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Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model[☆,☆☆]

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Abstract

Objective: To assess whether coronary graft flow patterns are affected differently by native coronary competitive flow or by stenosis of the coronary anastomosis. **Methods:** Nine pigs (65–70 kg) underwent off-pump grafting of the left internal mammary artery to the left anterior descending artery (LAD). Transit-time flow patterns in the mammary grafts were recorded under four different conditions: (1) baseline flow (proximal LAD occluded), (2) full competitive flow, (3) partial competitive flow and (4) after creation of a stenosis in the anastomosis. Competitive flow was achieved by an adjustable occluder on the left anterior descending artery. The mean luminal stenosis of the anastomosis was 75 ± 11%, calculated by epicardial ultrasound. Mean flow, systolic and diastolic antegrade and retrograde flow during different flow conditions were calculated as ratios of baseline flow and compared. Different derived flow indexes were calculated and compared in the same manner. Friedman's test and post hoc analyses by Wilcoxon signed-ranks were performed without correction for multiple comparisons. **Results:** Mean graft flow was more reduced by competitive flow than by a stenotic anastomosis of 75 ± 11%. Competitive flow significantly decreased diastolic antegrade flow and both diastolic and systolic maximum peak flows, but increased retrograde flow, compared with baseline and stenosis. Furthermore, competitive flow and stenosis could be distinguished by analysis of several derived indexes. Pulsatility index (maximum − minimum flow/mean flow) and insufficiency percent (retrograde flow as fraction of total flow) was increased significantly more by competitive flow than by stenosis. Diastolic filling percent was significantly reduced at competitive flow compared with stenosis and baseline. **Conclusions:** The mammary graft flow was significantly reduced by native coronary competitive flow, but marginally decreased by a stenotic anastomosis of 75% mean luminal stenosis. Reduction of graft flow due to competition was particularly evident in diastole. A detailed flow pattern analysis may differentiate between competitive flow and stenosis of the anastomosis.

Keywords: Heart surgery; CABG; Anastomosis; Coronary graft assessment; Transit-time flow measurement; Epicardial ultrasound

1. Introduction

Transit-time blood flow measurement has gained popularity for assessing patency of coronary bypass grafts. It is easy and convenient for intra-operative use and provides accurate graft flow measurements with few sources of technical error [1]. However, clear cut-off values to predict the patency for different types of grafts to different target vessels have not been reported because of a wide variability among patients and grafts. Generally, a mean graft flow of under 10–15 ml/min, pulsatility index >5 and a poor diastolic flow pattern have been accepted as indicating poor graft performance, necessitating further investigation of the graft and the anastomosis [2]. When interpreting transit-time flow measurements, it is important to take the hemodynamic conditions of the coronary system into consideration. Thus low flow within bypass grafts might have numerous causes, such as high coronary resistance, small target vessels, kinking, dissection or spasm in the graft, competitive flow and anastomotic failure. Hence the use of graft flow for assessing the anastomosis may give unreliable results and lead to unnecessary revisions.

This study aimed to assess the impairment of graft flows due to competitive flow from the coronary artery or stenosis

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of the coronary anastomosis, as well as the extent of their impact. Transit-time flow patterns were measured at four different flow conditions in a left internal mammary artery (LIMA) to left anterior descending coronary artery (LAD) in a porcine model.

2. Materials and methods

Ten Noroc pigs (hybrid of 1/4 Duroc, 1/4 Yorkshire and 1/2 Norwegian landrace, weight 65—70 kg) underwent off-pump coronary artery bypass grafting (OPCAB) with LIMA-to-LAD anastomosis through a median sternotomy. One pig was excluded from the study because of hemodynamic instability throughout the study so that nine animals were included in the final analysis. The animals received good care in accordance with the European convention on animal care and Norwegian national regulations. Approval was given by the Norwegian ethics committee on animal research. All animals were treated by the same anesthesiologist and surgical team. At completion of the experiments, the animals were killed with an intravenous injection of high dose pentobarbital and potassium chloride.

2.1. Anesthesia and surgical technique

All pigs received premedication with intramuscular azaperone 4 mg/kg and ketamine 0.20 mg/kg. Anesthesia was induced with intravenous atropine 1 mg, fentanyl 0.01 mg/kg and pentobarbital 10 mg/kg. General anesthesia was maintained by infusions of fentanyl 0.02 mg/kg/h and midazolam 0.3 mg/kg/h. Amiodarone 150 mg and hexamethonium chloride 20 mg/kg were given to avoid arrhythmias. Full heparinization was achieved with heparin 10—20 000 IE intravenously. The pigs were ventilated with room air through a tracheotomy tube, and ventilator settings were adjusted according to blood gas measurements. Central venous catheters were introduced into both internal jugular veins for infusions and measurements of central venous pressure. A catheter was placed in the descending thoracic aorta for continuous measurement of arterial pressure. The bladder was drained through a cystotomy. After median sternotomy, the LIMA was harvested with its pedicle. A 16 mm flow transit-time flow probe (VeriQ flowmeter, Medi-Stim ASA, Oslo, Norway) was placed around the pulmonary trunk to measure cardiac output. ECG leads were connected to the flowmeter. An Axius vacuum stabilizer (Guidant, Santa Clara, CA) was applied to immobilize the LAD at the site chosen for grafting. A 2 or 3 mm flow probe was placed immediately proximal to the coronary arteriotomy to assess native coronary flow. Adjacent to this flow probe, an adjustable vascular occluder (In Vivo Metric, US) was applied to create either occlusion of the LAD or partial competitive flow (Figs. 1 and 3). Full competitive flow was achieved by complete pressure release of the vascular occluder. Ischemic preconditioning was performed by five repeated cycles of 30 s of LAD occlusion with 30 s of reperfusion in between. After arteriotomy of the LAD, an intracoronary shunt was placed in the vessel lumen. The LIMA—LAD anastomosis was then sutured with a continuous 7-0 Prolene to create patent anastomoses without technical failures. Patency of the anastomosis was confirmed with epicardial ultrasound imaging. At completion of the anastomosis, a 3 mm flow probe was also placed on the LIMA graft to assess graft flow (Figs. 1 and 3).

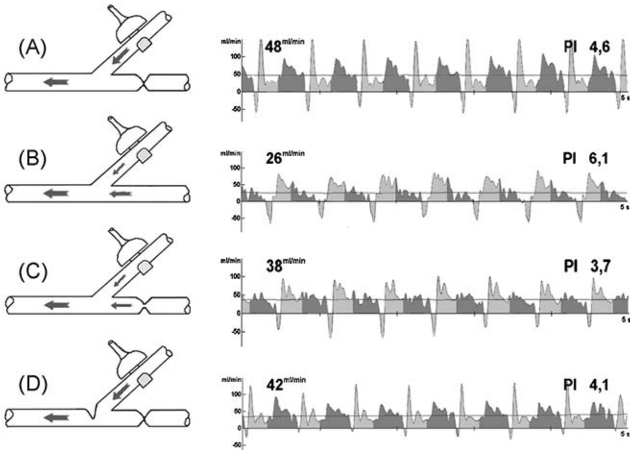


Fig. 1. Layout of the four flow conditions with typical corresponding flow curves. (A) Baseline flow with proximal LAD totally occluded. (B) Full competitive flow with no snaring of the proximal LAD. (C) Partial competitive flow with partial occlusion of LAD (approximately 50% of full competitive flow). (D) Stenotic anastomosis with no competitive flow.

2.2. Epicardial ultrasound imaging

The status of the anastomosis was assessed by epicardial ultrasound imaging before and after constructing a stenosis of the anastomosis, and with or without competitive flow.

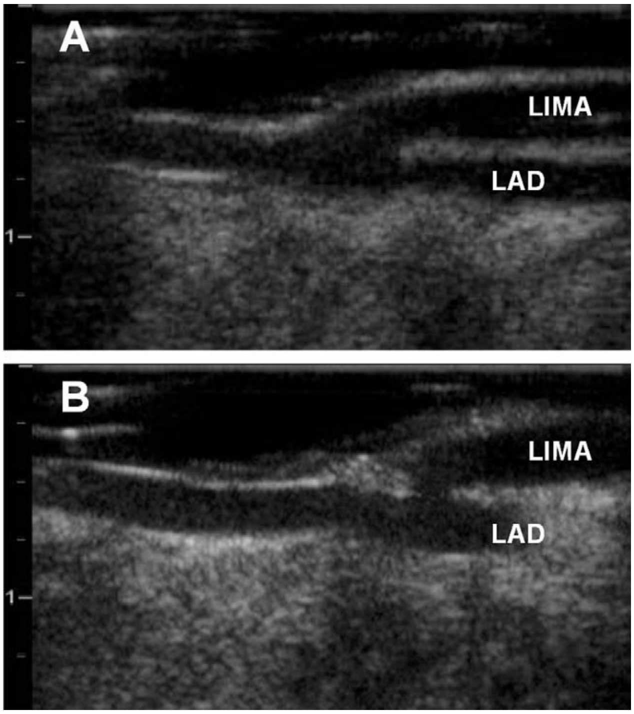


Fig. 2. B-mode ultrasound images of the same LIMA—LAD anastomosis. (A) Fully patent anastomosis. (B) Stenotic anastomosis after placement of a deep stitch at the toe.

The ultrasound imaging was performed with a GE Vivid 7 scanner (GE Vingmed, Norway) equipped with an i13L linear array probe (GE Healthcare, Waukesha, WI), capable of operating at frequencies from 7 to 14 MHz. Ultrasound gel was applied in the field of the anastomosis to get a proper stand-off, suitable for better images. The anastomosis was visualized in transverse and longitudinal scan planes using B-mode tissue imaging and a new ultrasound flow imaging modality termed 'blood flow imaging' (BFI). The BFI modality is based on conventional color Doppler imaging and can visualize blood flow in any direction of the two-dimensional image plane without limitations imposed by aliases [3] (Videos 1 and 2). The luminal stenosis was estimated with the use of MATLAB v7.0 (Mathworks Inc., USA).

2.3. Experimental protocol

Transit-time flow patterns in the LIMA grafts were recorded under four different conditions: (A) baseline flow: the proximal LAD was totally occluded; (B) full competitive flow: no occlusion of the proximal LAD; (C) partial competitive flow: partial occlusion of the LAD to roughly half its competitive flow; (D) stenotic anastomosis (Fig. 1). After a fully patent anastomosis was constructed and controlled by epicardial ultrasound, a stenosis of the anastomosis was made by placing a deep stitch at the anastomotic toe with the aim to reduce its cross sectional area (Fig. 2). The calculated mean degree of stenosis was 75 ± 11% as measured by epicardial ultrasound [3].

All flow and ultrasound measurements were made after 30 min stabilization and at similar and stable hemodynamic conditions (heart rate, cardiac output and blood pressure) after removal of the stabilizer from the epicardial surface. All recordings of flow values in the LAD, LIMA and pulmonary trunk were obtained simultaneously and stored in a database. The flow curves were analyzed off-line using the Medi-Stim 2.0 VeriQ software. The LAD flow represented the competitive flow (Figs. 1 and 3) (Videos 1 and 2).

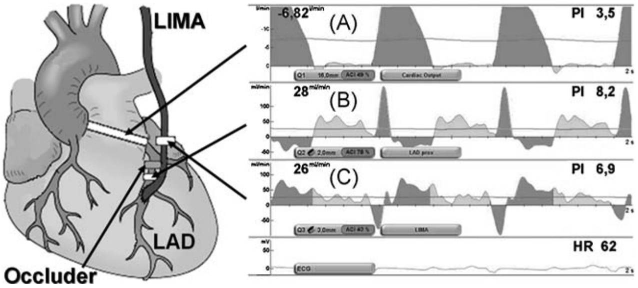


Fig. 3. Layout showing the position of the three flow probes during experiments and their corresponding flow curves by the Medi-Stim VeriQ flowmeter. (A) Pulmonary trunk flow. (B) LAD flow. (C) LIMA flow. The vascular occluder was applied around the proximal LAD to adjust competitive flow. These flow curves were recorded at full competitive flow; light gray represents diastolic flow, dark gray is the systolic flow. Antegrade and retrograde flow is the flow above and below the zero line, respectively.

For each flow condition five consecutive stable wavelets from each recording probe were stored for further analysis. The flow in the pulmonary trunk defined the systolic and diastolic flow phase. The following flow values were calculated in the LIMA graft under all four conditions: diastolic antegrade flow, systolic antegrade flow, total retrograde flow, diastolic maximum peak flow, and systolic maximum peak flow. The following values were used to calculate the following derived indexes:

$$\begin{aligned}
\text{Mean flow} &= \text{antegrade} - \text{retrograde flow}\\
\text{Insufficiency}\,(\%) &= (\text{retrograde flow}/\text{antegrade flow}) \times 100\\
\text{Diastolic filling}\,(\%) &= (\text{diastolic flow}/(\text{systolic} + \text{diastolic flow}) \times 100\\
\text{Pulsatility index (PI)} &= (\text{maximum peak flow} - \text{minimum peak flow})/\text{mean flow}.\\
&\quad \text{This is automatically calculated by the flowmeter.}
\end{aligned}$$

2.4. Statistics

Data were analyzed using SPSS, version 15.0 (SPSS Inc., Chicago, IL) and expressed as mean ± 1 standard deviation for normally distributed data and as median with range for data not normally distributed. Friedman's tests for non-normally distributed variables were applied. If the Friedman's test revealed significant changes, post hoc analyses by Wilcoxon signed-ranks were performed without correction for multiple comparisons. To compare the flow measurements between individual pigs, ratio values to baseline flow were calculated. A p value <0.05 was considered significant.

3. Results

The overall blood pressure, heart rate and cardiac output were 94 ± 14 mmHg, 102 ± 19/min and 7.0 ± 1.6 l/min,

Table 1
True values of mean flow and derived indexes. Median and range ($n = 9$).

Name	Baseline	Full competitive flow	Partial competitive flow	Stenosis of anastomosis	p
Mean flow	48 (35–50)	29 (3–38)*,†	38 (18–52)*	41 (19–60)	0.001
Pulsatility index	3.3 (1.6–10.1)	5.8 (2.2–12.8)*	4.0 (2.0–9.7)	3.9 (1.5–10.1)	0.006
Diastolic filling%	67 (56–85)	46 (31–58)*,†	56 (40–71)*	61 (46–75)	<0.001
Insufficiency%	2.3 (0–13.1)	9.4 (0.21–37.0)*,†	5.1 (0–14.5)	2.0 (0–14.6)	0.002

p refers to Friedman's test.

* $p < 0.05$ refers to comparison with baseline condition analyzed by post hoc test.

† $p < 0.05$ refers to comparison with a luminal LIMA–LAD stenosis of 75 ± 11%, analyzed by post hoc test.

Table 2
Flow values as ratios to baseline (=1). Baseline flow is defined as patent anastomosis with no competitive flow. Median and range ($n = 9$).

Flow	Full competitive flow	Partial competitive flow	Stenosis	*p*
Mean	0.63 (0.08–0.81)*,†	0.76 (0.51–1.17)*	0.88 (0.54–1.25)	0.001
Diastolic antegrade	0.52 (0.13–0.77)*,†	0.56 (0.50–1.07)*	0.83 (0.43–1.86)	0.008
Systolic antegrade	1.06 (0.39–1.40)	1.16 (0.49–1.54)	0.96 (0.67–2.54)	0.481
Diastolic maximum peak	0.59 (0.34–0.78)*,†	0.72 (0.40–1.08)*	0.83 (0.37–1.83)	<0.001
Systolic maximum peak	0.77 (0.50–1.04)*,†	0.76 (0.54–0.96)*,†	1.07 (0.71–2.83)	0.001
Retrograde	2.30 (1.15–10.55)*,†	1.37 (0.46–8.00)	0.60 (0.14–10.6)	0.018

p refers to Friedman's test.

[*] $p < 0.05$ refers to comparison with baseline conditions analyzed by post hoc test.

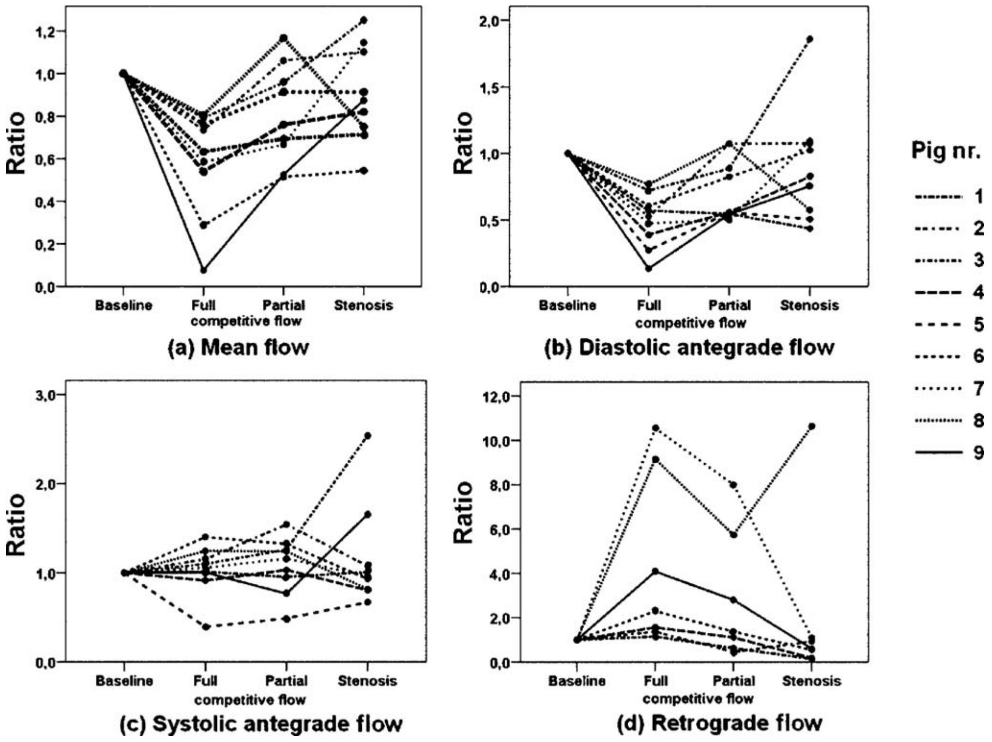
[†] $p < 0.05$ refers to comparison with stenosis analyzed by post hoc test.

respectively. The flow values and derived indexes at all four flow conditions are presented in Tables 1 and 2. A dot plot diagram (Fig. 4) illustrates the flow ratios under the four flow conditions.

The most important findings were the reduction of diastolic flow determined by full and partial competitive flow compared with baseline flow ($p = 0.008$ and 0.021, respectively), whilst the stenotic anastomoses influenced either the diastolic or the mean flow ($p = 0.314$ and 0.285, respectively) (Fig. 4; Tables 1 and 2). The mean flow was reduced during both full and partial competitive flow compared with baseline flow ($p = 0.008$ and 0.051, respectively). The systolic antegrade flow was not influenced by any of the flow conditions ($p = 0.481$) (Fig. 3). The PI and percentage of insufficiency increased only under full competitive flow ($p = 0.008$, both indexes) (Table 1). The diastolic filling % was lower in full and partial competitive flow compared with baseline ($p = 0.008$ and 0.011, respectively). Retrograde flow occurred in early systole under all four flow conditions, but was significantly increased only during full competitive flow ($p = 0.008$), (Table 2). The diastolic and systolic maximum peak flows were both reduced at competitive flow ($p = 0.008$ and 0.011, respectively), whilst a 75% anastomotic stenosis did not affect maximum peak flows ($p = 0.086$ and 0.314, respectively) (Table 2).

4. Discussion

Our study produced four major findings. Firstly, competitive flow led to a significant reduction of blood flow within the LIMA graft, mainly because of a considerable decrease of the diastolic flow. Secondly, the graft flow was not significantly decreased despite a major (75%) stenosis of the anastomoses. Thirdly, higher PI was observed at full competitive flow because lower mean flows were recorded. Finally, partial competitive flow generally had the same effect as full competitive flow on both the mean and



(a) Mean flow

(b) Diastolic antegrade flow

(c) Systolic antegrade flow

(d) Retrograde flow

Fig. 4. Dot plots presenting flow values at four different flow conditions, expressed as ratio of baseline flow (=1). (a) Mean flow, (b) diastolic antegrade flow, (c) systolic antegrade flow and (d) retrograde flow.

diastolic flow, whereas retrograde flow, PI and insufficiency were significantly influenced only under full competitive flow.

Our various experimental settings evoked three different flow conditions often encountered by the surgeon in practice. Full competitive flow mimics the situation of a graft placed distal to a less than critical stenosis of the coronary vessel. This may occur when coronary vessels with less than 50—70% stenosis are grafted, although such stenosis has no hemodynamic consequences at rest. Partial competitive flow occurs when a coronary artery is grafted distal to a significant stenosis providing about half the volume flow compared with the full value. The third condition was no-flow, an ideal situation for placing the graft distally on a totally occluded coronary.

This study showed that the LIMA graft was much influenced by competitive flow, as both the full and partial competitive flow conditions significantly altered the flow patterns. Despite the superior long-term patency of mammary grafts, the effect of competitive flow on the patency of LIMA grafts is still controversial [4—15]. The narrowing phenomenon (string sign) of the distal mammary graft is believed to be associated with competitive flow [4,7,16], because the blood flow within the mammary artery is so low that it cannot meet the metabolic requirements of its cell walls, causing the graft to narrow and eventually fail.

Clinical studies of competitive flow do not measure flows because they are retrospective and based on angiographic data. The occurrence of competitive flow has been inferred from the concomitant presence of a non-significant stenosis of the grafted vessel [7,9,17]. Furthermore, other studies suggest that arterial grafts such as LIMA are more influenced by competitive flow than are saphenous vein grafts [4,7,10—16]. The non-muscular saphenous vein grafts cannot adjust their lumens in response to metabolic requirements as much as arterial grafts. Thus, the response of vein grafts to low flow is limited.

To consider the effects of stenotic anastomoses we found that a 75% luminal stenosis of the anastomosis did not reduce blood flow through the grafts. This supports the findings of Morota et al. [18] and Jaber et al. [19], who also showed that blood flow measurements remained stable when anastomotic stenoses varied from mild (<25%) to moderately severe (<75%).

Our results are in line with the patho-physiological principles underlining blood flow in stenotic vessels described by Poiseuille's law. Nonetheless, this effect of a stenosis on blood flow is reduced in the LAD because of the autoregulation within the peripheral vascular bed. The LAD is characterized by the largest lumen and most extensive peripheral vascular bed of all coronary arteries. Therefore to reduce the LAD perfusion flow by stenosis, the vessel lumen must be considerably restricted (e.g. from 80 to 90%). With such narrowing autoregulation will soon be exhausted, and any subsequent small reduction will have major hemodynamic consequences [20]. Clinically, a stenosis of the LAD <75% will reduce maximal flow capacity, causing ischemic induced chest pain during exertion. During rest a stenosis >75% may significantly reduce blood flow, which can lead to chronic myocardial hypoxia.

A practical question raised by our findings is how to distinguish between competitive flows from a stenotic anastomosis, whenever low flows are recorded after CABG, since both conditions may decrease blood flow. We found that competitive flow altered mainly the diastolic phase of graft flow, whereas the systolic flow remained unchanged. Additionally, a smoother flow pattern might be present, because the maximum peaks in systole and diastole decrease during competitive flow in LIMA—LAD anastomoses. Thus, a careful analysis of flow patterns and their timing should always be carried out in situations with low graft flow. If the flow pattern is still difficult to interpret then snaring the coronary artery proximal to the anastomotic site might be of further help. Thus D'Ancona et al. strongly recommended that graft flow should be measured with and without proximal snaring of the coronary artery [2]. With competitive flow, as we found, occlusion of the coronary artery will increase graft flow; conversely, with a flow decrease an obstruction distal to the graft may be suspected (i.e. stenotic anastomosis, coronary stenosis distal to the anastomotic site or poor run-off). Temporary clamping of grafts directed to collateral coronaries may also aid in the interpretation of blood flow.

Hangler et al. strongly warned against the use of occluders during CABG, as they found evidence of coronary endothelial injury on electron microscopy after different occluding techniques [21]. To avoid vessel snaring, many surgeons measure the flow in the LIMA graft before removing the aortic cross clamp. Alternatively, as we have reported, epicardial ultrasound is fast and efficient for assessing coronary graft anastomoses [22]. In the present study the new blood flow imaging modality was used to evaluate the patency of the anastomosis by looking at its morphology and function, and particularly the degree of stenosis [3]. We believe that this technique has a great part to play in the intra-operative assessment of CABG as it is non-invasive and can easily detect stenoses and competitive flow [22].

The main limitations of this study were that the pigs had normal coronary arteries with good run-off, and that the animal model may not be directly comparable to patients with advanced coronary disease. The measured flow values may also be different in different species. Thus, the true flow values and derived indexes may not be directly applicable to humans, although the 75% degree of anastomotic stenosis in our model still represented a failed anastomosis likely to cause stable angina. The consequences of an even tighter stenosis on graft flow were not investigated. Finally, the statistical limitations were the multiple comparisons and a limited number of measurements. The widely used Bonferroni correction for multiple comparisons is designed for use with independent multiple measurements and does not fully apply to this situation. We instead report uncorrected p values for the Wilcoxon signed-ranks, which the readers may themselves more easily assess the relevance of the statistical differences described.

In conclusion, in a porcine model, the LIMA flow was significantly reduced by native coronary artery competitive flow but marginally decreased by an anastomotic mean luminal stenosis of 75%. Reduction of graft flow due to competitive flow was particularly evident in diastole. Thus a careful analysis of flow patterns may help to discriminate between competitive flow and an anastomotic stenosis. A detailed knowledge of different flow patterns by the surgeon is mandatory for a reliable interpretation of transit-time flowmetry. In a near future epicardial tissue and Doppler imaging assessment may be performed together with transit-time flowmetry because the combined information supplied by each technique might potentially improve intra-operative evaluation of coronary grafts.

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Appendix A. Conference discussion

Dr B. Walpoth (*Geneva, Switzerland*): Thank you for presenting an interesting experimental assessment of this new device from MediStim. Basically there are some problems with what you showed. First of all, it has been shown before, secondly, it is well known to all cardiac surgeons that you will never have full competitive flow. You need a relevant stenosis in order to make a bypass. And as you have shown and which was known that if you have a stenosis of the native vessels which is not in excess of 75 to 80%, you will not have major changes in your flow measurement.

However, I fully agree with you that the addition of imaging technique is an important feature, because sometimes you measure low-flow situations in grafts without any obvious reasons, but if imaging is available it can help on-site in the operating room to make a decision.

My question is the following. You said with 75% stenosis at the toe of your anastomosis you didn't see major flow changes. You saw some changes but not as much as you would have expected. How did you assess the 75% stenosis? To obtain a correct degree of stenosis you need a biplanar angiographic evaluation and 75% might not be sufficient.

Dr Nordgaard: We used our ultrasound images of the anastomoses. The images were afterwards analyzed using the MatLab software. Several diameters of each LIMA–LAD anastomosis were measured for calculation of the degree of luminal stenosis. In the operation field we assessed the anastomosis using ultrasound imaging since our aim was creating a stenosis of a significant degree at the toe of the anastomosis.

I do not agree with your comment that full competitive flow doesn't exist in coronary surgery. Often surgeons do graft vessels with about 50% luminal stenosis. Then the hemodynamic still acts as full competitive flow because the blood flow is not influenced at this degree of stenosis.

Dr Walpoth: This is correct, yes.

Dr A. Pavie (*Paris, France*): On your presentation I would like to make a small comment, and I am a little provocative. You suggest that it is more important to have good indication to avoid competitive flow, but it is still very important to do good surgery. I am not sure that we can follow you. It is certainly important to do a good indication, but if we do good surgery, it is probably better.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejcts.2009.02.036.