Coronary artery bypass grafting (CABG) has historically been considered the revascularization standard for patients with multivessel and left main coronary artery stenosis. The results of percutaneous coronary intervention (PCI) have been improved by drug-eluting stent technology and, consequently, the potential indications for revascularization with PCI have expanded.1 A strategy of targeted or ischemia-driven revascularization is advocated in major guidelines. 2 Untreated ischemia is an important determinant of an unfavorable outcome, and successful ischemia-driven revascularization improves prognosis.3,4 Recent studies examining the completeness of revascularization have demonstrated that residual ischemia after revascularization in multivessel coronary artery disease insights from measurement of absolute myocardial blood flow using magnetic resonance imaging compared with angiographic assessment

Jayanth R. Arnold, BMBCh, MA, MRCP, DPhil; Theodoros D. Karamitsos, MD, PhD; William J. van Gaal, MD; Luca Testa, MD, PhD; Jane M. Francis, DCRR, DNM; Paul Bhamra-Ariza, MBBS, BSc, MRCP; Ali Ali, MBBS, MRCPI, FCPS; Joseph B. Selvanyagam, MBBS, DPhil, FRACP, FESC; Steve Westaby, MBBS, FRCS, PhD, FESC, FECTS; Rana Sayeed, MBBS, FRCS; Michael Jerosch-Herold, PhD; Stefan Neubauer, MD, FRCP, FMedSci; Adrian P. Banning, MBBS, MD, FRCP, FESC

Background—Revascularization strategies for multivessel coronary artery disease include percutaneous coronary intervention and coronary artery bypass grafting. In this study, we compared the completeness of revascularization as assessed by coronary angiography and by quantitative serial perfusion imaging using cardiovascular magnetic resonance.

Methods and Results—Patients with multivessel coronary disease were recruited into a randomized trial of treatment with either coronary artery bypass grafting or percutaneous coronary intervention. Angiographic disease burden was determined by the Bypass Angioplasty Revascularization Investigation (BARI) myocardial jeopardy index. Cardiovascular magnetic resonance first-pass perfusion imaging was performed before and 5 to 6 months after revascularization. Using model-independent deconvolution, hyperemic myocardial blood flow was evaluated, and ischemic burden was quantified. Sixty-seven patients completed follow-up (33 coronary artery bypass grafting and 34 percutaneous coronary intervention). The myocardial jeopardy index was 80.7±15.2% at baseline and 6.9±11.3% after revascularization (P<0.0001), with revascularization deemed complete in 62.7% of patients. Relative to cardiovascular magnetic resonance, angiographic assessment overestimated disease burden at baseline (80.7±15.2% versus 49.9±29.2% [P<0.0001]), but underestimated it postprocedure (6.9±11.3% versus 28.1±33.4% [P<0.0001]). Fewer patients achieved complete revascularization based on functional criteria than on angiographic assessment (38.8% versus 62.7%; P=0.015). After revascularization, hyperemic myocardial blood flow was significantly higher in segments supplied by arterial bypass grafts than those supplied by venous grafts (2.04±0.82 mL/min per gram versus 1.89±0.81 mL/min per gram, respectively; P=0.04).

Conclusions—Angiographic assessment may overestimate disease burden before revascularization, and underestimate residual ischemia after revascularization. Functional data demonstrate that a significant burden of ischemia remains even after angiographically defined successful revascularization.


Key Words: bypass surgery ■ revascularization ■ stent
WHAT IS KNOWN

- Revascularization strategies for multivessel coronary artery disease include percutaneous coronary intervention and coronary artery bypass grafting.
- In large population-based studies, anatomic scores examining the completeness of revascularization have demonstrated that residual ischemia after revascularization increases the risk of adverse outcomes after either percutaneous coronary intervention or coronary artery bypass grafting.

WHAT THE STUDY ADDS

- Functional data demonstrate that a significant burden of ischemia remains even after angiographically defined successful revascularization.
- Angiographic assessment may underestimate residual ischemia after revascularization but overestimate disease burden before revascularization.
- These data demonstrate the potential complementary role of cardiovascular magnetic resonance–based functional assessment in managing patients with complex coronary disease.

revascularization increases the risk of adverse outcomes after either PCI or CABG.5–13

Insights from physiological assessment using the pressure wire to measure fractional flow reserve have confirmed the limitation of angiography to assess the functional significance of coronary stenosis.14 Because the functional consequences of revascularization may not correlate precisely with angiographic appearances, a potential limitation of these previous studies examining completeness of revascularization is their reliance on angiographic measures.15

Cardiovascular magnetic resonance (CMR) provides an ideal modality to examine the functional status of the whole myocardium. Absolute quantification of myocardial blood flow using CMR benefits from high spatial resolution and reproducibility. Furthermore, this method permits detailed quantitative characterization of both the scale and spatial extent of ischemia, beyond the binary assessment afforded by visual techniques. In this study, we measured absolute myocardial blood flow to evaluate the completeness of revascularization and ischemia relief comprehensively in patients randomized to treatment with either CABG or PCI.

Selection and Treatment of Patients

Patient selection, randomization, and revascularization procedures are fully described previously.17 In brief, patients referred for elective angiography for investigation of angina (stable or unstable) were recruited if they had 3-vessel (>50% stenoses) or 2-vessel coronary artery disease (including a type C left anterior descending and left main disease >50%), in whom it was determined that equivalent anatomic revascularization could be achieved with either PCI or CABG. Patients with no contraindication to perfusion imaging were studied (inclusion/exclusion criteria listed in Table 1). Subjects were treated with the intention of achieving complete revascularization of all vessels >1.5 mm in diameter with stenosis >50%, as defined by quantitative coronary angiography. Patients undergoing PCI were pretreated with dual antiplatelet therapy; post-PCI, clopidogrel was continued ≥12 months, and aspirin, indefinitely. The use of drug-eluting stents was the preferred strategy for all lesions. Patients undergoing CABG ceased antiplatelet agents ≥2 days before surgery. General anesthesia was administered according to standard practice, with coronary artery bypass using nonpulsatile flow and a membrane oxygenator. As is standard clinical practice in many cardiac centers, patients received ≥1 internal mammary artery graft. Post-CABG, aspirin was continued indefinitely.

angiographic jeopardy index (MJI) was calculated using the Bypass Angioplasty Revascularization Investigation (BARI) score and using the Duke jeopardy score.12,13 Using the post-PCI angiographic appearances and the surgeon’s operative report in conjunction with the baseline angiogram for CABG, the postprocedure residual MJI (RMJI) was also calculated using both methods. Complete revascularization was defined as RMJI=0, mildly incomplete revascularization as RMJI>0 and <33%, and moderate-to-severe incomplete revascularization as RMJI≥33%. Angiographic data were also evaluated in relation to the 17-segment AHA model and, using surgeon’s operative report, segments were characterized as to whether they had been revascularized, and whether the graft type was arterial or venous.14

CMR Procedures

Multiparametric CMR imaging (comprising assessment of myocardial perfusion and contractile function and late gadolinium enhancement [LGE]) was performed at 1.5-Tesla (Siemens Sonata) at baseline, and subsequently at 5 to 6 months after revascularization, corresponding to the standard interval for outcome assessment after PCI. Patients were instructed to avoid agents, which could antagonize the effects of adenosine (eg, caffeine, methylxanthines) for 24 hours before assessment.

For perfusion imaging, an ECG-gated T1-weighted fast gradient echo sequence was used (echo time, 1.04 ms; repetition time, 2 ms, saturation recovery time, 100 ms; voxel size, 2.1×2.6×8 mm³; flip angle, 17°) to acquire 3 short-axis images every heart beat (representing basal, midventricular, and apical segments) to track the first pass of a gadolinium-based contrast agent (0.04 mmol/kg intravenous bolus of Gadodiamide, Omniscan, GE Healthcare) injected at stress (after a 4-minute infusion of adenosine [140 μg/kg per minute]), and subsequently at rest (after 20 minutes). Patients were monitored by electrocardiography, sphygmomanometry, and pulse oximetry. For LGE imaging, after a further bolus of gadolinium (0.045 mmol/kg), images were acquired in the 3 long axes, and a short-axis stack using a T1-weighted segmented inversion-recovery turbo fast low-angle shot (true-FRASE) sequence (echo time, 4.8 ms; voxel size, 1.4x2.4x8 mm³; flip angle, 20°; interslice gap, 2 mm). For left ventricular (LV) function, steady-state free-precession cine images were acquired in the 3 long-axis views, and a short-axis stack (echo time/repetition time, 1.5/3.0 ms; flip angle, 60°; slice thickness, 7.0 mm, interslice, gap 3 mm).

All CMR images were analyzed in a masked fashion, presented in random order, for 16/17 segments (apical segment excluded) according to the 17-segment American Heart Association segmentation model.15 Processing time per case was 1 to 2 hours. For analysis

Study Design

Myocardial Injury following Coronary Artery Surgery versus Angioplasty (MICASA) is a prospective, single-center, randomized (1:1) trial comparing myocardial injury after PCI and CABG. IRCTN25699844: http://www.controlled-trials.com/IRCTN25699844. Methodology and results from this trial have been described previously.16,17 Differences in myocardial perfusion 6 months after PCI and CABG was a prespecified study comparison, approved by the Regional Institutional Ethics Committee. Written informed consent was obtained from each patient before enrollment.
of myocardial perfusion, signal intensity curves were generated by tracing endocardial and epicardial contours (MASS, Medis Medical Imaging Solutions, Leiden, The Netherlands), manually corrected for cardiac displacement. The myocardium was divided into equiangular segments (6 for basal and midventricular slices, and 4 for apical), and a region of interest placed at the center of the LV cavity to measure the arterial input of contrast, which was corrected for signal saturation by a contrast-enhancement calibration curve. Quantitative perfusion analysis was performed as previously described. Absolute myocardial blood flow (MBF) in mL/min per gram was calculated for each myocardial segment by model-independent deconvolution of myocardial signal intensity curves with the arterial input measured at the basal level. Segments with hyperemic MBF below 1.8 mL/min per gram were classified as ischemic. Ischemia burden was defined as the percentage of segments with ischemia. Complete revascularization at the patient level was defined as the absence of any residual ischemia at the segmental level after revascularization.

For analysis of LGE, areas of hyperenhancement were quantified using the full-width half maximum method (MASS, Medis Medical Imaging Solutions, Leiden, The Netherlands). For analysis of global LV function parameters, the short-axis steady-state free-precession images were analyzed using customized software (Syngo, Siemens, Erlangen, Germany), to determine end-diastolic volume index, end-systolic volume index, stroke volume index, ejection fraction, and mass index.

### Statistical Analysis

Data analysis was performed using Medcalc version 9.1.0.1 (Mariakerke, Belgium) and R (version 2.10.1; R Foundation for Statistical Computing, Vienna, Austria; URL http://www.R-project.org). Deviation from normality was tested using the D’Agostino–Pearson test. Continuous data (without repeated measures) are presented as mean±SD, and groups were compared using t tests (paired where appropriate). Non-normally distributed data are presented as median (interquartile range), and nonpaired data were compared using the nonparametric Mann–Whitney U test, while paired measurements were compared with the Wilcoxon signed-rank test. The frequency distributions of categorical data were compared using McNemar tests, and χ² test or Fisher exact test, as appropriate. Statistical tests were 2-tailed, and P<0.05 was considered significant.

The clinical end point was the composite of death/myocardial infarction/stroke/target lesion revascularization during up to 3 years of follow-up. Disease burden as assessed by CMR and by anatomic scoring methods (BARI, Duke scores) was compared within patients using 1-way repeated measures ANOVA. For segmental perfusion analysis, involving repeated measures within each patient, linear mixed effect models were used to account for the within-patient correlation of segmental flows (nlme: Linear and Nonlinear Mixed Effects Models; R package version 3.1–92). Linear mixed effect models for segmental baseline and hyperemic blood flows were used to analyze: (1) changes in segmental hyperemic MBF on follow-up examination relative to baseline, and (2) the difference in hyperemic MBF between the 2 patient groups, and the interaction between these 2 effects.

In the linear mixed effects models for resting and hyperemic MBF, 2 data strata were considered. At the lowest level, MBF measurements in myocardial segments within the same patient shared a common, patient-specific random intercept component, but the intercept component varied between patients. At the patient level, all regression coefficients other than the intercept were fixed across the cohort, because there was no evidence that allowing a between-patient variation of the regression coefficients other than the intercept would lead to better agreement with the measured data.

Stepwise selection of predictors using Akaike information criterion was used to build more parsimonious linear mixed effect models for hyperemic myocardial blood flow. The candidate variables were the following: sex, age, body mass index, diabetes mellitus, family history of heart disease, hypertension, hyperlipidemia, smoking status, CMR examination/intervention effect with levels baseline and postintervention, patient management or intervention type (PCI or CABG). Stepwise forward and backward selections of candidate variables were used to select a model from this set of candidate variables. The final model for segmental hyperemic MBF included, besides patient management, examination time point, and presence of ischemia at baseline, also SYNTAX score (P=0.134), family history (P=0.011), resting MBF (P<0.001e-6), and age (P=0.0013).

To assess the impact of LGE on perfusion, hyperemic MBF was modeled with linear mixed effects model, using LGE transmurality (categorized by 3 levels) as single fixed-effects predictor. ANOVA was then applied for testing the variation across the 3 LGE transmurality levels (0%, 0–50%, and 51–100%).

### Study Participants

Of 72 participants recruited, 67 (93%) completed the full imaging protocol and were included in the final analysis (Figure 1). Five subjects did not undergo follow-up imaging (contraindication to gadolinium administration in 1, failure of Gadolinium first-pass in 1, and 3 subjects declined follow-up perfusion imaging). One patient was randomized to PCI but received CABG, because of failed PCI (inability to pass a wire beyond a chronic total occlusion); in the perfusion analysis, this patient was included in the CABG cohort.

Patients in the 2 groups were matched with regard to most baseline demographic and clinical characteristics (Table 2). The median time between randomization and treatment was 33 days (5–55) for PCI and 20 days (13–73) for CABG (P=0.22). Follow-up imaging was performed at a median.

---

**Table 1. Patient Selection Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients with &gt;2-vessel CAD (≥50% stenosis), including the LAD and a functionally significant left main stem stenosis (≥50% stenosis)</td>
<td>1. Contraindication to aspirin or clopidogrel</td>
</tr>
<tr>
<td>2. Equivalent revascularization achievable by both PCI and CABG</td>
<td>2. Women of child-bearing potential</td>
</tr>
<tr>
<td>3. Angina (stable or unstable)</td>
<td>3. Patients requiring concomitant cardiac surgery</td>
</tr>
<tr>
<td>5. Contraindications to CMR (severe claustrophobia, metallic implants, including pacemakers, defibrillators, cerebral aneurysm clips, and ocular metallic deposits)</td>
<td>5. Contraindications to CMR (severe claustrophobia, metallic implants, including pacemakers, defibrillators, cerebral aneurysm clips, and ocular metallic deposits)</td>
</tr>
<tr>
<td>6. Contraindications to adenosine (second- or third-degree aortic valve block, obstructive pulmonary disease, diprydamole use)</td>
<td>6. Contraindications to adenosine (second- or third-degree aortic valve block, obstructive pulmonary disease, diprydamole use)</td>
</tr>
<tr>
<td>7. Contraindications to gadolinium (anaphylaxis, estimated glomerular filtration rate &lt;60 mL/min)</td>
<td>7. Contraindications to gadolinium (anaphylaxis, estimated glomerular filtration rate &lt;60 mL/min)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; LAD, left anterior descending; and PCI, percutaneous coronary intervention.
of 188 days (171–213) after revascularization in the CABG group and at 182 days (162–195) in the PCI group (P = 0.21). All CMR images were of sufficient quality for analysis, and no images were excluded.

**Procedural Data**

In the PCI group, 34 patients underwent PCI to 85 vessels (2.50 treated vessels per patient), using 142 stents (1.67 stents per vessel). Patients undergoing PCI received an average of 4.3±1.6 stents (total stent length 79.9±29.8 mm per patient). Aside from 1 lesion, all vessels were treated with drug-eluting stents. The median procedure time was 60.5 minutes (46–83). The procedure was uncomplicated in 31 cases; occlusive dissection occurred in 3, and was successfully managed percutaneously in all 3 cases.

In the CABG group, 33 patients underwent on-pump CABG using 80 grafts (2.42 grafts per patient). Conduit material used for grafting comprised 33 left internal mammary grafts, 45 saphenous vein grafts, and 2 free arterial grafts. The average time on bypass was 56.3±21.7 minutes, with cross-clamp time of 34.6±12.8 minutes.

**Angiographic Assessment of Disease Burden and Completeness of Revascularization**

In the 67 patients who completed the imaging protocol, the mean MJI (BARI) was 80.7±15.2% at baseline and 6.9±11.3% after revascularization (P<0.0001). The MJI was comparable in both groups at baseline (82.6±16.0% for PCI versus 78.8±14.4% for CABG; P=0.31) and postrevascularization (6.4±12.0% versus 7.4±10.7%, respectively; P=0.73). According to the BARI score, complete revascularization was achieved in 63% of subjects (60.6% of the CABG group and 65% of the PCI group; P=0.92), with 33% having 0% to 33% residual ischemia and 4.5% having >33% residual ischemia postrevascularization. Complete results and jeopardy index data derived from the Duke score are presented in Table 3 and Figure 2. Relative to the BARI score, the mean Duke score was lower at baseline (BARI 80.7±15.2% versus Duke 64.5±29.6%; P=0.0001) but comparable postprocedure (BARI 6.9±11.3% versus Duke 6.8±12.7%; P=0.99)

**Functional Assessment of Ischemia Burden and Completeness of Revascularization**

Ischemia burden as determined by CMR was 49.9±29.2% at baseline and 28.1±33.4% after revascularization (P<0.0001). Based on CMR criteria, complete revascularization was achieved in 39% of subjects, with 27% having 0% to 33% residual ischemia and 34% having >33% ischemic segments at follow-up.

Compared with CMR-determined ischemic burden, both angiographic scores overestimated disease burden at baseline (CMR 49.9±29.2% versus BARI 80.7±15.2% [P<0.0001] and Duke 64.5±29.6% [P=0.0019]; Table 3). However,
Clinical Outcomes

Three-year clinical follow-up was available in 100% of subjects. At 3 years postrevascularization (2.5 years after second CMR evaluation), there were 11 end points (1 death, 1 myocardial infarction, and 9 repeat revascularizations—6/34 PCI (18%) and 5/33 (15%) CABG (P=0.96). Before the second CMR assessment at 6 months, the composite end point occurred in 5 patients (1 myocardial infarction and 1 repeat revascularization in the CABG group, and 3 repeat revascularizations in the PCI group). After the second CMR scan, the composite end point occurred in 6 patients (1 death and 2 repeat revascularization in the CABG group, and 3 repeat revascularizations in the PCI group).

Table 2. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>CABG (n=33)</th>
<th>PCI (n=34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±9</td>
<td>65±7</td>
<td>0.69</td>
</tr>
<tr>
<td>Male</td>
<td>27 (82%)</td>
<td>30 (88%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (15%)</td>
<td>4 (12%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>9 (27%)</td>
<td>7 (21%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>18 (55%)</td>
<td>14 (41%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (67%)</td>
<td>21 (62%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22 (67%)</td>
<td>16 (47%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>7 (21%)</td>
<td>6 (18%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>30 (91%)</td>
<td>33 (97%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Rest heart rate, beats per minute</td>
<td>61±13</td>
<td>60±7</td>
<td>0.71</td>
</tr>
<tr>
<td>Rest systolic blood pressure, mmHg</td>
<td>135±20</td>
<td>138±21</td>
<td>0.48</td>
</tr>
<tr>
<td>Rest diastolic blood pressure, mmHg</td>
<td>73±11</td>
<td>80±12</td>
<td>0.03</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>22.8±6.1</td>
<td>23.8±6.5</td>
<td>0.52</td>
</tr>
<tr>
<td>End-diastolic volume index, mL/m²</td>
<td>76±18</td>
<td>76±12</td>
<td>0.87</td>
</tr>
<tr>
<td>End-systolic volume index, mL/m²</td>
<td>26±16</td>
<td>24±11</td>
<td>0.04</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>67±11</td>
<td>70±8</td>
<td>0.23</td>
</tr>
<tr>
<td>Myocardial mass index, g/m²</td>
<td>62±11</td>
<td>59±12</td>
<td>0.37</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

postprocedure, both angiographic scores significantly underestimated residual ischemia (CMR 28.1±33.4% vs BARI 6.9±11.3% [P<0.0001] and Duke 6.8±12.7% [P<0.0001]).

Effect of Revascularization on Segmental Myocardial Perfusion

Perfusion data for a total of 1072 myocardial segments were available. Because of the confounding influence of LGE on myocardial perfusion, segments with LGE at baseline (n=118; 11%) were excluded from this analysis. Of the remaining segments, 47% were deemed ischemic at baseline and 53% nonischemic.

In segments that were nonischemic at baseline (n=222 for CABG and n=277 for PCI), there was no significant change in hyperemic MBF after revascularization (2.40±0.46 mL/min per gram at baseline and 2.51±0.75 mL/min per gram postrevascularization [P=0.17]). At each time point, there was no significant difference in hyperemic MBF between the 2 groups (at baseline 2.44±0.53 for CABG versus 2.36±0.40 for PCI, P=0.80, and postrevascularization, 2.50±0.75 versus 2.51±0.77, respectively; P=0.26).

In segments that were ischemic at baseline (n=230 for CABG and n=223 for PCI), there was no significant difference in baseline hyperemic MBF (1.22±0.34 mL/min per gram in the CABG group, and 1.26±0.36 mL/min per gram in the PCI group; P=0.26; Figure 3). After revascularization, there was a significant increase in MBF both for CABG (from 1.20±0.33 mL/min per gram to 1.97±0.79 mL/min per gram; P<0.0001) and for PCI (from 1.23±0.34 mL/min per gram to 2.38±0.78 mL/min per gram; P<0.0001). However, hyperemic MBF was significantly higher after PCI than post-CABG (P=0.0002; Figure 3).

If the 5 subjects who underwent repeat revascularization before their follow-up CMR assessment, hyperemic MBF postrevascularization remained higher post-PCI (2.37±0.78 mL/min per gram [n=207 segments]) compared with post-CABG (1.96±0.80 mL/min per gram, [n=220 segments]; P=0.003).

Effect of Revascularization on Ischemia Burden

With exclusion of the 5 subjects who underwent repeat revascularization before their follow-up CMR assessment, at baseline, 44% of segments in the CABG group (220/496) were fully viable but deemed ischemic, and 42% (207/496) in the
by guest on June 21, 2017 http://circinterventions.ahajournals.org/Downloaded from

P higher after PCI (P = 0.003). MBF indicates myocardial blood flow.

In segments with LGE, hyperemic myocardial blood flow declined with increasing LGE transmurality, both at baseline and after revascularization (Figure 5). In segments with significant scar burden at baseline, there was evidence of improvement in hyperemic MBF after revascularization.

Impact of Graft Type and LGE on Segmental Perfusion

Analysis of the types of graft vessel used in the CABG cohort revealed that at baseline, there was no significant difference in MBF in segments subsequently revascularized by arterial or venous grafts (1.23±0.35 mL/min per gram versus 1.89±0.81 mL/min per gram; P = 0.67). However, postrevascularization, hyperemic MBF was significantly higher in segments supplied by arterial grafts than those supplied by venous grafts (1.23±0.35 mL/min per gram versus 1.89±0.81 mL/min per gram; P = 0.04; Figure 4).

In segments with LGE, hyperemic myocardial blood flow declined with increasing LGE transmurality, both at baseline and after revascularization (Figure 5). In segments with significant scar burden at baseline, there was evidence of improvement in hyperemic MBF after revascularization.

Effect of Revascularization on Global LV Indices

Baseline LV systolic function was well preserved in both groups (ejection fraction 67±11% for CABG and 70±8% for PCI; P = 0.13). After revascularization, there were no significant changes in ejection fraction, left ventricular end-systolic volume, and left ventricular end-diastolic volume, and no differences between the 2 cohorts (data not shown).

Discussion

This study compares existing anatomic scores reflecting the completeness of revascularization and absolute functional measurement of myocardial blood flow derived by CMR. Relative to functional assessment, angiographic scoring systems overestimate the degree of disease burden before revascularization and systematically underestimate the degree of residual ischemia after revascularization. These data demonstrate the potential complementary role of CMR-based functional assessment both before and possibly after revascularization, in patients with complex coronary disease.

The use of CMR perfusion imaging in our study enabled an in-depth and detailed quantitative characterization of ischemia, identifying not only the spatial extent of ischemia, but also the scale of the hyperemic response of that territory. Historically, the assessment of the functional consequences of obstructive coronary disease has required additional stress imaging after diagnostic coronary angiography. Insights from measurement of fractional flow reserve have shown that the significance of discrete lesions on angiography tends to be overestimated, and long diffuse lesions can be functionally significant but underestimated by angiography. These insights have direct implications when planning revascularization strategies as demonstrated by the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, where use of fractional flow reserve to identify ischemia resulted in improved clinical outcomes using fewer coronary stents.4

In this study, both the BARI and Duke angiographic scores overestimated the extent of ischemia at baseline and underestimated it postrevascularization. By their nature, these scores assume a perfect procedural result after revascularization, which inevitably cannot always be delivered in the real world. Assessment of perfusion in this study occurred 6 months after revascularization. The hemodynamic results of PCI may be compromised by procedural complications and limited stent expansion and incomplete

Figure 3. Segmental hyperemic MBF before and after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in segments with ischemia at baseline. Segmental hyperemic MBF in ischemic segments without late gadolinium enhancement at baseline (ischemia defined as hyperemic MBF <1.8). Hyperemic MBF did not differ significantly between the 2 patient groups before revascularization (P = 0.47) but was higher after PCI (P = 0.003). MBF indicates myocardial blood flow.

Figure 4. Segmental hyperemic MBF before and after coronary artery bypass grafting (CABG) according to graft type. Hyperemic MBF did not differ significantly between the 2 groups before revascularization (P = 0.67) but was higher after CABG in segments subtended by arterial grafts (P = 0.04). MBF indicates myocardial blood flow.
lesion coverage. Subsequent restenosis and nonculprit lesion progression are also possible causes of reduced myocardial perfusion. Graft occlusion after CABG occurs most frequently within the first few months of the procedure. Venous graft occlusion may be clinically occult but will obviously impair myocardial perfusion in the dependent territory.

Despite their inherent limitations, both anatomic scores are well established and, in large population–based studies, both scores have demonstrated the negative impact of residual non-revascularized myocardium on long-term prognosis after both PCI and CABG.5–13 Our preliminary data suggest potential for larger comparative studies of CMR-based functional assessment with these existing anatomic scores. This could potentially result in a more accurate risk prediction in the individual patient after revascularization.

Another advantage of using multiparametric CMR with LGE imaging is its potential to incorporate concurrent viability assessment. Using LGE imaging in this study, the tissue response to revascularization in ischemic territories was assessed, whereas avoiding the confounding influence of scar (which cannot be achieved with most alternative imaging modalities). Demonstrable LGE has been shown to have an adverse prognostic impact before revascularization, and previous studies have also shown that, at a segmental level, the likelihood of functional improvement after revascularization, and previous studies have also shown that, at a segmental level, the likelihood of functional improvement after revascularization declines with increasing LGE transmurality.27 However, previous studies have not assessed the relationship between LGE and myocardial perfusion. Our data demonstrate that the extent of the hyperemic response declines with increasing LGE transmurality. This is probably predictable, but it is noteworthy that revascularization augmented hyperemic MBF even in those segments with significant scar burden at baseline, which previously have been considered unworthy of revascularization. This suggests that revascularizing hypoperfused segments with some evidence of viability might be beneficial for the purpose of reducing the overall ischemic myocardial burden.

Our data provide a clear demonstration that arterial grafting achieves greater augmentation of flow in response to hyperemia than a venous conduit. The ability of arteries to dilate in response to increased demand is well recognized. Clinical data suggests improved longevity and better clinical outcomes after revascularization using internal mammary arteries.28 Despite this, revascularization with a single mammary artery and ≥2 veins is the standard practice in most cardiac surgical centers. Our data provide further support that complete revascularization with arterial grafts should be considered as the surgical technique of choice.

As anticipated, patients randomized to either CABG or PCI experienced a significant improvement in myocardial perfusion in ischemic territories. However, the scale of the hyperemic response after revascularization with PCI was greater than after CABG using mixed arterial and venous grafts. One potential explanation for this result is that restoring patency to native coronary arteries permits higher blood flow than the alternative strategy of diverting blood through a bypass conduit, with the consequences of competitive retrograde flow. Secondly, in the context of complex coronary artery disease, PCI has the potential to provide complete revascularization to the whole distribution of an epicardial vessel with multiple lesions in series. By contrast, bypass with a single graft may reperfuse only the distal segment, leaving areas upstream from the stenosis untreated, and this myocardium is left potentially ischemic. However, it must be noted that these data reflect a snapshot of revascularization at 6 months after the procedure. There is little doubt that despite advances in coronary stent technology, bypass surgery still provides a more durable clinical result in patients with diffuse coronary disease particularly if they are diabetic.29

Limitations
Our study is restricted by the small number of subjects involved, but it serves the purpose of hypothesis generation.
for larger future studies, which might characterize appropriate prognosis-defining thresholds of ischemia and to examine whether the achievement of higher hyperemic flows might improve clinical outcome. In our study, we defined ischemia as the presence of a perfusion deficit, which is an established and sensitive indicator of ischemia, most commonly used in clinical practice and, the presence of ischemia, as indicated by perfusion deficits, is also a strong predictor of future clinical events.\textsuperscript{8,9,10} We did not assess other, cellular, consequences of ischemia, such as ECG changes or wall motion abnormalities. Currently, there are limited published data involving CMR regarding the appropriate threshold to define ischemia and, although absolute perfusion CMR has been extensively validated, there are limited data on its use after CABG.\textsuperscript{26,32,33} In this study, we used a hyperemic myocardial blood flow threshold of 1.8 mL/min per gram, which, in a previous study, was defined and then prospectively validated.\textsuperscript{26} Previous studies using CMR perfusion have used myocardial perfusion reserve index, a ratio of hyperemic to resting flow.\textsuperscript{32,33} However, using CMR perfusion have used myocardial perfusion reserve index, although absolute perfusion CMR has been extensively validated, this study, we used a hyperemic myocardial blood flow threshold of 1.8 mL/min per gram, which, in a previous study, was defined and then prospectively validated.\textsuperscript{26} Previous studies using CMR perfusion have used myocardial perfusion reserve index, a ratio of hyperemic to resting flow.\textsuperscript{32,33} However, using this approach, small changes in resting perfusion can have a disproportionate effect on myocardial perfusion reserve index, and correction by rate-pressure product (which only 1 of these studies used) may be incomplete. We also used model-independent deconvolution, which enables an accurate representation of the physiological impulse response, free from assumptions regarding its shape or compartmental structure.

Conclusions

Angiographic estimation of the completeness of revascularization may overestimate disease burden at baseline and underestimate residual disease after revascularization. Functional data demonstrate that a significant burden of ischemia remains even after apparently successful revascularization. The use of functional techniques may help improve our understanding of the impact of incomplete revascularization on long-term cardiovascular outcomes and facilitate the assessment of residual disease after revascularization and clinical decision making regarding the choice of revascularization strategy.

Acknowledgments

The authors are grateful to Dr C. Antoniades for statistical support.

Sources of Funding

This work was supported by the British Heart Foundation, the UK Medical Research Council, and the Oxford NIHR Biomedical Research Center. Contributions to the cost of the study were made by unrestricted research donation from both Cordis, a Johnson & Johnson Company, and Boston Scientific Corp.

Disclosures

Prof Neubauer is supported by the Oxford British Heart Foundation Center of Research Excellence. Prof Banning has received honoraria from Abbott Vascular, Cordis, a Johnson & Johnson Company, and Boston Scientific Corp.

References


_Circ Cardiovasc Interv._ 2013;6:237-245; originally published online May 21, 2013; doi: 10.1161/CIRCINTERVENTIONS.112.000064

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2013 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/6/3/237

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Interventions_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Interventions_ is online at:
http://circinterventions.ahajournals.org//subscriptions/