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Intraoperative Ultrasound Assessment in Coronary Artery Bypass Surgery

- with special reference to coronary anastomoses and the ascending aorta

Doctoral Thesis

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Intraoperativ ultralyd som kvalitetskontroll ved åpen hjertekirurgi

Bakgrunn

Avhandlingen **"Intraoperative ultrasound assessment in coronary artery bypass surgery – with special reference to coronary anastomoses and the ascending aorta"** er en evaluering av ultralyd som kvalitetskontroll ved undersøkelse av bypass-årer til hjertets kransarterier, spesielt LIMA-LAD, samt aterosklerose i hovedpulsåren ved åpen hjertekirurgi. Doktoravhandlingen er basert på fem arbeider som alle er publisert i anerkjente internasjonale tidssskrifter. Arbeidet er en blanding av kliniske studier på pasienter og dyreeksperimentelle studier..

Resultater

I det første eksperimentelle arbeidet demonstreres at dimensjonene i den opererte åreforbindelsen på hjertet varierer lite gjennom hjertesyklus. Dette funnet styrker betydningen av ultralyd som en enkel kvalitetskontroll ved koronar bypass-kirurgi.

I et klinisk arbeid ble ulike deler av åreforbindelsen på hjertet (LIMA-LAD anastomosen) sammenlignet med bruk av ultralyd. Undersøkelsen viste at avløpet i en åreforbindelse kunne kvalitetssikres med ultralyd, og at operasjon på et stillestående hjerte ved hjelp av hjerte-lungemaskin ga et noe bedre resultat enn ved operasjon på et bankende hjerte.

I det tredje arbeidet ble en ny to-dimensjonal ultralyd modalitet, såkalt "blood-flow imaging (BFI)", sammenlignet med konvensjonell farge Doppler ultralyd i en dyreeksperimentell undersøkelse av bypass-kirurgi. BFI ga vesentlig bedre fremstilling av både retning og hastighet av blodstrømmen i bypass-årer på hjertets overflate.

I den fjerde studien ble første del av aorta undersøkt med både transøsofageal ekkokardiografi og ultralyd-undersøkelse direkte på aorta (epiaortal ultralyd). Ultralyd av aorta direkte i operasjonsfeltet var best for å påvise og gradere aterosklerose i aorta ascendens. Dette kan derved tenkes å redusere faren ved åpen hjertekirurgi hos pasienter som har atherosklerose i den første del av hovedpulsåren.

Det siste arbeidet er en pasient-kasuistikk som viser nytten av intraoperartiv kontroll av resultatet etter bypass-kirurgi. Ved kombinert bruk av ultralyd og blodstrømsmåling ble det avslørt at blodstrømmen gikk feil vei i bypass-åren, noe som medførte umiddelbar kirurgisk korreksjon med godt resultat for pasienten.

Gjennom eksperimentelle og kliniske undersøkelser bidrar avhandlingen til å demonstrere at intraoperativ ultralyd-undersøkelse er et enkelt og nyttig redskap ved åpen hjertekirurgi.

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Biveiledere:	*Professor Hans Torp, NTNU og*
	Overlege Idar Kirkeby-Garstad, NTNU og St Olavs Hospital

Overnevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i medisin.

Disputasen finner sted i Auditoriet, Medisinsk Teknisk Forskningssenter, NTNU, fredag 26. november 2010 kl. 12.15.

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LIST OF PAPERS

This thesis is based on the following original papers, which will be referred to by their Roman numerals:

I. Ibrahim KS, Lovstakken L, Kirkeby-Garstad I, Torp H, Vik-Mo H, Haaverstad R. Effect of the cardiac cycle on the coronary anastomosis assessed by ultrasound. Asian Cardiovasc Thorac Ann 2007;15:86-90.

II. Ibrahim KS, Vitale N, Kirkeby-Garstad I, Samstad S, Haaverstad R. Narrowing effect of off-pump CABG on the LIMA-LAD anastomosis: Epicardial ultrasound assessment. Scand Cardiovasc J 2008;42:105-109.

III. Løvstakken L, Ibrahim KS, Vitale N, Torsvik Henriksen S, Kirkeby-Garstad I, Torp H, Haaverstad R. Blood Flow Imaging – A new 2-D ultrasound modality for enhanced intraoperative visualization of blood flow patterns in coronary anastomoses. J Am Soc Echocardiogr. 2008;21:969-975.

IV. Ibrahim KS. Vitale N, Tromsdal A, Kirkeby-Garstad I, Fraser AG, Haaverstad R. Enhanced intraoperative grading of ascending aorta atheroma by epiaortic ultrasound vs echocardiography. Int J Cardiol 2008;128:218-223.

V. Ibrahim KS, Vitale N, Kirkeby-Garstad I, Haaverstad R. Quick intra-operative diagnosis of coronary subclavian steal syndrome after CABG by transit-time flowmetry and epicardial ultrasound imaging. Int J Angiol 2006;15:110-112.

ABBREVIATIONS

CABG	Coronary artery bypass grafting
OPCAB	Off-pump coronary artery bypass
BFI	Blood flow imaging
CDI	Colour Doppler imaging
CSSS	Coronary subclavian steal syndrome
EAU	Epiaortic ultrasound
TEE	Transesophageal echocardiography
VAS	Visual analogue scale

INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is the most common cardiovascular operation carried out in the world. About 350 000 and 3000 patients undergo CABG every year in the United States and Norway, respectively. Coronary artery by-pass surgery is indicated in selected groups of patients with significant stenosis and occlusion of the coronary arteries due to atherosclerotic disease. Through bypass surgery sufficient blood supply is delivered to the ischemic myocardium.

Coronary artery bypass surgery

Coronary surgery is usually performed on an arrested heart using cardio-pulmonary bypass (CPB) with the heart-lung machine, ie. on-pump coronary artery bypass grafting (CABG). The bloodless and motionless surgical field enables the surgeon to perform distal anastomoses with minimal risk of technical errors **(1).** The surgical result is of utmost importance since the success rate of coronary artery bypass grafting is determined by the long-term patency of the grafts. This depends mostly upon the quality of the distal anastomoses, particularly that between the left internal mammary artery (LIMA) and the left anterior descending artery (LAD) **(2).**

Unfortunately there are drawbacks related to the use of CPB, particularly the systemic inflammatory response and the risk of brain damage by aortic atherosclerotic debris and air embolism **(3).** Major surgery triggers an inflammatory response. With the use of CPB, inflammation is increased by the contact between the patient's own blood and foreign material within the tubes and membranes of the CPB circuit. The inflammatory response develops very rapidly through the activation of the bradykinin and kallikrain systems, along with a disarrangement of the coagulation cascade **(4).**

Embolism of atherosclerotic debris is mainly caused by surgical manipulation of the ascending aorta during cannulation, cross-clamping and whilst performing the proximal anastomoses. Air embolism is mainly caused by incorrect manoeuvres of cannulation and insufficient deairing. Embolism is most harmful when it causes occlusion of cerebral vessels. The consequences of embolism range from neurocognitive disorder to stroke **(5-7).**

Coronary surgery on the beating heart, ie. off-pump CABG, is an alternative method, with the aim to reduce the risk of complications by avoiding aortic cannulation, cross-clamping and CPB **(8).** In beating heart surgery the exposure of coronary vessels is obtained by application of stabilizers, directly on to the targeted native coronary artery or as an apical traction device to achieve a combination of hemodynamic stability and better exposure of the surface of the heart.

Despite some possible advantages of off-pump vs. on-pump CABG, there is still an open debate regarding the quality of distal anastomoses with conflicting results on graft patency rates **(8, 9).**

Quality control in coronary surgery

Coronary artery bypass surgery has a two-fold purpose:

a) Reduces symptoms and improves patients` quality of life

b) Increases life expectancy.

In order to achieve these goals, it is necessary to apply a strategy tailored for each individual patient, to guarantee the best long-term patency of coronary artery bypass grafts. This strategy involves sound medical decision-making, a good surgical technique and a fine quality assessment. Further, each of these measures is applied at two different stages: *preoperatively and intraoperatively.*

Pre-operatively, the surgeon decides whether the patient is suitable for on-pump or off-pump myocardial revascularization. The decision is based on several criteria such as the severity of coronary disease and its anatomy, left ventricular function, comorbidity and risk factors.

Intra-operatively, an initial evaluation is carried out to assess the likely presence of atherosclerotic plaques on the ascending aorta, its location and degree. This assessment will bring the surgeon into further operative planning, like the choice between on- and off-pump CABG, and whether to perform total arterial revascularisation to avoid manipulation of an atherosclerotic aorta. After the coronary bypass grafting is completed and prior to chest closure, graft flow and the quality of distal anastomoses should be assessed to avoid any technical failure. Off-pump surgery is potentially associated with a higher rate of technical errors than conventional CABG, because distal anastomoses are carried out towards a moving target on the beating heart. Early detection of a failed anastomosis enables the surgeon to perform a prompt revision of the graft, and may thereby effectively reduce the risk of postoperative mortality and morbidity **(10).**

Background studies

This thesis is a continuation of previous studies initiated at our institution in 1998. Briefly, the objectives and conclusions of these background studies are summarised below:

- In the first study epicardial ultrasound scanning with a new mini transducer was applied intra-operatively to evaluate coronary artery stenoses and the quality of distal graft anastomoses in on-pump CABG, with special emphasis to the left anterior descending artery (LAD). Epicardial colour Doppler ultrasound scanning with the new equipment was simple, fast, safe and allowed satisfactory imaging of coronary stenoses and graft anastomoses. Factors limiting the imaging quality were proximal lesions, intramyocardial vessels, vessel tortuosity, and extensive calcifications **(11).**

- The second study was performed to evaluate the use of intraoperative epicardial colour Doppler ultrasound for a quality assessment of the left internal mammary artery (LIMA) to left anterior descending coronary artery (LAD) anastomoses performed in off-pump CABG. This study concluded that intra-operative colour Doppler ultrasound allowed adequate imaging and quantitative analysis of off-pump LIMA-to-LAD anastomoses. One anastomosis was promptly revised due to a technical error detected by epicardial colour Doppler imaging **(10).**

- The third study evaluated the correlation between intra-operative colour Doppler ultrasound assessment of off-pump LIMA-to-LAD grafts and the assessment by angiography at a mean of 8 months follow-up. The study conclusions were that anastomotic dimensions and patency of intra-operative colour Doppler ultrasound correlated significantly with those of selective coronary angiography at 8 months follow up **(12).**

The encouraging results of these studies stimulated our group to carry out further research for the improvement of results in coronary artery bypass surgery. In detail our attention was focused into a better intra-operative quality assessment of coronary artery by-pass grafts and the ascending aorta by ultrasound.

OBJECTIVES OF THE INVESTIGATION

Off-pump myocardial revascularization may reduce some of the risks and complications observed after on-pump coronary surgery. However, it is technically more demanding and holds a higher incidence of technical failure of the anastomoses. Further, in the immediate postoperative period the patients undergoing off-pump CABG have less platelet dysfunction and are assumed to have increased coagulation tendency compared to patients operated on-pump. This may reduce the patency of the anastomoses.

1. A porcine model of coronary bypass surgery was run to test whether the cardiac cycle had an impact on the dimension of distal anastomoses in coronary surgery. The dimensions of the anastomosis of the internal mammary artery (LIMA) to the left anterior descending artery (LAD) were measured by means of B-mode and colour Doppler ultrasound. **(Paper I)**

2. During a CABG operation the surgeon takes great care suturing the toe of the distal coronary anastomosis, because this is generally recognized as the most important part. A technical failure of this area will impair greatly forward blood flow causing a poor run-off. On the other hand less attention is given to the heel of the anastomosis. However, this area may be equally important, especially if there are major diagonal and septal branches located within the ischemic myocardium proximal to the anastomosis. Thus, we aimed to compare the dimensions of the toe and heel portion of the LIMA-LAD anastomosis and their relations during on- and off-pump CABG, by means of epicardial ultrasound. **(Paper II)**

3. A novel 2-D ultrasound imaging modality named blood flow imaging (BFI) ameliorates colour Doppler imaging (CDI) by providing precise information on flow direction and velocity because it is not limited by angle-dependency or aliasing artefacts. Thus, our objective was to test the application of BFI versus CDI for visual assessment of blood flow patterns in the LIMA-LAD anastomosis in a porcine model. **(Paper III)**

4. There are some serious post-operative complications in coronary surgery among which cerebral ischemia causing neurological complications, ranging from neurocognitive disorders to stroke, is the most frequent. Cerebral ischemia is believed to occur mostly due to intraoperative embolisation of atheromatous plaques from the ascending aorta. Pre- or intra-operative diagnosis of the atheromatous aorta may guide the surgeon to use techniques reducing the risk of cerebral complications. In a group of patients operated upon of on-pump CABG, the atheromatous plaques in the ascending aorta were detected and their extension graded by means of epiaortic ultrasound and transesophageal echocardiography. The two modalities were compared to ascertain which one of the two was more reliable for routine intra-operative application. **(Paper IV)**

5. Coronary subclavian steal syndrome (CSSS) is the phenomenon of retrograde flow (steal) through the pedicled LIMA which may occur after CABG due to concurrent proximal stenosis or occlusion of the ipsilateral subclavian artery. In a clinical report we present the case of CSSS with a pedicled LIMA, which was diagnosed and successfully treated during the primary operation by means of combined transit-time flowmetry and epicardial colour Doppler imaging. **(Paper V)**

Methodological consideration

Surgical procedure

a. Off-pump CABG (Paper I, II, III, V)

Coronary bypass surgery on beating heart was performed fairly similarly in the clinical setting and in the porcine model. As the patients were operated upon by different surgeons over a long period of time, the surgical techniques and equipment applied varied over the years.

All patients were operated under general anaesthesia. In the first seven patients access to the heart was through a small left anterolateral thoracotomy in the fourth or fifth intercostal space. Since 1998 median sternotomy was used in all cases. Since 1999 Full heparinization (3 mg/kg) with activated clotting time (ACT) > 410 sec was given in most patients and in all animals. The left internal mammary artery (LIMA) was harvested with its pedicle. The left anterior descending artery (LAD) was identified and snared with 4-0 pledgeted polypropylene suture proximal to the coronary arteriotomy. An epicardial stabilizer was applied to immobilize the coronary artery chosen for grafting. As an aid in exposing the left side of the heart, a deep pericardial stitch and/or a vacuum stabilizer was applied to fascilitate this manoeuvre. An intracoronary shunt was also placed into the vessel lumen whenever needed. The coronary anastomosis was usually performed with a continuous 7-0 polypropylene suture. Following bypass grafting, the heart was repositioned into the pericardial cradle. Heparin was partially reversed with protamin following beating heart surgery.

Postoperatively all patients were given acetyl salicylic acid (ASA) as life-long medication.

b. On-pump CABG (Paper I, II, IV)

Approach to the heart and LIMA harvesting was through a median sternotomy. All subjects had full heparinization (3 mg/kg) to achieve ACT > 410 sec. Cardiopulmonary bypass was instituted by cannulation of the ascending aorta and the right atrium. After aortic cross-clamping a crystalloid cardioplegia solution was infused into the aortic root and CPB was run at 34 ^{0}C systemic cooling. The coronary anastomoses were performed as in off-pump CABG.

Antithrombotic regimens in off-pump patients (Paper II, V)

Throughout the years 1997-1998 all off-pump patients received 100 U/kg unfractionated heparin i.v. intraoperatively to reach ACT > 270 sec without reversal with protamine sulphate at the end of the operation. Since 1999 the patients were fully heparinised and the heparin was reversed to 1/3 of its activity with protamine sulphate after completion of the procedure.

The antithrombotic regimen before year 2000 was as follows: Acetyl salicylic acid (ASA) 75-160 mg was prescribed up to the day of surgery, postoperatively 500 ml of dextran were infused within 8 hours after surgery, ASA was continued at the preoperative dose and in addition low molecular weight heparin (LMWH) (enoksaparin 40 mg once daily) was administered. Since year 2000 all off-pump patients received a daily dose of clodipogrel 75 mg from postoperative day 1 for four weeks was added to the ASA, dextran and LMWH regimen. No loading dose of clopidogrel was administered.

Animal research model (Paper I, III)

Norwegian landrace pigs weighting 60-85 kg underwent coronary bypass grafting of the LIMA-LAD under general anaesthesia and through median sternotomy, either with or without use of the heart-lung machine. The pigs were artificially ventilated through a tracheotomy tube.

The pigs were premedicated with intramuscular azaperone 6 $mg \cdot kg^{-1}$ and diazepam 0.15 $mg \cdot kg^{-1}$. Anaesthesia was induced with intravenous atropine 0.15 $mg \cdot kg^{-1}$, ketamine 7 $mg \cdot kg^{-1}$ and thiopentone 3 $mg \cdot kg^{-1}$. Maintenance infusions were of fentanyl 63 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and midazolam 0.6 $mg \cdot kg^{-1} \cdot min^{-1}$ combined with isoflurane 1% in a 1:2 mixture of oxygen and air.

All animals were treated in accordance with the Norwegian Animal Research Authority. The animals were acclimatized at the facility for a minimum of three days before the experiments and were sacrificed with an i.v. injection of potassium chloride at the end of the procedure.

Transit-time flowmetry (Paper I-V)

All the transit-time flow measurements (Medi-Stim Butterfly Flowmeter, Medi-Stim ASA, Oslo, Norway) of the coronary bypass grafts were performed intra-operatively. Following on-pump CABG the measurements were done after weaning from the extracorporeal circulation. The flow probe (3 or 4 mm) was placed close to the distal anastomosis. Unfortunately there are no well defined evidence-based cut-off values for an adequate flow, but three parameters are taken into consideration for a thorough assessment: 1) mean blood flow, 2) the pulsatility index, 3) the diastolic flow pattern. **(8).**

The potential shortcoming of transit-time flowmetry lies in the fact that the flow depends on several physiologic variables, including blood pressure, peripheral vascular resistance and competitive flow from native vessels. Therefore, standard curves and flow values for different types of grafts and target vessels are not available. Standardization of flowmetry is difficult because of the large variability among different patients, as well as within the same patient. Thus, interpretation of flow findings is largely dependent on the surgeon's personal experience **(13, 14).**

Intraoperative ultrasound methods

a. Epicardial ultrasound (Paper I, II, III, V)

After completion of the LIMA-LAD anastomosis and with the stabilizer still in place, epicardial ultrasound imaging of the anastomosis was done with a GE Vingmed Vivid 7 ultrasound scanner and a GE i13L probe, in accordance to one of our previous reports **(11).** This probe is a linear array mini-transducer designed for intraoperative imaging with frequencies operating at 10-14 MHz. The ultrasound imaging system was optimized for high resolution colour flow imaging applications. With the use of gel as the conduction medium, the transducer was applied directly and gently on the anastomosis between the paddles of the stabilizer (Fig. 1).

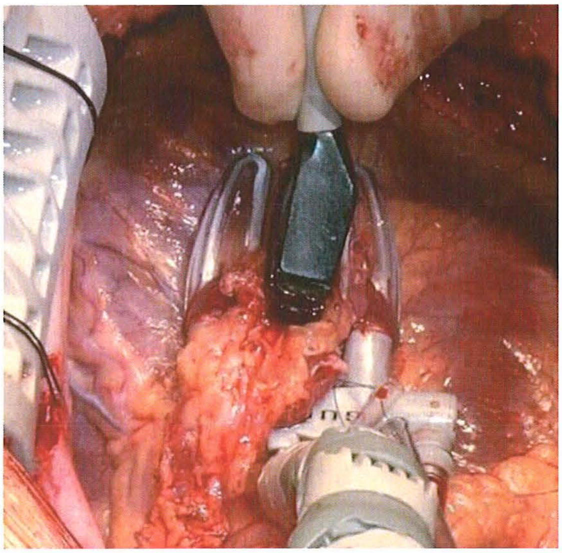


Fig. 1.

Epicardial ultrasound imaging with a handheld mini-transducer applied upon the LIMA-LAD anastomosis during beating heart surgery.

Real time ultrasound images showing the complete anastomosis as well as the distal run-off were stored as digital data for later analysis. The morphology of the anastomosis was assessed by measuring its dimensions, such as the length of the anastomosis proper (DA), the LAD diameter at the toe (D1) and heel (D3) of the anastomosis, as well as 5-10 mm distal to the toe (D2) (Fig 2).

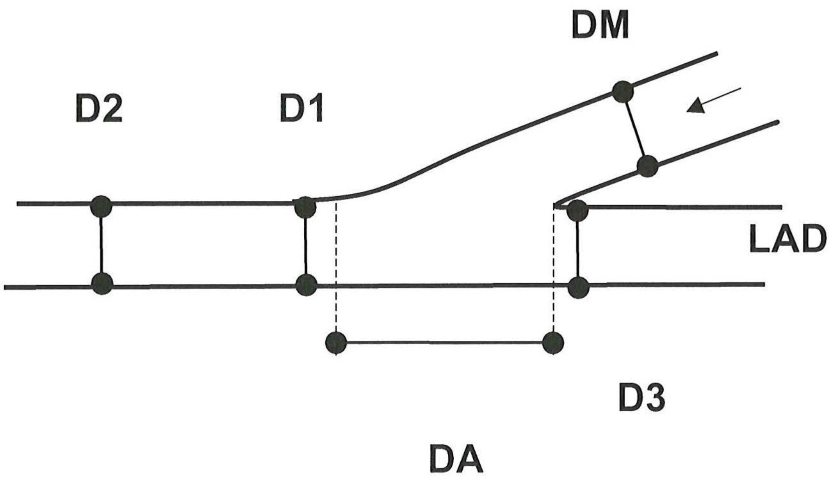


Fig. 2. Sketch of an anastomosis between the left internal mammary artery graft (LIMA) and the left anterior descending artery (LAD).

b. Blood Flow Imaging versus Colour Doppler Imaging (Paper III)

Blood Flow Imaging (BFI) is a real-time, ultrasound flow imaging modality able to visualize the blood flow in any direction of the image, not limited by velocity aliasing or the angle of the ultrasound beam, and therefore overcomes the fundamental colour Doppler imaging (CDI) limitations; i.e. angle-dependency and aliasing **(15).** This is achieved through the preservation and visualization of the speckle pattern originating from the blood signal echoes and is further explained in paper III.

The speckle pattern is present inside the vessel lumen, but is normally not visible due to weak echoes from blood. The movement of this blood speckle pattern is correlated to the blood flow scatter movement, and is captured by imaging with a very high frame rate, more than 2000 1000 Hz in our recordings. Using slow motion display of subsequent speckle images, the movement of speckle pattern can be tracked by the human eye.

The data acquisition with BFI is the same as for CDI. The two techniques have therefore been combined by modulating the parametric colour information in CDI with the speckle pattern. The combined modality includes both quantitative Doppler measurements as well as angle and velocity aliasing independent speckle movement. Thus, BFI provides a more intuitive display of the flow conditions requiring less interpretation than CDI images.

c. Transesophageal echocardiography (Paper IV)

After induction of general anaesthesia, transesophageal echocardiography (TEE) was carried out by a 5 MHz biplane TEE transducer (GE Vingmed, Horten, Norway) connected to a GE Vingmed System FiVe or GE Vivid 7 (GE Vingmed, Horten, Norway). Images of the thoracic aorta were obtained in both transverse and longitudinal view planes by a cardiologist familiar with aortic transesophageal echo.

d. Epiaortic ultrasound (EAU) (Paper IV)

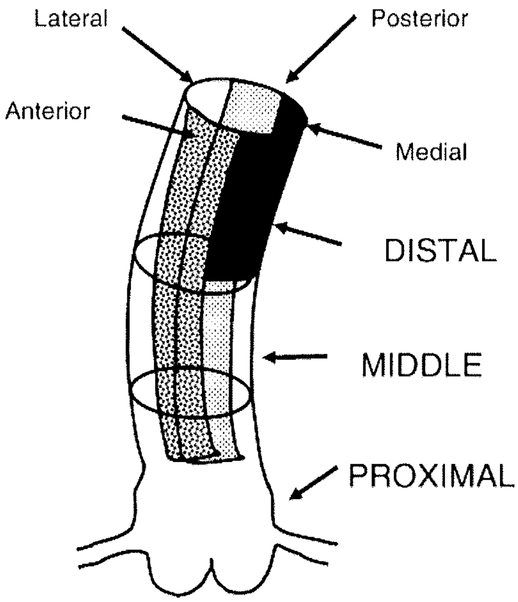
After median sternotomy and harvesting of the left internal mammary artery (LIMA), the ascending aorta from the aortic root to the origin of the brachiocephalic artery was scanned directly by the surgeon using a GE Vingmed i8.5L probe connected to a GE Vingmed Vivid 7 ultrasound scanner. The probe is a linear array transducer designed for intraoperative imaging with frequencies of 8.5 MHz. A finger glove filled with sterile saline solution was used as ultrasound medium between the aortic wall and the probe.

Images from longitudinal and transverse view planes were obtained and recorded together with TEE images for subsequent off-line evaluation. For the purpose of further analysis, the ascending aorta was divided into three sections:

- the proximal section was from the aortic annulus across the sinotubular junction and distally into the tubular portion just below the tract of the aorta overlapping the right pulmonary artery
- the middle section was considered as the tubular segment of the ascending aorta overlapping the right pulmonary artery
- the distal tubular section was defined from the upper limit of the middle section to the origin of the brachiocephalic artery

The whole circumference of the aorta was divided into four segments: anterior, posterior, medial and lateral. Thus the ultrasound scanning of each ascending aorta comprised 12 areas (3 sections × 4 segments) as illustrated in fig. 3.

Fig. 3.
Sketch of the ascending aorta divided into 12 segments for the purpose of analysing atheromatous degeneration of the aortic wall by means of epiaortic ultrasound



The degree of atherosclerosis was graded according to the morphology of atheromatous plaques by a modified Montgomery scale for aortic lesions as presented in table 1 **(16).**

Table 1. Modified Montgomery scale for aortic lesions:

Grade 1 = normal
Grade 2 = intimal thickening
Grade 3 = atheroma < 4 mm
Grade 4 = atheroma $\geq$ 4 mm (Fig 4)
Grade 5 = any mobile (a) or ulcerated atheroma (b).

Intimal thickening was considered as a smooth non-protruding lesion of the intimal lining the entire lumen of the aorta. Atheroma was a localized lesion protruding into the lumen. The images were reviewed by a cardiac surgeon and a cardiologist; the consensus within the two was reached by giving the highest grade for each area detected. An example of grade 4 severe atherosclerosis of the ascending aorta as assessed by EAU is shown in fig. 4.

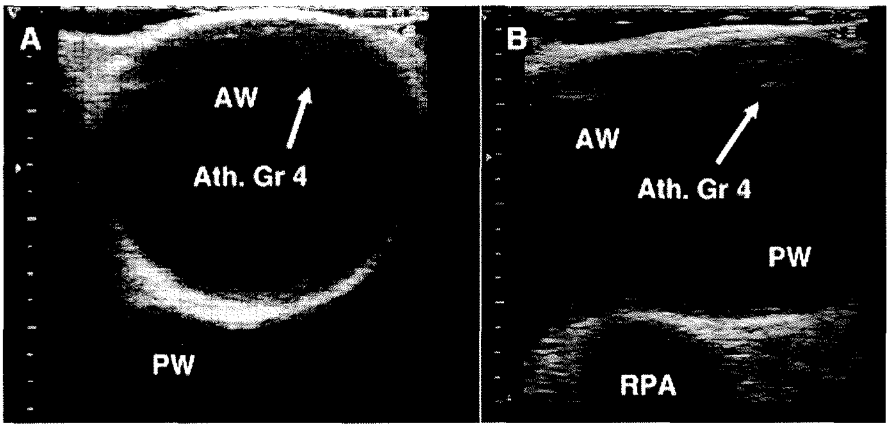


Fig. 4. A grade 4 atherosclerotic plaque in the aorta is seen both in the transverse (B) and the longitudinal (B) view as assessed by EAU. AW=anterior wall; PW=posterior wall; RPA=right pulmonary artery.

Intraoperatively the surgeon adjusted his surgical technique (e.g. site of insertion of the aortic cannula, cross-clamp and placement of vein grafts) if information gathered from the ultrasound investigations indicated atheromatous aortic areas.

Statistics

General considerations

Skewness test was used to assess the distribution of data. Data normally distributed are described as the arithmetic mean ± standard deviation (SD) as a measure of variability. Skewed data were presented as median with range. A P value < 0.05 was considered statistically significant. Most of the statistical analysis was carried out using the SPSS software (SPSS Inc, Chicago, Illinois).

Special considerations

Paper I

Analysis of variance (ANOVA) for repeated measurements was used to assess the impact of the ultrasound modality (B-mode or colour flow image), the cardiac cycle (end-systole or end-diastole) and the sites of measurement (D1, D2, D3 or DA) on the morphology of the anastomosis and the LAD. For variables significantly influencing the measured dimensions, we applied the paired t-test with Bonferroni correction according to the number of comparisons done, as post-hoc analyses for identification of the difference between values.

Paper II

Paired-samples t-test was used to compare the dimensions and ratios within the same group while independent-samples t-test was applied to compare dimensions and ratios between the two groups.

Paper III

Differences between the two modalities, BFI and CDI, were evaluated based on assessments of blood flow direction, aliasing and pulsatility. Statistical analysis was performed using the two-sided Wilcoxon signed rank test of paired measurements, with exact calculation of probabilities. Interobserver variability was calculated with the help of the interclass correlation coefficient. The statistical analysis was performed with SPSS software and dot-plots were made using the Matlab numerical software (The MathWorks, Natick, MA).

Paper IV

The results were presented as mean Montgomery grade ± SD for each area and method separately. The statistical significance of the observed difference in visualization between TEE and EAU for each single area was calculated from the McNemar`s test for paired samples. The areas with comparable visualization were further studied to assess statistically the difference in detection and grading of atherosclerosis between the two methods. The identification of a normal or an atherosclerotic intima (Montgomery ≥ 2 score) was compared using McNemar`s test, and the difference in Montgomery grading between TEE and EAU was analyzed by Wilcoxon's matched pairs signed rank sum test.

Summary of results

Paper I

In this study, we evaluated the effect of the cardiac cycle on the dimensions of the LIMA-LAD anastomosis as measured by EAU with the use of two ultrasound modes, two-dimensional ultrasound imaging (B-mode) and colour Doppler mode. There was no significant effect of the cardiac cycle on the LAD diameters at the toe (D1), heel (D3), anastomosis proper (DA) and downstream the native LAD (D2), neither by B-mode nor colour Doppler imaging.

The B-mode imaging modality yielded larger diameters than the colour Doppler flow modality regardless of the phase of the cardiac cycle. However, the diameter of the LAD at the toe (D1) was found similar by both ultrasound modes.

On clinical grounds, provided the scanning is directed perpendicular to the vessel, this study showed that the surgeon may assess the morphology of an anastomosis without paying much attention to the phase of the cardiac cycle or the mode of ultrasound applied. B-mode imaging complies fully with the peristaltic movement of the artery, whereas colour filling more easily enters the vessel boundaries.

B-mode images yielded more precise measurements because they provided a more detailed view of the anastomosis, enabling the surgeon to assess the intimal echo-pattern very clearly. The colour Doppler, however, evaluated graft patency with very useful information on the pattern and direction of blood flow within the anastomosis.

Paper II

The dimensions of LIMA-LAD anastomoses performed off-pump in 38 patients were compared to similar dimensions from 12 on-pump patients. The length of the anastomosis (DA), LAD diameters at the toe (D1) and heel (D3) of the anastomosis, as well as the reference downstream LAD (D2) were measured in diastole by two-dimensional ultrasound imaging (B-mode). As coronary artery dimensions differ between patients, we compared the ratios of the anastomotic dimensions to native vessel size between the two patient groups .

In off-pump patients, the dimension of the heel (D3) was smaller than the toe (D1) ($p=0.004$). Both D3 and D1 were smaller than the run-off LAD (D2) ($p<0.01$). In off-pump patients the D3/D2 ratio was smaller than D1/D2 ($p=0.009$), whereas these ratios were similar in on-pump patients. Although the D3/D2 ratio was smaller in off- than in on-pump patients ($p=0.01$), D1/D2 was similar in the two groups.

This study indicated that off-pump CABG may cause a narrowing of the coronaries, especially at the anastomotic heel. Further, as the heel position may have less priority compared to the toe of an anastomosis, we suggest that the anastomotic technique should be modified to improve its patency.

Paper III

Intraoperative ultrasound recordings of patent LIMA-LAD anastomoses were acquired from a porcine model (N=9). Three independent observers randomly evaluated colour Doppler imaging (CDI) and blood flow imaging (BFI) cine-loops with regards to different assessments of flow direction and velocity. Further, a selection of technical problems that might occur in clinical practice was induced in three pigs to investigate the resulting flow patterns. In all cases, reliable ultrasound B-mode and Doppler images could be obtained of the LIMA-LAD anastomosis.

By B-mode ultrasound the D_1/D_2 ratio in the initial nine anastomoses was 0.89 ± 0.17, indicating patent anastomoses and without any significant narrowing at the toe. The D_1/D_2 ratio was 0.52, indicating a stenosis at the anastomotic toe, in an anastomosis made faulty by applying an extra deep stitch at the toe. BFI was found to provide an improved visual assessment of blood flow patterns in the LIMA-LAD anastomosis compared to CDI. The modality may therefore increase the certainty and efficiency of flow evaluation for intra-operative quality control in coronary surgery. As conventional Doppler information is also available, the BFI modality may replace CDI in the evaluation of anastomosis flow in the future.

Paper IV

A total of 60 patients scheduled for elective conventional CABG underwent both TEE and EAU of the ascending aorta. The two ultrasound techniques were compared in terms of their ability to detect and grade atheromas in the ascending aorta.

The number of areas that were sufficiently visualized for a reliable assessment were higher for EAU than TEE, 664/720 (92%) vs. 398/720 (55.3%) respectively ($p<0.01$). Overall detection rate of units with Montgomery grade ≥ 2 by EAU only vs. TEE only in the areas sufficiently visualized by both methods was 88/334 (26%) vs. 37/349 (11%), respectively.

In detail, TEE was superior in detecting atheroma only in the anterior areas of the proximal segment of aorta. Further, TEE demonstrated fewer areas in the middle and almost no atheroma in the distal ascending aorta. In comparison, EAU detected almost similar numbers of diseased areas in all locations.

The posterior segment was the area most influenced by atheromatous disease along the whole length of the ascending aorta, this feature reaching statistical significance ($p<0.01$). The anterior segment was the second most diseased portion.

Taking all the sections of the ascending aorta together, EAU was superior in tracing areas and atheromas compared to TEE. Epiaortic ultrasound could detect five times grade 4 atheromas vs. TEE. Two areas with grade 5 were detected; these were only seen by EAU.

Paper V

In one patient a coronary subclavian steal syndrome (CSSS) occurred after completion of an off-pump CABG with a pedicled LIMA to the LAD. The steal phenomenon was diagnosed intraoperatively by means of combined transit-time flowmetry and epicardial ultrasound imaging. At the immediate revision, the LIMA was successfully anastomosed as a free graft to the ascending aorta so to avoid any further occurrence of CSSS. A postoperative MRI angiogram confirmed a moderate proximal stenosis of the left subclavian artery.

This case report shows the usefulness of the combined application of transit-time flowmetry and epicardial ultrasound scanning in routine surgical practice.

General discussion

Intraoperative assessment of coronary grafts and anastomoses

With the exception of coronary artery bypass surgery, virtually all other procedures on the heart, including valve surgery and coronary stenting, are accompanied by perioperative evaluations to ensure an adequate technical result. There is currently no standardized intraoperative approach for the identification of technical errors of coronary grafts and anastomoses (i.e. angiography, ultrasound Doppler scanning, transit-time flowmetry). Moreover the application of these methods is not routine clinical practice in most centres.

Intraoperative coronary angiography

Although angiography is considered the gold standard for the evaluation of coronary circulation, grafts and anastomoses, it has limitations as routine method of intraoperative control. Angiography is invasive and requires bulky and expensive equipments and these facilities are rarely available in operating theatres **(17).** Moreover, Hol et al. demonstrated that on-table angiograms can be difficult to interpret because not all findings are important for later patency. Optimal results on-table predicts good long-term results, whereas significant lesions on-table may have less impact on the follow-up results **(18).** However, if transcatheter valve replacements become routine clinical practice in the future, hybrid catheter suites will also be widely available for combined modalities of coronary intervention

Transit-Time Flow Measurements

Transit-time flowmetry (TTFM) is the most common intraoperative method used for the assessment of the patency of grafts and anastomoses. Transit-time flowmetry is based on the simple quantitative measurement of blood flow within the graft. Advantages of TTFM are an easy, plug-and-play application without pre-calibration and its reasonable cost. However, TTFM does not provide any anatomical information and can detect a technical failure only if there is a severe stenosis in the graft or in the anastomosis. This is because it is dependent on several factors like systemic blood pressure, diameter of the target vessel, size of the distal arterial bed and residual antegrade flow in the target vessel **(8,13,14)**. Finally, interpretation of measurements of blood flow of sequential grafts may be quite difficult with this method.

Thermal coronary artery imaging

Thermal coronary artery imaging with an infrared camera was introduced by Suma and colleagues as a non-invasive method for evaluation of graft anastomoses during off-pump CABG operations **(19)**. Unfortunately this technique detects grossly stenosed anastomoses only, and cannot be applied to intramyocardial vessels or to grafts directed to target vessels at the back of the heart.

Intraoperative fluorescence imaging technique

Intraoperative fluorescence is a relatively new imaging technique. It is based on capture by a charge-coupled device video camera of fluorescence of Indocyanine Green (ICG) contrast medium, when illuminated with near-infrared light using laser energy projected from the SPY imaging system (Novadaq Technologies Inc., Toronto, Canada).

The strengths of the technique are its simplicity and safety. It is minimally invasive because it does not require an arterial puncture and avoids the need for ionizing radiation. Further, its major attraction is that it provides information in a fashion similar to coronary angiography, with which the surgeon is familiar and can easily interpret. However, there are currently limitations to the technique. First, the technique is only semi-quantitative and divides assessment of graft flow into "excellent," "satisfactory," or "poor," and does not provide an exact measure of graft flow. Developments are underway that will permit the imaging system to give quantitative flow measurements. Second, the technique only allows precise definition of anastomotic quality in around 75% of grafts. This is because depth of penetration of the laser beam is only around 1 mm, and is therefore vulnerable to varying depths of the native coronary artery (e.g., when intramyocardial). For the same reason, imaging can only occur when the chest is open and pedicled conduits are less visualized than skeletonized ones. A more powerful, pulsed laser might resolve these limitations, but should be balanced against the fact that the device intentionally uses low-power laser energy so as to avoid thermal myocardial damage **(20).**

Epicardial ultrasound

Over the last 15 years several devices for intraoperative ultrasound visualization of coronary arteries and graft anastomoses have been tested in animal experiments as well as in clinical studies. Unfortunately none of the early ultrasound devices gained wide acceptance mainly due to their many technical limitations. Previously, the main technical reason for this was the cumbersome and large size of the ultrasonic probe, which allowed only visualisation of the LAD, diagonals and the proximal right coronary artery, as well as limited imaging quality **(21-23).** Further, epicardial scanning could only be carried out when the patient was on CPB and the early-generation transducers were only able to provide black and white images.

We have previously shown that a new generation epicardial imaging of coronary arteries and anastomoses with high frequency ultrasound is simple and safe **(11).** It has several advantages over angiography; it is non-invasive and requires no injection of contrast medium. Moreover, comparing epicardial ultrasound with angiography at an eight month follow-up showed that the former has a positive prognostic value **(12).**

While transit time flowmetry is the most widely used method in the assessment of grafts, it does not give direct information about the anatomy of the anastomosis. Epicardial coronary imaging using high frequency ultrasound probes may aid the surgeon performing coronary artery bypass procedures by localizing the coronary artery segments underneath epicardial fat, identifying the site of coronary stenosis to be bypassed and assessing the quality of anastomoses **(11).** So far, the use of epicardial ultrasound has been most appreciated in off-pump CABG where technical errors are supposed to be more common. In addition, epicardial ultrasound may be of value in scanning the target coronary site for grafting in order to avoid calcified regions, stented areas or where there are septal perforators which can hinder the procedure **(11).** These perforators might not be well delineated by angiography. In the present study, colour Doppler ultrasound, as well as further developments, have been valuable in the morphologic assessment of coronary anastomoses.

Effect of the cardiac cycle on LIMA-LAD anastomotic dimensions

Small changes of coronary diameters during the cardiac cycle have been found using intravascular ultrasound (IVUS); a 10 % increase was detected in healthy vessels **(24)**, and a 2-12 % increase in atherosclerotic vessels **(25-27)**. Although most of the coronary blood flow occurs in diastole, the systolic expansion of coronary vessels can be explained by the increase of the coronary intraluminal pressure during systole **(25)**.

In our study, no significant changes in diameter of the LAD at the heel (D3), toe (D1), anastomosis proper (DA) or distally in the LAD (D2) during the cardiac cycle were detected. We believe that the different outcome was most likely due to the following two reasons: Firstly, epicardial imaging is not as sensitive as IUVS to discriminate very minor changes; a systolic increase of coronary diameter of about 10 % is equivalent to a 0.1-0.15 mm increase in diameter. Secondly, grafting of the LAD caused stiffness of the vessel wall, and this may well have reduced systolic expansion of the coronary artery, whereas IVUS measurements are usually taken on coronary vessels that have not undergone any surgical manipulation.

B-mode imaging complies fully with the peristaltic movement of the artery, whereas colour filling more easily enters the vessel boundaries. Therefore, with the current standard ultrasound technology, we believe that B-mode yields more precise dimensional measurements because it gives a more detailed view of the anastomosis, enabling the surgeon to assess the intimal echo pattern easily, fast and clearly. The colour Doppler, however, enables the surgeon to evaluate graft patency because it provides useful information on the pattern and direction of blood flow within the anastomosis.

On clinical grounds, provided the scanning is directed perpendicular to the vessel, our study on the cardiac cycle (paper I) showed that the surgeon can assess the morphology of an anastomosis without paying much attention to the phase of the cardiac cycle. This is supposed to be essential for wide acceptance of epicardial ultrasound in clinical practise.

Importance of the heel of the LIMA-LAD anastomosis as assessed by ultrasound

The importance of the heel of the LIMA-LAD anastomosis is still far from being established. Our results from study II showed that the segment of the coronary artery involved in the anastomosis within the off-pump group underwent a degree of narrowing in comparison to patients operated on-pump. Both the toe (D1) and the heel of the anastomosis (D3) had smaller diameters in relation to the native distal run-off point of the artery (D2) in patients operated off-pump vs. patients operated on-pump CABG, where this difference did not exist. Further analysis of the anastomotic dimensions in off-pump patients showed that the heel of the anastomosis (D3) was the site mostly affected by stenosis. These results are supported by a previous study using postoperative quantitative angiography at 14 ± 5 days which showed that the diameter of the heel portion of the anastomosis was significantly smaller than that of the toe portion **(28).**

The reduction in the heel diameter is most probably related to technical issues. The importance of the toe must be emphasised because it is the exit point of the anastomosis to the ischemic myocardium so the surgeon pays more attention while suturing the anastomotic toe. On the other hand, the heel that represents the ''posterior'' suture line of the anastomosis may easily be under-estimated. Further, this part is more difficult to repair if bleeding occurs. Hence, surgeons tend to place large suture bites at the heel and this might increase the rate of narrowing.

It was only in off-pump patients that the segment of the coronary artery involved in the heel of the anastomosis had undergone significant narrowing. In other words, this was related to the beating heart technique since the same results were not found in the on-pump group. However, the better experience with on-pump surgery might have played a role since the off-pump cases also include our initial experience with this method.

We do not know whether this reduction in the diameter of the heel has any significant clinical outcome. In cases of stenotic, but non-occluded coronaries, retrograde blood flow from the heel might compete with antegrade blood flow from the native coronary. However, since the retrograde flow from the heel occurs in systole whereas antegrade blood flow from the native coronary is mainly diastolic, both might synergize with each other. In cases where the stenotic coronary anastomosis progresses to complete occlusion, the patent heel could eventually be of significance.

A new ultrasound modality: Bloodflow imaging versus Colour Doppler imaging

The assessment of the LIMA-LAD anastomosis is a complex issue as it includes both flow pattern and evaluation of the dimensions of the anastomosis in relation to the distal run-off, specially the toe. The assessment of the direction of blood flow can be carried out by CDI. This method is dependent on colour interpretation, which in turn is influenced by the angle of the probe applied on to the anastomosis. In addition high blood flow-rates induce aliasing, making evaluation of flow direction less intuitive. The BFI method shows blood flow as speckle patterns that are not dependent on the angle given to the probe at the time the anastomosis is scanned and is not affected by aliasing.

In study III visualization of blood flow direction was much enhanced by BFI compared to CFI, and this holds true for all conditions of flow which we encountered in our study. This was confirmed by the three observers that gave higher rates to BFI than CDI both in assessments of blood flow directions and its competitive patterns. As the BFI gives an intuitive impression of flow pattern and direction, this ultrasound modality is suggested to play an important role in future vascular imaging,

Clinical implementation of intraoperative ultrasound imaging – a case report

The case report presented in paper V shows the usefulness of transit-time flowmetry and epicardial ultrasound scanning for a rapid intraoperative diagnosis of coronary subclavian steal syndrome. CSSS may be a reason for early occurrence of angina after CABG; caused by retrograde blood flow (steal) from the LAD through the LIMA graft in patients with a left subclavian artery stenosis. Clinical features of subclavian artery stenosis are a difference of systolic blood pressure more than 20 mmHg between the arms, thrombo-embolism or ischemic pain to the arm.

In our patient a weaker left radial pulse and a reduced blood pressure to the left arm were reported by a junior doctor. CSSS developed immediately after grafting the LIMA on to the LAD, but it was quickly diagnosed intraoperatively by flowmetry and epicardial ultrasound scanning, despite any ischemic ECG changes. The combined application of these two modalities was relevant because each of them provided information, which coupled with those given by the other one, contributed to reach the diagnosis.

As a result of a quick intraoperative diagnosis prompt surgical revision was carried out, avoiding intra- or postoperative complications to the patient. On the other hand, missing the diagnosis of CSSS at surgery would have exposed the patient to unpleasant consequences in the follow-up, such as early recurrence of angina, subclavian artery PTA, carotid-subclavian by-pass or redo CABG surgery.

Assessment of atherosclerosis in the ascending aorta and clinical implications

Traditionally, the assessment of atherosclerosis of the thoracic aorta is carried out by the surgeon by reviewing the preoperative chest X-ray and the plain cine-loop of the angiogram, whereas intraoperatively a simple visual inspection and finger tip palpation are the routine methods. Unfortunately, all these methods are inaccurate and grossly underestimate aortic atheromas. Computer tomographic scanning (CT) may provide further preoperative information on the presence, degree and location of plaques in the aorta, especially in 3D images. However, CT scan was demonstrated to be less sensitive than EAU in detecting atheromatous plaques in the ascending aorta; 45 % vs. 60 % **(29).** Magnetic Resonance Imaging (MRI) is considered to have the same degree of sensitivity as transesophageal echocardiography **(30),** but has several disadvantages that reduce its application being less available, expensive and contraindicated in patients with implanted pacemaker/electro converter and with claustrophobia.

Previous studies reported that EAU, in comparison to TEE, was able to visualize satisfactorily the ascending aorta including the middle and distal parts **(31, 32)**. In a selected series of patients undergoing cardiac surgery, EAU visualized plaques in the ascending aorta in 50 % of cases and led to a change in the procedure in 24 % of cases because of atheromas **(33).**

Our results, as presented in paper IV, confirmed previous observations as EAU provided a more enhanced visualization of the wall of the ascending aorta in its entire length, and this allowed a reliable assessment of the atheromatous plaques. Epiaortic ultrasound scanned a far higher number of areas (92.3%) of the wall of the entire ascending aorta than TEE (55.3%).

The degree of visualization by TEE varied according to sections and segments of the aorta; being highest proximally and decreasing in the distal ascending aorta, where imaging is made difficult or impossible due to the interposition of the airways between the oesophagus and the upper part of the ascending aorta. The distal part of the ascending aorta is a site of great intra-operative manipulation as the aortic CPB cannula and the cross-clamp are placed in this area. Thus, through scanning of the distal ascending aorta with precise information on the likely location, extent and degree of atheromatous plaques are necessary to avoid embolization of atheroma debris from the aortic wall.

A further step of our study was the evaluation of the grading of atheromatous lesions by a modified Montgomery score in the areas sufficiently visualized by both EAU and TEE scanning. The two techniques were compared also. Compared to TEE, epiaortic ultrasound identified a higher number of areas with a Montgomery score ≥ 2. Moreover a similar number of diseased areas were detected by EAU over the three sections and four segments of the aortic wall. The few areas which were better assessed by TEE were those in the proximal section, especially in the anterior site, and in the anterior and posterior segments of the middle section. TEE was superior in the proximal anterior areas because of the limited visualization by EAU due to the imprecise positioning of the EAU probe over the unfavourably confined anatomic location of the scanned areas.

The application of EAU demonstrated the highest prevalence and severity of atheroma to be located in posterior segments of the ascending aorta, especially in the proximal section. The second most atheromatous segment was the anterior one, especially in the distal and proximal sections. The regional pattern of development of atheroma is probably determined by local variations in shearing forces and endothelial dysfunction **(34).**

A "clean" aorta can undergo surgical manipulation like clamping, cannulation and stitching of proximal anastomoses with a very low embolic risk due to dislodged atherosclerotic debris. The clinical implications of our study are important during surgery, as a careful placement of the aortic cross-clamp is relevant to avoid dislodgement and embolisation of atheromatous debris from the posterior aortic wall. When a heavily diseased posterior segment is demonstrated, a Fogarty cushion-shod clamp may be applied carefully, although not without risk. Unfortunately, atheromatous lesions of the anterior section of the aorta are more difficult to deal with. The detection of their location enables the surgeon to avoid those particular areas or to revise the operative strategy by applying methods that reduces the likelihood of embolization of atheromas, i.e. off-pump technique, ''no touch'' strategy, single clamp technique, etc.

Conclusions

1. The B-mode and colour Doppler imaging were not significantly influenced by the effects of the cardiac cycle during assessment of the LIMA-LAD anastomosis in an experimental animal model. Thus, for a thorough evaluation of a coronary distal anastomosis both modalities should be applied in addition to transit-time flowmetry. The B-mode may provide precise measurements of the anastomotic dimensions, whilst the colour flow should be applied to assess the flow pattern. Epicardial imaging of graft anastomoses may reliable and reach wide clinical application in the future.

2. Off-pump CABG might have a stenotic effect on the coronary arteries, particularly at the heel of the anastomisis. Whether modifications to the suture technique may change the results remains to be explored in future prospective studies.

3. Blood Flow Imaging is superior to colour Doppler imaging in the assessment of blood flow patterns through the LIMA-LAD anastomosis, specially the direction of blood flow. This is due to its ability to show blood flows as speckles which can be traced by the naked eye. The BFI modality is suggested to play an important role in future cardiovascular imaging.

4. Epiaortic ultrasound is the investigation of choice for detection of atheromatous lesions of the ascending aorta because it allows a detailed grading of atheromas over the entire length of the ascending aorta. A "clean" aorta can undergo surgical manipulation like clamping, cannulation and stitching of proximal anastomoses with a low embolic risk. If atherosclerotic plaques with the risk of embolic events are identified, the surgeon is given the opportunity to revise the operative strategy and in case of coronary surgery, beating heart surgery may be preferred.

5. The combined application of transit time flowmetry and epicardial ultrasound imaging was pivotal in the intraoperative diagnosis and treatment of a coronary subclavian steal syndrome avoiding further and dangerous consequences to the patient. This is an example on how intraoperative imaging may be implemented into clinical practice of coronary surgery.

Final remarks and further developments

Over the last years we have demonstrated the efficacy, usefulness and reliability of epicardial ultrasound scanning of coronary arteries and anastomoses. From the cardiac cycle study (paper I), we concluded that B-mode yields more precise measurements because it gives a more detailed view of the anastomosis, enabling the surgeon to assess the intimal echo pattern very clearly. Colour Doppler imaging provides important information on the pattern and direction of blood flow within the anastomosis and further into the run-off vessels.

For a thorough evaluation of a coronary distal anastomosis, both B-mode and colour flow imaging should be applied in addition to flowmetry: colour flow with the aim of assessing anastomotic patency, and B-mode to provide precise measurements of the anastomosis dimensions. The introduction of BFI may further enhance the clinical application of intraoperative cardiovascular ultrasound.

In a case report we have also shown the usefulness of the combined application of transit-time flowmetry and epicardial ultrasound scanning for a quick intraoperative diagnosis of coronary subclavian steal syndrome, avoiding technical failure and dangerous consequences to the patient.

We have believed that future intraoperative evaluation of coronary grafts and anastomoses will consist of a combined approach of flowmetry and epicardial ultrasound, which has recently been developed with collaboration by our research group. The introduction of new transducers for epicardial imaging of very small dimensions together with further improvements in imaging technology may also enhance the widespread use of epicardial scanning in cardiac surgery. In CABG patency of grafts is assessed by flow analysis, whereas ultrasound is applied to detect anastomotic failures more directly. As the cardiac cycle in an experimental study did not play any significant role in the assessment of epicardial ultrasound, epicardial imaging of graft anastomoses may be done rapidly and reliably and reach wide clinical application in the future.

A summary of the potential role of epicardial imaging in coronary surgery is presented in Tab 1.

Table 1. The potential role of intraoperative epicardial imaging in cardiac surgery
1. Localization of coronary artery embedded in epicardial fat
2. Visualization of the coronary artery underneath fibrotic scar tissue
3. Delineation of the intramural course of a coronary artery
4. Intraoperative assessment of the site and severity of coronary stenosis
5. Selection of arteriotomy site for bypass grafting
6. Localisation and extention of stents and dissection following PCI
7. Assessment of the integrity of distal coronary tree beyond an obstruction
8. Assessment of coronary anastomoses and grafts
9. Identification of the extent of coronary artery involvement in aortic dissection
10. Assessment of cardiac anatomy in congenital heart surgery
11. Epiaortic evaluation of the ascending aorta in cardiac surgery
12 Guidance in emerging novel surgical procedures for coronary artery disease

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Paper I

ORIGINAL CONTRIBUTION

Effect of the Cardiac Cycle on the Coronary Anastomosis Assessed by Ultrasound

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ABSTRACT

Anastomosis of the left internal mammary artery to the left anterior descending artery was performed in 9 pigs to evaluate the effect of changes in the cardiac cycle and the choice of ultrasound mode on assessment of graft morphology. The length of the anastomosis and the diameters of the left anterior descending artery at the toe and heel of the anastomosis, as well as downstream, were measured in end-systole and end-diastole with both B-mode and color Doppler imaging. None of the diameters were influenced by the cardiac cycle using either ultrasound mode. B-mode yielded larger diameters at all points except the toe of the anastomosis. It was concluded that provided the scanning is perpendicular to the vessel, the morphology of an anastomosis can be assessed without paying much attention to the phase of the cycle or the mode of ultrasound applied.

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INTRODUCTION

The success of coronary artery bypass grafting (CABG) is determined by the long-term patency of the graft. This depends mainly on the quality of distal anastomoses, particularly that between the left internal mammary artery (LIMA) and the left anterior descending artery (LAD).[1] Although off-pump CABG may reduce some of the risks and complications related to on-pump CABG, it is technically more demanding and carries a higher risk of technical failure.[2] Thus, quality control of distal anastomoses before completion of the operation is of the utmost importance, particularly during off-pump CABG. Detecting an anastomotic error enables the surgeon to revise the anastomosis, and so reduce postoperative morbidity and mortality.[3]

Distal anastomoses can be evaluated intraoperatively by graft flow measurements or by direct visualization using ultrasound scanning or angiography. Transit-time flowmetry is the most common intraoperative method used to assess coronary bypass grafts, but it is not very sensitive as blood flow is influenced by resistance in the peripheral coronary circulation. This technique detects a technical failure only if there is severe stenosis in the graft or at the site of anastomosis.[4-6] Epicardial imaging of coronary arteries and anastomoses with high frequency ultrasound is simple and safe.[7] It has several advantages over angiography; it is noninvasive, requiring no injection of contrast medium.[8] Moreover, comparing epicardial ultrasound with angiography at the 8-month follow-up has shown that the former has excellent prognostic value.[8] B-mode (Figure 1) and color-flow (Figure 2) imaging allow visualization of the anastomosis and its components (coronary artery and graft conduit) as well as the bloodstream.[7] However, the best modality for determining the morphology of the anastomosis has not been investigated. Moreover, the effects of the cardiac cycle on the coronary arteries are largely unknown. Hence, we assessed the morphology of LIMA-LAD anastomoses in the pig together with the changes induced by the cardiac cycle, using B-mode and color Doppler ultrasound scanning.

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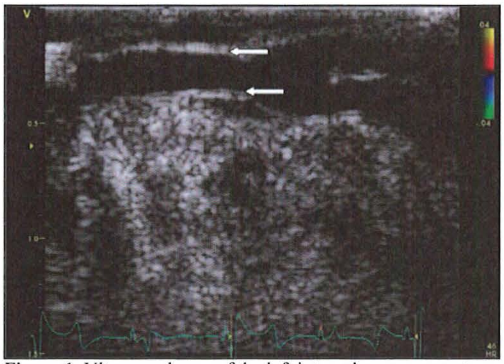

Figure 1. Ultrasound scan of the left internal mammary artery-left anterior descending artery anastomosis in longitudinal view by B-mode. The anterior and posterior intimal echo patterns are shown by arrows. The intimal echo pattern indicates that the ultrasound beam is perpendicular to the left anterior descending artery intima. The left internal mammary artery is seen top right and the flow direction is to the left of the picture.

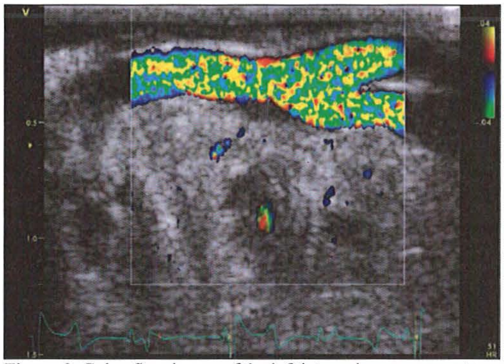

Figure 2. Color-flow image of the left internal mammary artery-left anterior descending artery anastomosis in longitudinal view. The left internal mammary artery is top right and the direction of blood flow is to the left of the picture.

Patients and Methods

Nine pigs weighing 60–85 kg underwent LIMA-LAD grafting under general anesthesia at the animal experimental laboratory at Trondheim University Hospital. Seven pigs had off-pump CABG, and 2 had LIMA grafting under cardiopulmonary bypass. All operations were carried out by the same surgeon (RH). Animals received humane care in accordance with the European Convention on Animal Care and the Norwegian national regulations; the Norwegian Ethics Committee on Animal Research approved the protocol. All pigs were premedicated with intramuscular azaperone 6 $mg \cdot kg^{-1}$ and diazepam 0.15 $mg \cdot kg^{-1}$. Anesthesia was induced with intravenous atropine 0.15 $mg \cdot kg^{-1}$, ketamine 7 $mg \cdot kg^{-1}$, and thiopentone 3 $mg \cdot kg^{-1}$. Maintenance infusions were of fentanyl 63 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and midazolam 0.6 $mg \cdot kg^{-1} \cdot min^{-1}$ combined with isoflurane 1% in a 1:2 mixture of oxygen and air. The pigs were artificially ventilated through a tracheotomy tube.

After a median sternotomy and full heparinization (3 $mg \cdot kg^{-1}$), the LIMA was harvested with its pedicle, and prepared. The LAD was identified and snared with 4/0 pledgeted polypropylene suture proximal to the coronary arteriotomy. After 3–5 min of ischemic preconditioning, the snare was released and an Axius Xpose access device (Guidant, Santa Clara, CA, USA) and an Axius vacuum stabilizer were applied to pull the heart and immobilize the LAD site chosen for grafting. After arteriotomy, an Axius coronary shunt was placed into the vessel lumen. The coronary anastomosis was performed with a continuous 7/0 polypropylene suture, aiming to create a patent anastomosis without technical failure. The snare was applied again to the LAD proximal to the anastomosis. Following epicardial ultrasound assessment of the anastomoses, the apical stabilizer was removed and the heart placed back into the pericardium.

For on-pump LIMA-LAD anastomosis, the approach to the heart, LIMA harvesting, and heparinization were the same as in the off-pump group. Cardiopulmonary bypass was instituted by cannulation of the left axillary artery and the right atrium. After aortic cross clamping, crystalloid cardioplegia solution was infused into the aortic root. The coronary anastomosis was performed with a continuous 7/0 polypropylene suture. The snare was applied again to the LAD proximal to the anastomosis. The 2 pigs were easily weaned off cardiopulmonary bypass without inotropic support so that LIMA-LAD scanning could be carried out.

After completion of the LIMA-LAD anastomosis and with the stabilizer still in place, epicardial ultrasound imaging was performed with a GE Vingmed Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) ultrasound scanner and a GE i13L probe. This probe is a linear-array mini-transducer designed for intraoperative imaging, operating at frequencies of 10–14 MHz. The ultrasound system was optimized for high-resolution color-flow imaging applications and achieved a frame rate of 16 frames per second. Using gel as the conduction medium, the transducer was gently applied directly on the anastomosis, between the paddles of the stabilizer. Real-time ultrasound images of the complete anastomosis as well as the distal run-off were stored as digital data for later analysis. The morphology of the anastomosis was assessed by measuring its dimensions (Figure 3): the length of the anastomosis proper (DA), the LAD diameter at the toe (D1) and heel (D3) of the anastomosis, and 5–10 mm distal to the toe (D2). The electrocardiogram was recorded continuously together with the images and

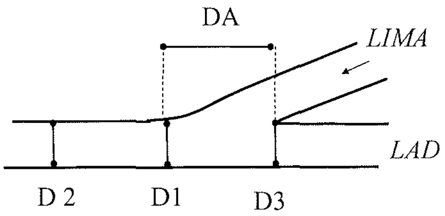

Figure 3. Diagram of the left internal mammary artery-left anterior descending artery anastomosis: diameters of the left anterior descending artery at the toe of the anastomosis (D1), 5-10 mm distal to the toe (D2), and at the heel (D3), DA = diameter of the anastomosis proper.

was used to define diastole. Intraoperatively and before the epicardial ultrasound, graft flow was monitored by transit-time flowmetry (Medi-Stim Butterfly Flowmeter, Medi-Stim AS, Oslo, Norway).

The results are presented as mean ± 1 standard deviation. Analysis of variance (ANOVA) for repeated measurements was used to assess the impact of the ultrasound modality (B-mode or color-flow), the cardiac cycle (end-systole or end-diastole), and the sites of measurement (D1, D2, D3, or DA) on the morphology of the anastomosis and the LAD. For variables significantly influencing the measured dimensions, we applied the paired t test with the Bonferroni correction, according to the number of comparisons carried out, as post hoc analyses for identification of the difference between values. A p value less than 0.05 was considered significant. The statistical analysis was carried out using SPSS version 12 software (SPSS Inc, Chicago, IL, USA).

Results

All animals remained hemodynamically stable throughout the operation, as confirmed by a satisfactory mean arterial pressure of 76 ± 6.3 mm Hg. The mean systolic blood pressure was 111 ± 8.1 mm Hg and the mean diastolic blood pressure was 57 ± 6.6 mm Hg. All 9 LIMA-LAD anastomoses were satisfactory and found to be fully patent by both ultrasound modalities.

There was no significant effect of the cardiac cycle on LAD diameters D1, D2, D3, and DA by either B-mode or color Doppler imaging ($p = 0.989$ by ANOVA; Table 1). B-mode imaging yielded larger diameters than color-flow Doppler, regardless of the phase of the cardiac cycle ($p \leq 0.0001$ by ANOVA). B-mode showed larger LAD diameters at the heel (D3) and downstream LAD (D2), as well as a longer anastomosis (DA) than that observed in color Doppler imaging. The diameter of the LAD at the toe was found to be similar with both ultrasound modes (Table 2).

Discussion

Although porcine coronary arteries have been measured by epicardial ultrasound, this study used the best available technology, emphasizing key technical aspects to obtain good quality images and reliable measurements.[9] Small changes in coronary diameters during the cardiac cycle have been found using intravascular ultrasound (IVUS); a 10% increase was detected in healthy vessels and a 2%–12% increase in atherosclerotic vessels.[10-13] Although most of the coronary blood flow occurs in diastole, the systolic expansion of coronary vessels can be explained by the increase in coronary intraluminal pressure during systole.[10] Instantaneous recording of coronary flow and pressure along with IVUS measurements of coronary internal diameters have demonstrated that systolic expansion is preceded by an increase in intraluminal pressure and a maximal increase in diameter occurring in mid to late systole. In our study, no significant changes in the diameter of the LAD at the heel, toe, anastomosis proper, or distally were detected during the cardiac cycle. We believe that the different outcome was most likely due to the following reasons. Firstly, epicardial imaging

Table 1. **Diameters of LIMA-LAD Anastomoses in End-Systole and End-Diastole in B-mode and Color Doppler**

		B-Mode Measurement (mm)			Color-Flow Measurement (mm)		
Measurement	N	Systole	Diastole	p*	Systole	Diastole	p*
D1	45	2.11 ± 0.33	2.10 ± 0.30	3.33	2.10 ± 0.39	1.96 ± 0.35	1.68
D2	45	2.30 ± 0.39	2.40 ± 0.70	2.96	2.18 ± 0.38	2.10 ± 0.35	0.808
D3	45	2.04 ± 0.58	2.19 ± 0.47	2.66	1.89 ± 0.43	1.88 ± 0.38	7.76
DA	45	3.37 ± 0.46	3.40 ± 0.41	6.22	3.19 ± 0.43	2.91 ± 0.52	0.0723

*Refers to the difference between measurements in systole and diastole after the Bonferroni correction. D1 = diameter of LAD at the toe of the anastomosis, D2 = diameter of LAD 5-10 mm distal to the toe of the anastomosis, D3 = diameter of anastomosis at the heel, DA = diameter of the anastomosis proper, LAD = left anterior descending artery, LIMA = left internal mammary artery.

Table 2. **Mean (Systolic and Diastolic) Diameters of LIMA-LAD Anastomoses in B-mode and Color Doppler**

		Mean Diameter (mm)		
Measurement	N	B-mode	Color-Flow	p*
D1	45	2.08 ± 0.20	2.00 ± 0.23	0.5
D2	45	2.35 ± 0.43	2.12 ± 0.29	0.004
D3	45	2.14 ± 0.36	1.88 ± 0.31	0.004
DA	45	3.39 ± 0.31	3.05 ± 0.33	< 0.01

*Refers to the difference between measurements in B-mode and color-flow after the Bonferroni correction. D1 = diameter of LAD at the toe of the anastomosis, D2 = diameter of LAD 5-10 mm distal to the toe of the anastomosis, D3 = diameter of the anastomosis at the heel, DA = diameter of the anastomosis proper, LAD = left anterior descending artery, LIMA = left internal mammary artery.

is not as sensitive as IVUS to discriminate very minor changes; a systolic increase of coronary diameter of 10% is equivalent to a 0.1–0.15-mm increase in diameter. Secondly, grafting of the LAD caused stiffness of the vessel wall, and this may well have reduced systolic expansion of the coronary artery, whereas IVUS measurements were taken on coronary vessels that had not undergone any surgical manipulation.

The color-flow image mode showed a slightly longer DA measurement in systole than in diastole. This morphological difference between the two phases of the cardiac cycle might be attributable to distension of the LIMA wall secondary to the increase in intraluminal pressure that occurs in the distal part of the mammary artery in systole. This hypothesis is supported by the results of an IVUS study demonstrating elongation and thinning of the vessel wall during systole.[9] Nonetheless, the length of the anastomosis proper is usually adequate throughout the cardiac cycle and is not likely to impair blood flow through the LIMA-LAD anastomosis. Changes in the dimensions of the coronary vessel wall during the cardiac cycle may be more accurately detected by IVUS, as this technique is better for visualizing the complete internal circumference of the vessel by transverse view plane and synchronous measurement of intracoronary blood pressure. On the other hand, intraoperative epicardial scanning is much easier to perform than IVUS, because the latter entails sophisticated equipment and invasive manipulations that greatly limit its routine application.

On clinical grounds, provided the scanning is directed perpendicular to the vessel, this study showed that the surgeon can assess the morphology of an anastomosis without paying much attention to the phase of the cardiac cycle or the mode of ultrasound applied. B-mode imaging complies fully with the peristaltic movement of the artery, whereas color filling more easily enters the vessel boundaries. Therefore, we believe that B-mode yields more precise measurements because it gives a more detailed view of the anastomosis, enabling the surgeon to assess the intimal echo pattern very clearly. Color Doppler, however, enables the surgeon to evaluate graft patency because it provides very useful information on the pattern and direction of blood flow within the anastomosis. For a thorough evaluation of a coronary distal anastomosis, both B-mode and color-flow imaging should be applied in addition to flowmetry; color-flow with the aim of assessing anastomotic patency, and B-mode to provide precise measurements of the anastomosis dimensions.

We believe that future intraoperative evaluation of coronary grafts and anastomoses will consist of the combined approach of flowmetry and epicardial ultrasound. Patency of grafts is assessed by flow analysis, whereas ultrasound is applied to detect anastomotic failures. In this animal study, the cardiac cycle did not play any significant role in the assessment by epicardial ultrasound. Thus, if this is confirmed clinically, combined flowmetry and epicardial ultrasound has the potential for complete graft assessment in CABG surgery.

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Paper II

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ORIGINAL ARTICLE

Narrowing effect of off-pump CABG on the LIMA-LAD anastomosis: Epicardial ultrasound assessment

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Abstract

Aim. Effects of off-pump CABG on LIMA-LAD anastomotic dimensions vs. on-pump CABG assessed by epicardial ultrasound imaging. *Material and methods.* LIMA-LAD anastomoses were performed off-pump in 38 patients and on-pump in 12. Intra-operative imaging was by a GE Vivid 7 ultrasound scanner and i13L transducer. Length of the anastomosis (DA), LAD diameters at the toe (D1) and heel (D3) of the anastomosis, the reference downstream LAD (D2) were measured in diastole by two-dimensional imaging (B-mode). Relationships between these dimensions were compared between on- and off-pump patients. *Results.* In off-pump patients, D3 dimension was smaller than D1 ($p = 0.004$). Both D3 and D1 were smaller than D2 ($p < 0.01$). Ratio D3/D2 was smaller than D1/D2 ($p = 0.009$). In on-pump patients, these ratios were similar. D3/D2 ratio was smaller in off- than in on-pump patients ($p = 0.01$), D1/D2 were similar in the two groups. *Conclusion.* Off-pump CABG may cause a narrowing of the coronaries, especially at the anastomotic heel. The anastomotic technique at the heel may have to be modified to improve its patency.

Key words: *Epicardial ultrasound, Coronary graft assessment, LIMA-LAD anastomosis*

Patency of the distal graft anastomoses after coronary artery bypass grafting (CABG) especially that between the left internal mammary artery and the left anterior descending artery (LIMA-LAD), is the most important determinant of operative success and long-term patient survival (1). Off-pump CABG is becoming an established alternative method for this anastomosis with the aim of reducing post-operative complications of the cardiopulmonary bypass machine, especially the neurological and somatic ones (2). However, as surgery on the beating heart is technically demanding, anastomotic errors are more likely to occur than with on-pump CABG, possibly as high as 9.9% (2). Hence it is important to monitor the quality of the anastomosis before the end of the operation.

Intraoperative monitoring can be done by flow measurement of the graft or by direct visualisation of the anastomosis by ultrasound scanning or angiography. Although transit-time flowmetry is the most common intraoperative method used, it is not very sensitive, as blood flow is influenced by resistance in the peripheral coronary circulation. Thus it detects a technical failure only if there is severe stenosis in the graft or anastomosis (4–6).

Even though intraoperative angiography is used for evaluation of the LIMA-LAD anastomosis, it has proved non-practicable since it needs fixed equipment that is both expensive and bulky (6); it is also invasive. Moreover, at 3 months it produced a high rate of false-negative results compared with follow-up angiography; hence it has a low predictive value (3).

Intraoperative fluorescence imaging technique is based on capture, by a charge-coupled device video camera, of fluorescence of Indocyanine Green (ICG) when illuminated with near infrared light using laser energy from the SPY imaging system (Novadaq

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Technologies Inc., Toronto, Canada). It is safe, simple, rapid and repeatable imaging technique for intraoperative assessment of coronary grafts. However, this technique is semiquantitative until now and can not provide objective measurements and since it uses laser, it can not visualise a depth of more that 1-mm. Another disadvantage is poor imaging of the anastomosis morphology.

Intra-operative epicardial ultrasound using high frequency ultrasound probe is a new method of evaluating LIMA-LAD anastomosis. It is considered very sensitive, non-invasive, not time consuming and safe (7). Furthermore, comparison between epicardial ultrasound and angiography at 8 months showed that the ultrasound examination had a positive prognostic value (8).

A recent study of the heel of the LIMA-LAD anastomosis, the site of the proximal suturing showed it to be the place most likely to become stenosed during surgery (9). In this study we aimed to evaluate and compare LIMA-LAD anastomoses in off- vs. on-pump CABG with special reference to the dimensional relations of the heel and the toe using intraoperative epicardial ultrasound.

Materials and methods

Off-pump patients

Thirty-eight consecutive patients scheduled for elective off-pump CABG were included; their clinical characteristics are shown in Table I. Patients had 1- or 2- vessel coronary disease and the average number of distal anastomoses was 1.74 ± 0.5 per patient (range 1–3). All patients received a LIMA graft anastomosed to the LAD. Nineteen patients received an additional vein graft; 11 patients received a saphenous vein graft (SVG) to the diagonal branch, seven received a SVG to a right coronary artery, and one received a SVG to the marginal branch.

On-pump patients

Twelve consecutive patients scheduled for elective on-pump CABG were included; their clinical characteristics are presented in Table I. Patients had 2- or 3- vessel coronary disease and all received a LIMA graft anastomosed to the LAD. The average number of distal anastomoses was 3.6 per patient. Nine patients received a SVG to the diagonal branch, 11 patients received a SVG to the right coronary artery, and 11 received a SVG to the marginal branch.

Table I. Patients' clinical characteristics.

	Off-pump 38 patients	On-pump 12 patients
Male/Female	29/9	9/3
CCS class:		
I	3	–
II	16	–
III	9	9
IV	10	3
Previous MI	5	5
Mean EF	70% ± 11	65% ± 10

The same surgeon (RH) operated upon all patients in both groups. The Norwegian Regional Committee in Medical Research approved the research protocol.

Off-pump LIMA-LAD

After median sternotomy and full heparinization (3 mg/kg), a pedicled LIMA graft was harvested. The activated coagulation time was not allowed to fall below 270 s. The LAD was identified and snared with 4-0 pledged polypropylene suture (Prolene, Ethicon, Somerville, NJ) proximal to the coronary arteriotomy. After 3–5 min of ischemic preconditioning, the snare was released and an epicardial stabiliser (Guidant, Santa Clara, CA, USA) was applied to immobilise the LAD site chosen for grafting and another apical stabiliser (Guidant) was applied to pull the heart. After arteriotomy an intracoronary shunt (Guidant) was positioned into the vessel lumen. The coronary anastomosis was performed with a continuous 7-0 or 8-0 polypropylene suture (Prolene). The LIMA pedicle was secured with an epicardial stitch on each side. Following epicardial ultrasound assessment of the anastomoses, the action of heparin was reversed with protamine and the apical stabiliser removed and the heart was placed back into the epicardial cradle.

On-pump LIMA-LAD

The approach to the heart, LIMA harvesting and heparinization were the same as in the off-pump group. The patients were fully heparinized (3 mg/kg) and the ACT was not allowed below 480 s. Cardiopulmonary bypass was instituted by cannulation of the ascending aorta and the right atrium. After aortic cross-clamping a crystalloid cardioplegia solution was infused into the aortic root. The coronary anastomosis was performed with a continuous 7-0 polypropylene suture (Prolene). The LIMA pedicle was secured with an epicardial stitch on each side. Following epicardial ultrasound assessment of the anastomoses, the patients were weaned from the heart-lung machine and the operation continued as usual.

Epicardial ultrasound scanning

After completion of the LIMA-LAD anastomosis and with the stabiliser still in place, two-dimensional

(B-mode) epicardial ultrasound imaging of the anastomosis was done with an i13L MHz linear array GE Vingmed transducer connected to a GE Vingmed System FiVe or a GE Vivid 7 ultrasound scanner (GE Vingmed, Horten, Norway). This probe is a linear array mini-transducer (footprint 27.3 × 9.6 mm) designed for intraoperative imaging with frequencies operating at 10–14 MHz. With the use of gel as conduction medium, the transducer was applied directly onto the epicardium between the paddles of the stabiliser. Real time ultrasound images showing the complete anastomosis as well as the distal run-off were stored as digital data for later analysis with the EchoPAC software (GE Vingmed). The ultrasound imaging and storage of data were obtained within approximately 5–10 min for each patient.

The quality of the anastomosis was rated good when both the anastomosis and the distal run-off in the coronary artery could be well visualised. The images obtained from the anterior-posterior and transverse planes were used to assess the quality and patency of the anastomosis. Only the images presenting the toe and the heel where the intima is shown clearly were considered because it guaranteed that the beam was perpendicular to the tissue (10). The dimensions of D1, D2, D3, DA, and DM were measured, see Figure 1. The D1/D2, D3/D2, D1/D3 and DM/DA ratios were also calculated to assess the geometry of the anastomosis. Ideally these ratios should be as close to 1 as possible, as described in our previous study (11). The ECG was recorded

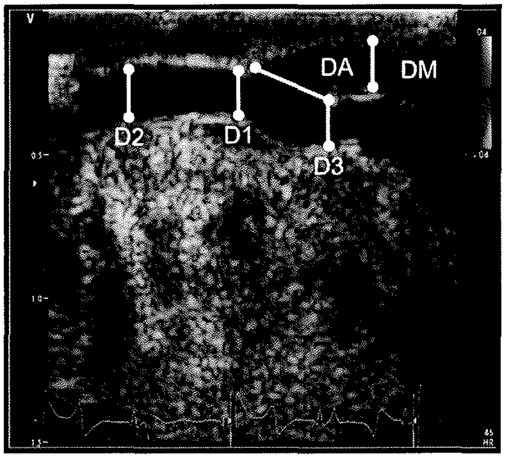

Figure 1. Two-dimensional (B-mode) ultrasound image of the LIMA-LAD anastomosis in longitudinal view. D1: diameter of the LAD at the toe of the anastomosis. D2: diameter of the LAD 5–10 mm distal to the toe of the anastomosis. D3: diameter of the LAD at the heel of the anastomosis. DA: length of the anastomosis proper. DM: diameter of the left mammary artery graft.

continuously on the monitor together with the images and was used for defining diastole. In the on-pump patients, epicardial imaging was done before termination of cardiopulmonary bypass.

Transit-time flowmetry

Intraoperatively and prior to epicardial ultrasound, graft flow was controlled with transit-time flowmetry (Medi-Stim Butterfly Flowmeter, Medi-Stim AS, Oslo, Norway) with sterile gel as the conduction medium. In on-pump patients the flow measurements were done after weaning the patient from the heart-lung machine.

Statistical analysis

Data normally distributed are described as the arithmetic mean ± standard deviation and range. Paired-samples t-test was used to compare the dimensions and ratios within the same group while independent-samples t-test was applied to compare dimensions and ratios between the two groups. A p-value <0.05 was considered statistically significant. The statistical analysis was carried out using the SPSS software version 13 (SPSS Inc, Chicago, Illinois).

Results

No operative mortality and no myocardial infarction occurred. Images of the LIMA-LAD anastomoses were rated good in all patients but six in the off-pump group and all but one in the on-pump group. In these seven cases the image quality did not allow measurements of anastomotic dimensions at the heel position. Thus, a total of 32 off-pump and 11 on-pump patients were considered for final analysis. Mean LIMA transit-time flow in the off-pump group was 29.8 ± 16.9 ml/min with a pulsatility index of 2.2 ± 0.4, whereas it was 34.4 ± 16.2 ml/min with a pulsatility index of 3.1 ± 0.8 in the on-pump group.

Coronary artery and anastomotic dimensions by off- vs. on-pump technique are presented in Table II. In the off-pump group, the dimension of the heel (D3) was significantly smaller than the toe (D1) ($p = 0.004$). Both D3 and D1 were smaller than the reference LAD (D2) ($p < 0.01$). These dimensions did not differ in the on-pump patients.

The ratios of the anastomotic dimensions by off- vs. on-pump technique are presented in Table III. The ratio of the heel to the distal run-off LAD (D3/D2) was smaller than the ratio between the toe and the run-off LAD (D1/D2) ($p = 0.009$). When compared in on-pump patients, these ratios were similar. Further, the D3/D2 ratio was smaller in off-pump

Table II. Different dimensions (cm) of the LIMA-LAD anastomosis in off- and on-pump CABG patients considered for final analysis.

	Off-pump (cm) n = 32	On-pump (cm) n = 11	p
D1	0.15 ± 0.04^{a}	0.17 ± 0.03^{f}	0.158
	(0.10–0.26)	(0.13–0.23)	
D2	0.16 ± 0.03^{b}	0.17 ± 0.04^{g}	
	(0.12–0.26)	(0.12–0.24)	0.348
D3	0.14 ± 0.02^{c}	0.18 ± 0.05^{h}	
	(0.10–0.19)	(0.11–0.28)	0.007
DM	0.19 ± 0.06^{d}	0.16 ± 0.03^{i}	
	(0.12-0.40)	(0.12–0.19)	0.009
DA	0.44 ± 0.14^{e}	0.38 ± 0.11^{j}	
	(0.21–1.00)	(0.22–0.64)	0.136

(D1: diameter of the LAD at the toe of the anastomosis; D2: diameter of the LAD 5-10 mm distal to the toe of the anastomosis; D3: diameter of the LAD at the heel of the anastomosis; DA: length of the anastomosis proper; Dm: diameter of the mammary artery graft).
Values (cm) are presented as mean ± standard deviation; values in brackets represent the range.
^{a} vs. ^{b}, ^{a} vs. ^{c}, ^{b} vs. ^{c}, ^{d} vs. ^{e}: $p < 0.01$.
^{f} vs. ^{g}, ^{f} vs. ^{h}, ^{g} vs. ^{h}: NS.
^{i} vs. ^{j}: $p < 0.01$.

than in on-pump patients ($p = 0.01$), whereas D1/D2 were similar in the two groups.

Discussion

Our results show that the coronary artery segment involved in the anastomosis of the off-pump group underwent a certain degree of narrowing in comparison to patients operated on-pump. In patients operated on beating heart, both ends of the anastomosis; the toe (D1) and the heel (D3), had smaller diameters compared to the distal run-off LAD (D2), which represent the reference native coronary artery. This difference was not seen in patients operated on-pump. Further, the heel (D3) is smaller in off-pump than in on-pump patients. Thus, is assumed that this might be related to the beating heart CABG technique, since the same results were not found in the on-pump group.

Table III. Ratios of different dimensions of the LIMA-LAD anastomosis in off- and on-pump CABG patients considered for final analysis.

	Off-pump N = 32	On-pump N = 11	p
D1/D2	0.94 ± 0.11^{a}	0.98 ± 0.09^{c}	0.23
	(0.75–1.17)	(0.83–1.11)	
D3/D2	0.85 ± 0.16^{b}	1.06 ± 0.22^{d}	0.01
	(0.52–1.25)	(0.85–1.64)	
DM/DA	0.46 ± 0.15	0.41 ± 0.15	0.79
	(0.17 -0.92)	(0.04–0.57)	

(D1: diameter of the LAD at the toe of the anastomosis; D2: diameter of the LAD 5–10 mm distal to the toe of the anastomosis; D3: diameter of the LAD at the heel of the anastomosis; DA: length of the anastomosis proper; DM: diameter of the mammary artery graft.)
Values are presented as mean ± standard deviation; values in brackets represent the range.
^{a} vs. ^{b}: $p < 0.01$, ^{c} vs. ^{d}: NS.

The analysis of the anastomotic dimensions in off-pump patients showed that the heel of the anastomosis (D3) was the site mostly affected by stenosis compared to the toe of the anastomosis (D1). Moreover, the diameter of the toe was significantly reduced as well. These results are supported by a previous study using postoperative quantitative angiography at 14 ± 5 days for patients operated on- and off-pump, showing that the diameter of the heel portion of the CABG anastomosis was significantly less than that of the toe portion (9). This reduction in the heel dimension is most likely related to technical issues. The importance of the toe may be over-emphasised because it is the anterior exit point of the anastomosis to the ischaemic myocardium; on the other hand, the heel represents the posterior suture line of the anastomosis and is the part that is more difficult to repair if bleeding occurs. Hence surgeons may tend to take relatively bigger bites at the heel site of the anastomosis, so increasing the stenosis rate.

As far as ratios are concerned, off-pump anastomotic ratios were smaller than the on-pump ones. In particular the D3/D2 ratio in off-pump patients reached the lowest score indicating the occurrence of narrowing at D3, whereas all the remaining ratios, especially those of on-pump patients, were much closer to the ideal value of 1. We do not know whether this reduction in the diameter of the heel has any unfavourable outcome on clinical grounds, therefore it deserves further long-term evaluation.

In the light of our results, we would suggest that the surgical technique might need to be modified in off-pump patients. For coronary artery anastomosis, the continuous suture technique is generally used because it is easy to perform, there is less anastomotic leakage, and it is quicker than the interrupted suture technique. However, the purse-string effect carries a potential risk of anastomotic stenosis, which does not occur with the interrupted suture technique (12). When performing the running suture technique one should be very cautious using small bites both at the toe and heel with the 7-0 or 8-0 tread and avoid hard pulling which may cause a snaring effect.

An alternative mechanical interrupted suture device (U-Clip device, Medtronic Inc.) has been designed presented to eliminate the need for standard suture management, knot tying, and surgical assistance. Despite the inherent difficulties, a multicenter study showed that the use of the U-Clip device resulted in excellent long-term graft patency and anastomotic quality as objectively assessed by use of quantitative, 6-month postoperative angiographic analysis (13). Whether widespread use is possible, taking into account the increased cost will depend on clinical outcome from future studies.

We also found that the diameter of the LIMA graft (DM) is smaller than that of the anastomosis proper (DA) in both groups. This might be determined by the surgeon to create an optimal angle of the anastomosis; alternatively, it is related to some spasm in the LIMA graft.

Visualisation of the anastomosis by epicardial ultrasound imaging was satisfactory and simple. However, high quality imaging of the heel showing vessel wall intima clearly was more difficult than looking at the toe of the anastomosis as seven out of 50 LIMA-LAD anastomoses were excluded to avoid unreliable measurements.

As explained in a previous report, we chose to make the measurements in the two-dimensional (B-mode) imaging modality as this was shown to be more reliable than colour-Doppler for doing these measurements (10). We also chose to do the measurements in the diastolic phase of the cardiac cycle to standardise the measurements. However, in a later experimental study, we found that the cardiac cycle does not affect these measurements (10).

Limitations of the study are the non-randomised design; nonetheless patients' clinical characteristics make the two groups quite homogenous. Furthermore it must be recognised that the study includes LIMA-LAD anastomoses in off-pump surgery performed at the early stages of our series with off-pump CABG and was thus part of our evolving experience.

Conclusion

Off-pump CABG might have a narrowing effect on the coronary arteries, especially at the heel position. The technique of anastomosis at the heel may have to be modified to improve its patency. However, the clinical significance of this is still to be explored.

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Paper III

Blood Flow Imaging: A New Two-Dimensional Ultrasound Modality for Enhanced Intraoperative Visualization of Blood Flow Patterns in Coronary Anastomoses

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Objectives: The study's objective was to evaluate a novel two-dimensional ultrasound imaging modality termed "blood flow imaging" (BFI) for intraoperative assessment of blood flow patterns in coronary anastomoses. The BFI modality extends color Doppler imaging (CDI) with information on flow direction and velocity that is not limited by angle dependency or aliasing artifacts.

Methods: Intraoperative ultrasound recordings of patent left internal mammary artery-left anterior descending anastomoses were acquired from an experimental porcine model (N = 9). Three independent observers randomly evaluated CDI and BFI cineloops with regard to different assessments of flow direction and velocity. Further, a selection of technical problems that might occur in clinical practice was induced in three pigs to investigate the resulting flow patterns.

Results: The BFI modality was found to provide an improved visual assessment of blood flow patterns in the left internal mammary artery-left anterior descending anastomosis compared with CDI.

Conclusion: The modality may therefore increase the certainty and efficiency of flow evaluation for intraoperative quality control in coronary surgery.

Keywords: Coronary artery bypass grafting surgery, Intraoperative quality control, Colour-doppler imaging, Blood flow imaging

The long-term survival of patients after coronary artery bypass grafting is directly related to the patency of distal anastomoses.[1] Modern coronary bypass series reported perioperative graft occlusion rates as high as 11%,[1,2] especially for off-pump coronary artery bypass grafting, which is technically more demanding.[2] The construction of a technically perfect anastomosis at the time of surgery is therefore an important determinant of graft patency. However, there is currently no standardized method or common clinical practice regarding intraoperative graft assessment, that is, angiography, ultrasound imaging, and transit-time flowmetry. Although the latter is the most widely used, it does not provide imaging of the anastomosis and may not be reliable unless there is a severe graft stenosis.

Epicardial imaging with high-frequency ultrasound is a reliable, simple, and safe method of intraoperative assessment of coronary grafts and anastomoses.[3] In previous studies we have reported on the clinical applications of epicardial B-mode and color Doppler imaging (CDI).[3,4] High-frequency B-mode ultrasound satisfactorily visualized the coronary anastomoses and allowed for measurements of the anastomosis and grafted coronary artery dimensions.[4] Moreover, a comparison between the evaluation of coronary anastomoses by intraoperative epicardial ultrasound and angiography at 8 months' follow-up demonstrated that the former had a positive prognostic value.[5]

Imaging of blood flow patterns in the anastomosis after completion provides an important source of information regarding graft patency. In previous studies, color Doppler ultrasound methods have been used to map the blood flow within the anastomoses.[6,7] However, these Doppler-based methods are only able to visualize the flow velocity component parallel to the ultrasound beam and are further limited by a maximum measurable velocity before aliasing phenomena occur,[7] which frequently obscure the color Doppler information. The angle dependency of CDI was studied in the context of anastomosis flow by Vera et al,[8] who through computer simulations reported how a more accurate and accessible image of flow conditions in an anastomosis could be

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obtained by the portrayal of the two-dimensional directions of flow.

A new real-time ultrasound flow imaging modality termed "blood flow imaging" (BFI) has recently been introduced. With BFI the blood flow in any direction of the image plane can be visualized without velocity aliasing limitations.[9] Further, by combining this new technique with conventional color Doppler measurements, the best properties of both modalities may be used. With this in mind, the aim of the present study was to evaluate the application of BFI versus CDI for assessment of blood flow patterns of the left internal mammary artery-left anterior descending (LIMA-LAD) anastomosis in a pig model.

MATERIALS AND METHODS

A total of nine pigs (weight 60-85 kg) underwent grafting of the LAD with LIMA under general anaesthesia. Seven pigs underwent operation via off-pump, whereas two pigs had LIMA grafting on cardiopulmonary bypass. All operations were carried out by the same surgeon (R.H.). The animals received good care in accordance with the European convention on animal care and the Norwegian national regulations, and the Norwegian Ethics Committee on animal research approved the protocol.

Anesthesia and Operative Technique

All pigs were premedicated with intramuscular azaperone 6 mg $\cdot$ kg^{-1} and diazepam 0.15 mg $\cdot$ kg^{-1}. Anaesthesia was induced with intravenous atropine 0.15 mg $\cdot$ kg^{-1}, ketamine 7 mg $\cdot$ kg^{-1}, and thiopentone 3 mg $\cdot$ kg^{-1}. Maintenance infusions were fentanyl 63 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} and midazolam 0.6 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} combined with isoflurane 1% in a 1:2 mixture of oxygen and air. The pigs were artificially ventilated through a tracheotomy tube.

Off-pump LIMA-LAD. After median sternotomy and full heparinization (3 mg $\cdot$ kg^{-1}), the LIMA was harvested with its pedicle and prepared. The LAD was identified and snared with 4-0 pledgeted polypropylene suture (Prolene, Ethicon, Somerville, NJ) proximal to the coronary arteriotomy. After 3 to 5 minutes of ischemic preconditioning, the snare was released and an Axius Xpose Access Device and Axius Vacuum Stabilizer (Guidant, Santa Clara, CA) were applied to pull the heart and immobilize the LAD site chosen for grafting. After arteriotomy, an Axius coronary shunt (Guidant) was placed into the vessel lumen. The coronary anastomosis was performed with a continuous 7-0 polypropylene suture (Prolene) with the aim of creating patent anastomoses without technical failures. The snare was applied again to the proximal LAD for the measurement of transit-time LIMA flow using a Medi-Stim Butterfly flowmeter (Medi-Stim ASA, Oslo, Norway).

On-pump LIMA-LAD. The approach to the heart and LIMA harvesting and heparinization were as in the off-pump group. Cardiopulmonary bypass was instituted by cannulation of the left axillary artery and the right atrium. After aortic crossclamping, crystalloid cardioplegia was infused into the aortic root. The coronary anastomosis was performed with a continuous 7-0 polypropylene suture (Prolene) with the intention to create a patent anastomosis without technical failures. The two pigs were easily weaned from cardiopulmonary bypass without inotropic support so that LIMA-LAD scanning could be carried out. The snare was applied again to the proximal LAD for the measurement of transit-time LIMA flow using the Medi-Stim Butterfly flowmeter.

Ultrasound assessment of the LIMA-LAD anastomosis. In all nine pigs, epicardial ultrasound assessment of the anastomosis was carried out with the LAD snared proximally from the anastomotic site, with the intention to simulate the standard condition of a graft anastomosis placed distal to a significant stenosis. Furthermore, in three pigs, after assessment of the standard condition, an untoward situation that might occur in clinical practice was experimentally created in each pig, referred to as special cases 1, 2, and 3:

1. In one pig the LAD was unsnared mimicking an anastomosis constructed distal to a nonsignificant stenosis.
2. By placing an extra deep stitch at the toe of the anastomosis, a failed stenotic anastomosis occurred in the second pig.
3. The LAD was snared distally to the anastomotic site in the third pig to reproduce an anastomosis placed proximally to a significant stenosis.

At the end of the procedure, the apical stabilizer was removed and the heart was placed back into the pericardial cradle.

Ultrasound Image Acquisition

The epicardial ultrasound images of the LIMA-LAD anastomoses were acquired using a Vivid 7 ultrasound scanner (GE Vingmed, Horten, Norway) equipped with an i13L linear array probe (GE Healthcare, Waukesha, WI) operating at frequencies of 7 to 14 MHz. The Axius Vacuum Stabilizer (Guidant, Santa Clara, CA) was used during epicardial imaging of the anastomosis in both off- and on-pump cases, the latter after weaning from bypass circulation. The epicardial imaging procedure (left) and a representative B-mode image (right) are shown in Figure 1.

For each B-mode recording, color Doppler and BFI data were stored. Cineloops using the two flow imaging modalities being evaluated were generated off-line from the same data recording, which allowed fair comparisons.

Blood Flow Imaging

BFI is a real-time ultrasound flow imaging modality that is able to visualize the blood flow in any direction of a two-dimensional image plane and that is not limited by velocity aliasing. The method thereby overcomes two fundamental limitations of CDI that often obscure the Doppler velocity information.

The visualization of blood flow in BFI is based on the enhancement and visualization of the ultrasound speckle pattern from blood signal echoes. This speckle pattern is present inside the vessel lumens but is normally not visible because of the weaker echoes from blood compared with the surrounding tissue structures. In BFI, the blood scatterer speckle pattern is produced by wall filtering as used in CDI to attenuate signal from tissue.

Movement of the blood speckle pattern between image acquisitions correlates to the movement of blood scatterers and can be captured by imaging with a high frame rate. In BFI this frame rate is achieved by using beam interleaving techniques in which smaller regions of the image are acquired separately, a technique that is also used in CDI to maximize the overall frame rate for a given user-chosen pulse repetition frequency. The frame rate of each image region acquired then equals the user-chosen pulse repetition frequency, typically 1000 to 2500 Hz in our recordings. One complete image frame is built by merging several contiguous image regions acquired subsequently in time.

After image acquisition, N speckle images are available for each image region (six in our recordings). These N speckle images are displayed simultaneously for all regions over the time it takes to acquire the next complete frame of data. The speckle images are

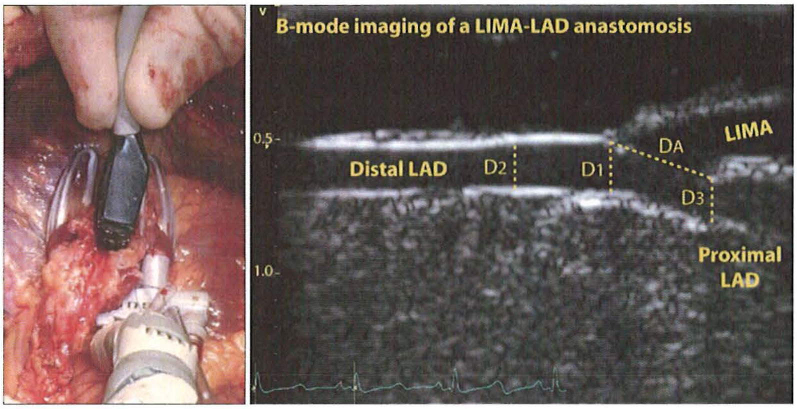

Figure 1 *Left:* Epicardial ultrasound imaging. A stabilized area around the LIMA-LAD anastomosis is imaged using a Vivid7 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) and high-frequency i13L linear array (GE Healthcare, Waukesha, WI). *Right:* B-mode image of the LIMA to LAD coronary anastomosis as obtained in the study. Diameter measurements indicated were used to determine the quality of the anastomosis. *LIMA*, Left internal mammary artery; *LAD*, left anterior descending.

thereby displayed in slow motion, which allows the human eye to track the speckle pattern movement in the image plane in real-time. To look at the detailed blood movement, the display frame rate can be slowed down in replay cineloops as in CDI for in-depth investigations.

The data acquisition in BFI is similar to that used for CDI, and the two techniques have been combined to include both quantitative color Doppler images and the qualitative angle- and aliasing-independent speckle visualization. As several speckle images are produced for each color Doppler image, the imaging frame rate of the speckle information is substantially higher compared with the Doppler information given in CDI (sixfold in our recordings).

The BFI technique shares similarities with the more established B-Flow modality[10] in that both modalities display speckle images of blood. However, the image acquisition scheme and display are significantly different. The frame rate required for the acquisition and display of the blood speckle movement is not provided in the B-Flow modality.

Ultrasound Image Analysis

The ultrasound images were rated good when the LIMA-LAD anastomosis and the proximal LAD and distal run-off could be well visualized by the B-mode and CDI mode in the longitudinal plane. An example of the B-mode image quality obtained is shown in Figure 1, where dimensions used to validate the quality of the anastomosis are also indicated.[5] The anastomosis was considered technically satisfactory if the following measurements could be decided: the length of the anastomosis proper (D_A), diameters of the LAD at the toe of the anastomosis (D_1), and 5 to 10 mm distally to the anastomosis (D_2). D_2 was defined as the reference diameter and a ratio D_1/D_2 was calculated; a D_1/D_2 value around 1 indicates a patent anastomosis without any stenosis at the toe.[5]

To compare the qualitative differences of BFI and CDI cineloops, both modalities were assessed by three independent observers, all familiar with CDI and the concept of BFI. Cineloops using CDI and BFI from the nine experiments with standard condition were presented to the observers in random order, and different aspects related to flow direction and velocity dynamics were evaluated for both modalities. The following questions were asked:

Question 1: Based on the flow information presented, to what degree of certainty can you assess the *direction of flow*:

a) from the LIMA to the distal part of the LAD?

b) from the LIMA to the proximal part of the LAD?

Question 2: Based on the flow information presented, to what degree of certainty can you assess *competitive flow* in the anastomosis?

Question 3: Based on the flow information presented, to what degree of certainty are you able to assess *flow pulsatility*?

Question 4: Based on the flow information presented, to what degree are you influenced by *velocity aliasing* in assessing:

a) flow direction?

b) flow velocity?

To quantify the visual evaluation of the observers a visual analogue scale was used, where each observer evaluation was rated between 0 and 100, and a value of 100 equaled the best score. For question 4a and b regarding the influence of *velocity aliasing*, the scale was reversed so that the method least influenced by aliasing was given a higher score.

Statistical Analysis

The general null hypothesis for the different observer evaluations was that there was no difference between CDI and BFI for the assessment of flow in the anastomosis. Statistical analysis was performed using the exact Wilcoxon signed-rank test for paired measurements. The outcome of the evaluations was displayed in dot-plots. The statistical analysis and plotting were performed using the numeric MATLAB software with the statistical toolbox (The MathWorks, Natick, Mass).

RESULTS

Because the BFI modality is best appreciated through cineloops, we encourage the reader to download example movie clips from the journal online service (http://journals.elsevierhealth.com/periodicals/ymje/home) where BFI and CDI cineloops are presented side by side (Videos 1 to 4) (Supplementary content).

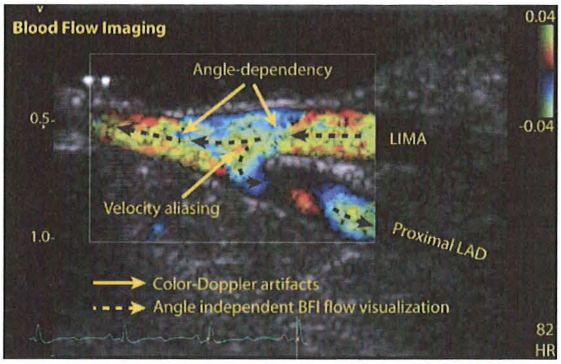

Figure 2 Standard imaging case of a technically perfect and fully patent LIMA-LAD anastomosis imaged with BFI. The artifacts in the color image related to angle dependency and velocity aliasing (*solid arrows*). The direction of the flow as observed by BFI (*dashed arrows*). *LIMA*, Left internal mammary artery; *LAD*, left anterior descending; *BFI*, blood flow imaging. View video clip online.

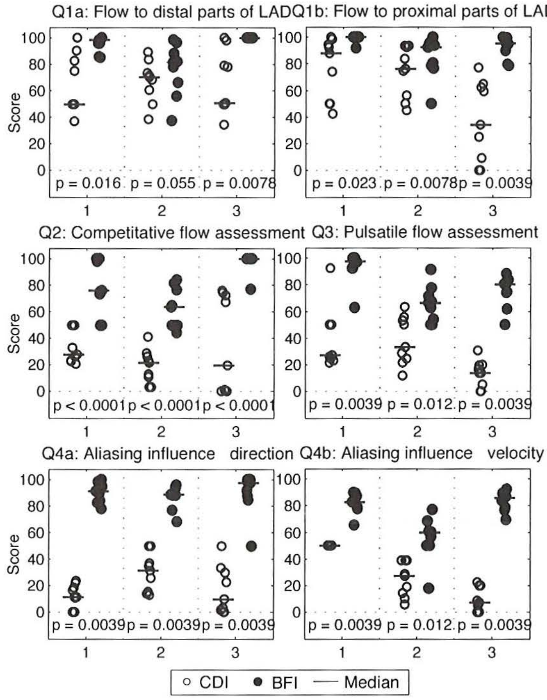

Figure 3 Dot plots presenting the visual analogue scores of the three observers when evaluating BFI versus CDI for the assessment of flow in the standard case (technically patent) LIMA-LAD anastomosis (N = 9). The corresponding Wilcoxon signed-rank test *P* values for each individual observer are shown for each evaluation. *LAD*, Left anterior descending; *CDI*, color Doppler imaging; *BFI*, blood flow imaging.

Quality of the Ultrasound Images and LIMA-LAD Anastomoses

In all cases, reliable ultrasound B-mode and Doppler images could be obtained of the LIMA-LAD anastomosis. Less than one minute was used by a trained surgeon to acquire useful images, whereas good-quality images for post-processing were acquired within approximatively 3 minutes.

All nine anastomoses were rated good and patent by B-mode ultrasound measurements as described above. Mean transit-time flow of LIMA grafts was 34.7 ± 4.2 mL/min, at a mean arterial blood pressure of 76 ± 6.3 mm Hg. The mean measurements of these anastomoses were as follows: D_A = 3.4 ± 0.3 mm; D_1 = 2.1 ± 0.2 mm; D_2 = 2.4 ± 0.4 mm. The D_1/D_2 ratio was 0.89 ± 0.17 mm, indicating patent anastomoses and without any significant narrowing at the toe.

In special case number 2, the mean measurements of this purposely failed anastomosis were as follows: D_A = 2.2 mm; D_1 = 1.1 mm; D_2 = 2.1 mm. The D_1/D_2 ratio was 0.52, indicating a stenosis at the anastomotic toe.

Comparisons of Ultrasound Modalities

In Figure 2 and Video 1, a BFI image of the standard case with a technically perfect and patent anastomosis is shown. In this case, a significant occlusion is induced proximally in the LAD by snaring. Artifacts in the color Doppler image information for this example, relating to the limitations of angle dependency and velocity aliasing, are indicated by solid arrows, and the dashed arrows indicate the movement of the speckle pattern as observed by BFI.

The results of the evaluations made by the three observers are presented in Figure 3. The corresponding *P* values as calculated using the Wilcoxon signed-rank test are given for each observer evaluation. A difference in favor of BFI can be observed with regard to median visual analogue scale scores. A nonsignificant result was found only for observer 2 in the assessment of flow from the LIMA graft directed into the distal LAD.

Special Cases

Case 1. The image of an anastomosis without proximal snaring of the LAD using BFI is shown in Figure 4 and Video 2. Complex flow patterns resulting from this competition were observed within the anastomosis.

Case 2. The image of a stenosed anastomosis using BFI is shown in Figure 5 and Video 3. In the systolic phase of the cardiac cycle, an increased flow rate was observed passing through the LIMA proximally into the LAD, caused by the increased resistance of the stenosis (pre-stenotic flow patterns). In the diastolic phase of the cardiac cycle, jet-like post-stenotic flow patterns were observed, as well as the formation of turbulence and small eddies distal to the stenosis.

Case 3. The image of a distally snared anastomosis using BFI is shown in Figure 6 and Video 4. A substantial increased flow rate from the LIMA directed proximally into the LAD was observed.

DISCUSSION

With the exception of coronary artery bypass surgery, virtually all other interventions on the heart, including heart valve surgery and coronary stenting, are usually accompanied by diagnostic imaging on completion to ensure a satisfactory result. There is currently no

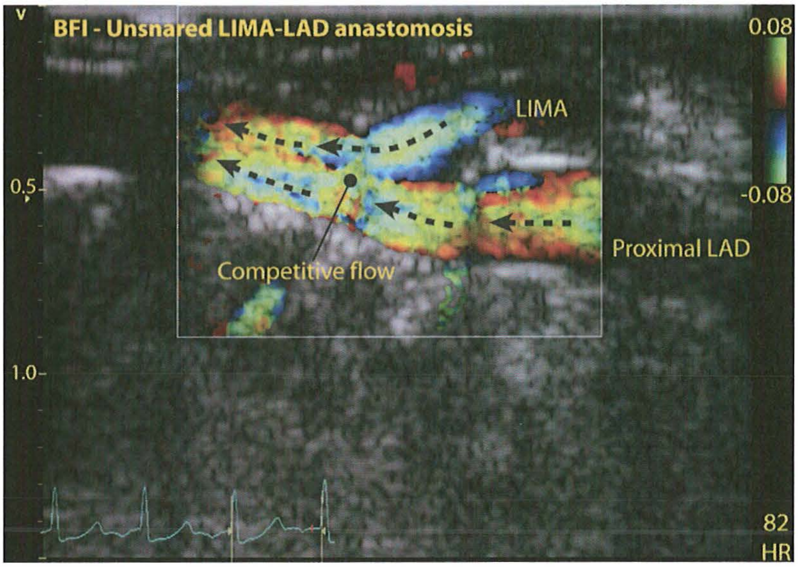

Figure 4 BFI image of the LIMA-LAD anastomosis with the LAD unsnared. Because no significant stenosis exists either proximally or distally in the LAD, competitive downstream flow could be observed (*dashed arrows*). *LIMA*, Left internal mammary artery; *LAD*, left anterior descending. View video clip online.

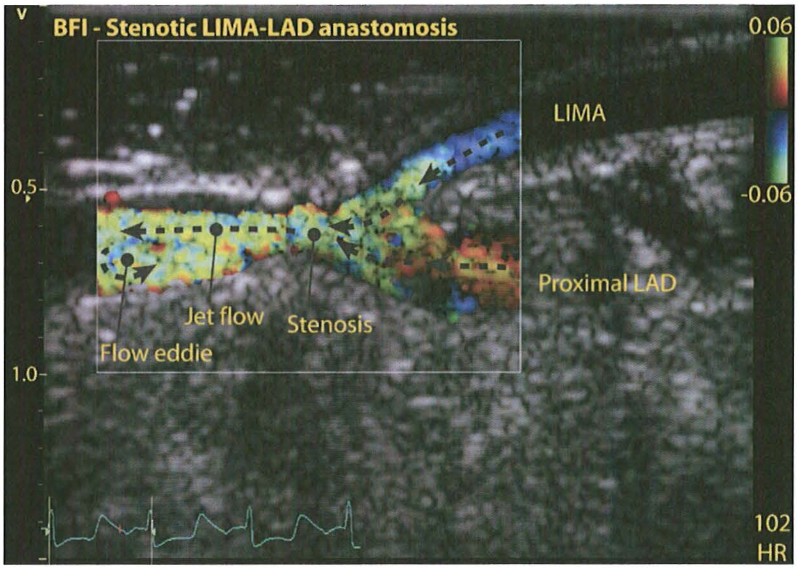

Figure 5 Stenosed LIMA-LAD anastomosis imaged with BFI. In the diastolic phase of the cardiac cycle (as shown here), jet flow through the stenosis in the toe of the anastomosis and flow turbulence and eddies distally to the anastomosis could be observed (post-stenotic flow patterns). In systole, an increased flow rate could be seen proximally into the LAD that can be attributed to the increased flow resistance because of the stenosis (pre-stenotic flow patterns). *BFI*, blood flow imaging; *LIMA*, left internal mammary artery; *LAD*, left anterior descending. View video clip online.

standard imaging method for intraoperative assessment in coronary surgery.

Intraoperative ultrasound has shown potential for clinical use in coronary artery bypass surgery,[3-5] and both B-mode tissue imaging and color Doppler flow imaging has been used to provide reliable information for the evaluation of the anastomosis geometry throughout the complete cardiac cycle.[11] In addition to the evaluation of the anastomosis geometry, the evaluation of flow patterns inside the

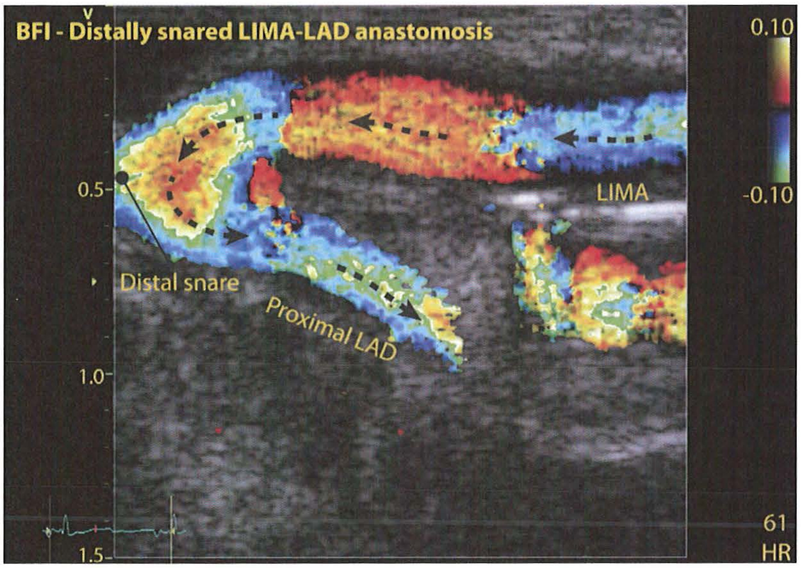

Figure 6 BFI image of the LIMA-LAD anastomosis with a distal snare on the LAD. Because of the distal occlusion, an increased flow rate from the LIMA directed proximally into the LAD could be observed (*dashed arrows*). *BFI*, Blood flow imaging; *LIMA*, left internal mammary artery; *LAD*, left anterior descending. View video clip online.

anastomosis is important. Ideally, when the anastomosis is correctly placed distal to a significant stenosis, the blood should run smoothly from the graft through the anastomosis and into both the distal and proximal segments of the coronary vessel, providing adequate blood supply to the ischemic myocardium. The small dimensions of the vessels involved (1-2 mm) coupled with the dynamic changes in the cardiac cycle increase the complexity of the flow fields, which requires both a high spatial resolution and a high frame rate for adequate imaging.

An epicardial stabilizer is usually used for performing the distal anastomosis off-pump. Subsequently the imaging is performed with the same stabilizer in place. An apical stabilizer is also recommended during imaging if the bypass operation is performed with the use of a heart-lung machine, but imaging can also be performed without an apical stabilizer by manually stabilizing the heart before weaning off the heart-lung machine.

Generally, the time required to obtain reliable images were within 1 minute, whereas for recording good-quality images, 2 to 3 minutes might be needed. It is easy to train a surgeon to obtain good images, and it does not require much knowledge in ultrasound. However, a technician, an anesthetist, or a cardiologist is needed outside the sterile field to handle the ultrasound unit.

In this study we compared CDI with the BFI modality, which in addition to Doppler images, provides a qualitative visualization of the movement of blood that is not affected by angle dependencies or velocity aliasing. For intraoperative assessment, one can argue that the use of the information presented in the color images is mainly qualitative, that is, to get an impression of overall flow patterns in the anastomosis. In this respect, the BFI modality may provide a more intuitive and detailed image of flow with less demand on interpretation. This was supported by the independent observer evaluations of different aspects related to imaging of flow direction and velocity dynamics. The new modality more adequately portrayed the complex flow in the anastomosis and may therefore increase the certainty and efficiency of flow assessment in the operating room.

The evaluation of flow direction in the anastomosis is important to validate satisfactory blood flow from the graft to the ischemic areas of the myocardium. A near perpendicular angle and the tortuous nature of the coronary artery versus the ultrasound beam may lead to unreliable Doppler measurements and an image that is prone to different interpretations because of angle dependencies. Specifically, the detailed flow path around the anastomotic toe and heel are considered hard to evaluate on the basis of color Doppler images.[9]

We asked the observers to evaluate the modalities with respect to imaging of flow directed from the LIMA distally and proximally into the LAD, and with respect to competitive flow in the anastomosis. As evident from Figure 5, the BFI modality was generally rated higher than CDI with regard to these aspects. All results were statistically significant, with the exception of one observation in the evaluation of distal flow direction.

Ultrasound assessment of changes in blood flow velocity, turbulence, and flow pulsatility is important to detect stenoses and abnormal changes in flow resistance. Pulsatility measurements have been used for the evaluation of flow conditions.[12] Although the speckle visualization technique provided by BFI is not based on quantified blood velocities, relative velocities in different parts of an image and throughout the cardiac cycle are well visualized. In fact, all observers rated BFI as superior in the assessment of flow pulsatility, which indicates that the speckle movement in BFI provides a display with a higher dynamic range of velocities. This may have potential benefits when assessing highly dynamic flow as seen in the coronary arteries.

Because of the high dynamics of the flow through the anastomosis, aliasing artifacts obscured the Doppler information in all clips at some stages of the cardiac cycle. Different pulse-repetition frequencies were used in the image recordings as presented to the observers, and the Doppler velocity range and amount of aliasing present in the images therefore varied. Because the color images were identical for both CDI and BFI in the clips generated offline, an equal amount of aliasing was present for both modalities. When asked how influenced they were with aliasing when assessing flow direction and velocity, the observers were consistently less influenced when the BFI speckle movement was included. This advantage of BFI may reduce the need to adapt the velocity scale during intraoperative evaluation of flow in the coronary arteries and anastomoses.

In ultrasound imaging, the demands of frame rate often compromise the image quality. This becomes particularly relevant when imaging the coronary arteries because of their small dimensions and the high flow dynamics. In our BFI application, six speckle images were generated for each color image. This six-fold increase in frame rate provided more information of the flow in the LIMA-LAD anastomosis, and an increase in spatial resolution was also confirmed applicable while retaining a sufficiently smooth display of flow information.

The results from the observer evaluation of flow conditions in the standard cases are expected also to be applicable clinically. The properties of BFI were further examined in three special cases in which realistic abnormalities had been induced, so that the observer evaluations can be put into perspective of what might happen in a clinical setting. When the LAD is left unsnared, flow from the proximal part of the LAD can be observed mixing with the LIMA flow in the anastomosis. Such competitive flow patterns might be an indication of placement of the graft below a nonsignificant stenosis. In the stenosed case, an increased flow into the proximal LAD in the systole and an accelerated stenotic flow in the diastole were clearly visualized. Further, in the post-stenotic flow, jet-like flow qualities and flow turbulence could be observed. For the distally snared anastomosis, the directional flow information provided by BFI clearly visualized an increased amount of blood moving from the LIMA proximally into the LAD.

STUDY LIMITATIONS

Because no gold standard is available to provide a reference regarding flow conditions, the evaluations were based on expert opinions, and the results must be viewed in light of this. Although all observers were experts in interpreting color flow images, they had different professional backgrounds that may have influenced the results. In this study only LAD anastomoses were investigated. For other less-accessible coronary arteries, a sufficient image quality for the evaluation of anastomosis patency may be more difficult to obtain. This aspect should be further investigated.

CONCLUSIONS

The BFI modality offers new information about flow conditions in the LIMA-LAD anastomosis not readily available using CDI. Because BFI is not limited by angle dependencies, a more intuitive and instant appreciation of flow conditions can be obtained in the operating room. As conventional Doppler information is also present, the BFI modality may replace CDI in the evaluation of anastomosis flow in the future. The BFI modality may also have potential for improved imaging of flow in other areas of cardiac surgery, for example, in valve surgery and aortic dissection. Further investigations should be performed to establish this potential.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.echo.2008.01.019.

Paper IV

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Enhanced intra-operative grading of ascending aorta atheroma by epiaortic ultrasound vs echocardiography

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Abstract

Aims: Intra-operative grading of atheromatous plaques in the ascending aorta by epiaortic ultrasound (EAU) and transesophageal echocardiography (TEE) in patients who have undergone CABG.
Methods and results: Sixty patients scheduled for elective CABG were prospectively enrolled to undergo intra-operative TEE and EAU ultrasound scanning of the ascending aorta. The ascending aorta was divided into three sections; proximal, middle and distal, and four segments; anterior, posterior, medial and lateral. Degree of atherosclerosis was graded according to a modified Montgomery scale.

Epiaortic ultrasound was unable to provide images for a reliable assessment in 56 areas (7.7%; 56/720) vs 322 non-visualized areas by TEE (44.7%; 298/720) ($p<0.01$). Out of 563 areas that scored ≥2, EAU visualized 379/720 areas (52.6%), whereas TEE visualized 184/720 areas (25.5%) ($p<0.01$). EAU mean scores were significantly higher for the mid ($p=0.0001$) and distal ($p=0.05$) sections and for the posterior segment ($p<0.01$) vs TEE. TEE had a higher mean score than EAU in the anterior segment. When all EAU areas were grouped the posterior segment reached a significantly higher mean score ($p<0.01$), and the anterior segment was the second mostly diseased.
Conclusions: EAU is the intra-operative investigation of choice because it allowed a detailed grading of atheromatous lesions over the entire length of the ascending aorta. Accurate grading by TEE was restricted only to those areas that could be sufficiently visualized. TEE has a reduced power of investigation that limits its use, especially in the distal ascending aorta, a site of great surgical manipulation.

Keywords: Epiaortic ultrasound; Aortic atheroma; Transesophageal echocardiography

1. Introduction

Coronary artery bypass grafting (CABG) surgery is the cardiac operation most frequently performed worldwide because of its excellent results in the long-term. Unfortunately there are some post-operative complications among which cerebral ischemia is the most frequent [1]. Cerebral ischemia is a broad definition of all the neurological complications, ranging from neurocognitive disorders to stroke, that may occur in the early postoperative time. The rate of neurocognitive disorder is estimated between 0.4 and 60% of patients, according to the definition and methods applied for its diagnosis [1]. Stroke has a rate of occurrence up to 9% [2–7], and it is considered one of the most serious complications after coronary surgery.

Cerebral ischemia is believed to be mostly due to intra-operative embolisation of atheromatous plaques from the ascending aorta [8–10]. Manipulation of the ascending aorta is required for cannulation, cross-clamping and suturing of proximal anastomoses. Pre- or intra-operative diagnosis of the atheromatous aorta may decrease the incidence of cerebral complications [5]. In one study, the use of intra-operative EAU aided changing the planned surgical strategy in 28% of the patients: 24% were converted from on-pump CABG to

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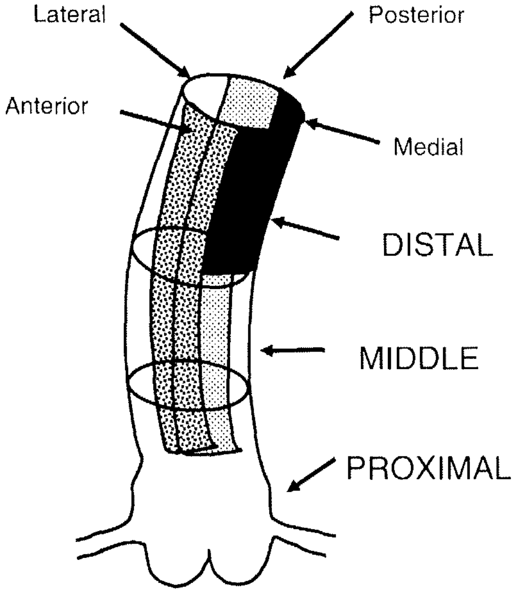


Fig. 1. Transverse and longitudinal partition of the ascending aorta into three sections (proximal, middle, distal) and four segments (anterior, posterior, lateral, medial) for purposes of the ultrasound analysis.

OPCAB, and it influenced the choice of the aortic cannulation, cross-clamping, and proximal anastomosis site in 4% of the patients [11], while in another study TEE aided major and minor changes in 26% of patients who underwent off-pump CABG [12]. Scanning of the ascending aorta can be carried out by means of computed tomography (CT) or magnetic resonance (MRI) scans, by trans-esophageal echocardiography (TEE) and more recently by epiaortic ultrasound (EAU).

Computer tomography scan has been demonstrated to be less sensitive than EAU in detecting atheromatous plaques in the ascending aorta [13], whereas MRI is considered to have the same degree of sensitivity as TEE [14]. Unfortunately MRI has several disadvantages that reduce its application, as being expensive and it is contraindicated in patients with claustrophobia. At the present time TEE and EAU are the techniques of choice for intra-operative detection of atheromatous plaques in the ascending aorta [15,16]. According to these studies EAU provided better visualization of the distal portion of the ascending aorta, whereas TEE showed better images of the proximal part of the aorta. Nonetheless, none of the techniques have been tested so far with regard to precise grading of aortic atheroma and detailed direct comparisons have not been reported. Most studies have simply assessed the presence or absence of atheroma with or without calcifications [4–6].

The purpose of the present study was to improve the intra-operative grading and assessment of atheromatous plaques in the ascending aorta by means of EAU and TEE in patients undergoing CABG, with the aim to ascertain which of the two modalities are more reliable for routine intra-operative use.

2. Materials and methods

A total of 60 patients scheduled for elective CABG were prospectively enrolled at the two cardiac centers participating in the study from 1998 to 2005. The patients were predominantly males (46; 76.6%) with a mean age of 69.6± 10.4 years. Four patients had a history of a cerebro-vascular accident (6.6%) and one patient had a carotid artery stenosis (1.6%). The patients were chosen on the basis of availability of both equipment and trained personnel on the day of surgery. Each patient underwent TEE and EAU of the ascending aorta. The study protocol was approved by the Regional Medical Ethics Committee on Human Research at the two institutions.

3. Ultrasound methods

3.1. Transesophageal echocardiography

After induction of general anesthesia, TEE was carried out by a 5-MHz biplane TEE transducer (GE Vingmed, Horten, Norway) connected to a GE Vingmed System FiVe or GE

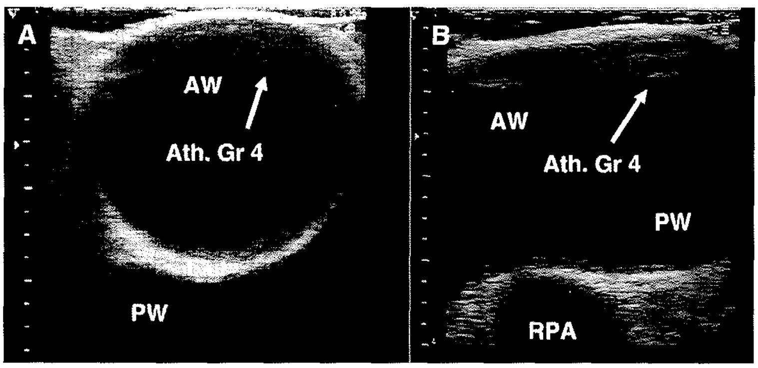


Fig. 2. Epiaortic ultrasound scanning of the middle section of the ascending aorta: cross- (A) and longitudinal section views (B). In both views the grade 4 atheroma lesion of the aorta anterior wall is clearly visible. Ath gr 4 = atheroma grade 4; AW = anterior wall; PW = posterior wall; RPA = right pulmonary artery.

Table 1
Number of areas sufficiently visualized for reliable assessment by EAU and TEE (McNemar's test)

	Distal			Middle			Proximal		
	EAU	TEE	*p*	EAU	TEE	*p*	EAU	TEE	*p*
Anterior *n*=60	55	2	0.0001	55	58	0.375	56	59	0.375
Lateral *n*=60	55	2	0.0001	55	19	0.0001	56	58	0.688
Medial *n*=60	55	2	0.0001	55	20	0.0001	56	58	0.688
Posterior *n*=60	55	2	0.0001	55	58	0.375	56	58	0.688
Total	220	10		220	154		224	233	

Vivid 7 (GE Vingmed, Horten, Norway). The TEE was performed by a cardiologist with experience in evaluation of the thoracic aorta with the aim to optimize images of the ascending aorta in both transverse and longitudinal view planes.

3.2. Epiaortic ultrasound

After median sternotomy and harvesting of the left internal mammary artery (LIMA), the ascending aorta from the aortic root to the origin of the brachio-cephalic artery was scanned directly by the surgeon using a GE Vingmed i8.5L probe connected to a GE Vingmed Vivid 7 ultrasound scanner (GE Vingmed, Horten, Norway). The probe is a linear array transducer designed for intra-operative epiaortic imaging with frequencies of 8.5 MHz. It has a foot-print dimension of 43 mm × 17 mm. A finger of a surgical glove filled with sterile saline solution was used as ultrasound medium between the aortic wall and the probe. The distance between the probe and the anterior aortic wall was around 2 cm.

EAU and TEE images from longitudinal and transverse view planes were obtained and recorded on 0.5-in S-VHS videotapes for subsequent off-line evaluation.

3.3. Ultrasound analysis

For the purpose of analysis, as adopted in a previous study [17], the ascending aorta was divided into three sections: the proximal section was from the aortic annulus to right below the tract of the aorta overlapping the right pulmonary artery, the middle section was considered as the segment of the ascending aorta overlapping the right pulmonary artery, and the distal section was defined from the upper limit of the middle section to the origin of the brachiocephalic artery. The whole circumference of the aorta was divided into four segments: anterior, posterior, medial and lateral; see Fig. 1. Thus the ultrasound scanning of each ascending aorta comprised 12 areas (3 sections × 4 segments), for a total of 720 units (60 patients × 12 areas) at the end of the study.

The degree of atherosclerosis was graded according to the morphology of atheromatous plaques by the Montgomery scale modified with the aim to detail aortic lesions [7]. The scale was as follows: grade 1 = normal; grade 2 = intimal thickening; grade 3 = atheroma < 4 mm; grade 4 = atheroma > 4 mm; grade 5 = any mobile (a) or ulcerated atheroma (b). Thickening was considered as a smooth non-protruding lesion of the intima lining the entire lumen of the aorta. Atheroma was a localized lesion protruding into the lumen.

The images were reviewed by a cardiac surgeon and two cardiologists; the consensus within the three assessors was reached for each area detected.

Intra-operatively the surgeon adjusted his surgical technique (e.g. site of insertion of the aortic cannula, cross-clamp and placement of vein grafts) if information gathered from the ultrasound investigations indicated atheromatous aortic areas.

3.4. Statistical analysis

Results were presented as mean Montgomery grade ± standard deviation (SD) for each area and method separately. The statistical significance of the observed difference in visualization between TEE and EAU for each single area was calculated from the McNemar's test for paired samples. The areas with comparable visualization were further studied to assess statistically the difference in detection and grading of atherosclerosis between the two methods. The identification of a normal or an atherosclerotic intima (Montgomery ≥ 2 score) was compared using the McNemar's test, and the difference in Montgomery grading between TEE and EAU

Table 2
Survey of areas scoring a Montgomery grade ≥ 2; areas sufficiently visualized by both EAU and TEE or by one method only (McNemar's test)

Area		Total number of areas with Montgomery grade ≥ 2		Number of areas identified by one method only		Likelihood of random distribution
	N	EAU	TEE	EAU	TEE	*p*
Proximal						
Anterior	55	34	46	3	14	0.004
Lateral	54	25	18	14	5	0.167
Medial	54	28	21	13	6	0.167
Posterior	54	45	33	14	2	0.004
Middle						
Anterior	54	30	20	18	8	0.078
Posterior	54	42	18	26	2	0.0001

Table 3
Comparison of severity grading in areas sufficiently visualized by both EAU and TEE (paired comparison: Wilcoxon's test)

Area	Pts	EAU					TEE					EAU vs TEE			
		Montgomery grade					Montgomery grade					EAU>TEE	EAU<TEE	EAU=TEE	
		1	2	3	4	5	1	2	3	4	5				
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	*P*
Proximal															
Anterior	55	21	28	3	3	0	9	31	12	3	0	5	20	30	0.004
Lateral	54	29	23	1	1	0	36	17	1	0	0	13	6	35	0.175
Medial	54	26	25	2	1	0	33	19	1	1	0	14	7	33	0.088
Posterior	54	9	37	5	3	0	21	27	5	1	0	19	7	28	0.020
Middle															
Anterior	54	24	26	1	3	0	34	20	0	0	0	22	8	24	0.006
Posterior	54	12	35	3	4	0	36	18	0	0	0	31	2	21	0.0001
Total				14	15				19	5		104	50		

was analyzed by Wilcoxon's matched pairs signed rank sum test. A *p* value <0.05 was considered significant. The analysis was carried out using the SPSS software version 14 (SPSS Inc., Chicago, Illinois).

4. Results

There was no operative mortality or myocardial infarction in any patient. Patients received a mean of 3.7 ± 1.1 distal and 1.9 ± 0.8 proximal anastomosis/patient. In one patient the procedure had to be converted to on-pump beating heart CABG to avoid cross-clamping because of grade 4 aortic atheroma, see Fig. 2. One patient developed left hemiparesis on post-operative day 1 despite having only a grade 2 aortic atherosclerosis.

The number of units that were sufficiently visualized for a reliable assessment by EAU was 664/720 (92%) vs TEE 398/720 (55.3%) ($p<0.01$). In detail, the aortic areas visualized by EAU were equally distributed over the three sections and four segments, whereas most of the areas not visualized by TEE were in the distal and middle part of the ascending aorta (see Table 1).

In those areas sufficiently visualized by both EAU and TEE, the overall number of areas recognized with a Montgomery grade >2 by only one of the two methods was: EAU 88/334 (26%) vs TEE 37/349 (11%), see Table 2. In detail, TEE was more sensitive in detecting atheroma in the anterior areas of the proximal segment of aorta only, showing few areas in the middle and almost no atheroma in the distal ascending aorta. In comparison, EAU detected almost similar numbers of diseased areas in all locations.

Table 4
Comparison of total number of units in the ascending aorta with a modified Montgomery score ≥ 2 as assessed by EAU vs TEE scanning

	Total units investigated	EAU	TEE
Grade 2	720	314	149
Grade 3	720	31	25
Grade 4	720	25	5
Grade 5	720	2	0

With regard to the severity of atheroma graded by the modified Montgomery criteria in areas sufficiently visualized by both methods (Table 3), TEE scored higher only in the proximal anterior area while EAU scored higher in all others although to a variable statistical power.

Taking all the sections of the ascending aorta together, EAU was superior in tracing atheromatous areas than TEE. Epiaortic ultrasound detected a far higher number of grade 4 atheromas than TEE; 25 vs 5, respectively. In addition the two atheromatous areas graded 5 were detected by EAU only (see Table 4).

The Bland–Altman test of agreement reflected the mismatch between lesion scores using the two ultrasound scanning techniques. These data suggest that the extent and degree of atheromatous lesions in the ascending aorta may be underestimated by TEE (Fig. 3).

The mean severity of atheroma in all the twelve areas of the ascending aorta scanned by EAU is illustrated in Fig. 4. The posterior section was the most atheromatous along the whole length of the ascending aorta, this feature reaching

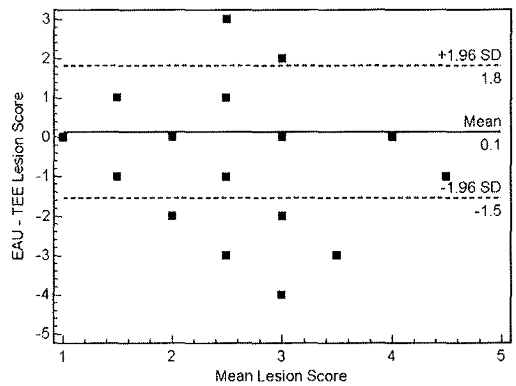
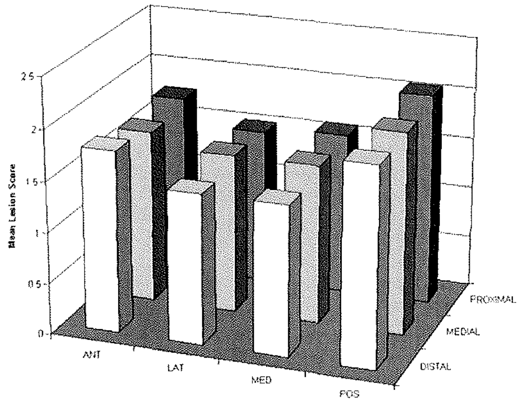


Fig. 3. Bland–Altman plot of atheromatous lesion scores by EAU vs TEE. Transesophageal echocardiography underestimates the extent and degree of lesions in the ascending aorta.



	ANT	LAT	MED	POS	p
DIS	1.78 ± 0.83	1.47 ± 0.66	1.47 ± 0.79	1.95 ± 0.65	<0.0001
MED	1.69 ± 0.77	1.56 ± 0.76	1.56 ± 0.71	1.98 ± 0.76	0.008
PROX	1.77 ± 0.79	1.52 ± 0.63	1.59 ± 0.65	2.07 ± 0.74	<0.0001
p	0.82	0.86	0.41	0.72	

Fig. 4. Overall grading of atheromatous lesions in the ascending aorta by EAU mean scores. The cross-matching of the three sections (proximal, middle, distal) and four segments (anterior, posterior, medial, lateral) divides the aorta in 12 square-shaped areas.

statistical significance ($p<0.01$). The anterior segment was the second most diseased portion.

5. Discussion

The first step of our study was to assess the number of areas sufficiently visualized by each of the two techniques as it has been shown that EAU visualized more areas than TEE [5,7]. Our results confirmed previous observations because EAU provided a more enhanced visualization of the wall of the ascending aorta in its entire length and this allowed a reliable assessment of the atheromatous plaques. Epiaortic ultrasound scanned a far higher number of areas along the aortic wall (92.3% of the entire ascending aorta) than TEE (only 55.3%). The degree of visualization by TEE varied according to sections and segments of the aorta; being highest proximally and decreasing to the distal ascending aorta where imaging is difficult or impossible due to the interposing airways between the oesophagus and the upper part of the ascending aorta [15]. This "blind spot" is a limitation of TEE that may be solved by the use of an aortic view technique [16]. The distal part of the ascending aorta is a site of great intra-operative manipulation as the aortic CPB cannula and the cross-clamp are placed in this area. Thus thorough scanning of the distal ascending aorta with precise information on the likely location, extent and degree of atheromatous plaques are necessary to avoid embolization of atheroma debris from the aortic wall.

As far as grading of the atheromatous disease in the sufficiently visualized areas of the ascending aorta was concerned, EAU identified a higher number of areas with a Montgomery score ≥2 compared to TEE. Epiaortic ultrasound scanning identified almost a similar number of diseased areas over the visualized areas. On the other hand TEE presented with some differences according to the areas being investigated. The areas which were better assessed by TEE were only those in the proximal anterior area. The diseased proximal anterior areas were better detected by TEE than by EAU because a thorough EAU scanning of the proximal–anterior area requires surgical dissection of the fat pad covering the aortic root for correct placement of the ultrasound probe. Removing the fat pad off the aortic root is not usually carried out in CABG surgery as it is unnecessary. The higher yield of positive diagnoses in the anterior and posterior segments than in lateral segments may in part be due to the better axial than lateral resolution of ultrasonic imaging.

A further step of our study was the evaluation of the atheroma grading severity in the sufficiently visualized areas as assessed by Montgomery grade by both EAU and TEE scanning and comparing the two techniques. Wilcoxon test gave us a good opportunity to detect in which areas were EAU superior and in which it was inferior to TEE. TEE was only superior in the proximal anterior areas, this is probably related to the limited visualization by EAU at these areas.

Finally the Bland–Altman method was used to test whether there was agreement between TEE and EAU with the aim to find out whether one of the two techniques underestimated atheromatous lesions. We did confirm that TEE underestimates the extent and degree of aortic wall lesions.

Using EAU, we observed the highest prevalence and severity of atheroma in the posterior segments of the ascending aorta, especially in the proximal section. The second most atheromatous segment was the anterior one, especially in the distal and proximal sections. The regional pattern of development of atheroma is determined initially by local variations in shearing forces and endothelial dysfunction [15]. We observed lower mean scores in the lateral and medial segments, probably because the EAU probe had to be placed in a suboptimal position (i.e. not perpendicular to the aortic wall) because of restricted space due to the pericardium (laterally) or the pulmonary artery (medially). In their extensive study [18], Linden et al. concluded that the distal–medial area was the one with fewest atherosclerotic lesions. However, we tend to believe that this finding may be influenced by the reduced power of EAU to investigate this area due to a suboptimal placement of the probe.

The clinical implications of our study are important during an operation when a careful placement of the cross-clamp is relevant to avoid dislodgement and embolisation of atheromatous debris from the inner aortic wall. When a heavily diseased posterior segment is demonstrated, a Fogarty cushion-shod clamp may carefully be applied. Unfortunately atheromatous lesions of the anterior section of the aorta are more difficult to deal with, but identifying their location enables the surgeon to avoid those particular areas or to adopt all the technical options that have the aim of reducing a likely embolization of atheromas (i.e. off-pump technique, "no touch" strategy, single clamp technique, distal aortic arch cannulation, etc.).

In conclusion, epiaortic ultrasonic scanning is the intraoperative investigation of choice to detect aortic atheroma, because it is superior in its ability to screen the entire length of the ascending aorta and provide a detailed grading of lesions. Grading by TEE is restricted to those areas that can be visualized, and it is most limited in the distal ascending aorta which is a site of great surgical manipulation. Cardiac surgeons who wish to employ ultrasonic imaging to detect atheroma before aortic cross-clamping and bypass circulation, so that they can use its results to modify operative techniques and minimise the risk of atheroembolism, should use epiaortic scanning rather than transesophageal echocardiography.

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Paper V

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Quick Intraoperative Diagnosis of Coronary Subclavian Steal Syndrome after CABG by Transit-Time Flowmetry and Epicardial Ultrasound Imaging: Case History

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Introduction

The left internal mammary artery (LIMA) remains the conduit of choice in coronary artery bypass grafting (CABG) surgery because of its documented long-term patency [1,2]. Coronary subclavian steal syndrome (CSSS) is the phenomenon of retrograde flow (steal) through the pedicled LIMA which may occur after CABG due to concurrent proximal stenosis or occlusion of the ipsilateral subclavian artery [3]. It was first recognized as a cause of early recurrent angina following CABG in 1974 (4), and may have an incidence of up to 3–4% [5].

Several clinical features may lead to the diagnosis of CSSS after CABG with the pedicled internal mammary artery; occurrence of early recurrent angina often increased by ipsilateral arm movement, ischemia of the ipsilateral arm along with reduction of systolic blood pressure of ≥20mmHg, cerebral ischemic events or bruits over the subclavian artery [6,7].

Aortic arch and coronary angiograms are the golden standards for diagnosis of CSSS, as the former shows late filling of the left subclavian artery through the circle of Wills, whereas the latter demonstrates retrograde flow in the internal mammary artery [8]. Treatment of CSSS is either by percutanous transluminal angioplasty (PTA) or surgery [9–12] of the subclavian artery stenosis.

In this report we present a case of CSSS after CABG with a pedicled LIMA which was diagnosed during the primary operation by means of combined transit-time flowmetry and epicardial ultrasound imaging. At the immediate revision, a free LIMA-graft was successfully anastomosed to the ascending aorta so as to avoid any of the complications of CSSS.

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Case History

A 61-year-old, hypertensive male patient with stable angina was referred for elective CABG due to a 70% LAD stenosis at its origin that was not suitable for a PTCA. On clinical examination after admission to our department, the left radial pulse was slightly weaker than the right one; blood pressure was 170/80 in the right and 130/70 in the left arm. However, the patient did not complain of ischemic deficits to his left arm.

At operation, off-pump grafting of a pedicled LIMA onto the LAD was performed. At the end, transit-time flowmetry (Medi-Stim flowmeter, Oslo, Norway) and epicardial ultrasound imaging were carried out as routine intraoperative graft assessment after off-pump CABG at our institute [13]. Transit-time flowmetry is a Doppler ultrasound method used to assess graft patency on the basis of mean graft flow and derived values, such as the pulsatility index. It is the most widely used method to assess the patency of bypass grafts intraoperativelv due to its simplicity and reliability. The epicardial imaging was obtained by a GE i13L (13 MHz) linear array transducer connected to a GE Vivid 7 ultrasound scanner. (Vingmed GE, Horten, Norway). The transit-time flow rate in the LIMA graft was −14 ml/min without any LAD snaring, but increased up to 40 ml/min when the LAD was snared proximal to the anastomosis. Epicardial color Doppler imaging showed retrograde flow through the LIMA graft (Fig. 1) that turned antegrade when the LAD was snared proximal to the anastomosis (Fig. 2). A quick diagnosis of a coronary subclavian steal syndrome was reached.

Immediate surgical revision was carried out by ligating and cutting the LIMA graft proximally and anastomosing its top-end to the ascending aorta as a free aorto-coronary conduit. Control-flow measurement in the LIMA graft was 39 ml/min. Epicardial ultrasound imaging confirmed normal antegrade blood flow through the anastomosis (Fig. 3). The postoperative course was uneventful and the patient was discharged home. A postoperative MRI angiogram showed a proximal stenosis of the left subclavian artery (Fig. 4). The patient is free of angina and without any CSSS complications 1 year after surgery.

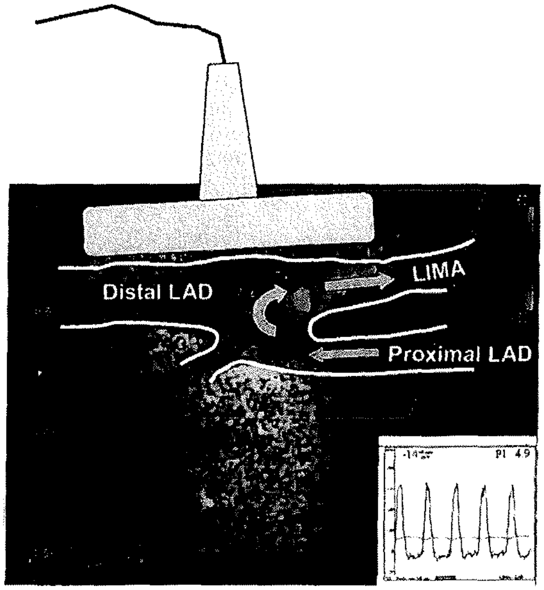

Fig. 1. Epicardial color Doppler imaging showing the steal phenomenon. The blue color shows the blood flowing retrograde into the LIMA (arrows). This observation was supported by the mean flow measurement of −14 ml/min in the pedicled LIMA graft (see inserted flowmetry diagram).

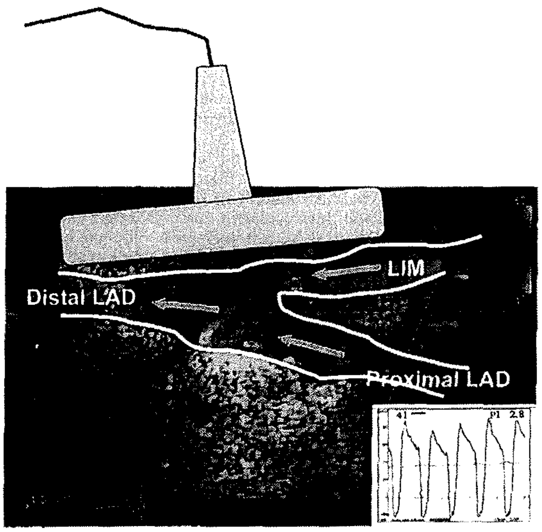

Fig. 2. After snaring the LAD proximally, epicardial color Doppler imaging showed the antegrade LIMA flow passing distally through the anastomosis (arrows). The mean LIMA flow rate was 41 ml/min (see inserted flowmetry diagram).

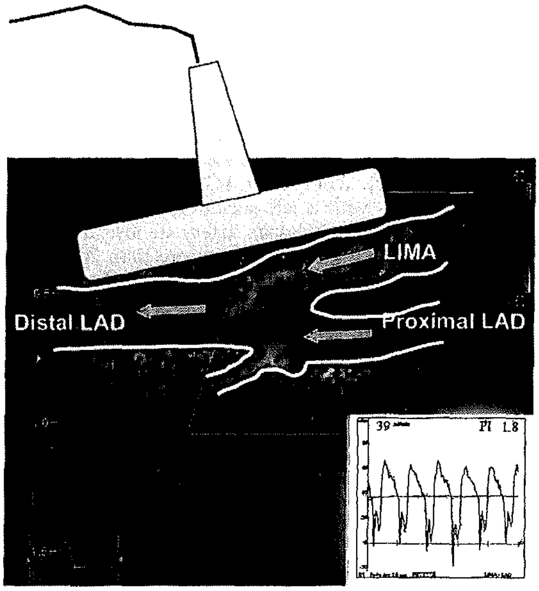

Fig. 3. Epicardial color Doppler imaging after creating a free LIMA graft as an aorto-coronary conduit. The antegrade flow direction in the graft and anastomosis is confirmed by the red color and the mean flow rate is 39 ml/min (see inserted flowmetry diagram).

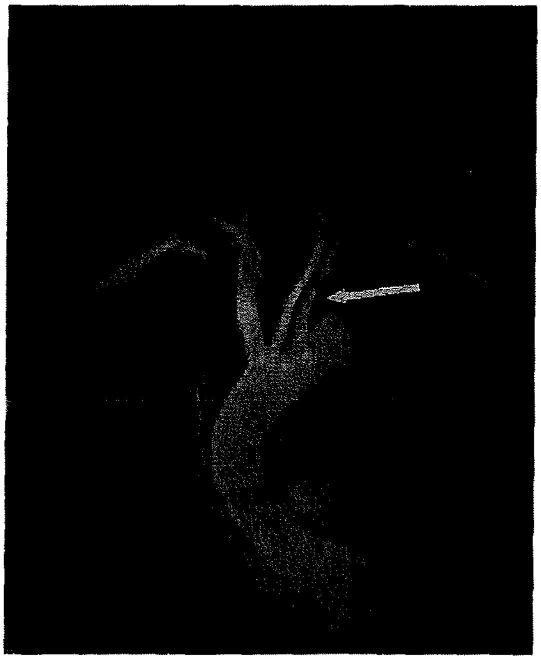

Fig. 4. The contrast-enhanced T1-weighted 3D MR angiography is showing irregular vessel contours in the left subclavian artery (arrow) indicating a stenosis.

Discussion

This case report shows the usefulness of transit-time flowmetry and epicardial ultrasound scanning for a quick intraoperative diagnosis of coronary subclavian steal syndrome. CSSS may be a reason for early occurrence of angina after CABG; this is caused by retrograde blood flow (steal) from the LAD through the LIMA graft in patients with a left subclavian artery stenosis. Clinical features of subclavian artery stenosis are a difference of systolic blood pressure more than 20 mmHg between the arms, thrombo-embolism or ischemic pain to the arm. Diagnosis is made by color Doppler ultrasound or angiography.

In our patient a weaker left radial pulse and a reduced blood pressure to the left arm were reported by a junior doctor. Unfortunately, these signs were initially left unnoticed and the patient underwent CABG without any further investigation for a subclavian artery stenosis. CSSS developed immediately after grafting the LIMA onto the LAD, but it was quickly diagnosed intraoperatively by transit-time flowmetry and epicardial ultrasound scanning despite no ECG ischemic changes. The combined application of these two investigations was relevant because each of them provided information, which coupled with those given by the other one, contributed focusing the diagnosis. Transit-time flowmetry demonstrated impaired flow rate within the graft whereas epicardial imaging enabled visualization of the anastomosis and \retrograde blood flow from the LAD through the LIMA. Of note, when proximal snaring of the LAD was applied, the change of direction of the blood flow through the anastomosis with a sudden increase of its rate were clearly demonstrated by the ultrasound scanning and transit-time flowmetry, respectively. As a result of a quick intraoperative diagnosis, prompt surgical revision was carried out, avoiding intra- or postoperative complications to the patient. On the other hand, missing the diagnosis of CSSS at surgery would have exposed the patient to very unpleasant consequences in the follow-up, such as early recurrence of angina, an aortic arch and selective coronary angiogram followed by subclavian artery PTA or carotid-subclavian bypass or redo CABG surgery.

In conclusion, both transit-time flowmetry and epicardial color Doppler ultrasound are useful in coronary surgery, especially when applied together These two investigations are reliable, easy and rapid tc apply and safe for the patient. The combined application of transit-time flowmetry and epicardial ultrasound imaging was pivotal in the intraoperative diagnosis and treatment of a coronary subclavian steal syndrome avoiding further and dangerous consequences to the patient.

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109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
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115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160.Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161.Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162.Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163.Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164.Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165.Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166.John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167.Geir Falck: HYPEROSMOLALITY AND THE HEART.
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169.Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170.Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171.Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172.Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173.Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174.Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175.Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176.Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177.Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178.Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179.Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180.Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181.Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182.Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183.Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184.Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185.Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186.Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187.Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188.Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189.Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION

190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
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228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
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238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY

243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
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254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE

271.Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272.Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273.Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274.Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275.Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276.Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277.Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278.Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279.Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280.Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281.Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282.Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283.Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284.Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285.Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286.Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287.Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288.Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289.Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290.Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291.Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
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