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REVIEW

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Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: a critical review

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Summary

Transit time flow measurement (TTFM) is a quality control tool for intraoperative graft evaluation in coronary artery bypass graft (CABG) surgery. A critical review of the literature available using TTFM in CABG surgery is the focus of this article. The main objectives will be to detail precise parameters for flow evaluation, to show limitations of TTFM and to prove its predictive impact on postoperative graft failure rate. Publications listed in the PubMed database were reviewed, searching for intraoperative graft verification in coronary surgery by TTFM, with postoperative imaging follow-up (FU) modality and with a special focus on publications released after European guidelines from 2010. Nine included publications revealed an overall graft failure rate of ∼12%. Mean graft flow had a positive predictive value in the largest study, and cut-offs, of at least 20 ml/min for internal mammary artery (IMA) grafts, therein partially confirming guidelines, and 30–40 ml/min for saphenous venous grafts (SVGs) were proposed. An explicit correlation between graft flow, patency rate and severity of coronary stenosis, by indicating the fractional flow reserve, was found for IMA grafts. Increased pulsatility index and increased systolic reverse flow probably predict worse outcome and may help identifying competitive flow. Diastolic filling, rarely indicated, could not be confirmed as the predictive marker. No significant correlation of TTFM and graft failure rate for radial and other arterial grafts could be found, partially due to the small number of these types of grafts analysed. Larger target vessels and lower postoperative CK-MB levels may predict better graft patency rates. Low sensitivity for TTFM to reliably detect graft failure is certainly a major issue, as found in randomized analyses. However, methodical limitations and varying threshold values for TTFM render a general consensus difficult. Influence of quantity (vessel territory distribution) and quality (myocardial scar) of the graft perfusion area, on TTFM and FU outcome, was not included by anyone and should be part of future research. TTFM is probably not the tool of choice to detect progressive late graft failure of SVG. Peroperative TTFM values should be correlated with one type of conduit, differentiating between early and late graft failure (by applying a uniform, appropriated definition), to precise and confirm threshold values.

Keywords: Coronary surgery • Quality control • Transit time flow measurement

INTRODUCTION

Coronary artery bypass graft (CABG) surgery continues to play a major part in the cardiac surgeon's daily activity. In addition to the already proved techniques of surgical revascularization, i.e. on-pump versus off-pump or minimal extracorporeal circulation circuits and predominantly used arterial grafts, there is a growing emphasis on the importance of immediate peroperative checking of the bypass grafts used, to identify peroperative and early postoperative complications due to graft failure. Since 2010, intraoperative graft evaluation has been mentioned 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 (class I recommendation, level of evidence C) [1]. The optimal technique for graft patency evaluation is not mentioned; however, recommended indicative values of a mean graft flow (MGF) of ≥20 ml/min and a pulsatility index (PI) of ≤5 refer to the peroperative transit time flow measurement (TTFM) as the method of choice, which is the focus of the present article. The aim of this review of available literature, investigating TTFM in CABG surgery, will be to resume current indications, focusing on reference values of TTFM. Particular attention will be paid to the impact of peroperative TTFM values on postoperative outcome, in terms of early and mid-term follow-up (FU) graft failure rate. This review prioritizes available literature published in the guidelines since 2010.

MATERIALS AND METHODS

Transit time flow measurement fundamentals

In 2007, the TTFM technique was described, among others, by Balacumaraswami and Taggart in a detailed review; therefore, a short overview will be given [2]. Transit time ultrasound technology uses two ultrasonic transducers fixed to one flow probe. The ultrasonic signal is transmitted from one sensor and will cross a fluid-filled pipe. The opposed fixed reflector will reflect the signal, which will be received by a second sensor. Transit time of the signal, i.e. the difference between upstream and downstream transit time of the ultrasound beam, will be subject to the flow velocity in the pipe. Transit time difference is directly proportional to the blood flow volume. Mean graft flow (MGF = Q_{mean}; ml/min) will depend on graft quality and diameter, target vessel quality and distal run-off of the bypass. The 'PI' estimates the resistance in the graft and, respectively, the distal target vessel run-off. Its value is calculated by the difference in the peak systolic flow minus the peak diastolic flow divided by the median flow (PI = [$Q_{max} - Q_{min}$]/Q_{mean}). The 'diastolic flow fraction (DF)' can be determined by connecting the TTFM console to an ECG, to calculate the percentage of the total flow during the diastole (DF = $Q_{diastole}$/[$Q_{systole} + Q_{diastole}$]), which should be higher than systolic flow, in particular for the left coronary system due to the higher transmyocardial pressure gradients of the left ventricle.

Search of papers

Publications listed in the PubMed database were reviewed, searching for intraoperative graft verification in coronary surgery by TTFM. Items of research were: TTFM, coronary TTFM and TTFM in CABG surgery.

Inclusion and exclusion criteria, type of studies and follow-up

Case reports and studies not dealing with post-CABG TTFM were excluded. Only studies with a postoperative FU by an imaging modality, coronary angiography (CAG), multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI) were incorporated in this review. Studies released after the EACTS/ESC–Guidelines for Myocardial Revascularization in 2010–were the main focus of the present review.

RESULTS

Nine studies have been identified in the PubMed database, having had systematic postoperative imaging control (by one of the above-mentioned modalities), and have been analysed in detail for this review (Table 1).

Types of studies

One randomized study compared the intraoperative graft patency, using TTFM and indocyanine green angiography (IGA), with a control group, without direct graft flow detection [11]. In four studies, patient data were collected retrospectively and the remaining four were realized as prospective studies [3–10]. Two of the latter were also randomized, but focused on the impact of different per- or postoperative treatment strategies (surgical U-clip versus standard sutured proximal bi-mammary T anastomosis; postoperative Aspirin + Clopidogrel versus Aspirin medication alone), not on TTFM [8, 10]. A total of 2654 anastomoses have been analysed by TTFM and have had successful postoperative FU by either CAG or MDCT. In one study, an MRI was performed for a small minority of the patients [3].

Follow-up duration and completeness

FU varied from 1 week up to 1 year. Indicated FU completeness ranged from 67 to 100%. In all retrospective studies, patients have been selected from larger collectives [3–5, 7]. Only Walker *et al.* [7] indicated the total collective of surgical patients before selection, corresponding to a *de facto* FU completeness of 62%.

Types of grafts

Arterial grafts were the preferred object of TTFM [3, 5–8]. Singh, Lehnert, Gao and Jokinen included all types of grafts, i.e. also saphenous venous grafts [4, 9–11]. Gastroepiploic artery (GEA) to right coronary artery (RCA) bypass grafts were in the focus of the retrospective analysis of Uehara *et al.* [6].

Graft failure rate

Overall graft failure rate was close to 12%. The definition of graft failure was not uniform: while graft occlusions and string signs were common parameters and applied by the majority of the authors, the definition of significant graft stenosis varied between more than 50% and more than 75% stenosis. Incidence of graft failure rate varied from 4% to up to 20%. Different selection criteria, including only specific types of grafts and target vessel anastomoses, are one potential explication. The highest graft failure rate of 20% (defined as occlusion, string sign and more than 75% stenosis) was observed by Handa *et al.* [5] in 12 of 59 *in situ* left internal mammary artery (LIMA) to left anterior descending artery (LAD) grafts at the 1-year FU.

Transit time flow measurement parameters/ systemic arterial pressure

Five studies systematically analysed MGF, PI and DF at TTFM [3, 5–7, 11]. In the remaining four studies, peroperative graft flow was based on either MGF and PI, or MGF alone [4, 8–10]. Handa *et al.* [5] introduced the 'maximal graft flow acceleration (max df/dt)' and Jokinen *et al.* [9] the 'insufficiency ratio (IR–percentage of backward flow)' as new 'reliable' indicators to determine graft failure. Analogous to the latter, Honda *et al.* [3] mentioned the importance of the 'systolic reverse flow' which corresponds to the percentage of the flow curve area below the zero line (should not exceed 3% of the total flow curve area) and which may predict early graft failure. Three studies indicated systemic arterial pressure during TTFM [4, 6, 9].

Table 1: Overview of the studies in the main focus of the review

Ref	Study	A Type of study (selection criteria)	A No. of patients / anastomoses **(anastomoses in FU)**	B FU duration + modality **(completeness)**	C Types of graft analysed	D Definition of graft failure/**failure rate in % (no. of grafts)** at FU	E TTFM parameters	E MAP/SP (mmHg)	F Definition of **TTFM cut-off values**/ recommendations + conclusions	G Operative results/remarks/ postoperative clinical outcome (CO)
[3]	Honda (2015)	Retrospective (selected with preoperative FFR)	72/72 **(69)**	MDCT/MRI/CAG: within 1 year **(96%)**	LIMA to LAD	String sign: **16% (11)**	MGF/PI/DF/ systolic reverse flow	n/a	*Abnormal*: MGF **<20 ml/min**, PI **>3**, DF **<25%**, systolic reverse flow **>3%**	Graft failure **16%**: correlated with FFR; significant MGF↓, PI↑ and systolic reverse flow↑; string sign in 4.2, 21 and 50% in severe, mild and non-stenotic lesions, respectively *CO*: FU mortality **3%**
[4]	Lehnert (2015)	Retrospective (selected from two randomized trials)	345/982 **(982)**	1-year: CAG **(100%)**	SVG, IMA, RA	String sign, stenosis >50%: **12% (119)**	MGF	MAP 63.1 ± 7.6	*Acceptable*: IMA: **>20 ml/min**, SVG: **>40 ml/min** MGF ↑ if coronary diameter **>1.5 mm** TTFM identify mainly IMA failure	Graft failure **12%** (6% IMA; 17% SVG; 17% RA) *LIMA*: 4%↑ risk of failure for every 1 ml/min↓ (MGF) (similar tendency for SVG, no correlation for RA). Largest study! *Selection criteria*: Surgeon used to perform TTFM! *CO*: **n/a**
[5]	Handa (2014)	Retrospective (selected with TTFM for LIMA–LAD)	59/70 **(59)**	1 year: CAG/MSCT **(84%)**	LIMA to LAD	Occlusion, string sign, stenosis >75%: **20% (12)**	MGF/PI/DF/ maximal graft flow acceleration (max df/dt)	n/a	*Abnormal*: MGF **<15 ml/min**, PI **>5**, DF **<50%** TTFM not predictive for graft failure	Graft failure **20%** (12 patients): • 6 normal TTFM (17% of all normal TTFM) • 6 abnormal TTFM (50% of all graft failures) No graft revision in abnormal TTFM, occluded grafts excluded, highest graft failure rate for IMAs! CO: n/a
[6]	Uehara (2015)	Prospective [gastroepiploic artery (GEA) to right coronary artery (RCA)]	83/83 **(83)**	1 week; CAG **(100%)**	GEA to RCA	Fitzgibbon B, 0: **15% (11)** Occlusion, string sign: **6% (5)**/bidirectional flow **19% (16)**	MGF/PI/DF	MAP 70–90 SP 100–150	No threshold values (comparing means) TTFM not predictive for graft failure	Graft occlusion 6%: mean (MGF **7.8 ± 1.5 ml/min;** PI **6.5 ± 1.9**) Bidirectional flow 19%: mean (MGF 14.5 ml/min, PI 5.5) *Normal grafts*: mean (MGF 24.2 ml/min, PI 2.9) No statistical difference of means, but pathological TTFM values in occluded grafts! *CO*: n/a
[7]	Walker (2013)	Retrospective (LIMA–LAD robotic-assisted minimally invasive, selected with complete FU!)	160/160 **(160)**	Peroperative/day 1–2: CAG in 160 of 259 patients (**62%**; **100%**)	LIMA to LAD	Fitzgibbon B: 2% (3); Fitzgibbon 0: 3% (5) = **5% (8)**	MGF/PI/DF	n/a	*Abnormal*: MGF **<15 ml/min**, PI **>5**, DF **<50%** TTFM not predictive for graft failure	Graft failure **5%**: significant differences mean MGF (24 vs 34 ml/min, *P* = 0.033) patent versus patent grafts, no difference for PI or DF Selected patients with complete FU (160 of 259 = FU 62%) Only 1 patient with PI >5 had normal angiography *CO*: **n/a**

Continued

Table 1: Continued

Ref	Study	A Type of study (selection criteria)	A No. of patients / anastomoses **(anastomoses in FU)**	B FU duration + modality **(completeness)**	C Types of graft analysed	D Definition of graft failure/**failure rate in % (no. of grafts)** at FU	E TTFM parameters	E MAP/SP (mmHg)	F Definition of **TTFM cut-off values**/ recommendations + conclusions	G Operative results/remarks/ postoperative clinical outcome (CO)
[8]	Bigdeli (2011)	Prospective randomized: LIMA–LAD + RIMA (15 T-graft vs 15 U-clip): 2-seq. CX-anastomosis	30/90 **(90)**	2 weeks + 6 months: MDCT **(100%)**	IMA	Occlusion: **0%** (2 weeks); **2%** (4 anastomoses = **2** RIMA sequential at 6 months)	MGF	n/a	n/a TTFM no in the focus of the study	Graft occlusion **4%**: no difference for MGF in two selected groups (mean MGF 94 ± 44 vs 108 ± 8 ml/min), highest MGF measured at common T-graft with excellent 6-month outcome *CO*: No in hospital and FU mortality
[9]	Jokinen (2011)	Prospective (all)	75/204 **(195)**	119 ± 42 days (≈6 months): CAG **(97%)**	All (n/a)	Occlusion: **15% (29)** Stenosis >50%: **5%** (**7** only SVG) of all SVG	MGF/PI/ insufficiency ratio (backward flow in %)	SP 100–120	No threshold values TTFM not predictive for graft failure	Graft occlusion 15% (17% SVG, 5% LIMA, 33% RA: only 3 RA included) CK-MB predict occlusion (89 ± 95 vs 35 ± 48 µg/l) *CO*: early mortality **3%;** *FU*: cardiac survival **85%**; graft occlusion not predictive for mortality
[10]	Gao (2010)	Prospective randomized (125 Aspirin vs 124 Aspirin + Clopidogrel) at least one SVG	248/? **(704)**	3 months MDCT: **(90%)**	SVG (68%), LIMA (31%), RA (1%)	Occlusion/ string sign: **8.4% (58)**	MGF/PI	n/a	*Abnormal*: MGF **<10 ml/min**, PI **>5** MGF↑ + PI↓ correlated with SVG patency↑	*Graft occlusion*: SVG 6.5% Aspirin + Clopidogrel/10% Aspirin (anastomosis redone + patient excluded if TTFM abnormal, despite redo!) *CO*: all alive during FU; TTFM not predictive for MACE (not precised!)
[11]	Singh (2010)	Prospective randomized (GRIIP trial): 78 TTFM + Indocyanine vs 78 control	156/? **(312)**	MDCT/CAG 12.1 ± 10.5/ 13.3 ± 9.8 months: **(71/69%)**	SVG **(49 + 53%)** IMA + RA **(47 + 51%)**	Occlusion: **13.8% (43)** Stenosis >50%: **3.8%** **(12)**	MGF/PI/DF	n/a	*Abnormal*: MGF **<10 ml/min**, PI **>5**, DF **<50%** TTFM (+indocyanine angio) not predictive for graft failure	Graft occlusion **13.8%**: (imaging: 30% SVG, 0 IMAs + RA/control: 21% SVG, 2.8% IMAs + RA) *CO*: MACE of 7.7% in imaging + control group; TTFM not predictive for MACE
[12]	*Une (2013)*	Retrospective 65 SVG from GRIIP trial	*44 (65)*		SVG	Occlusion 32% + stenosis 1.5% (SVG)			MGF <31 ml/min (in 50% of occluded SVG)	*CO*: non-elective surgery but not TTFM predictive for MACEs
	Total (no.)/ range		1230/>2677 **(2654)**	(**62%**) **69–100%**		Overall graft failure rate: **11.8% (314)**			Study [3, 4, 5, 7, 9] found no correlation between TTFM and graft failure rate	

FFR: fractional flow reserve; LIMA: left internal mammary artery; LAD: left anterior descending artery; RIMA: right internal mammary artery; CX: circumflex artery; SVG: saphenous vein graft; TTFM: transit time flow measurement; CABG: coronary artery bypass graft; MDCT: multidetector computed tomography; MRI: magnetic resonance imaging; CAG: coronary angiography; RA: radial artery; IMA: internal mammary arteries; MGF: mean graft flow; PI: pulsatility index; DF: diastolic flow fraction; MAP: mean arterial pressure; SP: systolic pressure; Ref: reference; GEA: gastroepiploic artery; RCA: right coronary artery; MACEs: major cardiac adverse events.

Transit time flow measurement parameters and cut-off threshold values

EACTS/ESC Guidelines recommend an MGF of ≥20 ml/min and a PI of ≤5 as acceptable peroperative results for TTFM. Some authors accepted lower threshold values, with an MGF of <15 ml/min and <10 ml/min, respectively, before labelling TTFM 'abnormal' [5, 7, 10, 11]. Four studies found that TTFM does not predict graft failure; of these, one obtained definite pathological TTFM values (MGF: 7.8 ± 1.5 ml/min; PI: 6.5 ± 1.9) for a subgroup analysis of occluded grafts at FU [5–7, 11]. A direct correlation between FU outcome and initial MGF could be proved in one study, with consecutively proposed cut-off values for acceptable flow rates of an MGF of ≥20 ml/min for LIMA grafts and an MGF of ≥40 ml/min for saphenous venous grafts (SVGs) [4]. The attribution of an increased PI and reduced graft patency rate at FU was found in another study; however, the only significant predictor for early graft occlusion was a high CK-MB release within 24 h after surgery [9]. A PI of <5, if analysed, was predominantly accepted by the authors, albeit excluding one study with a recommended PI of <3 [6]. An explicit correlation between severity of LAD stenosis and MGF, PI and systolic flow reverse was found by another group [3]. DF does not predict graft failure; however if indicated, generally a DF of >50% was valued as acceptable in all but one study with a recommended DF of at least 25% [3, 5–7, 11]. Two studies found a correlation of an increased backward flow through the grafts and a worse outcome at FU. A 'systolic reverse flow' of ≥3% and an increased 'IR' were proposed parameters to detect graft failure [3, 9].

Postoperative clinical outcomes

In four studies, the reader did not get any information concerning the clinical postoperative results: early, late mortality, morbidity or major cardiac adverse events (MACEs) [4–7]. A FU mortality rate of 3% has been observed in two studies [3, 9]. Jokinen *et al*. [9] stated further that occluded grafts did not predict long-term survival. Bigdeli *et al*. [8] precised that all included patients survived during FU.

Only the GRIIP trail mentioned, with an incidence of 7.7%, the rate of MACE (death, myocardial infarction and repeat revascularization), which was identical for the imaging (TTFM + IGA) and the control group [11]. The authors concluded accordingly that a systematic graft control did not lead to a significant reduction in MACE at 1-year FU [11]. Une *et al*. [12] found, in their retrospective subgroup analysis of venous grafts from the GRIIP trial, that only the non-elective surgery but not TTFM results was significantly associated with MACE.

DISCUSSION

Previous literature and general considerations

In 2010, the task force on myocardial revascularization of the EACTS/ESC mentioned the '... graft flow measurement, related to graft type, vessel size, degree of stenosis, quality of anastomosis, and outflow area ... at the end of surgery ...' as a class I recommendation (level of evidence C) [1]. An MGF of <20 ml/min and a PI of >5 may indicate 'technically inadequate grafts' [1]. None of the present studies confirmed or included precisely both cut-off values (Table 1). On the contrary, some authors concluded that TTFM is not reliable and does not predict graft failure [5–7, 9, 11].

According to a review from 2007 (including seven studies with more than 100 patients having had intraoperative TTFM), 3.2% of a total of 1411 grafts (8.8% of all CABG patients) had been directly revised intraoperatively based on abnormal TTFM [2]. Graft patency rate and FU modalities have not been indicated and thresholds for MGF, PI and DF have not been defined [2].

In this review, authors tend to precise reference values for TTFM after CABG surgery and their impact on postoperative outcome in terms of graft patency rate.

Randomized trial

The only randomized study (GRIIP trial), comparing TTFM with a non peroperative imaging control group, could not prove any benefit concerning graft patency rate [11]. FU completeness was, with 71% and 73%, respectively, poor for both groups [11]. A high percentage of venous bypasses (~50%) and late graft occlusion that occurred nearly exclusively in these venous grafts may limit general conclusions (early versus late graft failure in IMA versus SVG) [11].

Mean graft flow of internal mammary arteries

Lehnert *et al*. [4], including 354 patients, found a graft failure rate of 6.5% for single IMA at 1-year FU by CAG. MGF was directly correlated with the FU outcome, with an observed 4% decreased risk of graft failure for every 1 ml/min increase in MGF, and the following threshold was defined: MGF should at least achieve 20 ml/min for IMA grafts, confirming current recommendations [4].

A correlation between TTFM and the degree of coronary stenosis, focusing on LIMA and RIMA to LAD bypasses, was found by Honda *et al*. [3]. Severe (fractional flow reserve, FFR <0.70), mild (0.70 ≤ FFR < 0.75) and non-stenotic lesions (FFR ≥0.75) referred directly to TTFM [3]. Corresponding mean MGF rates of 24.7 ± 10.6, 19.2 ± 14 and 16 ± 9.7 ml/min indicated better bypass flow in cases of more severe LAD stenosis [3]. A cut-off of 20 ml/min for IMA grafts seems to be plausible: string signs were observed in 4.2, 21 and 50%, in cases of severe, mild and non-stenotic lesions, respectively [3].

Walker *et al*. [7] found a significant difference in the mean MGF between patent and non-patent LIMA–LAD grafts.

Bigdeli *et al*. [8] did not indicate distal graft flow rates, but the mean MGF of 93.7 ± 44.0 and 108.1 ± 68.4 ml/min, respectively, at the level of the common T graft (free RIMA on LIMA), may underline, with a graft failure of 2% at 6 months, the good results in both groups.

Six LIMA–LAD grafts with peroperative reduced MGF of <15 ml/min (50% of all abnormal TTFM) were found to be non-patent at FU by Handa *et al*. [5].

According to these results, one may conclude that in the majority of the reviewed studies, a direct correlation between MGF and IMA graft could be observed: an acceptable threshold value for MGF of IMA grafts should be close to 20 ml/min.

Pulsatility index of internal mammary artery

Increasing mean PIs of 2.4 ± 0.6 and 3 ± 1.1, in severe (FFR <0.70) and mild (0.70 ≤ FFR < 0.75) coronary lesions, and pathological PI values (5.5 ± 8.2) in non-stenotic lesions (FFR ≥0.75) were associated with increased graft failure rates at FU, due to the increased

competitive native coronary blood flow [3]. Walker *et al*. [7] could not find any significant differences for patent and non-patent grafts (contrary to MGF values), but according to their observations the PI has probably the best predictive value to exclude false-positive results: only 1 patient with a PI of >5 had a normal angiography.

Mean graft flow and pulsatility index of saphenous venous grafts

Lehnert *et al*. [4] observed a 16.9% graft failure rate for single venous grafts. Increased MGF was significantly associated with a better outcome (a 2% decreased risk of graft failure for every 1 ml/min increase in MGF) and an MGF of at least 40 ml/min was recommended for SVG [4].

The second largest study (248 patients with 68% SVG), focusing on postoperative treatment by Aspirin versus Aspirin and Clopidogrel, revealed a graft failure rate of 8.4% [10]. Predictors for SVG patency were, next to a double anti-platelet therapy, a higher MGF and a lower PI [10].

Une *et al*. [12] realized a retrospective subgroup analysis of 65 SVGs from the GRIIP trial: an MGF of <31 ml/min was associated with 50% late SVG occlusion.

According to this, acceptable MGF for SVG should probably be higher than for IMA grafts (at least 30–40 ml/min).

Mean graft flow and pulsatility index of other arterial conduits (radial artery and gastroepiploic artery)

No statistical differences in mean TTFM values in occluded versus patent GEA to RCA grafts have been found by Uehara *et al*. [6]. Contrary to IMA grafts and SVGs, Lehnert *et al*. did not find any correlation between TTFM and RA failure, but general conclusions are limited due to the small number of RAs included [4, 10, 11].

Diastolic flow fraction, systolic reverse flow, CK-MB release and target vessel diameter

The DF is rarely indicated, but may be useful. Pagni *et al*. [13] could prove in an experimental animal model that competitive blood flow will have a greater impact (i.e. a decreased blood flow rate) on IMA than on SVG, which is particularly evident during diastole. The systolic reverse flow may allow to identify an 'oscillatory flow' through the graft [3, 14].

The only relevant predictor of graft occlusion, found by Jokinen *et al*., was a higher CK-MB release within 24 h after surgery (89 vs 35 μg/l), a well-established predictive parameter, not applied by any other group [9, 15]. The impact of the target vessel diameter, a parameter found to be next to the graft perfusion area (i.e. the extension of the LAD, circumflex artery and RCA territories) significantly associated with the bypass flow, was analysed by Lehnert *et al*. [4, 16]. The correlation between smaller coronary arteries (diameter <1.5 mm), a generally reduced MGF and a higher risk for vein graft failure, leads to the recommendation for an MGF of ≥40 ml/min for SVG [4].

Limitations of transit time flow measurement

A randomized trial reported a low sensitivity of 25% and a specificity of 98% to detect a greater than 50% graft stenosis or occlusion by TTFM (cut-off values: MGF >10 ml/min, PI <5 and DF >50%) [17]. Nine of 139 grafts had normal TTFM although they had a pathological angiogram and CAG revealed, among others, a one-sided target coronary artery stenosis in LIMA to LAD grafts [17]. Walker *et al*. [7] stated accordingly that normal TTFM values were observed in cases of distal anastomotic occlusion with pathological antegrade, but preserved retrograde coronary flow. TTFM may be therefore normal in cases of correct graft outflow and reflects one major limitation of the technique: it will be impossible to detect a proximal or distal coronary stenosis or a one-sided flow restriction due to a partially failed anastomosis in cases of unrestricted flow.

The highest incidence of string signs (50%) for isolated IMA–LAD grafts was observed in patients without significant coronary stenosis [3]. Nonetheless, MGF may be also normal in non-stenotic coronary lesions with increased collateral flow (mean 16.0 ± 9.7 ml/min; range 1.0–35.0 ml/min) [3]. The PI and systolic reverse flow may help to identify 'oscillatory blood flow' in these cases [3].

Early versus late graft failure in internal mammary artery versus saphenous venous grafts

Varying outcome and threshold values may result from diverse definitions of graft stenosis (50 or 75% occlusion of the cross-sectional area). Guidelines mention that the '... Early graft failure ... (is) evaluated by intra-operative angiographic control ...', but a common definition for critical graft stenosis remains obscure [18].

Progressive stenosis after 1 year may be an ongoing process, principally affecting venous grafts, and due to the factors other than surgical skills. Halabi *et al*. [19] proposed the classification in no (<25%), non-critical (25–74%), critical (75–99%) or occlusive (100%) disease for SVG. Ongoing arteriosclerosis or intimae fibrosis of the arterialized low pressure venous conduits may be the main mechanisms [9, 20]. The GRIIP trial underlines the problematic application of TTFM for predicting late venous graft failure [11, 12]. A late graft occlusion rate of 30% of almost exclusively venous grafts could be predicted neither by initial TTFM nor by IGA [11]. The authors admitted that the: '... results also indicate that 1-year graft failure was likely to fibrointimal hyperplasia as opposed early technical errors ...' [11]. According to this, the correlation between TTFM and late graft failure remains questionable, in particular when predominantly venous and initially patent grafts (fully patent grafts at 10-week CAG have been selected for a long-term FU by Tokuda *et al*. [21]) were re-examined by a late CAG.

In contrast, TTFM may help in identifying grafts at risk during the early postoperative period [22]. Early graft failure may occur as a consequence of reduced initial graft blood flow (anastomotic narrowing, lesions of the conduit, competitive flow, insufficient distal run-off due to a reduced target vessel diameter and perfusion area) [22]. IMAs remain, in general, free of arteriosclerosis and failure will be due to early 'technical' problems. Nakajima *et al*. evaluated the patency of arteries and classified: antegrade (A), competitive (B), reversed (C) blood graft flow or occlusion (O), to describe 2-week and long-term CAG, similar to the Fitzgibbon classification, applied by some authors [3, 8–10, 23, 24]. Seventy-five percent of the grafts with competitive flow at initial CAG were occluded after 56 ± 31 months [23].

Limitations of the included studies

A graft failure rate of up to 20% for the surgical 'gold standard' isolated LIMA–LAD bypass, as observed by Handa *et al*. [5], may raise the question of technical limitations. Interestingly, the authors (concluding that TTFM does not predict graft failure) defined cut-off values (MGF >15 ml/min, PI <5 and DF <50%), but no graft revision was realized in cases of 'abnormal' results [5]. Six grafts with pathological TTFM (50% of all abnormal TTFM) were found to be non-patent at FU [5].

Similar to this, explicit 'abnormal' TTFM parameters (mean MGF: 7.8 ± 1.5 ml/min; mean PI: 6.5 ± 2.3) were found in 6% occluded grafts, borderline values (MGF 14.5 ± 2.3 ml/min; PI 5.5 ± 1.9) in 19% of grafts, presenting a bidirectional flow, contrary to 75% of patent GEA to RCA grafts (MGF 24.2 ± 2.3 ml/min, PI 2.9 ± 0.4) [6]. Uehara *et al*. [6] concluded that no correlation between graft patency and TTFM exists, due to a missing significant statistical difference of mean and given examples of normal values in all three groups. The solely comparison of means of definite threshold values appears methodically questionable.

Highly selective patient populations and biased inclusion criteria ('... TTFM was performed ... where the surgeons operating method included TTFM ...') limit the interpretation of the results [4, 6]. A mean overall graft failure of ∼12% seems to be acceptable and in congruence with the available literature, but FU criteria are not clear for the retrospective studies [3, 4, 7].

The complexity to define cut-off values in TTFM may arise from the dynamic flow properties of the heart. Jokinen *et al*. stated that: '... accuracy of TTFM is high under good hemodynamic and graft flow conditions, but may be biased when hemodynamic is poor and blood flow low ...' analogous to previous publications [2, 9, 25, 26]. Distal run-off and bypass flow resistance may be, in addition to quantity, determined by the quality of the myocardium and flow towards scarred myocardium may be reduced [27]. Localization of TTFM probe application and an individual graft flow curve analysis for different types of grafts should be discussed. While different compliances between arterial and venous grafts (a pressure drop along LIMA grafts of 2.9 ± 2.2 mmHg versus SVG of 0.4 ± 0.7 mmHg was found by Glineur *et al*.) will be probably negligible, patent venous valves in SVG may wrongly eliminate competitive backwards flow [28, 29]. Therefore, TTFM should be realized close to the distal anastomosis of SVG.

Transit time flow measurement and clinical impact

Only the GRIIP trial investigators indicate 7.7% MACE, occurring in both the imaging and the control group, and concluded accordingly that peroperative graft control did not lead to a significant reduction in MACE [11]. However, general conclusions are limited, due to the few, currently available data, and, as aforementioned, the high percentage of included venous grafts (s. early versus late graft failure in IMA versus SVG) [11].

Own, practical experience of transit time flow measurement during off-pump CABG surgery

(i) Flow characteristics may change over time: observed in venous bypass grafts during repetitive early TTFM (probably due to air embolism).

(ii) MGF may increase, PI decrease with increased blood pressure: observed in IMA to left coronary arteries, in cases of less severe proximal coronary stenosis.

(iii) Competitive flow may be observed between side grafts or venous versus arterial grafts bypassing similar coronary territories. Flow may be initially correct or may alternate between the conduits and may wrongly indicate low TTFM values for one territory.

To resume, the following aspects should be pointed out

(i) Current guidelines recommend TTFM for direct intraoperative quality control in CABG surgery (class I recommendation, level of evidence C).

(ii) An MGF of <20 ml/min and a PI of >5 are proposed threshold values indicating technically inadequate grafts (EACTS/ESC guidelines 2010). DF should probably exceed 50% and will be more important for the coronary blood supply of the left ventricle.

(iii) One randomized trial, comparing TTFM with other quality control modalities, could prove a high specificity, but low sensitivity thus indicating one major limitation of the technique.

(iv) An MGF of ≥20 ml/min for IMAs grafts and an MGF of ≥30–40 ml/min for venous grafts were associated with an improved long-term outcome.

(v) PI >5 seems to have a predictive value to exclude false-positives and may help to detect competitive flow in IMA grafts.

(vi) In IMA to LAD grafts, more severe proximal LAD stenoses (indicating the FFR) were associated with an improved graft flow and better FU results, contrary to non-significant LAD lesions (graft failure up to 50%).

(vii) Normal TTFM reflects a normal graft (out-) flow, but no visualization of the anastomosis. One-sided outflow restriction may be undetectable without cardiac stress testing (systemic pressure should be monitored).

(viii) TTFM alone may be insufficient to detect graft failure and other parameters should be indicated. Several studies could not prove any statistical differences, comparing TTFM of patent and non-patent grafts; however, methodical limitations in their majority were evident.

(ix) SVGs should be measured close to the distal anastomosis to detect competitive flow (patent valves).

(x) Quantity (vessel territory distribution) and quality (myocardial scar) of the graft perfusion area, as well as the target vessel diameter, may have an impact and should be part of future analyses.

(xi) A detailed direct flow curve analysis including the percentage of the systolic reverse flow should be part of TTFM.

(xii) TTFM is probably not the tool of choice to detect progressive late graft failure of SVG. Different pathological entities during FU (early versus late graft failure, graft occlusions and string signs versus progressive stenosis) of different conduits (IMA and RA versus SVG) should be separately correlated with TTFM, using a uniform definition for graft failure.

(xiii) Future studies should systematically include a clinical FU, indicating MACE, to obtain (predictive?) values for TTFM.

Magnetic resonance imaging control/future studies

A systematic, repetitive FU may be possible by MRI, quantifying bypass flow at mid- and long term and comparing it with TTFM [30]. The main advantage (next to reduced invasiveness and no

exposure to X-rays) will be the option to obtain supplementary information of the myocardial perfusion. Blood flow behaviour, after performing CABG to ischaemic or scarred myocardial territories, can be analysed over time.

Further larger studies should be randomized, comparing TTFM with other or none peroperative control methods, analysing the outcome by respecting the above-mentioned criteria.

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