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CLINICAL RESEARCH
Coronary artery disease

Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial

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Aims Visual estimation is the most commonly used method to evaluate the degree of coronary artery stenosis prior to coronary artery bypass grafting. In interventional cardiology, the use of fractional flow reserve (FFR) to guide revascularization decisions has become routine. We investigated whether the preoperative FFR measurement of coronary lesions is associated with anastomosis function 6 months after surgical revascularization using a multiarterial grafting strategy.

Methods and results In this prospective double-blind study, 67 patients were enrolled from two institutions in Europe and Canada. From these patients, 199 coronary lesions were assessed visually and with FFR at the time of the preoperative angiogram. All patients received coronary revascularization using multiple arterial grafts. A post-operative 6-month angiogram was performed to assess anastomosis functionality using a described angiographic method. The primary outcome was the association between preoperative FFR values and anastomosis function 6 months after surgery. Preoperative FFR was significantly associated with 6-months anastomotic function for all conduits and for all targets ($P < 0.001$). An FFR value of ≤0.78 was associated with an anastomotic occlusion rate of 3%.

Conclusion We found a significant association between the preoperative FFR measurement of the target vessel and the anastomotic functionality at 6 months, with a cut-off of 0.78. Integration of FFR measurement into the preoperative diagnostic workup before multiarterial coronary surgical revascularization leads to improved anastomotic graft function.

Clinical Trials.gov Identifier NCT02527044.

Keywords FFR • CABG • Arterial graft • Flow competition

Introduction

The objective of surgical coronary revascularization is to restore blood supply to a myocardial territory that is ischaemic or at risk of infarction through the interposition of a low-resistance conduit to the diseased coronary artery segment. The compliance of this bypass conduit must be sufficient to accommodate the high flow demands of systemic pressure with minimal pressure drop at the site of distal implantation.[1]

Competitive flow occurs when the resistance of the coronary bypass graft closely matches that of the native coronary artery target.[1,2]

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In this situation, both the native coronary artery and the bypass graft contribute to distal perfusion, each providing their own resistance to blood flow. For saphenous vein grafts, the pressures at the two ends of the circuit are identical, with only minor phasic variations, due to their large diameter and absence of muscular layers. In arterial grafts instead, due to the smaller diameter and higher vasomotor tone, the pressure at the proximal ostium is higher than at the distal anastomosis. Studies have demonstrated that pressure gradients between the aorta and bypass grafts are three to six times greater in arterial grafts compared to venous grafts.[1] Competitive flow between the native coronary artery and the arterial graft can result in further reductions of blood pressure through the conduit, which can cause the muscular layer to spasm and potentially close. This phenomenon has been widely reported in the literature.[1,3–5] Given the near-universal use of the left internal thoracic artery (LITA) to graft the left anterior descending (LAD) territory and the fact that current guidelines recommend the use of the right internal thoracic (RITA) and radial arteries (RA), the importance of the assessment of competitive flow should not be underestimated.

Current methods to estimate the severity of the coronary stenosis and the potential for competitive flow include visual inspection,[6] quantitative coronary angiography (QCA),[7] and fractional flow reserve (FFR).[8] Fractional flow reserve is the only direct method to assess the haemodynamic effect of a stenosis by measuring pressure ratios in order to determine the ischaemic potential of the stenosis. Several studies have shown that both visual inspection and QCA have poor correlation with FFR,[9–13] and the 2018 European Guidelines for myocardial revascularization recommend that coronary artery lesions be measured with a FFR when evidence of ischaemia is not available (Class I, Level of Evidence A).[14]

Fractional flow reserve evaluation, however, has not been widely adopted during the diagnostic workup of patients referred for surgical revascularization and only limited evidence exists on the role of preoperative FFR in patients undergoing coronary artery bypass grafting (CABG) surgery.

The Impact of Preoperative FFR on Arterial Bypass Graft Function (IMPAG) study was designed to evaluate the correlation between target vessel pre-operative FFR value and anastomotic function 6 months after surgery.

Methods

Study design

We devised a prospective double-blind observational study performed in two different institutions in Belgium and Canada. The trial was registered (ClinicalTrials.gov Identifier: NCT02527044) and approved by the local research ethics boards in both institutions. All patients enrolled in the study provided written informed consent.

Outcomes

The primary outcome was the association between target vessel pre-operative FFR value and anastomotic function (defined as below) 6 months after surgery. Secondary outcome was the association between target vessel pre-operative FFR value and anastomosis occlusion at 6 months after surgery.

Study procedures

Patients were eligible for the study if they had multivessel coronary artery disease (CAD) and were referred for isolated CABG using multiple arterial grafts. Patients were excluded if they had previous cardiac surgery, or were not candidate for the use of multiple arterial bypass grafts. The full list of eligibility criteria can be found in Supplementary material online, *Table S1*. Patients were enrolled at the time of the diagnostic angiogram, or at the time of the pre-operative consultation with a cardiac surgeon.

Diagnostic angiography using either radial or femoral access was performed following the usual standard of care at each institution. Fractional flow reserve measurements of all major disease vessels were performed using a PressureWire Certus Agile Tip (Abbot St. Jude Medical, Minneapolis, MN, USA) with the use of intravenous adenosine as a hyperaemic stimulus. Fractional flow reserve values were recorded by a study coordinator and blinded to the patient, interventional cardiologist, and surgeon. Angiographies were graded independently by two expert reviewers. Disagreements were resolved by a third reviewer, if needed.

The sequence and strategy of arterial revascularization was left to the operating surgeon. After surgery, all patients received therapies as recommended by the current American College of Cardiology and American Heart Association guidelines, including smoking cessation counselling and the administration of antiplatelet agents, beta blockers, lipid medications, and angiotensin-converting enzyme inhibitors.[15,16]

Patients underwent follow-up angiography of all bypass grafts and anastomoses 6 months after surgery. Nitroglycerine (2 mg) was injected into each graft before filming. At least, two orthogonal views of each internal thoracic or RA graft imaging were obtained, with continued exposure as required to visualize distal run-off and the size of the target coronary bed. Angiographic evaluations were performed by two observers (one interventional cardiologist and one cardiac surgeon) blinded to the pre-operative FFR values. In the case of disagreement between observers, a third observer (interventional cardiologist) decided the value. Following a described method,[3] anastomotic function was scored as 0 for an occluded graft, 1 when the flow from the native coronary artery was dominant, 2 when flow supply from the native coronary and from the graft was balanced, and 3 when the native coronary was fully opacified by the graft. An anastomosis was considered 'non-functional' for scores of 0–2 and 'functional' for score of 3. Angiographic patency was graded according to the FitzGibbon classification[4] (A: widely patent, B: patent with flow limited, and O: occluded). The coronary run-off was graded using a previously described semi-quantitative scale based on the importance of the coronary bed beyond the area of the stenosis (A: excellent run-off, B: moderate run-off, and C: poor run-off).[1]

Sample size

A pilot phase was conducted to assess feasibility and allow sample size calculation. Twenty patients were recruited, and all patients had a follow-up angiogram 6 months after CABG. An average number of 3.8 FFR measurements and arterial anastomoses per patient was observed, with no loss to follow-up. Patients of the pilot phase were included in the full trial. Sample size calculation was based on the results of the pilot phase and of a previously published trial.[17] We estimated a rate of 6-months anastomosis failure (i.e. occlusion) of 5% in patients with FFR <0.75 and 15% in patients with FFR >0.75. With a power of 0.90 at an alpha level of 0.05, 414 anastomoses would be required to detect a statistically significant difference between groups. Assuming a 10% dropout rate and an average of 3.8 anastomosis per patient, sample size was defined at 456 anastomoses. Based on the data of the pilot phase, 120 patients were deemed necessary.

An interim efficacy analysis was pre-established at 50% of the sample size including a total of 64 patients and 199 anastomoses. The rate of non-functional grafts in the group with FFR > 0.75 (n = 83) and FFR < 0.75 (n = 116) was 53% and 5%, respectively with a *post hoc* power estimation of 100%. Accordingly, the Steering Committee decided to describe the results of the trial in the present report.

Analytic design and statistical analysis

Continuous variables were reported as mean and standard deviation (SD) while categorical variables were reported as count and percentage. The relationship between specific target FFR and degree of stenosis (DS) was investigated using linear regression, and r^2 was used to quantify the degree of correlation between the two variables. Receiver operating characteristic (ROC) curves was used to identify the FFR and DS cut-off points with the highest discriminative power to predict non-functional anastomoses at the 6-month angiogram, and the two variables were dichotomized accordingly. Areas under the ROC curves (AUC) was used to compare the accuracy of FFR over the angiographic DS to predict non-functional anastomosis. If 95% confidence interval (CI) AUC lower limit was <0.5, the variable was considered not predictive.

Patient characteristics, graft configuration, and target details including FFR and DS between functional and non-functional anastomoses were compared using Student's *t*-test and χ^2 test for continuous and categorical variables, respectively. A multivariable model was then built using all variables associated with a *P*-value <0.1. As additional analysis, a mixed effect generalized linear model (logit) was implemented with the same set of variables as fixed effect to account for clustering within patient (multilevel model). To investigate the robustness of cut-off identified, predicted probability of anastomotic non-function was obtained by bootstrap simulations of multivariable model predictions (R = 1000).

Recursive partitioning (classification tree) was used to explore relationship between graft status (balanced, occluded, perfect, reverse flow) and graft characteristics listed in *Table 1*. The *recursive partitioning* algorithm works by splitting the dataset recursively, which means that the subsets that arise from a split are further split until a predetermined termination criterion is reached. At each step, the split is made based on the independent variable that results in the largest possible reduction in heterogeneity of the dependent (predicted) variable. The minimum number of observations in a node before attempting a split was 15 and that a split must have decreased the overall lack of fit by a factor of 0.01 (cost complexity factor) before being attempted. This statistical approach was used to account for the multiple and complex interactions that determine anastomotic function.

Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA) and R software, version 3.2.3 (R Foundation). *P*-value <0.05 was considered statistically significant.

Results

Overall 64 of 68 patients underwent the planned 6-month angiographic control. Mean angiographic follow-up was 6.6 months (SD 0.9).

During the follow-up period, 7 patients (10.2%) required eight elective percutaneous coronary interventions (PCIs). Details of these patients are given in Supplementary material online, *Table S2*.

From 64 patients, 199 anastomoses from 150 grafts were evaluated. There were 36 patients with double sequential and 7 patients with triple sequential grafts. The Y graft configuration was used in 172 anastomoses (86.4%).

Table 1 Characteristics of functional and non-functional grafts

		Functional *n* = 150	Non-functional *n* = 49	*P*-value
DS > 87.5	No	120 (72.7)	45 (27.3)	0.056
	Yes	30 (88.2)	4 (11.8)	
FFR < 0.78	No	27 (38.0)	44 (62.0)	<0.001
	Yes	123 (96.1)	5 (3.9)	
Sequential	No	96 (74.4)	33 (25.6)	0.67
	Yes	54 (77.1)	16 (22.9)	
Y graft	No	19 (70.4)	8 (29.6)	0.52
	Yes	131 (76.2)	41 (23.8)	
Target	CX	54 (70.1)	23 (29.9)	0.018
	DIA	20 (90.9)	2 (9.1)	
	LAD	53 (84.1)	10 (15.9)	
	PDA	23 (62.2)	14 (37.8)	
Conduit	LITA	69 (85.2)	12 (14.8)	0.029
	RA	6 (66.7)	3 (33.3)	
	RITA	75 (68.8)	34 (31.2)	
N sequential	0	76 (83.5)	15 (16.5)	0.11
	1	11 (68.8)	5 (31.2)	
	2	48 (67.6)	23 (32.4)	
	3	15 (71.4)	6 (28.6)	
Age	Mean (SD)	65.4 (10.3)	67 (11.0)	0.30
Cholesterol	No	30 (71.4)	12 (28.6)	0.50
	Yes	120 (76.4)	37 (23.6)	
Diabetes	No	87 (70.7)	36 (29.3)	0.053
	Yes	63 (82.9)	13 (17.1)	
Smoking	No	81 (75.0)	27 (25.0)	0.89
	Yes	69 (75.8)	22 (24.2)	
PVD	No	115 (74.7)	39 (25.3)	0.67
	Yes	35 (77.8)	10 (22.2)	
CKD	No	146 (76.4)	45 (23.6)	0.09
	Yes	4 (50.0)	4 (50.0)	
MI	No	110 (74.3)	38 (25.7)	0.56
	Yes	40 (78.4)	11 (21.6)	
EF	Mean (SD)	62 (10.5)	64.9 (14.1)	0.08
Prior PCI	No	104 (72.7)	39 (27.3)	0.17
	Yes	46 (82.1)	10 (17.9)	
SYNTAX score	Mean (SD)	22.9 (6.8)	21.1 (6.6)	0.26
Target diameter	Mean (SD)	1.9 (1.9)	1.8 (0.4)	0.47
Run-off	A	127 (73.8)	45 (26.2)	0.058
	B	23 (88.5)	3 (11.5)	
	C	0 (0.0)	1 (100.0)	
Off-pump	No	35 (85.4)	6 (14.6)	0.10
	Yes	115 (72.8)	43 (27.2)	

CKD, chronic kidney disease; DS, degree of stenosis; EF, ejection fraction; FFR, fractional flow reserve; MI, myocardial infarction; N, number; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation.

The median percentage of DS was 70 (interquartile range (IQR) 70–80) for LITA anastomoses, 80 (IQR 70–81.25) for RITA anastomoses, and 82.5 (IQR 65–95) for RA anastomoses (P = 0.01). Median

FFR was 0.73 (IQR 0.67–0.80) overall, 0.71(IQR 0.65–0.75) for LITA anastomoses, 0.77 (IQR 0.69–0.82) for RITA anastomoses, and 0.72 (IQR 0.64–0.84) for RA anastomoses ($P = 0.001$).

Angiographic patency rate was 85.2% for the LITA, 68.8% for the RITA, and 76.7% for the RA anastomoses (P-value for LITA vs. RITA = 0.052, LITA vs. RA = 0.38, and RITA vs. RA = 0.62). Forty-nine anastomoses were found to be non-functional (24%); of these, 27 (14%) were occluded, 13 (6%) presented a balanced flow, and 9 presented reverse flow (4%). The proportion of functional anastomoses was 85.2% for the LITA, 68.8% for the RITA, and 66.7% for the RA (P-value for LITA vs. RITA = 0.01, LITA vs. RA = 0.16, and RITA vs. RA = 0.89).

Among the 49 anastomoses found to be non-functional, the preoperative target vessel FFR was significantly lower for those who required PCI ($n = 8$) vs. those who did not ($n = 41$) (median/IQR 0.80/0.76–0.81 vs. 0.83/0.81–0.89, $P = 0.01$). Detailed description of the patients, the grafts, and the anastomoses are given in Supplementary material online, *Tables S3–S5*.

Primary endpoint analysis

Preoperative FFR and angiographic DS presented a significant but very weak correlation ($R^2 = 3\%$, *Figure 1*). Fractional flow reserve but not DS were found predictive of non-functional anastomosis (FFR AUC 0.92; 95% CI 0.87–0.96 vs. DS AUC 0.57, 95% CI 0.48–0.66; P-value for comparison <0.001). Fractional flow reserve best cut-off value was >0.78 with a specificity of 0.78 and a sensitivity of 0.90 for non-functionality (*Figure 2*), while the DS best cut-off value was <87.50 with a specificity of 0.20 and a sensitivity of 0.92 for non-functionality.

Table 1 compares patients, target, and graft configuration between non-functional and functional anastomoses at the 6-month angiogram. In non-functional anastomoses, the preoperative FFR value was significantly higher than in functional anastomoses (0.83 ± 0.07 vs. 0.66 ± 0.19; $P < 0.001$) while DS distribution did not differ between the two groups (73 ± 12 vs. 76 ± 14; $P = 0.12$).

At univariate and multivariable analyses (*Table 2*), FFR < 0.78 was associated with a 98% relative risk reduction of non-functional anastomosis (odds ratio 0.02, 95% CI 0.00–0.05), and this was also confirmed by the multilevel analysis. Angiographic diameter stenosis of >87.5% was not significantly associated with the risk of non-functional anastomosis. We also found that anastomosis to the posterior descending artery (PDA) was associated with a 4-fold time increase in the risk of non-function. An increasing number of sequential anastomoses was found to be protective against anastomosis non-function at univariate but not at multivariate analysis. The identified FFR cut-off of <0.78 was evaluated by bootstrapping models including vessel targets (*Table 3*). Anastomosis to the CX with FFR < 0.78 had 2% graft non-functionality rate and was used as reference. All anastomoses with FFR > 0.78 presented a significantly higher risk of non-function. Only anastomoses to the PDA presented a marginally significant trend toward an increased risk of non-function also in case of FFR < 0.78. Bootstrapping analysis confirmed a marginal, non-statistically significant benefit with increasing number of sequential anastomoses per graft. Classification tree algorithm selected FFR, target, and number of sequential anastomoses as the variables which

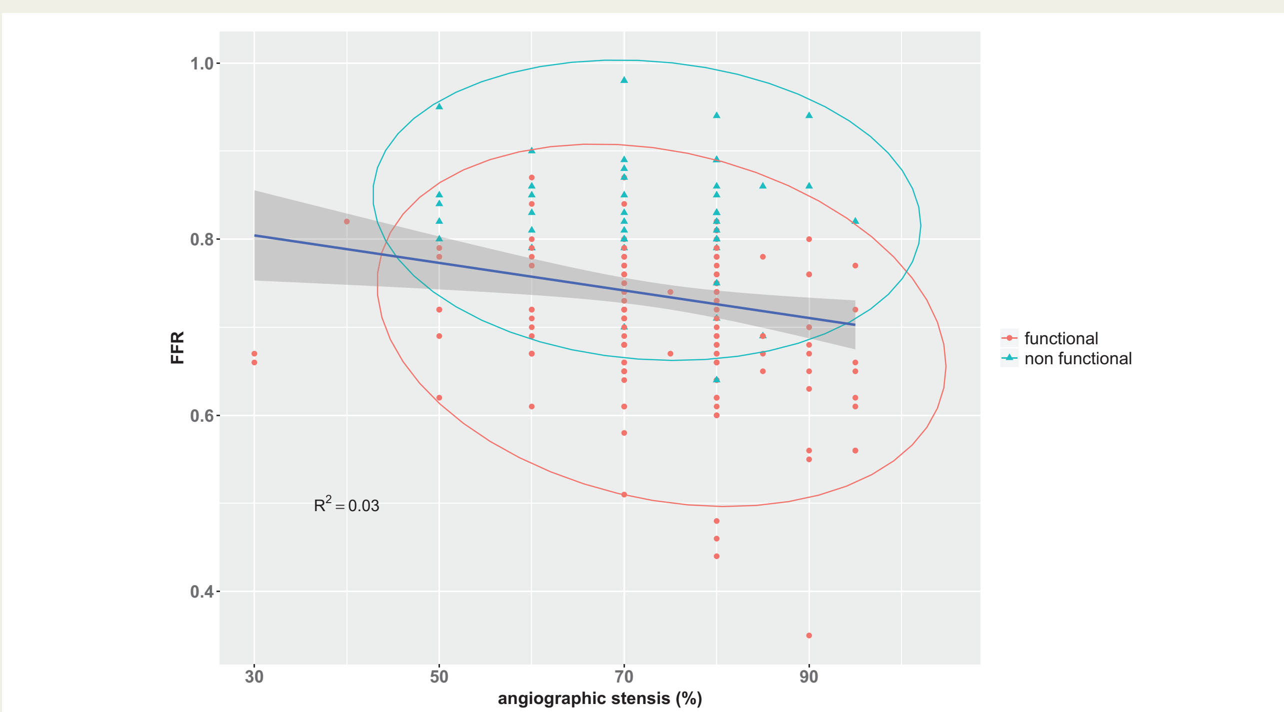


Figure 1 Dotplot and regression line representing the relationship between fractional flow reserve and angiographic stenosis in grafts that are functional (red) and non-functional (blue) at 6-month angiography. A prediction ellipse is presented indicating a region for predicting the location of a new observation. The centre of the ellipse is the sample mean, a prediction ellipse gives a visual indication of skewness and outliers in the data.

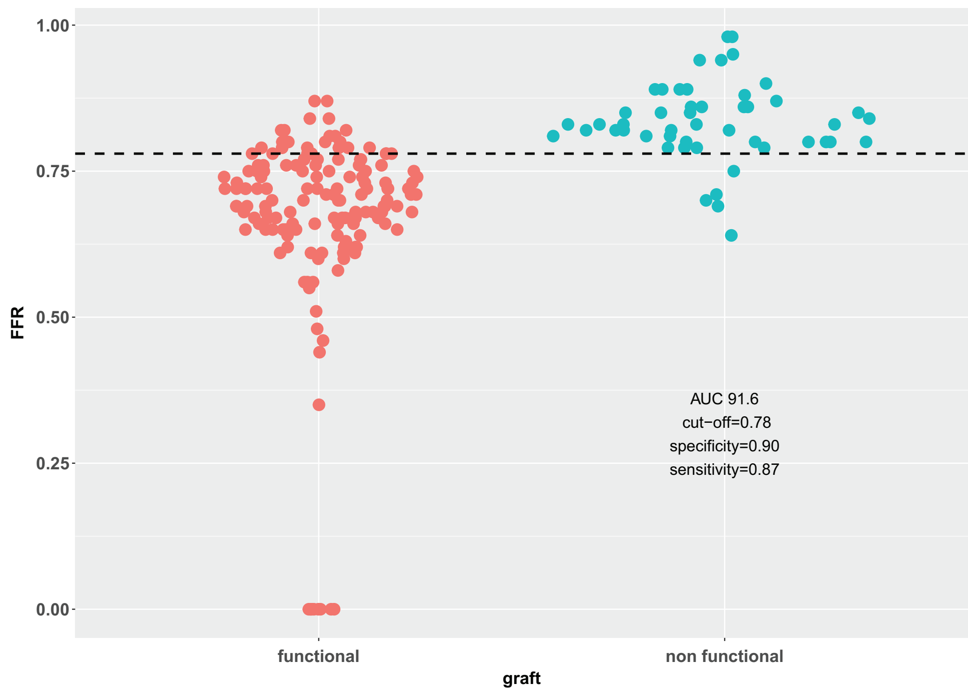


Figure 2 Sinaplot conveying information of both the number of data points, the density distribution, outliers of fractional flow reserve value in non-functional vs. functional anastomosis at 6-month angiography.

best identify patterns of graft status (*Figure 3*). This analysis confirmed that anastomoses to the CX with FFR < 0.78 presented the best outcome (96% functional grafts). Anastomoses to CX with higher FFR achieved a 68% rate of function only in presence of multiple sequential anastomoses. For FFR values >0.78 in grafts to LAD, DIA, or PDA the rate of non-functional anastomoses was very high (71%, 54%, and 82%, respectively).

Details of the association between anastomoses function and FFR quartiles are provided in Supplementary material online, *Figure S1*.

Secondary endpoint analysis

Fractional flow reserve but not DS was found to be predictive of anastomosis occlusion (FFR AUC 0.86 95% CI 0.78–0.93; vs. DS AUC 0.59 95% CI 0.49–0.70; *P*-value for comparison <0.001). The FFR best cut-off value was >0.78 with a specificity of 0.77 and a sensitivity of 0.92 for occlusion, while the DS best cut-off value was <87.50 with a specificity of 0.19 and a sensitivity of 0.92 for occlusion.

Supplementary material online, *Tables S6* and *S7* detail the analysis of occluded and non-occluded anastomoses at 6-month angiography.

Fractional flow reserve but not DS was found to be significantly higher in non-functional anastomoses (0.83 ± 0.06 vs. 0.68 ± 0.18; *P* < 0.001).

Discussion

We found a significant association between the preoperative FFR measurement and anastomotic function in arterial bypass grafts 6 months after surgery. The best FFR cut-off value was 0.78; less than 2% of the anastomosis to target vessels with preoperative FFR <0.78 were found to be non-functional at the follow-up angiogram.

The superior long-term functionality of arterial over venous graft is thought to result from favourable biological properties of the endothelium to protect this vessel against vasospasm, thrombus formation, and atherosclerosis. In two previous studies, we have demonstrated that the resistance in venous graft appears negligible and therefore the pressure at the distal graft anastomosis is nearly equal to the aortic pressure, minimizing risk of competitive flow.[1–3] Arterial grafts have a higher pressure drop and are more vulnerable to chronic competitive flow. In contrast, venous grafts are less subject to competitive flow but are prone to stenosis and occlusion over time which results in decreasing patency rates in the mid- and long-term.

Fractional flow reserve measurement has been validated as the most accurate invasive method of assessing the physiologic significance of a coronary artery stenosis.[13] This is reflected in studies such as the DEFER trial, which found that stenoses that were non-significant by FFR (≥0.75) were associated with a <1% risk of cardiac death or myocardial infarction whether or not they were stented.[18] Another key trial evaluating FFR was the FAME study, which found that FFR-guided PCI reduced the risk of death, repeat revascularization, and non-fatal myocardial infarction in the first year after the procedure.[19] Taken together, these prospective, randomized trials indicated clearly that FFR could identify lesions that warranted intervention, and that lesions that were not significant by FFR could safely be left alone. As a result of these trials, the use of FFR is supported by the professional guidelines, and has been widely adopted by interventional cardiologists during PCI.

Table 2 Risk factors at univariate, multivariate, and multilevel (random effect individual ID) analysis for non-functional grafts

Variable	OR (univariate)	OR (multivariate)	OR (multilevel)
DS	0.36 (0.10–0.96, P = 0.07)	0.69 (0.12–3.30, P = 0.66)	0.71 (0.05–9.17, P = 0.79)
FFR	0.02 (0.01–0.06, P < 0.001)	0.02 (0.00–0.05, P < 0.001)	0.01 (0.00–0.91, P = 0.047)
Sequential	0.86 (0.43–1.69, P = 0.67)	—	—
Y graft	0.74 (0.31–1.92, P = 0.52)	—	—
Target DIA vs. CX	0.23 (0.04–0.90, P = 0.06)	1.42 (0.06–23.13, P = 0.82	0.67 (0.00–197.26, P = 0.89)
Target LAD vs. CX	0.44 (0.19–1.00, P = 0.056)	2.52 (0.22–36.91, P = 0.47	10.09 (0.01–13 621.23, P = 0.53)
Target PDA vs. CX	1.43 (0.62–3.25, P = P = 0.40)	4.05 (1.15–16.43, P = 0.037)	7.75 (0.70–85.43, P = 0.09)
Conduit RA vs. LITA	2.88 (0.55–12.58, P = 0.17)	2.57 (0.12–62.79, P = 0.55)	12.19 (0.01–29 320.96, P = 0.53)
Conduit RITA vs. LITA	2.61 (1.28–5.62, P = 0.011)	2.75 (0.16–55.88, P = 0.50)	5.48 (0.01–4828.03, P = 0.62)
N sequential	1.38 (1.03–1.86, P = 0.032)	0.66 (0.27–1.64, P = 0.37)	0.90 (0.13–6.42, P = 0.92)
Age	1.01 (0.98–1.05, P = 0.35)	—	—
Cholesterol	0.77 (0.37–1.70, P = 0.50)	—	—
Diabetes	0.50 (0.24–1.00, P = 0.056)	0.42 (0.15–1.10, P = 0.08)	0.21 (0.01–3.08, P = 0.25)
Smoking	0.96 (0.50–1.83, P = 0.90)	—	—
PVD	0.84 (0.37–1.81, P = 0.67)	—	—
CKD	3.24 (0.74–14.23, P = 0.11)	—	—
MI	0.80 (0.36–1.67, P = 0.56)	—	—
EF	1.02 (0.99–1.05, P = 0.13)	—	—
Prior PCI	0.58 (0.26–1.22, P = 0.17)	—	—
Syntax score	0.96 (0.91–1.01, P = 0.11)	—	—
Target diameter	0.94 (0.51–1.15, P = 0.70)	—	—
Run-off B	0.37 (0.08–1.12, P = 0.12)	—	—
Run-off C	–	—	—
Off-pump	2.18 (0.91–6.09, P = 0.10)	—	—

CKD, chronic kidney disease; CX, circumflex; DIA, diagonal; DS, degree of stenosis; EF, ejection fraction; FFR, fractional flow reserve; LAD, left anterior descending; LITA, left internal thoracic artery; MI, myocardial infarction; N, number; OR, odds ratio; PCI, percutaneous coronary intervention; PDA, posterior descending artery; PVD, peripheral vascular disease; RA, radial artery; RITA, right internal thoracic artery.

Table 3 Predicted probability of non-functional graft from bootstrap simulations of model predictions (R = 1000)

FFR	Target	Predicted probability of non-functional graft	Absolute risk difference
<0.78	CX	0.02 (0.00–0.06)	Reference
≥0.78	CX	0.53 (0.36–0.69)	0.51 (0.35–0.65, P < 0.001)
<0.78	PDA	0.08 (0.02–0.17)	0.05 (0.00–0.14, P = 0.020)
≥0.78	PDA	0.82 (0.64–0.95)	0.81 (0.60–0.95, P < 0.001)
<0.78	DIA	0.02 (0.00–0.06)	0.00 (-0.04 to 0.03, P = 0.95)
≥0.78	DIA	0.54 (0.00–0.85)	0.53 (-0.03 to 0.84, P = 0.25)
<0.78	LAD	0.04 (0.00–0.10)	0.02 (-0.02 to 0.08, P = 0.23)
≥0.78	LAD	0.71 (0.44–0.93)	0.69 (0.41 to 0.92, P < 0.001)

CX, circumflex; DIA, diagonal; FFR, fractional flow reserve; LAD, left anterior descending; PDA, posterior descending artery.

However, FFR evaluation is not part of the standard assessment of patients referred for CABG, and limited information on the role of FFR in cardiac surgery is available. Botman *et al.*[17] examined the correlation between FFR measurement and graft patency, and found that grafting a stenosis with FFR > 0.75 significantly increase the risk of graft occlusion (P < 0.0001). Honda *et al.*[20] evaluated the association between the preoperative FFR in the LAD and the intra-operative flow measured in the LITA-LAD graft and observed that FFR was positively correlated with graft flow, and systolic reverse flow. The authors concluded that when a coronary lesion measured between 0.70 and 0.75 by FFR, there was a greater likelihood of competitive flow.

Fournier *et al.*[21] performed a retrospective trial of 627 patients having at least one intermediate stenosis assessed as intermediate by

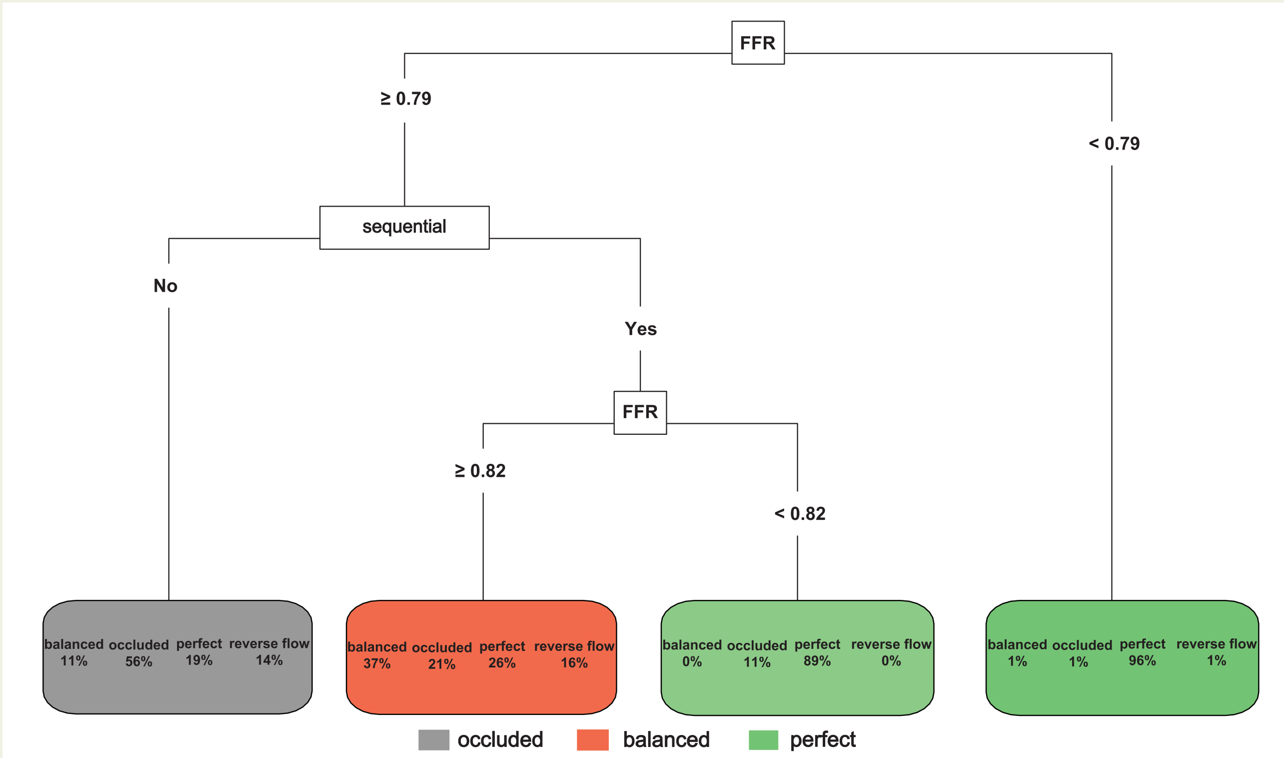


Figure 3 Classification tree. Ach node shows the predicted class, the predicted probability for each class (from left to right: balanced, occluded, perfect, reverse flow), and the percentage of observation in the node.

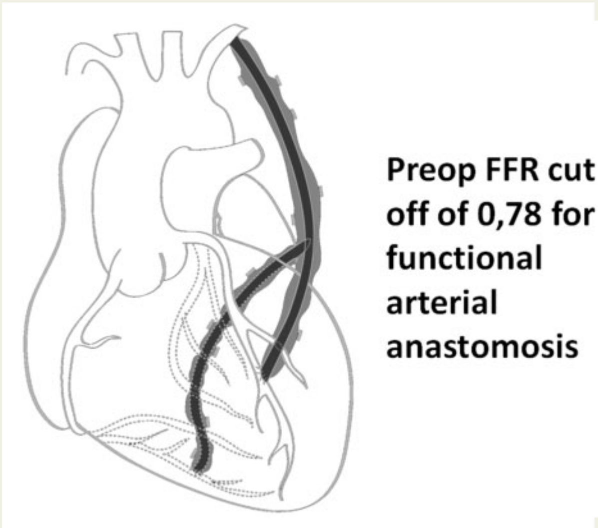
Table 4 Comparison between the Fractional Flow Reserve vs. Angiography Randomization for Graft Optimization (FARGO) trial and the Impact of Preoperative FFR on Arterial Bypass Graft Function (IMPAG) study

	FARGO	IMPAG
Patients	100	68
Anastomoses	267	199
Arterial anastomoses	100	199
Mean number of anastomoses per patient	2.6 FFR/3.0 angio	2.9
Predicted power	80	90
Mean follow-up (months)	6	6
Follow-up (patients)	72	64
Graft occlusion rate	16% FFR/12% angio	13.6%
Calculated power	<10%	100
Main findings	FFR-guided bypass surgery had similar graft failure rates and clinical outcomes as angiography-guided bypass surgery	FFR predict graft patency at 6 months significantly better than angiography

FFR, fractional flow reserve.

either coronary angiography alone or angiography plus FFR. The authors found that patients in the FFR-guided group had fewer anastomoses, and a lower rate of death and myocardial infarction 6 years after surgery (hazard ratio 0.59, 95% CI 0.38–0.93).

Of note, the recent Fractional Flow Reserve vs. Angiography Randomization for Graft Optimization (FARGO) trial[22] found that FFR-guided CABG had similar graft failure rates and clinical outcomes as angiography-guided CABG. Reasons for the difference compared



Take home figure In the IMPAG trial, pre-operative FFR <0.78 was associated with anastamotic functionality 6 months after CABG.

to our findings are likely the low power of the FARGO trial (the study was prematurely stopped at 58% of the planned enrolment and angiographic control was available in only 74% of the enrolled sample) and the prevalent (67%) use of vein grafts (much less sensitive to competitive flow than arterial grafts). A comparison between the two studies is provided in *Table 4*. It is of note that in FARGO, there was a good correlation between the visual estimation of coronary artery stenosis and the FFR value, which contradict our findings and most of the published literature.[10]

Currently at least two prospective randomized trials are evaluating the role of FFR in CABG. The GRAFFITI trial,[23] is a prospective, randomized, double-blind, multicentre study examining the rate of occluded bypass grafts 1 year after surgery between angiographic vs. FFR-guided CABG. The FFR-Guided Percutaneous Coronary Intervention and CABG Surgery in patients with multivessel CAD (FAME) 3 Trial is a prospective, multicentre, randomized study with major adverse cardiovascular and cerebrovascular events (MACCE) at 1 year as the primary outcome, and enrolment is ongoing.[24] The results of these trials will help to define the role of FFR in improving the outcome of CABG patients.

Our results suggest that preoperative FFR is associated with anastomotic function at 6 months in CABG patients receiving arterial grafts. Further studies are necessary to evaluate if the increase in anastomotic function translates to improved clinical outcomes.

Limitations

Our study's short follow-up is a very important limitation. Even more importantly, this analysis was performed after inclusion of slightly more than 50% of the planned sample size so we cannot exclude that the study is underpowered and a type I error cannot be ruled out. However, the high level of significance for all the outcomes and the very high power at *post hoc* calculation make us confident in the solidity of our findings. The study was performed at two specialized care centres with expertise in performing both FFR and CABG with arterial grafts, and both the efficacy and safety results may not reflect the results in other centres and for surgeons using venous grafts. Finally, the study is obviously underpowered to detect differences in clinical outcomes.

Conclusion

We describe a highly significant association between preoperative FFR and anastomotic arterial graft function at 6 months in CABG patients. Arterial grafts to target vessels with FFR <0.78 had extremely high patency rate at 6 months. These results suggest that FFR may play an important role in pre-operative planning of CABG procedures and should be utilized whenever possible, particularly for surgeons utilizing multiple arterial conduits.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: F.F.R. wires used in this study were provided by Abbot Medical Inc. Abbot Medical was not involved in the study design, data collection, or data analysis. None of the authors has any other conflict of interest to declare.

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