($P \leq 0.018$). A significant decrease was found 2 minutes after hyperaemic response and diastolic velocities showed a significant linear relation ($P \leq 0.032$).

Conclusions: String sign LIMA grafts were found in 9/52 (17.3 %) patients. All patent and all string sign grafts showed a shift towards a coronary flow profile in the proximal segment postoperatively. The study revealed the ‘functionality’ of the patent and the (distal) string sign LIMA graft in regard to myocardial oxygen demand. String sign grafts are ‘recruitable’ on demand.

## Introduction

The use of internal mammary arteries (IMAs) is accepted as the best choice in coronary artery bypass grafting (CABG) because of the longer graft patency and patient survival than venous grafts [1-3]. It is well known that postoperative LIMA graft velocity patterns are typically biphasic with lower antegrade systolic and higher antegrade diastolic values compared to preoperative values. This velocity pattern is due to the IMA grafts adaptation to the coronary artery stream bed with an increasingly diastolic flow portion.

IMA grafts can develop into string sign grafts or can occlude and the causes of these findings are still discussed. It remains unclear how and when patent LIMA grafts become string sign LIMA grafts and their behaviour at rest and in hyperaemic response is still unknown. Studies have suggested that using this conduit in mild to moderate stenosis in the target vessel lead to decreased anterograde flow in the arterial bypass and may cause string sign IMA grafts or disuse atrophy [4-7]. Moreover, there is still no consensus in the assessment of the severity of the LAD stenosis related to the IMA conduit patency [8-10].

Control arteriography is the current gold standard method for the assessment of the IMA conduit patency especially for patients at rest. Analysing the functionality or adaptability of the patent, string sign- or occluded LIMA grafts in myocardial hyperaemic tests with control angiography has not been performed or described to our knowledge. Limitations of control arteriography are its costs, its risks in clinically stable patients of 0.7 - 4.0 % [11-12] and the possible disruption of baseline haemodynamics by contrast injection [13].

Echo Doppler ultrasonography is nowadays a frequently used non-invasive method for preoperative IMA screening and postoperative assessment of the LIMA graft function. This method can be used at rest and in contrast to angiography also during hyperaemic response. In this study we evaluate the patency and functionality of the patent, partial- and total string sign LIMA graft at rest and during hyperaemic myocardial response. To our knowledge, this is the first report analysing LIMA string sign grafts versus patent LIMA grafts by supraclavicular Doppler.

## Materials and methods

Fifty-three patients (40 M), mean age of 61 ± 7 years were scheduled for LIMA bypass grafting to the LAD area and prospectively entered in a follow-up study.
Control arteriography was performed at 1.4 ± 0.8 years and mid-term supraclavicular ultrasonography follow-up at 1.8 ± 0.8 years.
The angiograms were analysed by two observers and assessed for native coronary artery stenoses, stenosis of coronary anastomoses and the patency of LIMA grafts. The LIMA grafts and the native coronary arteries were studied by selective injections in order to assess the patency and run-off of the LIMA grafts and the stenoses of the native coronary system. LIMA patency and contrast run off were classified in 3 categories; Group I: patent and functional LIMA grafts (Fig. 1d). Group II: sequential LIMA distal string sign graft; no narrowing of the LIMA graft and high flow of contrast from the origin to the first anastomosed branch with narrowing and no or very low contrast flow into the distal graft segment (Fig. 2d). Group III: total LIMA string sign graft; narrowing of the LIMA graft and no or very low flow of contrast into the LIMA graft (Fig. 3d).

Figure 1. Mid-term follow-up supraclavicular duplex of a patent LIMA graft at angiography (1d) at rest (1a), during hyperaemic response (1b) and 2 minutes after hyperaemic response (1c). * note the scale. 1d: Patent LIMA graft (A) to the LAD (B). sy = systolic, di = diastolic

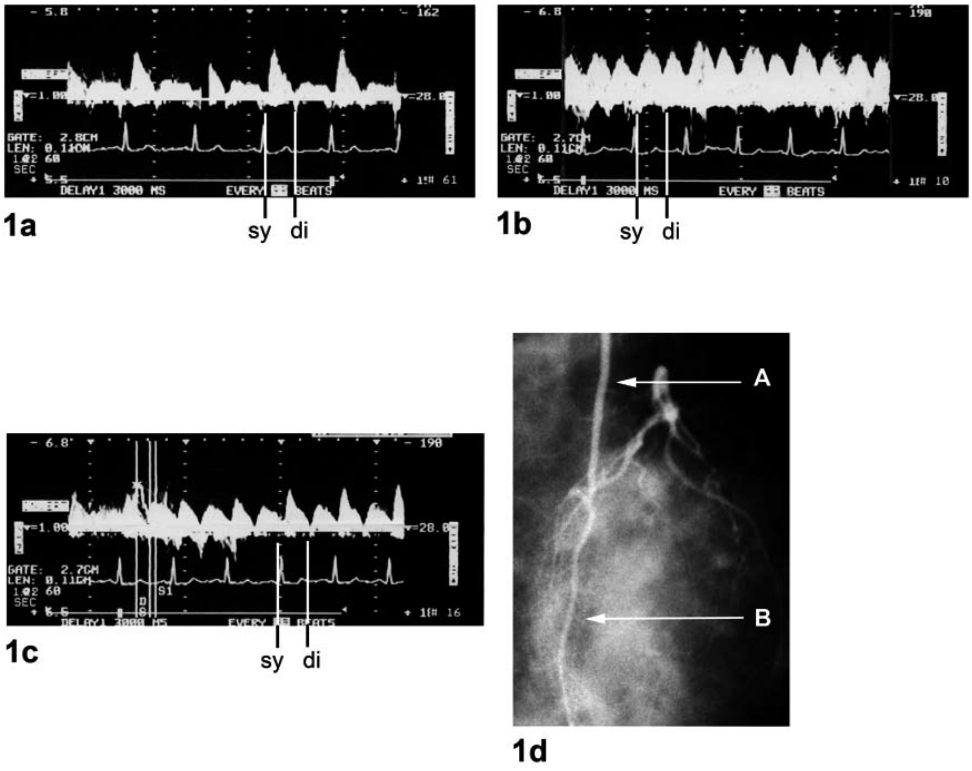
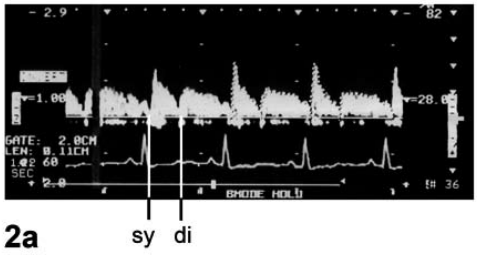
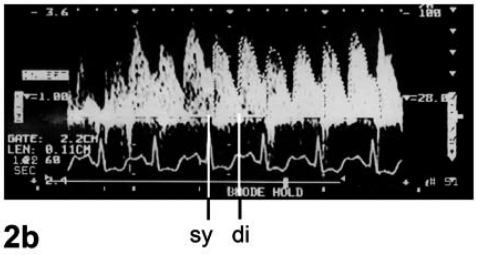


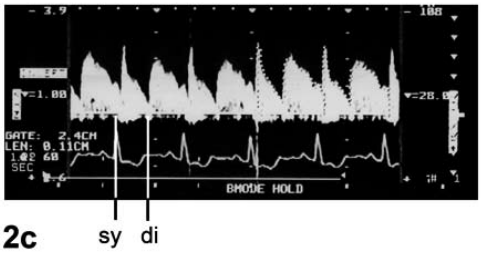
Figure 2. Mid-term follow-up supraclavicular duplex of a distal LIMA string sign graft at angiography (2d) at rest (2a), during hyperaemic response (2b) and 2 minutes after hyperaemic response (2c). * note the scale. 2d: LIMA jump graft (A) to the diagonal branch (B) with distal LIMA string sign graft (C) to the LAD (D). sy = systolic, di = diastolic



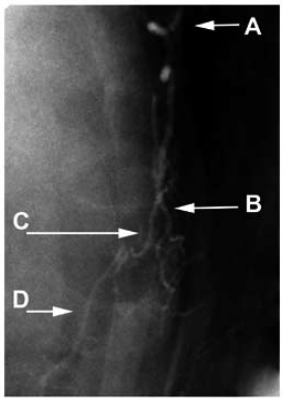

2a sy di




2b sy di

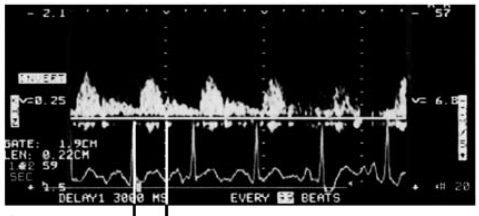



2c sy di

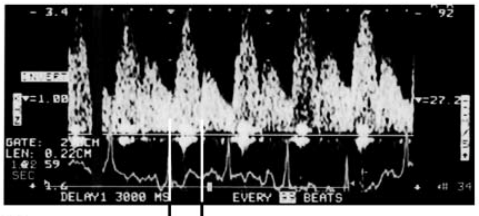



2d

Figure 3. Mid-term follow-up supraclavicular duplex of a total LIMA string sign graft at angiography (3d) at rest (3a), during hyperaemic response (3b) and 2 minutes after hyperaemic response (3c). * note the scale. 3d: Total LIMA string sign graft (A) to the LAD (B). sy = systolic, di = diastolic




3a sy di

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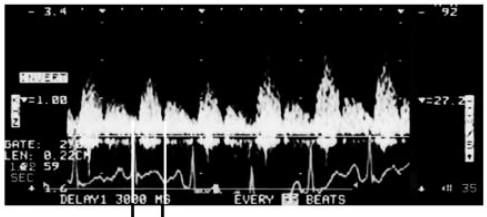
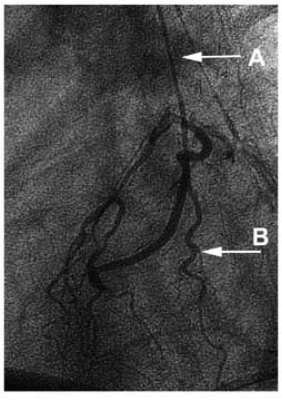



3c sy di




3d

In order to analyse differences between fully patent sequential LIMA grafts to the LAD area and sequential LIMA distal string sign grafts of group II we constituted a subgroup of group I with only the sequential LIMA grafts (Group IB).
The LIMA origin ultrasonographic parameters were analysed by two independent observers. The observers were blinded for the angiography results. Ultrasonography was performed at rest, during a stress test using 0.14 mg/kg/min infusion of adenosine [14] for 6 min and 2 min after the stress test. All patients were monitored electrocardiographically during ultrasonography. From all patients informed consent was obtained.

*Duplex ultrasonography technique*

Initially a Sonos 2000 (Hewlett Packard, Andover, Mass.) and later a Sonos 2500 ( Hewlett Packard, Andover, Mass.) duplex scanner was used that combined both B-mode imaging and pulsed Doppler ultrasound to evaluate blood velocity parameters of the LIMA. Duplex ultrasound investigations and recordings were performed by two trained and experienced technicians. The ultrasound investigation was performed in supine position of the patients under continuous electrocardiographic control. A 7.5 MHz sector scanner was positioned in the supraclavicular fossa and duplex velocities were measured and recorded at an angle of approximately 60 degrees distal to the origin of the LIMA. Software with correction for insonation angle was used. Spectral analysis of LIMA duplex velocity recording was performed during 3-5 consecutive cardiac cycles and data were analysed off-line and interpreted by two physicians. The intraobserver variability was 1.9 %. The following velocity parameters were analysed: peak diastolic and peak systolic velocity (DPV and SPV), diastolic and systolic velocity time integral (DVI, SVI), peak diastolic/peak systolic velocity ratio (DSVR) and diastolic/total (diastolic + systolic) velocity integral ratio (DTVIR). The velocity-time integral is the integral of the instantaneous velocity (Vi) over the time interval (T).

*Statistical analysis*

Data entry and univariate statistical analyses were performed with the use of Epi Info 6.04c (CDC, Atlanta, Georgia). Data within groups were tested by paired t-tests and between groups by unpaired t-tests and ANOVA tests. All data were expressed as mean ± standard deviation. Data were considered statistically significant when the *P* value was 0.05 or less.

## Results

*Control arteriography*

The mean time intervals between operation and control arteriography (group I; 1.5 ± 0.9 years, group II; 1.0 ± 0.04 years, group III; 1.7 ± 1.4 years, $P = 0.64$) and between control arteriography and mid-term follow-up ultrasonography (group I; 0.33 ± 1.4 years, group II; 0.53 ± 0.4 years, group III; 0.67 ± 0.8 years, $P = 0.91$) did not differ significantly between the groups.

In 17.3 % of the patients (distal) string sign LIMA grafts were observed.

Group I consisted of 43 patients (35 M, 62 ± 8 years), with 10 single LIMA to LAD and 33 sequential LIMA grafts to the LAD area (82.7 %). Subgroup IB consisted of the 33 patients (28 M, 60 ± 7 years) with all patent sequential LIMA grafts.

Group II contained 4 patients (2 M, 66 ± 4 years), all with LIMA sequential grafts to the LAD area (7.7 %). Group III contained 5 patients (4 M, 66 ± 5 years), with 3 single LIMA to LAD and 2 LIMA sequential grafts to the LAD area (9.6 %).

The degree of stenosis of the left anterior descending arteries and diagonal branches at control arteriography are shown in Table 1.

*Table 1. Degree of native coronary vessel stenosis of the anterior wall at control arteriography*

| | Group I | Group I B | Group II | Group III | *P* | *P** |
|---|---|---|---|---|---|---|
| LAD stenosis | 88 ± 16 | -- | 76 ± 31 | 83 ± 13 | 0.36 | -- |
| LAD stenosis | -- | 87 ± 18 | 76 ± 31 | -- | -- | 0.06 |
| First diagonal branch stenosis | 83 ± 16 | -- | 88 ± 25 | 35 ± 50 | 0.004 | -- |
| First diagonal branch stenosis | -- | 83 ± 16 | 88 ± 25 | -- | -- | 0.327 |
| Second diagonal branch stenosis | 91 ± 11 | -- | -- | -- | -- | -- |

LAD: left anterior descending artery. Group I, patent and functional LIMA grafts; Group II, distal LIMA string sign grafts; Group III, total LIMA string sign grafts; Group IB, patent and functional sequential grafts. *P*: ANOVA *P*-test for differences between groups. *P**: unpaired *P* values for differences between groups. Data are mean ± standard deviation.

No stenoses of the distal anastomoses could be detected either at selective LIMA graft arteriography or native coronary arteriography. No patient presented angina and no electrocardiographic changes appeared.

*Ultrasonography mid term follow-up of the LIMA origin*

One patient was excluded from the study because obesity hampered ultrasonography. In 52 patients (98 %) ultrasonographic detection of the origin of the LIMA was successful and all registrations could be used for analysis. The time interval between surgery and mid term follow-up did not differ significantly between groups (group I; 1.87 ± 0.99 years, group II; 1.5 ± 0.4 years, group III; 1.8 ± 0.7 years, $P = 0.52$). Neither the heart rate nor the systolic or diastolic blood pressure was significantly different between the groups. All patients were in sinus rhythm. Parameters were statistically

studied in order to analyse the differences and relationships between the groups. No ischemia could be detected electrocardiographically during ultrasonography and no patient had complaints of angina.

*Table 2. Postoperative supraclavicular LIMA duplex velocities at rest in mid-term follow-up*

| | | Group I n = 43 | Group II n = 4 | Group III n = 5 | *P* | *P** | *P*** | *P*§ |
|---|---|---|---|---|---|---|---|---|
| DPV | (cm/sec) | 38 ± 14 | 26 ± 8 | 20 ± 8 | NS | 0.005 | NS | 0.006 |
| DVI | ($cm^2$) | 13 ± 5 | 11 ± 3 | 6 ± 2 | NS | 0.002 | 0.01 | 0.005 |
| SPV | (cm/sec) | 58 ± 19 | 36 ± 8 | 29 ± 7 | 0.03 | 0.002 | NS | 0.001 |
| SVI | ($cm^2$) | 10 ± 4 | 7 ± 1 | 6 ± 2 | NS | 0.013 | NS | 0.013 |
| DSVR | | 0.7 ± 0.2 | 0.8 ± 0.3 | 0.7 ± 0.3 | NS | NS | NS | NS |
| DTVIR | | 0.6 ± 0.1 | 0.6 ± 0.1 | 0.5 ± 0.1 | NS | NS | 0.046 | NS |

DPV, diastolic peak velocity; DVI, diastolic velocity integral; SPV, systolic peak velocity; SVI, systolic velocity integral; DSVR, diastolic/systolic peak velocity ratio; DTVIR, diastolic/total (diastolic + systolic) velocity integral ratio Group I, II and III as described in Table 1. *P*: values for differences between group I and II, *P**: values for differences between group I and III, *P***: values for differences between group II and III, $P^{\S}$: values for the linear relation between the three groups. Data are mean ± standard deviation. NS: not significant.

*At rest*

All velocities of the functional LIMA grafts (Fig. 1a) are higher than LIMA string sign grafts (Fig. 3a) and differ significantly (Table 2). Comparing the velocities of the functional grafts with the distal LIMA string sign grafts a clear tendency can be noticed (Fig. 1a and Fig. 2a). All functional LIMA graft velocities are higher but do not differ significantly except for peak systolic velocity (Table 2). Comparing the velocity parameters of distal LIMA string sign grafts with total LIMA string sign grafts only the DVI is significantly higher whereas all velocities in group II

are higher. The linear relations for all velocities between the three groups are highly significant (Table 2).
As expected, the subgroup IB shows higher velocities than group II (Table 5).

*Hyperaemic response*

Nor the heart rate or the systolic or diastolic blood pressure differs significantly between the three groups during 6 minutes of hyperaemic response.
In all groups, in contrast to values at rest, the DSVR is > 1. Within all groups, a highly significant increase of all velocities is present (*P*I, *P*II and *P*III in Table 3). Remarkably, total string sign LIMA grafts do respond and velocities and time integrals increase significantly. However, maximal velocities in this group remain lower compared to the other groups (Table 3).

*Table 3. Maximal hyperaemic response values during 6 min of adenosine*

| | | Group I n = 43 | Group II n = 4 | Group III n = 5 | *P* | *P** | *P*** |
|---|---|---|---|---|---|---|---|
| DPV | (cm/sec) | 103 ± 27 | 83 ± 16 | 67 ± 25 | 0.012 | NS | 0.007 |
| DVI | ($cm^2$) | 31 ± 10 | 22 ± 4 | 17 ± 4 | 0.007 | NS | 0.005 |
| SPV | (cm/sec) | 91 ± 24 | 80 ± 13 | 76 ± 18 | NS | NS | NS |
| SVI | ($cm^2$) | 19 ± 5 | 16 ± 3 | 15 ± 3 | NS | NS | NS |
| DSVR | | 1.3 ± 0.3 | 1.3 ± 0.2 | 1 ± 0.2 | NS | NS | NS |
| DTVIR | | 0.7 ± 0.1 | 0.6 ± 0.0 | 0.6 ± 0.0 | 0.042 | NS | 0.014 |

| | | | *P*I | *P*II | *P*III | *P*§ |
|---|---|---|---|---|---|---|
| DPV | (cm/sec) | NS | 0.00 | 0.006 | 0.006 | NS |
| DVI | ($cm^2$) | NS | 0.00 | 0.007 | 0.001 | NS |
| SPV | (cm/sec) | NS | 0.00 | 0.018 | 0.007 | NS |
| SVI | ($cm^2$) | NS | 0.00 | 0.014 | 0.006 | NS |
| DSVR | | NS | 0.00 | 0.021 | 0.010 | 0.049 |
| DTVIR | | NS | 0.00 | NS | 0.009 | NS |

DPV, DVI, SPV, SVI, DSVR and DTVIR as described in Table 2. *P*: values for the linear relation between the three groups for absolute maximal hyperaemic values. *P**: values for differences of absolute values between group I and II. *P***: values for differences of absolute values between group I and III. *P****: values for differences of absolute values between group II and III. *P*I: values for differences of maximum hyperaemic values versus values at rest within group 1. *P*II: values for differences of maximum hyperaemic values versus values at rest within group II. *P*III: values for differences of maximum hyperaemic values versus values at rest within group III. *P*§: values for the linear relation of maximum hyperaemic values versus values at rest between the groups. Data are mean ± standard deviation. NS: not significant.

Comparing the hyperaemic responses between all groups, only the diastolic values differ significantly between group I and III (*P**, *P*** and *P**** in Table 3). However, these parameters increase significantly during hyperaemic response within all groups (*P*I, *P*II and *P*III in Table 3). Analysing the subgroup IB versus group II only the diastolic parameters differ significantly although a significant increase is clear within both groups (Table 5).

*Two minutes after hyperaemic response*

There are no significant differences in heart rate, systolic or diastolic blood pressure between the groups. All velocities decrease within the three groups in 2 min. In group I and III all values decreases significantly and in group II all but the peak systolic velocity decrease significantly (*P**, *P*** and *P**** in Table 4).

In group I, velocities decreased to values at rest whereas velocities in group II and group III are still higher compared to values at rest. The linear relation between the three groups for differences of maximal hyperaemic response versus values after 2 min is significant for diastolic parameters. All values in group IB decrease as well. In contrast to the hyperaemic response diastolic velocities do not differ significantly compared to group II (Table 5).

*Table 4. Two minutes after the adenosine hyperaemic response test*

| | Group I n = 43 | Group II n = 4 | Group III n = 5 | *P* | *P** | *P*** | *P**** | *P*§ |
|---|---|---|---|---|---|---|---|---|
| DPV (cm/sec) | 47 ± 17 | 42 ± 13 | 33 ± 10 | NS | 0.000 | 0.038 | 0.007 | 0.032 |
| DVI ($cm^2$) | 14 ± 5 | 13 ± 3 | 8 ± 2 | NS | 0.000 | 0.035 | 0.002 | 0.010 |
| SPV (cm/sec) | 56 ± 21 | 45 ± 17 | 46 ± 10 | NS | 0.000 | NS | 0.004 | NS |
| SVI ($cm^2$) | 10 ± 4 | 8 ± 1 | 8 ± 2 | NS | 0.000 | 0.016 | 0.004 | NS |
| DSVR | 0.9 ± 0.3 | 1 ± 0.2 | 0.7 ± 0.2 | NS | 0.000 | 0.007 | NS | NS |
| DTVIR | 0.6 ± 0.1 | 0.6 ± 0.0 | 0.5 ± 0.1 | NS | 0.000 | NS | 0.023 | NS |

DPV, DVI, SPV, SVI, DSVR and DTVIR as described in Table 2. *P*: values for the linear relation between the three groups. *P**: values for differences of maximal hyperaemic response and 2 min. after the response test within group I. *P***:values for differences of maximal hyperaemic response and 2 min after the response test within group II. *P****: values for differences of maximal hyperaemic response and 2 min after the response test within group III. *P*§: values for the linear relation for differences of maximal hyperaemic response minus values 2 min after the response test between groups. Data are mean ± standard deviation. NS: not significant.

*Table 5. Postoperative supraclavicular LIMA duplex velocities in mid-term follow-up*

| | Group IB n = 33 | Group II n = 4 | *P* | Group IB n = 33 | Group II n = 4 | *P* |
|---|---|---|---|---|---|---|
| | at rest | | | hyperaemic response | | |
| DPV (cm/sec) | 39 ± 14 | 26 ± 8 | NS | 108 ± 24 | 83 ± 16 | 0.048 |
| DVI ($cm^2$) | 14 ± 5 | 11 ± 3 | NS | 33 ± 10 | 22 ± 4 | 0.042 |
| SPV (cm/sec) | 58 ± 19 | 36 ± 8 | 0.034 | 93 ± 22 | 80 ± 13 | NS |
| SVI ($cm^2$) | 10 ± 4 | 7 ± 1 | NS | 19 ± 5 | 16 ± 3 | NS |
| DSVR | 0.7 ± 0.2 | 0.8 ± 0.3 | NS | 1.3 ± 0.3 | 1 ± 0.2 | NS |
| DTVIR | 0.6 ± 0.1 | 0.6 ± 0.1 | NS | 0.7 ± 0.1 | 0.6 ± 0.0 | NS |

| | Group IB n = 33 | Group II n = 4 | *P* |
|---|---|---|---|
| | after the response | | |
| DPV (cm/sec) | 48 ± 17 | 42 ± 13 | NS |
| DVI ($cm^2$) | 14 ± 5 | 13 ± 3 | NS |
| SPV (cm/sec) | 58 ± 21 | 45 ± 17 | NS |
| SVI ($cm^2$) | 10 ± 4 | 8 ± 1 | NS |
| DSVR | 0.9 ± 0.3 | 1 ± 0.2 | NS |
| DTVIR | 0.6 ± 0.1 | 0.6 ± 0.0 | NS |

Group IB, patients with patent sequential LIMA grafts; Group II, as described in Table 2. *P*: values for differences between the groups. Data are mean ± standard deviation. NS: not significant.

## Discussion

Takagi et al. [15] tested and compared the ultrasonographic method from the supraclavicular fossa with Doppler catheter measurements and found significant correlations in SPV ($P < 0.01$), DPV ($P < 0.01$), and the diastolic to systolic peak flow velocity ratios ($P < 0.01$) between the methods. Therefore, we can assume that ultrasonography from the supraclavicular fossa permits assessment of the LIMA graft patency.

Patent LIMA grafts and their transthoracic ultrasonographic patterns have been widely described. LIMA grafts can develop into string sign grafts and it is interesting to study the response in velocity patterns of these string sign LIMA grafts in different myocardial conditions. Song et al. [16] stated that the 'occluded' grafts showed transthoracic diastolic velocity time integral fractions of less then 0.60 in all grafts.

A (partial) LIMA string sign graft was observed in 17.3 % (9 pts.) of our study population (52 pts.). At rest, in all groups the DSVR was < 1.0. this confirms that peak systolic velocities were higher than peak diastolic velocities in the proximal part of the LIMA graft. In all groups, the DTVIR was equal to or higher than 0.5 which implicates that the diastolic fraction of the cardiac cycle is equal to or predominant to the systolic fraction. Analysing the velocity patterns and the highly significant differences of the linear relations between the groups, it is remarkable that a diastolic pattern can be obtained in the proximal part of the string sign LIMA graft. This is remarkable because of the "non functional state" of the string sign LIMA graft. Therefore, these findings implicate that a total string sign LIMA graft at rest is not totally occluded but in a "low functional state".

We found diastolic velocity time integral fractions of 0.6 in group I and II and 0.5 in total LIMA string sign grafts. However, our measurements were taken from the supraclavicular approach which can explain the higher systolic and lower diastolic values in occluded grafts and therefore lower diastolic fraction values.

Jones et al. [12] described in their review report that the diastolic fraction of less then 0.5 was shown to be the best criterion for prediction of stenosis. In our data the patent LIMA conduit and the partial string sign LIMA graft had a diastolic fraction (DTVIR) of > 0.5. In total LIMA string sign grafts diastolic fractions were 0.5 ± 0.07. In our opinion (borderline) values should be interpreted carefully especially

when patients do not have complaints because of the physiological state of the string sign LIMA graft.

In all groups during the stress test, in contrast to values at rest, the DSVR became equal to or higher than 1. This means that peak diastolic velocities were higher than peak systolic velocities which implicates a more pronounced coronary profile (Table 3). All string sign LIMA graft velocities increased significantly. The diastolic peak velocity equals to the systolic peak velocity and the diastolic fraction becomes predominantly (DTVIR > 0.5) as in the patent – and partial string sign- LIMA grafts. However, the diastolic values remained significantly lower compared to the patent LIMA grafts. Some explanations may be put forward in this regard. First, there is no difference in the degree of stenosis of the LAD but there is a significant difference in stenosis of the diagonal branch. However, there were only 2 patients with sequential LIMA grafts in the string sign group. Secondly, we already reported [17] that at multivariate analyses the maximal diastolic peak velocity in hyperaemic response correlated significantly with the LIMA run-off area. These LIMA run-off areas can also contribute to the findings but we did not take these in account. Nevertheless, the LIMA grafts do respond in the stress test demonstrating to be a "reactive conduit".

After the stress test, all velocities within group I and III decreased significantly and DSVR became equal to or lower than 1. Adenosine is rapidly metabolized [14] and all LIMA grafts, even the total string sign LIMA grafts, responded well and immediate to their function on demand of the decreased myocardial stress circumstances. After 2 min, all diastolic values were lowered by 50 % in all groups. So, this finding enhanced the statement that string sign LIMA grafts can be considered as "living conduits".

We did not transform our data into flow because of the poor correlation of the diameter at angiography versus ultrasonography [17]. We agree with Driever et al. [18] that calculations of the diastolic flow values contain errors especially in determining the diameter of the LIMA which is a significant part of the flow calculation. We used the supraclavicular approach and although Driever et al. [18] assessed LIMA graft patency through the second intercostal space both approaches showed a DSVR of < 1.0. So, systolic peak velocity remained higher than diastolic peak velocities in the proximal part of the LIMA as also described by Bach et al. [19]. They mentioned a diastolic/systolic peak velocity ratio of 0.6 ± 0.2.

Gaudino et al. [20] showed the increase of the systolic and diastolic peak velocity in myocardial stress conditions with a decrease of the systolic/diastolic peak velocity ratio to 0.85 ± 0.28 compared to 1.51 ± 0.33 at rest.
Mauric et al. [21] described the significant increase of the diastolic peak velocity after leg exercise compared to values at rest whereas the systolic peak velocity was unchanged.
Katz et al. [22] described the dominant diastolic flow pattern in patent grafts at transthoracic Doppler. Occluded grafts had absent flow or a dominant systolic pattern. Adenosine induced increase of LIMA diastolic peak velocity from 48 to 105 cm/s. He did not measure adenosine effects in occluded LIMA vessels.
There are only a few reports describing the string sign or no flow LIMA graft to the LAD area. Akasaka et al. [6] described, using a guide wire, that the no flow state in IMA grafts at rest were temporary and that these IMA grafts functioned as conduits during hyperaemic states.
In our opinion, a non-invasive method –as the supraclavicular ultrasonography- to assess LIMA graft patency could be useful for clinical diagnosis and long term follow-up of graft outcome.

*Limitations*
First, the number of patients with (partial) LIMA string sign graft is small which hampers statistical analyses. Secondly, no control group with an occluded and non-responding LIMA graft was present.

## Conclusions

Our findings suggest that LIMA string sign grafts are in a “low functional state” at rest and can adapt to myocardial stress conditions when myocardial oxygen demand is increased. So, in our opinion, LIMA string sign grafts are “living conduits”.

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*CHAPTER 8*

# EPICARDIAL CORONARY ARTERY DOPPLER: VALIDATION IN THE ANIMAL MODEL

G D'Ancona
JM Hartman
F Bartolozzi
E van Deel
DJGM Duncker
AJJC Bogers
M Pilato
AP Kappetein

***Interact Cardiovasc Thorac Surg 2008;7:634-637.***

## Abstract

Background: Aim of the study was to validate the use of a newly designed epicardial coronary artery Doppler probe and test its detection of changes in coronary blood flow velocity.

Materials and methods: Left anterior descending (LAD) coronary blood flow and flow-velocity were evaluated in 4 adult pigs by using respectively a pericoronary transit time flow (TTF) probe and a newly designed epicardial Doppler micro-probe. Four consecutive measurements were taken for each of the following condition: basal, partial stenosis, occlusion, and reperfusion of the LAD. Values were recorded and compared by means of ANOVA analysis and multiple range testing.

Results: Mean TTF value (ml/min) was 23.2 ± 6.6 in basal condition, 16.2 ± 5.7 after partial LAD stenosis, 0.1 ± 0.3 during LAD occlusion, and 67.4 ± 23.3 at reperfusion ($P < 0.001$). Similar patterns were recorded in terms of Doppler velocity (cm/s) with values of 4.0 ± 1.9 in basal condition, 3.5 ± 2.3 after partial LAD stenosis, 0.5 ± 1.4 during LAD occlusion, and 11.1 ± 5.5 at reperfusion ($P < 0.001$).
When multiple range testing was performed within groups, no significant differences in both TTF and Doppler velocity were seen between basal condition and partial LAD stenosis ($P$ = ns).

Conclusion: Epicardial coronary arterial Doppler is a valuable means to detect coronary arterial flow velocity in basal condition. Although changes in flow velocity are easily recorded after coronary occlusion and reperfusion, modifications after partial coronary stenosis are not clearly defined. Epicardial coronary Doppler could serve as an armamentarium to assist cardiac surgeons in the identification and assessment of coronary targets, and, as an adjunct to TTF technology, as a means to better assess the patency of coronary graft anastomosis.

## Introduction

Since the 1980's intraoperative epicardial coronary ultrasound has been proposed as a possible tool to guide cardiac surgeons on selection of appropriate coronary targets and to assess coronary anastomosis quality [1-2]. In spite of initial enthusiasm, this technology was soon abandoned due to its limitations in terms of technological designing and interpretation of findings. Some authors have recently started to consistently dedicate their research on epicardial coronary Doppler performed with custom-made Doppler probes in both the porcine model and in the ex-vivo human beating heart [3-5].

We herein report our initial experience, in a porcine model, with a newly designed epicardial coronary Doppler micro-probe (X-plore®, Medistim, Oslo, Norway) and discuss the possible future applications of this technology.

## Materials and methods

Four adult pigs (50 kg) were sedated with ketamine (30 mg $kg^{-1}$i.m.), anaesthetized with thiopental (10 mg $kg^{-1}$i.v.), intubated and ventilated. Anaesthesia was maintained with midazolam (2 mg $kg^{-1}$+ 1 mg $kg^{-1}$ $h^{-1}$i.v.) and fentanyl (10 μg $kg^{-1}$ $h^{-1}$i.v.). Animals were treated accordingly to the existing ethical regulations on animal experimentation. Median sternotomy and pericardiotomy was performed. The left anterior descending (LAD) coronary artery was isolated and a pericoronary snare was placed proximally around the vessel. LAD absolute flow (ml/min) and flow velocity (cm/s) values were simultaneously measured using respectively a 2-mm pericoronary transit time flow probe (Transonic Systems Inc. ®, Ithaca, New York, USA) and a newly designed epi-coronary Doppler probe (X-plore®, Medistim, Oslo, Norway). The Doppler probe used has a 7,5 MHz -3 by 6 mm unfocused crystal. When an ultrasound beam is reflected by a moving object, the frequency of the reflected pulse is changed. An object moving towards the ultrasound beam will compress the wave form and increase the frequency. Correspondingly, an object moving away from the beam will lengthen the waveform and decrease the frequency.

The change in frequency, also called Doppler shift, represents the velocity and direction of the moving target. To limit problems relating to the ultrasound beam's angle of incidence with the blood, the X-plore® probe has a built-in angle of 45 degrees. Holding the probe perpendicular to the vessel direction will ensure accurate velocity measurements. Note that this causes the probe to measure the velocities in front or behind the actual probe position, but never right under the probe.

The Doppler probe is connected with a flowmeter device (Veri-Q, Medistim, Oslo, Norway) that works as measuring and data storage mean. The device applies a pulsed Doppler, allowing the user to control the depth from where the velocity should be measured. Additionally, sample volume is adjustable, and selected as a range around the depth setting. The default settings are a depth of 5 mm, and a volume of 6 mm. These settings allow for sampling flow velocities at depths from to 2 to 8 mm from the probe surface. The Veri-Q will display the Doppler spectrum at the default 5 seconds sweep rate as soon as a probe is connected. The crystal is arranged in a 45 degree angle when the probe is held perpendicular to the measured surface. The velocity scales are compensated for the same 45 degree angle (Fig. 1 and Fig. 2). The

sample volume can be adjusted in size and position.

The TTF probe was placed immediately distally to the snare and the epicoronary Doppler probe was placed more distally on the LAD and away from the point of stenosis to avoid extreme velocity peeks secondary to a condition of blood flow vorticosity. Adequate contact between the probe and the vessel was achieved by means of aqueous gel. Simultaneous measurements of TTF and Doppler flow velocity were recorded during 4 different phases: in basal condition, after creating a stenosis of the LAD with the proximal snare, during coronary occlusion, and during coronary reperfusion.

Four consecutive measurements were recorded during each phase of the experiment. Similarly, invasive blood pressure (BP), heart rate (HR), and left ventricular end diastolic pressure (LVEDP) were recorded.

Data were stored and analyzed. Data were expressed in terms of means ± standard deviation. ANOVA was used in the analysis to evaluate significant differences in TTF, Doppler flow velocity, BP, HR, and LVEDP between the 4 different stages of the experiment (basal, partial stenosis of LAD, occlusion LAD, and reperfusion). Whenever significant differences between the groups were reported, multiple range testing was adopted to identify if the differences persisted even in the comparison within coupled groups. Pearson's correlation coefficient was calculated to test relationship between coronary flow and coronary flow velocity values. Statistical significance was stated for $P$ values < than 0.05.

All experiments were performed and funded by the Erasmus University Hospital in Rotterdam, NL.

At the end of the experiments, animals were used for other investigations and eventually sacrificed in the operating room.

## Results

Values of blood pressure, heart rate, and left ventricular end diastolic pressure were recorded during the 4 different phases of the experiment (Table 1) and no statistically significant differences were noticed in mean blood pressure ($P = 0.2$), heart rate ($P = 0.4$), and left ventricular end diastolic pressure ($P = 0.8$).

There were statistically significant differences when comparing TTFM and Doppler

flow velocity measurements during the four stages of the experiment. Doppler Velocity in cm/s was 4.0 ± 1.9 in basal condition, 3.5 ± 2.2 during partial coronary stenosis, 0.50 ± 1.4 at occlusion, and 11.0 ± 5.5 during reperfusion ($P < 0.0001$) (Table 2). Similarly, TTF in ml/min was 23.1 ± 6.6 in basal condition, 16.2 ± 5.7 during partial coronary stenosis, 0.0 ± 0.2 at occlusion, and 67.4 ± 23.2 during reperfusion ($P < 0.0001$) (Table2).

Furthermore, with multiple range testing, no differences were found within the groups, in TTF and Doppler flow velocity within the basal condition and partial LAD stenosis ($P$ = ns).

A strong correlation was found between mean coronary flow and mean Doppler velocity values (P coefficient 0.99; $P < 0.001$) (Table 3).

## Discussion

The current referral pattern for coronary artery bypass grafting (CABG) has changed including patients with more complex coronary pathology and anatomy and associated co-morbidities. In the light of this, there has been a revived interest in methods for intraoperative coronary graft patency verification and coronary target selection. Although TTF has been widely demonstrated as a sensitive tool for intraoperative quality assessment of newly constructed grafts [6-9], its application can not be extended to the evaluation of coronary targets due to limitations that are intrinsic to transit time technology and for which transit time probes can function only when placed around the coronary artery or graft. Furthermore, TTF allows for a purely functional analysis of the graft-anastomosis unit and does not add any anatomical information about the degree of patency of the anastomosis.

In this regard Doppler technology has recently resurged as a valuable intraoperative armamentarium to help cardiac surgeons selecting adequate coronary targets for revascularization and depicting both anatomical and functional features of newly constructed anastomosis.

The possible applications of a custom-made 13 MHz epicardial coronary Doppler probe were investigated previously demonstrating its ability to successfully visualize and assess coronary arteries and anastomoses on all sides of the heart in both the animal model and ex-vivo in humans [4].

Moreover, micro-probe Doppler has allowed for safe graft vessel harvesting (left internal mammary artery) and for selection of optimal anastomotic target site [5].
In the present study we validated a newly designed Doppler micro-probe that allows for recording of purely functional values (flow velocity) at the level of the anastomosis and directly on the coronary vessel.
Although the X-plore ® probe technical features are based on the same specifications of the most commonly available Doppler probes with a similar frequency – i.e., a center frequency of 7,5 MHz and a wide bandwidth of +/- 30 % - some small adaptations have been performed:

1) The angle of incidence between ultrasound and direction of blood flow is crucial for the accuracy of the velocity measurement. Standard Doppler probes must be angled correctly by the operator, while the X-plore ® probe has an inbuilt angle of 45 degrees allowing the probe to be placed perpendicular to the vessel.

2) In the X-plore ® probe a rectangular 3 by 6 mm crystal has been used allowing the ultrasound beam to cover the full cross section of the vessel. Differently, standard probes have round crystals with a focused beam that measures only part of the vessel cross section.

3) The 2 features above allow for a direct placement of the X-plore® probe directly on the coronary vessel with minimal wall compression (preventing in this way to create vessel's stenosis).

4) Lastly, the X-plore ® probe has been adapted with a suction system to stabilize the device on the myocardium avoiding Doppler noise caused by the heart movements.

The existing model does not permit any Doppler image reconstruction and our analysis was limited to the flow velocity values.
Although this may be considered as a limitation of the study, we do believe that coronary flowdynamics as recorded by epicardial Doppler can give simple and immediate information to the surgeon concerning the possible status of the coronary

artery and its anastomosis.

In our analysis the X-plore ® probe ® seemed to immediately detect adequate Doppler signals even for high heart rates as those often encountered in the pig model. Eventual disturbances in the signal wave were automatically filtered by the system. A more advanced model of this micro-probe has been recently designed and includes a suctioning system that maintains the probe on top of the vessel in order to further reduce any signal disturbance associated with heart movements (Fig. 2).

In basal condition Doppler velocity values were easily obtained and showed consistence during the four consecutive measurements. Interestingly both flow velocity, as detected by the epicardial Doppler probe, and absolute flow values, as detected by the pericoronary TTF probe, did not show any significant change after partial snaring of the LAD, confirming the fact that changes in coronary rheology may not happen until levels of vessel sub-occlusion are achieved.

As demonstrated in the occlusion phase of the experiment, zero flow velocity can be easily detected with epicardial coronary Doppler technology and represent a total coronary occlusion situation. Furthermore, in the reperfusion phase, the Doppler micro probe detected brisk increases in blood flow velocity documenting the occurrence of significant increases in coronary absolute flow values. To translate these findings clinically: if epicardial coronary Doppler technology is used as a sole means to record flow velocity, some valuable conclusions may be deducted concerning the coronary status, location, and the successful reperfusion after graft anastomosis.

Although the initial indication for the X-plore ® probe was for identification of intra-myocardial coronary targets, we do believe that its application should be enlarged.

When searching for intramuscular vessels, the surgeon places the probe in the approximate area of the vessel, and listens for the audible Doppler signal. The operator should select an appropriate volume setting that enables the surgeon to hear the signal, and possibly help differentiate arterial flow (pulsatile waveform as in Fig. 3) or venous flow (continuous flow) from noise originating from probe movements.

When looking for a stenosis, the surgeon first needs to measure a normal, patent segment of the vessel. When a stable curve is displayed, the operator should store it in the Veri-Q system. The system will display a reference line, demonstrating the recorded reference peak velocity. When the surgeon relocates the probe, the measured

peak velocity will be compared with the reference line. The system will display the change in peak velocity as a percent of stenosis (Fig. 3). The velocity scale may also need to be changed when the probe is on top of a narrow stenosis, causing the peak velocity to increase by four times (Fig. 3). As the probe is moved further down the stenosis, the velocity will go back down again and become much lower than the reference value (as reported in our experiments where the probe was placed very distally from the stenosis).

Practically, epicardial Doppler technology could also be applied in dubious situations to distinguish between arterial and venous coronary branches and guide adequate anastomotic targeting.

In this regard, routine use of Doppler technology could be advocated to evaluate adequate delivery of antegrade and retrograde cardioplegia and to locate coronary artery branches during mitral valve surgery and radiofrequency ablation procedures for atrial fibrillation.

Furthermore, this technology can be used to document coronary flow velocity after aortic root surgery with reimplantation of coronary ostia and standard aortic valve replacement with stented valves.

Moreover, in a second part of the present study, we have started investigating the use of coronary Doppler in detecting changes in coronary flow velocity after administration of intravenous cardio- and vaso-active medications, during elevation and stabilization of the beating heart, and while using intracoronary shunting. Final results of this analysis will be presented in a second stage.

As demonstrated in our study, reperfusion after coronary revascularization may be easily detected with Doppler devices. In this context we suggest to use a combined approach by associating peri-graft TTF measurements and epicardial coronary Doppler to record simultaneously coronary graft absolute flow and coronary flow velocity. As already described, TTF measurements may show faulty values if proximal coronary snaring is not applied in the experimental setting [9]. As a matter of fact almost normal TTF findings are documented in some cases where a stenosis at the toe of the anastomosis is present together with a perfectly patent anastomotic heel. In this particular situation the absolute values as detected with the perivascular TTF probe are representative of the sole flow going towards the proximal part of the

coronary. In this situation the proximal snaring would imply significant reduction of the TTF values and document the anastomotic failure. Snare omission may be obviated by the routine use of epicardial coronary Doppler and documentation of flow velocity direction and its increase proximally and distally to the anastomosis. In addition, improvements in coronary perfusion may be selectively and specifically identified even in sequential grafts where measurement of TTF values at the level of the main graft may not be fully representative of the status of the different sequential anastomosis.

## Conclusions

In the present study we have validated, in a pig model, the use of a newly designed epicardial coronary Doppler micro-probe. Although the X-plore® probe allows for detection of purely functional measurements (in terms of coronary flow velocity), its application is of interest in evaluating flow dynamics in different clinical conditions. We do believe that, in the near future, multiple features should be included in the same device to allow for simultaneous coronary graft flow measurement, epicardial coronary blood flow velocity and direction detection, and ultrasound representation of coronary targets and coronary anastomosis.

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*Table 1. Hemodynamic values during the 4 experimental phases*

| | BP mmHg | HR bpm | LVEDP mmHg |
|---|---|---|---|
| Baseline | 69.1 ± 8.7 | 98.8 ± 19.7 | 22.1 ± 24.5 |
| Partial Coronary Stenosis | 64.1 ± 2.0 | 86.9 ± 23.5 | 31.2 ± 28.4 |
| Coronary Occlusion | 64.2 ± 6.0 | 87.8 ± 24.6 | 20.8 ± 22.6 |
| Reperfusion | 64.9 ± 8.6 | 88.4 ± 25.0 | 23.5 ± 25.5 |
| *P* | 0.2 | 0.4 | 0.8 |

*Table 2. Coronary blood flow and blood velocity values during the 4 different experimental phases*

| | Mean TT Flow (cc/min) | Mean Doppler Flow Velocity (cm/s) |
|---|---|---|
| Baseline | 23.2 ± 6.6* | 4.0 ± 1.9* |
| Partial Coronary Stenosis | 16.2 ± 5.7* | 3.5 ± 2.2* |
| Coronary Occlusion | 0.1 ± 0.2 | 0.50 ± 1.4 |
| Reperfusion | 67.4 ± 23.2 | 11.0 ± 5.5 |
| *P* | <0.0001 * ns | <0.0001 * ns |

*Table 3. Correlation between mean coronary blood flow and velocity during the 4 different experimental phases*

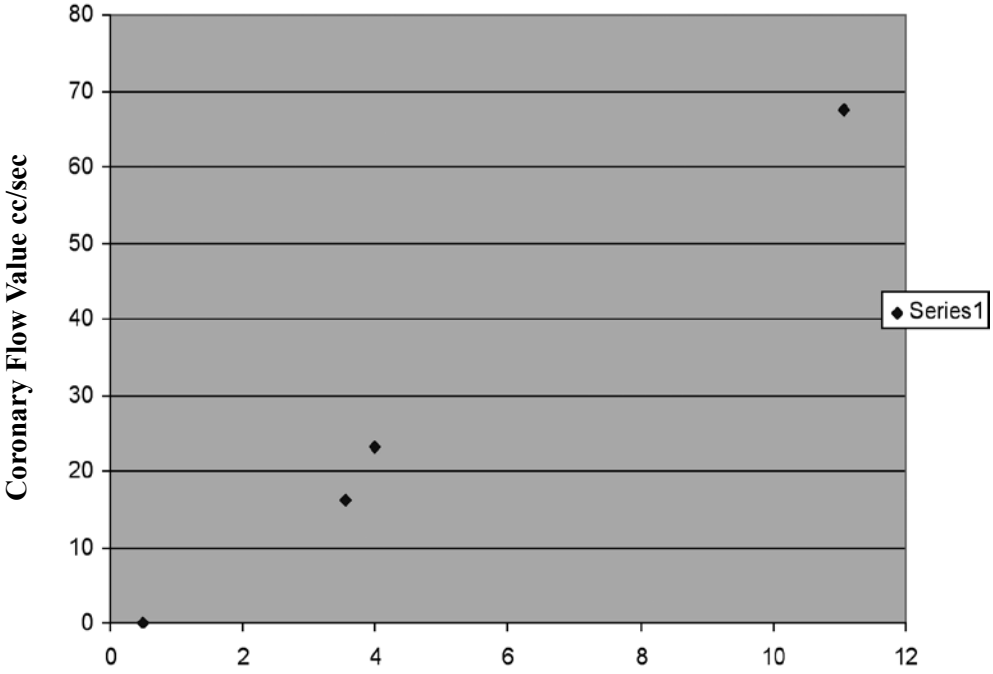


*Figure 1. 7.5 MHz X-plore ® Doppler probe. Note the orientation at 45 degrees of the unfocused crystal and the default 6 mm sample volume and 5 mm at the center of the probe*

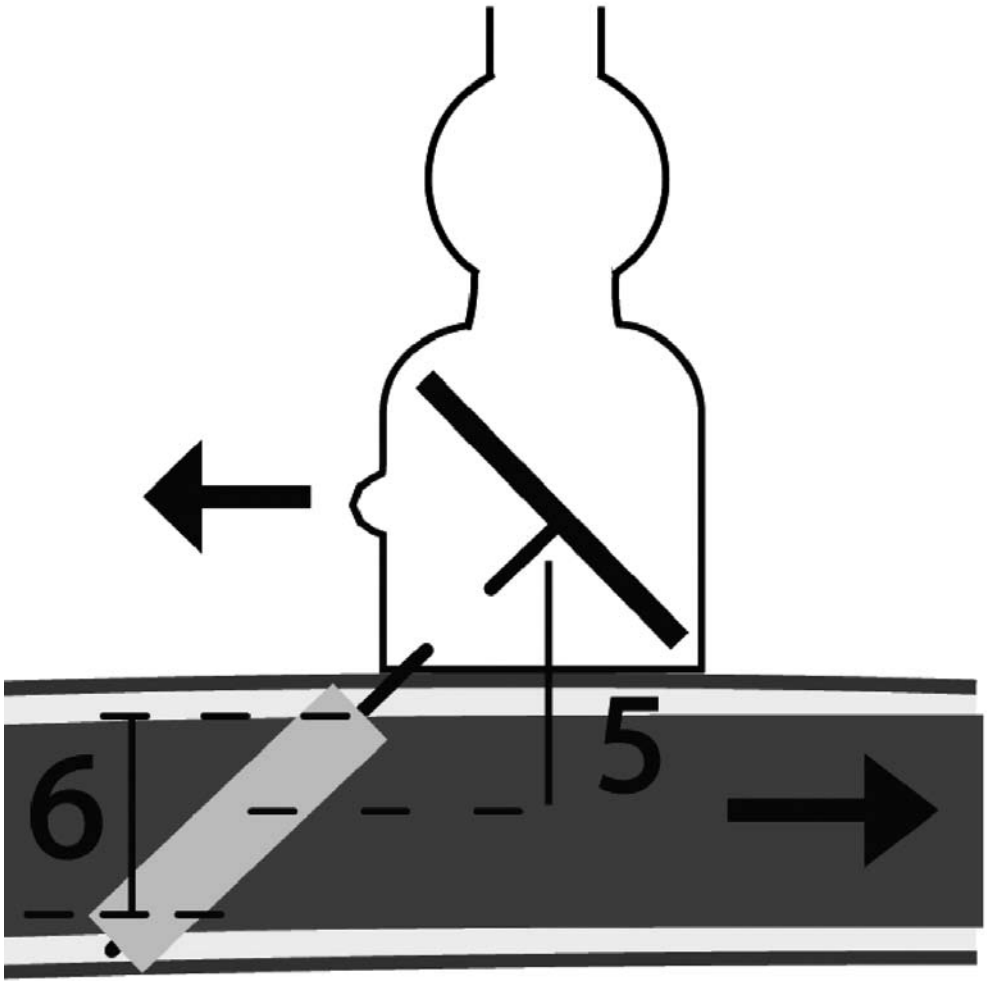
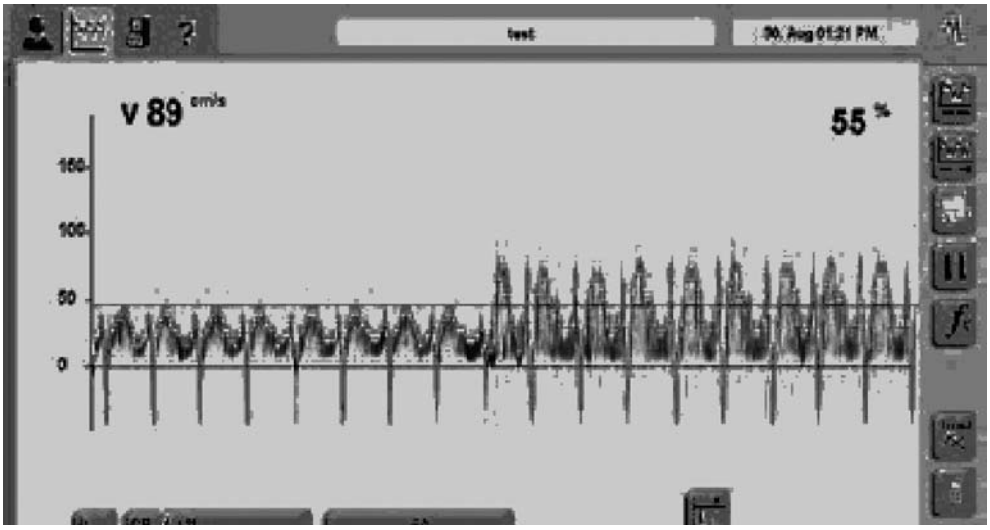


*Figure 2. Suction type epicardial coronary Doppler probe*

*Figure 3. Coronary flow velocity as measured by epicoronary X-plore ® Doppler probe: on the left side of the panel the velocity is measured before the stenosis; the right side shows flow velocity immediately at the level of the stenosis where vorticosity is increased and peak velocity is 55% higher than reference value*



*CHAPTER 9*

# ULTRASONOGRAPHIC AND DSCT SCAN ANALYSIS OF SINGLE LIMA VERSUS ARTERIAL T-GRAFTS 12 YEARS AFTER SURGERY

JM Hartman
WB Meijboom
TW Galema
JJM Takkenberg
AM Schets
PJ De Feyter
AJJC Bogers

***Submitted***

## Abstract

Objective: To investigate the long term outcome in patients with left internal mammary artery to left anterior descending coronary artery (LIMA-LAD) and T-grafts by ultrasonography and dual source computed tomography (DSCT) and to analyse if ultrasonography can determine graft patency.

Methods: Thirty-two patients, 28 male, 50.8 ± 8.8 years at operation, were studied. Fifteen patients with single LIMA-LAD and additional vein grafts (group I) and seventeen patients with LIMA-free right internal mammary artery (FRIMA) T-grafts (group II) underwent DSCT, transthoracic ultrasonography of the LIMA and left ventricle, an electrocardiogram and a short questionnaire. Differences were tested with unpaired and paired t-tests.

Results: In group I, 4.1 ± 1.1 and in group II, 4.5 ± 1.1 anastomoses/pt were performed. DSCT showed three string sign LIMA (20 %) grafts and 6 occluded venous anastomoses (13 %) in group I and three (distal) string sign LIMA grafts (18 %), seven occluded LIMA anastomoses (23 %) and nine occluded FRIMA anastomoses (23 %) in group II. Ultrasonographic variables in the proximal part of the LIMA graft did not differ between the groups. No effect was found of left ventricular function, proximal string sign LIMA grafts and previous myocardial infarction on ultrasonographic graft performance. Four patients in group I and one patient in group II suffered angina within the last six months.

Conclusions:Ultrasonography can not distinguish between string sign and patent single LIMA or T-grafts nor demonstrate distal anastomosis patency in T-grafts twelve years after surgery. We do favour T-grafts because of the low incidence of recurrent angina.

## Introduction

The use of the left internal mammary artery (LIMA) as a bypass graft has improved the durability of coronary artery bypass grafting (CABG)[1].

The free right internal mammary artery (FRIMA) can be anastomosed end-to-side to the LIMA, known as arterial composite T-graft with the proximal LIMA as the only source of inflow, to revascularize the anterior, lateral and/or inferior wall. Positron emission tomography as well as angiographic, intravascular and transthoracic ultrasonographic analyses have been reported for short and mid-term follow up of these T-graft configurations [2-4].

Invasive native coronary and bypass angiography is still the gold standard to determine patency of bypass grafts. However, invasive angiography also has disadvantages such as difficulties in finding the origin of the graft, inadequate contrast filling especially into distal coronary arterial parts and small side branches, catheter-induced spasm of the LIMA, underestimation of eccentric plaques and overprojection of coronary arteries.

To evaluate the long-term performance of the LIMA and the arterial T-graft accurate non-invasive tests would be useful. Non-invasive duplex (combination of 2D-mode ultrasonography and pulsed Doppler system) flow measurements of the LIMA have been performed in the past decade by several groups [5-6].

CT coronary angiography has become an accurate noninvasive method to detect or rule out coronary stenosis. Especially the analysis of stenosis and patency of arterial and venous bypass grafts are very promising [7-9].

We performed quantitative analyses of single LIMA-LAD versus arterial composite T-grafts by transthoracic ultrasonography compared to Dual Source computed tomography (DSCT) scans in order to investigate the long term outcome of these grafts and to analyse whether ultrasonographic findings can determine the patency of these grafts in patients long-term after CABG.

## Materials and Methods

*Patients*

Between September and December 2007, we screened seventy-three patients who were operated with single LIMA to the LAD and additional vein grafts or with composite arterial T-grafts in the period of 1994 until 1997. We scheduled these patients for inclusion in a protocol to compare transthoracic ultrasonographic LIMA variables with DSCT scans. Excluded were patients over 85 years of age, previous allergic reaction to contrast, serious co-morbidity, impaired renal function (creatinine $\geq$ 120 µmol/l) and an irregular cardiac rhythm. Renal dysfunction (14 pts), deaths (8 pts), co-morbidity (8 pts), refusal to participate (5 pts), lost in follow-up (5 pts) and allergy to contrast (1 pt) were the drop-out reasons.

The Institutional Review Board of the Erasmus MC Rotterdam approved this study (NL 13011-078-06). Informed consent was obtained from all patients.

Thirty-two patients, 28 male and 4 female, mean age of 50.8 ± 8.8 years at the time of operation, were included in this transectional study. Group I consisted of 15 patients (12 male and 3 female, mean age at operation of 54.0 ± 10.4 years) with a single LIMA graft to the LAD and additional vein grafts. Group II consisted of 17 patients with LIMA-FRIMA-T-grafts (16 male and 1 female, mean age at operation of 48.0 ± 6.1 years).

All patients underwent DSCT, an electrocardiographically controlled duplex scanning of the proximal LIMA through the second or third intercostal space, transthoracic echocardiography (TTE) of the left ventricle, an electrocardiogram and a short questionnaire within one day in order to compare data without time interference. All patients were permitted to continue their cardiovascular medication including ß-blockers. Diabetic patients were not allowed to take metformine medication during this day to prevent lactic acidosis induced by impaired renal function after iodinated contrast injection during the DSCT scan.

All patients were studied by DSCT scans in order to assess the patency of the grafts and were classified into (sub)groups:

Group I: single LIMA grafts to the LAD with additional vein grafts (n=15)

Subgroup I A: patent single LIMA grafts to the LAD with good contrast run-off into the coronary system (n=12)

Subgroup I B: string sign single LIMA grafts to the LAD with contrast run-off into the coronary system (n=3)
Group II: composite LIMA-FRIMA-T-grafts (n=17)
Subgroup II A: patent LIMA-FRIMA-T-grafts (n=11)
Subgroup II B: distal string sign LIMA grafts (n=3)

*Transthoracic ultrasonography protocol*

We used the IE 33 208 ultrasound system (Philips, Best, The Netherlands) which combined 2-D imaging and pulsed Doppler ultrasound to evaluate blood velocity variables of the LIMA as well as left ventricular function. TTE evaluation of the single LIMA and the main stem of the T-graft were performed in all thirty-two patients with a 9 MHz linear array vascular probe (Philips, Bothell, WA, USA). The probe was placed at an angle of approximately 60 degrees in the second or third intercostal space with the patient in supine position. LIMA duplex recordings were electrocardiographically controlled during 3-5 cardiac cycles and data were quantified both online and off-line and were interpreted by 2 physicians. The ultrasonographic LIMA variables analysed were: systolic and diastolic peak velocity (SPV and DPV), systolic, diastolic and total velocity integral (SVI, DVI and TVI), diastolic/systolic velocity integral ratio (DSVIR), diastolic/total (diastolic + systolic) velocity integral ratio (DTVIR) and peak diastolic/peak systolic velocity ratio (DSPVR).
The following echocardiographic standard views, using the S5-1 broadband phased array transducer (Philips, Bothell, WA, USA), were obtained in order to classify segmental wall motions and consecutively left ventricular function: parasternal long and short axis, apical four and two chamber and apical long axis.
The analyses of the LIMA ultrasonograhic variables and the segmental wall motion score of the left ventricle were performed by two blinded observers.

*Dual-Source Computed Tomography scan protocol*

*Patient preparation*

No oral or intravenous ß-blockers nor nitroglycerin were administered prior to the scan.

*DSCT Scan*

All patients were scanned using a Somatom Definition DSCT scanner (Siemens Medical Solutions, Forcheim, Germany). The system is equipped with two X-ray tubes and two corresponding detectors mounted on a single gantry with an angular offset of 90 degrees and a gantry rotation time of 330 ms. CT angiography scan parameters were: number of X-ray sources 2, detector collimation 32 x 0.6 mm with double sampling by rapid alteration of the focal spot in the longitudinal direction (z flying focal spot), rotation time 330 ms, tube voltage 120 kV.

Automatic tube current modulation in x,y,z-direction with Care Dose 4D® software, (Siemens Medical Solutions, Forcheim, Germany) was applied in all patients. The coronary arteries were scanned with 380 reference mAs/rot. In all patients, we used a relative wide ECG pulsing window (30-65% of the R-R-interval) during which full tube current was applied to include both the mid-diastolic and the end-systolic phases. A bolus of Ultravist® 370 mg l/ml iodinated contrast material (Schering AG, Berlin, Germany), which varied between 80-100 ml depending on the expected scan time, was injected (flow rate: 4.0-5.0 ml/s) in the right antecubital vein.

All CT coronary angiography datasets were reconstructed using a single-segmental reconstruction algorithm: slice thickness 0.75 mm; increment 0.4 mm; medium-to-smooth convolution kernel (B26); resulting in a spatial resolution of 0.6-0.7 mm in-plane and 0.5 mm through-plane.

*DSCT Image Reconstruction*

The reconstruction algorithm uses data from a single heart beat, obtained during a quarter X ray tube rotation by two separate X-ray tubes, resulting in a temporal resolution of 83 ms. Initially, a single dataset was reconstructed during the mid-diastolic phase (350 ms before the next R-wave). In case of impaired image quality datasets were reconstructed in the end-systolic phase (275 ms after the previous R-wave).

*DSCT Image Evaluation*

Axial views and multi-planar reconstructions (MPR) were used to identify patency of grafts and anastomoses of grafts to coronary run-offs. One experienced observer scored all DSCT coronary angiography datasets and quantified the lumen. Analyses

were performed in the proximal part of the LIMA just distal from the subclavian artery, in the LIMA at the level of the second or third intercostal space and proximally and distally from each anastomosis of the graft with a coronary insertion. Visually the coronary branches (distal run-offs) supplied by a patent graft were separately evaluated.

*Electrocardiogram*

Additional electrocardiograms were taken from all patients and analysed by two blinded observers.

*Statistical Analysis*

Data entry and statistical analysis were performed with the use of Epi Info 6.04c (CDC, Atlanta, Georgia). Continuous variables are displayed as means ± standard deviation and considered statistically significant when the *P*-value was 0.05 or less. Discrete variables are displayed as counts or proportions. Data within and between the groups were tested by paired and unpaired *t*-tests. Sample size calculation showed that at least 10-11 patients in each group are necessary to detect a significant difference in diastolic peak velocity between the 2 groups, assuming that diastolic peak velocity in single LIMA to LAD grafts is on average 22 cm/sec (range 15-30 cm/sec) [10] versus 35 cm/sec (range 25-45) [11] in T-grafts (assuming equal variances, SD = 10, $\alpha = 0.05$, power = 0.80).

## Results

Patients characteristics are shown in Table 1. In group I, fifteen single LIMA to the LAD bypasses were constructed and one right internal mammary artery (RIMA) to the right coronary artery (RCA) and one single, one jump, six triples, five quadruple and one quintuple venous bypass grafts, a total of sixty-two anastomoses, 4.1 ± 1.1/patient, were performed. Two re-explorations due to excessive blood loss postoperatively and one percutaneous coronary intervention (PCI) of the LAD artery four years after surgery were performed.

In group II, six single, nine jump and two triple jump LIMA grafts to the LAD area with two single, eight jump and seven triple FRIMA bypass grafts were performed.

In six patients, an additional single gastroepiploic artery (GEA) bypass graft to the posterior descending artery (PDA, n=4) or the RCA (n=2) and one additional vein graft to the RCA were performed, in total seventy-six anastomoses, 4.5 ± 1.1/patient. Re-exploration because of excessive blood loss postoperatively was done in one patient, one PCI of the RCA was done three years after surgery and in the same patient PCI of the circumflex artery (CA) ten years after surgery was performed.
No patients had complaints of angina during the investigations.

*DSCT scan follow-up*

DSCT-scan findings are shown in Table 2. In group II, one FRIMA anastomosis (2.6 %) could not be judged. Also in group II, one patient with a distal string sign LIMA graft has severe left main stenosis but did not suffer angina.

*Ultrasonographic follow- up of the LIMA variables*

In all thirty-two patients transthoracic ultrasonography of the LIMA was successful with adequate Doppler velocity profiles. No ischaemia could be detected electrocardiographically and all patients were in sinus rhythm. All LIMA variables of the LIMA to the LAD and the composite T-grafts are comparable (Table 3) without significant differences. Ultrasonographic differences between subgroups were also not observed: patent grafts between the groups (Table 3), preserved versus impaired LVF, string sign versus patent LIMA grafts within group I (Table 4) and versus all patent main stem LIMA grafts and patent LIMA grafts without myocardial infarction did also not reveal significant differences. Noticeably, proximal string sign LIMA grafts were only observed in group I.

*Echocardiography*

All patients underwent TTE in order to determine left ventricular function (Table 1). In two patients, no adequate window could be obtained.

*Electrocardiogram*

No ischemia could be detected in any patient electrocardiographically.

*Questionnaire*

Sixteen patients are still controlled by their cardiologist. Eleven patients routinely and five patients because of recurrent complaints. Twenty-two patients do not suffer from any physical limitation.

Four patients in group I and one patient in group II have suffered recurrent angina during exercise within the last six months. DSCT of these patients in group I showed one patient with a string sign LIMA graft with a patent quadruple venous graft, three patent LIMA grafts with two patent triple venous grafts and in one patient three occluded venous anastomoses in the quadruple venous graft. DSCT of the patient in group II showed a string sign LIMA graft and a partial occluded FRIMA graft. This patient underwent PCI of the CX but suffers from recurrent angina.

## Discussion

Follow-up of bypass grafts is important for quantitative and qualitative analyses and coronary arteriography is the gold standard to perform this follow-up. However, costs, the invasive nature and the risks in clinically stable patients of 0.7-4.0 % [12-13] limit the routine use of this method and for these reasons, non-invasive methods have been developed for graft follow-up purposes.

Postoperative ultrasonographic follow-up of the in situ LIMA graft has been extensively described in the last decade [4-6, 14] and it is well known that a shift from a predominantly systemic profile towards a coronary flow profile is present in these bypass grafts [14]. Until now, ultrasonographic LIMA analyses compared to DSCT scans have not been performed in a late follow-up setting (Fig. 1,2 and 3).

LIMA (sequential) bypass grafting and arterial composite T-grafting are accepted methods for coronary revascularisation [15-16]. However, there are concerns surrounding composite arterial bypass grafting related to perioperative hypoperfusion, their ability to supply sufficient blood flow (especially in a composite T-graft and during hyperaemic response), and the unknown long-term effects on arterial conduit luminal size [2-4, 17].

Despite these concerns, arterial T-bypass grafting has been expanded in the last decade using the right GEA, the radial artery and the RIMA as (free) additional arterial conduits. Many strategies for arterial composite T-grafting have been described but

we restrict to T-grafts with the FRIMA connected end-to-side to the attached LIMA graft.

It is remarkable that six anastomoses in venous grafts (13%) and not a single LIMA-LAD anastomosis were occluded in group I while seven LIMA anastomoses (23.3 %) and nine free RIMA anastomoses (23.1 %) were occluded in the T-grafts (group II). However, one of the crucial questions concerning these findings is whether or not these findings affect the patients.

Five patients (15.6%) have suffered angina within the last six months but were free of complaints during the investigations: four patients in group I (26.7 %) and one patient in group II (5.9 %). These findings suggest that patients from our study population with T-grafts suffer less angina compared to patients with a conventional operation twelve years after CABG in spite of the much higher number of occluded anastomoses. We realise that this suggestion is based on a small population and without analysing the circumstances and causes of the occluded grafts.

The DSCT scans showed that twelve LIMA single bypasses were patent and three LIMA grafts were string sign in group I. Many reports analysed the influence of competitive flow on the cause of string sign or occluded LIMA grafts but, so far, no consensus could be obtained concerning this association [18-21]. Previous reports describe that diastolic velocity measurements in string sign LIMA grafts are lower compared to patent LIMA grafts [5, 22] in a short - or mid - term follow up. In our data, all ultrasonographic measurements appeared to be more pronounced in string sign LIMA grafts (Table 4). Jones et al. [13] stated in a review that the diastolic fraction (DTVIR) of less then 0.5 is the best predictor of stenosis of the LIMA. Song et al. [23] stated that “occluded” LIMA grafts show diastolic fractions of less than 0.6. Our data differ from these findings: string sign LIMA grafts showed a DTVIR of $0.39 \pm 0.04$ versus patent LIMA grafts $0.36 \pm 0.1$ (Table 4).

Ultrasonographic analyses of the main stem of total patent T-grafts (n=11) also show this remarkable finding of a diastolic fraction of less then 0.5 namely $0.38 \pm 0.1$ (Table 3).

Early- and mid-term follow-up reports describe that systolic and diastolic peak velocities at rest are significantly higher in patent LIMA grafts compared to string sign LIMA grafts [24-25]. These data do not correspond to our long term follow-up findings: diastolic and systolic peak velocities are comparable in both groups

although SPV in both groups remains much higher compared to DPV as confirmed in other mid-term and long-term follow-up reports (Table 3) [5, 10, 26].

In our opinion, it is reasonable to assume that T-grafts have a larger myocardial perfusion area compared to single LIMA grafts. The myocardium is mainly perfused during the diastolic phase [27] and therefore we expect higher diastolic values in main stem of the T-grafts compared to the single LIMA grafts [11]. Remarkably, all variables in the proximal part of the single LIMA grafts are as high as in the main stem of the T-grafts without statistical significant differences (Table 3), not even when only patent grafts are taken into account (Table 3). We found no effect of LVF, proximal string sign LIMA grafts, and previous myocardial infarction on ultrasonographic graft performance.

The important questions remain why all proximal LIMA ultrasonograhic variables do not differ between LIMA to LAD and composite T-grafts and also not differ between string sign LIMA and patent LIMA grafts and whether the extent of the LIMA perfusion area influences ultrasonographic variables at rest in the late postoperative period. The IMA graft patency is highest and most durable when performed as single bypass to the LAD. This finding is consistent with reports describing the patency of vein grafts to the LAD exceeding the patency to the CX and RCA [28-29]. These findings can be explained by the more direct course of the bypass to the target area as well as by the extent of the target area. The perfusion area supplied by the LAD is larger compared to other coronary arteries resulting in larger blood flow demands in LIMA grafts to the LAD compared to other coronary areas resulting in less tendency to fail or become string sign [18-21]. For this reason, diastolic blood flow in proximal LIMA grafts and also in T-grafts will be mainly relevant for the anterior and septal wall perfusion area. Consequently, the areas depending on the more distal anastomoses are probably less well perfused. When the distal LIMA branch in the T-graft shows string sign or is less functional, the flow competition in the proximal part of the LIMA graft will be minimal and the blood flow through the main stem can simply flow into the FRIMA branch.

In the long-term follow-up, the ‘dynamic’ LIMA seems to create a ‘fixed’ or ‘steady’ state, at least at rest, expressed in equal values of the ultrasonographic variables from different perfusion areas in the proximal part of the LIMA. This consideration may also be an explanation for the equalisation of the ultrasonographic variables between

all subgroups and for our different findings in the late follow-up setting compared to reports which describe short- and mid-term follow-up.

Limitations: First, the crosssectional design of our study does not allow to draw further conclusions on patient cohort level. Ultrasonography was performed at rest and additional studies should include hyperemic response tests to analyse ultrasonographic behaviour of the LIMA grafts for different myocardial perfusion areas.

## Conclusions

Non-invasive transthoracic ultrasonography allows detecting velocity patterns in the proximal part of a single or composite LIMA graft. However, these patterns can not determine differences between string sign and patent single LIMA or T-grafts and can not demonstrate patency of distal anastomoses in T-grafts in patients twelve years after surgery.
LIMA grafts remodel into a 'fixed' or 'steady' state at rest in which all ultrasonographic variables equalize between (subdivided) groups twelve years after CABG in contrast to early and mid-term follow-up findings. Despite the increased number of occluded anastomoses in T-grafts we do favour these composite grafts because of the low incidence of recurrent angina.

Acknowledgement

Special thanks to M. Rengo for preparing the DSCT images and A. Weustink for the scanning protocol as well as the actual scanning.

*Table 1. Characteristics of the patients in group I and II*

| Variable | Group I<br>N = 15 | Group II<br>N = 17 | *P* |
|---|---|---|---|
| Age at investigation (years) | 65.9 ± 10.2 | 59.6 ± 6.2 | 0.04 |
| Age at operation (years) | 54.0 ± 10.4 | 48.0 ± 6.1 | 0.05 |
| Time after CABG (years) | 11.8 ± 0.7 | 11.6 ± 1.0 | 0.47 |
| Male | 12 | 16 | |
| LIMA anastomoses/pt | 1.0 ± 0.0 | 1.8 ± 0.7 | |
| Total LIMA anastomoses | 15 | 30 | |
| FRIMA anastomoses/pt | 0 | 2.4 ± 0.8 | |
| Total FRIMA anastomoses | 0 | 39 | |
| Total venous anastomoses/pt | 3.2 ± 1.1 | 0* | |
| Total GEA anastomoses/pt | 0 | 0.4 ± 0.5 | |
| RIMA (in situ) | 0** | 0 | |
| Total anastomoses/pt | 4.1 ± 1.1 | 4.5 ± 1.1 | 0.33 |
| Intimectomie | 1 (LAD) | 1 (RCA) | |
| Preoperative anterior wall infarction | 6 | 3 | |
| Preoperative inferior infarction | 2 | 3 | |
| Preoperative inferoposterior infarction | 1 | 2 | |
| Preoperative lateral infarction | 1 | 1 | |
| Postoperative PCI (LAD) | 1 | 0 | |
| Mean systolic blood pressure (mmHg) | 135 ± 15 | 142 ± 18 | 0.28 |
| Mean diastolic blood pressure (mmHg) | 77 ± 11 | 83 ± 14 | 0.20 |
| Mean heart rate (beats/min) | 72 ± 12 | 66 ± 11 | 0.14 |
| Angina within last 6 months | 4 | 1 | |
| Diabetes | 4 | 4 | |
| Normal LVF | 6 | 8 | |
| Impaired LVF | 6 | 5 | |
| Abnormal relaxation LV | 2 | 3 | |
| Length (m) | 1.76 ± 0.09 | 1.77 ± 0.06 | 0.56 |
| Weight (kg) | 85 ± 12 | 88 ± 11 | 0.40 |

Group I; Patients with a single LIMA graft to the left anterior descending artery LAD) and additional vein grafts, Group II; Patients with LIMA-free right internal mammary artery (FRIMA)-T-graft, GEA; gastroepiploic artery, PCI; percutaneous intervention. *P* = unpaired *P*-values for differences between the groups, data are ± standard deviation. * in 1 patient a single venous bypass was additionally performed ** in 1 patient a single right internal mammary artery was additionally performed.

*Table 2. DSCT findings in patients from group I and II*

| Variable | Group I<br>N = 15 | Group II<br>N = 17 |
|---|---|---|
| Patent LIMA graft | 12 | 12 |
| (distal) String sign LIMA graft | 3 (20 %) | 3 (17.6 %) |
| (distal) String sign FRIMA graft | - | 0 |
| Occluded LIMA grafts | 0 | 2 (11.8 %)* |
| Occluded LIMA anastomoses | 0 | 7 (23.3 %) |
| Occluded FRIMA anastomoses | - | 9 (23.1 %) |
| Occluded venous anastomoses | 6 (13 %) | - |
| Stenotic regions in venous jump grafts | 7 (15.2 %) | - |
| String sign GEA graft | - | 1 (16.7 %) |
| Occluded GEA anastomoses | - | 1 (16.7 %) |

Group I, II, FRIMA and GEA as described in Table 1. * patent main stem with occluded distal LIMA grafts.

*Table 3. Transthoracic ultrasonographic proximal LIMA variables and only patent LIMA grafts in group I and II twelve years after CABG*

| Variable | Group I N = 15 | Group II N = 17 | *P* | Group I * N = 12 | Group II * N = 11 | *P* |
|---|---|---|---|---|---|---|
| DPV (cm/s) | 18 ± 7 | 21 ± 7 | 0.26 | 17.0 ± 7.0 | 22 ± 7.0 | 0.15 |
| SPV (cm/s) | 57 ± 19 | 62 ± 30 | 0.59 | 56.2 ± 15.9 | 67 ± 28 | 0.27 |
| DVI ($cm^2$) | 7 ± 3 | 8 ± 4 | 0.34 | 6.6 ± 3.48 | 7.9 ± 3.2 | 0.38 |
| SVI ($cm^2$) | 12 ± 5 | 12 ± 5 | 0.97 | 11.7 ± 4.0 | 12.4 ± 3.9 | 0.70 |
| TVI ($cm^2$) | 17 ± 6 | 21 ± 9 | 0.17 | 16.2 ± 4.2 | 21.4 ± 6.6 | 0.04 |
| DSVIR | 0.6 ± 0.2 | 0.7 ± 0.2 | | 0.56 ± 0.3 | 0.66 ± 0.2 | |
| DTVIR | 0.37 ± 0.1 | 0.39 ± 0.1 | | 0.36 ± 0.1 | 0.38 ± 0.1 | |
| DSPVR | 0.33 ± 0.1 | 0.37 ± 0.1 | | 0.31 ± 0.1 | 0.35 ± 0.1 | |

Group I, patients with single LIMA grafts to the LAD and additional vein grafts; Group II, patients with LIMA-free RIMA composite T grafts; * only patent grafts; DPV, diastolic peak velocity; SPV, systolic peak velocity; DVI, diastolic velocity integral; SVI, systolic velocity integral; TVI, total (diastolic + systolic) velocity integral; DSVIR, diastolic/systolic velocity integral ratio; DTVIR, diastolic/total (diastolic + systolic) velocity integral ratio; DSPVR, peak diastolic/peak systolic velocity ratio. *P* = unpaired *P*-values for differences between the groups. Data are ± standard deviation.

*Table 4. Proximal LIMA variables in patent and proximal string sign LIMA grafts in group I*

| Variable | Patent LIMA N = 12 | String sign LIMA N = 3 | *P* |
|---|---|---|---|
| DPV (cm/s) | 17.0 ± 7.0 | 22.1 ± 6.0 | 0.27 |
| SPV (cm/s) | 56.2 ± 15.9 | 60.0 ± 33.6 | 0.76 |
| DVI ($cm^2$) | 6.6 ± 3.48 | 8.1 ± 3.2 | 0.52 |
| SVI ($cm^2$) | 11.7 ± 4.0 | 13.3 ± 8.6 | 0.64 |
| TVI ($cm^2$) | 16.2 ± 4.2 | 21.5 ± 11 | 0.19 |
| DSVIR | 0.56 ± 0.3 | 0.67 ± 0.2 | |
| DTVIR | 0.36 ± 0.1 | 0.39 ± 0.04 | |
| DSPVR | 0.31 ± 0.1 | 0.41 ± 0.1 | |

Ultrasonographic variables and group I as described in Table 3. *P* = paired *P*-values for differences within the group. Data are ± standard deviation.

Figure 1. Late follow-up main stem transthoracic ultrasonography (1a) and DSCT coronary angiography of a patent composite arterial T-graft from the transverse (1b), lateral (1c) and anterolateral view (1d). (a) main stem of the T-graft; (b) LIMA branch of the T-graft; (c) FRIMA branch of the T-graft; (d) native obtuse margin branch. DSCT, Dual-source computed tomography; LIMA, left internal mammary artery; FRIMA, free right internal mammary artery.

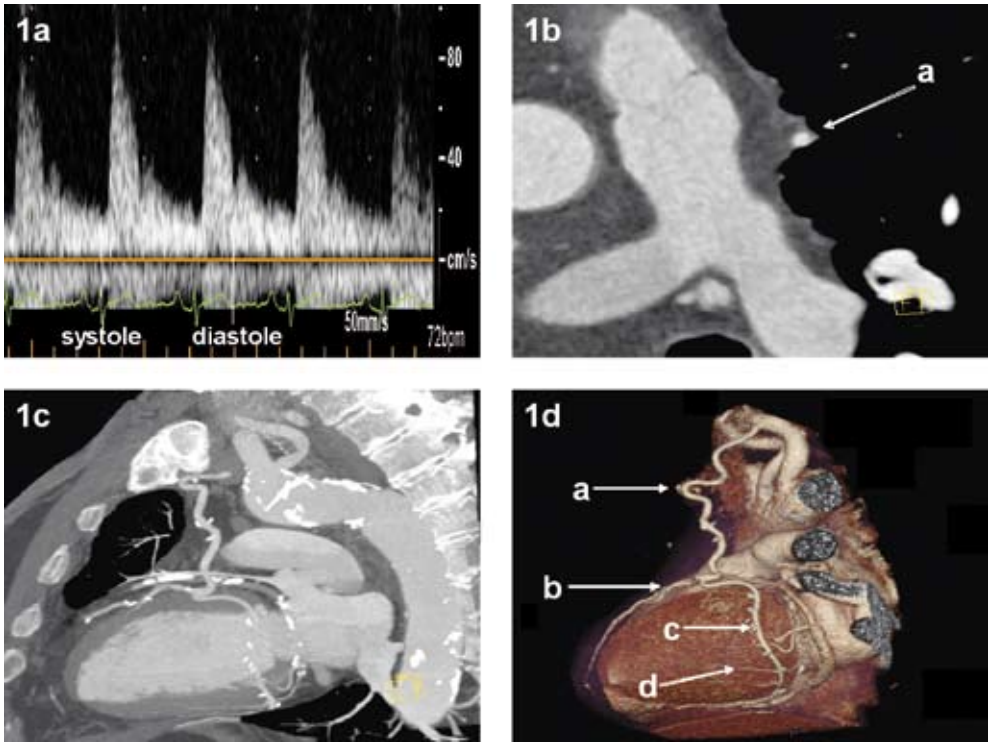


Figure 2. Late follow-up main stem transthoracic ultrasonography (2a) and DSCT coronary angiography of a composite arterial T-graft from the transverse (2b), anterolateral (2c) and lateral view (2d). (a) main stem of the T-graft; (b) LIMA branch of the T-graft; (c) occluded FRIMA branch of the T-graft. Abbreviations as in Figure 1.

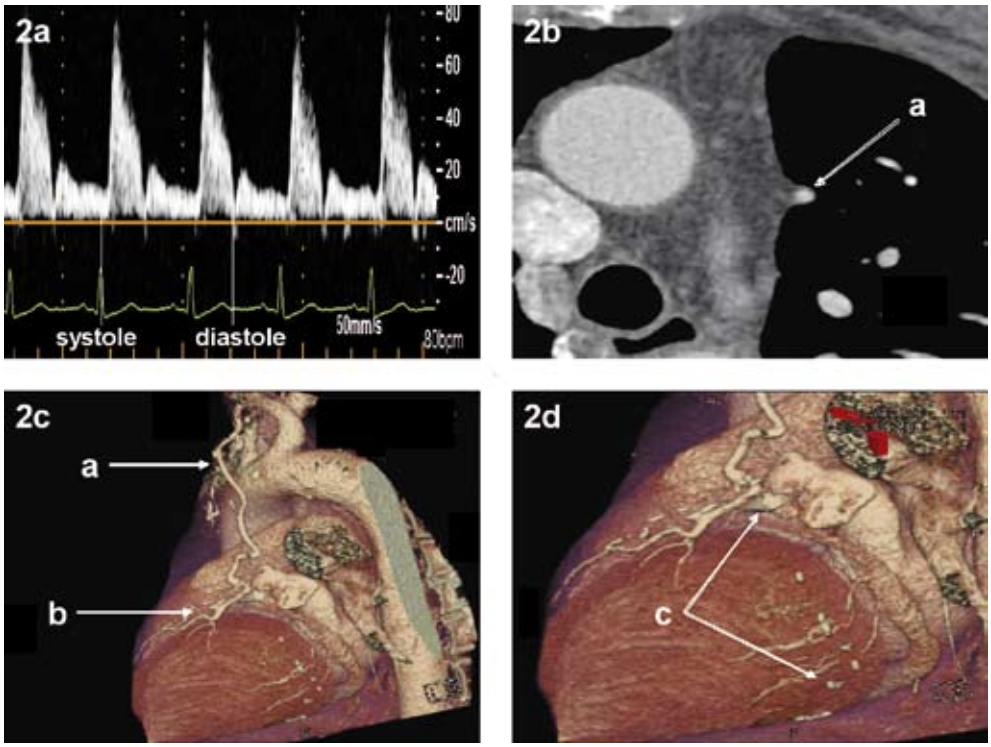
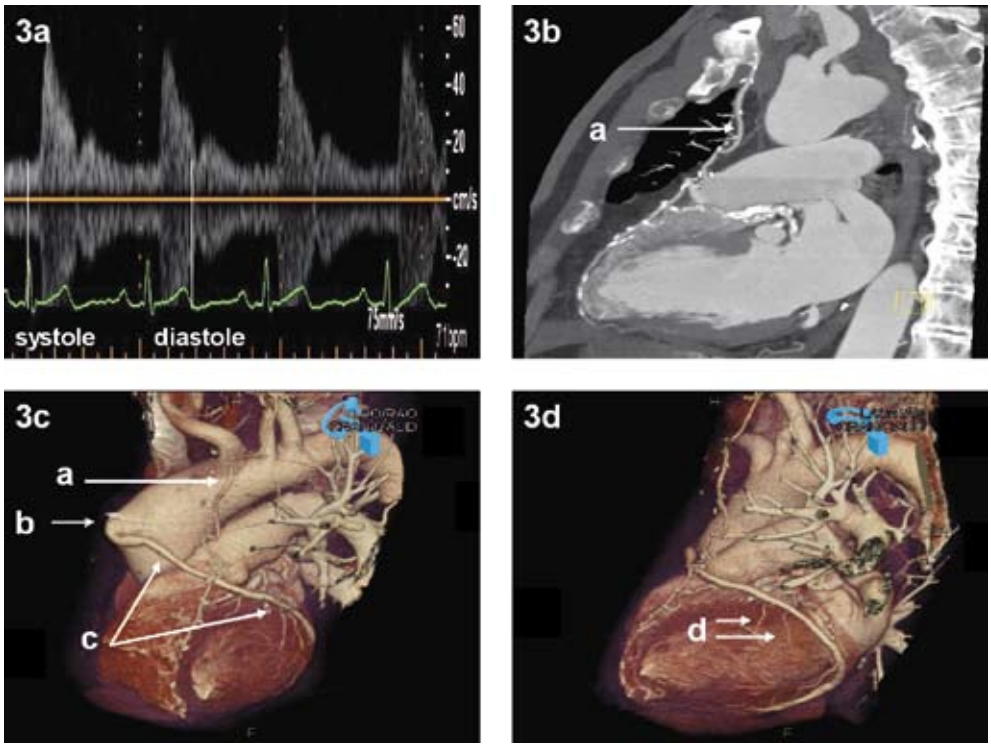


Figure 3. Late follow-up transthoracic ultrasonography (3a) and DSCT coronary angiography of a patent single LIMA graft to the LAD with an additional patent venous graft from the lateral (3b,3d) and anterolateral (3c) view. (a) LIMA graft; (b) proximal venous graft anastomoses to the aorta; (c) patent venous jump graft to the lateral and inferior wall; (d) native obtuse margin branches. LAD, left anterior descending artery. Abbreviations as in Figure 1.



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*CHAPTER 10*

# ANATOMICAL AND FUNCTIONAL ASSESSMENT OF SINGLE LIMA VERSUS ARTERIAL COMPOSITE T-GRAFTS 12 YEARS AFTER CORONARY BYPASS SURGERY

JM Hartman
WB Meijboom
TW Galema
JJM Takkenberg
AM Schets
PJ de Feyter
AJJC Bogers

***Submitted***

## Abstract

Objective: To determine whether functional ultrasonographic LIMA findings correspond with 64-MSCT in patients 12 years after CABG.

Methods: We entered thirty-four patients (63.2 ± 9.2 years), sixteen with conventional single LIMA (group I) and eighteen composite arterial T-grafts (group II), in a cross-sectional study. Patients underwent transthoracic proximal LIMA ultrasonography at rest and during the Azoulay maneuver, LV TTE and 64-MSCT, 11.5 ± 1.4 years postoperatively. Differences were tested with paired and unpaired T-tests.

Results: MSCT scans showed three string sign LIMA grafts (19 %) and six occluded venous anastomoses (12 %) in group I and three distal string sign LIMA grafts (17 %) and sixteen occluded T-graft anastomoses (22 %) in group II. LIMA diameters and areas are significantly larger in group II compared to group I in the origin, 3.5 ± 0.7 vs 2.5 ± 0.5 mm, $P = 0.00007$ and 0.09 ± 0.04 vs 0.05 ± 0.02 $cm^2$ , $P = 0.00019$ and in the third intercostal space, 3.4 ± 0.7 vs 2.5 ± 0.5 mm, $P = 0.00009$ and 0.09 ± 0.03 vs 0.05 ± 0.02 $cm^2$ , $P = 0.000047$ whereas most ultrasonographic LIMA findings do not differ between and within the groups, even not adjusted for differences in LVEF.

Conclusions: Proximal LIMA diameters and areas are significantly larger in T-grafts compared to single LIMA grafts, probably due to larger myocardial perfusion areas, which can explain the equalization of ultrasonographic variables between and within both groups at rest and during the Azoulay maneuver 12 years after surgery.

## Introduction

The in situ left internal mammary artery (LIMA) has become the first choice of conduit in coronary artery bypass grafting (CABG) to the left anterior descending artery (LAD) because of reduced cardiac events, superior graft patency, and enhanced short and long-term survival [1-2]. Due to these findings, composite arterial T-grafts (in situ LIMA grafts with another arterial conduit attached) are used in daily practice with good clinical results [3-5]. However, questions remain both on whether the main stem of the in situ LIMA of these T-grafts is able to supply sufficient blood flow at rest and during stress and as well as on the unknown long-term effects on arterial conduit luminal size [6-8]. In this regard, LIMA graft patency in patients with recurrent angina is usually assessed by angiography although other diagnostic techniques are additionally used nowadays and very promising, for example multislice computed tomography (MSCT) [9].

To investigate the long-term outcome of single LIMA to the LAD versus arterial T-grafts we assessed and compared anatomical and functional graft characteristics by 64-MSCT (DSCT) scan at rest and transthoracic ultrasonography at rest and during the Azoulay maneuver 12 years after bypass surgery.

## Materials and methods

Between September 2007 and January 2008, we entered thirty-four patients in a cross-sectional study who were operated with single LIMA to the LAD and additional vein grafts and with T-grafts in the period of 1994 until 1997. Group I consisted of 16 patients (13 Male, 3 Female), mean age of 55.4 ± 11.5 years at the time of operation, with a single LIMA graft to the LAD and additional vein grafts. Group II consisted of 18 patients (17 Male and 1 Female), mean age of 48.5 ± 6.3 years at the time of operation, with LIMA-free right internal mammary artery (FRIMA)-T-grafts. Excluded were patients over 85 years of age, previous allergic reaction to contrast, serious co-morbidity, impaired renal function (creatinine ≥ 120 μmol/l) and an irregular cardiac rhythm.

The Institutional Review Board of the Erasmus MC Rotterdam approved this study

(NL 13011-078-06). Written informed consent was obtained from all patients.

All patients underwent a DSCT scan, transthoracic duplex scanning of the proximal LIMA, transthoracic echocardiography (TTE) of the left ventricle, an electrocardiogram and a short questionnaire within one day.

The DSCT scans were performed to assess the anatomical function (patency) of the arterial grafts and were classified into patent or (distal) string sign grafts. Grafts larger or equal to 2 mm in diameter with good contrast run-off into the coronary system were classified as patent grafts. Small grafts with a diameter of less then 2 mm in diameter with contrast run-off into the coronary system were classified as string sign grafts.

*Transthoracic ultrasonography protocol*

The IE 33 208 ultrasound system (Philips, Best, The Netherlands) was used, which combined 2-D imaging and pulsed Doppler ultrasound to evaluate blood velocity variables of the LIMA as well as left ventricular function. TTE evaluation of the single LIMA and the main stem of the T-graft were performed in all thirty-four patients with a 9 MHz linear array vascular probe (Philips, Bothell, WA, USA). The probe was placed at an angle of 60 degrees in the second or third intercostal space with the patient in supine position. LIMA duplex recordings were electrocardiographically controlled during 3-5 cardiac cycles and data were quantified both online and off-line and were interpreted by 2 physicians. The ultrasonographic LIMA variables analysed were: systolic and diastolic peak velocity (SPV and DPV), systolic, diastolic and total velocity integral (SVI, DVI and TVI), diastolic/systolic velocity integral ratio (DSVIR), diastolic/total (diastolic + systolic) velocity integral ratio (DTVIR) and peak diastolic/peak systolic velocity ratio (DSPVR).

Echocardiographic standard views, parasternal long and short axis, apical four and two chamber and apical long axis, using the S5-1 broadband phased array transducer (Philips, Bothell, WA, USA), were obtained in order to classify left ventricular function and left ventricular ejection fraction (LVEF). Manual tracing of LV end-systolic and end-diastolic frames was perfomed offline according to Simpson's method [10] using commercially available Enconcert software (Philips, Best, The Netherlands).

We performed the Azoulay maneuver at the end and measured the ultrasonographic

LIMA variables afterwards at the same (marked) position as at rest. The Azoulay maneuver is a test which induces hypervolaemia and increases cardiac output by lifting up both legs of the patient [11].

We ultrasonographically analyzed and compared different (sub) groups: (a) distal string sign LIMA grafts versus patent LIMA grafts in Group II at rest and during the Azoulay maneuver. (b) LVEF smaller then 50 % ( n = 6) versus LVEF greater or equal to 50 % (n = 25) at rest and during the Azoulay maneuver. (c) proximal string sign LIMA grafts (n = 3 in group I) versus all proximal patent grafts (n = 31) at rest and during the Azoulay maneuver. (d) All patients in group I versus group II.

The analyses of the LIMA ultrasonograhic variables, left ventricular function and LVEF were performed by two blinded observers.

*Dual-Source Computed Tomography scan protocol*

*DSCT Scan*

Neither ß-blockers nor nitroglycerin were administered prior to the scan. All patients were scanned using a Somatom Definition DSCT scanner (Siemens Medical Solutions, Forcheim, Germany). The system is equipped with two X-ray tubes and two corresponding detectors mounted on a single gantry with an angular offset of 90 degrees and a gantry rotation time of 330 ms. CT angiography scan parameters were: number of X-ray sources 2, detector collimation 32 x 0.6 mm with double sampling by rapid alteration of the focal spot in the longitudinal direction (z flying focal spot), rotation time 330 ms, tube voltage 120 kV.

Automatic tube current modulation in x,y,z-direction with Care Dose 4D® software, (Siemens Medical Solutions, Forcheim, Germany) was applied in all patients. The coronary arteries were scanned with 380 reference mAs/rot. In all patients, we used a relative wide ECG pulsing window (30-65% of the R-R-interval) during which full tube current was applied to include both the mid-diastolic and the end-systolic phases. A bolus of Ultravist® 370 mg l/ml iodinated contrast material (Schering , Berlin, Germany), which varied between 80-100 ml depending on the expected scan time, was injected (flow rate: 4.0-5.0 ml/s) in the right antecubital vein.

All CT coronary angiography datasets were reconstructed using a single-segmental reconstruction algorithm: slice thickness 0.75 mm; increment 0.4 mm; medium-to-

smooth convolution kernel (B26); resulting in a spatial resolution of 0.6-0.7 mm in-plane and 0.5 mm through-plane.

*DSCT image reconstruction*

The reconstruction algorithm uses data from a single heart beat, obtained during a quarter X ray tube rotation by two separate X-ray tubes, resulting in a temporal resolution of 83 ms. Initially, a single dataset was reconstructed during the mid-diastolic phase (350 ms before the next R-wave). In case of impaired image quality datasets were reconstructed in the end-systolic phase (275 ms after the previous R-wave).

*DSCT image evaluation*

Axial views and multi-planar reconstructions (MPR) were used to identify patency of grafts and anastomoses of grafts to coronary run-offs. Analyses were performed in the proximal part of the LIMA, at the level of the second or third intercostal space and proximally and distally from each anastomosis of the graft with a coronary insertion. Distal run-off supplied by a patent graft was separately evaluated.

*Electrocardiogram*

Additional 12-leads electrocardiograms were taken from all patients and analysed by two blinded observers.

*Statistical Analysis*

Data entry and statistical analysis were performed with the use of Epi Info 6.04c (CDC, Atlanta, Georgia). Continuous variables are displayed as means ± standard deviation. Discrete variables are displayed as counts or proportions. Data within and between the groups were tested by paired and unpaired *t*-tests. A *P*-value of 0.05 or less was considered statistically significant. Sample size calculation showed that at least 10-11 patients in each group are necessary to detect a significant difference in diastolic peak velocity between the 2 groups, assuming that diastolic peak velocity in single LIMA to LAD grafts is on average 22 cm/sec (range 15-30 cm/sec) [12] versus 35 cm/sec (range 25-45) [13] in T-grafts (assuming equal variances, SD = 10, $\alpha = 0.05$, power = 0.80).

## Results

In Group I, sixteen single LIMA to the LAD anastomoses were constructed with a total of sixty-six distal anastomoses, 4.1 ± 1.1/patient. In group II, thirty-one LIMA anastomoses, fourty-three FRIMA anastomoses, six gastro-epiploic artery anastomoses and one additional venous anastomoses were constructed, a total of eighty-one distal anastomoses, 4.5 ± 1.1/patient, $P = 0.26$ between the groups.
The mean age of the 34 patients at the time of surgery differed significantly between the groups: $P = 0.034$. The time interval between operation and late follow-up is not significant: 11.5 ± 1.7 (Group I) versus 11.5 ± 1.1 years (Group II), $P = 0.91$.
Except for the heart rate, 74 ± 14 (Group I) versus 66 ± 11 b/min (Group II), $P = 0.046$, hemodynamic variables did not differ between both groups.

*DSCT scan*
In all thirty-four patients the DSCT scans were of diagnostic value. Examples are shown in Fig. 1, Fig. 2 and Fig. 3.
DSCT scans showed three string sign LIMA grafts (19 %) and six occluded venous anastomoses (12 %) in group I and three distal (downstream from the T-anastomose) string sign LIMA grafts (17 %), two string sign FRIMA grafts (11 %), seven occluded LIMA anastomoses (23 %), nine occluded FRIMA anastomoses (21 %), one string sign GEA graft (17 %) and one occluded GEA anastomose (17 %) in group II.
Diameters and cross-sectional areas of the proximal LIMA grafts in group I are shown in Table 1. As expected, both variables differ significantly between the patent and string sign LIMA grafts. Diameters and cross-sectional area's of the proximal T-grafts in group II are shown in Table 2. As expected, both variables also differ significantly between both patent LIMA and FRIMA and distal string sign LIMA and distal string sign FRIMA grafts.
Finally, we selected only the patients with patent proximal LIMA grafts from group I and II to compare diameters and cross-sectional area's. Data are shown in Table 2.
DSCT scans showed no proximal string sign LIMA grafts nor occluded LIMA grafts in the main stem of the T-grafts.

*Ultrasonographic findings*

Adequate Doppler profiles could be obtained from all 34 patients. Examples are shown in Fig. 1a, Fig. 2a and Fig. 3a. In 1 patient TTE and the Azoulay maneuver could not be performed due to time constraints.

No ultrasonographic differences could be obtained between the string sign LIMA grafts and the patent LIMA grafts within group I at rest nor during the Azoulay maneuver (Table 3). Even within these subgroups no differences appeared. Proximal string sign LIMA grafts were only observed in group I.

When only patent grafts in both groups were selected, only diastolic peak velocity at rest and total velocity integral values differs. Nevertheless, all variables are more pronounced in T-grafts at rest and during the Azoulay maneuver (Table 4).

Remarkably, ultrasonographic LIMA findings do not differ between and within the subgroups at rest and during the Azoulay maneuver and also hemodynamic observations do not differ between (sub) groups at rest and during the maneuver.

*Echocardiography*

All but one patient underwent TTE to determine LVEF. In two patients, no adequate window could be obtained. In group I, the overall EF was 57 ± 16 versus 59 ± 9 % in group II, $P = 0.71$.

*Electrocardiogram*

All patients were in sinus rhythm and no ischemia could be detected in any patient.

*Questionnaire*

All but six patients (82 %) remained free of recurrent angina in the postoperative period until these late follow-up investigations. Four patients in group I and two patients in group II have suffered recurrent angina during exercise within the last six months but remained free of complaints during the investigations including during the Azoulay maneuver. Four patients already used ß-blockers and 5 patients are controlled by their cardiologist. One patient in each group was already treated with stenting but still had complaints of angina. This patient in group II has three anastomoses on a string sign graft and 1 occluded FRIMA anastomose. The other patient in group II has four patent distal bypasses. Two patients from group I have

string sign LIMA grafts with four respectively three patent distal venous bypasses. The other two patients in this group have a patent LIMA graft, one with three patent distal venous bypasses and one with one patent venous bypass and three occluded venous bypasses.

## Discussion

The intrinsic properties of internal mammary arteries explain the long term survival of these bypass grafts [14-15] which results in the statement that arterial composite T-grafts also would have a good long-term graft patency. It can be employed in patients with a severe sclerotic aorta which favours complications due to aortic manipulations and complete revascularization can also be achieved in ventricular fibrillation with the use of extracorporeal circulation or in the beating heart reducing aortic manipulations [4].

Coronary arteriography (CA) is still the accepted method for quantitative evaluation of bypass grafts irrespectable whether the patient suffers angina. However, CA is an invasive procedure which in patients with T-grafts may result in serious events (hypoperfusion) due to induced spasm of the main stem. Therefore, we performed two different control methods in order to determine functional and anatomical patency of (T-) grafts.

With the introduction and development of cardiac CT scans in recent years, imaging of moving coronary arteries and bypass grafts has become feasible. Sensitivities and specificities above 90 % have been reported for coronary artery stenosis compared to coronary angiography [16-18]. However, cardiac CT scans are essentially a morphologic and not a functional diagnostic method in coronary artery bypass control. So, we performed additionally ultrasonography at rest and during the Azoulay maneuver to assess the functionality of single LIMA grafts and the main stem of T-grafts. One of the aims of the study was to determine whether TTE can play a role in the assessment of different LIMA perfusion areas whereas TTE of T-grafts have not been described over a follow-up period over 10-years.

Adequate Doppler profiles of the single LIMA and the main stem of the T-grafts at rest and during the Azoulay maneuver were obtained in all patients which is extremely successful [19]. However, no overall ultrasonographically significant differences were

obtained between the groups nor between subgroups at rest or during the Azoulay maneuver. With respect to the larger perfusion area of the T-grafts, one should expect higher ultrasonographic values in these grafts compared to single LIMA grafts. Even the number of occluded T-graft anastomoses does not influence Doppler profiles.

It is remarkable to notice that the Azoulay maneuver did not have any influence on the Doppler profiles. This finding strengthens the assumption that the 'dynamic' LIMA graft progresses into a 'fixed' or 'steady' (ultrasonographic) state. One of the explanations why the Azoulay maneuver does not affect patients from both groups may be related to the fact that physiological exercise does not appear to be as complete as pharmacological inducement [20].

Prifti et al. [21] stated in a short follow-up study that peak systolic and diastolic velocity ratios are good variables for demonstrating the functional T-graft status. Ratios of greater than 0.85 demonstrated good flow through both distal branches of the T-graft. This means that systolic and diastolic peak velocities equalize in contrast to preoperative values [22]. In spite of the in situ RIMA graft in their study, our findings in the in situ LIMA grafts are different. We found in patent T-grafts values of $0.3 \pm 0.1$ and we also measured these values in patent single LIMA grafts. So, these values are not discriminative in our long-term follow-up study. We did not extrapolate the values of main stems of patients with occluded FRIMA grafts because of the small number of these patients ($n = 2$).

Lemma et al. [23] described in a short term follow-up study their angiographic- and guide wire findings in the proximal and distal arterial composite T-grafts using radial arteries versus single LIMA to the LAD grafts. They found significant differences between the groups for proximal time-average peak velocities. We did not calculate this variable but in patent grafts DPV at rest appeared also significant with higher values in the T-grafts ( $P = 0.03$) while SPV did not ($P = 0.07$). The ratio of these variables remains equal in our study, $0.3 \pm 0.1$ in both groups, while significant differences appear in their study: $0.9 \pm 0.4$ for single LIMA grafts versus $1.1 \pm 0.2$ for T-grafts, ($P = 0.03$), suggesting a higher diastolic part in the cardiac cycle in T-grafts. However, our data were derived from the transthoracic approach in a late follow-up setting. Nevertheless, angiography showed significantly greater proximal LIMA diameters in T-grafts than in single LIMA grafts ($2.8 \pm 0.4$ versus $2.4 \pm 0.5$ mm, $P = 0.019$). Our DSCT findings are similar for the origin of the LIMA graft as well as

for the third intercostal space. Diameters in the T-graft group in our study appeared higher compared to the study of Lemma et al. (3.5 ± 0.7 versus 2.8 ± 0.4 mm). An explanation for this finding can be the higher number of anastomoses with T-grafts per patient in our study although this should be interpreted carefully while we used another method to measure diameters and we performed the study in a different follow-up setting. However, Gurne et al. [24] already described the ability of the IMA graft to adapt its dimension to flow demand in the late postoperative period.

These findings probably explain the equalization of the Doppler profiles between the groups. We assume that the overall myocardial perfusion area of T-grafts is larger compared to single LIMA grafts. Therefore, we suppose that overall blood flow through the T-grafts is larger compared to the single LIMA grafts. This statement was enhanced by the DSCT findings. It would be interesting to perform also a DSCT scan during hyperemic response or the Azoulay maneuver. This was however not included in our protocol.

The number of occluded T-graft anastomoses in our study seems relatively high [25-26]. According to Pevni and Nakajima [25-26], besides technical problems, occluded bypass grafts can be the results of competitive flow, especially in patients with moderate stenoses in coronary arteries. This should be a subject for further detailed analysis in comparison with the findings of sequential LIMA grafts [25-27].

Limitations: We were interested in absolute values of TTE variables in proximal LIMA grafts to discriminate between single LIMA and T-grafts. We did not consider the severity of coronary stenosis nor estimated competitive flow between these systems although we assume that these factors can influence absolute values. Cardioactive medication was continued during the study. This could affect ultrasonographic measurements during the Azoulay maneuver.

## Conclusions

Ultrasonography can detect adequate Doppler profiles in the proximal part of single LIMA bypass grafts as well as in T-grafts.
Proximal LIMA diameters and areas, assessed by DSCT, are significantly larger in T-grafts compared to single LIMA grafts, probably due to larger perfusion areas, which can explain the equalization of ultrasonographic variables with no significant differences between and within both groups at rest and during the Azoulay maneuver 12 years after surgery.

Acknowledgement

Special thanks to M. Rengo for preparing the DSCT images and A. Weustink for her contribution both to the scanning protocol as well as the actual scanning.

*Table 1. Diameters and cross-sectional areas in proximal LIMA to LAD grafts*

| | LIMA-LAD | Patent LIMA graft | String sign LIMA graft | *P* |
|---|---|---|---|---|
| | N = 16 | N=13 | N = 3 | |
| Diam origin (mm) | 2.49 ± 0.5 | 2.7 ± 0.3 | 1.6 ± 0.44 | 0.00004 |
| Area origin ($cm^2$) | 0.05 ± 0.02 | 0.06 ± 0.01 | 0.02 ± 0.01 | 0.00024 |
| Diam 2-3 ic (mm) | 2.48 ± 0.47 | 2.66 ± 0.26 | 1.67 ± 0.25 | 0.00003 |
| Area 2-3 ic ($cm^2$) | 0.05 ± 0.02 | 0.06 ± 0.01 | 0.02 ± 0.01 | 0.00005 |

Diam : diameter, *P*: unpaired value for differences between patent en string sign LIMA grafts. Data are ± standard deviation.

*Table 2. Diameters and cross-sectional areas in proximal T-grafts and patent single LIMA grafts*

| | T-graft N = 18 | LIMA-LAD N = 13* | *P* |
|---|---|---|---|
| Diam LIMA origin (mm) | 3.47 ± 0.7 | 2.7 ± 0.3 | 0.001 |
| Area LIMA origin (cm²) | 0.09 ± 0.04 | 0.06 ± 0.01 | 0.002 |
| Diam LIMA 2-3rd i.c. (mm) | 3.4 ± 0.7 | 2.7 ± 0.3 | 0.001 |
| Area LIMA 2-3rd i.c. (cm²) | 0.09 ± 0.03 | 0.06 ± 0.01 | 0.001 |
| Diam LIMA before T anastomose (mm) | 3.4 ± 0.7 | | |
| Area LIMA before T anastomose (cm²) | 0.09 ± 0.04 | | |
| | *T-graft* | *T-graft* | |
| | Patent LIMA graft N = 13 | Distal string sign LIMA graft N = 3 | *P** |
| Diam LIMA behind T anastomose (mm)** | 3.0 ± 0.5 | 1.8 ± 0.1 | 0.003 |
| Area LIMA behind T anastomose (cm²)** | 0.07 ± 0.02 | 0.04 ± 0.01 | 0.033 |
| | Patent FRIMA graft N = 14 | Distal string sign FRIMA graft N = 2 | |
| Diam FRIMA behind T anastomose (mm)# | 3.1 ± 0.5 | 1.8 ± 0.2 | 0.001 |
| Area LIMA behind T anastomose (cm²)# | 0.08 ± 0.02 | 0.03 ± 0.01 | 0.009 |

LIMA, left internal mammary artery; FRIMA, free right internal mammary artery.
* proximal string sign LIMA grafts deleted. *P*: unpaired value for differences between proximal patent single LIMA and proximal patent T-grafts.
** 2 occluded distal LIMA grafts. # 2 occluded FRIMA grafts. *P**: paired value for differences between patent and distal string sign T-grafts. Diam : diameter. Data are ± standard deviation.

*Table 3. Ultrasonographic variables for string sign- and patent LIMA grafts in group I*

| Variable | Patent LIMA at rest N = 13 | String sign LIMA at rest N = 3 | *P* | Patent LIMA Azoulay N = 13 | String sign LIMA Azoulay N = 3 | *P* |
|---|---|---|---|---|---|---|
| DPV (cm/s) | 16.5 ± 7.0 | 22.1 ± 6.0 | 0.22 | 17.2 ± 9.2 | 16.4 ± 5.1 | 0.89 |
| SPV (cm/s) | 56.2 ± 15.2 | 60.0 ± 33.6 | 0.76 | 57.6 ± 13.9 | 53.0 ± 31.3 | 0.68 |
| DVI ($cm^2$) | 6.3 ± 3.5 | 8.1 ± 3.2 | 0.44 | 6.3 ± 3.9 | 6.6 ± 4.3 | 0.90 |
| SVI ($cm^2$) | 11.7 ± 3.8 | 13.3 ± 8.6 | 0.61 | 12.0 ± 3.1 | 12.6 ± 8.7 | 0.85 |
| TVI ($cm^2$) | 16.1 ± 4.0 | 21.5 ± 11 | 0.16 | 17.7 ± 5.7 | 18.9 ± 12.6 | 0.80 |
| DSVIR | 0.54 ± 0.3 | 0.67 ± 0.2 | 0.43 | 0.53 ± 0.28 | 0.55 ± 0.15 | 0.90 |
| DTVIR | 0.35 ± 0.13 | 0.39 ± 0.04 | 0.60 | 0.34 ± 0.12 | 0.36 ± 0.07 | 0.81 |
| DSPVR | 0.3 ± 0.1 | 0.41 ± 0.1 | 0.09 | 0.3 ± 0.1 | 0.35 ± 0.14 | 0.49 |

DPV, diastolic peak velocity; SPV, systolic peak velocity; DVI, diastolic velocity integral; SVI, systolic velocity integral; TVI, total (diastolic + systolic) velocity integral; DSVIR, diastolic/systolic velocity integral ratio; DTVIR, diastolic/total (diastolic + systolic) velocity integral ratio; DSPVR, peak diastolic/peak systolic velocity ratio. *P*: paired values for differences within the groups. Data are ± standard deviation.

*Table 4. Ultrasonographic variables in patent grafts in group I and II at rest and during the Azoulay maneuver*

| Variable | Group I at rest N = 13 | Group II at rest N = 13 | *P* | Group 1 Azoulay N=13 | Group II Azoulay N=13 | *P* |
|---|---|---|---|---|---|---|
| DPV (cm/s) | 16.5 ± 7.0 | 23.5 ± 8.8 | 0.03 | 17.2 ± 9.2 | 25.4 ± 13.1 | 0.08 |
| SPV (cm/s) | 56.2 ± 15.2 | 76.8 ± 36.2 | 0.07 | 57.6 ± 13.9 | 97.7 ± 75.2 | 0.07 |
| DVI ($cm^2$) | 6.3 ± 3.5 | 9.0 ± 4.1 | 0.09 | 6.3 ± 3.9 | 9.3 ± 4.4 | 0.09 |
| SVI ($cm^2$) | 11.7 ± 3.8 | 14.2 ± 5.8 | 0.20 | 12.0 ± 3.1 | 18.7 ± 11.8 | 0.06 |
| TVI ($cm^2$) | 16.1 ± 4.0 | 24.8 ±10.3 | 0.01 | 17.7 ± 5.7 | 25.9 ± 10.4 | 0.02 |
| DSVIR | 0.54 ± 0.3 | 0.66 ± 0.23 | 0.24 | 0.53 ± 0.28 | 0.56 ± 0.21 | 0.77 |
| DTVIR | 0.35 ± 0.13 | 0.37 ± 0.1 | 0.58 | 0.34 ± 0.12 | 0.34 ± 0.1 | 0.87 |
| DSPVR | 0.3 ± 0.1 | 0.34 ± 0.1 | 0.33 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.97 |

Group I, patients with single LIMA grafts to the LAD and additional vein grafts; Group II, patients with LIMA-free RIMA composite T-grafts. *P*: unpaired value for only patent grafts between the groups. Abbreviations as described in Table 3. Data are ± standard deviation.

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Figure 1. Late follow-up main stem transthoracic ultrasonogaphy (1a) and DSCT coronary angiography of a patent composite arterial T-graft from the transverse (1b) and anterolateral view (1c). (a) main stem of the T-graft; (b) LIMA branch of the T-graft; (c) too large, not kinking, patent FRIMA branch of the T-graft. DSCT, Dual-source computed tomography; LIMA, left internal mammary artery; FRIMA, free right internal mammary artery; SPV, systolic peak velocity (cm/s); DPV, diastolic peak velocity (cm/s).

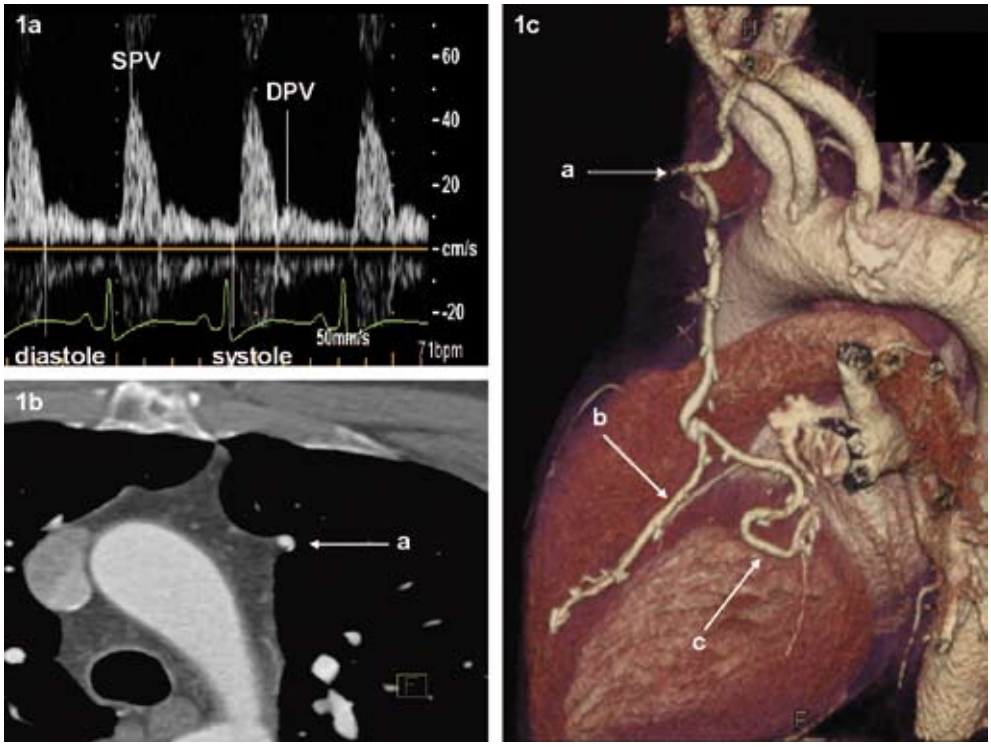
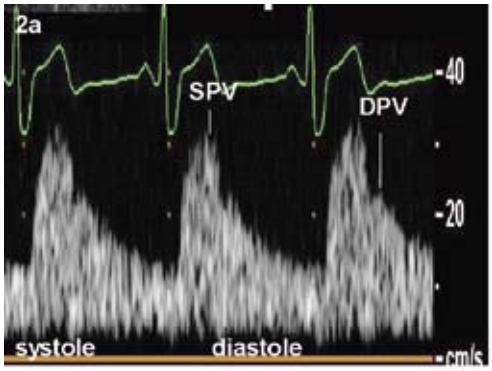
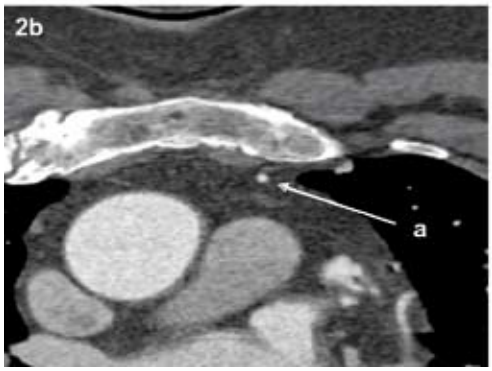


Figure 2. Late follow-up main stem transthoracic ultrasonogaphy (2a) and DSCT coronary angiography of a composite arterial T-graft from the transverse (2b) and anterolateral view (2c). (a) main stem of the T-graft; (b) string sign LIMA branch of the T-graft; (c) patent FRIMA branch of the T-graft. Abbreviations as in Figure 1.



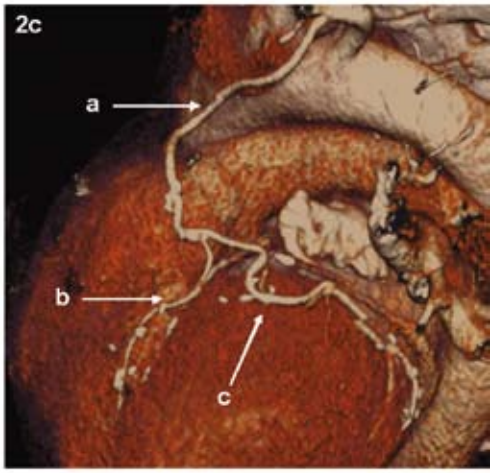
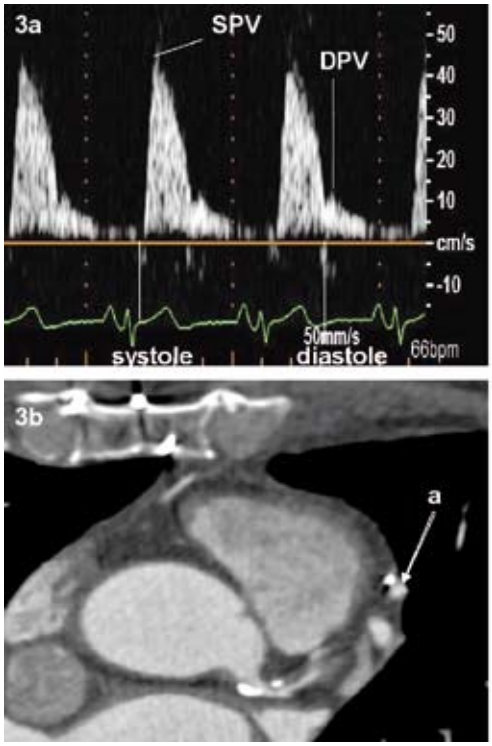
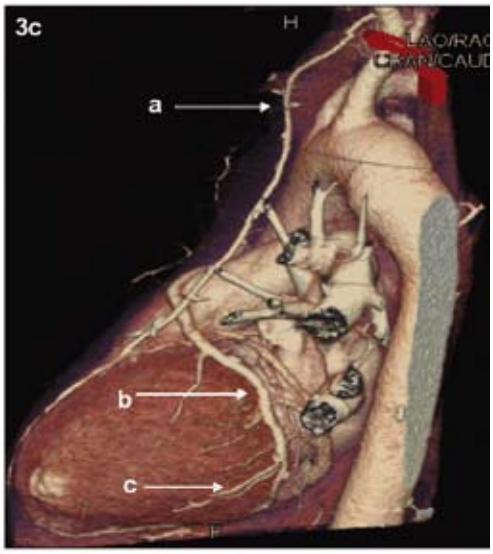



Figure 3. Late follow-up transthoracic ultrasonogaphy (3a) and DSCT coronary angiography of a patent single LIMA graft to the LAD from the transverse view (3b) with an additional patent venous graft from the lateral view (3c). (a) patent LIMA graft. (b) patent venous jump graft to the lateral and inferior wall. (c) native obtuse margin branches. Abbreviations as in Figure 1.



*CHAPTER 11*

# GENERAL DISCUSSION

Non-invasive methods in observational and diagnostic studies have increasingly been used over the years in medicine. In this regard, we investigated whether ultrasonography can play a role in the assessment of the patency of left internal mammary artery (LIMA) used as a bypass graft in coronary surgery.

Supraclavicular ultrasonography of the LIMA, as described in this thesis, was used to analyze single and sequential LIMA bypass grafts in an early- and mid-term follow-up period. Transthoracic ultrasonography of the LIMA was used to assess single LIMA grafts and LIMA grafts in a LIMA-free right internal mammary artery (FRIMA)-T-graft reconstruction in a late follow-up period.

We found in 92 % of the LIMA's adequate Doppler profiles preoperatively. Adequate Doppler profiles of the in situ LIMA graft ranges from 80 to nearly 100 % postoperatively [1-5]. It is well known that preoperatively LIMA Doppler profiles show predominantly systolic velocity patterns as can be expected from a systemic artery and that postoperatively LIMA graft echo Doppler profiles show a shift towards coronary artery spectra with higher diastolic velocities and lower systolic velocities compared to preoperative.

Single LIMA grafts to the left anterior descending artery (LAD) are discussed in the early follow-up period at rest and in the mid-term follow-up period at rest and during adenosine infusion. These analyses are followed by analyses of sequential LIMA grafts in the same periods with comparison of the ultrasonographic findings between single and sequential LIMA grafts. We also discuss the single LIMA to LAD grafts and T-grafts at rest and during the Azoulay manoeuvre in the late follow-up period. We compared the ultrasonographic findings between these groups and also compared these findings with the early- and mid-term ultrasonographic single LIMA-LAD and sequential LIMA graft findings.

*Single LIMA grafts to the LAD*

In the early postoperative period, an average of 5 months after the operation, diastolic ultrasonographic values increased significantly compared to preoperative values in single LIMA bypass grafts. At the same time systolic values decreased significantly in these grafts which confirm earlier described observations [6-8]. These values did not differ significantly in the mid-term postoperative follow-up, 1.8 years, at rest. We also analyzed individual single LIMA grafts and classified these grafts in patent

LIMA grafts and string sign LIMA grafts based on angiographic findings in this mid-term follow-up period.
Early postoperative ultrasonographic values did not show differences between the groups. In both groups diastolic values increased after the operation while systolic values decreased significantly. In this time interval no control angiography of the LIMA grafts was performed.
We conclude, based on ultrasonographic findings, that in this early follow-up period no string sign LIMA grafts were present.

The causes of the development of string sign LIMA grafts have been discussed extensively in literature [9-18]. However, there is no agreement on the cause of a string sign LIMA graft. One of the issues is the influence of competitive flow between native coronary arteries and LIMA bypass grafts. We conclude from our findings, that if competitive flow plays a role in the development of string sign LIMA grafts, it does not influence the patency of LIMA bypass grafts within the first half year after LIMA bypass surgery.
However, ultrasonographic values differ in the mid-term follow-up of 1.7 years. Patent LIMA grafts preserve the same ultrasonographic values while of all string sign LIMA grafts ultrasonographic values decrease compared to early postoperative values [19].
The decrease of the ultrasonographic values can be explained by less blood flow through the LIMA graft caused by competitive flow which can be an explanation studying the angiogram. However, this finding can also be explained by an increase of shear-stress in the run-off area of the LIMA graft caused by progressive increase of distal coronary atherosclerosis which results in a decreased run off-area. We should keep in mind that several factors, not included in our studies, influence blood flow velocity such as flow resistance and pressure gradient across stenotic coronary lesions, length of stenotic lesions, blood viscosity and laminar flow [20].
We additionally performed a hyperaemic response test using adenosine and studied the performance of the LIMA grafts after the test to assess the functionality of the LIMA grafts in the mid-term follow-up period. All ultrasonographic values increased significantly during the hyperaemic response test in all patients in both groups with higher or equal diastolic values compared to systolic values. The diastolic/systolic

peak velocity ratio increased in patent LIMA grafts as well as in string sign LIMA grafts. Together with the other diastolic and systolic variables taken into account, this implies that the LIMA graft extensively adopts to the coronary flow profile. We conclude that not only patent LIMA grafts but also string sign LIMA grafts are able to adapt to the needs of the myocardium and therefore have to be considered as patent and functional grafts.

This statement is supported by the fact that 2 minutes after the stress test the ultrasonographic values decreased in all patients in both groups. In patent LIMA grafts, all overall values decreased significantly compared to the hyperaemic response values while values in string sign LIMA grafts also decreased.

We emphasize that these findings and statements are based on early- and mid-term follow-up research and should only be extrapolated carefully for the functionality of the patent and string sign LIMA grafts during late follow-up.

*Sequential LIMA bypass grafts to the LAD area*

We also studied patients with sequential LIMA bypass grafting to the LAD area. Pre- and postoperative ultrasonography and angiography time scheduling was the same as in single LIMA grafts.

Preoperative Doppler profiles of the LIMA also shows predominantly systolic patterns as can be expected from a systemic artery. In two patients, Doppler profiles could not be used. Early postoperative Doppler profiles show a shift towards diastolic coronary Doppler spectra. All diastolic ultrasonographic variables overall increased significantly and all systolic ultrasonographic variables decreased significantly.

In contrast to single LIMA grafts, all mid-term ultrasonographic variables except systolic peak velocity, increased further in time at rest compared to early postoperative variables. This progressive increase towards a coronary Doppler profile is remarkable. It may be related to the complexity and unknown hemodynamic interactions between native coronary arteries and multiple anastomosis of the LIMA grafts as well as the mutual interferences between LIMA graft segments. The aim of the study was not to analyse this association but we perceived that this influence also may affect ultrasonographic variables.

As described for single LIMA grafts, all duplex variables increased significantly during the hyperaemic response test. So, sequential LIMA grafts are also able to adapt

to the needs of the myocardium and therefore have to be considered as functional grafts. In consequence of the findings of the coronary angiogram we divided the sequential LIMA grafts into patent sequential LIMA grafts and sequential distal string sign LIMA grafts.
Except for systolic peak velocity, none of the variables showed significant differences between the groups in the mid-term follow-up at rest. Adenosine hyperaemic response showed a significant increase of all variables within both groups. However, diastolic variables were significantly more pronounced in the patent LIMA grafts compared to distal string sign LIMA grafts.
In multivariate analyses the maximal diastolic peak velocity in hyperaemic response correlates significantly with the LIMA run-off area [21]. This may indicate that even in stress situations, the partial string sign LIMA graft does not need to perform the maximum capacity to deliver the increased oxygen needs for the perfused myocardium run-off area. This assumption is reasonable while no patients had complaints of angina during the adenosine infusion. Based on these findings, we conclude that native blood flow also play a role in the delivery of oxygenated blood to the LIMA graft run-off area which indicates competitive blood flow.
After the stress test, almost all variables decreased significantly towards values at rest in both groups [22]. From these findings we conclude that sequential LIMA grafts are also functional grafts and can adapt to the needs of the myocardium and therefore should be considered as 'living conduits'.

Considering only patent LIMA grafts to the anterior wall, no differences can be measured between single and sequential LIMA grafts at rest in mid-term follow-up. The hyperaemic test induces significant increase of the ultrasonographic variables in both groups with slightly pronounced ultrasonographic values in the sequential LIMA grafts while differences can not be observed. Ultrasonographic values 2 minutes after the stress test also did not reveal differences between the groups. So, the number of LIMA anastomosis (single LIMA or sequential LIMA grafts) does not influence the overall ultrasonographic values of patent LIMA grafts. One of the most important contributions to the ultrasonographic results in LIMA grafts to the anterior wall seems to be the run-off area and these values are independent of the number of anastomosis. However, correction of the competitive flow should be calculated

to determine the effective perfused area of the LIMA graft which become the final result of the ultrasonographic values [21]. As shown in Chapter 3, the number of anastomosis is not related to the extend of the perfused myocardial areas.
Considering the ultrasonographic values of the LIMA grafts during the adenosine hyperaemic response test and the fact that during the test no patients suffered angina, we concluded that this conduit is not restrictive in oxygen delivery to the increased demand of the myocardium. Revascularization of the anterior myocardial wall can be performed safely using the LIMA graft.

*Single LIMA grafts to the LAD in late follow-up*
We also performed a long-term analysis with a mean of 12 years after surgery. Single LIMA to the LAD anastomosis with additional venous grafts and LIMA-free-right internal mammary artery (FRIMA)-T-grafts were compared. Transthoracic ultrasonographic analyses were performed at rest and during the Azoulay manoeuvre [23]. Dual Source Computed Tomography (DSCT) scans were performed at rest and classified as the gold standard.
Ultrasonographic single LIMA-LAD variables at rest were as high as values in string sign single LIMA grafts. Diastolic peak velocities are low compared to systolic peak velocities resulting in low diastolic/systolic peak velocity ratios. Diastolic values are higher compared to preoperative values although differences are small. The Azoulay manoeuvre did not affect ultrasonographic values in patent nor in string sign single LIMA grafts (Chapter 10). One would expect that an increase of blood flow towards the heart increases cardiac output and an increased myocardial oxygen demand. An explanation for these equal ultrasonographic LIMA values may be an increase in native coronary artery blood flow or an increase in diameter of the single LIMA grafts during the Azoulay manoeuvre. Unfortunately, we did not perform DSCT scans during the stress test.

*T-grafts in late follow-up*
Diastolic peak velocities in T-grafts are significantly higher compared to values in single LIMA grafts while diastolic velocity integrals are close to significance (Chapter 10) at rest. This can be expected by the assumption of a larger run-off in T-grafts compared to single grafts [21]. However, the Azoulay manoeuvre also

does not affect the ultrasonographic values of these grafts. No differences could be measured between values at rest and during the manoeuvre. Explanations of these findings can be the same as for single LIMA grafts: native coronary artery blood flow increases or the diameter of the main stem of the T-grafts enlarge.
Another explanation why the Azoulay manoeuvre does not affect Doppler profiles may be that physiological exercise does not appear to be as complete as pharmacologic induction [24]. In addition, patients were allowed to take their medication during the day of investigation, such as ß-blockers. This medication could also have influenced the values of physical exercise.

Overall T-graft diastolic values are lower compared to early and mid-term follow-up values of sequential LIMA grafts even when only patent T-grafts are taken into account. Although we stated above that run-off areas are not determined by the number of anastomosis, we expected overall ultrasonographic values as high as the values of sequential LIMA grafts. Our findings indicate that ultrasonographic values of 'living' LIMA grafts throughout the years of follow-up may be influenced by several physiological and anatomical interactions. No effect of LVF, string sign LIMA grafts or previous myocardial infarction could be found on ultrasonographic graft performance (Chapter 9).

In a review article, Jones et al. [25] stated that the diastolic fraction of less than 0.5 is the best predictor of stenosis of the LIMA. This statement is not based on late follow-up measurements. Our measurements show values of less than 0.5: not only in string sign single LIMA grafts but also in patent single LIMA grafts, overall T-grafts, distal string sign LIMA grafts in T-grafts as well as in all subgroups.
We learned from DSCT scans the appearance of differences in the proximal diameter between single LIMA grafts and T-grafts and conclude that this finding can play a role in the different ultrasonographic values between these grafts.

Our ultrasonographic research was performed in a late follow-up setting. It appears that 'living' LIMA grafts are exposed to many different influences throughout the years, of which a lot of these are quantitatively and qualitatively unknown. So, meaningful comparisons to earlier follow-up data (from other groups) cannot be

performed without understanding and knowing the hemodynamic, anatomical and physiological changes and circumstances within the single and sequential LIMA grafts as well as the possible progressive coronary atherosclerosis and myocardial conditions throughout the years which all reflect the ultrasonographic values.

*Prospects*

It is obvious that pre- and postoperative LIMA velocity patterns can be obtained by echo Doppler from the non-invasive transthoracic and supraclavicular approach.

We described that single LIMA graft function can be assessed by interpreting diastolic variables from ultrasonography at rest and during stress tests.

From this research, with a relatively small number of patients, it is not possible to determine the function of the distal LIMA anastomosis in sequential- or T-grafts. To refine the functional assessment of these grafts, studies with a large number of patients should be investigated periodically in a follow-up setting at rest and during stress tests. These findings should be compared to data from the same patient in different time settings with respect to (progressive) native coronary sclerosis while maximal diastolic peak velocity in hyperaemic response is the strongest predictor in determining the LIMA run-off area.

In this way ultrasonography may turn out to be a valuable non-invasive tool to screen for patency of the LIMA graft.

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*CHAPTER 12*

**SUMMARY**

**SAMENVATTING**

**CURRICULUM VITAE**

**LIST OF PUBLICATIONS**

**DANKWOORD**

**PORTFOLIO**

## SUMMARY

### Chapter 1 General introduction

Chapter 1 comprises the introduction to this thesis. It describes the advantages of the LIMA in CABG as well as the need for follow-up in patients undergoing CABG. Doppler echocardiographic systems are illustrated and advantages of these methods are summarized. Differences between preoperative and postoperative LIMA ultrasound blood flow patterns are explained at different anatomical levels. The causes for the development of the "string sign" IMA graft are pointed out and finally, the aims of the studies in this thesis are outlined.

### Chapter 2 Different behaviour of sequential versus single left internal mammary artery to left anterior descending area grafts

In Chapter 2, a comparison is made for patients with a different number of anastomosis performed with the LIMA graft to the anterior wall of the left ventricle. In 17 patients, a single LIMA anastomosis to the LAD and in 45 patients, a sequential LIMA bypass graft to the LAD area was performed. Supraclavicular ultrasonographic findings are compared at rest in a mid-term follow-up period and at rest and during and after a stress test using adenosine with control angiography as the gold standard in a late follow-up period.
Ultrasonographic diastolic values are significantly higher in sequential LIMA grafts which may influence long-term patency.

### Chapter 3 Differences in LIMA Doppler characteristics for different LAD perfusion areas.

Chapter 3 describes whether LIMA Doppler velocity characteristics at late follow-up correlate with LIMA perfusion areas of the anterior myocardial wall determined at control angiography. First, the "target" or "potential" area to be revascularized by the LIMA graft was judged from the preoperative coronary angiogram. Secondly,

the perfused area was calculated from the late native coronary and LIMA graft angiography with competitive flow taken into account. Multivariate linear regression analyses shows that the maximal diastolic peak velocity in the stress test correlates significantly with the LIMA run-off area and is the strongest predictor of the LIMA run-off area.

**Chapter 4** **Postoperative changes of duplex ultrasound velocity characteristics in the nonmobilized right internal mammary artery in patients with left internal mammary artery bypass grafting.**

Chapter 4 evaluates postoperative changes of the Doppler variables in the nonmobilized RIMA in different intercostal spaces in 41 patients undergoing CABG with the LIMA graft. All postoperative RIMA Doppler variables, including the proximal diameter, increased significantly compared to preoperative values suggesting a hyperaemic response after LIMA harvesting after median sternotomy. The increase was most marked in diastolic parameters and decreased at longer follow-up time intervals.

**Chapter 5** **Can late supraclavicular echo Doppler reliably predict angiographical string sign of LIMA to LAD area grafts?**

Chapter 5 investigates whether Doppler of the LIMA to the LAD area grafts can reliably predict (distal) string sign LIMA grafts identified at angiography 1.4 years after surgery. Angiography demonstrated in 46 patients functional LIMA grafts, in 4 patients sequential distal string sign LIMA grafts and in 5 patients total string sign LIMA grafts. From the multivariate logistic regression analyses we developed a formula, consisting of systolic and diastolic peak velocity, to assess the probability of (partial) string sign LIMA grafts. This predictive formula appeared not refined enough to determine the status of all LIMA grafts with high accuracy.

**Chapter 6** **Preserved hyperaemic response in supraclavicular ultrasonography demonstrates function on demand of the LIMA to LAD string sign graft after CABG**

Chapter 6 demonstrates in a small number of patients the response to increased myocardial oxygen demand in patent and in string sign single LIMA grafts. Control angiography showed in 13 patients a patent LIMA graft and in 3 patients a string sign LIMA graft to the LAD at 1.5 years postoperatively. Both groups showed a shift towards coronary type diastolic Doppler profile at rest and at hyperaemic response which proves the functionality of the string sign single LIMA graft.

**Chapter 7** **Preserved hyperaemic response in (distal) string sign left internal mammary artery grafts.**

In Chapter 7, Doppler variables at rest, during and after a stress test are correlated with angiographically patent and (distal) string sign LIMA grafts to the LAD area. Fifty-two patients were studied 1.8 years after bypass surgery at rest, in hyperaemic response and after the hyperaemic response. Arteriography demonstrated functional LIMA grafts in 43 patients, sequential distal string sign LIMA grafts in 4 patients and total string sign LIMA grafts in 5 patients. (Partial) String sign LIMA grafts were found in 9/52 (17.3 %) patents. Between the groups all ultrasonographic velocities showed a significant linear relation at rest and during maximal hyperaemic response all velocities increased significantly within all groups while a significant decrease was found 2 minutes after the hyperaemic response. So, (partial) string sign LIMA grafts are in a “low functional state” at rest and can adapt to myocardial stress conditions when myocardial oxygen demand increases.

**Chapter 8** **Epicardial coronary artery Doppler: validation in the animal model**

Chapter 8 describes the validation of a newly designed epicardial Doppler probe in 4 adult pigs. A pericoronary transit time flow probe and the newly designed probe measured coronary blood flow and flow velocities in different conditions

of the LAD. The newly designed Doppler probe can detect coronary arterial flow velocities and can possibly play a role in the assessment of the patency of coronary graft anastomoses.

## Chapter 9 Ultrasonographic and DSCT scan analysis of single LIMA versus arterial T-grafts 12 years after surgery

Chapter 9 compares transthoracic Doppler variables of 15 single LIMA to LAD grafts and 17 T-grafts with DSCT scans as the gold standard in a late follow-up period. DSCT scans showed three string sign single LIMA grafts and in the T-graft group three string sign LIMA grafts, seven occluded LIMA anastomoses and nine free-RIMA anastomoses.
Ultrasonographic variables in the proximal part of the LIMA graft did not differ between the groups. Left ventricular function, proximal string sign LIMA grafts nor previous myocardial infarction affected ultrasonographic graft performance. So, ultrasonography can not distinguish between string sign and patent single LIMA or T-grafts nor demonstrate distal anastomosis patency in T-grafts 12 years after surgery.

## Chapter 10 Anatomical and functional assessment of single LIMA versus arterial composite T-grafts 12 years after coronary bypass surgery

In Chapter 10, we investigated whether the ultrasonographic function of the LIMA graft correspond with the DSCT scan findings in patients 12 years after bypass surgery. Sixteen patients with a single LIMA graft and eighteen patients with a composite arterial T-graft underwent proximal LIMA ultrasonography at rest and during the Azoulay manoeuvre, transthoracic ultrasonography of the left ventricle and a 64-MSCT scan. The DSCT scans showed three string sign single LIMA grafts and three distal string sign LIMA grafts and sixteen occluded anastomoses in T-grafts. Proximal LIMA diameters and areas are significantly larger in T-grafts, probably due to larger myocardial perfusion areas, which can explain the equalization of ultrasonographic LIMA variables with no significant differences between the groups.

# Chapter 11 General discussion

Chapter 11 includes the general discussion of this thesis in which the results and conclusions of this thesis are reviewed.

## SAMENVATTING

### Hoofdstuk 1 Algemene introductie

Hoofdstuk 1 is de introductie van dit proefschrift. Het beschrijft de voordelen van de LIMA graft in patiënten welke een bypass operatie moeten ondergaan. Tevens wordt het belang om deze graft te vervolgen in de periode na de operatie uiteengezet.
De verschillende Doppler methoden met hun voor- en nadelen worden uitgelegd. De bloedstroom patronen van de LIMA voordat deze als graft is aangelegd en de bloedstroom patronen van deze graft nadat deze als bypass is aangelegd worden geanalyseerd. De mogelijke redenen van het ontstaan van de "string sign" LIMA graft worden puntsgewijs weergegeven. Tenslotte worden de doelen van de verschillende studies in dit proefschrift besproken.

### Hoofdstuk 2 Verschillen tussen meerdere- en enkele linker arteria mammaria interna omleidingen op de voorzijde van het hart

Hoofdstuk 2 vergelijkt 2 patiëntengroepen met een verschillend aantal LIMA anastomosen op de voorzijde van het hart. Zeventien patiënten hebben 1 anastomose met de LIMA graft op de LAD en 45 patiënten hebben meerdere omleidingen met de LIMA graft op de voorzijde van het hart. Supraclaviculair gemeten geluidsgolven worden tussen beide groepen vergeleken 5 maanden na de operatie in rust. Deze metingen worden herhaald na ruim anderhalf jaar bij dezelfde patiënten. Deze metingen worden in rust en tijdens een stress test en direct na deze stress test uitgevoerd. Om een gouden standaard te verkrijgen ondergaan deze patiënten in dezelfde periode een angiogram van de kransslagaderen en een angiogram van de omleidingen.
Het blijkt dat de LIMA grafts met meerdere omleidingen significant hogere diastolische waarden hebben in vergelijking met de LIMA grafts met een enkele omleiding. Deze hogere diastolische waarde zou een rol kunnen spelen op de lange termijn patency van deze graft.

**Hoofdstuk 3** **De grootte van het perfusie-gebied van de LIMA graft correleert met verschillende Doppler variabelen**

Hoofdstuk 3 beschrijft de overeenkomsten tussen de Doppler variabelen van de LIMA graft en de grootte van het perfusie-gebied van deze LIMA graft. Om de grootte van het perfusie-gebied van de LIMA graft te bepalen wordt in eerste instantie het potentiële te revasculariseren gebied met behulp van het preoperatieve angiogram vastgesteld. Het uiteindelijke postoperative perfusie-gebied van de LIMA graft wordt berekend met behulp van het controle angiogram van het natieve coronair systeem en van de LIMA graft. Bij de berekening van dit perfusie-gebied wordt rekening gehouden met de competitieve bloedstroom tussen de twee systemen. De multivariate lineaire regressie analyse toont aan dat de maximale diastolische Doppler snelheid in de adenosine belastingstest een significante correlatie vertoont met de grootte van het perfusie-gebied van de LIMA graft. Deze variabele heeft tevens de grootste voorspellende waarde voor de grootte van het perfusie-gebied van deze LIMA graft.

**Hoofdstuk 4** **Doppler veranderingen in de rechter arteria mammaria interna na coronair chirurgie met behulp van de linker arteria mammaria interna**

Hoofdstuk 4 beschrijft de postoperatieve Doppler veranderingen in de RIMA na coronair chirurgie met de LIMA graft. Alle Doppler variabelen, inclusief de diameter van de RIMA, nemen significant toe in vergelijking met de preoperatieve waarden. Deze toename kan een uiting zijn van een hyperemische reactie in het borstbeen na het vrij prepareren van de LIMA na een mediane sternotomie. De diastolische Doppler variabelen nemen procentueel het meeste toe en nemen af naarmate de periode na de operatie toeneemt.

**Hoofdstuk 5** **Kan echo Doppler het vóórkomen van string sign LIMA grafts, welke vastgesteld zijn met angiografie, voorspellen?**

Hoofdstuk 5 onderzoekt of de echo Doppler een betrouwbare methode is om de functionaliteit van LIMA grafts 1.4 jaar na de operatie vast te stellen. Angiography toont 46 open en goed functionerende LIMA grafts, 4 jump grafts met een distale string sign LIMA graft en 5 LIMA grafts met over de gehele lengte een string sign. Middels de multivariate logistische regressie analyse hebben we een formule ontwikkeld om de aanwezigheid van een (gedeeltelijke) string sign LIMA graft te voorspellen. Het blijkt dat deze formule niet nauwkeurig genoeg is om met een hoge betrouwbaarheid voorspellingen te doen.

**Hoofdstuk 6** **Met behulp van de echo Doppler wordt vastgesteld dat de hyperemie stress test aantoont dat de string sign LIMA graft op de LAD als functionele graft beschouwd moet worden**

Hoofdstuk 6 toont in open en string sign LIMA grafts de reactie van de inspanningstest in een kleine patiëntenpopulatie. Angiografie toont anderhalf jaar na de operatie in 13 patiënten een open en in 3 patiënten een string sign LIMA graft aan. In beide grafts ontstaan in rust en tijdens de stress test een Doppler profiel met een coronair flowpatroon. Dit bewijst dat de string sign LIMA graft functioneert.

**Hoofdstuk 7** **(distale) String sign LIMA grafts kunnen zich aan de stress condities van het myocard aanpassen**

Hoofdstuk 7 correleert de waarden van het Doppler signaal in rust en tijdens de stress test met de op angiografie gevonden doorgankelijkheid van de LIMA graft. Tweeenvijftig patienten werden in rust, tijdens en direct na een stress test 1.8 jaar na de operatie bestudeerd. Het angiogram toonde in 43 patiënten open LIMA grafts, in 4 patiënten een deels open en deels string sign LIMA graft en in 5 patiënten een gehele string sign LIMA graft. In 9/52 (17.3 %) patienten werden er (deels) string sign

LIMA grafts aangetroffen. Alle Doppler variabelen tonen in rust een significante lineaire relatie tussen de drie verschillende patiënten groepen. Tijdens de stress test nemen alle Doppler variabelen in alledrie de groepen significant toe en nemen allen significant af direct na de stress test. Met deze gegevens bewijzen we dat de (deels) string sign LIMA grafts in rust niet maximaal functioneren maar dat deze grafts zich kunnen aanpassen indien de myocardiale stress een toename van het zuurstofaanbod eist.

**Hoofdstuk 8** **Validatie van een nieuw ontwikkelde epicardiale Doppler probe in een diermodel**

Hoofdstuk 8 beschrijft de validatie van een nieuw ontwikkelde epicardiale Doppler probe. Voor deze validatie werden 4 volwassen varkens gebruikt. Een transit time flow probe en de nieuw ontwikkelde Doppler probe werden met elkaar vergeleken tijdens bloedstroom metingen onder verschillende omstandigheden in de LAD. Het blijkt dat de nieuwe epicardiale probe adequate metingen van coronaire bloedstroomprofielen kan verrichten waardoor het mogelijk ook een rol kan gaan spelen in de bepaling naar de functionaliteit van anastomosen op de kransslagaderen.

**Hoofdstuk 9** **Vergelijkingen van ultrageluidsgolven met DSCT scans tussen LIMA grafts met een enkele omleiding en arteriële T-grafts 12 jaar na coronair chirurgie**

Hoofdstuk 9 vergelijkt transthoracaal gemeten Doppler waarden tussen 15 LIMA grafts met een enkele omleiding en 17 T-grafts in een periode lang na de operatie. De DSCT scan wordt bij deze vergelijking als gouden standaard gebruikt. Deze scan toont dat er drie string sign LIMA grafts aanwezig zijn in de groep patiënten met een enkele LIMA anastomose en in de patiëntengroep met T-grafts drie string sign LIMA grafts, negen afgesloten LIMA anastomosen en negen vrije-RIMA-graft anastomosen. Proximaal in de LIMA gemeten ultrageluidsgolven tonen geen verschil tussen de beide groepen. De linker ventrikelfunctie, de aanwezigheid van een proximale string sign LIMA noch een doorgemaakt infarct van de voorwand van het hart heeft invloed op de waarden van de Doppler. We concluderen dat de Doppler methode geen onderscheid kan maken tussen string sign en open en functionerende

LIMA grafts of T-grafts. Na 12 jaar kan de functie van de distale anastomosen in T-grafts niet middels Doppler onderzoek aangetoond worden.

**Hoofdstuk 10 Anatomische en functionele vergelijking tussen single LIMA grafts en arteriële T-grafts 12 jaar na bypass chirurgie**

Hoofdstuk 10 beschrijft of de met ultrageluidsgolven vastgestelde functie van de LIMA graft overeenkomt met de bevindingen van de DSCT scan 12 jaar na operatie.
Zestien patiënten met een enkele LIMA omleiding en achttien patiënten met een T-graft ondergingen een Doppler onderzoek van de proximale LIMA in rust en tijdens de Azoulay manoevre alsmede een transthoracaal echocardiogram van de linker ventrikel en een DSCT scan.
De DSCT scan toonde drie string sign LIMA grafts in de groep van patiënten met een enkele LIMA anastomose en drie string sign LIMA grafts en zestien afgesloten anastomosen in de patiënten met een T-graft. De proximale diameters en oppervlakten van de LIMA grafts in T-grafts zijn significant groter dan in de LIMA grafts met een enkele omleiding. Dit kan het gevolg zijn van het grotere te perfunderen gebied van het hartspierweefsel door de T-grafts. Deze bevinding kan de verklaring zijn waarom er geen significante Doppler waarden tussen de verschillende proximale LIMA grafts wordt gevonden.

**Hoofdstuk 11 Discussie**

Hoofdstuk 11 bevat de discussie van dit proefschrift. De resultaten en de conclusies van dit proefschrift worden hierin beschreven.

## CURRICULUM VITAE

Joost Michael Hartman was born on January 30th , 1965, in Bussum, The Netherlands. After graduating from "Scholengemeenschap Katwijk de Breul" in Zeist, he studied one year Pharmacy at the State University Utrecht. After this year, he started his medical training at the State University Utrecht. During his medical study his interest in cardio-thoracic surgery was stimulated when he worked as a research investigator at the department of Cardio-Thoracic and Cardio-Vascular Surgery in the St. Antonius Hospital in Nieuwegein. In January 1995 he obtained his Medical Degree at the State University Utrecht. He started working as a resident in Cardio-Thoracic Surgery in several hospitals. In this period he started this thesis.

In April of 2001 he started his training as a Cardio-Thoracic Surgeon, first spending two years residency at the department of Surgery at the "Medisch Centrum Leeuwarden" (Head subsequently dr. D.C. Busman and dr. W.J.H.J. Meijerink). In 2007 he finished his training in Cardio-Thoracic Surgery at the Erasmus MC Rotterdam (head: Prof. dr. A.J.J.C. Bogers). After completing his training, he stayed in the Erasmus MC Rotterdam as a consultant at the Department of Cardio-Thoracic Surgery till December 2008.

In December 2008 he started as a consultant at the Department of Cardio-Thoracic Surgery at the University Medical Centre Groningen.

## LIST OF PUBLICATIONS

**J. Hartman**, B. Meijboom, T. Galema, H. Takkenberg, A. Schets, P. de Feyter, A. Bogers. Anatomical and functional assessment of single LIMA versus arterial composite T-grafts 12 years after bypass surgery. **Submitted**

**J. Hartman**, B. Meijboom, T. Galema, H. Takkenberg, A. Schets, P. de Feyter, A. Bogers. Ultrasonographic and 64-MSCT analysis of single LIMA versus arterial T grafts 12 years after surgery. **Submitted**

CA den Uil, D Reis Miranda, WK Lagrand, **JM Hartman**, C Ince, AJ Bogers, PE Spronk, ML Simoons. Visualization of human pulmonary alveoli in vivo: A faesibility study. **Submitted**

G. D'Ancona, **JM Hartman**, F Bartolozzi, E. van Deel, DJGM Duncker, AJJC Bogers, M.Pilato, AP Kappetein. Epicardial coronary artery Doppler: Validation in the animal model. **Interact Cardiovasc Thorac Surg 2008;7:634-7.**

**M Hartman**, J Kelder, R Ackerstaff, H van Swieten, F Vermeulen, A Bogers. Preserved hyperaemic response in (distal) string sign LIMA grafts. **Eur J Cardiothorac Surg 2007;31:283-9.**

**M Hartman**, J Kelder, R Ackerstaff, H van Swieten, F Vermeulen, A Bogers. Can late supraclavicular echo Doppler reliably predict angiographical string sign of lima to lad grafts?. **Echocardiography 2007;24:689-96.**

**M Hartman**, J Kelder, R Ackerstaff, H van Swieten, F Vermeulen, A Bogers. Preserved hyperaemic response in supraclavicular ultrasonography demonstrates function on demand of the LIMA to LAD string sign graft after CABG. **J Cardiovasc Surg 2007;48:59-66.**

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**M Hartman**, J Kelder, R Ackerstaff, E Bal, F Vermeulen, A Bogers. Different behavior of sequential versus single left internal mammary artery to left anterior descending area grafts. **Cardiovasc Surg 2001;9:586-94.**

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## DANKWOORD

Hooggeleerde heer Bogers, ik wil u bedanken dat u in de totstandkoming van dit proefschrift bent gaan geloven. Ik kwam op uw afdeling als ‘agnio’ en nam een, mijns inziens, wel aardig onderzoek mee uit een ander ziekenhuis. U heeft zich verdiept in dit onderzoek en bent er enthousiast over geworden. In de loop der jaren bent u mijn steun en toeverlaat geweest in de gemakkelijke en moeilijke tijden welke het schrijven van een proefschrift met zich meebrengt. Ik mocht u altijd ‘lastigvallen’ als het niet liep en uw goede adviezen hebben mij in de juiste richting voor het completeren van dit proefschrift gestuurd. De rust en het vertrouwen welke u bleef uitstralen hebben mij geraakt. Ik hoop dat ik een deel daarvan naar de toekomst kan meenemen.

Weledelzeergeleerde heer Kappetein, beste Arie Pieter, dank dat ik je op de momenten ‘dat het nooit uitkwam’ toch kon storen. Ondanks je drukke professionele bestaan heb je altijd de tijd voor me genomen als dat nodig was. Blij dat jij diegene was die me zo nu en dan een spiegel voorhield. Ik zal het nooit vergeten, Stockholm 2006. Misschien heb je gelijk, misschien ook niet. Ik denk dat het niet gaat om het gelijk hebben maar wel om respect voor elkanders visie.

Hooggeleerde heer Duncker, beste Dirk Jan, ik heb geleerd van jouw systematische en gecontroleerde aanpak om problemen op te lossen. De passie die jij uitstraalt als ‘onderzoek’ je pad kruist is bewonderenswaardig en bijna onvoorstelbaar. Ik ben zeer verheugd jouw persoonlijkheid en enthousiasme te hebben mogen ervaren. Ik wil hier een deel van meenemen in mijn carrière. Ik ben blij dat jij je visie over dit proefschrift hebt laten schijnen.

Hooggeleerde heer van Swieten, u bent één van de weinigen die mij vanaf het allereerste begin, in ‘mijn wereld’ van de cardiothoracale chirurgie, heeft meegemaakt. Ik begon als student geneeskunde in het St. Antonius Ziekenhuis te Nieuwegein reeds met onderzoek. Ik heb daar twee jaar als ‘agnio’ op uw afdeling mogen werken en tevens een voorzichtige aanzet gemaakt voor dit proefschrift alsmede een start gemaakt met mijn professionele carrière. U heeft een kritische blik ten aanzien van

het functioneren van individuen in een groep alsmede het op consequente wijze uitvoeren van onderzoek. Mede dankzij uw visie, adviezen en toewijding is het project dat de basis vormt voor dit proefschrift tot een goed einde gebracht. Ik ben er trots op dat u in de 'kleine commissie' heeft willen plaatsnemen.

Hooggeleerde heer de Feyter, beste Pim, door jouw rustige houding en vakbekwaamheid heb ik er nooit aan getwijfeld dat het laatste deel van dit proefschrift er zou komen. Ik kon je altijd, op welke locatie dan ook, aanspreken waarbij de problemen binnen een paar minuten opgelost waren. Jouw heldere blik op de realiteit heeft me verbaasd en tegelijkertijd was ik daar erg van onder de indruk. Ik ben blij dat dit proefschrift daar ook van heeft kunnen profiteren.

Hooggeleerde heer Mochtar, beste Bas, ik heb nooit met jou binnen één afdeling gewerkt. Ik vind dat vreselijk jammer omdat ik naast jouw vakbekwaamheid tevens jouw visie over belangrijke wereldkundige zaken had willen ervaren. Ik heb je leren kenen als een persoon met een eigen visie. Ik herken me deels in jouw persoonlijkheid en ik hoop dat we nog veel 'filosoferende' momenten tegemoet kunnen zien. Ik verheug me er in ieder geval op. Ik ben zeer vereerd dat je kritisch naar mijn proefschrift hebt willen kijken.

Hooggeleerde heer Verhagen, beste Hence, ik ben blij dat jij tijd hebt willen nemen om mijn proefschrift te analyseren. Zoveel Rotterdammers hebben nu ook weer niet een belangrijke fase van hun studentenleven in de mooiste studentenstad van Nederland doorgebracht.

Weledelzeergeleerde heer Morshuis, beste Wim, jij bent ook één van cardio-thoracaal chirurgen die mij vanaf het begin van mijn professionele carrière hebt meegemaakt. Ik dank je voor de kritische noten en voor de momenten dat ik je onder vier ogen kon spreken. Ik ben blij dat jij vakkundig naar mijn proefschrift hebt willen kijken.

Ik wil graag mijn collegae cardio-thoracaal chirurgen bedanken voor wat zij de laatste jaren voor mij vakkundig hebben betekend. Door jullie geduld, vakbekwaamheid, openheid, feedback en toewijding ben ik geworden tot de cardio-thoracaal chirurg

welke ik nu ben. Ik ben heel blij dat ik mijn opleiding in Rotterdam heb mogen volgen. Ik zal de vrijdagmiddagborrels niet snel vergeten en hoop dat dit 'routinebezoekje' in de toekomst nog vele malen mag plaatsvinden. Professor Bogers, Arie Pieter, Jos, Lex, John, Charles, Frans en Peter, heel veel dank.

Mijn kamergenoten in het ziekenhuis wil ik tevens bedanken. Zij hebben moeten afzien als ik weer eens achter de computer zat met de muziek misschien niet op de laagste stand. Ik hoop dat ze inmiddels mijn muziekstijl zijn gaan waarderen. In ieder geval heb ik ze ruim de tijd gegeven. Özjekakan, dank dat ik af en toe in je boekje mocht kijken hoe jij het gedaan hebt. Ik hoop dat ik je nog vaak zal tegenkomen. Als jij rijdt dan zet ik een muziekje op….ts ts ts ts. Frans, ik wens je heel veel succes met je carrière. Ik weet zeker dat je een mooie plek hebt bemachtigd. Pieter, ik vind je een prettige collega die nooit te beroerd is om een stap extra te zetten. Ik hoop en verwacht dat je een mooie carrière tegemoet gaat. Martijn, je bent inmiddels elders aan het werk. Ik hoop van harte dat je een goede stap gemaakt hebt. Ik hoop dat ook jouw boekje niet al te lang meer op zich laat wachten.

Geachte Dokter Vermeulen, u bent de initiator achter het eerste deel van dit proefschrift. U heeft de subsidies, de organisatie alsmede de verschillende specialismen warm laten lopen voor, in mijn ogen, uw project. Ik zal nooit vergeten dat u mij benaderde met de vraag of ik eens wou kijken naar Doppler data in een computer. Twee assistenten hadden reeds een aanzet gemaakt doch waren om verschillende redenen gestopt. Aanvankelijk had ik geen idee waar het over ging en wat nu eigenlijk belangrijk aan dit project was. Ik heb me in het onderwerp, de data en de uitwerking verdiept, niet wetende dat dit project een groot deel van mijn leven zou gaan beheersen. Ik denk nog regelmatig terug aan de lange avondsessies welke we samen hebben doorgemaakt na een lange werkdag. Uw enthousiasme en gedrevenheid waren onuitputtelijk. Als ik op het einde van de avond naar huis wilde omdat ik het genoeg vond kwam u weer met nieuwe inzichten en ideeën welke op dat moment geanalyseerd moesten worden. Zonder uw kennis, doorzettingsvermogen en geloof in een goede afloop had ik dit project niet kunnen voortzetten op de manier zoals het nu gelopen is. Ik ben zeer blij dat ik u in een vroeg stadium van mijn carrière heb mogen ontmoeten en dat u vertrouwen in mij gehad heeft om dit enorme project uit te werken. Dankwoorden

schieten hiervoor te kort. Ik hoop van harte dat het u en uw familie zeer goed gaat. Dit proefschrift had nooit tot stand kunnen komen als collega's uit andere specialismen niet actief geparticipeerd hadden. Weledelzeergeleerde heer Ackerstaff, veel dank voor uw zeer kritische blik op de manuscripten. Als ik u om hulp vroeg had u altijd tijd voor mij. U heeft een zeer gedreven persoonlijkheid met een enorme kennis van de 'Doppler materie' waar ik gelukkig gebruik van mocht maken. Zonder uw toewijding was dit project gedoemd geweest te mislukken. Weledelgeleerde heer Kelder, beste Hans, wat was je druk met je eigen projecten. Toch wist je tussen alle projecten en polibezoeken tijd voor mij in te ruimen. Of het nu overdag of 's avond laat was maakte jou niet uit. Je kennis over methodologie en statistiek heeft indruk op me gemaakt. Ik ben blij dat jij één van de steunpilaren van dit project was. Weledelgeleerde heer Bal, dank u voor de beoordeling van de electrocardiogrammen. Uw analyse heeft in belangrijke mate bijgedragen aan dit proefschrift. Beste Vincent en Gert, jullie inspanningen zijn niemand ontgaan. Vincent, ik heb jouw gedrevenheid gemist. Helaas werd je ziek en kon je het project niet meer afmaken. Ik hoop dat het goed met je mag gaan. Gert, hartelijk dank dat jij bereid was om het werk van Vincent voort te zetten. Jouw participatie was onontbeerlijk voor het onderzoek. Weledelgeleerde heer Meijboom, beste Bob, zonder jouw kennis was het tweede deel van mijn proefschrift nooit tot stand gekomen. Samen hadden we eigenlijk nooit tijd om gegevens van patiënten te analyseren. Toch hebben we samen tijd kunnen maken om de DSCT scans te analyseren. Achteraf gezien is dit gelukkig vlot verlopen. Ik heb je leren kennen als een toegewijd en secuur werkende dokter. Ik wens je veel succes met je opleiding en verwacht dat je snel de 's' kwijtraakt. Weledelgeleerde heer Galema, beste Tjebbe, jouw kritische blik en onbevangenheid zijn belangrijk geweest voor de totstandkoming van dit proefschrift. Je opvallend heldere blik op mijn onderzoek heeft mij in de juiste richting gestuurd. Ik dank je voor je openheid en je kritische noten. Beste Anne-marie, wat heb jij veel werk achter de schermen verricht. Ik heb gemerkt dat als jij je zinnen ergens opzet jezelf er ook helemaal in vastbijt. Alle echo analyses welke jij verricht hebt zijn essentieel voor het tweede deel van dit proefschrift. Ik bewonder je doorzettingsvermogen en ben erg blij dat jij je hebt opgesteld om in het onderzoek te participeren. Op naar het volgende wetenschappelijke project.....

Dear Giuseppe, we spent some time in the laboratory at the University of Rotterdam. Your personality and your clear view on research has impressed me. I hope you will be able to ‘join life”. Beste Elza, we wisten nooit wanneer we precies zouden komen. Toch zorgde jij er altijd voor dat alle voorbereidingen reeds getroffen waren en dat we direct aan de slag konden met de varkens experimenten. Dank voor je toewijding. Marianne en Annemarie, dank dat jullie je ontfermden over de extracorporele circulatie tijdens de varkens experimenten. Jullie ondersteuning heeft geleid tot een mooie validatie.

Dit proefschrift en mijn professionele ontwikkeling is mede tot stand gekomen door de ondersteuning van verpleegkundig personeel, de afdeling echocardiologie alsmede de secretaresses uit het St. Antonius Ziekenhuis in Nieuwegein en het Erasmus Medisch Centrum Rotterdam in Rotterdam. Ik ben een ieder veel dank verschuldigd.

Ik ben de afdeling Algemene Heelkunde van het Medisch Centrum Leeuwarden veel dank verschuldigd voor de twee geweldige jaren van mijn vooropleiding. Ik was er nog maar net en had al 2 congressen geboekt over de grens. Dit werd mij op een prettige manier kwalijk genomen. Ik wil een ieder bedanken voor de zeer prettige samenwerking en verhelderende borrels. Er werd zelfs gezegd dat ik me wel heel positief ontwikkelde: ”Hartman, jij moet een plasje gaan inleveren”.

Wanneer iemand tijd en energie in een project stopt gaat dit ten koste van andere elementaire zaken in het leven. Ik besef terdege dat ik niet altijd thuis heb kunnen geven naar mensen toe die ik lief heb. Vriendschap houdt ook in dat je er niet altijd voor anderen kunt zijn al klinkt dit tegenstrijdig.

Vrienden Steven C., Jeroen L., Marc R., Wim de S., Marc N., Rogier K., Arend van Z., Michel K., Jur P. en Allard S., dank voor jullie begrip. Quality time is essential and will come again.

Lief ‘tennisteampje’, dank voor jullie begrip dat ik de laatste tijd wel heel erg geestelijk en lichamelijk afwezig was. Ik vond de momenten in ‘Ahoy’ onvergetelijk.

Filosoferen over ‘time sceduling’ en vooral niet naar het tennis kijken. Dank voor jullie steun.

Lief en apart ‘voetbalteampje’, dank voor jullie steun en begrip als ik er weer eens niet was. Altijd dienst, congres of tijd nodig voor mijn onderzoek. Zeeltje en Alex, bedankt voor de interesse die jullie altijd in mij toonde. Ik heb het nooit laten merken maar het deed me veel.

Lieve Jos, Deb en Pat, dank voor jullie onvoorwaardelijke steun. Ik besef dat het voor jullie niet altijd even gemakkelijk is geweest. Ik hoop dat na de afronding van dit project alles duidelijk geworden is.

Lieve Ellis, wat heb jij moeten afzien. Ik heb me dat ten tijde van ons samenzijn nooit gerealiseerd. Wijsheid en begrip komt met de jaren. Jij hebt me meerdere malen vele spiegels voorgehouden. De laatste jaren ben ik gaan inzien wat voor een mooi mens je bent. Ik heb veel respect voor je gekregen en ik ben blij dat ik je ken. Wat hadden we een mooi project…..called Janssen…..Heel veel liefs.

## PHD PORTFOLIO

| **Research School: COEUR**<br>**PhD period: 2000-2008** | | |
|---|---|---|
| **1 PhD training** | **Year** | **Workload (ECTS)** |
| **- General academic skills** | | |
| Labaratory animal science | 2007 | 1.5 |
| **- Reasearch skills** | | |
| Statistics | 2005 | 0.3 |
| **- In-depth courses** | | |
| Pathophysiology of ischemic heart disease (Coeur Ph.D.) | 2003 | 1.5 |
| Cardiovascular imaging and diagnostics (Coeur Ph.D.) | 2004 | 1.5 |
| European School for Cardio-Thoracic Surgery Bergamo (cardiac level two course) | 2005 | 1.8 |
| Annual courses for trainees in Cardio-Thoracic Surgery of the Dutch association for Thoracic Surgery | 2002-2007 | 3.6 |
| Introductory course, “Mitral valve repair”, Barcelona, Spain, May 9-11 | 2005 | 0.9 |
| Course “Valve surgery and AF treatment in the 21th century”. Leiden, The Netherlands, November 24-25 | 2005 | 0.6 |
| Course “Minimal invasive thoracoscopy”, Elancourt, Paris, France, May 29-30 | 2006 | 0.6 |

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|---|---|---|
| **- Presentations** | | |
| *Ultrasonographic and 64-MSCT analysis of single LIMA versus arterial T-grafts 12 years after surgery | | |
| 18th WSCTS World Congress, Kos, Greece | 2008 | 0.6 |
| Dutch Society for Thoracic Surgery, Nieuwegein, The Netherlands | 2008 | 0.6 |
| *Preserved hyperaemic response in (distal) string sign left internal mammary artery grafts | | |
| The joint 20th annual meeting of the European Association for Cardio-Thoracic Surgery and the 14th Annual Meeting of the European Society of Thoracic Surgeons, Stockholm, Sweden | 2006 | 0.6 |
| *Preserved hyperaemic response in supraclavicular ultrasonography demonstrates function on demand of the LIMA to LAD string sign graft after CABG | | |
| 11th WSCTS World Congress, Sao Paulo, Brasil | 2001 | 0.6 |
| Dutch Society for Thoracic Surgery, Nieuwegein, The Netherlands | 2005 | 0.6 |
| *Can late supraclavicular echo Doppler reliably predict angiograhical string sign of LIMA to LAD area grafts? | | |
| 50th International Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary | 2001 | 0.6 |

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| *Postoperative changes of duplex ultrasound velocity characteristics in the nonmobilized right internal mammary artery in patients with left internal mammary artery bypass grafting<br>25th World Congress of the International Society for Cardiovascular Surgery, Cancun, Mexico | 2001 | 0.6 |
| *Differences in LIMA Doppler characteristics for different LAD perfusion areas<br>14th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Frankfurt, Germany | 2000 | 0.6 |
| *Different behavior of sequential versus single left internal mammary artery to left anterior descending area grafts<br>49th International Congress of the European Society for Cardiovascular Surgery, Dresden, Germany | 2000 | 0.6 |
| **- International conferences**<br>49th International Congress of the European Society for Cardiovascular Surgery, Dresden, Germany, June 24-27 | 2000 | 0.9 |
| 14th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Frankfurt, Germany, October 7-11 | 2000 | 1.2 |
| 25th World Congress of the International Society for Cardiovascular Surgery, Cancun, Mexico, September 9-13 | 2001 | 1.2 |

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|---|---|---|
| 50th International Congress of the European Society for Cardiovascular Surgery, Budapest, Hungary, June 20-23 | 2001 | 0.9 |
| 11th World Congress of the World Society of Cardio-Thoracic Surgeons, Sao Paulo, Brazil, August 12-15 | 2001 | 0.9 |
| 4th EACTS-ESTS Joint Meeting, Barcelona, Spain, September 25-28 | 2005 | 0.9 |
| 20th Annual Meeting of the European Association for Cardio-Thoracic Surgery and the 14 Annual Meeting of the European Society of Thoracic Surgeons, Stockholm, Sweden, September 10-13 | 2006 | 0.9 |
| 18th World Congress of the World Society of Cardio-Thoracic Surgeons, Kos, Greece, April 30-May 3 | 2008 | 0.9 |
| 22nd Annual Meeting of the European Association for Cardio-Thoracic Surgery, Lisbon, Portugal, September 13-17 | 2008 | 1.2 |
| **- Seminars and workshops** | | |
| Stentless versus homograft workshop LUMC, Leiden | 2004 | 0.3 |
| Course "Video assisted thoracoscopy", Elancourt, Paris, France, January 19-21 | 2005 | 0.9 |
| International Scientific Meeting of Cardiothoracic Surgeons, Zurs am Arlberg, Austria, March 4-10 | 2007 | 1.8 |

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|---|---|---|
| International Scientific Meeting "Aortic valve repair", Haga Hospital Leyenburg, The Hague, The Netherlands, October 19 | 2007 | 0.3 |
| 10th Thoracic course of the Hoytema foundation, Enschede, The Netherlands, December 14 | 2007 | 0.3 |
| 6th Annual Meeting of the Dutch Society for Endoscopic Surgery, Rotterdam, The Netherlands, March 27-28 | 2008 | 0.6 |
| Annual OLV-College on "Advanced valve interventions", Aalst, Belgium, June 16-18 | 2008 | 0.9 |
| 13th Advanced Course "Master of valve repair", London, England, October 13-15 | 2008 | 0.9 |
| | | |
| **- Didactic skills** | | |
| Flow measurements in coronary bypass surgery | 2005-2007 | 1.5 |
| Video microscopy of alveoli in vivo | 2006-2008 | 1.5 |
| | | |
| **- Others** | | |
| Meetings of the Dutch Association for Thoracic Surgery | 2003-2008 | 3.6 |
| Organisation of the 6th Annual Meeting of the Dutch Society for Endoscopic Surgery, De Doelen, Rotterdam, The Netherlands, March 27-28 | 2008 | 1.5 |

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| **2 Teaching activities** | | |
| **- Lecturing** | | |
| Teaching activities nursing staff intensive care, high care, medium care and coronary care unit. Teaching pathogenesis, pathophysiology, indications and surgical treatment of diseases of the chest | 2003-present | 9 |
| Teacher "Opleidingsinstituut Erasmus MC" Nursing school | 2003-present | 9 |
| "CarVasz" Congress, Ede-Wageningen, The Netherlands, November 18 | 2005 | 1.2 |
| **- Supervising practicals** | | |
| Teacher "Dissecting room" medical students | 2003-2004 | 1.2 |
| **- Others** | | |
| Reviewer "European Journal of Cardio-Thoracic Surgery" | 2006-present | 1.5 |
| Reviewer "Vascular Medicine" | 2008-present | 0.6 |
| Reviewer "Echocardiography" | 2008-present | 0.3 |