CORONARY ARTERIES

Limited Flow Reserve in Non-Obstructed Bypass Grafts Supplying Infarcted Myocardium: Implications for Cardiovascular Magnetic Resonance Imaging Protocols

Christian Spies, MD,1 Oliver K. Mohrs, MD,2 James R. Madison, DO,3 Andreas Fach, MD,2 Bernd Nowak, MD, FESC,2 and Thomas Voigtländer, MD2

Rush University Medical Center, Section of Cardiology, Chicago, Illinois, USA,1 Cardioangiologisches Centrum Bethanien (CCB), Frankfurt/Main, Germany,2 University of California Davis, Division of Nephrology, Sacramento, California, USA3

ABSTRACT

We evaluated flow reserve in non-obstructed bypass grafts supplying infarcted and non-infarcted myocardium. Bypass grafts were examined by phase-contrast flow measurements and myocardial viability was assessed with late enhancement technique. Flow reserve was higher in bypasses supplying normal myocardium compared to those supplying infarcted myocardium (2.9 vs. 1.5, p < .0001). This difference remained significant after adjusting for co-variables. Bypass grafts supplying infarcted myocardium were more likely to have lower flow reserve than those supplying normal myocardium (flow reserve ≤ 2, 84% vs 18%, p = .0003). Flow reserve is reduced in non-stenosed bypasses supplying infarcted myocardium, likely due to altered microcirculation. Thus, cardiovascular magnetic resonance based bypass assessment must include myocardial viability testing.

INTRODUCTION

Coronary artery bypass grafting (CABG) is one of the mainstays of coronary revascularization with 515,000 performed procedures in the US annually (1, 2). With bypass patency rates of 61–85% at 10 years follow-up recurrent angina in post-CABG patients is a frequently encountered clinical scenario (3, 4). Conventional coronary angiography is considered the gold standard for evaluation of subsequent graft disease. However, its invasiveness, X-ray exposure, and risk for complications make an alternative non-invasive diagnostic modality desirable (5). Cardiovascular magnetic resonance (CMR) is a promising alternative surveillance tool for patients with suspected graft disease following CABG. Several reports demonstrated the ability of CMR to discriminate between grafts with significant stenosis (≥50% or ≥70% luminal diameter by cine conventional angiography) from those without stenosis by combining CMR derived, anatomic information of 2D-angiography, and physiologic characteristics with flow reserve (FR) estimates using phase-contrast flow mapping (6–9).

However, since FR is a function of epicardial blood flow and coronary microcirculation, not only bypass or native coronary artery stenosis can cause reduced FR. Among several factors known to reduce coronary microcirculation is the presence of left ventricular hypertrophy, hypertension, diabetes mellitus, left ventricular dysfunction, prior myocardial infarction, smoking, hyperlipidemia, and obesity (10–15). To which extent these factors influence the FR in bypass grafts is unknown. Prior studies have either not addressed this potential limitation of CMR based FR measurement, or patients with these conditions were excluded from the studies. This would seemingly create an artificially selected subgroup, since the majority of patients...
undergoing CABG likely have at least one of the aforementioned co-factors (6–9, 16).

The goal of the present study was to evaluate the role of myocardial scarring on FR measured with CMR phase contrast flow mapping in bypass grafts without significant stenosis.

METHODS

Study population

We retrospectively identified patients with a history of CABG who underwent a complete CMR based bypass graft evaluation between December 2002 and August 2004. Patients were required to have a recent conventional coronary angiogram within 3 months of the time of CMR bypass evaluation, which showed no evidence for significant stenosis in the bypass graft evaluated with CMR. No change in the patients’ clinical status or medication regimen could occur between procedures. All patients were in sinus rhythm. We excluded patients with irregular heart rhythms or unstable angina. Written informed consent was obtained from all participants. Initial screening of our database revealed 45 potential bypass grafts in 29 patients (Fig. 1). After reviewing the CMR and conventional angiography data files and images, 15 bypass grafts had to be excluded because either the bypass graft or runoff vessels had significant stenosis (n = 9), as defined in the following paragraph or were occluded (n = 3), the CMR image quality was inadequate due to artifact from vascular clips (n = 1), or the vascular territory of the bypass grafts was supplied by large collateral flow (n = 2). The remaining 30 bypass grafts in 19 patients were included in the present analysis.

Conventional coronary angiography

Selective X-ray angiography was performed using the Judkins technique with standard 4–6F catheters. All native vessels, saphenous vein grafts, internal mammary grafts and stumps were visualized in 2 orthogonal views. Grafts with a stenosis more than 20% in diameter of the bypass or run-off vessel as well as grafts supplying vascular territory receiving significant collateral blood flow by cine angiography were excluded. Collateral blood flow was analyzed subjectively as present or absent.

Cardiovascular magnetic resonance imaging

Prior to CMR evaluation the surgical report was reviewed to identify number of proximal anastomoses and their corresponding sites of distal anastomoses in all patients. CMR was performed on a 1.5-T MRI system (Magnetom Sonata Mastro Class, Siemens Medical Solutions, Erlangen, Germany). For signal detection the combination of a six-channel body phased-array coil and a two-channel spine phased-array coil was used. ECG-signal was received from an external system (Magnitude 3150, InVivo Research Inc., Orlando, FL, USA). Patients were monitored throughout the procedure with non-invasive blood pressure, heart rate and continuous electrocardiographic measurements.

First, for visualization of the graft origin and course, a multi-slice two-dimensional breath-hold, ECG-gated, double inversion, black blood turbo spin-echo sequence (echo time 44 ms; acquisition window 800 ms, field of view 230 to 350 mm; matrix 176 × 256, slice thickness 5 mm) was applied in axial and individual planes. ECG-gated, breath-hold, contrast-enhanced 3D-gradient-echo angiography was applied using gadolinium–diethylene triamine pentaacetic acid (DTPA, dosage 0.1 mmol/kg body weight) to evaluate patency and course of each graft. Typical sequence parameters for MR angiography were the following: TR 3.1 ms, TE 1.2 ms; voxel-size 1.2 × 0.9 × 2.0 mm³, flip angle 20°, matrix 240 × 384, partitions 52, slab-thickness 104 mm.

Second, ECG-gated, breath-hold, phase-contrast flow mapping was performed based on different localizer planes (typical sequence parameters: TE 4.2 ms, temporal resolution 70 ms, segmentation 7, breath-hold of approximately 20–30 seconds, flip angle 30°, velocity encoding 75 cm/s, voxel-size 1.4 × 0.8 × 6.0 mm³) (Fig. 2). Flow data of each visible graft were acquired at rest and during adenosine-induced hyperemia (dosage 140 µg/min/kg body weight, first measurement 3 minutes after start of infusion). Flow mapping was performed in the proximal third of saphenous vein grafts (SVG) to minimize motion due to cardiac pulsations, while left internal mammary artery (LIMA) grafts were evaluated in the mid third as more proximal measurements would be inaccurate due to a larger proximity to the isocenter.

Third, an ECG-gated, breath-hold, segmented inversion-recovery-turboFLASH-sequence “TrueFISP-cine-sequence” (TE 4.4 ms; acquisition window 800 ms, segmentation 25, TI optimized to null the myocardium, typical at 200 to 300 ms; flip angle 30°, voxel-size 1.7 × 1.3 × 6.0 mm³) served for

![Figure 1. Flow chart of included bypass grafts. Initial database search revealed 45 potential bypass grafts. After review of the CMR and conventional angiography images 15 grafts had to be excluded. Thirty bypass grafts remained which underwent complete CMR evaluation and which were found to have at most 20% stenosis on conventional angiography. Grafts were separated into two groups based on presence or absence of prior myocardial infarction in the vascular territory of the bypass as determined by late enhancement CMR imaging.](image-url)
detection of non-viable myocardium in a stack of contiguous long axis views and short axis planes (Fig. 3). Images were acquired approximately 15 minutes after administration of a second bolus of 0.1 mmol/kg gadolinium-DTPA (total dosage 0.2 mmol/kg).

**Data analysis**

Conventional angiography and CMR bypass data were reviewed separately by two experienced readers (C.S. and O.K.M.) at different time points. The readers were blinded to the results of the other imaging modality. Flow velocity analysis and quantification of left ventricular mass and ejection fraction was performed using an analytic software package (Argus Software, Siemens Medical Solutions, Erlangen, Germany). FR was calculated as the ratio between flow velocity at maximal hyperemia and baseline. Vascular territory supplied by the bypass graft and area of myocardial scarring on late enhancement were categorized following the AHA 17-segment model (17).

To allow analysis of regional myocardial function, percent myocardial thickening (PMT) was analyzed in segments 1 to 16 of the AHA 17-segment model. PMT was calculated as end-systolic myocardial thickness (ESMT) minus end-diastolic myocardial thickness (EDMT) divided by EDMT × 100. Further, as a surrogate marker for regional myocardial mass, EDMT was evaluated separately. Measurements in the 16 segments were taken in three representative short axis views (basal, mid-ventricular, and apical), thus excluding the apical segment 17 from the analysis. According to the vascular territory supplied by the bypass graft as determined on conventional angiography, PMT and EDMT was calculated as the mean of all segments within this territory. Further, PMT and EDMT was calculated for the entire heart (segments 1 to 16) as a reference value.

According to the presence of myocardial scarring in the bypass distribution as seen on late enhancement imaging, grafts were categorized into 2 groups: 1) grafts supplying normal, completely viable myocardium, and 2) grafts supplying either partially or completely non-viable myocardium due to prior myocardial infarction (Fig. 1). Bypass grafts supplying normal myocardium were required to have no segmental overlap between the vascular territory served by the bypass graft and abnormal
late enhancement in the same territory, whereas grafts supplying infarcted myocardium had at least one segmental overlap.

**Statistical analysis**

Continuous data is presented as median and range, except for the unadjusted and adjusted variables in the analysis of variance (ANOVA), which is presented as mean with standard deviation (SD) and mean with 95% confidence interval (CI), respectively. Differences in baseline characteristics between the two groups were compared with Mann-Whitney U-test for continuous data and chi-square test for dichotomous variables. We used ANOVA to compare the mean flow reserve adjusting for variables that were associated with FR (at p < .15) and for variables known to affect FR (diabetes mellitus, hypertension, and obesity).

To determine an independent association of the presence or absence of myocardial scarring with FR, we used binary logistic regression analysis. FR was divided in two groups, either ≤2, or >2. The same confounders were entered in a sequential analysis as described above for the ANOVA. Analyses were performed with SPSS software (Version 13.0, SPSS Inc., Chicago, IL).

**RESULTS**

Of 30 grafts included in the present analysis, 12 were LIMAs and 18 SVGs. Nineteen bypass grafts were found to supply normal, non-infarcted myocardium, while 11 grafts had a vascular distribution which had at least one segment overlap with an infarcted territory as seen on late enhancement. Median age of the predominantly male patient population was 67 (range 54–82) years (Table 1). Patients with bypass grafts supplying normal myocardium were more likely to have diabetes mellitus and were more frequently prescribed nitrates and renin-angiotensin system inhibitors, although these differences did not meet statistical significance. Further, patients with grafts supplying normal myocardium had a higher ejection fraction (67% [24–78] vs 45% [24–75], p = .035) and a higher PMT in both the graft area (96% [−18–200] vs 54.5% [−15–143], p = .11) and in all myocardial segments combined (87% [21–123] vs 53% [15–105], p = .03).

Flow reserve in bypass grafts supplying normal myocardium was almost twice as high (2.9 ± 0.9 vs. 1.5 ± 0.7; p < .0001) compared to the group of bypasses with myocardial scar formation in its vascular distribution (Table 2). The difference in FR between the two groups remained significant even after adjusting for potential confounders (2.6 [2.0–3.1] vs 2.2 [1.3–3.2], p = .03), including usage of nitrates and renin-angiotensin system inhibitors, presence of diabetes mellitus, hypertension, and obesity, left ventricular ejection fraction, and PMT in the graft area and in all myocardial segments.

Bypass grafts supplying infarcted myocardium were more likely to have a FR < 2 than those supplying normal myocardium (84% vs 18%, p = .0003; Fig. 4). In logistic regression analysis, the presence of infarcted myocardium in the graft distribution was associated with a lower FR (OR 24, 95% CI 3.4–171.5, p = .002), although this association weakened after adjusting for...
and PMT in all segments.

hypertension, body mass index, ejection fraction, PMT in graft area, nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, diabetes mellitus, hypertension, and body mass index; C

\[ A = \text{Adjusted for nitrate and renin-angiotensin system inhibitor use,} \]

\[ B = \text{Adjusted for nitrate and renin-angiotensin system inhibitor use,} \]

diabetes mellitus, hypertension, and body mass index; C = Adjusted for nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, hypertension, body mass index, ejection fraction, PMT in graft area, and PMT in all segments.

potential confounders and became statistically non-significant (Table 3).

**DISCUSSION**

The present study finds that FR in non-obstructed bypass grafts supplying normal myocardial tissue was almost twice as high compared to non-obstructed bypasses supplying partially infarcted myocardium. Our finding has significant impact on the strategy of CMR-based bypass evaluation, as infarcted myocardium in the distal territory of the normal bypass graft might lead to falsely low FR values. This would lead to the false assumption that an “epicardial” bypass stenosis is present. A concept prior described in an animal model evaluating regional perfusion with magnetic resonance first-pass measurements after selective administration of adenosine and microspheres in the left circumflex territory (18).

However, an ideal non-invasive surveillance test, used to evaluate bypass grafts demands the precise distinction between stenosed and not-stenosed bypass grafts. Hence, a comprehensive bypass evaluation is warranted when using CMR technologies, which not only evaluates patency and FR of the bypass graft but also localizes myocardial scar tissue in relation to the bypass graft distribution. This becomes imperative since prior myocardial infarction is a common finding in patients with prior CABG.

The difference in FR between grafts supplying normal and infarcted myocardium remained statistically significant, even after adjusting for several confounders including left ventricular ejection fraction and PMT. The latter parameter, as well as EMDT, was included in the analysis as they are surrogate markers for regional function and mass. Bypass grafts supply only a portion of the left ventricle, but left ventricular ejection fraction and mass are parameters representing the entire left chamber. The observed loss of statistical significance of the association of presence of myocardial scarring with low FR after adjusting for confounders is not surprising, given the small sample size of the study, also leading to a wide confidence interval in the regression analysis.

Prior studies evaluating bypass grafts with CMR flow mapping have not adequately addressed the importance of myocardial scar formation and the role of microcirculation. Bedaux et al (7) addresses the impact of stenosis in the native coronary vascular structure by dividing groups based on bypass grafts with normal or abnormal runoff; however, the influence of the vascular bed distal to the epicardial vascular structure is not considered. Although Langerak et al (8) discuss the importance of the microcirculation in FR, they conclude that there is a good correlation between CMR flow characteristics and conventional angiography, minimizing the role of microcirculation in the estimation of FR. Consequently, FR alone was unable to differentiate more than 50% stenosed from non-stenosed sequential grafts. Perhaps, because sequential bypass grafts usually supply larger areas of myocardium, the influence of altered microcirculation contributes in a greater manner to these FR estimations. Additionally, Ishida et al (6) were unable to differentiate stenosed from non-stenosed grafts with CMR based coronary flow reserve measurements in internal mammary artery grafts with distal anastomosis to the left anterior descending artery.

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**Table 2. Flow reserve by presence/absence of infarcted myocardium in graft distribution**

<table>
<thead>
<tr>
<th></th>
<th>Normal myocardium (n=19)</th>
<th>Infarcted myocardium (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted mean ± SD</td>
<td>2.9 ± 0.9</td>
<td>1.5 ± 0.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted mean (A) [95% CI]</td>
<td>2.9 [2.5–3.4]</td>
<td>1.6 [0.9–2.2]</td>
<td>.008</td>
</tr>
<tr>
<td>Adjusted mean (B) [95% CI]</td>
<td>2.5 [2.1–3.0]</td>
<td>2.3 [1.5–3.1]</td>
<td>.002</td>
</tr>
<tr>
<td>Adjusted Mean (C) [95% CI]</td>
<td>2.6 [2.0–3.1]</td>
<td>2.2 [1.3–3.2]</td>
<td>.03</td>
</tr>
</tbody>
</table>

A = Adjusted for nitrate and renin-angiotensin system inhibitor use, B = Adjusted for nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, hypertension, and body mass index; C = Adjusted for nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, hypertension, body mass index, ejection fraction, PMT in graft area, and PMT in all segments.

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**Table 3. Association of flow reserve with the presence/absence of infarcted myocardium in graft distribution**

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>24 [3.4–171.5]</td>
<td>.002</td>
</tr>
<tr>
<td>Adjusted model (A)</td>
<td>19.3 [1.7–222]</td>
<td>.02</td>
</tr>
<tr>
<td>Adjusted model (B)</td>
<td>2.4 [0.07–86]</td>
<td>.63</td>
</tr>
<tr>
<td>Adjusted model (C)</td>
<td>2.6 [0.06–122.6]</td>
<td>.63</td>
</tr>
</tbody>
</table>

*Odds ratio from binary logistic regression representing the independent association between the predictor variable (presence of infarcted myocardium in the distribution of the bypass graft) and the outcome variable (flow reserve) divided into two groups (<2 and ≥2).

A = Adjusted for nitrate and renin-angiotensin system inhibitor use, B = Adjusted for nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, hypertension, and body mass index; C = Adjusted for nitrate and renin-angiotensin system inhibitor use, diabetes mellitus, hypertension, body mass index, ejection fraction, PMT in graft area, and PMT in all segments.

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**Figure 4. Proportion of bypass grafts with flow reserve greater than 2 by presence/absence of infarcted myocardium in graft distribution.**
or diagonal branches. It is possible that this finding is related to the fact that mammary arteries commonly are used regardless of myocardial viability in the vascular distribution of the grafts, but simply because their patency rates are excellent and a CABG is being done regardless. This might as well increase the importance of an altered microcirculation on the flow pattern under rest and stress in these bypasses. Finally, Nagel’s approach of excluding all patients with myocardial infarction, left ventricular hypertrophy, micro-vessel disease, cardiomyopathy, or severe valvular disease in the evaluation of native coronary vessels following stent placement does not appear to be practical, since several patients following CABG would be excluded from CMR bypass evaluation as most of them have at least on of the above listed factors potentially influencing FR (17).

The mechanism by which scarred myocardium in the territory of a non-obstructed bypass graft causes reduced FR is obvious. It is well accepted that destruction of the morphologic integrity and scar formation of the myocardium as caused by myocardial infarction negatively affects the coronary microcirculation (17, 19). Increased vascular resistance and abnormal viscosity are the purposed pathomechanisms by which hypertrophy or dysfunction of the left ventricle, hypertension, diabetes mellitus and hyperlipidemia reduces microcirculatory blood flow, secondarily leading to a reduction of FR as well (11–13, 20, 21).

In addition to describing the association between myocardial infarction and reduced FR, our study has further implications on CMR based protocols evaluating bypass grafts. It appears crucial to identify the localization of myocardial scar formation in order to reliably calculate FR, which should translate into less false-positive test results potentially further improving the specificity of CMR based bypass evaluation. A score system to calculate FR, weighting the pertinent variables FR, presence of myocardial scarring, left ventricular ejection fraction, PMT, and various comorbidities such as diabetes mellitus or hypertension, would be optimal. However, our sample size is not sufficient to develop such a model. Further, redefining the cut off value for FR in CMR based flow mapping seems warranted. However, the presented data does not allow such a modification as we have excluded stenosed bypass grafts as a comparative group. Future studies should be able to clarify these uncertainties.

Nevertheless, CMR based bypass evaluation is an intriguing approach as it provides anatomic and functional information from CMR-angiography, bypass flow characteristics and myocardial properties, by visualizing reduced microcirculation and myocardial scarring via wash-in and wash-out characteristics of a single bolus of intravenous contrast agent (Gadolinium-DTPA) during early and late enhancement, respectively (22–27). Our imaging protocol omitted early imaging after contrast administration; thus, we have no direct evidence of “pure” diminished microcirculation. However, it is reasonable to assume that with documented late enhancement limited microcirculation is present.

Since CMR is the only technology which evaluates bypass flow reserve and microcirculation, it appears superior to other tests. It provides data which otherwise can only be obtained by combining different invasive tests, as in the case for FR with transcatheter technique using Doppler or thermodilution tipped catheters, with non-invasive modalities used for assessment of myocardial perfusion or viability, such as contrast echocardiography or PET imaging (28–31). Further, adding late enhancement imaging to the regular CMR based bypass evaluation protocol, barely prolongs the scanner time if timed optimally. At our institution, gadolinium was given immediately before the flow measurements at rest and following a 6 minute adenosine infusion, a process taking about 15 minutes after which late enhancement can be documented without delay.

Several limitations apply to our study. First, as outlined above, myocardial perfusion was not measured directly, enabling us only to assume an altered microcirculation if myocardial scarring was present. Second, our sample size was not sufficient to evaluate the importance of the transmural extent of myocardial scar tissue. It is intuitive to assume that subendocardial scarring would influence FR to a lesser extent than transmural infarcts; however, this remains to be proven. Third, a history of hypertension and diabetes mellitus is a crude estimate of the actual blood pressure and glycemic control at the time examination. Although actual values of blood pressure and serum glucose would have been superior for data analysis, these data were unavailable. Further, despite being potential confounders for FR, lipid levels and smoking status were unavailable and thus not included in the analysis. Fourth, inclusion of the left ventricular ejection fraction prior to bypass surgery would have been desirable; however, this value was frequently unavailable or obtained by other modalities than CMR, preventing direct comparison.

In summary, FR in bypass grafts evaluated by CMR phase contrast flow mapping is influenced by the presence of scarring in the supplied myocardium. Thus, myocardial viability testing with late enhancement technique appears to be crucial in order to obtain a comprehensive and reliable coronary bypass evaluation with CMR.

REFERENCES
