Title

Beyond patency: functional assessment of adequacy using internal mammary artery grafting to the left anterior descending artery

Running title

Graft functional assessment

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Abstract

Introduction: Arterial graft physiology influences the long-term outcome of coronary artery bypass grafting (CABG). We studied factors that can affect the overall resistance to flow using internal mammary artery grafting to the left anterior descending artery.

Methods: This was a prospective, non-randomized observational study of 100 consecutive patients who underwent elective on-pump isolated or combined valve surgery and CABG. Coronary stenoses were assessed using conventional and quantitative coronary angiography assessment. The flow and pulsatility index (PI) of the grafts were assessed by transit time flowmetry during cardioplegic arrest and at the end of the operation. Fractional polynomials were used to explore linearity, followed by multivariable regression analysis.

Results: Univariate analysis demonstrated higher flows at the end of the operation in patients who had higher flows with the cross clamp on ($p<0.001$), in males ($p=0.004$), in patients with a low PI at the end of the operation ($p=0.04$) and in patients with a larger size of the recipient artery ($p=0.005$). Multivariable regression analysis showed that the graft flow at the end of the operation was significantly associated with the mean flow with the cross clamp on ($p<0.001$), sex ($p=0.003$) and PI at the end of the operation ($p=0.003$). Concomitant valve surgery did not influence flows. Male patients had 18ml/min higher flow.

Conclusions: The graft flow at the end of the operation can be determined by the flow with the cross clamp on, the PI with the cross clamp off and coronary artery. We reported differences in the graft flows between sexes, and for first the time, we introduced the concepts of “adequate flow” and “resistance-to-forward-flow” for patent coronary grafts.

Keywords: CABG, coronary, bypass, surgery, TTFM, flow, LIMA, graft, effectiveness, adequacy, resistance

Introduction

During the gold-standard technique of coronary artery bypass grafting (CABG), the internal mammary artery (IMA) is most commonly anastomosed to the left anterior descending artery (LAD) [1] [2]. A patent IMA-to-LAD graft is associated with an improved survival benefit and a reduction in subsequent myocardial infarction, recurrent angina and the need for repeat revascularization [2-4] with patency rates >90% [5-9]. Surgeons who understand the physiology of coronary revascularization may be able to perform better surgical revascularization procedures [10].

The benefit of the LIMA-to-LAD appears to persist long after most non-arterial conduits have lost their efficacy [11]. This benefit has been attributed to the in situ nature of the conduit, endothelial production of endogenous vasodilators (NO, prostacyclin [PGI₂] and epoxyeicosatrienoic acids), closer size matching between the graft and target vessel, the absence of atherosclerotic disease and reduced disease progression.

Graft failure is generally associated with the severity of the proximal stenosis, which in turn affects competitive flow from native vessels, other bypass grafts or collateral vessels [12], and the quality of the grafted vessel and tandem myocardium perfused by the grafted vessel [13-20]. Differences between microvascular health and microvascular disease, as described by Gutterman et al [10] may also play a fundamental role.

The effectiveness of a graft can be directly evaluated by the intraoperative transit time flow measurement (TTFM) using the VeriQ transit time flowmetry system CardioMed-MediStim (Medistim ASA Økernveien 94 N-0579 Oslo Norway) which yields the mean graft flow (MGF), pulsatility index (PI) and diastolic flow fraction (DF). Intraoperative TTFM assessment during CABG is recommended by the European Association for Cardio-Thoracic Surgery and European Society of Cardiology.

Maximum flow across a patent IMA-to-LAD anastomosis is achieved when the native artery and heart chambers are empty of blood (cross clamp on). In such a state, the only resistance to blood flow is dependent on the radius of the grafted vessel and perfused vascular bed. However, this scenario is artificial. Therefore, in this study we sought to determine the degree of overall resistance to flow relative to several factors that have previously been postulated to influence resistance and adversely affect forward flow through the IMA-to-LAD bypass graft.

Materials and Methods

The study was performed as a prospective, single-surgeon, single center, observational study over a period of 24 months. One hundred consecutive patients who underwent elective isolated CABG or combined CABG and valve surgery, with IMA grafting to the LAD as one of the conduits were included. This study was conducted as part of a Registered Clinical Audit with Datix Number ID: 5559, and individual consent was not required.

The surgical indication and approach for patients with coronary artery disease were determined via institutional heart-team meetings, to achieve consistency in the institutional surgical care independent of individual treating physicians or surgeons. Evaluation of the coronary anatomy was primarily based on conventional fluoroscopic coronary angiography. All the patients underwent a median sternotomy, and IMAs (either RIMA or LIMA) were harvested using a skeletonized extra-pleural technique. All IMAs were of good quality with adequate flow and were used as a pedicle. Complete revascularization using a conventional on-pump, cold-blood cardioplegic arrest technique was achieved under general anesthesia and right heart catheter monitoring. There was 0% revision of the IMA to LAD grafts and a limited 5% revision of all other grafts following VeriQ assessment.

The operating surgeon graded the quality of the grafted LAD as good (no evidence of atherosclerotic plaques at the anastomosis point or distal vessel), moderate (only some diffuse

disease at the anastomosis or distal to it), and poor (extensive atherosclerotic plaque at the anastomosis or distal to it). This gross evaluation of coronary artery disease, although subjective, is equally a commonly used method that surgeons use to evaluate the area of anastomosis macroscopically.

The LAD diameter was estimated intraoperatively by the surgeon in increments of 0.25 mm with the heart in cardioplegic arrest and the arteries empty of blood using dedicated probes and/or shunts.

The degree of proximal stenosis within the proximal LAD was assessed by a co-investigator, blinded to the operative technique, using quantitative coronary angiography (QCA) [15].

The IMA-LAD flow and pulsatility index (PI) were assessed by transit time flow measurement (TTFM) first with the cross clamp on (systemic pressure of 70-80 mmHg on the pump), and then with the heart completely empty, with the native vessels as empty as possible and without any other graft (even if attached to the heart) being operational (excluded from the circulation), to achieve minimal possible resistance to forward flow through the patent anastomosis (FXCon & PIXCon).

The forward flow through the patent IMA-LAD anastomosis was re-assessed at the end of surgery, with the heart off bypass, fully re-perfused with all grafts completed and at a MAP of 70-80 mmHg (FXCoff & PIXCoff).

Change in flow through the IMA-to-LAD (ΔFlow) was defined as the difference between the flow achieved with the cross-clamp on and with the cross-clamp off ($\Delta\text{Flow} = \text{FXCon} \text{ minus } \text{FXCoff}$). Similarly, the change in PI (ΔPI) was defined as the difference between the PI measured with the cross-clamp off and PI achieved with the cross-clamp on ($\Delta\text{PI} = \text{PIXCoff} \text{ minus } \text{PIXCon}$). Patients requiring an intra-aortic balloon pump and/or inotropes (other than noradrenaline at a maximum dose of 0.5 $\mu\text{g/kg/min}$) to maintain systemic blood pressure were excluded from analysis.

The published minimum acceptable flow for IMA grafts at the end of the operation (equivalent to FXCoff for this study) was 15-20ml/min [21-22], while the minimum acceptable for vein grafts was 30-40ml/min [23] although unpublished data from our unit suggest that flows greater than 26ml/min were associated with higher patency rates for both arterial and venous grafts. Based on these, we chose flow using an IMA-LAD <28 mL/min as low (poorer) flow and ≥ 28 mL/min as high flow.

Postoperatively, dual antiplatelet therapy was started at 4-6 hours after the end of the operation and all other secondary prevention therapies were re-initiated on the first postoperative day.

Statistical methods

The baseline characteristics are described using means and standard deviation or numbers and percentages, where appropriate.

The relationships between flow-off (FXCoff) and several key variables (FXCon, PIXCoff, size of the target coronary artery, quality of the target coronary artery, degree of proximal stenosis, and length of proximal stenosis) were first explored using univariable linear regression analysis. We kept the variables in their original continuous nature to not lose information by categorizing the data [24, 25]. Due to skewness, we log transformed the flow-off for all analyses.

Using fractional polynomials we then examined whether non-linear relationships between the variables and outcome of interest (log flow in the IMA-to-LAD graft, or log(FXCoff)) existed. Finally using multivariable regression analysis adjusting for all variables of interest, we explored whether potential relationships with log(FXCoff) still existed when adjusting for other variables.

For sensitivity analysis, we carried out the same analysis as described above, but using a binary outcome of FXCoff <28 in logistic regression models.

All statistical analyses were performed using STATA14 SE. All tests were two-sided and α was set at 0.05.

Results

The data from all one hundred patients were included in the analysis (Table 1). The distribution of FXCoff and PIXCoff for all the patients included in the cohort is presented in Figure 1.

Identifying predictors of low IMA-to-LAD flow on a continuous scale:

Univariable linear regression models (Table 2) showed that a higher logFXCoff was associated with higher flow in the IMA-to-LAD graft with the cross clamp on (FXCon; $p < 0.001$) (Figure 2), male sex ($p = 0.004$), and the size of the grafted LAD ($p = 0.005$) and was inversely associated with the PI with the cross clamp off (PIXCoff; $p = 0.04$).

Higher flow rates (FXCoff) at 18ml/min were observed in males than in females (Figure 2); however the number of females within the study population was small and a larger, more balanced sample size would be needed to confirm this observation.

When all other variables were included in the multivariable linear regression model (Table 3), we found that higher FXCon ($p < 0.001$), the PI with the cross clamp off (PIXCoff, $p = 0.003$) and male sex ($p = 0.003$) were associated with higher flow (FXCoff) but the size of the grafted LAD was no longer associated.

Identifying predictors of low IMA-to-LAD flow, defined as $< 28 \text{ ml/min}$:

Univariable models to assess the binary outcome of low IMA-to-LAD flow after removal of the cross clamp ($< 28 \text{ ml/min}$) showed that sex ($p = 0.043$), PIXCoff ($p = 0.01$) and FXCon ($p = 0.045$) were significantly related (Table 2). The multivariable model (Table 3) confirmed PIXCoff ($p = 0.022$) and FXCon ($p < 0.001$) as variables that remained significantly associated

with lower flows at the end of the operation. These findings were, of course, based on dichotomization [24, 25] of the data at 28ml/min.

Assessment of the relationship between Δ Flow (and Δ Flow%) and the size of the LAD:

No significant association was found between Δ Flow and the LAD size only a trend toward higher Δ Flow for larger diameter LADs (>1.75mm), likely due to the arteries having a higher FXCon (Figure 3).

Assessment of the relationship between Δ Flow (and Δ Flow%) and the degree of proximal stenosis (high degree of stenosis = less antegrade flow down the native artery flow and less backwards “leak” of flow with the cross clamp on):

No correlation was found between the degree of proximal stenosis (%DS) assessed by QCA analysis of the preoperative coronary angiogram and Δ Flow (Figure 4), with only the lesion length being a more important determinant of Δ Flow (Figure 5) and without reaching statistical significance, likely because all the patients included in the study already had angiographically significant proximal LAD disease.

Discussion

Coronary artery bypass grafting is the most effective treatment for complex coronary artery disease. The IMA-to-LAD graft is currently considered the optimal mode of coronary revascularization and is the best standardized form of cardiac surgery performed worldwide. For many years, researchers emphasized creating patent anastomoses with little thought given to assessing the functional capacity of the grafts. The intraoperative use of TTFM is the recommended way to assess the functional capacity of coronary artery by-pass grafts and is currently the only widely used system of intraoperative quality assurance [22].

A successful CABG operation with patent grafts will reduce the ischemic burden within the myocardium and will provide both symptomatic and prognostic benefits. However, perhaps a more important point to consider is to what extent is a patent graft an adequate graft? Are all patent grafts optimally adequate? Furthermore, what are the factors that determine patency and adequacy? In this study, by combining several techniques and using the IMA-to-LAD graft as a point of reference, we addressed those questions to better understand how to predict the longevity and adequacy of our grafts.

In CABG surgery, early graft failure is not infrequent, with an occurrence rate of 5-20% [26-28]. With the introduction of TTFM, the cardiac surgeon can now not only document the patency of their anastomoses at the end of the operation but can also better assess the functional capacity of the grafts they perform. In a recent review of published TTFM studies, Niclauss et al. concluded that the mean graft flow positively predicts long-term patency (minimum threshold of 20 ml/min for IMA grafts and 30-40 ml/min for vein grafts) [23]. Coronary artery bypass graft failure has been associated with the following: high FFR (which was also associated with high mean PI, probably due to competitive, antegrade flow from the native coronary artery) [17]; TTFM measurements in the early diastolic phase [29]; smoothness of the graft-flow curve for arterial grafts [27] and high PI and high systolic reverse flow [26]. Published work from our group has shown that differences of TTFM parameters between left- and right-sided vein grafts were small and unlikely to be of clinical relevance [30].

Competitive flow is most commonly due to non-significant proximal coronary vessel stenosis, which allows native blood flow to compete with the flow down the graft. Furthermore, competitive flow appears to be a particularly important determinant of graft failure for arterial conduits [13]. We believe that the term competitive flow in this context is limited and does not adequately describe the “resistance to forward flow” downstream from a patent graft. As we summarized in figure 6, other factors that might contribute to resistance and forward flow are

as follows: the degree of proximal stenosis, flow from other grafts to the area, flow from coronary collaterals (particularly in the setting of chronically occluded arteries), size and quality of the grafted vessel, filling pressures of the heart chambers and mean arterial perfusion pressure [13, 14, 16, 18-20].

Our findings revealed a significant reduction in flow from the time that the heart is empty and on cardiopulmonary by-pass with the cross clamp on (FCXon) to the time that the heart is fully functioning off the bypass (FCXoff). It could be argued that FCXon represents the maximum flow of blood (per min) that a particular IMA can provide to a given vascular bed under conditions of minimum resistance and close to maximum hyperemia. The results of our study confirmed that FCXoff was inversely associated with PIXCoff, which represents the resistance to forward flow downstream of the graft anastomosis within the run-off of the native LAD and under standardized loading conditions. Because the PIXCoff may change relative to several factors, the LIMA-to-LAD graft can operate up to a maximum FCXon, the result of minimum possible resistance to forward flow (PIXCon) for that particular LIMA-to-LAD graft. Thus, ΔFlow represents the “range of operation” for that particular IMA in that particular vascular bed. Does it make any difference if an IMA-to-LAD is “operating” between 32ml/min and 100ml/min or between 32ml/min and 60ml/min? This is a difficult question to answer and it is more difficult to prove which of the two is more “adequate” than the other. However, after decades of performing millions of successful CABG operations, we have the means to interrogate our work, better understand our results and possibly further refine and optimize our procedures.

We observed that the end procedure flow (FXCoff) of the IMA-to-LAD graft was higher for males by 18ml/min, questioning the proposed threshold of 20 ml/min for a well-functioning ITA graft by Niclauss et al [23]. These differences between males and females may be related to a lower body mass index, smaller heart muscle and smaller coronary arteries. Thus, although

we fully agree that an IMA to LAD graft should be offered to all patients who need CABG, we could argue that the threshold of 20ml/min (the current minimum acceptable flow at the end of the operation for arterial grafts) may also be variable and dependent on the the heart size, sex and body mass index and will require further investigation and verification in future studies. Additionally, we showed that no differences exist in the end procedure flow (FXCoff) of the IMA-to-LAD graft for isolated CABG compared with combined CABG and valve procedures. Our findings suggest that coronary arteries less than 1.75mm at the site of the anastomosis are associated with lower flows, agreeing with previously published data [23], although this finding should be confirmed in larger studies. Thus, it is likely that the more proximal is the anastomosis, the greater is the chance of the graft being adequate.

Our data demonstrated no association between Δ Flow and the maximal stenosis in the native vessel, probably due to most of the grafted vessels showing significant proximal stenosis. The length of the stenosis could be an important determinant of the Δ Flow, although not statistically significant in our analysis. In this study we used QCA to quantify the severity of the proximal coronary artery lesion, although the use of an alternative angiographic scoring tool that incorporates the minimal lumen diameter, lesion length, and subtended myocardial area, such as DILEMMA score, may better predict the functional significance of lesions [31]. Moderate proximal native coronary artery stenosis and high fractional flow reserve (FFR) are known to affect the bypass graft flow [12, 17] due to competitive antegrade flow from the native vessel. Currently, cardiac surgeons tend to understand competitive flow as the flow that comes down the native coronary artery via non-significant proximal narrowing. We believe that the flow of a constructed coronary artery bypass graft, affecting its performance and long-term patency, may also be influenced by the quality and quantity of the peripheral vascular bed, collateral flow from other native coronary arteries and flow from adjacent coronary artery bypass grafts. We believe that the use of the term “resistance to flow” is probably more appropriate and

representative of the flow dynamics at the end of a coronary artery bypass procedure. If and when a constructed coronary artery bypass graft encounters significant resistance to flow, we believe that this should be adequately documented and communicated to the clinicians involved with the patients care. Currently, most cardiac surgeons decide their intended procedural strategy based on coronary angiography alone, that, particularly in the modern era of multiple arterial grafts may result in high resistance to flow in certain grafts with a potential compromise to long-term patency. Preoperative assessment with FFR as an adjunct to conventional angiography and CT coronary angiography with CT-FFR may allow the integration of physiological data. Further studies may open new avenues in the assessment of coronary artery disease and help cardiac surgeons to utilize adequate revascularization strategies for every patient with coronary artery disease.

Limitations

Several limitations exist that, if addressed appropriately with further studies, can help us understand to perform and assess CABG better. Our patients did not undergo routine FFR assessments of their coronary artery disease, and we did not assess the IMA-to-LAD diameter ratio. Thus, we could not include this data in our analysis. None of our patients had undergone CT of their coronary artery disease preoperatively, although several had undergone postoperative CT angiogram and CMR assessment as part of different study protocols, the results of which will be presented in a complete format and a later publication. We had an imbalance in the male-to-female ratio in our sample, with only 15 female patients included in the current study; thus, our findings regarding the higher observed flows in males would need to be further investigated in future studies. The intention of this manuscript was not to investigate early or long term patency but to determine factors that can influence the resistance to forward flow and adequacy of the performed graft. The effect of adequacy and resistance to

flow concepts have on the early and long-term patency of coronary artery by-pass surgery is an important question that will require further investigation.

Conclusion

With this prospective study, we evaluated the functional outcomes of the IMA-to-LAD graft at the end of the operation. We have shown a positive correlation between the flow achieved with the cross clamp on (FXCon) and that at the end of the operation (FXCoff), and we confirmed that the IMA-to-LAD graft performs better when the IMA graft operates against low resistance to forward flow (expressed by PI). For the first time, we have shown that the expected flow at the end of the procedure (FXCoff) can be 18ml/min higher for males and it is higher when the anastomosis is performed on a larger diameter (possibly to a more proximal part) native coronary artery. In this article, we introduced the novel concepts of “adequate grafts” and “resistance to flow” and questioned the current, non-sex-specific lowest acceptable threshold of flow for arterial grafts. We believe that the findings of this study will open new avenues for clinical research and scientific argument, ultimately helping the clinical community to refine and optimize the effectiveness of coronary artery by-pass surgery.

Figure legends

Figure 1: Distribution of all TTFM Flow and PI measurements at the end of the operation (FXCoff, PIXCoff)

Figure 2: Positive correlation between FXCon and FXCoff for males and females

Figure 3: Correlation of ΔFlow (and $\Delta\text{Flow}\%$) with the size of the LAD artery graft

Figure 4: ΔFlow (and $\Delta\text{Flow}\%$) was not correlated with %DS, as assessed by QCA

Figure 5: ΔFlow (and $\Delta\text{Flow}\%$) was not correlated with lesion length, as assessed by QCA

Figure 6: Multifactorial influence on the adequacy and longevity of a graft. FXCoff = flow measured with the cross-clamp off; FXCon = flow measured with the cross-clamp on

Author contributions

George Krasopoulos: [1] research design, interpretation of data; [2] drafting the paper and revising it critically; [3] approval of the submitted version

Andrea D'Alessio: [1] interpretation of data; [2] revising the paper critically; [3] approval of the submitted version

Danilo Verdichizzo: [1] interpretation of data; [2] revising the paper critically; [3] approval of the submitted version

Mirko Muretti: [1] interpretation of data; [2] revising the paper critically; [3] approval of the submitted version

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Table 1: Demographics and surgical characteristics of the study population

Age distribution, mean (SD)	67.0 ± 0.9
Other Characteristics	%
Participant number	N = 100
Male sex (%)	85
Valve surgery (%)	25
Hypertension (%)	83
Hypercholesterolaemia (%)	96
Diabetes mellitus (%)	19
CCS score	
- 0 (%)	4
- 1 (%)	19
- 2 (%)	59
- 3 (%)	14
- 4 (%)	4
NYHA class	
- 1 (%)	26
- 2 (%)	59
- 3 (%)	15
- 4 (%)	0
Previous AMI (%)	44
Smoking	

-	Never (%)	45
-	Ex (%)	55
-	Active (%)	0
	COPD (%)	18
	PVD (%)	32
	Poor LV function (%)	15
	Grafted vessel quality	
-	Good (%)	73
-	Moderate (%)	12
-	Poor (%)	15

AMI: Acute myocardial infarction; COPD: Chronic obstructive pulmonary disease; PVD: Peripheral vascular disease; LV: Left ventricle.

** please note that as N=100 the percentage values are always equal to the corresponding N values.

Table 2: Univariable regression results

Variable	Continuous outcome		Binary outcome	
	(log F _X Coff)		(F _X Coff < 28ml)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Degree of stenosis (DS)				
Lesion length	-0.008 (-0.020, 0.004)	0.188	0.025 (-0.033, 0.083)	0.398
Artery size	0.38 (0.12, 0.65)	0.005	-1.82 (-3.66, 0.02)	0.053
Sex	0.37 (0.12, 0.62)	0.004	-1.22 (-2.40, -0.04)	0.043
F_XCon	0.003 (0.001, 0.005)	<0.001	-0.014 (-0.027, -	0.045
		<0.001	<0.001<0.001)	
PI_XCoff	-0.14 (-0.28, -0.01)	0.040	1.01 (0.24, 1.77)	0.010
Quality of LAD				
<i>Moderate vs good</i>	0.00 (-0.28, 0.29)	0.572	0.34 (-1.09, 1.77)	0.897
<i>Poor vs good</i>	0.14 (-0.12, 0.40)		0.05 (-1.34, 1.44)	

Table 3: Multivariable regression results

Variable	Continuous outcome		Binary outcome	
	(log F _X Coff)		(F _X Coff < 28ml)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Degree of stenosis (DS)	0.003 (-0.002, 0.007)	0.282	-0.018 (-0.052, 0.017)	0.321
Lesion length	-0.008 (-0.019, 0.003)	0.145	0.011 (-0.067, 0.090)	0.773
Artery size	0.22 (-0.04, 0.48)	0.103	-2.13 (-4.55, 0.29)	0.084
Sex	0.35 (0.13, 0.58)	0.003	-1.53 (-3.11, 0.046)	0.057
F _X Con	0.003 (0.001, 0.005)	<0.001	-0.023 (-0.043, -0.003)	0.022
		<0.001		
PI _X Coff	-0.19 (-0.32, -0.07)	0.003	1.87 (0.86, 2.88)	<0.001
				<0.001
Quality				
Moderate vs good	0.06 (-0.21, 0.33)	0.274	0.35 (-1.53, 2.23)	0.870
Poor vs good	0.19 (-0.04, 0.43)		-0.26 (-2.07, 1.55)

Distribution of all TTFM Flow and PI measurements at the end of the operation (FXCoff, PIXCoff)

Correlation of ΔFlow (and $\Delta\text{Flow}\%$) with the size of the LAD artery graft

Δ Flow (and Δ Flow%) was not correlated with %DS, as assessed by QCA

Δ Flow (and Δ Flow%) was not correlated with lesion length, as assessed by QCA

Multifactorial influence on the adequacy and longevity of a graft. FXCoff = flow measured with the cross-clamp off; FXCon = flow measured with the cross-clamp on

98x83mm (300 x 300 DPI)