Intraoperative transit time flow measurements during off-pump coronary artery bypass surgery: The impact of coronary stenosis on competitive flow

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Abstract

Background: Combining preoperative angiography findings with intraoperative transit time flow measurements (TTFM) may improve patency of coronary artery bypass grafts. Nevertheless, graft flow might be impaired by native coronary flow based on the severity of stenoses, with inferior long-term outcomes. This study investigates the impact of left anterior descending artery (LAD) stenosis on competitive flow measured in left internal mammary artery (LIMA) grafts during off-pump coronary artery bypass grafting.

Methods: Fifty patients were included in this prospective single-center cohort study. LAD stenosis was assessed with quantitative coronary analysis (QCA) and stratified into three groups based on its severity. TTFM of LIMA grafts were performed with LAD open and temporarily occluded. Change in mean graft flow after LAD snaring was the primary endpoint. Secondary endpoints included further TTFM parameters, clinical outcomes, and competitive flow index (CFI), defined as the ratio of mean graft flow with open or closed LAD.

Results: Mean LAD stenosis as objectified with QCA was 58 ± 15%. Mean LIMA graft flow increased from 20 ml/min with open LAD to 30 ml/min with snared LAD (p < .001). TTFM cut-off values for graft patency improved in 26%–42% of patients after LAD occlusion. Median CFI was 0.66 (IQR: 0.56–0.82). Postoperative myocardial infarction occurred in 2.0% of patients, 120-day mortality was 0%, and 2-year mortality was 6.0%.

Conclusions: Routine snaring of the LAD with CFI calculation during coronary artery bypass grafting is useful to detect significant competitive flow in LIMA grafts, potentially preventing unnecessary intraoperative graft revisions.

KEYWORDS
arterial grafts, CABG, coronary artery disease, minimally invasive surgery, off-pump coronary artery bypass grafting

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1 | INTRODUCTION

Myocardial revascularisation by percutaneous coronary intervention or coronary artery bypass graft (CABG) is an effective strategy to improve symptoms, quality of life, and survival in patients suffering from severe coronary stenosis. Indication for revascularisation is mainly based on visual quantification of the stenosis performed by an interventional cardiologist. Notwithstanding, this method is affected by a high intra and interobserver variability with low concordance on clinical relevant cut-off points.

Quantitative coronary analysis (QCA) using cardiac angiography has been applied for anatomical evaluation of coronary stenoses but its predictive value in terms of graft patency is yet not comparable to functional assessment methods such as the more invasive fractional flow reserve (FFR) measurement. Consequently, the degree of coronary stenosis can be misjudged impacting short- and long-term outcomes of coronary artery bypass grafts. This is particularly true for arterial grafts. On one side, arterial grafts demonstrated excellent long-term disease-free survival, low myocardial revascularisation rates, and high graft patency. On the other side, they require proper handling to avoid early technical failure and their patency can be significantly affected by the presence of competitive flow from native coronaries. Therefore, early detection of competitive flow on arterial grafts might be relevant to predict their long-term patency.

Competitive flow is defined as bypass graft flow impaired by native coronary flow, or as bypass graft flow that progressively lessens as proximal coronary artery stenosis decreases. In detail, competitive flow occurs when the resistance of the graft matches or exceeds native coronary artery resistance and is related to the degree of proximal stenosis. Thus far, the impact of stenosis and competitive flow on arterial grafts was observed only in animal studies. Small canine and porcine studies showed a decrease in left internal mammary artery (LIMA) flow in patent coronary arteries. Furthermore, a human study investigating the use of LIMA grafting in moderately stenotic coronary arteries showed similar results.

1.1 | Intraoperative flow measurements

Intraoperative evaluation of competitive flow can be performed through transit time flow measurements (TTFM). Studies showed that TTFM detects intraoperative graft occlusion in up to 5%-11% of cases and improves short-to-middle term outcomes in both on-pump and off-pump CABG (OPCAB). Moreover, the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularisation recommend the routine use of intraoperative graft flow assessment through TTFM. Nevertheless, clinical relevant TTFM cut-off values for graft failure vary between studies and are still debated.

Combining preoperative angiography findings with intraoperative TTFM may significantly impact graft patency. This becomes particularly important for grafts such as the LIMA to left anterior descending coronary (LAD), which has the highest influence on clinical outcomes. This study investigates the impact of coronary stenosis on competitive flow in LIMA to LAD bypass grafts during OPCAB surgery with the hypothesis that competitive flow increases with a lower degree of LAD stenosis.

2 | METHODS

2.1 | Study design and setting

This is a prospective single-center cohort study, reported as per the STROBE recommendations for observational research. Adult patients undergoing OPCAB with LIMA to LAD anastomosis for coronary artery disease between September 2016 and January 2017, and after interim analysis also from June to August 2017 were recruited at Medisch Spectrum Twente (Enschede, The Netherlands).

Patients with previous CABG, chronic total occlusion of the LAD, and patients requiring emergency surgery were excluded. The number of OPCAB surgeries during the study period determined the study size. Follow-up data were retrieved from the Netherlands Heart Registry. Follow-up regarding revascularization and myocardial infarction ended on December 31, 2020. Follow-up on mortality ended on February 1, 2021, as part of routine follow-up to prevent information bias. Patient records from referring hospitals were retrieved to complete routine follow-up. This study was exempted from the Medical Research Involving Human Subjects Act by the Medical Ethics Committee Twente (METC Twente: K16–63) and approved on August 11, 2016, by the local institutional review board. Written informed consent was obtained from study participants.

2.2 | Coronary stenosis evaluation and surgical procedure

Indication to surgical myocardial revascularisation was based on heart team consensus after evaluation of clinical data, visual quantification (eyeballing) of coronary stenosis, or FFR, according to guidelines. Preoperative LAD stenosis was quantified with QCA using QAngio XA (Medis) software for research purposes after surgery. The choice of best angiographic recording was based on image-plane, background contrast, and LAD runoff. LAD stenosis as defined by QCA was stratified into three groups: <50%, 50%–70%, and >70%.

All surgical procedures were performed by three experienced OPCAB surgeons. LIMA was harvested as pedicle. For flow measurements, 1–2 cm of distal LIMA was skeletonized. After harvesting, LIMA was injected with 1 mg/ml papaverine diluted in 50 ml saline solution to prevent spasm. Graft composition, that is, single, sequential, and/or composite graft, was at the surgeon’s discretion. A dedicated OPCAB stabilizer (ACROBAT SUV Vacuum, Maquet) was used for constructing the anastomosis.
After completion of the LIMA to LAD graft, the stabilizer was removed, and TTFM were performed with a VeriQ C (MediStim) system. The LAD was temporarily closed by placing a metal bulldog proximally to the anastomosis and remained closed until stable MAP and mean graft flow (MGF) in the LIMA graft were achieved. TTFM of LIMA flow with closed LAD were recorded and the bulldog clamp was removed. After stabilization of the flow, a new measurement was performed with proximal LAD open. For Y-graft configurations with a radial artery, the proximal radial Y-branch was temporarily occluded before flow measurements. Revision of the anastomosis was based on abnormal TTFM findings regarding flow profile. Only measurements with an acoustic coupling index (ACI) over 50% were included. If despite efforts contact could not be improved by skeletonizing the LIMA or increasing the amount of ultrasound gel, a suboptimal contact (ACI: 30%–50%) was accepted. TTFM were matched with electrocardiography to distinguish systolic from diastolic flow.

### 2.3 Primary and secondary endpoints

Primary endpoint of this study was the change in mean LIMA graft flow (ml/min) measured with open and closed LAD. Secondary TTFM endpoints were pulsatility index (PI), backflow (BF), diastolic filling (DF), peak systolic flow, and peak diastolic flow. A full description of these TTFM parameters can be found in previous publications. Secondary clinical endpoints included postoperative cardiac enzymes, early mortality after cardiac surgery which continues up to 120 days, as well as 2-year mortality, myocardial infarction, and need for revascularization according to Netherlands Heart Registry definitions.

A new parameter named competitive flow index (CFI) was developed to quantify competitive flow and it was defined as follows:

$$\text{Competitive flow index} = 1 - \frac{\text{MGF}_\text{LIMA Open}}{\text{MGF}_\text{LIMA Closed}}$$

where $\text{MGF}_\text{LIMA Open}$ is mean LIMA graft flow with LAD open (ml/min) and $\text{MGF}_\text{LIMA Closed}$ is mean LIMA graft flow with LAD snared. A CFI of 1 indicates high competitive flow and a CFI of 0 indicates the absence of competitive flow.

### 2.4 Statistical analysis

Continuous variables were tested for normality with visual inspection of histograms and skewness/kurtosis measures. A $p$ value of less than .05 was set as statistically significant.

Patients were analyzed by intention-to-treat. Primary and secondary endpoints were converted into clinically relevant dichotomous values and analyzed with a $\chi^2$ test or Fischer’s exact test when less than five events occurred.

Dichotomous cut-off values for graft patency were determined as MGF > 20 ml/min, PI < 3, BF > 3%, and DF > 50%. A strict composite endpoint cut-off for graft patency of MGF > 15 ml/min and PI < 3 as proposed by previous studies was also applied.

Variables were analyzed with a paired t test or Wilcoxon signed-rank test for comparison within individual patients. A Kruskal–Wallis test was used for group analysis based on QCA. A post hoc analysis with Holm–Bonferroni correction was performed. A linear mixed model was used to determine differences in TTFM parameters between open and closed LAD and between QCA groups. Survival was examined by a Kaplan–Meier curve. Follow-up was protocolized as standard care and missing data or loss to follow-up were thus not expected.

Indication for revascularization was sometimes based on a significant LM stenosis in the absence of significant LAD stenosis. A sensitivity analysis with and without LM stenosis was, therefore, performed. Sequential grafts might impact graft flow, and a sensitivity analysis excluding LIMA sequential grafts was performed to evaluate the impact of coronary territories extension on grafts runoff and competitive flow.

Results are reported as mean ± SD or median with interquartile range (IQR). Frequencies are reported as n (%). Whiskers show the 25th and 75th percentile ± 1.5 times IQR in the Tukey box-and-Whiskers plot.

### 3 RESULTS

#### 3.1 Baseline characteristics and quantitative coronary analysis

A total of 50 patients were included in this study and received a LIMA to LAD graft. All patients completed the 2-year follow-up analysis on mortality. Baseline characteristics of this study are given in Table 1. Mean age was 68 ± 9.1 years, 96% of patients were men, and mean body mass index (BMI) was 28 ± 4.6 kg/m² with 98% of cases diagnosed with multivessel disease.
All patients had significant LAD disease as determined by heart team discussion with eyeballing, FFR, or LM equivalent stenosis. Mean LAD stenosis objectified with QCA was 58 ± 15%. Detailed lesion characteristics are shown in Table S1.

LAD stenosis was stratified by QCA into three groups as follows: <50% stenosis (n = 14, 28%), 50%–70% stenosis (n = 22, 44%), >70% stenosis (n = 14, 28%). Patients with <50% LAD stenosis had a significant LM stenosis (9/14, 64%), or significant FFR under 0.80 (5/14, 36%).

Thirteen patients (26%) received a sequential graft on the diagonal branch (LIMA-D-LAD) with mean LAD-D stenosis of 55% ± 16%.

Intraoperative MGF and other TTFM parameters of LIMA to LAD graft with native LAD open or temporarily snared are displayed in Figure 2 and Table 2. Technical complications of LAD snaring were not observed. No significant variations in mean arterial pressure and heart rate were recorded during TTFM. All flow profiles had a diastolic flow waveform. Overall, MGF increased significantly from 20 (14–30) ml/min with open LAD to 30 (22–41) ml/min with snared LAD (Figures 3A,B, p < .001). In 26 patients (52%), MGF was under 20 ml/min with LAD open and increased in 16 patients over 20 ml/min after snaring the LAD. Normal flow profiles in the other patients were observed and no revisions were performed.

All other parameters, except for DF, showed a significant change in absolute values (p < .001, peak systolic flow p = .005) with LAD snared. After LAD occlusion, improved clinical cut-off values for MGF ≤ 15 and PI ≥ 3 were observed in 26% and 42% of patients. Three patients with LAD open and a PI over 5 shifted to a PI under 5 with LAD snared.

### 3.3 Stratification of TTFM parameters on severity of LAD stenosis

All LAD stenosis groups showed significantly higher values of LIMA MGF measured with snared LAD (Figure 3). No differences in LIMA MGF were noticed among QCA groups in the overall population (Figure 3A; p = .18) nor in the analysis performed after exclusion of patients diagnosed with an LM stenosis (Figure 3B; p = .52). Similar results were found for other TTFM parameters except for PI, where a significant difference between QCA groups was noticed (p = .04).

Results from linear mixed model analysis for all measurements and without LM stenosis are depicted in Table T2 and were consistent with sensitivity analyses without sequential grafts.
Only peak systolic flow in nonsequential grafts showed no difference between LAD open and closed ($p = .16$).

A post hoc analysis demonstrated only a significant pairwise comparison for PI between the 50% and 70% stenosis group and >70% stenosis ($p = .01$).

### 3.4 CFI and absolute difference in MGF

Median CFI as ratio of LIMA MGF with LAD open and snared was 0.33 (0.18–0.44). Although theoretically not possible, five patients had a CFI below 0. These patients had an MGF over 20 ml/min and a slightly higher MGF in the open LAD compared to closed LAD (mean difference: 2.6 ml/min). A significant difference in CFI was observed among QCA groups ($p = .03$) and patients without LM stenosis (Figure 4A; $p = .02$). Post hoc analysis showed a significant difference in CFI between <50% and >70% stenosis (overall: $p = .04$; without LM stenosis $p = .03$).

Absolute change in LIMA MGF between open and snared LAD was 11 (4.8–14) ml/min in the <50% stenosis group, 11 (8.8–16) ml/min in the 50%–70% group, and 4.5 (2–15) ml/min in the >70% group. There was no difference between stenosis groups (Figure 4B; $p = .19$) in the analysis including the overall population, but only in the subgroup analysis after exclusion of patients with LM stenosis ($p = .03$). Here, post hoc analysis showed a significant difference between 50% and 70% versus >70% stenosis groups ($p = .04$).

### 3.5 Clinical outcomes

Median follow-up was 1486 days. Incidence of postoperative myocardial infarction during follow-up was 2%, 120 days mortality was 0% and 2-year mortality was 6.0% (Table 3 and Kaplan–Meier survival curve in Figure S2).

Five patients died during follow-up. Two patients died of cerebrovascular embolism related to atrial fibrillation, one died of progression of multiple myeloma and two died of progressive heart failure. One patient received drug eluting stent implantation in the LM to circumflex artery due to incomplete revascularization of the marginal obtuse artery two years after OPCAB with an open LIMA to LAD graft.

One postoperative myocardial infarction occurred 36 days after OPCAB in an 83-year-old patient with recent myocardial infarction and previous percutaneous coronary intervention. The patient was accepted for OPCAB with three-vessel disease with LAD stenosis of 34% (QCA) and moderate LM stenosis (visual evaluation 40%). LIMA MGF with open LAD was 9 ml/min and 20 ml/min with snared LAD.

The intraoperative competitive flow was accepted based on other acceptable TTFM values with LAD snared and mild coronary stenosis (Table S4 and Figure S3).

### 4 DISCUSSION

This is the first study to investigate the impact of LAD stenosis on competitive flow measured in LIMA grafts during OPCAB. Mean LIMA graft flow increased by 11 ml/min after LAD snaring, in case of proximal stenosis quantified as <50% or 50%–70%. In patients with a >70% proximal stenosis, mean LIMA graft flow increased by 4.5 ml/min after LAD occlusion. A lower mean LIMA flow in sequential grafts was observed compared to single grafts because of LAD-D runoff. This phenomenon was present for both LAD open and snared and did not affect TTFM interpretations. LAD snaring is a common technique to obtain a bloodless field and is well tolerated, and comparable to shunting regarding postoperative cardiac enzyme rise. Atherosclerotic plaques or calcified coronary arteries might prove technical difficulties. Animal studies showed intimal injury with
In the present study, as the LAD was already snared for opening and closing of the LAD. These experiences are minimised without alternating snaring. Intra-operative competitive flow during follow-up, based on coronary angiography. These data are in line or even lower compared to those reported in the Netherlands Heart Registry or in other TTFM studies presenting a one-year myocardial infarction rate of 5.1%.

| TABLE 2 | Perioperative measurements of graft flow in closed versus snared LAD (n = 50) |
|---------|---------------------------------|----------------|-----------------|----------------------------|
|          | LAD, open | LAD, snared | p value          |
| Heart rate, beats per minute | 63 (56–78) | 63 (56–72) | .19 |
| Systolic blood pressure, mmHg | 101 (90–107) | 101 (93–108) | .26 |
| Diastolic blood pressure, mmHg | 51 ± 7.6 | 51 ± 7.9 | .75 |
| Mean arterial pressure, mmHg | 66 ± 8.5 | 66 ± 8.6 | .78 |
| Acoustic coupling index, % | 55 ± 16 | 54 ± 16 | .69 |

**TTFM** parameters and clinical cut-off values

| Mean graft flow, ml/min | 20 (14–30) | 30 (22–41) | <.001 |
| Mean graft flow, ≤20 ml/min | 26 (52) | 10 (20) | <.001 |
| Mean graft flow, ≤15 ml/min | 17 (34) | 4 (8) | .01 |
| Pulsatile index | 3 (2.2–4.0) | 2.1 (1.7–2.5) | <.001 |
| Pulsatile index, ≥3, n (%) | 26 (52) | 5 (10) | <.001 |
| Diastolic filling, % | 73 ± 6.5 | 73 ± 6.0 | .931 |
| Diastolic filling, <50% | 0 (0) | 0 (0) | 1.000 |
| Backflow, % | 3.6 (0.9–7.8) | 0.40 (0–1.2) | <.001 |
| Backflow, >3% | 26 (53) | 7 (14) | .01 |
| Peak systolic flow, ml/min (n = 32) | 27 (14–42) | 32 (23–45) | .005 |
| Peak diastolic flow, ml/min | 40 (28–59) | 54 (38–77) | <.001 |
| Mean graft flow, ≤15 ml/min and P1 ≥ 3, n (%) | 13 (26) | 1 (2) | <.001 |

Note: Values are expressed as n (%), mean ± SD, or median (interquartile range).
Abbreviations: LAD, left anterior descending coronary; TTFM, transit time flow measurements.

In the case of intraoperative borderline TTFM values, the calculation of CFI as described in this study might unmask significant competitive flow and prevent unnecessary graft revision. However, while CFI is a tool to evaluate the graft quality, patency, and flow, it cannot be used as predictor of clinical outcome as this ratio is independent of the absolute flow needed to perfuse the heart.

The intraoperative TTFM strategy applied in this study showed good outcomes in terms of myocardial infarction and mortality in the long-term follow-up. Only one patient (2%) diagnosed with intraoperative competitive flow experienced a postoperative myocardial infarction and none of our patients had myocardial revascularisation related to competitive flow during follow-up, based on coronary angiography. These data are in line or even lower compared to those reported in the Netherlands Heart Registry or in other TTFM studies presenting a one-year myocardial infarction rate of 5.1%.

4.1 Limitations

Preoperative QCA for surgical revascularization is rarely used for heart team discussions. In this study, LAD stenosis was quantified by QCA as 58% ± 15%, traditionally named moderate stenosis when visually estimated by a cardiologist. This is in line with an average left territory diameter stenosis of 64% reported in a previous TTFM study. The PROMISE trial identified that visual estimation of coronary stenosis was higher compared to QCA, with the highest differences for the LAD (24%). Indeed, 36/50 patients in our study had a QCA objectified LAD stenosis <70%, including 12/36 patients with a significant FFR < 0.80, 13/36 had a significant LM stenosis (LAD equivalent), and 10/36 patients stenosis visually estimated by experienced interventional cardiologists as >70%.

Patients with LM stenoses were regarded as LAD/Circumflex equivalent but might not have significant LAD stenosis based on QCA. Stratification of patients for LAD stenosis is thus biased and an unplanned subgroup analysis of patients with no LM stenosis was performed where intraoperative TTFM parameters were comparable (Figures 3 and 4). Although competitive flow is expected for moderate stenoses, we showed that not only a significant increase in graft flow is observed with LAD snared for LAD stenosis <50%, but also for 50%–70%, as well as >70% LAD stenosis (Figure 3).
Mean arterial pressure is rarely reported in clinical TT FM studies, and our MAP of 66 mmHg is comparable to the rare studies reporting these. Some centers aim for a MAP of 75–85 mmHg. Although univariate models determined a significant relationship between MAP and MGF, only a small part of MGF can be attributed to MAP ($r^2 = .08$, see Figure S4).

For this study, 50 patients were included to characterize the relationship of competitive flow from LAD with LIMA MGF. Although this is sufficient to determine this relationship, clinically relevant cut-off values on acceptable MGF or other parameters are underpowered. Last, women ($n = 2$, 4%) were underrepresented in this study compared to the reported Dutch data for isolated CABG (women: 20%).
To conclude, routine snaring of the LAD during OPCAB demonstrated an increase in MGF among all coronary stenosis groups. With LAD snared, 26%-42% of clinical cut-off TTFM values for graft failure shifted to acceptable values. Therefore, routine application of the CFI according to the method described in this study can be useful to identify competitive flow in case of intraoperative borderline TTFM parameters. Further studies are needed to establish definitive evidence regarding the role of CFI and routine snaring of the LAD during off-pump CABG, with special focus on the prevention of unnecessary intraoperative graft revisions and postoperative myocardial infarction.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

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