An Investigation of Transit-time Flowmetry Parameters in Coronary Artery By-pass Grafting

A dissertation for the degree of

Doctor of Philosophy

Sanaz Amin, MD

Wolfson College, University of Oxford

To my parents

Acknowledgements

"Let us be grateful to people who make us happy, they are the charming gardeners who make our souls blossom"
~ Marcel Proust ~ (1871-1922)

Although the successful completion of a doctoral thesis is dependent on the individual effort, the road to its realisation is heavily dependent on the people that surround and support you. In this regard, I have been very fortunate as I have many people to thank.

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Declaration

I declare that the work presented in this thesis is completely of my own and has not been submitted for any other degree, diploma, certificate or other qualifications in this or in any other University or Institute of learning.

Abstract

Coronary artery disease (CAD) remains the leading cause of early death and illness in developed countries. Today, patients with CAD are treated either with medical therapy, percutaneous coronary intervention, or with coronary artery by-pass grafting (CABG). Although CABG remains the reference-standard for revascularisation of multi-vessel CAD, long-term patency of by-pass grafts continues to be a major challenge. Literature suggests that perioperative graft failure occurs in up to 11% of by-pass grafts, affecting roughly 10% of all CABG patients, and hence numerous interventions have over the years been investigated to prolong graft patency and to identify grafts that may eventually go on to fail. Potentially failing grafts should ideally be identified during the operation to enable graft revision, before the chest is closed.

The conventional approach of visual inspection or palpation of the graft to assess flow can be deceiving, and European guidelines on myocardial revascularization now recommend intraoperative determination of graft flow with Transit time flowmetry (TTFM). Today, TTFM is the most commonly applied technique for intraoperative graft flow assessment. TTFM measures four flow parameters, mean graft flow (MGF), pulsatility index (PI), percentage of diastolic filling (%DF), and percentage of backward flow (%BF), but guidelines only provide cut-off values for MGF and PI, with no further distinction on how these parameters are affected in different CABG settings, and hence without a deeper understanding of the interrelation of measured parameters.

The work comprising this dissertation has sought to evaluate the utility of the TTFM technique by assessing the accuracy and precision of the technique in measuring

blood flow in addition to assessing all TTFM parameters in different CABG settings. In a retrospective observational study of 60 CABG patients, the accuracy and precision of the TTFM technique was evaluated by correlating measured TTFM blood flow to routinely determined free blood flow of the left internal mammary artery prior to grafting. In this study, it was found that (1) Overall overestimation was 7.1%, with a standard deviation of TTFM to true flows of 16.3%, with largest deviations from true flow seen with oversized TTFM probes. (2) TTFM probe oversizing was associated with poor acoustic coupling, reflecting poor probe to graft contact. (3) The study suggests that flow overestimation may be suspected with flows above 68 ml/min, but a true low flow is rarely deemed normal/too high.

In three separate observational studies of a total of 268 patients, all TTFM parameters were evaluated according to surgical approach (on- *vs.* off-pump CABG), choice of conduit (arterial *vs.* venous conduits), and grafted coronary territory (by-pass grafts to the right or left sided coronary arteries, respectively). The results of these three studies were as follows: (1) compared to off-pump surgery, MGF is higher for arterial grafts (50±35 *vs*. 38±26 ml/min, $p<0.001$) and %BF is lower for saphenous vein grafts (1.8±6.2 *vs*. 2.6±6.2%, $p=0.003$) during on-pump surgery, (2) arterial grafts have significantly higher %DF (71±8 *vs*. 64±11%, $p<0.001$) and %BF (2.3±3.2 *vs*. 1.7±3.2%, $p=0.002$) than venous grafts, but comparable MGF and PI, and (3) flow parameters are comparable between left- and right-sided saphenous vein by-pass grafts.

Finally, in a randomized clinical study of 35 patients, TTFM parameters of externally stented vein grafts were compared to non-stented vein grafts. In this study, it was demonstrated that external stenting of saphenous vein grafts does not affect intraoperative flow parameters.

The conclusions of this body of work are that, with a slight overall overestimation, TTFM is a good indicator of blood flow with a clinically acceptable precision only if appropriate angulation and probe size is ensured prior to measurement. Overestimation may be expected with flows >68 ml/min, but most importantly in situations with oversized TTFM probes. Furthermore, external stenting and coronary territory does not significantly affect TTFM parameters of saphenous vein grafts. However, research aiming to delineate TTFM cut-off values for graft patency must take into account the choice of conduit (arterial *or* venous) as well as the surgical approach (on- *or* off-pump).

Publications

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Amin S, Pinho-Gomes AC, and Taggart D. *Relationship of intraoperative Transit time flowmetry findings to angiographic graft patency at follow-up.* **Ann Thorac Surg**, **2016. 101(5): p. 1996-2006.**

Taggart DP, Amin S, Djordjevic J, Oikonomou EK, Thomas S, Kampoli AM, et al.. *A prospective study of external stenting of saphenous vein grafts to the right coronary artery: the VEST II study.* **Eur J Cardiothorac Surg, 2017. 51(5): p. 952-958.**

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List of Abbreviations

ACI	Acoustic Coupling Index
BF	Backward Flow
CABG	Coronary Artery By-pass Grafting
CAD	Coronary Artery Disease
CPB	Cardio-pulmonary By-pass
DF	Diastolic Filling
GEA	Gastroepiploic Artery
HFUS	High-Frequency Ultrasound
IMA	Internal Mammary Artery
LIMA	Left Internal Mammary Artery
MAP	Mean Arterial Pressure
MGF	Mean Graft Flow
NPV	Negative Predictive Value
ONCABG	On-pump Coronary Artery By-pass Grafting
OPCABG	Off-pump Coronary Artery By-pass Grafting
PI	Pulsatility Index
PPV	Positive Predictive Value
RA	Radial Artery
RCA	Right Coronary Artery
RIMA	Right Internal Mammary Artery
SVG	Saphenous vein Graft
TTFM	Transit-time Flowmetry
VEST	Venous External Stenting Trial

1

Introduction

Chapter 1 – General background

Coronary Artery Disease

Coronary artery disease (CAD), giving rise to the more general problem of ischaemic heart disease (IHD), refers to a narrowing or blockage of the epicardial coronary arteries that provide oxygen and nutrients to the heart muscle. CAD is caused by atherosclerosis, an intraluminal accumulation of fatty and calcified materials, that together with an inflammatory process narrow the intraluminal diameter. The resulting blockage restricts myocardial perfusion hereby leading to an imbalance between oxygen supply and demand in the resting state and especially so when the demand for flow is augmented (i.e. during exercise).

CAD remains the leading cause of death globally estimating over 7 million deaths worldwide [1]. Today, CAD of sufficient magnitude to lead to significant IHD is treated either with medical therapy, percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG). The clinical presentation, the nature and severity of CAD, the degree of inducible ischaemia on stress testing, and the ventricular function are all taken into consideration prior to determining whether the patient is an appropriate candidate for an interventional procedure [2]. CABG is often

considered when PCI is not feasible or when the short- and long-term benefits of CABG are superior to PCI, i.e. severe left main stenosis, 3 vessel disease and complex 2 vessel disease situations associated with a significant amount of myocardium at jeopardy [3-7]. Today, cardiac surgeons and cardiologists can use the SYNTAX (**SYN**ergy between percutaneous coronary intervention with **TAX**us and cardiac surgery) II score; a tool developed in connection with the SYNTAX trials [8-10] to aid clinicians in choosing the optimum revascularization approach in patients with complex coronary artery disease [8, 10-12].

Coronary artery by-pass grafting

The first successful CABG was performed in 1967 [13, 14]. During the past 50 years, the short- and long-term results of CABG have continued to improve thanks to better perioperative care and successive technical advances; improved cardiopulmonary by-pass (CPB) techniques, advanced anaesthesia techniques, shorter operating times, use of cardioplegia, more refined suturing techniques, and perioperative assessment of graft patency, which have all contributed to reducing the amount of myocardial injury [13-18]. Today, CABG is a cornerstone of invasive treatment of CAD [5, 6, 10].

In short, during open-heart surgery, venous or arterial conduits are used to by-pass areas of flow limiting calcification and stenosis in the epicardial coronary arteries, typically determined by coronary angiography or by fractional flow reserve (FFR) measurement, where the functional severity of a coronary artery stenosis is calculated as the ratio between the maximum achievable blood flow in a diseased coronary artery and the theoretical maximum flow in a normal coronary artery, during routine coronary angiography. For routine coronary angiography, a narrowing of the

coronary lumen diameter of 70% or greater (typically by visual estimation) is usually considered flow limiting [19]. For FFR measurement, an FFR lower than 0.75-0.80 is considered to be associated with myocardial ischaemia [20]. The main aim of CABG surgery is thus to restore perfusion of the ischaemic myocardium distal to the narrowing of the epicardial artery(-ies) lumen. CABG is performed either with the use of CPB followed by cardioplegic arrest providing a stable and bloodless surgical field to allow construction of the anastomosis under optimal conditions ('on-pump'). Alternatively CABG can be performed on the beating heart with the use of cardiac stabilizing devices that reduce motion around a small section of the coronary artery, which eliminates the need for CPB ('off-pump'). Insertion of small shunts into the coronary artery allows continuous myocardial perfusion of the beating heart during construction of the anastomoses.

On-pump and off-pump coronary artery by-pass grafting

Historically CABG was almost exclusively performed with the use of a CPB followed by cardioplegic arrest. The initial rationale for off-pump coronary artery by-pass grafting (OPCABG) where an extracorporeal circuit is avoided was mainly driven by economic considerations in developing countries due to the economic cost of the CPB [16]. Despite much scepticism by its opponents, OPCABG was gradually introduced into developed countries as surgeons recognized its potential to mitigate the adverse effects of extracorporeal circulation [21-24]. Two recent randomized clinical trials, with highly experienced participating surgeons in both on-pump coronary artery by-pass grafting (ONCABG) and OPCABG, have now showed that there is no difference between ONCABG and OPCABG in the incidence of death, stroke, myocardial infarction, new renal failure or repeat revascularisation at 30 days and 1 year after

surgery [22, 23]. Today, most CABG procedures are still performed ONCABG [25], however, some still consider OPCABG to be the choice of treatment for high-risk patients [24-26].

Although I do not intend to compare the benefits of these alternative surgical techniques in this thesis, I will attempt to establish whether there is a significant difference in intraoperative blood flow parameters of by-pass grafts in ONCABG *vs.* OPCABG surgery, which will be of importance for future guidelines on TTFM cut-off values (Chapter 4 – On- *vs.* off-pump surgery).

Arterial and venous conduits in CABG

Revascularisation with CABG has always been performed with the use of arterial as well as saphenous vein grafts (SVGs), however, only the use of internal mammary arteries (IMAs) and SVGs were practiced until the early 1970s [27-31]. Later, several other arterial conduits were introduced as alternative vessels for CABG revascularisation: the radial artery (RA) was introduced in 1973 [32, 33]; the gastroepiploic artery in 1987 [34, 35]; and the inferior epigastric artery in 1990 [36, 37]. Despite a large volume of observational studies, recommendations on the choice of particular conduits for revascularisation during CABG remain controversial [15, 38, 39]. However, revascularisation of the left anterior descending (LAD) artery territory with a left internal mammary artery (LIMA) is widely considered the 'reference-standard' in CABG [25, 38, 40, 41].

Given the different physiological roles of arteries and veins, there are some clear histo-pathological differences between the two. Suited to their tolerance of higher blood pressures, arteries possess thicker elastic muscular walls with smaller intravascular lumina [42]. Furthermore, arterial conduits produce much greater levels

of nitric oxide and decreased release of vasoconstrictors compared to the SVG, resulting in significantly less atheromatosis [42-44]. Together, these differences may well explain the superior long-term patency rates of arterial conduits compared to SVGs, reporting >90% for IMAs [45], >80% for the RA [46], and >65% for the gastroepiploic artery (GEA) [47] at 10-25 years after surgery, based on angiographic follow up. In comparison, SVG patency has been shown to decline from 75-80% at 1-year to 65% at 5-years, and less than 50% at 10-years after surgery with significant atheroma in most of the remaining grafts [48-50], prompting the necessity to assess all differences between arterial grafts and SVGs in the aim of better understanding how to overcome this obstacle.

Although I do not intend to assess conduit patency post CABG procedure, I will compare blood flow parameters in arterial *vs.* SVGs in this thesis (Chapter 5 – Arterial *vs.* venous grafting).

By-pass grafts to the left and the right coronary territory

The trans-myocardial pressure on the left side of the heart is higher than that of the right, as the left ventricle is required to provide circulatory support for the high-pressure systemic circulation. Such a pressure difference does indeed influence coronary blood flow [51]. Despite the obvious differences between the two territories, very few studies have specifically addressed blood flow parameters in left- *vs*. right-sided grafts, and current evidence for any difference is contradictory [52-54]. In this thesis, I will assess blood flow parameters in left *vs*. right-sided vein grafts (left anterior descending artery, diagonal artery, intermediate artery, circumflex coronary artery territory *vs*. the posterior descending artery and the right coronary artery, respectively) in Chapter 6 – Left- *vs.* right-sided venous by-pass grafting.

Saphenous vein grafts in CABG

Despite well-documented benefits of multiple arterial grafts [55-57], saphenous veins remain the most widely used by-pass conduits in CABG [58] and, in fact, their use appears to be on the rise [59]. This is likely due to a number of factors including: abundance, ease of harvest, versatility and reduced susceptibility of venous conduits to competitive flow [60]. Nevertheless, progressive SVG failure frequently occurs following CABG, limiting the long-term success of the operation [39, 48, 50, 61].

Attempts to mitigate SVG failure have been the focus of intense clinical research. Currently, only statins and β-blockers are routinely administered to reduce vein graft failure [61-63]. The use of an external support for SVGs has been explored on numerous occasions over the past 50 years [64-66], but limited clinical data in addition to poor results have precluded the use of external devices for SVGs as standard clinical practice in CABG. With the first generation of external SVG stents Murphy *et al.* [67] described 100% SVG occlusion at 6 months; Schoettler *et al.* [68] reported a 72% occlusion rate at 9 months; and Rescigno *et al.* [69] described a 67% occlusion rate at 12 months of SVGs supported with nitinol mesh. All of these external stents required gluing or suturing of the stent to the vein graft during the implantation procedure, which may have compromised SVG patency [70, 71]. A newly developed external device consisting of cobalt-chromium, the VEST stent (Vascular Graft Solutions Ltd, Tel Aviv, Israel), does not require fixation, and has shown promising results in both animal and human studies with significantly reduced diffuse intimal hyperplasia by improved lumen uniformity and haemodynamic flow patterns in externally stented SVGs [72-74]. Furthermore, the VEST stent has demonstrated patency rates of 85-90% at 1-year angiographic follow-up of SVGs to the left coronary territory [59] and 86% to the right coronary territory [71].

A multi-centre randomised trial investigating the benefits of external stenting of SVGs (the VEST III trial; *Venous External Stenting Trial*) is now in a 2-year follow-up process. If this trial successfully proves that the VEST stent reduces intimal hyperplasia and improves SVG patency, this will undoubtedly become a "game-changer" in CABG.

In this thesis, I have conducted a sub-study of the VEST III trial investigating whether the presence of an external stent affects intraoperative graft flow parameters of SVGs (Chapter 7: External stenting of venous grafts).

Coronary artery by-pass graft patency

Although both ONCABG and OPCABG are successfully performed in most patients, intraoperative graft failure occurs in up to 11% of by-pass grafts, affecting roughly 10% of all CABG patients [18, 75-78]. Intraoperative graft failure can be due to technical problems, for example, kinking or twisting of the graft, linear tension due to insufficient graft length, or thrombus or stenosis in the conduit, but intraoperative graft failure is most frequently due to inappropriate construction of the anastomosis [77]. Graft patency is a key predictor of survival outcome, and its importance has been emphasized in the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT IV) trial, where a composite end point of death or new myocardial infarction was 0.9% in patients with patent SVGs compared with 13.9% for patients with at least 1 occluded SVG [79]. Given these facts, developing and validating techniques for assessing graft patency intraoperatively is important, as perioperative graft occlusion is not always immediately apparent by traditional methods: palpitation of graft pulsation, assessment of hemodynamic stability, and electrocardiographic (ECG) changes [75, 80].

Techniques for intraoperative graft patency assessment

Since 1972 [81], several different techniques for intraoperative graft flow assessment have been introduced and validated (**Table 1.1**), and although conventional coronary angiography remains the "reference-standard" technique for graft patency assessment [82], its requirements for additional equipment and personnel, the need for arterial puncture, use of potentially nephrotoxic contrast agents, bi-dimensional representation without any direct functional information, and increased operating time usually precludes it from the operating room [83-85]. In some centres transesophageal echocardiography (TOE) is almost routinely used during cardiac surgery with the aim of detecting potentially life-threatening hemodynamic events [86]. Although intraoperative TOE assessment allows immediate and direct visualization of the anatomy and function of the heart, which may in particular prove helpful during valve replacement/repair, evidence-based practice guidelines only support this technique with Category 2 indications (possibly beneficial, but appropriate clinical indications are less certain) for CABG surgery [87]. This is most probably due to the fact that TOE alone cannot differentiate between a graft problem and other hemodynamic events in case of low cardiac output or new regional wall motion abnormality, and thus surgical confidence in the graft(s) to the affected region will determine the decision for graft revision. In contrast, Transit time flowmetry (TTFM) during CABG surgery allows immediate interpretation of the quality of each graft individually. Currently, TTFM is the most commonly applied technique for intra-operative graft flow assessment [76, 88-90]. TTFM measures four pertinent flow parameters: mean graft flow (MGF), pulsatility index (PI), percentage of diastolic filling (%DF), and percentage of backward flow (%BF). A more detailed explanation of the TTFM technique will be provided in Chapter 2 – General methods.

Table 1.1: Different Techniques for Intraoperative Graft Assessment

Technique	Year	Reference article	Patients (n)	Strengths	Limitations	Current use
Conventional angiography.	1988	Elbeery et al. [91]	50	Precise definition of graft patency	Invasive, requires contrast, rarely available in operating room	–
Electromagn-etic flowmetry.	1994	Louagie et al. [92]	262	Ease of use, Noninvasive	Motion artifacts, Interference	–
Transit-time flowmetry.	1994	Canver et al. [93]	63	Accurate graft flow value	Inability to define degree of stenosis	+
Thermal angiography.	1995	Falk et al. [94]	370	No contrast or radiation	No clarity with increasing depth	–
Doppler velocity measurements.	2000	Lin et al. [95]	35	Ease of use, Noninvasive	Flow values affected by angle of insonation	–
Epicardial color doppler scanning.	2002	Haaverstad et al. [96]	23	Noninvasive	Imprecise definition of all coronary territories	–
Intraoperative flourescence imaging.	2003	Taggart et al. [97]	84	Real-time "angiographic images"	Semiquantitative	+

Reproduced from; Balacumaraswami et al. Ann Thorac Surg 2007;83:2251–7.

Since 2010, intraoperative graft assessment has been recommended in the Guidelines for Myocardial Revascularization of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), as one part of the evidence-based technical recommendations for CABG surgery [98, 99]. Despite no mention of the optimal technique for intra-operative graft assessment, recommended indicative values of a MGF of ≥20 ml/min and a PI of ≤5 refer to TTFM as the method of choice (Class I recommendation, level of evidence C) [98] (**Table 1.2**). However, the guidelines do not take into account the remaining parameters as obtained by this technique (%DF and %BF), potential influence of surgical technique (ONCABG *or* OPCABG), choice of conduit (arterial *or* venous), or the effect of grafted coronary territory (grafts anastomosed to the left *or* the right coronary territory), which may indeed influence parameters [53, 100, 101], as discussed in Chapters 4-6. In keeping with this, the TTFM technique has been recommended in the NICE Guidelines (2011) [102] with similar cut-off values for MGF and PI, as recommended in the European guidelines. In addition to the recommendation, the NICE guidelines suggest that the TTFM technique is cost effective and may reduce the incidence of graft occlusion, and perioperative morbidity and mortality:

1.1 "The case for adopting the MiraQ system in the NHS for assessing graft flow during coronary artery bypass graft (CABG) surgery is supported by the evidence. The evidence suggests that intra-operative transit time flow measurement is effective in detecting imperfections that may be corrected by graft revision. This may reduce the incidence of graft occlusion and may reduce perioperative morbidity and mortality."

1.2 "The MiraQ system is associated with an estimated cost saving of £141 per patient compared with clinical assessment, when it is used routinely for assessing coronary artery bypass grafts during surgery."

Citations from: NICE medical technology guidance 8. Issued: November 2011 and renewed January 2018.

Despite these recommendations, there is no clear consensus on when to revise a graft (except in the situation where graft flow is completely absent) (**Table 1.2**).

In this thesis I will present, evaluate, and assess the TTFM technique in a variety of CABG settings, as presented in the respective chapters. None of the studies include follow-up data, as they are all designed as observational studies.

Table 1.2: Guidelines on intraoperative graft patency assessment.

Guideline	Recommendation	COR	LOE	Reference(s)
EACTS 2010 [98]	Yes	I	C	Kieser et al. [76]
EACTS 2014 [99]	Yes	IIa	C	Kieser et al. [76] Jokinen et al. [88]
NICE 2011 [103]	Yes	I	C	Kieser et al. [76] Becit et al. [18]
ACCF/AHA 2011 [104]	Yes – However, further research is warranted to identify a 'reference-standard' technique.	IIb	C	Taggart et al. [84]
ACCF/AHA 2014 [105]	No mention	N/A	N/A	N/A
ACC/AHA/AATS/PCNA/SCAI/STS Focused update	No mention	N/A	N/A	N/A

2012, 2014 [106, 107]				
STS 2016, 2017 [25, 108]	No mention	N/A	N/A	N/A
ESC guidelines 2013 [109]	No mention	N/A	N/A	N/A
CCS 2014 [110]	No mention	N/A	N/A	N/A

CCS: Canadian cardiovascular society, ESC: European society of cardiology, ACC: American college of cardiology, ACCF: American college of cardiology foundation, AHA: American heart association, EACTS: European association of cardiothoracic surgery, NICE: National institute for health and care excellence, AATS: American association for thoracic surgery, STS: Society of Thoracic surgeons.

Transit time flowmetry

The first Transit-time flowmeter was described in 1962 [111]. However, due to technological limitations, the technique was never put to clinical use. Only in 1983, when initial limitations of the technique had been resolved did the TTFM technique become available for clinical use [112]. As previously noted, TTFM is now the most commonly employed technique for intraoperative graft assessments, and may result in improved short-term and mid-term graft patency, morbidity and mortality [18, 52, 88, 101, 113-116]. There is however scant evidence regarding long-term outcomes that prevents drawing definite conclusions [114].

TTFM is an easy, fast, non-invasive technique, and the device does not consume a large amount of space in the operating room. Furthermore, flow measurements are independent of haematocrit level, heart rate, and vessel wall thickness [117]. Notwithstanding this, incongruent reports on sensitivity and specificity based on cut-off values of 15-20 ml/min for MGF and <3-5 for PI to predict patent or occluded grafts at angiographic short- *or* mid-term follow up (**Table 1.3**) [53, 77, 89, 118] along with lack of clear cut-off values of derived parameters have precluded it from becoming the "reference-standard" technique for intraoperative graft flow assessment [114, 119, 120].

Table 1.3: Reported sensitivity and specificity for graft patency according to different TTFM cut-offs

Author	Cut-off	Angiographic follow-up	Sensitivity	Specificity
Di Giammarco et al. [77]	MGF ≤ 15 ml/min	6.7 ± 4.8 months	87%	87%
	PI ≥ 3	–	66%	67%
	%BF ≥ 3	–	100%	67%
Kim et al. [53]	MGF ≤ 15 ml/min, PI > 3 (LCA), PI > 5 (RCA), %BF > 2%	1.1 ± 0.4 days	96%	77%
Tokuda et al. [118]	MGF ≤ 15 ml/min, PI ≥ 5.1 (LCA)	16.5 ± 7.6 months	26%	98%
	MGF ≤ 20 ml/min, PI ≥ 4.7 (RCA)	–	60%	98%
Quin et al. [89]	MGF < 20 ml/min	1-year	39%	81%
	PI > 5	–	19%	92%
	PI ≥ 3	–	38%	80%

LCA; left coronary artery; RCA; right coronary artery

Several studies have aimed at demonstrating the reliability of TTFM as an intraoperative measure to control the quality of coronary anastomoses and to define cut-off values for predicting graft failure at follow up [17, 18, 52, 77, 79, 88, 89, 101, 113, 118, 121-124]. Different cut-off values for graft revision, however, have been applied in the different studies, thereby yielding inconsistent findings regarding correlation of flow measurements with clinical endpoints including graft patency. Besides having applied different cut-off values, these studies did not report the level

of expertise of the operators, had limited sample sizes, short-term, and often incomplete follow-up, with failure to control for conduit type (arterial *or* venous), surgical technique (ONCABG *or* OPCABG), and target coronary artery territory (left *or* right sided by-pass grafts) [17, 18, 52, 53, 79]. Nonetheless, accumulative evidence suggests the following cut-off values for graft patency:

- MGF: >20 ml/min for arterial grafts and >35-40 ml/min for SVGs [114].
- PI: <5, ideally < 3 [114].
- %DF: >50% for right-sided grafts and higher for left-sided grafts [114].
- %BF: < 3% [114]

Keeping in mind, clinical useful recommendations on when to revise a graft can not be solely based on individual TTFM variables, as the patency of a by-pass graft is influenced by multiple factors such as patient comorbidities, the anatomy of the coronary vessel and the size of its vascular bed, the quality and type of the conduit, the degree of persistent flow through the native coronary artery, and the construction of the anastomosis [125]. As only some of these variables can be modified by surgical intervention, graft revision should be based on a combination of clinical criteria and intraoperative patency assessment (like TTFM).

Despite being the most commonly used technique for intraoperative graft flow assessment, available data on the accuracy of the TTFM technique in measuring actual graft flow is limited, suggesting only small variability and error of measurement both *in-vivo* and *in-vitro* [126, 127]. However, the first study [127] was conducted in sheep, and the second study [126] only included 12 patients subjected to CABG with the LIMA as one of the conduits. In this thesis, the accuracy of the TTFM technique will be evaluated in a larger *in-vivo* in-human study (Chapter 3).

High frequency ultrasound imaging

A new technique of high frequency ultrasound (HFUS) imaging has recently been implemented in the intraoperative graft verification procedure (introduced to the market in 2009), with the aim of increasing the diagnostic accuracy of the TTFM technique [128]. This newly added feature provides direct visualization of the anastomoses through a 3x2x1.5 (L/H/W) 15 MHz probe, thereby potentially prompting fewer unnecessary graft revisions. HFUS imaging can be used on the Aorta, conduits, and native coronary vessels, providing "real-time" images of vital vessels (**Figure 2.5**).

In a retrospective study of 333 patients with 717 grafts [128], and based on TTFM cut-off values of 15 ml/min for MGF and <3 for PI, 39 grafts (5.4%) were deemed as failed grafts by TTFM but only 2 (0.3%) were reclassified as failed anastomoses after HFUS imaging evaluation, leading to avoidance of 37 unnecessary graft revisions. In all 37 false positive cases, low run-off and high %BF were evident, suggesting that these grafts were exposed to competitive flow (competitive flow will be explained in the next chapter). In keeping with this, in 3 grafts (0.4%) the HFUS detected 'false negative' findings with TTFM. All 3 grafts had an intimal flap, which determined an intermittent good flow at TTFM. Thus, according to this study [128], the addition of HFUS imaging may enhance the sensitivity of isolated TTFM to detect by-pass graft errors from 26% to 33% and the specificity from 95% to 100%. Likewise, the positive predictive value (PPV) and the negative predictive value (NPV) may also improve, from 10% to 100% and from 98% to 99%, respectively [128].

The HFUS imaging technique will only be briefly explained in Chapter 2 – General methods, as the utility of this technique is not the aim of this thesis.

Conclusions and aims of this thesis

Despite the survival benefit of CABG over PCI in complex coronary artery disease [5], one of the major challenges of CABG remains the maintenance of long-term graft patency. With the aim of improving graft patency, intraoperative graft assessment techniques have been implemented almost since the initiation of CABG [30] with TTFM being the most commonly applied technique today. However, reported low sensitivity (**Table 1.3**) along with inconsistent cut-off values of the TTFM flow parameters (MGF, PI, %DF, and %BF) has precluded the technique from becoming the "reference-standard" for intraoperative graft patency assessment during CABG. What these studies perhaps failed to elicit is that any clinically useful recommendations on when to revise a graft cannot be solely based on individual TTFM variables due to each their limitation when evaluated separately [114], and that the ability to correctly interpret TTFM measurements needs to be acquired with clinical and experimental experience with all aspects of the surgery considered (surgical technique, conduit type, severity of the coronary disease, etc.). Previously published studies on the sensitivity and specificity of the TTFM technique [52, 53, 77, 89] have failed to control for these potential confounders. In addition, the studies did not always consider the level of expertise of the operators, which may further explain the conflicting results. As a consequence, current guidelines on the utility and cut-off values for when to revise a graft during CABG with TTFM are either scant or non-existent.

This thesis will thus evaluate the accuracy of the TTFM technique in measuring actual blood flow in addition to assessing MGF, PI, %DF, and %BF, as assessed by TTFM, in a variety of CABG settings: ONCABG *vs.* OPCABG, arterial *vs.* venous, left- *vs.* right-sided venous by-pass grafts, and the presence of an external

venous stent on intraoperative blood flow parameters, in the aim of assessing whether future studies on cut-off values of the derived parameters should control for these potential confounders and thus be included in future guidelines.

2

Methods

Chapter 2 – General methods

General Study Design and Population

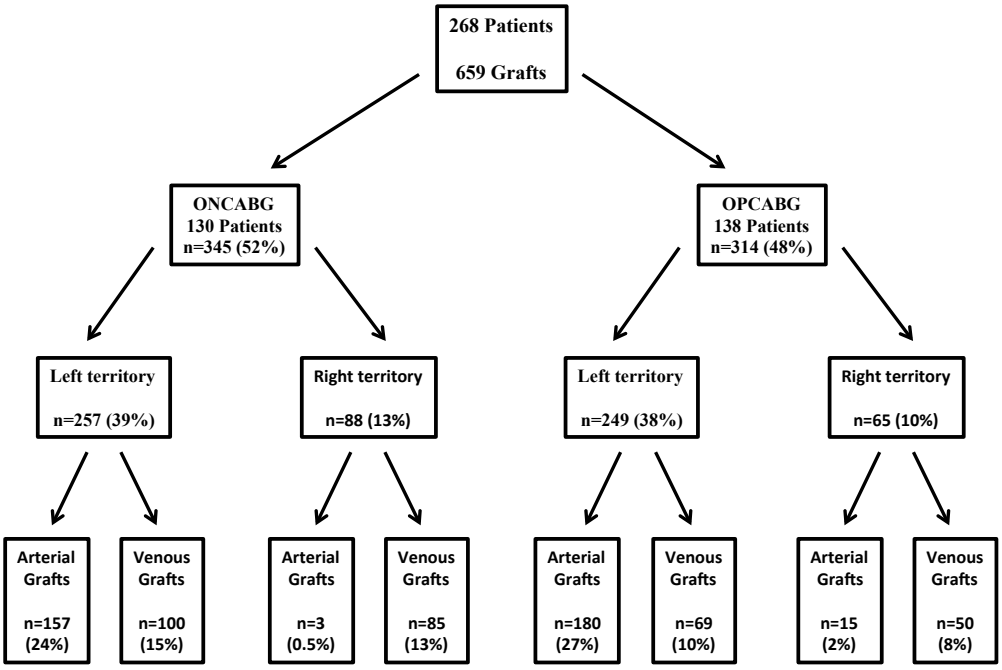
This thesis is mainly based on a two-surgeon (DPT and GK) single centre clinical practice of non-randomized observational studies (except for Chapter 7, which is a sub-study of a multi-centre randomized clinical trial) evaluating both the accuracy of the TTFM technique as well as assessing TTFM parameters in a variety of CABG settings. The studies in chapters 3, 4, 5, and 6 were discussed with the Health Research Authority (HRA) and confirmation was received from the HRA that ethical review from the NHS Research Ethics Committee (REC) was not required for these projects. However, the randomised study in chapter 7 was approved by a UK Research Ethics Committee (clinicaltrials.gov identifier: NCT02511834) and all subjects gave informed consent. It is crucial to emphasise from the outset that this thesis only reports the findings from formal measurement of the standard practice of both these surgeons. A detailed study design of each study will be addressed separately in the respective chapters.

General Procedure

All patients underwent CABG via a median sternotomy. IMAs were harvested as skeletonized conduits. To avoid peri-procedural spasms, topical papaverine and/or raising the systolic blood pressure to 150 mmHg for 5-10 minutes was routinely applied. RAs and SVGs were endoscopically harvested as skeletonized conduits and stored in heparinized blood prior to coronary artery anastomosis. CABG was subsequently performed either ONCABG *or* OPCABG. Where possible, composite multi-vessel grafting was performed in OPCABG cases to achieve total arterial grafting with complete avoidance of aortic manipulation. The routine practice of one surgeon (DPT) was OPCABG surgery, while the routine practice of the other surgeon (GK) was ONCABG. Overall, DPT performed 141 CABG procedures with 37 ONCABG and 104 OPCABG, and GK performed 127 CABG procedures with 93 ONCABG and 34 OPCABG (**Figure 2.1**).

TTFM measurement, mean arterial pressure (MAP), demographic data, and risk profiles recorded from July 2015 to April 2017 in 268 patients with a total of 659 by-pass grafts (**Figure 2.1**) undergoing elective or urgent isolated ONCABG *or* OPCABG procedure were included in the studies. Only composite and single grafts were included in the studies. A total of 6 sequential grafts where excluded from the entire cohort. In general, GTN was used to lower the blood pressure while Metaraminol boluses or noradrenalin infusions were used to increase the blood pressure. All measurements were performed with the VeriQC device (Medistim ASA, Oslo, Norway) and operated by the same person (SA). The extent of native coronary artery vessel disease was assessed by one blinded operator (SA) using quantitative coronary angiography (Horizon Cardiology version 12.2, McKesson, Israel).

Figure 2.1: Flow diagram of the entire cohort



2.1 *– Flow diagram showing the configuration of the entire cohort and all conduits in ONCABG and OPCABG coronary artery by-pass grafting to both the left and the right coronary territory. n depicts the number of patients in each limb.*

Off-pump CABG

Complete anticoagulation with heparin was achieved as in the ONCABG group. Following sternal splitting, lateral and inferior walls of the heart were exposed by means of a combination of a deep pericardial "stay suture", Trendelenburg and right decubitus positions, and opening of the right side of the pericardium down to the inferior caval vein. Regional myocardial immobilization was achieved with a suction stabilizer (TS2500, Medtronic Inc.). The target coronary vessels were snared proximally with a silastic sling. Intracoronary shunts (Clearview 31175, Medtronic Inc.) were used routinely in all OPCABG cases. A surgical blower-mister device was applied to enhance visualization for the surgeon (Clearview 22150, Medtronic Inc).

Proximal anastomoses to the ascending aorta were performed at a controlled systolic pressure of 70-80 mm Hg using a side-biting vascular clamp.

On-pump CABG

Cardiopulmonary by-pass was instituted by cannulation of the ascending aortic cannulation and a 2-stage venous cannula inserted into the right atrium. A standard cardiopulmonary by-pass circuit incorporated a roller-pump (Jostra HL 20) and a hollow-fibre membrane oxygenator (Inspire Sorin, Fusion Medtronic). The extracorporeal circuit was primed with 1000 ml of Hartmann solution, 500 ml Gelespan, 100 ml mannitol (20% Baxter solution), and 2500 IU of heparin. Non-pulsatile flow was maintained with a flow-rate of 2.4 l/min/m^2. Arterial filtration was not used, and cardiotomy suction was used in all patients. Acid-base balance was managed with alpha-stat control. The temperature was allowed to drift to 34°C during construction of anastomoses before rewarming. The myocardium was protected with intermittent antegradely infused cold blood-based cardioplegia solution (a mixture of the patients' blood and Harefield cardioplegia solution at a ratio of 4:1 during induction and of 8:1 for maintenance). On completion of distal anastomoses, the aortic cross-clamp was removed, and the proximal anastomosis was performed with partial clamping.

Principle of TTFM measurement

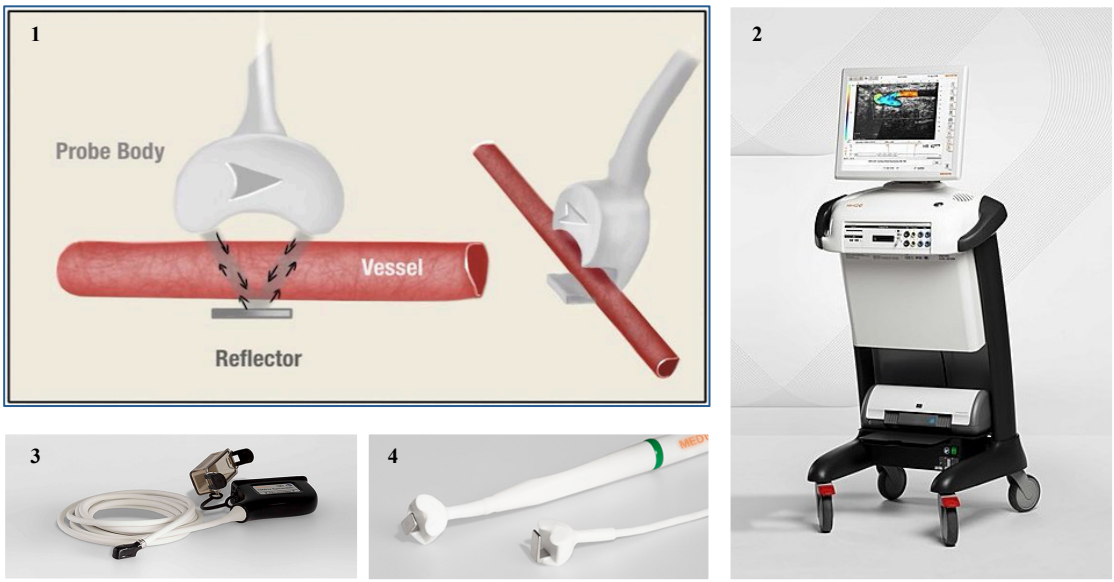
Prior to TTFM measurements, an appropriately sized probe was selected based on visual estimation of the external diameter of the conduit. For arterial grafts a probe size of 3 or 4 mm was used, and for SVGs a probe size of 4 or 5 mm was used. Ultrasound gel was applied to the probe-lumen ensuring that the graft occupied >75%

of the probe-lumen. Prior to TTFM measurement, adequate systemic blood pressure of 75-85 mmHg was secured, and during TTFM measurement, the probe was placed as close as possible to the distal coronary anastomosis, to ensure the most accurate reading of the flow dynamics across the anastomosis. Although this is easy for the left anterior descending artery, it may prove more difficult for right-sided grafts and for grafts going to the obtuse marginal when the heart is back in the chest cavity. For composite grafts, the probe was similarly placed close to the distal anastomosis without occluding the other limb. Traction on the pericardium was released, and the stabilizer was removed from the pericardial surface to allow the heart to return to its natural anatomic position. All TTFM parameters were subsequently assessed after protamine administration. The rational for measuring TTFM after reversal of heparin was to ascertain that the TTFM reading reflected the most accurate interpretation of the graft quality prior to sending the patient out of the operating room. Of note, grafts were revised if MGF <20 ml/min and/or PI>5 with obvious or detectable issues either by visual inspection or by HFUS imaging. Only post-revision TTFM measurements were included for analysis.

Principle of TTFM technique

The principle of the TTFM technique is based on ultrasound technology. The flow probe, which holds the graft perpendicular to two ultrasonic transducers and a fixed acoustic reflector housed within the probe, transmits pulsed ultrasound signals from the transducers both up- and downstream of the blood direction through the reflector (**Figure 2.2**). The time taken for the ultrasound waves to travel from one transducer to the other ("transit-time") is used as a direct estimate to calculate the actual blood flow given in ml/min.

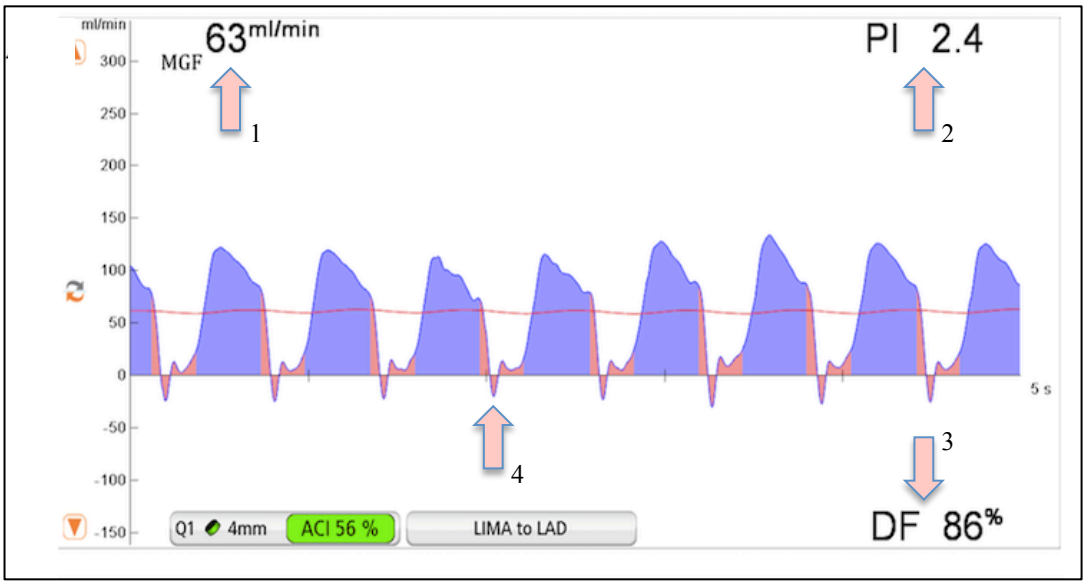
Figure 2.2: The principle of the TTFM technique



2.2.1: *The transducers in the TTFM probe are up- and downstream of each other. Both transducers act as a transmitter and a receiver.* ***2.2.2:*** *The VeriQC machine (Medistim ASA, Oslo, Norway).* ***2.2.3:*** *the HFUS probe (only available in one size).* ***2.2.4:*** *The TTFM probe. Probes are available in sizes 1.5mm to 7mm.*

Adherence to a recommended technique is important to ensure reliability and validity of the measurement, as bending and incorrect angulation of the vessels during measurement may lead to either over- or underestimation of blood flow (this will be discussed in Chapter 3 – Accuracy and precision of TTFM). Moreover, flow assessment should always be coupled with the electrocardiograph tracing to correctly differentiate between systolic (light red) and diastolic (light blue) flow (**Figure 2.3**).

Figure 2.3: example of a normal TTFM measurement in OPCABG



2.3: *TTFM measurement of LIMA to LAD. Main TTFM variables are provided and pointed out with pink arrows (1; MGF, 2; PI, 3; %DF, 4; %BF). The colour difference distinguishes between the diastolic (light blue) and the systolic (light red) phase of a cardiac cycle. Information on %DF and %BF is only available when the device is connected to an ECG.*

The acoustic coupling index (ACI) measures the adequacy of probe contact, with colour changing from green to yellow and red as contact deteriorates. Q1 refers to input 1, where the flow-probe was plugged in (in this case a 4-mm probe was used).

Mean Graft Flow (MGF)

As previously explained, the time taken for the ultrasound waves to travel from one side of the transducer to the other ("transit-time") is used to calculate the actual blood flow, as will be discussed in Chapter 3 – Accuracy and precision of TTFM.

Low flow will result in low shear stress, which is known to predispose grafts to develop intimal hyperplasia, resulting in graft failure [129]. MGF is not per se an adequate indicator of the quality of the anastomosis, as it is dependent on a number of independent factors, including blood viscosity, the size and quality of the graft,

arterial graft spasms, competitive flow, and the size and quality of the native coronary artery [77]. Thus, low flow values can be expected in fully patent anastomosis whenever the target territory has a poor run-off. In contrast, high flow is not necessarily a good indicator of good run-off either, as MGF may be 'normal' in cases of a distal anastomoses occlusion with pathological ante-grade, but preserved retrograde coronary flow, giving false impression of graft patency. The MGF parameters should therefore always be coupled with PI, %DF, %BF, and even the flow curve pattern (as explained below: Flow curves).

Pulsatility Index (PI)

The PI, expressed as an absolute number, represents an estimate of the resistance to forward graft flow and is considered an adequate indicator of the flow dynamics. The PI is obtained by dividing the difference between the maximum and the minimum flow by the value of the mean flow:

$$\frac{Q_{Maximum} - Q_{Minimum}}{Q_{Mean}}$$

Any factor that increases the resistance to distal flow, including graft stenosis or occlusion, distal native coronary artery stenosis, and poor run-off in the distal microvasculature will have an adverse influence on the PI value (i.e. result in high PI values).

Diastolic Filling (%DF)

DF% expresses the proportion of diastolic graft flow of the entire graft flow based on ECG information that can separate flow into its systolic and diastolic components.

%DF is obtained by dividing the flow in diastole by the value of one complete cardiac cycle (i.e. flow in diastole plus flow in systole):

$$\frac{Q_{diastole}}{(Q_{diastole} + Q_{systole})}$$

Flow in by-pass grafts follows the same haemodynamic rules of the flow in the native coronary arteries. During diastole, blood flows into both the native coronary artery and the by-pass graft; during systole, as the native coronary artery is compressed retrograde blood flow may be detected in the graft (i.e. 'backward' flow, as explained next). Diastolic filling is lower in grafts anastomosed to the right coronary territory compared to left-sided by-pass grafts due to the lower transmyocardial pressure gradient of the former [117, 119, 130], as will be discussed in Chapter 6: Left *vs*. right-sided venous by-pass grafting.

Backward Flow (%BF)

The %BF expresses the percentage of blood flow directed backward across the anastomotic site compared with the total forward flow during one complete cardiac cycle. The %BF parameter can only be obtained when the TTFM device is coupled to an ECG tracer and is illustrated on the screen as the area below the 0 curve line (**Figure 2.3.4**). Indeed, %BF is calculated as the integral of the area under the curve below the x-axis:

$$Area = \int_a^b f(x)dx$$

Physiologically, %BF occurs in diastole in the peripheral arteries due to the rapidly decreasing pulse pressure while %BF in coronary arteries and grafts occur in

systole as a result of the contracting myocardium. However, most often %BF in a graft occurs due to competitive flow [77, 131]. Thus, if the stenosis of the native coronary artery is not significant, blood flow in the graft will not exceed flow in the native coronary artery resulting in backward flow through the graft (this phenomenon is often referred to as "competitive flow") [121, 131, 132].

Acoustic Coupling Index (ACI)

The acoustic coupling index (ACI) depicts the percentage of ultrasound waves that are transmitted successfully from one side of the transducer to the other (**Figure 2.2.1**). The ACI value is displayed on the screen (**Figure 2.3**) with colour changing from green over yellow to red, as the contact deteriorates (red: 0-34, yellow: 35-50, green: 51-100). The ACI index will be further explained in Chapter 3 – Accuracy and precision of TTFM.

Flow curves

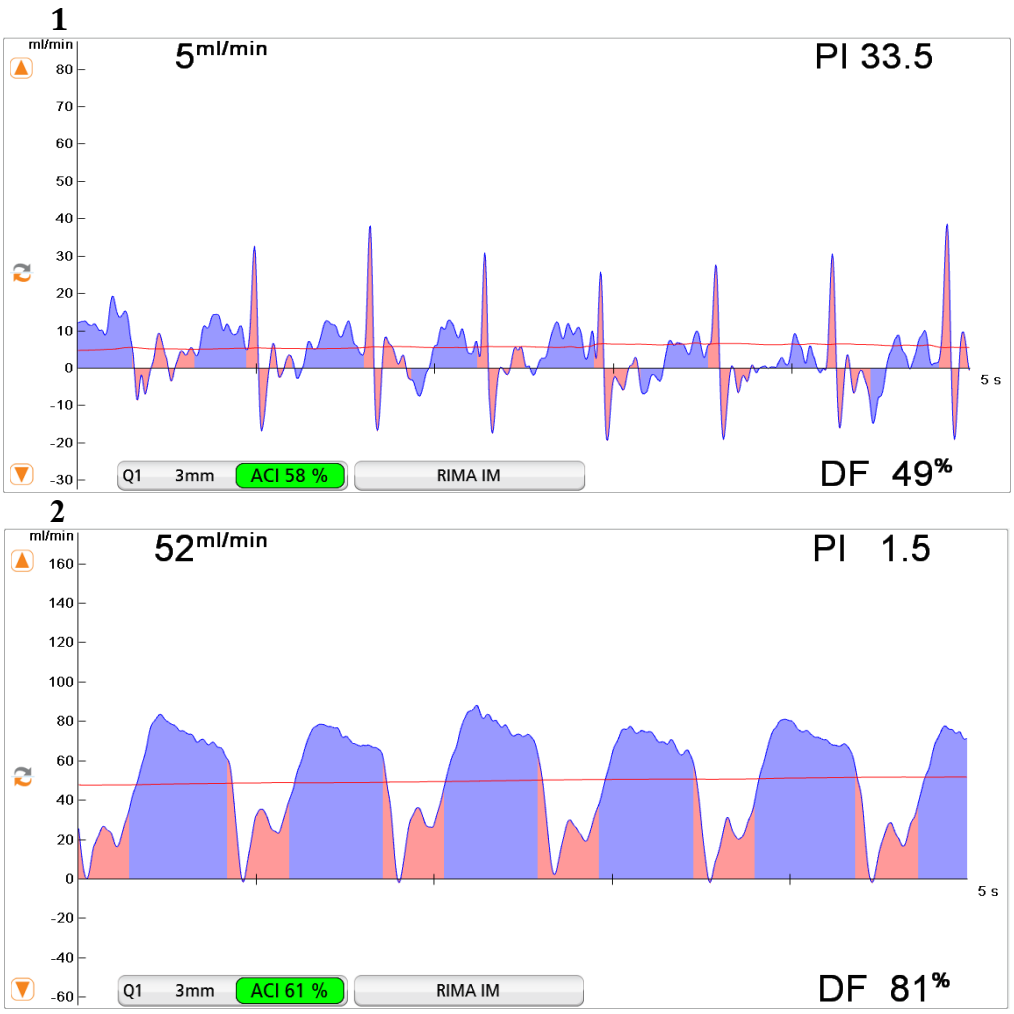
As formerly annotated, in a patent by-pass graft, the haemodynamics are physiologically similar to those observed in the native coronary arteries: blood flow mainly occurs in diastole with minimal systolic peaks taking place during the isovolumetric contraction. As such, observation of the flow curve, may help detect situations where a prominent systolic forward flow is present e.g. in cases of stenosis where forward flow is prohibited. In such cases, a particular spikey tracing occurs, which we collectively define as 'stenotic' curve morphology (**Figure 2.4**).

The value of the flow curves is often not considered and has only been briefly discussed in a few studies [133, 134]. In an attempt to quantify the value of the

waveform, few studies have succeeded in demonstrating the use of fast Fourier transformation (FFT) technique to determine the quality of a by-pass graft during CABG [135, 136]. The FFT analysis is based upon the principle that all periodic waveforms can be broken into a series of waves. Theses waves exist as frequencies that are multiplies of the original waveform ("the fundamental frequency") and are described in terms of amplitude and phase. The pulsatile waveforms of by-pass graft flows can be considered as periodic waveforms possessing a fundamental frequency, and thus the FFT technique can be used to quantify the quality of a by-pass anastomosis.

Although visual inspection of the flow curves and FFT may prove valuable, these are not the main aim of this thesis and will thus not be further discussed.

Figure 2.4: Example of a stenotic problem in a graft



2.4.1 – Off-pump case of twisted graft; RIMA to IM.

Pre-revision: Spikey systolic forward and backward flow, which we collectively define as 'stenotic' curve morphology, with subsequent poor TTFM parameters. Exploration of the entire graft showed that the conduit was twisted. The anastomosis was thus revised.

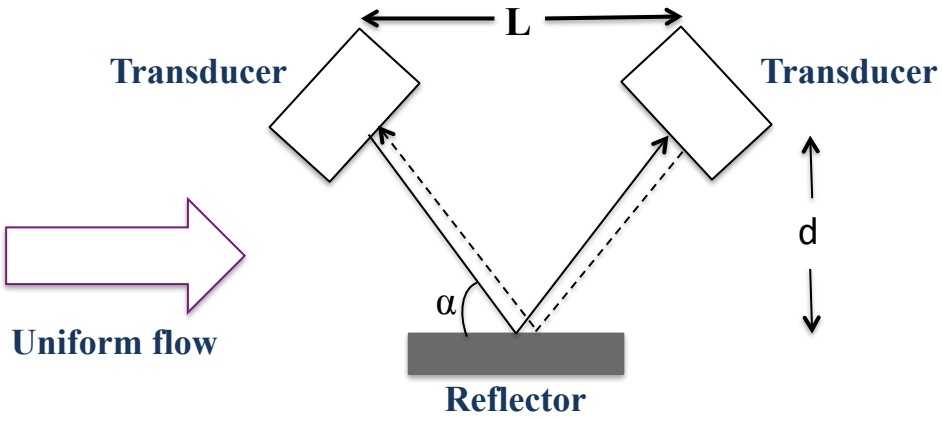
2.4.2 – Post revision: Significant improvement of all TTFM parameters and subsequent flow curves.

RIMA; right internal mammary artery**, IM;** Intermediate artery

Mechanism and mathematics behind the TTFM technique

As previously explained, the principle of TTFM is based on ultrasound technology. The device uses a flow probe, which holds the graft perpendicular to two ultrasonic transducers and a fixed acoustic reflector (Figure 2.5).

Figure 2.5: Principle of TTFM technique



***2.5** – L = length between transducer (kindly do not confuse with length in the equation below), α = angle, and d = diameter.*

Pulsed ultrasound signals are transmitted from the transducer both up- and downstream of the blood direction through the reflector. The time taken for the ultrasound waves to travel (*"transit-time"*) is then used to estimate the flow.

The equations for the up- and downstream flow in uniform flows are:

(1) $$t = \frac{2d}{c \cdot sin\alpha}$$

(2) $$t_{up} \frac{2d}{(c - v\ cos\alpha)\ sin\alpha}$$

(3) $$t_{down} \frac{2d}{(c + v\ cos\alpha)\ sin\alpha}$$

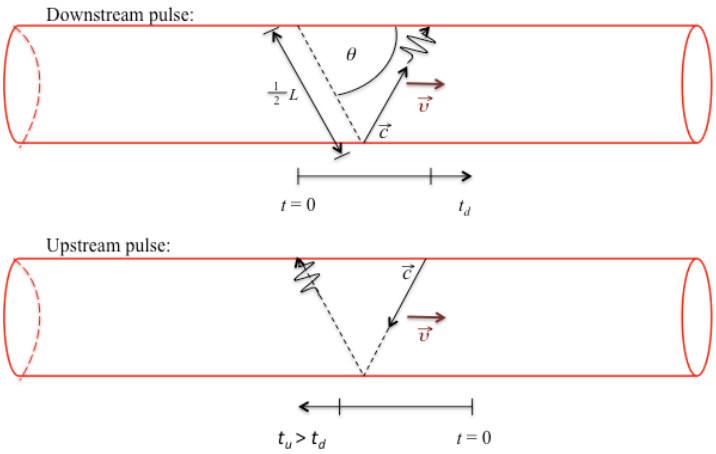
Equation (1) provides the "transit-time" from one transducer to the other, via the reflector, where *t* denotes the time, *c* denotes the speed of sound in a medium, and *v* denotes the flow velocity. Equation (2) and (3) provide the "transit-time" from one transducer to the other both up- (2) and downstream (3) the blood direction. Flow velocity is considerably negligible in comparison with the speed of sound in a medium, and therefore the term $v^2\cos\alpha^2$ is taken out of the equations providing the following equation for both up- and downstream:

$$\Delta t_{real} = \frac{4d(v\cos\alpha)}{(c^2 - v^2\cos^2\alpha)\sin\alpha} \approx \frac{4dv\cos\alpha}{c^2\sin\alpha} = \Delta t_{approx} \quad (4)$$

Δt_{real} denotes the precise formula for the transit time, and the Δt_{approx} denotes the approximation used by the TTFM flowmeter to estimate blood flow.

Notably, the system assumes a constant length L for a straight vessel. Below is a sketch showing a perfectly straight vessel, which provides the most accurate reading of the actual blood flow (**Example (1)**).

Example (1): Illustration of the down- (t_d) and upstream (t_u) 'transit-time' calculation



$$t_d = \frac{L}{c+\vec{v}\cos\theta}$$

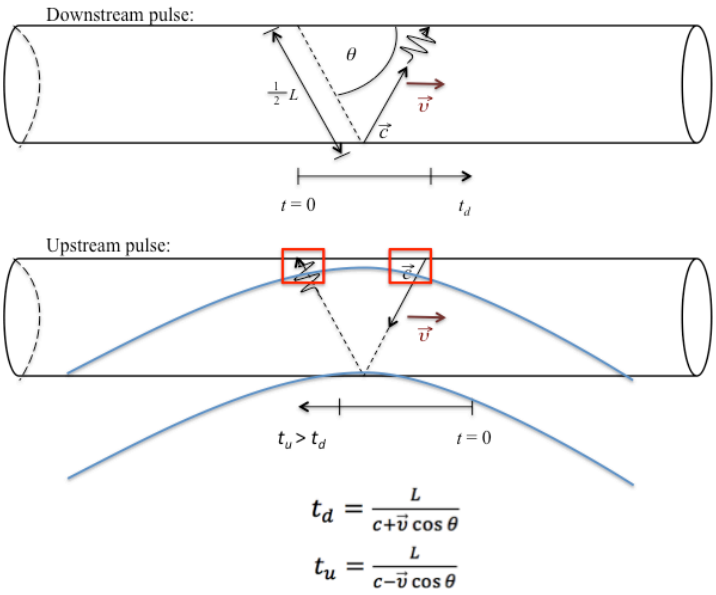
$$t_u = \frac{L}{c-\vec{v}\cos\theta}$$

E.1 *– The upstream pulse wave will always travel against the flow direction and thus result in a higher 'transit-time' compared to the downstream pulse wave (t_u>t_d). L; length, c; speed of sound in a medium, v; the flow velocity, cosθ; angle of the ultrasound beam.*

If the vessel is however pulled or pushed, the length (L) that the ultrasound waves travel inside the vessel lumen will be changed potentially affecting the calculated time-difference.

Below is a sketch (**Example (2)**) that highlights an area where the ultrasound pulse is not affected by the blood stream:

Example (2): Illustration of how bending of a vessel may affect the down- (t_d) and upstream (t_u) 'transit-time' calculation



As illustrated above, if the vessel is pulled the length (L) that the ultrasound signals travel inside the vessel lumen will change, and thus alter the calculated time-difference. More examples are illustrated in **Figure 3.5** in Chapter 3.

Transit time flowmetry as the preferred technique

Intraoperative graft patency verification techniques should be fast, easy, be able to save data for clinical evaluation, minimally invasive, easily meaningful, reproducible, and provide objective parameters rather than qualitative criteria. As previously discussed, many different techniques for intraoperative graft patency assessment have been introduced and validated (**Table 1.1**) each with their strengths and limitations.

Although conventional angiography remains the gold standard technique for graft patency verification, the technique has little value in assessing the hemodynamic function. Conventional angiography purely provides biplane anatomic evaluation. In addition, its requirements for additional equipment and personnel, need of arterial puncture, potentially nephrotoxic contrast agents, and increased operating time usually precludes it from the operating theatre.

Doppler velocity measurements use the principle of changes in frequency relative to the position of the probe (”*Doppler shift*”). The technique is easy to use, however, the range of resolution prohibits precise graft flow evaluation while the pulsed wave technique provides flow velocities that vary depending on the angle [95].

Electromagnetic flowmetry flow values vary with movement and are dependant on the haematocrit and other interference, and are thus no longer used in the operating theatre [92].

Thermal coronary angiography uses infrared light to detect temperature differences. By injection of cold/warm saline or cardioplegic solutions, the device provides images based on temperature differences between the myocardium and the vessels. However, the resolution of the images are often unsatisfactory [93]

Intraoperative fluorescence imaging is based on the fluorescent properties of indocyanine green (ICG) dye. After intravenous injection, ICG binds to plasma proteins and when illuminated with a near infrared laser light, it emits fluorescence light. This fluorescence is subsequently captured on a couple device video camera. Although the technique provides close-to angiographic images, fluorescence imaging does not produce precise measurements of flow in grafts but gives semiquantitative and monoplane assessment of graft patency [83, 84, 137]

TTFM is based on ultrasound technology, which gives immediate and close to precise measure of the actual flow [126, 127], in addition to other hemodynamic parameters (PI, %DF, %BF, and the flow curves). Furthermore, flow measurements are independent of haematocrit level, heart rate, and vessel wall thickness [117]. Unfortunately, the technique has been reported with low sensitivity and specificity (**Table 1.3**). Nonetheless, the ease of use and close to precise assessment of actual graft flow makes the technique an excellent tool for intraoperative graft flow assessment [114].

Overall, imaging modalities have little value in assessing the hemodynamic function while flow-assessment devices do not provide imaging of the anastomosis and may either over- or underestimate the need for graft revision. As both methods have clear limitations, a combination of these techniques would be preferred. As previously discussed, a recent study has shown that the addition of HFUS imaging to the TTFM technique may indeed increase the diagnostic value of the TTFM technique [128], but more research is now warranted to address the full potential of the combination.

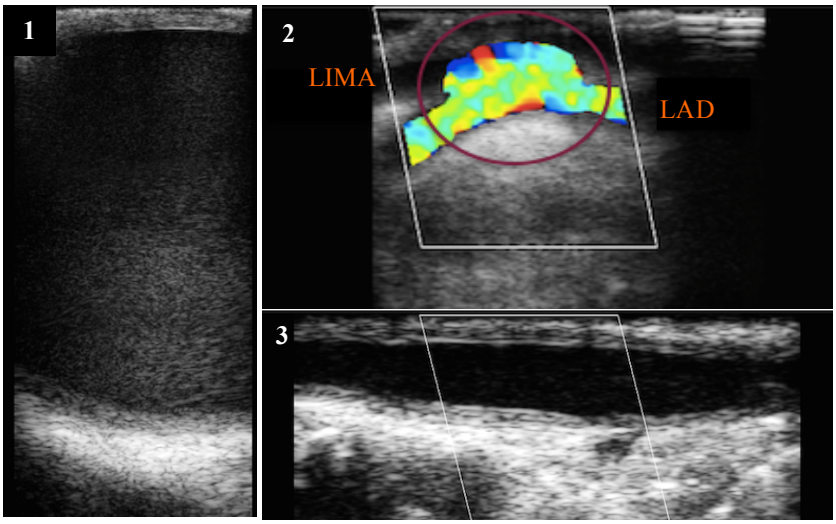
Principle of high-frequency ultrasound imaging

Similar to the TTFM technique, HFUS uses ultrasound waves (15 MHz) to visualize the vessel by means of a small probe measuring 3x2x1.5 cm (length/height/width) [128]. However, this technique is based on Doppler technology rather than ultrasound. The difference between these two technologies is that the Ultrasound technique relies on a specific depth (the reflector will reflect the ultrasound waves

back at a certain distance) making it a more accurate tool for flow measurements while in Doppler the ultrasound waves are transmitted in one direction and only reflected back from blood cells and tissues, making this technique less consistent for flow measurements.

The colour-flow mapping of the HFUS imaging technique along with a two-dimensional module allows a fast and easy detection of even small defects and can be used on grafts, distal anastomoses, and even the aorta (**Figure 2.6**).

Figure 2.6: Examples of high-frequency ultrasound images



2.5.1: *Normal aorta.* ***2.5.2:*** *HFUS image of a patent LIMA to LAD anastomosis. The anastomosis is shown within the red circle (LIMA anastomosed to LAD).* ***2.5.3:*** *Normal HFUS image of LIMA still attached to the chest-wall (in-situ).*

General statistics

Continuous variables are reported as mean ± standard deviation and were compared using the unpaired t-test for normal distributions and the Mann-Whitney U-test for non-normal distributions. Normality was tested with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages and were compared using the Chi^2-Pearson test. Multivariable linear regression was used to

investigate the effect of ONCABG and OPCABG, arterial and venous, and left coronary territory and right coronary territory on MGF, PI, %DF, %BF whilst controlling for potential confounding variables. Variables were incorporated into the multivariable analysis if associated with MGF in a univariable regression analysis at a significance level of $p<0.10$. Significance of the multivariable regression model was assessed using the *F*-test. Results of the regression model are presented as regression coefficients (β) with 95% confidence intervals (95% CI) and the corresponding p-values. A p-value<0.05 (two-sided) was considered statistically significant. Data analysis was performed in IBM SPSS Statistics Version 22 (SPSS Inc, Chicago, IL).

Statistical power calculations were based on pilot data on MGF from our group and the assumption that for any conduit-related difference to be of clinical importance, it should change MGF by >10% [114]. With an α-value of 0.05 (double-sided) and a β-value of 0.80, changing MGF from 48 ml/min by at least 5 ml/min (estimated sigma of 10 ml/min) requires at least 63 patients in each group. Potential changes in other parameters were considered exploratory. A more detailed description of the power analysis is provided in the respective chapters.

3

An assessment of the accuracy and precision of the TTFM technique

Chapter 3 – Accuracy and precision of TTFM

Introduction

As previously noted, current literature suggests that up to 11% of by-pass grafts, affecting roughly 10% of all patients, are occluded early after surgery [18, 75-77]. To potentially overcome this problem, current European guidelines on myocardial revascularization recommend intraoperative monitoring of graft flow [99][138], with TTFM currently being the most commonly applied technique [114, 119]. Curiously, however, there are only a few *in-vitro* and *in-vivo* studies actually assessing the accuracy and precision of TTFM determination of graft blood flow.

In 1993, Lundell *et al.* [127] conducted *in vitro* and *in vivo* experiments on TTFM in sheep and concluded that the TTFM was a good technique for graft flow assessment with a small variability in measurements of blood flow. In 1996, Laustsen *et al.* [126] conducted a study on the accuracy of the TTFM technique in patients. The study included 13 patients (35 measurements) undergoing *in situ* SVGs for chronic critical leg ischaemia and 12 patients (21 measurements) subjected to myocardial

revascularization with the internal thoracic artery as one of the conduits for CABG surgery. The study concluded that the technique was simple to use and gave fast, precise measurements of the actual blood flow [126]. Both studies used free blood flow as the reference-standard.

We considered that to understand the accuracy of TTFM and to determine in which situations measurements may be potentially less accurate, a larger scale study on TTFM co-variation with more directly determined graft flow was important. Hence, in an observational study, we evaluated TTFM's accuracy and precision in quantifying blood flow measurement of LIMA grafts by comparison with free flow into a collection vessel during surgery in a larger cohort of CABG patients. The results of this analysis does not only evaluate the accuracy and precision of TTFM, but provides further information on which TTFM measurement parameters are of importance for adequate estimation of graft flow.

Methods

This study was a single Centre retrospective observational study of 60 consecutive patients undergoing elective myocardial revascularization using the LIMA as one of the conduits (study period November 2015-April 2016). The patients were excluded if the LIMA was extensively diseased, had obvious sign of haematoma, or was damaged in any way that could potentially adversely affect flow. In this study, the primary study outcomes were co-variation of blood flow measured by TTFM and the free blood flow with the aim of assessing the accuracy and precision of TTFM flow measurement in an arterial graft. As secondary outcomes, the study intended to additionally assess the effect of TTFM's ACI value and the probe-to-conduit size

mismatch on accuracy of flow measurement. Based on a visual estimation of external graft diameter, the surgeon decided on probe size (3 or 4 mm).

Procedure

CABG was performed via a median sternotomy by two surgeons using their standard techniques. After dissection of the endothoracic fascia, the LIMA was skeletonized from its origin to 1-2 cm proximal to its bifurcation. Subsequently, TTFM measurement was performed proximally and distally on the LIMA prior to clipping and distal division of the conduit. To avoid peri-procedural spasm, topical papaverine and/or raising the systolic blood pressure to 150 mmHg for 5-10 minutes was routinely applied. With a total of 60 patients and conduit flow and diameter measurements both pre- and post-vasodilation in each patient, our study is based on 120 paired intraoperative measurements**.**

Flow measurements

After clipping and distal division of the LIMA, free blood flow was determined by collection into a measuring cup in a fixed time window of 20 seconds. The time-window had been chosen to ensure a potential maximum 2.5% error in absolute flow measurement in case the time-window was measured with up to 0.5 second inaccuracy over 20 seconds. TTFM was measured at the same time as the free flow at a fixed MAP of 75-85 mmHg. After the antispasmodic intervention, the distal clip was again removed, and TTFM and free flow were reassessed. Both are determined in ml/min. Collected blood was returned to the patients' circulation via the cell-saver in off-pump cases (n=38) and directly back to the cardiopulmonary by-pass circulation in on-pump cases (n=22). In the co-variation analysis by regression, flow over- or

underestimation was defined as any difference in TTFM flow compared to free flow (e.g. TTFM flow of 110 ml/min compared to free flow of 100 ml/min was considered flow overestimation of 10 ml/min or 10%), and in the Bland-Altman analysis over- or underestimation was determined from Bland and Altman's original approach using the average of TTFM and free flow as the denominator.

HFUS imaging

Following each blood flow measurement (pre- and post-vasodilation), the external conduit diameter was measured by HFUS imaging. Ultrasound gel was applied to the 15 MHz probe [128]. Subsequently, the probe was gently placed on top of the conduit, a longitudinally-oriented image was captured, and the exact diameter was measured on the screen. Any probe-to-conduit size mismatch (probe > or < conduit diameter) was considered probe over- or undersizing and provided in the results as percentage difference.

Acoustic Coupling Index (ACI) value

As the ACI value depicts the percentage of ultrasound waves that travel successfully from one end of the probe to the other (for example an ACI value of 68% means that 68% of the ultrasound waves have travelled successfully from one end to the other), in theory, a higher ACI value will provide a more reliable reading. ACI values are displayed on the screen for each TTFM flow measurement.

Statistical analysis

The general statistics have been discussed in Chapter 2 – General methods. Flow mismatch between TTFM flow and free flow are presented as the percentage TTFM

flow compared to free flow. Similarly, the probe-to-conduit size mismatch is shown as the percentage of probe size compared to the external LIMA conduit size measured by HFUS imaging. Multivariable logistic regression analysis was applied to determine the association of TTFM flow, probe size, probe oversizing, and ACI with flow overestimation and the association of probe size and ACI with probe oversizing. The results of the regression models are presented as odds ratios (*OR*) with 95 % confidence intervals (CI) and corresponding p-values. To evaluate the predictability of TTFM flow, probe oversizing, and ACI on flow overestimation, receiver operating characteristic (ROC) curves and the C statistic (area under the curve (AUC)) were constructed. Cut-off values maximising sensitivity and specificity were obtained by Youden's index. Further, to evaluate under- and overestimation, a Bland-Altman analysis was applied for pre- and post-vasodilatation results separately and with separate analyses for 3 and 4 mm probes and for probes demonstrated to be mis-matched.

Results

No LIMA was visually deemed unsuitable for grafting, and hence with a total of 60 patients, 120 TTFM paired flow measurements and 120 paired free flow measurements (60 pre- and 60 post-vasodilation measurements each) were included in the analysis. Based on the surgeons' visual inspection before vasodilation, in 61% (n=73) of all TTFM flow measurements the 3 mm probe was used, and in 39% (n=47) the 4 mm probe was used. Based on the regression analysis, TTFM flow was higher than actual free flow in 64% (n=77) of all measurements (**Figure 3.1**). Oversizing of the TTFM probe (probe size > external conduit diameter as determined by HFUS) occurred in 87% (n=104) of all measurements. The average pre-vasodilation proximal

and distal diameters were 1.9±0.4 and 1.5±0.4 mm, respectively, and the average post-vasodilatory proximal and distal diameters were 2.5±0.4 and 2.2±0.4 mm, respectively (both p<0.001). The relative changes with vasodilatation amounted to 31±25% for the proximal segment of the LIMA and 49±32% for the distal segment, respectively.

Multivariable logistic regression demonstrated that probe oversizing (*OR*=9.56 (95% CI 2.03-45.10), p=0.004) and higher TTFM flow (*OR*=1.02 (95% CI 1.01-1.04), p<0.001) were independent determinants of a higher TTFM than free flows. Probe size and ACI did not reach statistical significance in the regression model (**Table 3.1**). ACI values <40% (based on ROC cut-off values mentioned below) (*OR*=0.33 (95% CI 0.11-0.97), p=0.043), and probe size 4 mm (*OR*=5.55 (95% CI 1.54-20.01), p=0.009) independently predicted probe oversizing. ACI values were significantly lower in oversized probes compared to accurately sized or undersized probes (45±16% *vs*. 60±18%, p<0.001). When comparing the 3 and 4 mm probe sizes, the 4 mm probe was found to be associated with a significantly higher rate of probe oversizing determined as percentage of probe size compared to the external LIMA conduit size ((149±33% *vs*. 128±30%, p<0.001). Further, the 4 mm probe had lower values of ACI (41±14% *vs*. 50±18%) than the 3 mm probe (p=0.003) (**Figure 3.2**).

The ROC curves of TTFM flow, ACI, and probe oversizing for flow overestimation are shown in **Figure 3.3A**. The AUC was 0.76 for TTFM flow (95% CI 0.67-0.84, p<0.001), 0.40 for ACI (95% CI 0.30-0.51, p=0.07), and 0.68 for probe oversizing (95% CI 0.58-0.78, p=0.001). In direct comparison with the free flow, the optimal cut-off value of TTFM flows for assuming flow overestimation was 68 ml/min, resulting in a sensitivity of 71% and a specificity of 71% as determined with Youden's index. The ROC curve for ACI as an indicator of probe oversizing is shown

in **Figure 3.3B** with an AUC of 0.73 (95% CI 0.60-0-86, p=0.003). Emphasising high sensitivity, the optimal cut-off value for ACI was 0.36, which had a sensitivity of 100% but now a low specificity of 32%.

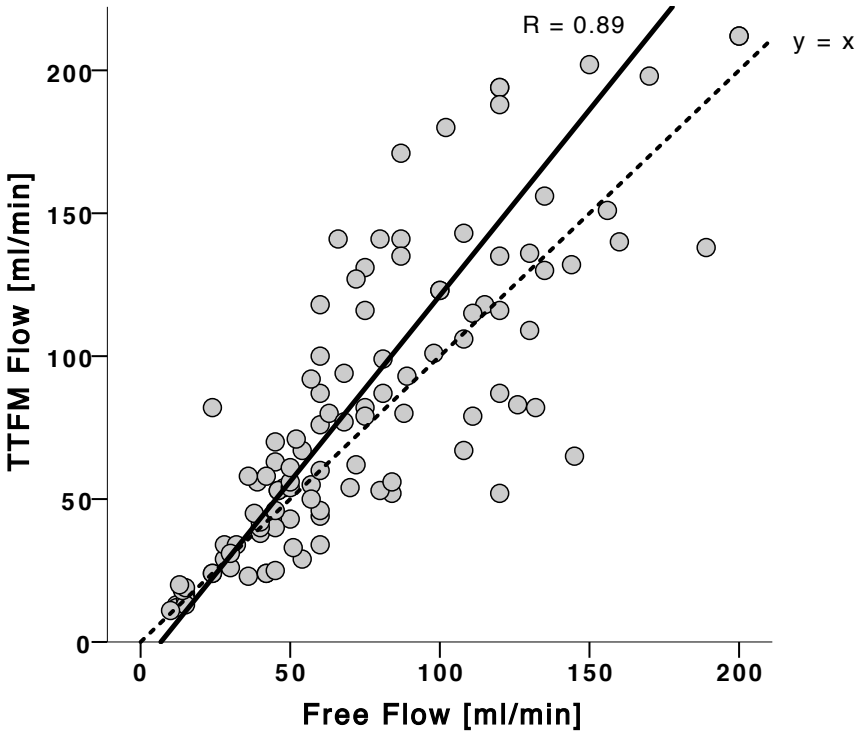
The Bland-Altman analysis showed that the TTFM technique may underestimate slightly at low flows and overestimate at higher flows. Overall, the TTFM technique systematically overestimated free flow by 7.1±16.3% (mean±SD, p=0.0012) in the pre-vasodilation situation, but did not systematically over- or underestimate free flow in the post-vasodilatation situation (**Figure 3.4**). The overall systematic overestimation in the pre-vasodilation situation was driven by the overestimation with 4 mm probes (13.3±15.4%, p=0.0002) whereas no systematic difference was noted with 3 mm probes (**Figure 3.4**). Absolute flow changes by vasodilatation were significantly overestimated by TTFM (98±45%, p<0.0001) (**Figure 3.4**). Probe-to-conduit diameter mismatch (undersizing) was only observed in the post-vasodilatation situation with the 3 mm probe, but no systematic flow over- or underestimation was noted in this situation albeit only 11 patients were evaluable (**Figure 3.4**).

Table 3.1: Multivariable logistic regression analysis for flow overestimation

	Unstandardized coefficients			95% CI for OR		
	B	SE	OR	Lower	Upper	p-value
Probe oversizing	2.257	0.792	9.558	2.026	45.096	0.004
Probe size (3 mm vs. 4 mm)	-0.097	0.568	0.907	0.298	2.762	0.864
ACI	-0.015	0.014	0.985	0.959	1.012	0.283
TTFM flow	0.023	0.006	1.023	1.012	1.035	<0.001

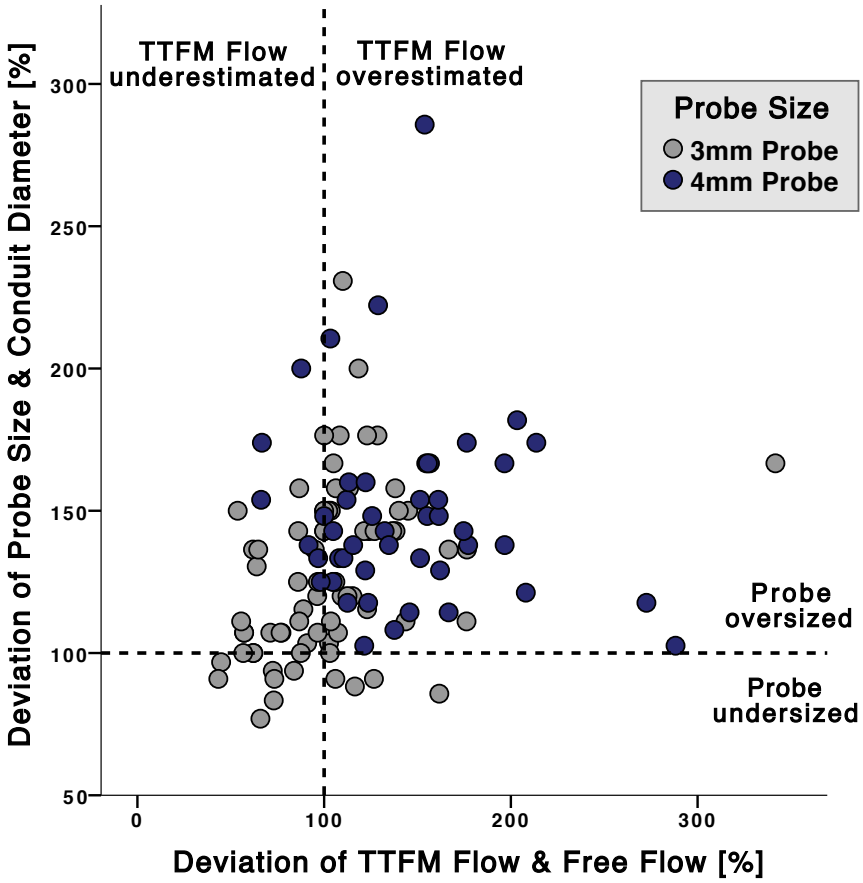
ACI: Acoustic coupling index, **CI:** Confidence interval, **OR:** Odds ratio, **SE:** Standard error.

Figure 3.1: Correlation of free flow and TTFM flows



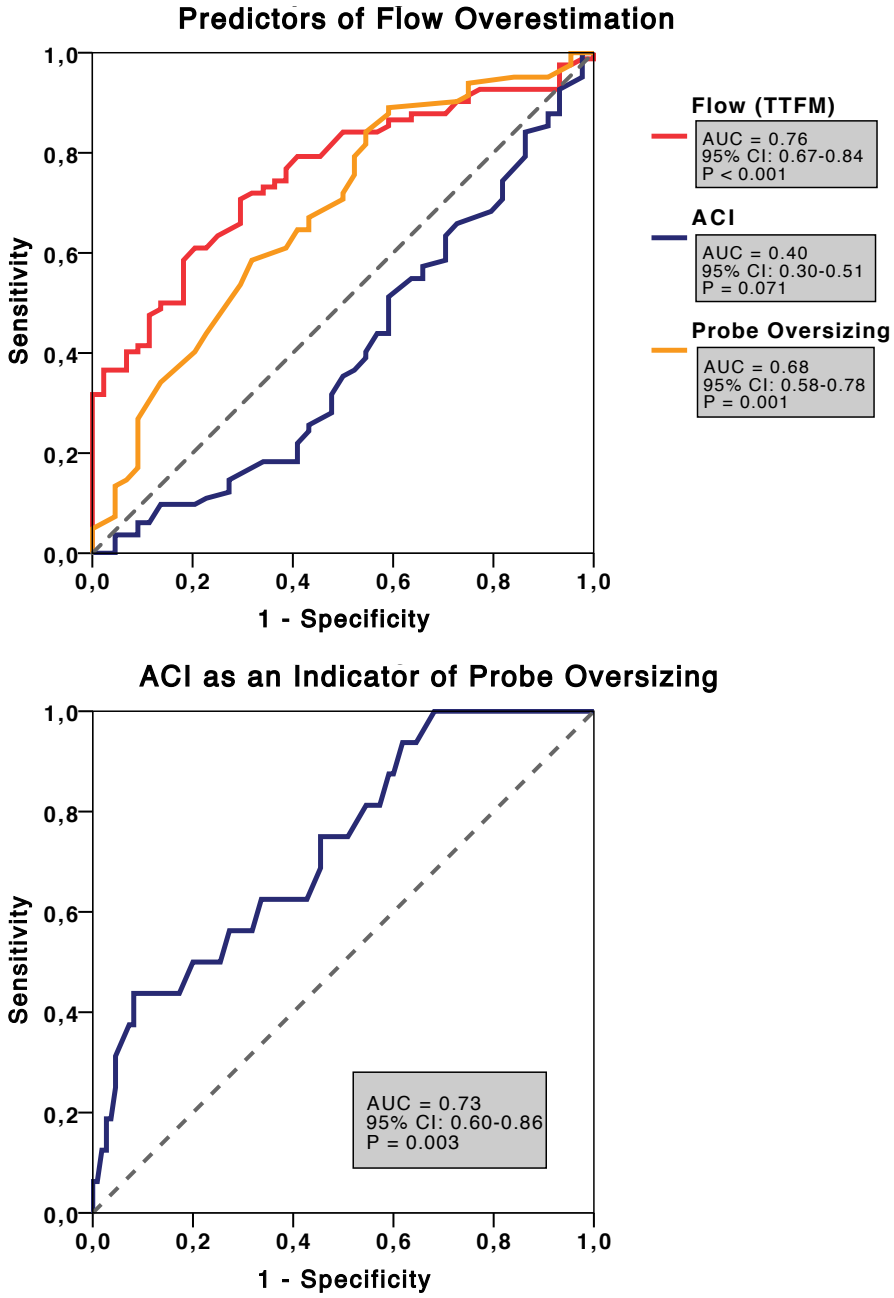
3.1 *– Scatter plot and interpolation line depicting the correlation between Free flow and TTFM flow (R=0.89). The dotted line indicates a perfect overlap of Free flow and TTFM flow (y=x). Flow measurements greater than 200 ml/min are not shown.*

Figure 3.2: Distribution of measurements in different probe sizes



3.2 *– Scatter plot depicting the distribution of measurements between probe-to-conduit size mismatch and TTFM accuracy with respect to the different probe sizes (3mm (n= 73) and 4mm (n=47)). Please note, both pre- and post-vasodilatory measurements of the 60 patient recruited are included in this figure.*

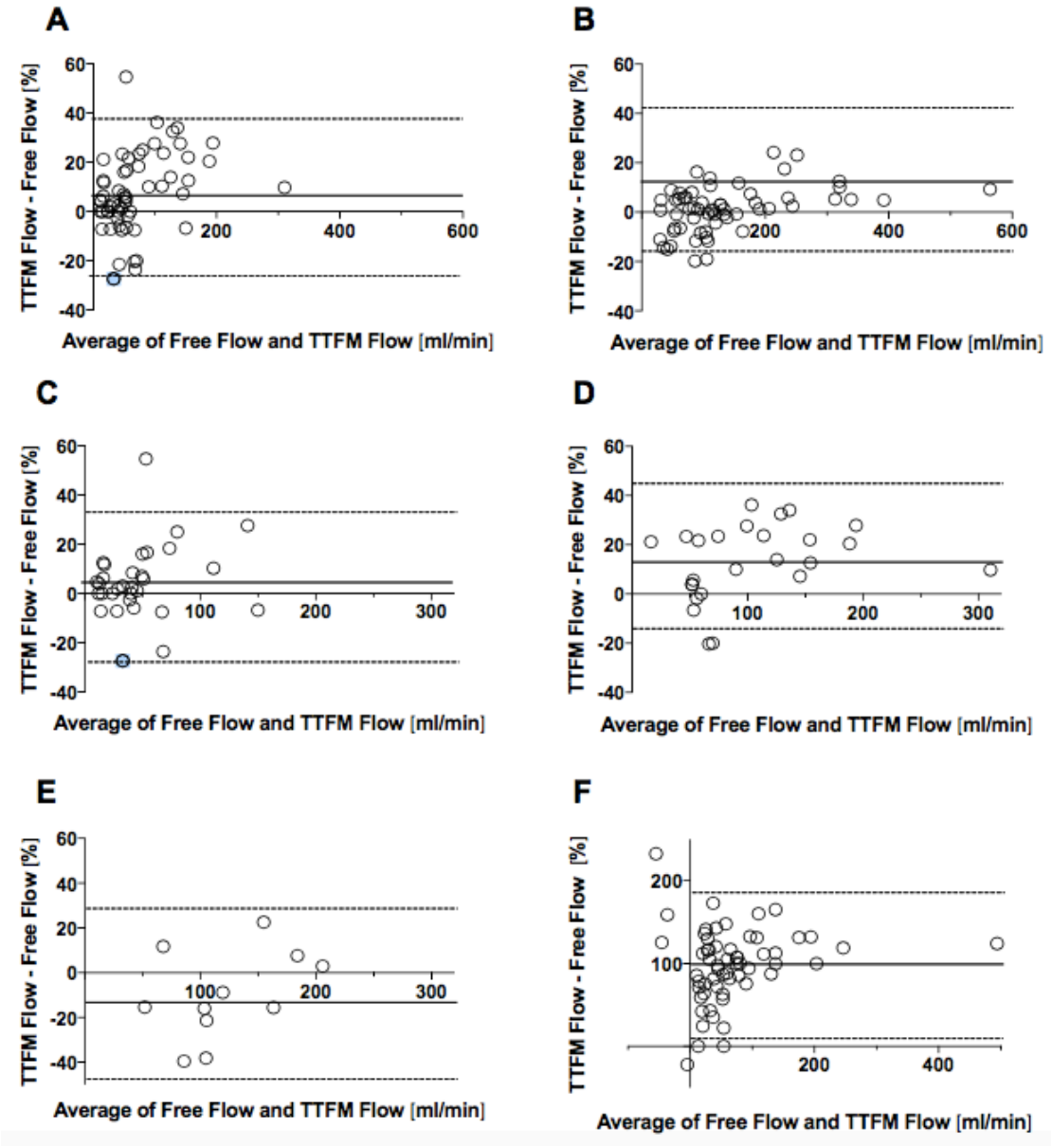
Figure 3.3: Receiver operating characteristics



3.3 – A: Receiver operating characteristic (ROC) curves of TTFM flow, ACI, and probe oversizing for flow overestimation. The area under the curve (AUC) was found to be 0.76 for TTFM flow (95% CI: 0.67-0.84; p<0.001), 0.40 for ACI (95% CI: 0.30-0.51; p=0.071), and 0.68 for probe oversizing (95% CI: 0.58-0.78; p=0.001).

B: ROC curves for ACI as an indicator of probe oversizing. With an AUC of 0.73 (95% CI: 0.60-0-86; p=0.003), ACI is a fair indicator for probe oversizing.

Figure 3.4: Bland-Altman plots of difference between free and TTFM flows



3.4 – A: Overall difference pre-vasodilatation.

B: Overall difference post-vasodilatation.

C: Difference in pre-vasodilatation in 3 mm probes.

D: Difference in pre-vasodilatation in 4 mm probes.

E: Difference in patients with undersized probes. Of note, all measurements in figure 3.4.E are in the post-vasodilatation situation and measured with a size 3 mm probe.

F: Overall

Where statistically significant difference from the zero line was found, horizontal lines indicating average deviation (with 95% confidence intervals) are inserted.

Discussion

To evaluate accuracy and precision of TTFM for evaluation of LIMA graft flow, co-variation of TTFM and free flows were determined during CABG in 60 patients. TTFM flows were higher than free flows in 64% of evaluations, and in comparison with their average, TTFM overestimated flow by 7.1% in the pre-vasodilation situation, but did not overestimate flow after vasodilatation. The standard deviation of TTFM to average flows was 16.3%. This overestimation was mainly seen with oversized probes and therefore often with 4 mm probes. Moreover, oversizing was more often seen with poor acoustic coupling index (ACI<40%). Our study further suggests that flow overestimation may be suspected with flows above 68 ml/min.

While the value of the TTFM technique and graft patency at follow-up has been evaluated [114], the accuracy of the TTFM blood flow measurement has not been fully addressed in the clinical setting. As previously denoted, only two studies have evaluated the *in vivo* accuracy of TTFM [126, 127]. However, both studies consisted of very small cohorts and one study was indeed conducted in sheep [127]. Nevertheless, both studies concluded that TTFM was a good technique for graft flow assessment [126, 127], albeit with a small variability in both *in vivo* and *in vitro* measurements [127]. In this study, we found that the TTFM technique accuracy is high with only a systematic overestimation noted of 7.1% driven by measurements with the 4 mm probe in higher flows (here 13.3%) in comparison with the average of TTFM and free flows, and a clinically acceptable precision corresponding to a standard deviation of 16.3% in the overall cohort. In the vasodilation situation, no systematic overestimation was noted. Clinically far larger systematic overestimation of 98% was noted if the absolute difference between the pre- and post-vasodilation situations were considered. Of note, any clinical setting where a perfect match was

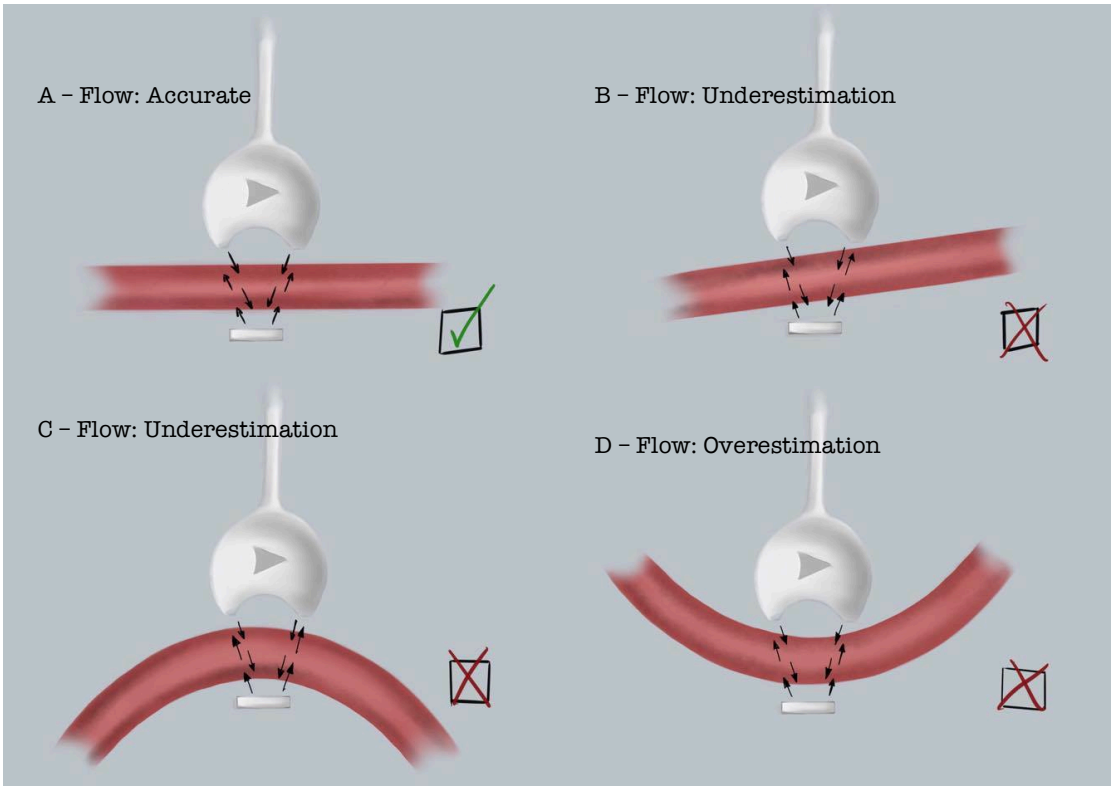
not met, e.g. a difference of even 5ml/min between TTFM and free flows was considered a mismatch, and was analysed as flow over- or underestimation. In reality a small variance in measurement should always be accounted for. Allowing a mismatch of 5 or 10% would further support the TTFM technique as an accurate and reliable technique for intraoperative graft flow assessment. Overall however, we found that TTFM flow >68 ml/min and probe oversizing were independent determinants of flow overestimation in comparison with free flow. The ACI value and the probe size (3 or 4 mm) did not reach statistical significance in this correlation.

A low ACI value arises due to poor signal transmission and the most common reason for low ACI values are probe damage or degradation or thick vessel walls and non-skeletonized vessels that attenuate ultrasonic energy. We found that probe oversizing was an independent variable for poor ACI value, but ACI was not associated with flow overestimation. Thus, a poor ACI does not lead to flow overestimation but can guide for correct probe sizing. In theory, the issue of probe oversizing can be solved by placing ultrasound gel around the conduit to increase the ACI, but even slight movement of the conduit (especially during beating-heart CABG) may expel gel and attenuate the ultrasound transmission. The ACI value is rarely low in undersized probes as the probe will cover the conduit completely, allowing all ultrasound waves to travel through the conducting media (human soft tissue and blood), but in this situation some ‘squeezing’ of the conduit may occur and is not recommended.

The probe size (3 or 4 mm) was not an independent variable for flow overestimation, but a 4 mm probe size was an independent variable for oversizing and thus may lead to flow overestimation. Indeed no overestimation of flow with TTFM was noted in the vasodilation situation, most likely because the graft, by increasing

some 31% to 49% in diameter, then more accurately complimented the size of the 4 mm probes and was, therefore, no longer clinically oversized. Overestimation of blood flow may be seen with larger probes due to angular misalignment between the conduit and the probe (Figure 3.5). As illustrated in Figure 3.5, bending of the conduit within the probe may lead to either over- or underestimation of flow. As explained earlier, with large probes, the risk of conduit to probe misalignment is higher due to more space between the vessel wall and the probe head despite the use of gel.

Figure 3.5: The principle of TTFM measurement



A: The probe head should be held perpendicular to the vessel for the most accurate reading.
B: This kind of angulation will result in flow underestimation.
C: Downward bending may result in flow underestimation, as explained in Example 2 below.
D: Upward bending of the vessel may result in flow overestimation.
The mechanism and mathematics behind Figure 3.5 has been explained in Chapter 2 – Methods.

We further found that the TTFM technique may overestimate the actual blood flow in higher flows (> 68 ml/min). In an attempt to explain this finding, we examined the mathematical equation as given in equation (4), which was discussed in Chapter 2 - Methods:

(1) $$t = \frac{2d}{c \cdot sin\alpha}$$

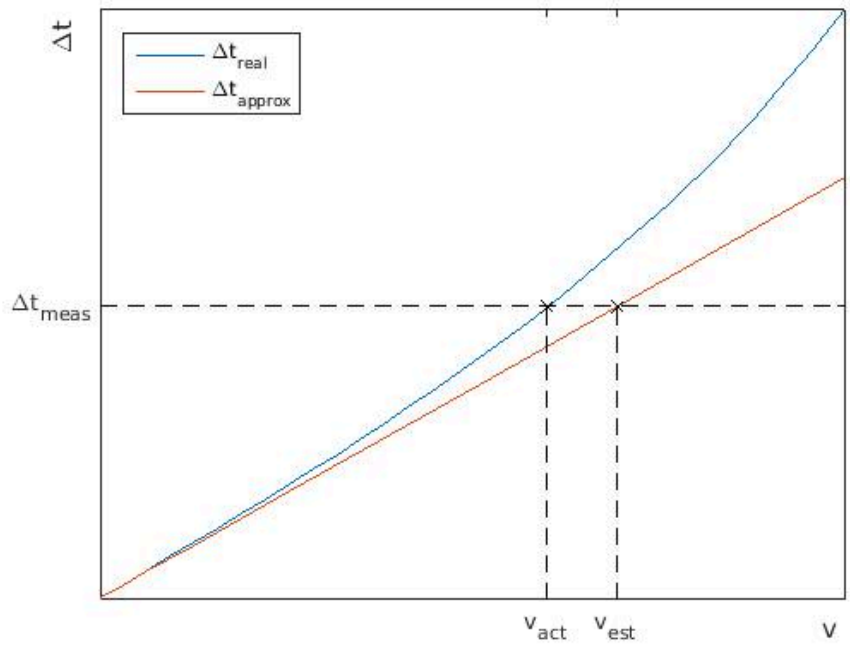
(2) $$t_{up} \frac{2d}{(c - v\ cos\alpha)\ sin\alpha}$$

(3) $$t_{down} \frac{2d}{(c + v\ cos\alpha)\ sin\alpha}$$

(4) $$\Delta t_{real} = \frac{4d(vcos\alpha)}{(c^2 - v^2 cos^2\alpha)\ sin\alpha} \approx \frac{4dvcos\alpha}{c^2 sin\alpha} = \Delta t_{approx}$$

As illustrated in **Figure 3.6** (below), we plotted the 2 expressions Δt_{real} and Δt_{approx}, as functions of v to show their qualitative behaviour. Assuming that we ran the experiment with the actual flow velocity (v_{act}), the machine would measure a 'transit-time' (Δt_{meas}) for the time difference and estimate a flow velocity (v_{est}). We can then see from the graph (**Figure 3.6**), that this corresponds to a higher flow velocity for the estimated velocity value (v_{est}) compared to the actual flow velocity (v_{act}), which hereby leads to an overestimation of the actual blood flow. Please note that this explanation is highly exaggerated, and the correct plot would show much less difference between v_{est} and v_{act}.

Figure 3.6: Illustrative graph for flow overestimation



Please notice, this is only an illustrative graph and is highly exaggerated compared to how the real graph with the correct numbers would look like.

MatLab R2016a.

LIMITATIONS

Only TTFM and free flow of internal mammary arteries were assessed in this study. This may not reflect accuracy of flow measurement of other conduits (SVG, RA, GEA). However, as formerly annotated, the TTFM technique is independent of haematocrit level, heart rate, and vessel wall thickness [117].

Another limitation of the study was the definition of probe sizing and flow over- or underestimation. In our study, any setting where a perfect match was not met was considered over- or underestimation. In reality, some inaccuracies (e.g. +/-10%) should be accounted for.

RECOMMENDATIONS

While we found no independent correlation between probe size and flow overestimation, probe size 4 mm was found as an independent variable for probe oversizing and may thereby result in flow overestimation more often than probe size 3 mm. Thus, we recommend use of probe size 3 mm or smaller (1.5 or 2 mm) for the LIMA graft. Alternately, the diameter of the conduit could be measured with HFUS imaging prior to TTFM measurement to more accurately assess the proper probe size. Surgeons must make sure that they use sufficient amount of ultrasound gel and aim for an ACI value >40%. The vessel should always be held perpendicular to the probe, as misalignment of the vessel to probe can lead to either over-, or underestimation of blood flow. Overall, however, the TTFM technique seems to have accuracy and precision adequate for flow assessment.

Conclusions

The TTFM technique is associated with blood flow overestimation in greater TTFM flows and in oversized probes. Probe size 3 and 4 mm or poor ACI value were not independent predictors of flow overestimation. Overall, TTFM is a good indicator of actual blood flow when appropriate angulation and probe size is ensured prior to measurement. Systematic double check by free flows is not necessary. Future studies addressing the accuracy of the TTFM in measuring correct blood flow could include the use of a 1.5 or 2 mm probe to potentially assess whether undersizing results in flow over- or underestimation.

4

Influence of on- vs. off pump surgical technique on TTFM parameters in CABG

Chapter 4 – On- *vs.* off-pump surgery

Introduction

Although CABG remains the reference revascularization procedure in case of complex coronary artery disease [5], the relative benefits of ONCABG *vs*. OPCABG surgery remain controversial. Recent clinical trials have reported similar clinical endpoints including death, stroke, myocardial infarction, new renal failure, or repeat revascularisation at 1 year [22, 23], but concerns remain that with OPCABG lower graft patency and higher rates of repeat target-vessel revascularisation may be seen [139-141]. These concerns have encouraged assessment of intraoperative graft flow with TTFM, and although guidelines advocate cut-off values, these are only provided for MGF and PI, and do not distinguish between ONCABG and OPCABG technique [99].

There are few studies available on intraoperative flow parameters in ONCABG *vs*. OPCABG and these have reported a trend for lower MGF [100, 142-144] and higher PI with OPCABG surgery [144]. However, no studies have assessed %DF or %BF in ONCABG *vs*. OPCABG, and have generally not distinguished

between arterial and venous grafts. The aim of this study was to compare all TTFM parameters in a cohort of primary CABG patients operated ONCABG *or* OPCABG and with arterial grafts as well as SVGs. Since ONCABG surgery promotes coronary artery vasodilatation, because of reactive hyperaemia following myocardial ischaemia [100], we hypothesized that graft flow and diastolic parameters would be higher with ONCABG than OPCABG surgery. Substantiation of any influence of surgical technique (ONCABG *vs*. OPCABG) on TTFM graft flow measurements may be of importance in establishing normal values.

Methods

The general procedure, ONCABG and OPCABG technique, and the principle of TTFM measurement have all been described in Chapter 2 – General methods and **Figure 2.1**.

Statistical analysis

The general statistics have been discussed in Chapter 2 – General methods. To ensure appropriate statistical power, we aimed for >110 grafts in each group for the ONCABG *vs*. OPCABG analysis.

Results

Patient baseline characteristics including target vessel disease

Overall, the study cohort included 268 patients with a total of 659 grafts performed by two surgical teams using their standard surgical practice. 138 patients underwent OPCABG (314 grafts) and 130 patients underwent ONCABG (345 grafts).

In the OPCABG group, 249 (38%) grafts were to the left coronary territory (180

arterial grafts, 69 SVGs), and 65 (10%) grafts were to the right coronary territory (15 arterial grafts, 50 SVGs) (**Figure 2.1**). In the ONCABG group, 257 (39%) grafts were to the left coronary territory (157 arterial grafts, 100 SVGs), and 88 (13%) were grafts to the right coronary territory (3 arterial grafts, 85 SVGs) (**Figure 2.1**). Arterial grafts were used significantly more often in OPCABG *vs.* ONCABG (62.1% arterial versus 46.4% arterial, $p<0.001$).

Patient demographics and baseline characteristics are presented in **Table 4.1**. The distribution of conduit type and grafted target vessel is shown in **Table 4.2**. The extent of native vessel disease, as judged by QCA, for the corresponding graft type, territory and surgical approach (ONCABG *vs*. OPCABG) were comparable (**Table 4.3**).

Comparison of TTFM parameters between ONCABG and OPCABG cohorts

TTFM measurements, MAP at time of measurement, and by-pass time are presented in **Table 4.4** and **Figure 4.1**. As intended, MAP at the time of TTFM measurement was similar between ONCABG and OPCABG.

During OPCABG surgery, MGF was significantly higher in SVGs both to the left (39±27 ml/min in arterial grafts *vs*. 49±35 ml/min in SVGs, $p=0.003$) and to the right coronary territories (25±14 *vs*. 73±31 ml/min, $p<0.001$).

No significant differences between ONCABG and OPCABG cohorts were noted for PI or %DF. In the OPCABG group, a slightly higher %BF was found for SVGs compared to the ONCABG group, but only if the right and left coronary territories were considered together (2.6±6.2 *vs*. 1.8±6.2%, $p=0.003$). There was no difference in %BF between ONCABG and OPCABG cohorts for the arterial conduits, but N was too low for meaningful conclusions.

Impact of arterial vs. venous conduit on TTFM parameters in the left and right territory

A significantly lower MGF was found for arterial grafts *vs*. SVGs during OPCABG in grafts anastomosed to the right territory (25±14 *vs*. 47±28 ml/min, p=0.003). No significant difference was found for PI. A significantly higher %DF was found for arterial *vs*. venous grafts in both ONCABG and OPCABG in the left territory (69±9 *vs*. 64±12% during ONCABG, and 72±8 *vs*. 63±12% during OPCABG; both p<0.001). No significant difference was noted for %BF (**Table 4.4**).

Multivariable linear regression models: MGF, PI, %DF, and %BF

The results of the multivariable linear regression model for all four TTFM parameters are shown in **Table 4.5**. ONCABG was an independent predictor of higher MGF by 5.77-point (95% CI 0.69-10.84; p=0.026) and of lower %DF by -3.28-point (95% CI -5.19 to -1.38; p=0.001). Male gender (p=0.029), extent of host coronary artery stenosis (p<0.001), and the use of a SVG (p=0.008) were independently associated with increased MGF. The use of a SVG was associated with higher PI (p=0.032), and lower %DF (p=0.004), and %BF (p<0.001).

Table 4.1: Patient demographics and preoperative risk profile for both groups

Variable	OPCABG	ONCABG	*p*-value
Total patients	138 (51%)	130 (49%)	-
Total grafts	314 (48%)	345 (52%)	-
Age (yrs)	67±9	67±8	0.8
Male	115 (83%)	113 (87%)	0.1
Body Mass Index (kg/m^2)	28.5±4.2	28.5±4.2	0.9
Diabetes mellitus			0.3
Insulin dependent	5 (4%)	8 (6%)	-
Noninsulin dependent	39 (28%)	29 (22%)	-
No history	94 (68%)	93 (72%)	-
Chronic obstructive pulmonary disease	18 (13%)	17 (13%)	0.9
Peripheral vascular disease	22 (16%)	13 (10%)	0.1
New York Heart Association class			0.037
I	34 (25%)	31 (24%)	-
II	87 (63%)	66 (51%)	-
III	16 (12%)	32 (25%)	-
IV	1 (1%)	1 (1%)	-
Canadian Cardiovascular Society class			0.5
I	27 (19%)	18 (14%)	-
II	82 (59%)	81 (62%)	-
III	18 (13%)	23 (18%)	-
IV	6 (4%)	7 (5%)	-
Left ventricular ejection fraction (%)	58±8	57±8	0.7
Composite grafts	70 (22%)	11 (3%)	<0.001
By-pass time (min)	-	96±26	-
Cross-clamp time (min)	-	67±21	-
Surgeon			
"DT"	104 (75%)	37 (28%)	<0.001
"GK"	34 (25%)	93 (72%)	<0.001

Table 4.2: Distribution of target vessels grafted using IMAs, RAs, and SVGs

Conduit (No.)	LAD	DIAG	IM	OM	RCA	PDA
LIMA (n=261)	213	5	5	38	0	0
RIMA (n=72)	38	9	13	11	0	1
RA (n=22)	0	2	0	4	5	11
SVG (n=304)	5	35	12	117	38	97

Table 4.3: Native vessel disease: Quantitative coronary angiography data

Variable	Host coronary artery diameter (mm)	Average lumen diameter at stenosis (mm)	Host coronary artery stenosis (% area)	Lesion length (mm)
Averaged overall (n=659)				
Arterial conduits (n=355)				
ONCABG (n=160)	2.2±0.7	0.77±0.41	86±11	10.4±4.7
OPCABG (n=195)	2.2±0.7	0.79±0.36	85±14	10.6±5.7
p-value	0.8	0.7	0.3	0.7
Venous conduits (n=304)				
ONCABG (n=185)	2.0±0.7	0.68±0.39	89±10	9.3±4.3
OPCABG (n=119)	2.0±0.7	0.69±0.36	88±12	9.4±4.9
p-value	0.9	0.8	0.4	0.9
p-value*	0.018	0.039	0.035	0.039
p-value**	0.024	0.030	0.080	0.086
Left territory (n=506)				
Arterial conduits (n=337)				
ONCABG (n=157)	2.2±0.7	0.77±0.41	86±11	10.4±4.8
OPCABG (n=180)	2.2±0.7	0.79±0.37	84±14	10.6±5.7
p-value	0.9	0.7	0.2	0.8
Venous conduits (n=169)				
ONCABG (n=100)	2.0±0.7	0.67±0.36	87±10	9.6±4.4
OPCABG (n=69)	2.0±0.7	0.71±0.38	85±14	9.2±5.1
p-value	0.8	0.5	0.1	0.6
p-value*	0.014	0.052	0.5	0.2
p-value**	0.065	0.1	0.9	0.077
Right territory (n=153)				
Arterial conduits (n=18)				
ONCABG (n=3)	2.0±0.5	0.62±0.41	93±8	8.6±4.0
OPCABG (n=15)	1.9±0.5	0.75±0.38	90±11	10.3±6.5
p-value	0.9	0.7	0.7	0.7
Venous conduits (n=135)				
ONCABG (n=85)	2.0±0.9	0.69±0.44	90±10	9.0±4.2
OPCABG (n=50)	1.9±0.5	0.65±0.33	92±9	9.9±4.5
p-value	0.5	0.6	0.4	0.3
p-value*	0.9	0.8	0.6	0.9
p-value**	0.8	0.4	0.7	0.9

*, comparing arterial and venous conduits in ONCABG

**, comparing arterial and venous conduits in OPCABG

Table 4.4: Comparison of intraoperative TTFM parameters between ON- and OPCABG

Variable	Mean graft flow (ml/min)	Pulsatility Index	Diastolic filling (%)	Backward flow (%)	By-pass time (min)	Mean arterial pressure at TTFM (mmHg)
Averaged overall (n=659)						
Arterial conduits (n=355)						
ONCABG (n=160)	50±35	2.3±0.9	69±9	2.6±6.1	95±27	81±6
OPCABG (n=195)	38±26	2.4±1.2	71±10	2.7±5.2	-	81±5
p-value	<0.001	0.5	0.08	0.9	-	0.6
Venous conduits (n=304)						
ONCABG (n=185)	50±29	2.5±1.6	61±12	1.8±6.2	96±6	81±6
OPCABG (n=119)	45±35	2.5±1.6	62±12	2.6±6.2	-	81±9
p-value	0.2	0.3	0.4	0.003	-	0.3
p-value*	0.8	0.3	<0.001	0.2	0.6	0.5
p-value**	0.047	0.097	<0.001	0.9	-	0.8
Left territory (n=506)						
Arterial conduits (n=337)						
ONCABG (n=157)	49±35	2.4±0.9	69±9	2.7±6.2	95±27	81±5
OPCABG (n=180)	39±27	2.4±1.1	72±8	2.6±5.0	-	81±6
p-value	0.003	0.7	0.09	0.9	-	0.4
Venous conduits (n=169)						
ONCABG (n=100)	52±28	2.5±1.9	64±12	2.0±7.9	95±23	81±6
OPCABG (n=69)	44±40	2.7±1.4	63±12	3.4±7.8	-	81±11
p-value	0.1	0.3	0.8	0.3	-	0.9
p-value*	0.5	0.5	<0.001	0.5	0.8	0.9
p-value**	0.3	0.065	<0.001	0.3	-	0.8
Right territory (n=153)						
Arterial conduits (n=18)						
ONCABG (n=3)	73±31	2.0±1.3	65±9	-	73±23	81±4
OPCABG (n=15)	25±14	2.8±2.0	62±17	3.6±6.8	-	82±4
p-value	<0.001	0.6	0.8	-	-	0.7
Venous conduits (n=135)						
ONCABG (n=85)	49±30	2.5±1.3	57±11	1.6±3.2	99±28	80±5
OPCABG (n=50)	47±28	2.6±1.2	60±10	1.6±2.6	-	82±7
p-value	0.7	0.7	0.3	0.9	-	0.07
p-value*	0.2	0.5	0.3	-	0.1	0.9
p-value**	0.003	0.6	0.3	0.3	-	0.2

*, comparing arterial and venous conduits in ONCABG

**, comparing arterial and venous conduits in OPCABG

Table 4.5: Multivariable linear regression model

Factors associated with MGF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	-1.864	16.40	-	0.9	-34.07	30.34
ONCABG	5.768	2.584	0.092	0.026	0.694	10.84
Surgeon	-2.699	2.628	-0.043	0.3	-7.860	2.463
Age	0.131	0.128	0.036	0.3	-0.120	0.382
Male	7.271	3.312	0.079	0.029	0.767	13.77
Composite graft	-1.452	3.727	-0.015	0.7	-8.771	5.868
PI	-8.363	1.476	-0.304	<0.001	-11.26	-5.465
%DF	0.233	0.126	0.080	0.064	-0.014	0.479
%BF	-0.804	0.492	-0.083	0.1	-1.771	0.162
Host coronary artery stenosis (% area)	0.392	0.097	0.146	<0.001	0.201	0.582
Venous graft	6.803	2.539	0.108	0.008	1.817	11.79

F=19.84, p<0.001

Factors associated with PI

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	4.417	0.539	-	<0.001	3.360	5.475
ONCABG	0.014	0.070	0.006	0.8	-0.123	0.151
Surgeon	0.068	0.070	0.030	0.3	-0.070	0.206
Age	-0.007	0.003	-0.054	0.041	-0.014	-0.002
Composite graft	0.024	0.100	0.007	0.8	-0.172	0.219
MGF	-0.006	0.001	-0.157	<0.001	-0.008	-0.004
%DF	-0.021	0.003	-0.202	<0.001	-0.028	-0.015
%BF	0.211	0.010	0.602	<0.001	0.191	0.231
MAP at TTFM	-0.002	0.005	-0.011	0.6	-0.011	0.007
Host coronary artery stenosis (% area)	-0.003	0.003	-0.027	0.3	-0.008	0.002
Venous graft	0.147	0.068	0.064	0.032	0.013	0.281

F=88.09, p<0.001

Factors associated with %DF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	56.37	7.346	-	<0.001	41.90	70.84
ONCABG	-3.287	0.968	-0.196	0.001	-5.194	-1.380
Male	4.567	1.393	0.192	0.001	1.823	7.310
BMI	0.328	0.118	0.162	0.006	0.095	0.561
Left territory	-6.273	2.990	-0.131	0.037	-12.161	-0.384
MGF	0.005	0.017	0.019	0.8	-0.030	0.039
PI	-1.395	0.805	-0.158	0.084	-2.980	0.189
%BF	0.172	0.230	0.065	0.5	-0.281	0.626
MAP at TTFM	0.153	0.071	0.131	0.032	0.013	0.293
Venous graft	-5.982	2.036	-0.183	0.004	-9.992	-1.972

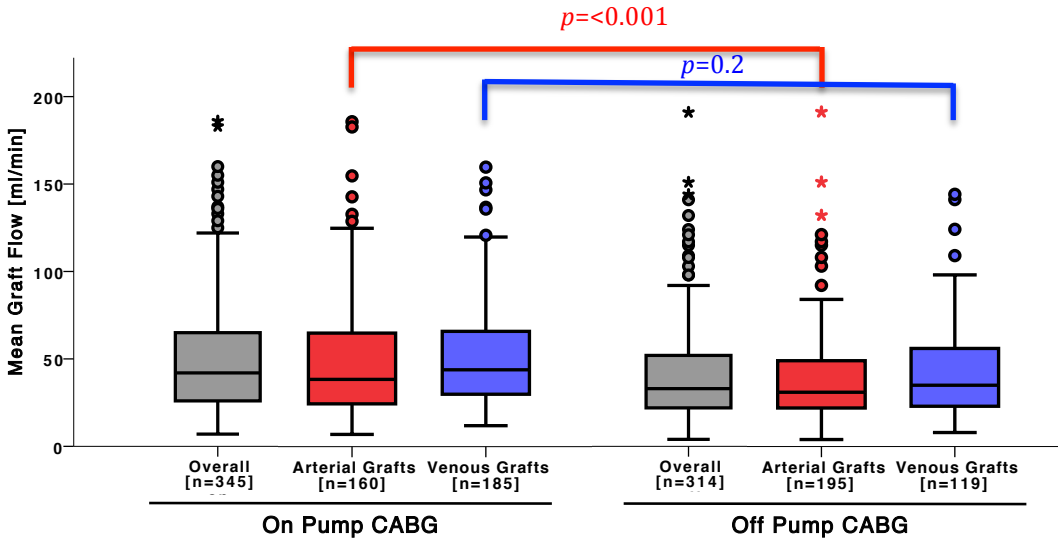
F=6.53, p<0.001

Factors associated with %BF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	-2.196	1.112	-	0.049	-4.380	-0.013
ONCABG	0.009	0.212	0.001	0.9	-0.407	0.425
Surgeon	0.039	0.214	0.006	0.9	-0.382	0.460
Composite graft	0.389	0.302	0.039	0.2	-0.203	0.982
MGF	-0.005	0.003	-0.053	0.093	-0.012	0.001
PI	1.962	0.093	0.689	<0.001	1.779	2.145
%DF	-0.004	0.010	-0.012	0.7	-0.024	0.016
Host coronary artery stenosis (% area)	0.003	0.008	0.011	0.7	-0.012	0.019
Venous grafts	-0.856	0.205	-0.132	<0.001	-1.258	-0.454

F=86.45, p<0.001

Figure 4.1: Box-plots depicting averaged overall mean graft flow and pulsatility index in ON- and OPCABG



N, number of grafts in each group. The dots and stars reflect data outliers.

Discussion

When compared to OPCABG, our study shows that ONCABG is associated with significantly higher MGF in arterial grafts but not in SVGs. In keeping with this, the multi-variable linear regression analysis found that ONCABG was an independent predictor of higher MGF. For SVGs, ONCABG is associated with a lower %BF than is seen during OPCABG. Moreover, our comparison of arterial grafts *vs.* SVGs demonstrated a higher %DF in arterial grafts during both ONCABG and OPCABG in the overall cohorts and in grafts anastomosed to the left territory.

Our study substantiates the results of a smaller study from our own group in 2008 [100] including a total of 266 grafts in 100 patients (20 ONCABG and 80 OPCABG). The study [100] found that, despite a lower MAP, MGF was overall higher in ONCABG surgery when compared to OPCABG surgery, and suggested that

these findings were related to vasodilatation resulting from a period of myocardial ischaemia that led to reactive hyperaemia. Indeed, it has been well documented that cross-clamping during ONCABG, despite the use of cardioplegia, leads to global myocardial ischaemia and acidosis [145] with subsequent coronary artery vasodilatation and hence a more substantial "run-off" for by-pass grafts. We only found a statistically significant higher MGF in arterial conduits, however, and speculate that this finding may reflect the adaptive response of arterial conduits to increase flow in response to myocardial demand (flow-mediated vasodilatation). In keeping with this notion, an angiographic study in three patients [146] showed that intact vascular smooth muscle is responsible for the physiological adaptability of internal mammary arteries, which can adjust calibre and blood flow according to myocardial demand [146]. In contrast, in veins only a slight increase in blood flow may be detected compared to arterial conduits [147].

In contrast to our results of comparable PI in ON- and OPCABG cohorts, Schmitz *et al*. [144] suggested an overall higher PI with OPCABG surgery. In theory, a higher PI may be expected in OPCABG grafts, as this is associated with lower MGF, and a correlation between lower MGF and higher PI has been reported not only in previous studies [52, 114, 117] but also by multi-regression analysis in this current study (**Table 4.5**). However, whether this difference is of any actual clinical relevance in predicting long–term graft patency is still not clear and further research is warranted to address this topic.

As previously noted, no previous studies have addressed %DF and %BF in ONCABG *vs.* OPCABG. In our study, no significant difference was found in terms of %DF, though a statistically significant higher %BF was found in SVGs in OPCABG *vs.* ONCABG when the right and left coronary territories were considered together.

The difference in %BF is of limited clinical importance, as it was <1% and both results are within the recommended cut-off value of <3% for %BF to predict short-term graft patency [77], however this finding will be discusses in the next chapter..

The multi-regression analysis demonstrated an association between lower %DF and ONCABG. This result is most probably due to the higher percentage of arterial grafts used during OPCABG. Indeed %DF is higher in arterial conduits, as the greater elasticity of arterial compared to venous vessel walls [146, 147] may allow more diastolic blood flow ("Windkessel effect") [148, 149], as further explained in the next chapter.

Comparing arterial grafts and SVGs in terms of MGF, our data demonstrate a higher MGF in SVGs during OPCABG, driven by the results to the right territory. However, only 15 arterial grafts were anastomosed to the right territory vs. 50 SVGs, and further research is now warranted to establish clinically relevant differences. No significant difference was found between the two conduit types in the ONCABG groups.

Our study demonstrates, as previously discussed, that arterial conduits are able to alter their blood supply more so than SVGs. In keeping with this, SVGs had a higher PI, albeit non-significant, and lower %DF, while a significantly higher %BF was found in SVGs in the overall and in the OPCABG cohorts. These findings are consistent with SVGs performing worse than arterial grafts in terms of graft failure at follow-up, as higher PI, lower %DF and higher %BF are all independently associated with an increased risk of graft failure [83, 114, 119]. As such, our results physiologically support the potential benefit of arterial grafting in CABG [45, 55, 56] and may, at least in part, explain the difference in terms of long-term graft patency between these graft types, with a patency rate of >90% for internal mammary arteries

at 10-years [45] *vs.* >50% for SVGs [48, 50].

LIMITATIONS

This was an observational study of two different but standard practices of two surgeons and confounding cannot be excluded due to lack of randomisation. The number of arterial grafts to the right coronary territory was small (3 ONCABG and 15 OPCABG). Nevertheless, a strong correlation for higher MGF in ONCABG was found in the overall as well as in the left territory cohorts, and in the multi-variable linear regression model. Our study also found a lower %DF in SVGs both during ONCABG and OPCABG, but not in grafts anastomosed to the right territory. However, lack of statistical significance may relate to the small number of grafts to the right territory.

Composite grafts were constructed in 22% of all OPCABG grafts vs. 3% of ONCABG grafts ($p<0.001$). According to the multi regression analysis, composite grafting may be weakly associated with lower MGF ($p=0.7$), which would weaken our finding of higher MGF in ONCABG *vs*. OPCABG arterial grafts. In contrast, 2 different studies on intraoperative flow dynamics of composite grafts demonstrated a marginal trend toward higher MGF in composite vs. single by-pass grafts [100, 150]. Overall, we do not believe that separation of single *vs*. composite grafts would have altered our results significantly.

Generally, there is a tendency to use more catecholamines in ONCABG procedures, which could result in lower MGFs due to constriction of the vessels (but at the same mean blood pressure). However, a constriction of the vessels would inversely affect our results and thus strengthen the correlation of higher MGFs in ONCABG.

Conclusions

Mean graft flow is higher in arterial conduits during on-pump coronary artery by-pass surgery than in off-pump coronary artery by-pass surgery, which may reflect the adaptive response of internal mammary arteries to increased flow in response to myocardial hyperperfusion (reactive hyperaemia) following a period of myocardial ischaemia. Future studies on cut-off values for graft patency should take into account the surgical approach and conduit type when addressing Transit time flowmetry parameters.

5

Perioperative flow profiles of arterial and venous by-pass grafts to the left coronary territory

Chapter 5 – Arterial *vs.* venous grafting

Introduction

The superiority of CABG for revascularization in complex multi-vessel coronary artery disease relies on the continuous patency of by-pass grafts [5, 7], revascularization by arterial conduits [55, 56, 151], and meticulous perioperative optimisation of conduit flow, which are all considered important first steps in achieving this goal [18, 76, 152]. As previously noted, current guidelines only provide recommended values for MGF and PI, and without regards to neither surgical technique (ONCABG vs. OPCABG) or conduit type (arterial *vs*. venous) [99].

In comparison with veins, and due to higher arterial blood pressure, arteries possess thicker, elastic, muscular walls, with a smaller intravascular lumen, and actively constrict/dilate to a larger degree than veins [146]. Studies on graft flow in arterial grafts *vs.* SVGs have suggested higher MGF in SVGs [100, 143, 144], but only one of these studies assessed PI [144], suggesting a higher PI in grafts anastomosed by OPCABG technique. No studies have addressed differences in

diastolic flow and backward flow, which may indeed differ between arterial and venous conduits, based on each their different mechanical and vasodilatory properties.

As current recommendations on graft flow profiles suggest all TTFM parameters must be taken into account [114], the aim of this study was not only to corroborate previous findings but to compare all TTFM parameters in arterial and venous grafts anastomosed to the left coronary territory both during ONCABG and OPCABG surgery, with the aim of depicting whether arterial grafts and SVGs have different flow profiles when used for CABG despite being exposed to similar distal (myocardial) resistance.

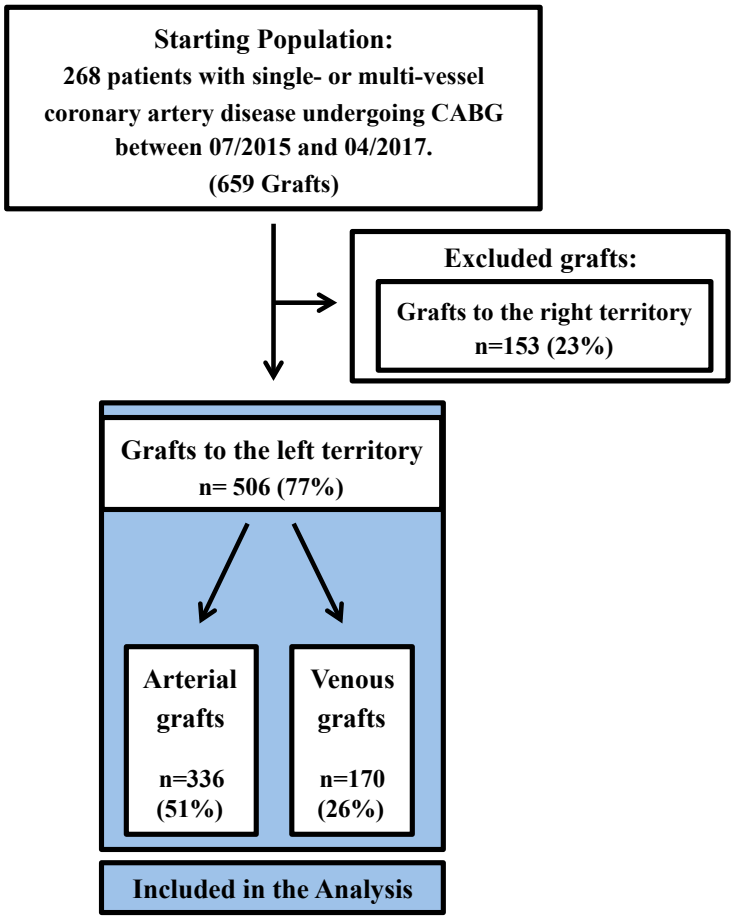
Methods

The general procedure, ONCABG and OPCABG technique, and the principle of TTFM measurement have all been described in Chapter 2 – General methods and **Figure 2.1**. To avoid potential influence of the different transmyocardial pressure of the left and the right ventricle on by-pass graft flow [52], grafts anastomosed to the right coronary territory were excluded, and hence the study population included a total of 506 by-pass grafts, 336 arterial and 170 venous. The study-group breakdown is depicted in **Figure 5.1**.

Statistical analysis

The general statistics have been discussed in Chapter 2 – General methods. In furtherance of the power analysis, to provide the possibility of further exploration of data, we aimed for 63 patients in each group.

Figure 5.1: Flow diagram showing the study group breakdown



5.1 – The analysis compares 336 arterial conduits and 170 venous conduits grafted to the left coronary territory.

Results

Patient baseline characteristics including target vessel disease

The analysis included 268 patients receiving a total of 659 grafts, 336 (66%) arterial and 171 venous grafts (**Figure 5.1**). 257 (51%) grafts (156 arterial; 61%) were anastomosed during ONCABG, while 249 (49%) grafts (180 arterial; 72%) were anastomosed during OPCABG. Patient demographics and preoperative risk profile are presented in **Table 5.1**. The distribution of conduit type and grafted target vessel is shown in **Table 5.2**.

The extent of native coronary artery disease is shown in **Table 5.3**. In the overall and in the ONCABG cohorts, the target coronary arteries receiving SVGs had smaller diameters (non-obstructed) and smaller average lumen diameters when compared to the target coronaries receiving arterial grafts (overall host coronary artery diameter: 2.0±0.7 *vs*. 2.2±0.7 mm, p=0.003; overall average lumen diameter at stenosis, 0.68±0.37 *vs*. 0.78±0.39 mm, p=0.008). However, no significant difference in the target vessel stenosis (%-area) was found between target vessels receiving arterial and venous grafts (overall, p=0.4).

*Comparison of flow profiles between arterial and venous grafts (**Table 5.4**).*

In both the overall, and in the ONCABG and OPCABG cohorts, MGF and PI were comparable between arterial grafts and SVGs. However, %DF was significantly higher in arterial grafts as compared to SVGs (overall, 71±8 *vs*. 64±11%; ONCABG, 70±7 *vs*. 64±10%; OPCABG, 72±8 *vs*. 63±12%; all p<0.001). Also, %BF was significantly higher in arterial grafts compared to SVGs in the overall (2.3±3.2 *vs*. 1.7±3.2%, p=0.002) and in the ONCABG cohorts (2.3±3.2 *vs*. 1.3±2.5%, p<0.001) but not in the OPCABG cohort (2.3±3.2 *vs*. 2.6±3.9%, p=0.8).

*Influence of ONCABG vs. OPCABG on graft flow profiles (**Table 5.4**).*

In arterial grafts, ONCABG was associated with significantly higher MGF (49±35 *vs.* 39±27 ml/min, p=0.003) and significantly lower %DF (70±7 *vs.* 72±8%, p=0.018) compared to OPCABG. In SVGs, ONCABG was associated with a lower %BF than in OPCABG cases (1.3±2.5 *vs.* 2.6±3.9%, p=0.016).

Regression models for factors influencing graft flow profiles

Table 5.5 shows the results of the overall multivariable linear regression model.

MGF

The use of SVGs had a significant positive influence on MGF by 7.89-point (95% CI 2.10-13.6, p=0.008). Some covariates used to adjust for the effect of graft type on MGF were also independently associated with a higher MFG: male sex (p=0.029), lower PI (p<0.001), and more significant target vessel stenosis (%-area; p<0.001).

PI

The use of a SVG had a significant positive albeit small influence on PI by 0.17-point (95% CI 0.03-0.31; p=0.02). Some of the covariates used to adjust the effect of the graft type on PI were also independently associated with a greater PI: lower MGF (p<0.001), lower DF% (p<0.001), and higher BF% (p<0.001).

%DF

The use of a SVG had a significant negative influence on DF% by -6.32-point (95% CI -7.97- -4.68, p<0.001). Some covariates used to adjust the effect of the graft type on %DF were also independently associated with a greater %DF: male sex (p=0.001), non-composite grafts (p=0.019), lower PI (p<0.001), and OPCABG surgery (p=0.002).

%BF

The use of a SVG had a significant negative influence on %BF by -0.64-point (95% CI -1.08- -0.21, p=0.004). Among covariates used to adjust for the effect of graft type on %BF only a higher PI was independently associated with a higher %BF (p<0.001).

Table 5.1: Patient demographics and preoperative risk profiles

Variable	Study population
Total patients	268
Age (y)	67±9
Male	229 (85%)
Body Mass Index	28.5±4.2
Diabetes mellitus	
Insulin dependent	13 (5%)
Noninsulin dependent	70 (26%)
No history	185 (69%)
Chronic obstructive pulmonary disease	35 (13%)
Peripheral vascular disease	35 (13%)
New York Heart Association	
I	66 (25%)
II	153 (57%)
III	47 (18%)
IV	2 (1%)
Canadian Cardiovascular Society	
I	47 (17%)
II	166 (62%)
III	42 (16%)
IV	13 (5%)
Left ventricular ejection fraction	57±8%
By-pass time (min)	95±26
Cross-clamp time (min)	66±21
Surgeon	
Procedures by "DT"	141 (53%)
Procedures by "GK"	127 (47%)
Total grafts	506
ONCABG	
Arterial grafts	156 (31%)
Venous grafts	101 (20%)
OPCABG	
Arterial grafts	180 (36%)
Venous grafts	69 (14%)

Table 5.2: Distribution of target vessels grafted using IMAs, RAs, and SVGs

Conduit (No.)	LAD	DIAG	IM	OM	PDA
LIMA (261)	212	5	5	38	1
RIMA (69)	38	8	13	10	0
SVG (170)	5	37	11	117	0
RA (6)	0	2	0	4	0

Table 5.3: Native vessel disease: Quantitative coronary angiography data

Variable	Host coronary artery diameter (mm)	Average lumen diameter at stenosis (mm)	Host coronary artery stenosis (% area)	Lesion length (mm)
Left territory				
Overall (n=506)				
Arterial grafts (n=336)	2.2±0.7	0.8±0.4	85±13	10.5±5.3
Venous grafts (n=170)	2.0±0.7	0.7±0.4	86±12	9.4±4.7
p-value	0.003	0.008	0.4	0.023
ONCABG (n=257)				
Arterial grafts (n=156)	2.2±0.7	0.8±0.4	86±11	10.4±4.8
Venous grafts (n=101)	2.0±0.6	0.7±0.4	87±10	9.6±4.4
p-value	0.014	0.041	0.4	0.16
OPCABG (n=249)				
Arterial grafts (n=180)	2.2±0.7	0.8±0.4	84±14	10.6±5.7
Venous grafts (n=69)	2.0±0.7	0.7±0.4	85±13	9.2±5.0
p-value	0.08	0.1	0.9	0.07
p-value*	0.9	0.7	0.2	0.8
p-value**	0.7	0.5	0.1	0.6

*, comparing arterial grafts in ON- vs. OPCABG

**, comparing venous grafts in ON- vs. OPCABG

Table 5.4: Comparison of intraoperative TTFM parameters between arterial and venous grafts supplying the left coronary territory

Variable	Mean graft flow (ml/min)	Pulsatility Index	Diastolic filling (%)	Backward flow (%)	By-pass time (min)	Mean arterial pressure at TTFM (mmHg)
Left territory						
Overall (n=506)						
Arterial grafts (n=336)	44±31	2.4±1.0	71±8	2.3±3.2	95±27	81±6
Venous grafts (n=170)	48±34	2.5±1.3	64±11	1.7±3.2	94±23	81±8
p-value	0.1	0.2	<0.001	0.002	0.7	0.9
ONCABG (n=257)						
Arterial grafts (n=156)	49±35	2.4±0.9	70±7	2.3±3.2	95±27	81±5
Venous grafts (n=101)	51±28	2.4±1.3	64±10	1.3±2.5	94±23	81±6
p-value	0.6	0.9	<0.001	<0.001	0.7	0.8
OPCABG (n=249)						
Arterial grafts (n=180)	39±26	2.4±1.1	72±8	2.3±3.2	-	81±6
Venous grafts (n=69)	44±40	2.7±1.4	63±12	2.6±3.9	-	81±11
p-value	0.34	0.07	<0.001	0.8	-	0.7
p-value*	0.003	0.7	0.018	0.7	-	0.4
p-value**	0.2	0.081	0.7	0.016	-	0.9

*, comparing arterial grafts in ON- *vs*. OPCABG

**, comparing venous grafts in ON- *vs*. OPCABG

Table 5.5: Multivariable linear regression model

Factors associated with MGF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	6.422	16.17	-	0.691	-25.36	38.20
Venous graft	7.893	2.947	0.117	0.008	2.102	13.69
Surgeon	-4.996	3.153	-0.078	0.114	-11.19	1.200
Male	8.352	3.811	0.091	0.029	0.864	15.84
Composite graft	-0.882	4.137	-0.010	0.831	-9.011	7.248
PI	-8.610	1.861	-0.287	<0.001	-12.27	-4.953
%DF	0.258	0.156	0.077	0.099	-0.049	0.565
%BF	-0.968	0.609	-0.095	0.113	-2.165	0.229
ONCABG	4.720	3.095	0.074	0.128	-1.362	10.80
Host coronary artery stenosis (% area)	0.396	0.111	0.148	<0.001	0.178	0.614

F=16.948, p<0.001

Factors associated with PI

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	3.879	0.421	-	<0.001	3.052	4.707
Venous graft	0.167	0.072	0.074	0.020	0.026	0.308
Surgeon	0.001	0.069	0.001	0.991	-0.134	0.136
Age	-0.002	0.004	-0.018	0.547	-0.009	0.005
Composite graft	0.007	0.099	0.002	0.943	-0.187	0.201
MGF	-0.005	0.001	-0.145	<0.001	-0.007	-0.003
%DF	-0.019	0.004	-0.167	<0.001	-0.026	-0.012
%BF	0.219	0.011	0.643	<0.001	0.197	0.240
Host coronary artery stenosis (% area)	-0.004	0.003	-0.045	0.139	-0.009	0.001

F=87.668, p<0.001

Factors associated with %DF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	69.35	3.215	-	<0.001	63.03	75.66
Venous graft	-6.322	0.836	-0.313	<0.001	-7.965	-4.679
Male	3.948	1.131	0.142	0.001	1.725	6.171
Composite graft	-2.784	1.185	-0.103	0.019	-5.112	-0.456
MGF	0.015	0.014	0.049	0.282	-0.012	0.041
PI	-2.892	0.545	-0.325	<0.001	-3.964	-1.820
%BF	0.148	0.181	0.049	0.416	-0.209	0.504
ONCABG	-2.531	0.825	-0.133	0.002	-4.153	-0.910

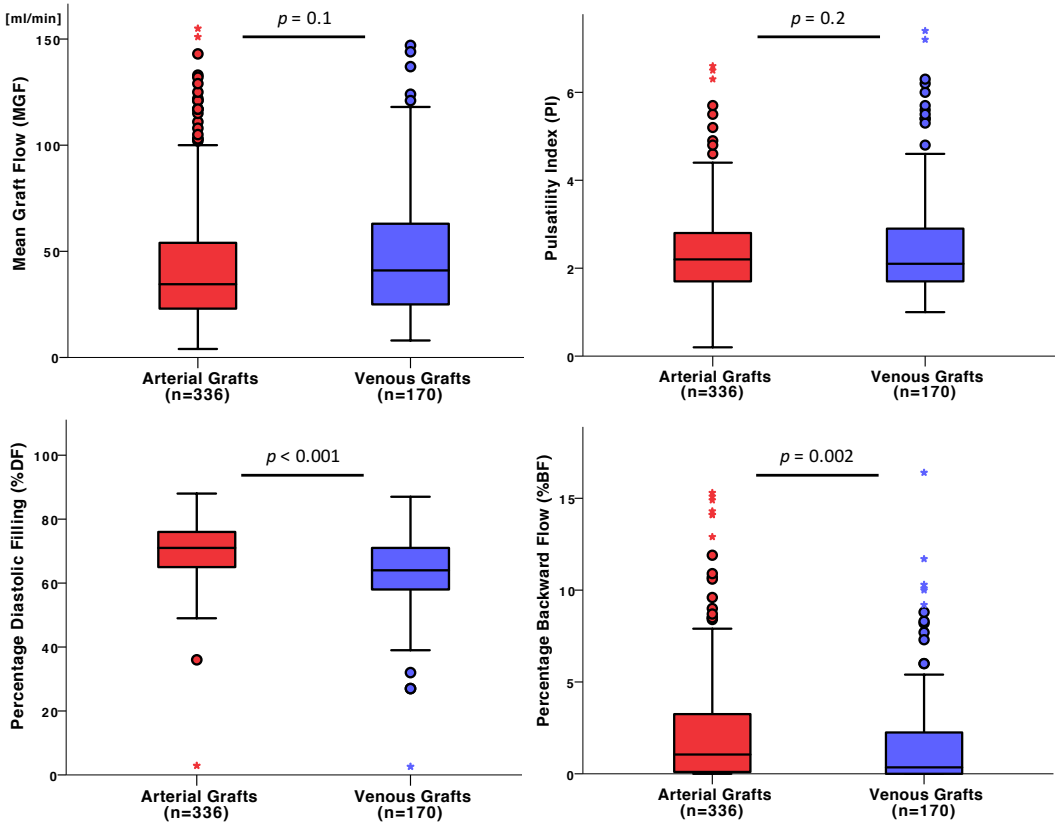
F=20.822, p<0.001

Factors associated with %BF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	-3.172	1.426	-	0.027	-5.973	-0.370
Venous graft	-0.643	0.222	-0.097	0.004	-1.080	-0.206
Surgeon	0.169	0.238	0.027	0.479	-0.299	0.636
Age	-0.010	0.011	-0.029	0.359	-0.032	0.012
Composite graft	0.565	0.309	0.063	0.068	-0.043	1.172
MGF	-0.005	0.003	-0.055	0.121	-0.012	0.001
PI	2.099	0.105	0.714	<0.001	1.893	2.306
%DF	0.012	0.012	0.035	0.317	-0.011	0.035
ONCABG	0.124	0.234	0.020	0.595	-0.335	0.584
Host coronary artery stenosis (% area)	0.004	0.008	0.015	0.633	-0.012	0.020

F=64.766, p<0.001

Figure 5.2: Overall differences between arterial grafts and SVGs



5.2: *Boxplots depicting overall differences in MGF, PI, %DF, and %BF between arterial (n=336) and venous (n=170) grafts.*

Discussion

As demonstrated by Transit-time flowmetry, overall there was no significant difference in MGF or PI between arterial grafts and SVGs to the left coronary territory. However there was an independent association between SVGs and higher MGF, as demonstrated in the regression analysis, irrespective of whether operated ONCABG or OPCABG.

A higher %DF was found in arterial grafts both in the ONCABG and in the OPCABG cohorts, and, driven largely by the difference in the ONCABG group, the %BF was also significantly higher in arterial grafts *vs*. SVGs. If considered in isolation, in SVGs a higher %BF was noted after OPCABG, and in arterial grafts a higher MGF and lower %DF (~2%) was found with ONCABG surgery.

The multi-regression analysis was in keeping with previous studies demonstrating that SVGs have higher MGF than arterial grafts (**Table 5.5**), but overall no significant difference between graft types was noted. A higher MGF might be expected in SVGs due to the generally larger calibre of veins [38, 100].

In studies aiming to define TTFM cut-off values for graft-revision, the higher MGF in SVGs has been linked to improved graft patency [101, 113]. In the study by Lehnert *et al*. [101], with a cut-off value for MGF of >20 ml/min for arterial conduits the risk of graft failure at 1-year decreased by 4% for every 1 ml/min increase, while the corresponding cut-off value for SVGs was twice as high (>40 ml/min) with a 2% decrease in graft failure risk for every 1 ml/min increase [101]. Although we did not demonstrate an overall difference in MGF between SVGs and arterial grafts, these studies in combination with our multi-regression analysis do suggest that MGF should be considered separately in arterial and venous grafts [114, 119, 130].

One previous study has assessed PI in arterial grafts and SVGs to the left coronary territory, and found no significant difference between the conduit types [54]. In keeping with this, we found a comparable PI between arterial grafts and SVGs both during ONCABG and OPCABG (**Table 5.4**). The multi-regression analysis did however suggest an association between higher PI and SVGs, but with a mere 0.17 point, making this finding questionable in terms of clinical relevance. Thus, this study does not suggest changing guidelines with respect to PI.

On the other hand, we found differences between diastolic and backward flow patterns between arterial and venous conduits. It is well-known that due to the higher transmyocardial pressure in the left coronary territory, diastolic flow differs between left- and right-sided by-pass grafts, (left-sided fill 60-70% during diastole while right-sided only fill about 50% [52, 53, 76]), but studies on %DF in arterial *vs.* venous conduits to the left and right territories are still missing in literature. Our data have demonstrated a significantly higher %DF in arterial (71%) compared to venous grafts (64%) anastomosed to the left territory (**Table 5.4**), and the multi-regression analysis supported that grafting of a SVG was associated with a lower %DF. This finding may reflect the superior elasticity of arterial walls when compared to veins [146, 147], allowing arterial grafts to expel blood more effectively during diastole ("Windkessel effect") [148, 149]. Keeping in mind, a large proportion of arterial grafts were anastomosed to the LAD (74%), usually the largest vessel with the largest vascular bed, which could also positively affect MGF and %DF.

Most often %BF in grafts occur due to "competitive flow" [77]: If the stenosis of the native coronary artery is not significant, blood flow in the bypass graft will not exceed flow in the native coronary artery resulting in backward flow across the anastomosis [121]. This is physiologically expected in all by-pass grafts and is 'normally' <3% [114]. Indeed, higher %BF has been associated with increased risk of graft failure [53, 77, 116]. No previous studies have specifically examined %BF in arterial grafts *vs.* SVGs. Our study demonstrates that %BF is overall higher in arterial grafts and predominantly driven by a larger difference during ONCABG since no difference was noted during OPCABG. The higher %BF found for SVGs between the ONCABG and OPCABG cohorts will be discussed below.

As previously noted, only three studies have specifically assessed intraoperative flow-profiles of arterial grafts and SVGs in ONCABG *vs.* OPCABG separately [100, 143, 144], all suggesting a lower MGF in grafts performed by OPCABG technique. In the study by Balacumaraswami *et al*. [100] comparing MGF in arterial grafts and SVGs in ONCABG *vs.* OPCABG, a lower MGF was found in both arterial grafts and SVGs after OPCABG, despite a higher mean arterial pressure with OPCABG [100]. Similarly, in the study by Schmitz *et al*. [143], including a total of 2247 by-pass grafts in 896 patients (695 ONCABG *vs.* 201 OPCABG), a lower MGF was demonstrated in grafts performed OPCABG compared to grafts performed ONCABG [143]. In contrast, our study only found a higher MGF in arterial grafts in the ONCABG *vs.* OPCABG cohorts. This finding is probably related to the cross-clamping during ONCABG surgery that despite the use of cardioplegia results in myocardial ischaemia [145]) with resultant native coronary artery dilation and subsequent higher myocardial perfusion [100]. As previously explained, arterial conduits can adjust their calibre and blood flow according to myocardial demand [146] ("flow-mediated vasodilatation"), and as the native coronary arteries dilate, arterial by-pass grafts are more capable of increasing blood supply.

Only one previous study has compared PI in arterial grafts and SVGs in ONCABG *vs.* OPCABG [144]. The strength of this study was the inclusion of a total of 890 patients with 445 performed ONCABG and a similar number of patients performed OPCABG. Each ONCABG patient was matched to an OPCABG patient with similar number of by-pass grafts and similar target coronary artery territory [144]. In that study, a higher PI was found in the OPCABG group, except for grafts anastomosed to the left anterior descending artery territory [144]. However, from a clinical perspective, the differences were small, as most PI values remained within the

normal accepted range (<3). In keeping with this, we did not demonstrate any significant difference relative to surgical procedure (Table 5.5).

No previous study has addressed %DF in ONCABG *vs.* OPCABG, but our study has now suggested a higher %DF in OPCABG *vs.* ONCABG arterial grafts. However, the difference was only ~2%, making this finding of little obvious clinical relevance.

Furthermore, as previously noted, for SVGs a lower %BF was noted in the ONCABG *vs.* the OPCABG group. This finding is most probably due to the dilation of native coronary vessels during ONCABG [145]. When the native coronary arteries dilate, they allow more blood to perfuse the by-pass graft [100]. In ONCABG situations, the SVG provides blood to the ischemic myocardium at a maximum capacity and high pressure, which may prevent significant backward flow. Another explanation for higher %BF in arterial grafts compared to SVGs might be that the target vessels for arterial grafts had a slightly larger average lumen diameter at stenosis compared to those for SVGs (0.8 vs. 0.7, respectively) (**Table 5.3**), resulting in higher competitive flow in arterial grafts.

Of note, an association between higher MGF, PI and lower %DF and %BF for SVGs was found in the multi-regression analysis (Table 5.5), which may further emphasize that arterial and venous conduits should be considered separately in studies addressing intraoperative flow-profiles of by-pass grafts.

LIMITATIONS

We were unable to adjust for potential influence of competitive flow, which could have adversely affected some of the TTFM parameters. Moreover, we found a significant difference between average lumen diameter at stenosis and host coronary diameter in the baseline cohort, which could affect %BF. Furthermore, as the vast majority of the arterial grafts were anastomosed to the LAD, and the vast majority of SVGs were anastomosed to the circumflex territory the target vessel could therefore potentially confound the comparisons of arterial and venous grafts.

According to the multi regression analysis, composite grafting may have a negative impact on %DF by 2.78-points. Since the vast majority of composite grafts were arterial, this may strengthen the correlation of higher %DF in arterial grafts vs. SVGs.

Conclusions

Overall, mean graft flow and pulsatility index are comparable between arterial and venous grafts, though SVGs can be demonstrated to have higher mean graft flow in multivariate analysis. On the other hand, diastolic flow and backward flow are more prominently seen in arterial compared to venous by-pass grafts ("windkessel effect"). A demonstration of higher MGF in arterial grafts during on-pump *vs*. off-pump CABG probably reflects a superior adaptability of arterial grafts to comply with the resistance to forward flow. The overall differences between conduits are clinically small in comparison with already established TTFM cut-off points, except for %DF, but should be taken into account in studies on cut-off points for graft patency.

6

Influence of coronary territory on perioperative flow profiles of saphenous vein grafts

Chapter 6 – Left- *vs.* right sided venous by-pass grafting

Introduction

As previously discussed, the transmyocardial pressure is higher on the left side of the heart compared to the right, as the left ventricle provides circulatory support for the high-pressure systemic circulation, and hence a larger fraction of the myocardial blood flow in the left coronary territory takes place during ventricular diastole [51, 83, 117]. These differences in coronary blood flow of the left and right coronary territory might therefore be expected to influence flow in by-pass grafts. Few studies, however, have specifically addressed flow in left- *vs*. right-sided grafts, and have included cohorts of both arterial and venous conduits. Hence, current evidence for any potentially clinically relevant difference is scarce and contradictory [52-54].

The aim of this study was to compare all TTFM parameters (MGF, PI, %DF, and %BF) in SVGs supplying the left and right coronary territories in a larger cohort of CABG patients. Results were then analysed according to ONCABG *vs*. OPCABG.

We hypothesized that the higher pressure on the left side would particularly influence diastolic run off in SVGs.

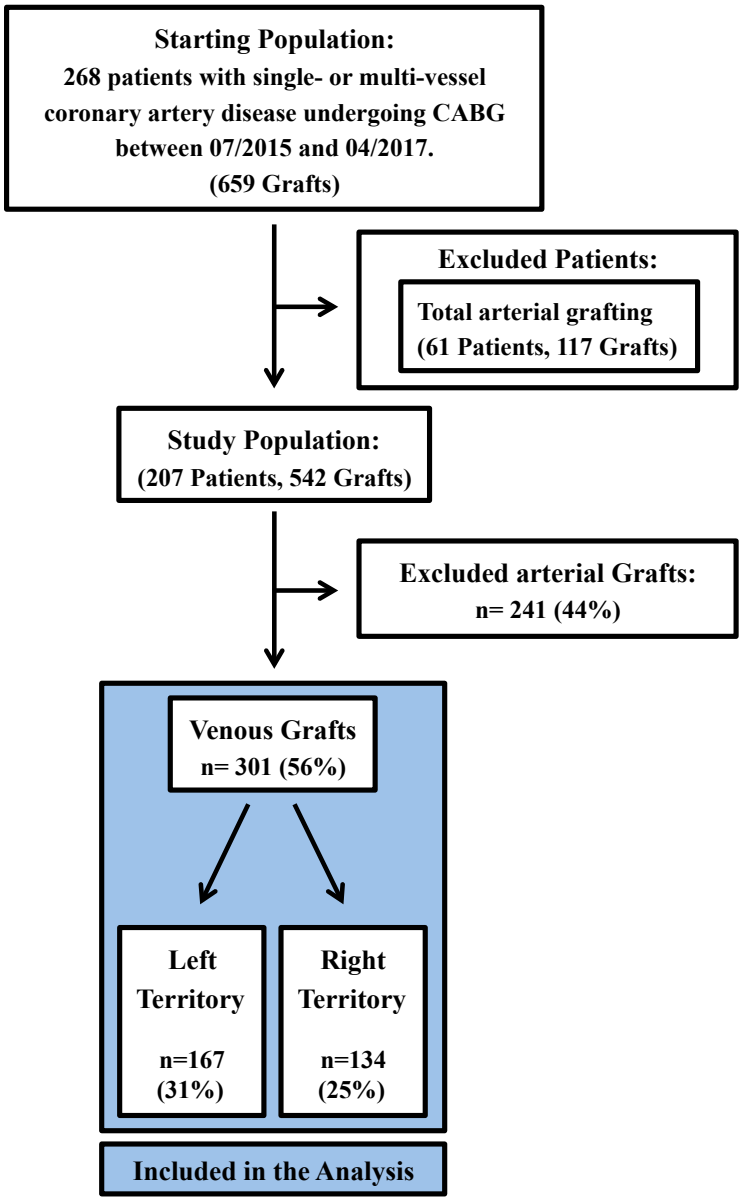
Methods

The general procedure, ONCABG and OPCABG technique, and the principle of TTFM measurement have all been described in Chapter 2 – General methods and **Figure 2.1**. Due to low number of arterial grafts to the right coronary territory, only SVGs were included. After exclusion of arterial conduits and 3 composite grafts, the study population included 207 CABG patients with a total of 301 SVGs. The study group breakdown is depicted in **Figure 6.1**.

Statistical analysis

The general statistics have been discussed in Chapter 2 – General methods. For a robust statistical power analysis, including multivariate analysis, we aimed for at least 130 SVGs in each group for the left *vs*. right-sided venous graft analysis.

Figure 6.1: Flow diagram showing the study group breakdown



6.1 – The analysis compares 167 SVGs going to the left coronary territory versus 134 SVGs going to the right coronary territory. N depicts number of grafts.

Results

Patient baseline characteristics including target vessel disease

207 patients receiving a total of 301 SVGs were included in the final analysis (**Table 6.1**). 167 SVGs (55%) were grafted to the left territory, and 134 SVGs were grafted to the right territory (**Figure 6.1**). 121 patients were operated ONCABG (184 SVGs, 61%), and 86 patients were operated OPCABG (117 SVGs). Patient demographics and their pre-operative risk profile are presented in **Table 6.1**. The distribution of the target vessels grafted is shown in **Table 6.2**.

The extent of native coronary artery vessel disease is shown in **Table 6.3**. Target vessel stenosis severity, as judged by QCA, was significantly lower in the left coronary territory compared to the right coronary territory both in the overall cohort (86±12% *vs*. 91±10%, p<0.001) and in the OPCABG cohorts (85±13 *vs*. 92±9%, p<0.04) and ONCABG (87±10% *vs*. 90±10%, p=0.002) cohorts. Non-obstructed target coronary artery diameter, average lumen diameter at stenosis, and lesion length were comparable between coronary territories.

Comparison of TTFM parameters between left and right coronary territory

TTFM measurements, MAP at the time of measurement, and by-pass times are presented in **Figure 6.2** and **Table 6.4**. As intended, MAP at the time of TTFM measurement was similar between grafts anastomosed to the left and the right territories. No significant differences between SVGs supplying the two coronary territories were found for MGF, PI, and %BF. However, a higher %DF was noted in left-sided SVGs in comparison to right-sided SVGs in the overall (63±12% *vs*. 58±11%, p<0.001), OPCABG (63±12% *vs*. 60±10%, p=0.07), and ONCABG (64±12% *vs*. 57±11%, p<0.001) cohorts.

Impact of OPCABG vs. ONCABG on TTFM parameters in the left and right territory

No significant territory-related difference was found for MGF, PI, and %DF between OPCABG and ONCABG cohorts. However, for the left territory, a significantly higher %BF was found in OPCABG SVGs compared to ONCABG SVGs (2.3±3.0% *vs*. 1.2±2.5%, p=0.023) (**Table 6.4**).

Multivariable linear regression model

The results of the multivariable linear regression models for MGF, PI, %DF, and %BF are shown in **Table 6.5**. The grafted coronary territory did not have a significant influence on MGF. However, the coronary territory had a significant influence on PI and %DF: Thus, grafting to the left territory led to higher PI and %DF of SVGs (*B* =0.36, 95% CI 0.04-0.67, *p*=0.026 and *B*=5.1, 95% CI 2.86-7.34, p<0.001, respectively). No significant influence of grafted territory was found for %BF. Moreover, no significant association was found between TTFM parameters and OPCABG *or* ONCABG technique (**Table 6.5**).

Some of the covariates used to adjust for the effect of the grafted territory were also independently associated with the TTFM parameters: older age was associated with higher MGF (p=0.034), and lower %DF (p<0.05), and male gender was associated with higher %DF (p=0.025). Furthermore, higher MGF was associated with lower %BF and greater %DF, while higher PI was associated with greater %BF and lower %DF. Moreover, higher %DF itself was associated with lower %BF (**Table 6.5**).

Table 6.1: Patient demographics and preoperative risk profiles

Variable	Study population
Total patients	207 (100%)
Age (yrs)	67±8
Male	176 (85%)
Body Mass Index (kg/m^2)	28.7±4.0
Diabetes mellitus	
Insulin dependent	9 (4%)
Noninsulin dependent	61 (29%)
No history of diabetes	137 (66%)
Chronic obstructive pulmonary disease	24 (12%)
Peripheral vascular disease	22 (11%)
New York Heart Association class	
I	50 (24%)
II	115 (56%)
III	40 (19%)
IV	2 (1%)
Canadian Cardiovascular Society class	
I	32 (15%)
II	132 (64%)
III	32 (15%)
IV	11 (5%)
Left ventricular ejection fraction (%)	58±7
By-pass time (min)	96±26
Cross-clamp time (min)	67±21
Surgeon	
"DT"	176 (85%)
"GK"	31 (15%)
Total grafts and territory	542 (100%)
Venous	301 (56%)
Left territory	167 (31%)
Right territory	134 (25%)

Table 6.2: Distribution of grafted target vessels

Conduit (No.)	LAD	DIAG	IM	OM	RCA	PDA
SVG (301)	5	35	12	115	38	96

Table 6.3: Native vessel disease: Quantitative coronary angiography data

Variable	Host coronary artery diameter (mm)	Average lumen diameter at stenosis (mm)	Host coronary artery stenosis (% area)	Lesion length (mm)
Venous grafts				
Overall (n=301)				
Left territory (n=167)	2.0±0.7	0.7±0.4	86.1±11.8	9.4±4.7
Right territory (n=134)	2.0±0.8	0.7±0.4	90.6±9.8	9.3±4.3
p-value	0.9	0.8	<0.001	0.9
ONCABG (n=184)				
Left territory (n=99)	2.0±0.7	0.7±0.3	87.2±10.4	9.6±4.4
Right territory (n=85)	2.0±0.9	0.7±0.4	90.4±10.1	9.0±4.2
p-value	0.5	0.4	0.002	0.5
OPCABG (n=117)				
Left territory (n=68)	2.0±0.7	0.71±0.38	84.5±13.5	9.2±5.1
Right territory (n=49)	1.9±0.5	0.65±0.33	91.7±9.4	9.9±4.5
p-value	0.6	0.4	0.040	0.4
p-value*	0.8	0.5	0.1	0.6
p-value**	0.5	0.6	0.5	0.3

*, comparing ON- and OPCABG to the left territoty.

**, comparing ON- and OPCABG to the right territory.

Table 6.4: Comparison of intraoperative TTFM parameters between SVGs supplying the left and the right coronary territory

Variable	Mean graft flow (ml/min)	Pulsatility Index	Diastolic filling (%)	Backward flow (%)	By-pass time (min)	Mean arterial pressure at TTFM (mmHg)
Saphenous vein grafts						
Overall (n=301)						
Left territory (n=167)	48±34	2.6±1.7	63±12	1.8±3.2	95±23	81±8
Right territory (n=134)	48±29	2.5±1.2	58±11	1.6±3.0	99±28	81±6
p-value	0.9	0.7	<0.001	0.8	0.3	0.9
ONCABG (n=184)						
Left territory (n=99)	52±28	2.5±1.9	64±12	1.2±2.5	95±23	81±6
Right territory (n=85)	49±30	2.5±1.3	57±11	1.6±3.2	99±28	80±5
p-value	0.5	0.9	<0.001	0.4	0.3	0.3
OPCABG (n=117)						
Left territory (n=68)	44±40	2.7±1.4	63±12	2.3±3.0	-	81±11
Right territory (n=49)	47±27	2.6±1.2	60±10	1.6±2.6	-	82±7
p-value	0.6	0.5	0.071	0.2	-	0.6
p-value*	0.1	0.3	0.8	0.023	-	0.9
p-value**	0.7	0.7	0.3	0.9	-	0.095

*, comparing ON- and OPCABG to the left territoty.

**, comparing ON- and OPCABG to the right territory.

Table 6.5: Multivariable linear regression model

Factors associated with MGF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	-48.09	32.66	-	0.1	-112.4	16.23
Left territory	3.04	3.87	0.05	0.4	-4.58	10.66
Age	0.47	0.22	0.12	0.034	0.04	0.89
Male	8.68	5.03	0.1	0.086	-1.23	18.59
Diabetes	-3.31	2.02	-0.93	0.1	-7.3	0.67
ONCABG	2.37	3.71	0.04	0.5	-4.94	9.67
Host coronary artery stenosis (% area)	0.41	0.22	0.14	0.067	-0.03	0.85
Mean lumen diameter	-3.07	6.33	-0.37	0.6	-15.53	9.39
PI	-3.02	1.58	-0.14	0.058	-6.14	0.1
DF%	0.55	0.21	0.19	0.009	0.14	0.96
%BF	-1.96	0.78	-0.18	0.012	-3.49	-0.43

F=8.68, p<0.001

Factors associated with PI

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	7.03	1.24	-	<0.001	4.57	9.48
Left Territory	0.36	0.16	0.11	0.026	0.04	0.67
Diabetes	0.01	0.08	0.01	0.9	-0.15	0.18
Host coronary artery stenosis (% area)	-0.02	0.01	-0.11	0.1	-0.03	0.003
Mean lumen diameter	-0.21	0.26	-0.05	0.4	-0.72	0.31
MAP at TTFM	-0.01	0.01	0.03	0.6	-0.03	0.01
Surgeon	-0.02	0.15	-0.01	0.9	-0.32	0.27
MGF	-0.01	0.003	-0.1	0.067	-0.01	0.001
DF%	-0.05	0.01	-0.34	<0.001	0.06	-0.03
%BF	0.19	0.03	0.36	<0.001	0.13	0.25

F=21.06, p<0.001

Factors associated with %DF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	70.26	10.53	-	<0.001	49.52	91.01
Left Territory	5.1	1.14	0.23	<0.001	2.86	7.34
Age	-0.14	0.07	-0.1	0.041	-0.27	-0.005
Male	3.5	1.55	0.12	0.025	0.45	6.56
Diabetes	0.5	0.62	0.04	0.4	-0.72	1.72
Host coronary artery stenosis (% area)	-0.07	0.07	-0.07	0.3	-0.2	0.07
Mean lumen diameter	-0.61	1.93	-0.02	0.8	-4.42	3.19
Surgeon	-0.12	1.1	-0.005	0.9	-2.28	2.04
MAP at TTFM	0.09	0.07	0.06	0.2	-0.06	0.23
MGF	0.05	0.02	0.15	0.011	0.01	0.09
PI	-2.87	0.45	-0.4	<0.001	-3.76	-1.99
%BF	-0.69	0.23	-0.18	0.004	-1.15	-0.22

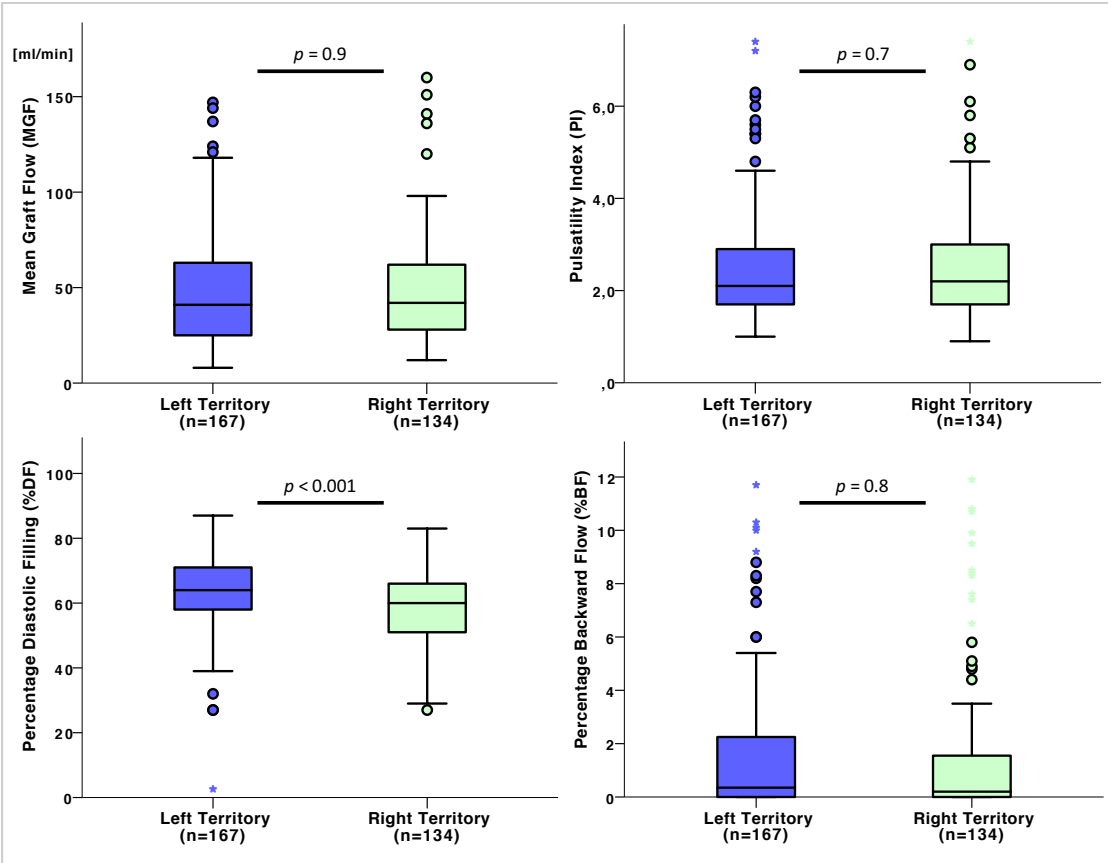
F=15.80, p<0.001

Factors associated with %BF

Model	Unstandardized coefficients		Standardized coefficients β	p-value	95% CI for *B*	
	B	SE			Lower	Upper
Constant	2.87	1.21	-	0.018	0.49	5.25
Left territory	0.37	0.3	0.06	0.2	-0.22	0.95
Diabetes	0.15	0.15	0.04	0.3	-0.16	0.46
ONCABG	-0.22	0.35	-0.04	0.5	-0.91	0.46
Surgeon	0.23	0.34	0.04	0.5	-0.44	0.89
MGF	-0.01	0.005	-0.12	0.018	-0.02	-0.002
PI	0.84	0.12	0.41	<0.001	0.62	1.07
DF%	-0.05	0.02	-0.18	0.002	-0.08	-0.02

F=25.47, p<0.001

Figure 6.2: Overall differences between SVGs to the left- and the right territory



6.2: *Boxplots depicting differences in MGF, PI, %DF, and %BF between grafts going to the left and right coronary territory, respectively.*

Discussion

As demonstrated by Transit-time flowmetry in patients undergoing CABG, our study has shown that SVGs anastomosed to the left and right coronary territory have comparable MGF, PI, and %BF irrespective of surgical technique (OPCABG *or* ONCABG). However, SVGs anastomosed to the left territory have a significantly higher %DF than SVGs anastomosed to the right territory both during OPCABG and ONCABG. This is consistent with the known fact that there is a higher % DF in left sided coronary vessels because of the higher transmyocardial pressure during systole

compared to the right side of the heart. Moreover, compared to ONCABG, a significantly higher %BF was found in OPCABG SVGs supplying the left coronary territory (**Table 6.4**). In a multi-regression analysis, grafting to the left territory was weakly associated with higher PI and strongly associated with higher %DF of SVGs (**Table 6.5**).

In keeping with our finding of no significant difference between territories with respect to MGF, the study by Tokuda *et al.* [52], including a mixture of arterial and venous grafts, found no statistically significant difference in MGF between grafts anastomosed to the left or the right coronary territory [52]. On the other hand, the study by Kim *et al*. [53], including a total of 117 arterial conduits (all operated OPCABG), found a higher MGF in grafts anastomosed to the left than to the right territory. However, as only arterial grafts were assessed, the structural and physiological differences between arterial and venous conduits [146, 147] may explain these conflicting results, and further research is thus warranted to address this topic.

In further concordance with our results of no significant territory-related difference in PI, the study by Tokuda *et al.* [52] also found no statistically significant difference between grafts anastomosed to the left or the right territory with respect to PI [52]. In contrast to this finding, the study by Kim *et al*. [53] found a higher PI in grafts anastomosed to the right coronary territory. Again, since the study by Kim *et al.* [53] only included arterial conduits, this may well explain these conflicting results. Another explanation for why a higher PI may be found in right-sided grafts may be due to the position of the TTFM probe during measurement. Repositioning of the heart into anatomical position at the end of surgery will cover the distal end of the graft. Consequently, TTFM measurement is often performed proximally on right-

sided grafts, where PI is usually higher, as the high pressured forward flow from the aorta results in higher systolic peak flows in the proximal segment of a by-pass graft and thereby in a larger difference between maximum flow and minimum flow, as further explained in the following [134]. In theory, a slightly higher PI may well be expected in grafts anastomosed to the left territory, as the PI is obtained by dividing the difference between maximum and minimum flow by the mean flow: $\frac{(Q_{Max} - Q_{Min})}{Q_{Mean}}$. Therefore, a larger difference between maximum and minimum flow, resulting in a higher PI value, may be expected on the left side of the heart where the higher transmyocardial pressure results in a higher pressure amplitude between systole and diastole [153]. Indeed, the multi-regression analysis suggested that grafting to the left territory was weakly associated with higher PI in SVGs (**Table 6.5**).

In agreement with our study suggesting a higher %DF in SVGs anastomosed to the left territory, the study by Tokuda *et al*. [52] and the study by Kim *et al*. [53] both demonstrated a higher %DF in grafts anastomosed to the left coronary territory compared to grafts anastomosed to the right territory. As previously denoted, a higher %DF is indeed expected on the left side of the heart due to the higher transmyocardial pressure, which lowers systolic coronary flow, irrespective of conduit type (arterial or venous) or surgical technique (**Table 6.5**). However, it is important to acknowledge that the established differences in %DF found in our study is of mere 5%. Although this difference may reach statistical significance, it is unlikely to be of any clinical relevance.

Similar to our study, Tokuda *et al.* [52] found no significant difference in %BF in left *vs*. right-sided by-pass grafts. In contrast, however, the study by Kim *et al*. [53] found a higher %BF in grafts anastomosed to the left coronary territory. As previously noted, only arterial grafts performed by OPCABG technique were included

in the study [53], however, their result [53] falls in line with our finding of higher %BF only in OPCABG grafts anastomosed to the left coronary territory (**Table 6.4**). A higher %BF may well be expected on the left side due to the higher transmyocardial pressure, which would force blood backward during the isovolumetric contraction. Another explanation could be, as in the previous chapter, that OPCABG SVGs to the left territory had slightly larger average lumen diameter at stenosis and could therefore be more exposed to competitive flow (**Table 6.3**).

No other parameters were found significantly different in grafts anastomosed OPCABG *vs*. ONCABG. Notwithstanding this however, previously published papers on TTFM parameters in OPCABG *vs.* ONCABG found a higher MGF in grafts performed with the latter technique [100, 143, 144]. In a prospective study [100] including a total of 266 grafts (203 OPCABG *vs.* 63 ONCABG) in 100 patients, a lower MGF was demonstrated in SVGs performed by OPCABG technique despite a higher mean arterial pressure when compared to ONCABG ($p<0.05$) [100]. The authors suggested these findings might be related to vasodilatation resulting from a period of myocardial ischaemia. As explained in the previous chapters, it has been well documented that despite usage of cardioplegia, cross-clamping in ONCABG leads to global myocardial ischaemia and subsequent acidosis with resultant dilatation of coronary arteries [145]. Thus, a higher MGF may be expected in ONCABG *vs.* OPCABG by-pass grafts. Although our results did demonstrate a numerically higher MGF in the ONCABG SVG cohort, this difference did not reach statistical significance.

Of note, the multi-regression analysis of this study showed significant associations between the four TTFM parameters (this will be further illustrated in **Table 8.1**), which suggests that these parameters should thus be considered

complementary rather than in isolation when assessing the quality of grafts intraoperatively [83, 114, 117]. This is supported by studies demonstrating that high quality grafts, as determined by angiographic graft patency assessment, have high MGF due to good run-off with concomitant low PI, predominant %DF, and little %BF [52, 76, 77, 101, 113, 118].

LIMITATIONS

While the statistical power-analysis allowed for clinically significant changes to be excluded, we cannot exclude if smaller changes may have occurred, differences that may be of importance for long-term patency. Furthermore, the extent of host coronary artery stenosis was statistically higher to the right coronary territory (**Table 6.3**). However, the mean host coronary artery stenosis was over 80% in both territories, which should make the difference between the two territories clinically irrelevant and thus comparable [121].

Conclusions

Saphenous vein grafts supplying the left coronary artery territory have a higher %DF when compared to right-sided SVGs, irrespective of whether the procedure is performed ONCABG or OPCABG. Furthermore, multi-regression analysis suggests that SVGs grafted to the left coronary territory are weakly associated with higher PI and strongly associated with higher %DF. The established difference in %DF between territories is not substantial, but do demonstrate that research aiming to delineate a cut-off value for graft patency with Transit-time flowmetry may need to take into account the target coronary territory.

7

Influence of external stenting on venous graft flow parameters in CABG: A randomized study

Chapter 7 – External stenting of venous grafts

Introduction

Although arterial grafts have demonstrated compelling benefits regarding surgical outcomes including long-term patency [55, 56], autologous SVGs remain the most widely used conduits in CABG [58], and their use appears to be on the rise [59][154]. To improve SVG patency, recent clinical studies have demonstrated the benefits of external stenting of SVGs with a newly developed external device consisting of cobalt-chromium, the VEST stent [59, 73, 74], as described in Chapter 1 – Introduction. It is not known to what extent external stenting changes perioperative flow-characteristics of SVGs, which is of importance for studies on graft patency and future guidelines on cut-off values for such by-pass grafts [99].

As previously noted, TTFM is a quality control tool for intraoperative graft assessment in CABG [114] and has been recommended in the most recent European guideline on myocardial revascularisation [99]. Although TTFM measures four flow

parameters (MGF, PI, %DF, and %BF), only one previous study has directly compared MGF and PI in stented and non-stented SVGs and found no significant difference between the two groups [59]. However, it later became apparent that the initially applied surgical technique of stent deployment was incorrect, as the stent was fixated with sutures and the side branches were ligated with metallic clips, which may have potentially altered SVG patency [71], and no studies exist on flow-parameters with the improved technique (avoidance of fixation and the use of 5.0 prolene to ligate side branches).

The aim of this study was to determine, in a randomised fashion, intraoperative blood flow parameters in stented and non-stented SVGs to the left and the right coronary territory as determined by TTFM technique. CABG patients from one centre participating in a multicenter, randomized, clinical trial of external stenting of SVGs were included. Patients were eligible if scheduled for at least one SVG to each of the two coronary territories (the right and the left), and each patient received external stenting of a single SVG, randomly allocated intraoperatively, to either the right or the left coronary territory. We hypothesized that external stenting would not significantly alter blood flow in a SVG as determined by TTFM.

Methods

This study was part of a multicentre, randomised, clinical study with patients serving as their own controls (the *VEST III* trial). The study was approved by a UK Research Ethics Committee (clinicaltrials.gov identifier: NCT02511834) and all subjects gave informed consent. Furthermore, a CONSORT 2010 checklist was used for this study. A total of thirty-five patients from one centre (John Radcliffe Hospital, Oxford, UK) were enrolled from October 2015 to the set deadline on January 2017. Each CABG

procedure was specially designed for each patient to compliment both preclinical risk factors as well as coronary anatomy. Patients were eligible if scheduled for on-pump multi-vessel CABG including LIMA to LAD and SVG to both the right and the left coronary territory. Patients with only left-sided or only right-sided coronary disease were excluded. Eligibility required a target vessel diameter of 1.5 mm or greater with a coronary artery stenosis greater than 75% and with an adequately dimensioned distal vascular bed as assessed from preoperative angiography. Each patient received one external stent (VEST stent, Vascular Graft Solutions Ltd, Tel Aviv, Israel), consisting of a cobalt-chrome braid with axial plasticity and radial elasticity, to a single SVG, randomly assigned intraoperatively by the opening of a sealed non-transparent envelope, to either the right or the left coronary territory. One or more SVGs remained non-stented and served as control. All SVGs were performed as single grafts. No revisions were needed based on adequate TTFM findings (MGF >20 ml/min and PI<5).

The degree of native coronary artery stenosis was measured by an independent observer using quantitative coronary angiography (Horizon Cardiology version 12.2, McKesson, Israel). Data from quantitative coronary angiography included host coronary artery diameter, average lumen diameter at stenosis, host coronary artery stenosis, and lesion length.

The primary end-points were MGF, PI, DF, and %BF measured by TTFM in stented as well as in non-stented SVGs. All flow measurements were carried out with the VeriQC device (Medistim ASA, Oslo, Norway).

Procedure

Routine on-pump CABG was performed by two surgeons, DPT (n=21) and GK (n=14). The study protocol was followed in all patients. SVGs were harvested by endoscopic technique (100%) and sutures (5.0 prolene) were used to ligate their side-branches. SVGs were preserved in heparinized blood buffered saline. After completing the distal anastomoses of the SVG, the sealed randomisation letter was opened and an adequately sized VEST device was selected from twelve available models based on diameter and length of the SVG. The device was threaded over the non-pressurized SVG. After completion of the proximal anastomosis, the device was expanded to cover the entire SVG. Gaps of 5-10 mm were intentionally maintained from the device to the distal and proximal anastomoses. No fixation of the device is required, as it is meant to maintain its shape post-deployment without compression of the vessel lumen [59, 71].

Principle of TTFM measurement

Prior to TTFM measurement, an appropriately sized probe was selected according to the external SVG diameter. Mainly probe sizes of 4 or 5 mm were used. Ultrasound gel was applied to the probe-lumen before positioning it on the SVG, such that the graft occupied a minimum of 75% of the probe-lumen. The probe was placed as close as possible to the distal anastomosis during TTFM measurement in non-stented SVGs but close to the proximal anastomosis in the 5-10 mm gap intentionally maintained in stented SVGs. Prior to measurements, a systemic MAP of 75-85 mmHg was maintained. Traction on the pericardium was released, and the stabilizer was removed from the pericardial surface to allow the heart to return to its natural anatomic position. TTFM parameters and MAP were determined after reversal with heparin.

Statistical analysis

The general statistics have been discussed in Chapter 2 – General methods. However, the statistical power-analysis of this study was based on the assumption that for a flow-measurement to become clinically significant, external stenting should change MGF to <40 mL/min or PI to >3 (Table 1). The power-analysis was based on previous values for MGF (58±26 mL/min) and PI (2.1±1.0) from our group. We conservatively assumed SD for the difference comparable to the SD of the population. With 31 and 33 patients in each group such difference will be detected with a beta of 0.90 and an alpha of 0.05 (double-sided). To allow for a dropout/non-analysable rate of at least 5%, we included 35 patients in each group.

Results

A total of 35 patients (mean age 68.0±6.9 years, 88.6% males) were enrolled between October 2015 to the set deadline on January 2017. All stent deployments were successful. A total of 115 bypass grafts, including 42 arterial conduits, 73 grafts were included in the analysis (35 stented SVGs and 38 non-stented SVGs). Of the stented SVGs, 17 (49%) were grafted to the left coronary territory and 18 (51%) were grafted to the right coronary territory. Five patients received bilateral internal mammary artery treatment. The clinical profile of the cohort is presented in **Table 7.1**.

Target vessel disease

The extent of native vessel disease and the length of the conduit used for CABG are shown in **Table 7.2**. Stented and non-stented SVGs were comparable with respect to host coronary artery stenosis (left territory, p=0.2; right territory, p=0.09), host coronary artery diameter (left territory: p=0.9, right territory: p=0.9), average lumen

diameter at stenosis (left territory, p=0.3; right territory, p=0.4), and lesion length (left territory, p=0.5; right territory, p=0.9). The mean length of stented and non-stented SVGs was identical in the two coronary systems (left territory, p=0.7; right territory, p=0.3).

Intraoperative TTFM

TTFM measurements and mean arterial pressure at TTFM are presented in **Table 7.3** and **Figure 7.1**. There were no significant differences between stented and non-stented SVGs in MGF (left territory, p=0.9; right territory, p=0.3), PI (left territory, p=0.2; right territory, p=0.1), % DF (left territory, p=0.6; right territory, p=0.3) and % BF (left territory, p=0.4; right territory, p=0.6). As intended, MAP at the time of TTFM measurement was similar in stented and non-stented SVGs (left territory, p=0.9; right territory, p=0.8).

Table 7.1: Patient demographics

Characteristic (n=35)	**Mean (±SD) or n (%)**
Age (yrs)	68.0±6.9
Male	31 (89%)
Body Mass Index	28.5±3.4
Diabetes mellitus	
Insulin dependent	4 (11%)
Non-insulin dependent	5 (14%)
No history of diabetes	26 (74%)
Chronic obstructive pulmonary disease	5 (14%)
New York Heart Association class	
I	7 (20%)
II	18 (52%)
III	8 (23%)
IV	2 (6%)
Canadian Cardiovascular Society class	
I	2 (6%)
II	25 (71%)
III	3 (9%)
IV	5 (14%)
Left ventricular ejection fraction (%)	57±6
Number of conduits	3.3±4.6
By-pass time (min)	100±21
Cross-clamp time (min)	64±17

Table 7.2: Native vessel disease: Quantitative coronary angiography data

Variable	Host coronary artery diameter (mm)	Average lumen diameter at stenosis (mm)	Host coronary artery stenosis (% area)	Lesion length (mm)	Graft length (cm)
Averaged overall (n=115)					
Stented SVG (n=35)	2.1±0.7	0.6±0.3	93±9	10.1±5.7	15.3±3.3
Non-stented SVG (n=38)	2.1±0.8	0.7±0.4	89±10	9.2±3.7	15.5±2.8
Arterial grafts (n=42)	2.2±0.7	0.8±0.5	87±11	10.9±3.6	-
p-value	0.9	0.9	0.2	0.6	0.8
Left territory (n=79)					
Stented SVG (n=17)	2.1±0.6	0.5±0.2	94±6	10.3±6.1	13.8±3.4
Non-stented SVG (n=20)	2.1±1.0	0.7±0.5	89±8	8.9±3.5	14.2±2.8
Arterial grafts (n=42)	2.2±0.7	0.8±0.5	87±12	10.9±3.6	-
p-value	0.9	0.3	0.2	0.5	0.7
Right territory (n=36)					
Stented SVG (n=18)	2.1±0.9	0.7±0.4	92±11	9.9±5.6	16.5±2.8
Non-stented SVG(n=18)	2.1±0.6	0.6±0.3	90±12	9.6±4.0	17.4±1.4
Arterial grafts (n=0)	-	-	-	-	-
p-value	0.9	0.4	0.09	0.9	0.3

p-value: comparing stented and non-stented SVGs.

Table 7.3: Comparison of intraoperative Transit time flowmetry data

Variable	Flow (ml/min)	Pulsatility index	Diastolic Filling (%)	Backward flow (%)	MAP at TTFM (mmHg)
Averaged overall (n=115)					
Stented SVG (n=35)	51±26	2.2±1.0	61±13	1.2±3.2	82±6
Non-stented SVG (n=38)	59±35	2.2±0.9	60±9	1.0±2.2	82±6
Arterial grafts (n=42)	45±35	2.3±0.8	70±7	1.8±2.2	82±7
p-value	0.5	0.9	0.9	0.9	0.9
Left territory (n=79)					
Stented SVG (n=17)	53±31	2.4±1.2	61±17	1.8±4.5	82±6
Non-stented SVG (n=20)	57±27	2.0±0.7	64±6	0.8±1.3	82±6
Arterial grafts (n=42)	45±34	2.3±0.8	70±7	1.8±2.2	82±7
p-value	0.9	0.2	0.6	0.4	0.9
Right territory (n=36)					
Stented SVG (n=18)	48±22	2.0±0.6	60±9	0.6±1.1	82±5
Non-stented SVG (n=18)	60±43	2.4±1.0	57±10	1.2±3.0	81±7
Arterial grafts (n=0)	-	-	-	-	-
p-value	0.3	0.1	0.3	0.6	0.8

p-value: comparing stented and non-stented SVGs.

Discussion

As literature does not address influence of external stenting of SVGs on perioperative flow characteristics, we sought to assess perioperative blood flow parameters in stented *vs*. non-stented SVGs in a randomised clinical study of CABG patients during on-pump surgery. As determined by transit-time flowmetry, our study showed no statistically significant difference in terms of MGF, PI, %DF or %BF between stented and non-stented SVGs, in neither the left nor the right coronary territory (**Table 7.3**).

In keeping with our findings, the VEST I trial [59], which enrolled a total of thirty-five patients with external stenting of SVGs going to either the right coronary artery (RCA) or the circumflex coronary territory, found a MGF of 67±28 mL/min *vs*. 66±33 mL/min (ns) and a PI of 2.2±1.1 *vs*. 2.2±1.0 (ns) in stented *vs*. non-stented SVGs. In the VEST I trial [59] %DF and %BF were not assessed, and it was later suggested that the initially applied surgical technique of how the stents were deployed was incorrect, which has now been improved [71]. With modern technique of external stenting, we can now confirm that external stenting is of no clinically significant concern for any aspects of haemodynamics of SVGs as assessed by TTFM.

In general, one might have hypothesized some improvement of flow dynamics in stented SVGs, since previous studies have demonstrated that external stenting of SVGs improve lumen uniformity and hemodynamic flow patterns, as determined by angiography and intravascular ultrasound (IVUS) at 1-year follow-up [73]. In a report of the VEST trial [73], post-hoc computational fluid dynamics analysis of grafts from patients in the VEST I trial were used to calculate and compare three haemodynamic parameters: time-averaged wall shear stress, oscillatory shear index, and relative residence time using a technique established in a previous study by the same group [59, 155]. With this technique a significantly reduced mean oscillatory shear index

was found in the stented group compared to the non-stented group. Pertinently, it was also found that mean oscillatory shear index correlated with the development of diffuse intimal hyperplasia [155], suggesting that external stenting of SVGs improve graft patency at follow-up. In fact, the key finding of the VEST I trial [59] was the potential of mechanical external stents to reduce intimal hyperplasia area in SVGs 1-year after CABG by approximately 15% ($p=0.04$) [59].

Although we did observe a trend towards higher flows in non-stented SVGs, this was statistically insignificant, and the high SD prevents drawing any definite conclusions. Furthermore, PI was higher in stented vs. non-stented SVGs going to the left coronary territory but conversely so in stented vs. non-stented SVGs going to the right coronary territory, and overall there was no statistically significant difference. Lack of statistical significance in our study may be due to the fact that stents do not compromise the vessel lumen but simply support the vascular wall [71]. In fact, most stents are deployed loosely at first, as repositioning of the heart back to anatomical place in combination with restoring normal blood pressure following CABG results in an increase of vessel diameter hereby eliminating any gap between the vessel wall and the stent without compromising the vessel lumen [71]. As such, a change in hemodynamic flows of stented SVGs may potentially arise post CABG when the vein graft has adjusted to the stent.

Taken together with our findings, external stenting seems to improve long term flow characteristics irrespective of initial changes, and demonstrate that external support with VEST stents is safe and may improve graft patency, at least in the short to mid-term with favourable changes in vessel structure.

LIMITATIONS

Our statistical power-analysis was based on the ability to see changes that, based on previously established cut-off points for TTFM parameters, would have been associated with clinically relevant compromised flows, but we may not have been able to see much smaller changes, which may eventually translate into significant changes including the development of hyperplasia.

Lastly, the different position of the TTFM probe (proximally in stented SVGs and as close as possible to the distal anastomosis in non-stented SVGs) may have potentially affected our results. However, this would potentially lead to a higher PI in stented SVGs, as we know that proximal measurement results in higher PI values [134], but this was only observed in stented SVGs going to the left coronary territory. Overall, we do not expect that the position of the probe has altered our results significantly.

Conclusions

External stenting of saphenous vein grafts with the VEST stent does not affect intra-operative flow parameters and does not deteriorate the vessels' haemodynamics in the perioperative period in coronary artery by-pass surgery. Further results from randomised clinical studies are warranted to address whether changes of flow dynamics in stented SVGs arise post CABG. Based on our results, cut-off points for native and externally stented saphenous vein grafts should be the same.

8

General discussion

Chapter 8 – Discussion

General discussion

The aim of this thesis was to assess the accuracy and precision of the Transit-time flowmetry (TTFM) technique for flow-determination in by-pass grafts during CABG, and to improve the understanding and clinical integration of all measured TTFM parameters (MGF, PI, %DF, and %BF) in different CABG settings in arterial as well as venous by-pass grafts. I believe that I have demonstrated that the TTFM technique, with a slight overestimation, especially at higher flows, is an accurate indicator of actual blood flow with a clinically acceptable precision. Most importantly, appropriate angulation and probe size must be secured prior to measurement to ensure the most accurate reading. Furthermore, I have assessed how ONCABG *or* OPCABG, the use of arterial *or* venous conduits, the grafted coronary territory, and external stenting of saphenous veins (with the VEST stent) may affect TTFM parameters during CABG. However, to provide a clear and coherent discussion about each parameter, I have decided to merge discussions about each separately, as presented in the following.

In this thesis, I have demonstrated that MGF is affected by surgical technique (ON- *or* OPCABG) and by choice of conduit (arterial *or* venous). However, grafted coronary territory and external stenting does not seem to have an effect on MGF in SVGs. Further research is now warranted to assess the effect of grafted coronary territory on arterial by-pass grafts both during ONCABG and OPCABG surgery.

In keeping with studies showing higher MGF in grafts anastomosed during ONCABG [100, 142-144], my data demonstrated that ONCABG is an independent predictor of higher MGF. However, I could only find a statistically significant higher MGF for arterial grafts and only numerically higher for SVGs in ONCABG *vs.* OPCABG. Interestingly, I found that MGF was overall higher in venous *vs.* arterial grafts performed by OPCABG technique, but no difference was found in ONCABG. I believe my results substantiate the different mechanical and vasodilatory properties of arterial and venous conduits. In theory, a higher MGF could be expected in venous compared to arterial by-pass grafts, regardless of surgical technique, due to the commonly larger calibre of veins with subsequent grafting to larger native coronary vessels [38, 100]. However, as arterial conduits have thicker and more elastic vessel walls, they are able to adjust calibre and hence blood flow according to myocardial demand [146, 147]. Consequently, a higher MGF in venous *vs.* arterial grafts in OPCABG is not surprising, as the veins may already be providing blood to the ischaemic myocardium at "maximum capacity"; however, when CABG is performed ONCABG, the vasodilatory effect of cross-clamping (as explained in chapter 4 – On- *vs.* off-pump surgery) and subsequent increased blood flow in arterial grafts eliminates major differences in MGF between the two conduit types.

Albeit with smaller differences, my results demonstrate that PI is comparable between arterial and venous by-pass grafts regardless of surgical technique. Moreover, PI is comparable for SVGs regardless of grafted coronary territory and external stenting. Further research is now warranted to address whether grafted territory affects PI in arterial conduits. According to one study [53], PI is higher in OPCABG arterial conduits anastomosed to the right coronary territory, however, no studies have assessed PI in ONCABG arterial by-pass grafts. Nevertheless, in concordance with previously published studies aiming to define a cut-off value for predicting graft failure, by short- and mid-term angiographic follow-up [77, 88, 89, 121], my PI results are all < 3, making any detectable PI difference between evaluated parameters in this thesis small and clinically irrelevant.

Most importantly, however, is the fact that PI is affected by MGF, %DF, and %BF, as I have demonstrated by multi-regression analysis, which will be discussed below (**Table 8.1**). This finding supports general recommendation of making sure that the PI value of each TTFM measurement is within the recommended cut-off value of <5 (ideally <3) [114], as a high PI often reflects poor by-pass graft quality [52, 76, 77, 101, 113, 118].

According to published literature, %DF is not correlated to graft patency at follow-up [114]. Nonetheless, it is commonly known that coronary arteries fill during diastole, hence a predominant systolic flow indicates poor graft quality [133]. The usual recommendation for %DF is 60-70% in grafts anastomosed to the left coronary territory and >50% for grafts to the right [52, 53, 76]. However, no studies have addressed %DF in arterial *vs.* venous conduits in ONCABG and OPCABG.

In this thesis, I found that the difference in %DF in SVGs between the left and the right coronary territory, albeit statistically significant, was not clinically

substantial. In contrast, however, %DF was both clinically and statistically higher in arterial *vs.* venous grafts, regardless of the surgical technique, both in the overall group and in grafts anastomosed to the left coronary territory (**Table 4.4** & **Table 5.4**). Further research is now warranted to establish whether this is true for arterial grafts to the right coronary territory. For now, our study suggests a %DF of 60% for venous grafts and 70% for arterial grafts (**Table 5.4**). Moreover, %DF was higher during OPCABG surgery, but this finding may well be due to the larger number of arterial by-pass grafts in the OPCABG groups. Further research in now warranted to establish whether %DF is clinically higher in arterial by-pass grafts anastomosed to the left coronary territory compared to those anastomosed to the right.

Finally, although %BF in arterial grafts was comparable between ONCABG and OPCABG, I found a higher %BF in arterial grafts *vs.* SVGs. However, these results were mainly driven by grafts anastomosed by ONCABG technique. In fact, %BF is only higher in arterial grafts *vs.* SVGs in ONCABG, as these differences are eliminated during OPCABG, where %BF increases for SVGs. As previously noted, this finding is probably due to the more passive vessel walls of SVGs being affected by the increased run-off. During ONCABG, the SVGs provide blood to the ischemic myocardium at a maximum capacity and high pressure, which prevents significant backward-flow.

Moreover, no difference was found for %BF for arterial grafts *vs.* SVGs to the left and the right territory (Chapter 4 – on- vs. off-pump surgery), but a higher %BF was found in OPCABG SVGs compared to ONCABG SVGs anastomosed to the left coronary territory (Chapter 6 - Left- vs. right sided venous by-pass grafting). Further research is now warranted to fully assess the effect of %BF in left- *vs.* right-sided arterial by-pass grafts.

As determined from findings by multi-regression models reported in the respective chapters, significant associations exist between the four TTFM parameters (Table 8.1), thus suggesting that these parameters should be considered complementary rather than in isolation when assessing quality of bypass grafts during CABG [83, 114, 117]. This is supported by further evidence that demonstrated that high quality grafts, as determined by angiographic graft patency assessment, have high MGF due to good run-off with subsequently low PI, predominant DF, and less BF [52, 76, 77, 101, 113, 118].

Table 8.1: Individual associations between all TTFM parameters

Variable	MGF	PI	%DF	%BF
MGF		−−−	+/++	−/−−
PI	−−−		−−−	+++
%DF	+/++	−−−		−/−−
%BF	−/−−	+++	−/−−	

8.1: *Based on multivariable linear regression analysis of the respective chapters (Chapter 4-6), this table shows the individual associations between all TTFM parameters. The table further shows whether the parameters are negatively or positively related. E.g. a high PI (>5) is likely seen in TTFM measurements with low MGF (<15-20 ml/min), low %DF (<50%), and high %BF (>3%). The strength of the associations is based on p-values (>0.05, <0.001 – 0.05, and <0.001 going from weak to moderate to strong, respectively), as provided in the respective tables (**Table 4.5, 5.5, and 6.5**).*

−/+: weak negative or positive association, −−/++: moderate negative or positive association, −−−/+++: strong negative or positive association.

In furtherance of the multi-regression models, we found a tendency for higher MGF in male patients, albeit non-significant (**Table 4.5, 5.5, and 6.5**). This finding has been supported in previous studies [54, 142] both attributing this finding to the 'obvious' reason, that men on average have larger calibre vessels supplying larger myocardial areas.

Moreover, the multi-regression models showed an independent association between higher %DF and male gender (**Table 4.5, 5.5, and 6.5**). Notably, the analysis also showed an independent association between higher MGF and greater %DF, which falls back to our previous observation of higher flows in male patients. In contrast, a lower %DF was associated with older age, which may be due to the lower diastolic blood pressure that is typical in elderly patients [156]. This lower diastolic pressure seems to carry an increased risk of myocardial infarction and death, likely due to a compromise of myocardial perfusion [157]. In addition, predominant systolic flow appears to have a negative impact on graft patency [53]. Altogether, these findings reinforce the importance of adhering to the recommended minimum cut-off value of 50% for %DF [84, 114], particularly in high-risk patients such as the elderly. However, further research may be warranted to fully establish the current observation.

As discussed in Chapter 1 – Introduction, TTFM measurements are influenced by multiple factors such as patient comorbidities, the anatomy of the coronary vessel, the magnitude of the native coronary vessels vascular bed, the quality and type of the conduit, the degree of persistent flow through the native coronary artery, and the construction of the anastomosis [125]. As such, surgeons should be wary of drawing extended conclusions with flow measurements, as there are numerous confounding factors that may affect the flow dynamics. *In general,* surgeons should always assess

all TTFM parameters to compliment each other, as strict application of the cut-off values advocated in the literature would likely result in overzealous and indeed unnecessary graft revisions [114]. Furthermore, TTFM operators should keep in mind that poor results might be due to mechanical problems (such as: kinking, twisting, extra suture, etc.) that require revision, or due to non-mechanical problems (such as: spasm, competitive flow, etc.), which do not require revision. In case of poor TTFM results, surgeons are advised to leave the graft and reassess TTFM after 5-10 minutes before making any hasted decisions. The effect of specific mechanical and non-mechanical problems have not been addressed in this thesis, as separate full studies are indeed required to fully assess these issues in CABG.

Moreover, although the value of the HFUS imaging was not evaluated in this thesis, the addition of 'visual' inspection of the by-pass grafts may prove valuable in situations with poor TTFM parameters. The two modalities may in fact be equally important, as TTFM provides functional information, and in a complementary way, HFUS imaging provides morphological information [120, 137]. In combination, these two modalities may increase diagnostic accuracy of failed or potentially failing grafts [128].

Interestingly, all our overall mean results for all four TTFM parameters (MGF, PI, %DF, and %BF) were safely within current recommended cut-off values (MGF: >20 ml/min for arterial grafts, and >35-40 ml/min for SVGs, PI: < 3, %DF: >50%, and %BF: < 3% [114]). It would be of interest to see how many of these 659 grafts have remained patent by subsequent follow up studies.

Of note, our overall graft revision rate based on poor TTFM parameters (MGF <20 ml/min, and/or PI>5) was 2.3%. All cases, except one, were detected in OPCABG.

The problems in the OPCABG cases were: Twisted graft (1), stretched graft (2), purse string effect (1), tight venous conduit side branch clips (1), dissection (4), intimal flap after endarterectomy (1), problem with proximal anastomosis (1). The problem in the ONCABG case was: purse string effect (1). Post revision, all parameters improved significantly with clinically acceptable results. In 3 cases, however, the grafts were revised erroneously, most probably due to competitive flow or spasm, which was deemed insufficient by TTFM. Only post revision TTFM measurements were included for analysis.

GENERAL LIMITATIONS

Most of our data is observational and not randomized (except Chapter 7 – external stenting of venous grafts), and based on the routine practice of 2 surgeons. Although the baseline characteristics of the studies are overall comparable, smaller differences with potential influence on TTFM parameters cannot be excluded.

The studies comprising this thesis only describe intraoperative graft flow parameters; hence, the results obtained may not necessarily reflect the long-term flow rates or graft patency at follow-up.

Although comparison of TTFM parameters in ONCABG vs. OPCABG, arterial grafts vs. SVGs, and left- vs. right-sided grafts have been extensively discussed and further analyzed by multi-regression analysis, we did not assess the effect of; the magnitude of the native coronary artery's vascular bed, spasm, different peri-procedural spasm prevention techniques, conduit length, heart rate, the quality of the anastomosis, and the quality of the conduit on TTFM parameters.

9

General conclusions and future directions

Chapter 9 – Conclusion

General conclusions

Cumulative evidence suggests that TTFM is a promising quality control adjunct to the surgeon's judgment with the potential to aid decision making when considering whether to redo an anastomosis. In keeping with, I have successfully demonstrated that TTFM is a good indicator of actual blood flow, when appropriate angulation and probe size is ensured, with a clinically acceptable precision. However, I believe that the ability to correctly interpret TTFM parameters in each measurement should be acquired with clinical and experimental experience, combining baseline characteristics of each case with both background knowledge on how these parameters are affected in different CABG settings as well as clinical criteria (electrocardiogram, trans-esophageal echo, and haemodynamic compromise).

Although this thesis clearly demonstrates the effect of different CABG settings on all TTFM parameters (MGF, PI, %DF, and %BF), except for arterial grafts to the left and the right coronary territory, these studies are based on observational studies and

randomized clinical trials are now warranted to support these results (except for chapter 7 – External stenting of venous grafts). For now, surgeons should keep in mind that on- *or* off-pump and conduit type are independent parameters that will affect the final results of a TTFM measurement. Based on my results, a higher cut-off value for MGF in venous *vs.* arterial by-pass grafts performed by OPCABG technique may be suggested. However, the cut-off value for MGF in ONCABG should be similar for both graft types. For PI, current recommended cut-off values of <5, ideally <3, seem acceptable and probably accurate. Moreover, the proposed different cut-off values for %DF in left- and right-sided by-pass grafts may need adjustment. According to the results of this thesis, the cut-off value for venous grafts anastomosed to either coronary territory are clinically comparable, however, further research in now warranted to assess whether the same is true for arterial by-pass grafts. Nonetheless, a separate cut-off value for %DF in arterial *vs.* venous by-pass grafts should be aimed for with a lower %DF in the latter. For %BF, a cut-off value of <3% seems reasonable, as even significant differences detected in this thesis are within the recommended cut-off value. However, surgeons should expect higher %BF in OPCABG *vs.* ONCABG SVGs. Thus, future research aiming to delineate cut-off values for all TTFM parameters by follow-up studies (e.g. CT-angiography) should, in a larger cohort, take into account the surgical technique, conduit type, and potentially the grafted coronary territory.

Future directions

As the data on TTFM parameters in this thesis only describe graft flows measured in the operating theatre, the results obtained in the respective chapters may not reflect the long-term flow rates of these grafts. However, the data on TTFM parameters

collected in this thesis will most probably be incredibly valuable in 5 or 10 years' time, if an assessment of graft patency was performed at that time. Such data would provide what is really useful to both surgeons and patients: an ability to predict long-term graft patency. Potentially, the subsequent findings would alter practice and be included in the international guidelines. Until then, further research is warranted to demonstrate the true potential of the TTFM technique. In particular, the potential of combined imaging and flow assessment techniques (e.g. TTFM and HFUS imaging). A comparison of centres/surgeons that use intraoperative flow assessment *vs*. centres/surgeons that don't, to examine any differences in patient instability on first evening post-surgery (including surgeon call-out or cardiac catheterisation laboratory visits), would most probably also emphasize the clinical benefits of the TTFM technique. Overall, the future for the TTFM technique looks promising and will probably increase in popularity.

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