

# Impact of target coronary artery stenosis severity measured by instantaneous wave-free ratio on bypassed graft patency

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## Abstract

**Background:** This study aimed to assess the impact of the measurement of the degree of target coronary artery stenosis using the instantaneous wave-free ratio (iFR) on patency of attached grafts.

**Materials and methods:** A total of 86 grafts were assessed by computed tomography angiography after coronary artery bypass grafting in 24 patients with multivessel coronary artery disease. The iFR was evaluated for all target coronary arteries. The coronary artery stenoses were divided into three groups based on the iFR value: iFR < 0.86 (group 1); iFR 0.86–0.90 (group 2); and iFR > 0.90 (group 3).

**Results:** Computed tomography angiography was performed at 192±44 days (range: 80–318 days). The correlation coefficient (r) between iFR and failed grafts was 0.332 (p=0.035). Graft failure was detected in three grafts (8.1%) for group 1, in two grafts (8.3 %) for group 2, and in four grafts (16%, all arterial grafts) for group 3. Statistically significant differences were found between groups 1 and 3 (p=0.041) and between groups 2 and 3 (p=0.044). No significant differences were found between groups 1 and 2 (p=0.228).

**Conclusion:** The degree of coronary artery stenosis measured by iFR is a risk factor for attached graft failure. In a coronary artery where the iFR was haemodynamically non-significant, a higher rate of graft failure was detected.

**Key words:** coronary artery bypass grafting, instantaneous wave-free ratio, graft failure, computed tomography angiography

## Introduction

Invasive coronary angiography (ICA) used to be the gold standard for decision making in guiding myocardial revascularisation, and was used as a benchmark to compare new methods to. However, limited correlations between angiographic findings and functional stenosis severity [1] enabled the development of functional assessment of coronary stenoses using intracoronary guidewires.

In the last decade, there has been renewed interest in the field of coronary physiology, driven by the introduction of a new, non-hyperaemic, pressure-based index of stenosis severity: the instantaneous wave-free ratio (iFR) [2]. In 2018, European cardiologists recommended iFR for the assessment of intermediate-grade stenosis [3]. There are currently no powerful data to assess the clinical benefits of iFR in guiding coronary

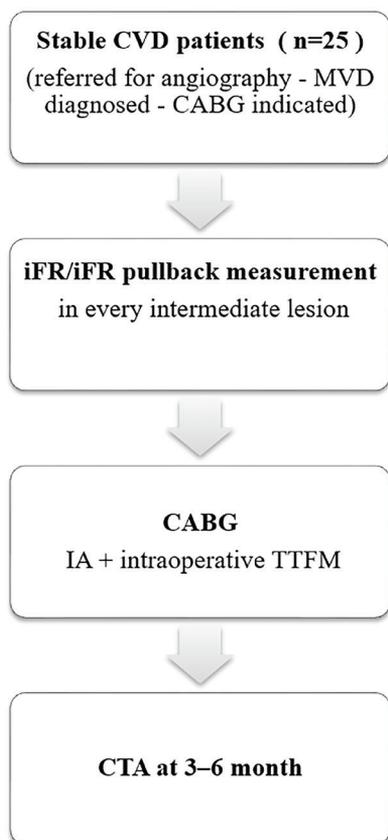
artery bypass grafting and no data showing that iFR can be a direct strong predictor of graft patency. Given the close association between iFR and flow in the coronary artery, and considering effect of the competitive flow on the graft patency, iFR may be suitable for guiding bypass grafting [4]. The aim of our study is to evaluate the impact of the iFR-determined coronary lesion severity as a factor for predicting graft failure.

## Material and methods

### Study population

Our prospective study included 25 patients with stable multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) surgery (Figure 1). This study is a follow-up to an article we previously published, where we investigated the correlation between

**Figure 1** - Flow chart of study design. CVD—coronary vessel disease; MVD—multivessel disease; iFR—instantaneous wave-free ratio; CABG—coronary artery bypass grafting; IA—intraoperative angiography; TTFM—transit time flow measurement; CTA—computed tomography angiography.



preoperative coronary artery stenosis severity measured by iFR and intraoperative transit time flow measurement (TTFM) of attached grafts [5].

iFR was measured in all angiographically intermediate (40–75% by diameter) stenoses of coronary arteries. The attached grafts were divided into three groups according to the preoperative iFR degree: group 1 (iFR < 0.86), group 2 (iFR 0.86–0.90), and group 3 (iFR > 0.90). Consensus about target arteries based on angiography findings was reached before iFR measurements were taken, and grafts in this study were attached despite negative iFR results. The standard medical treatment according to the European Society of Cardiology (ESC) guidelines on chronic coronary syndrome was provided for all patients [6]. The enrollment of the patients was consecutive. Computed tomography angiographies (CTA) were performed in 24 patients.

Permission for the study was confirmed by the Kaunas Regional Biomedical Research Ethics Committee on 9 September 2019 (Nr. BE-2-70).

### iFR measurement

iFR was performed using a standard technique, at the catheterisation laboratory. Physiological measurements were taken using a coronary pressure guidewire (Verrata, Philips Volcano, San Diego, CA, USA). To avoid vasomotor reactions, intracoronary nitrates were administered before every measurement. The iFR cut-off point was 0.90, where stenosis with iFR > 0.9 was considered haemodynamically non-significant [2,7], while stenosis with an iFR of 0.86–0.90 was considered to be the “gray zone” and iFR < 0.86 was considered

severe coronary stenosis [8]. All iFR measurements were done by the same operator, and iFR was measured distally and with pullback to localise the most severe lesion in each targeted vessel.

### Revascularisation

All CABG procedures were performed in a hybrid operating room, via median sternotomy on cardiopulmonary bypass (CPB), with heparinisation and ensuring activated clotting time (ACT) > 480 s. In all cases, we used antegrade cardioplegia (cold St. Thomas solution). Harvesting of internal mammary artery (IMA) grafts was performed with diathermy cautery coagulation on pedicle clips. For the second and third graft, a saphenous vein graft (SVG) was used. Harvesting for SVG was performed using the complete continuous open technique and interrupted bridging skin incision with skeletonisation. IMA distal anastomosis was performed using 8-0 Prolene (Ethicon, monofilament) sutures using the “parachute” technique. For SVG distal anastomoses, 7-0 Prolene (Ethicon, monofilament) sutures were used, using the “parachute” technique, and for proximal anastomoses on the ascending aorta, 6-0 Prolene (Ethicon, monofilament) was used. All attached grafts were assessed by intraoperative completion angiography and TTFM.

### Computed tomography angiography

The CTA was performed within 3–6 months of CABG on a 320 slice multidetector computed tomography (MDCT). All patients were given sublingual 0.3–0.4 mg nitroglycerin and/or beta-blockers (oral metoprolol 30–70 mg) 2 minutes prior to CTA, with Electrocardiography (ECG) heart rate control. The contrast agent was administered intravenously using an injector. Scans were undertaken with collimation of 0.6–0.625, a gantry rotation time of 275–350 ms, and a voltage of 120 kV. All patient data were rendered on a workstation using multiplanar reconstructions and three-dimensional volume rendering. Any stenosis of more than 70% within the grafts was considered as a loss of graft patency.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23 (Armonk, NY, USA: IBM Corp. Software). We calculated statistical characteristics such as the total observation number, mean, median, and standard deviation using descriptive statistics. Continuous variables are presented as the mean and standard deviation (SD), or median and interquartile range (IQR), while categorical data are expressed as numbers (percentages). After testing for normality, group differences were tested using Student’s t-test and Kruskal–Wallis analysis of variance (ANOVA) to compare samples. The correlation between graft patency and iFR was evaluated by one-way ANOVA analysis. The qualitative analysis of the groups was performed using the chi-square test. Variables with a two-sided p value < 0.05 were considered statistically significant.

## Results

### Study population

The participant characteristics (Table 1) and graft characteristics (Table 2) of this study were discussed in our previous article [5]. The left internal mammary artery (LIMA) was used in situ for bypassing the left coronary territory. The right internal mammary artery (RIMA) and bilateral internal mammary artery (BIMA) were not used in this study. SVG were mainly used for the right coronary artery or circumflex artery.

**Table 1** Patient characteristics

Variable	Value
Age	63.8 ± 8.9 (48–78)
Body mass index (kg/m <sup>2</sup> )	27.2 ± 4.79
Sex	
Male	23 (92%)
Hypertension	23 (92%)
Diabetes mellitus	2 (8%)
Dyslipidemia	22 (88%)
Arrhythmia	4 (16%)
Previous PCI	9 (36%)
Previous MI	15 (60%)
History of smoking	15 (60%)
LV EF %	47.12 ± 6.4
NYHA	
II	19 (76%)
III	6 (24%)
Euro score II	1.38 ± 0.75
Syntax score	31.38 ± 4.33
Distal anastomoses per pt.	3.56 ± 0.82 (2–5)

Abbreviations: PCI—percutaneous coronary intervention; MI—myocardial infarction; LV EF—left ventricular ejection fraction; NYHA—New York Heart Association; and pt—patient.

**Table 2** Graft characteristics

Variable	Group 1 (iFR < 0.86)	Group 2 (iFR 0.86–0.90)	Group 3 (iFR > 0.90)
Distal anastomosis	40	24	25
Grafts	36	22	23
SVG to RCA	7 (17.5%)	4 (16.6%)	3 (12%)
SVG to PDA	8 (20%)	5 (20.8%)	2 (8%)
SVG to OM	11 (27.5%)	6 (25%)	9 (36%)
SVG to diagonal	3 (7.5%)	2 (8%)	4 (16%)
LIMA to LAD	11 (27.5%)	7 (29%)	7 (28%)
Sequential grafts	4	2	2

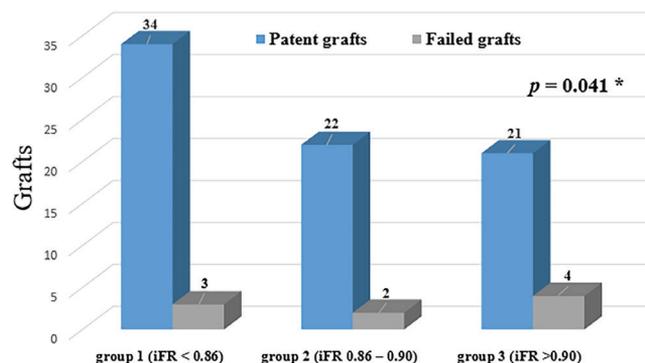
Abbreviations: SVG—saphenous vein grafts; RCA—right coronary artery; PDA—posterior descending artery; OM—obtuse marginal artery; LIMA—left internal mammary artery; LAD—left anterior descending artery; results reported as total number and percentage of all grafts.

## CTA results

Perioperative mortality was documented for one patient. CTA was performed at 192±44 days (range 80–318 days) after CABG for 86 attached grafts in 24 patients. There were 37 grafts (27 SVG and 10 LIMA) in group 1 (iFR < 0.86), 24 grafts (17 SVG and 7 LIMA) in group 2 (iFR 0.86–0.90), and 25 grafts (18 SVG and 7 LIMA) in group 3 (iFR > 0.90).

The correlation coefficient (r) between iFR and graft failure was 0.332 (p=0.035). Graft failure was detected in 3 grafts (8.1%, 2 SVG and 1 LIMA) for group 1, in 2 grafts (8.3 %, 1 SVG and 1 LIMA) for group 2, and in 4 grafts (16%, all LIMA) for group 3 (Figure 2). Statistically significant differences were found between groups 1 and 3 (p=0.041) and between groups 2 and 3 (p=0.044). No significant differences were found between groups 1 and 2 (p=0.228).

**Figure 2** - This graph shows the proportion of failed grafts in each group. \* Significant difference between group 1 and group 3.



## Discussion

This was a small prospective pilot study of 25 patients (aged 63.8±8.9 (48–78)) who underwent preoperative iFR measurement of the target arteries and postoperative follow-up by CTA (in 24 patients) of the attached grafts. Globally, coronary artery disease (CAD) has become the most common cause of death in countries from all income groups [9]. Even though CABG remains the mainstay in the treatment of symptomatic CAD patients [3,10], graft failure after CABG is a determining factor for morbidity and mortality [11,12]. CTA has recently become the standard clinical tool in graft assessment after CABG procedures. A meta-analysis of more than 2000 combined grafts showed 97.6% sensitivity and 96.7% specificity of the results of graft obstruction in CTAs with both 16 and 64 sections [13]. In another prospective study, graft patency was assessed using a 64-slice CTA followed by an invasive coronary angiography. This showed a sensitivity of 97%, specificity of 97%, and positive and negative prognostic values of 93% and 99% [14].

Despite the fact that ICA has long been the gold standard in assessing graft patency after CABG, it carries a 0.08% risk of myocardial infarction and a 0.7% risk of minor complications in clinically stable patients [15]. A significantly higher radiation exposure was observed for CTA (18–45 mSv) than ICA (7–9 mSv), but the volume of contrast agent was lower for 64-slice CTA (130–148 mL) than for ICA (110–223 mL) [14,16]. CTA with 128 slices showed low radiation exposure (2.3 ± 0.3 mSv), comparable to ICA [17]. There are limitations to CTA, with difficulties in accurate visualisation of distal anastomoses and clip associated artifacts [18]. The development of technology and integration of CTA with the fractional reserve flow (FFR) improved the visual assessment of graft patency and perfusion with a functional indicator [19,20]. At the moment, there is little FFR CT data to assess graft patency in patients after CABG. However, this is undoubtedly a promising direction, and perhaps with the development of scanning technology, it will replace ICA in the near future.

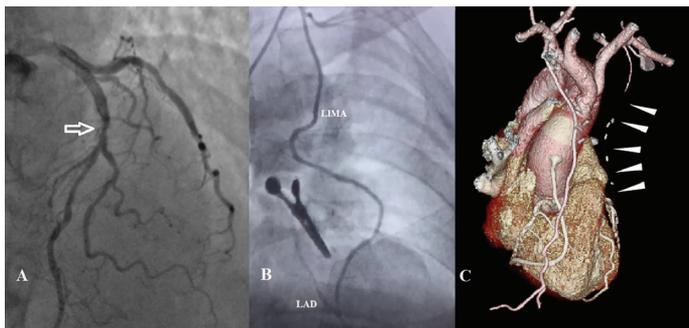
Our results show that non-significant coronary artery stenosis (iFR > 0.90) is associated with an increased risk of graft failure. In addition, all of the lost grafts were arterial grafts (LIMA) in group 1 (iFR > 0.90), which is possibly related to the sensitivity of arterial grafts to competitive flow from the native coronary artery [21,22]. However, the LIMA graft demonstrated superior patency compared with other grafts and the strategy of grafting to the left anterior descending artery is considered the “benchmark” for coronary revascularisation [23,24]. The internal mammary artery endothelium possesses a number of properties

that make it resistant to the development of atherosclerosis [25]. Current data recommend skeletonised internal mammary artery harvesting for revascularisation, with low thermal damage providing an improved endothelial layer and better integrity of the vessel wall [26]. IMA graft failure most commonly results from damage during mobilisation or harvesting, spasm, inflammation or suboptimal target vessel anastomosis [22]. In our study, we excluded technical errors due to errors of the surgeon by means of intraoperative angiography and TTFM. Interestingly, the degree of target vessel stenosis does not impact on SVG patency rate, as perfusion was directly from the aorta with higher pressures compared to arterial grafts [27]. Nevertheless, the process of SVG atherogenesis begins with early circumferential intimal thickening within the first year, followed by multilayered foam-cell accumulation. Between two and five years after bypassing, a necrotic core develops in the SVG intima and after 5–10 years the plaque will usually rupture; this corresponds to the period of SVG patency [22]. Acute thrombosis is usually the cause of an early SVG failure that occurs within days or months [28]. After harvesting of the vein with skeletonisation, there is disruption and damage to the adventitia and nutritional disturbance of the vessel occurs, which in turn leads to the development of acute thrombosis with intimal hyperplasia [29–31]. After bypass, the vein is exposed to wall stress, increasing the vein diameter and reducing blood velocity [32,33]. The data show that over-distension of the vein to check for leakage also contributes to the removal and/or dysfunction of the endothelium and medial damage [34]. Venous valves with turbulent flow can also cause intimal hyperplasia and thrombosis [35].

In a previous study, Wada et al. assessed the impact of iFR on graft failure after CABG, showing that target vessels with iFR 0.90–0.94 or 0.95–1.0 had a 28% and 50% ( $p = 0.002$ ) failure rate of attached arterial grafts at one year post-treatment [36]. In group 3 (iFR > 0.90) of our study, the loss rate of arterial grafts was 40% (Figure 3).

**Figure 3** - 65-year old female with three-vessel disease. Coronary angiography before coronary artery bypass grafting. Proximal LAD had 75% stenoses angiographically and the iFR was 0.92 (A, white arrow). Selective intraoperative angiography demonstrated attached LIMA graft patency (B). CTA showed that the LIMA to LAD graft had failed (C, white arrowheads).

*iFR—instantaneous wave-free ratio; LAD—left anterior descending coronary artery; LIMA—left internal mammary artery; CTA—computed tomography angiography.*



The iFR is a promising method for evaluation of coronary physiology. Based on comparisons to FFR, the cut-off point for iFR is 0.90 [2,7]. Define-Flair and iFR Swedeheart are prospective, randomised trials, which have compared FFR and iFR for the guided revascularisation strategy, and iFR showed similar results [37,38]. The Define-Flair trial demonstrated deferral from revascularisation in the iFR group, affecting 54%

(677) of patients and 50% (625) of patients in the FFR group [38]. The significant advantages of iFR compared to the existing methods for the evaluation of coronary physiology have been shown [4]. These advantages include: being adenosine-free, the time of the study is quicker than for FFR, the low level of discomfort for patients, ability to assess serial lesions, and superior signal-to-noise ratio compared to Pd/Pa. However, Rey et al. noted the importance of collateral blood flow to the target vessel and correct assessment of coronary physiology (iFR) to guide decision-making for CABG, which can reduce the risk of early graft failure [39].

Coronary revascularisation is crucial in the treatment of patients with coronary artery disease [3] and well-coordinated heart teamwork is required to avoid subjecting patients to inappropriate revascularisation of functionally insignificant stenoses.

## Limitations

Our study has several limitations. The cohort consisted of a small number of participants in a single-center study. This study combines the cardiologists' and surgeons' efforts, and recruiting a large sample of patients within a set period of time was a limitation of our study. For the calculations, we used data from both arterial and venous grafts and no separation of the revascularisation area. Graft patency on CTA was assessed over an average of  $192 \pm 44$  days (range, 80–318 days), with no data collected on long-term outcomes.

## Conclusion

The degree of coronary artery stenosis measured by iFR is a predictor of attached graft failure. In coronary arteries where the iFR was haemodynamically non-significant, a higher rate of graft failure was detected.

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