Background—Absolute quantification of perfusion with cardiovascular magnetic resonance has not previously been applied in patients with coronary artery bypass grafting (CABG). Owing to increased contrast bolus dispersion due to the greater distance of travel through a bypass graft, this approach may result in systematic underestimation of myocardial blood flow (MBF). As resting MBF remains normal in segments supplied by noncritical coronary stenosis (<85%), measurement of perfusion in such territories may be utilized to reveal systematic error in the quantification of MBF. The objective of this study was to test whether absolute quantification of perfusion with cardiovascular magnetic resonance systematically underestimates MBF in segments subtended by bypass grafts.

Methods and Results—The study population comprised 28 patients undergoing elective CABG for treatment of multivessel coronary artery disease. Eligible patients had angiographic evidence of at least 1 myocardial segment subtended by a noncritically stenosed coronary artery (<85%). Subjects were studied at 1.5 T, with evaluation of resting MBF using model-independent deconvolution. Analyses were confined to myocardial segments subtended by native coronary arteries with <85% stenosis at baseline, and MBF was compared in grafted and ungrafted segments before and after revascularization. A total of 249 segments were subtended by coronary arteries with <85% stenosis at baseline. After revascularization, there was no significant difference in MBF in ungrafted (0.82 ± 0.19 mL/min/g) versus grafted segments (0.82 ± 0.15 mL/min/g, \(P = 0.57\)). In the latter, MBF after revascularization did not change significantly from baseline (0.86 ± 0.20 mL/min/g, \(P = 0.82\)).

Conclusions—Model-independent deconvolution analysis does not systematically underestimate blood flow in graft-subtended territories, justifying the use of this methodology to evaluate myocardial perfusion in patients with CABG. (Circ Cardiovasc Imaging. 2011;4:312-318.)

Key Words: coronary artery bypass grafting • myocardial blood flow • cardiovascular imaging

In the noninvasive assessment of coronary artery disease (CAD), several approaches are available for the evaluation of myocardial perfusion.1 Although the diagnostic performance of qualitative methods is well established, the use of quantitative measures potentially offers improved accuracy when diagnosing multivessel disease and greater objectivity in the serial assessment of myocardial perfusion.2–5

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All tracer-based imaging methods used for quantification of myocardial blood flow (MBF) use an arterial input function (AIF), which is conventionally approximated by tracer changes within the left ventricular blood pool.6 Although this methodology is valid for perfusion quantification in territories of native coronary arteries, before or after percutaneous coronary intervention, the same may not apply after coronary artery bypass grafting (CABG).4,7,8 Accurate assessment of MBF is critically dependent on the fidelity of the AIF: after CABG, the kinetics for the dynamic passage of contrast through the vasculature may be altered, resulting in distortion of the AIF. Specifically, compared with native coronary vessels, the increased length of bypass grafts may

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result in increased dispersion of contrast, thereby distorting the arterial input to myocardium supplied by a functioning bypass graft.

Hence, estimation of MBF by any imaging modality that defines the AIF in the left ventricular blood pool may be susceptible to systematic error in graft-subtended territories. Our objective was to test this hypothesis by using cardiovascular magnetic resonance (CMR) in this study.

Absolute quantification of perfusion by CMR is conventionally performed by using deconvolution models.\(^9\)–\(^{12}\) This methodology has been validated in animal models by comparison with microsphere assessment of myocardial perfusion and in human subjects by comparison against invasive measures of myocardial perfusion.\(^{10}\)–\(^{13}\) Although quantitative assessment of perfusion by CMR has been applied in patients undergoing percutaneous coronary intervention, it has not been attempted after CABG, and the validity of the latter remains undetermined.\(^7\)–\(^8\)

Previous studies have shown that unlike stress MBF, resting MBF remains unchanged with increasing coronary stenosis, until critical narrowing is reached (>85% to 90%).\(^{14}\)–\(^{16}\) Therefore, when considering segments subtended by less severe coronary stenoses (<85%), resting MBF is normal (ie, the same as in segments subtended by normal coronary arteries) and remains unchanged after revascularization. Using this observation, it is possible to test whether MBF after CABG is systematically underestimated, by comparing in segments subtended by noncritical stenoses (<85%), (1) resting MBF in grafted versus ungrafted segments after revascularization and (2) resting MBF in grafted segments before and after revascularization.

Methods
Patient Population
The study population comprised patients with multivessel or left main coronary artery disease who had been referred for elective CABG. In a recently published study involving 80 patients with multivessel coronary disease, we compared periprocedural myocardial injury in subjects randomly assigned to percutaneous coronary intervention or CABG (randomization ratio, 1:1).\(^7\) Taking advantage of the latter subgroup in this cohort, we assessed perfusion using CMR in patients undergoing CABG. Patients were eligible for the study if there was angiographic evidence of at least 1 myocardial segment subtended by a noncritically stenosed coronary artery (<85%). Exclusion criteria were severe claustrophobia, metallic implants or foreign bodies, and contraindications to gadolinium (anaphylaxis, estimated glomerular filtration rate, <60 mL/min). The study was conducted according to the Declaration of Helsinki and was approved by the regional ethics committee. All participants gave written informed consent before participation.

Revascularization Procedures
All subjects underwent on-pump CABG, according to standard practice. General anesthesia was administered according to usual care, with coronary artery bypass using nonpulsatile flow and a membrane oxygenator. Core patient temperature was allowed to drift down to a minimum of 32°C. All patients received a pedicled left internal mammary graft to the left anterior descending coronary artery. Saphenous vein was used for grafts to the right and circumflex coronary arteries. All patients received aspirin indefinitely after revascularization.

CMR Procedures
CMR imaging was performed at 1.5 T (Sonata, Siemens Medical Solutions Erlangen, Germany) at baseline and subsequently at 4 to 6 months after revascularization.

After piloting, left ventricular functional imaging was performed using a steady-state free-precession sequence. Cine images (TE/TR, 1.5/3.0 ms; flip angle, 60°; in-plane resolution, 1.5×1.5 mm; slice thickness, 7 mm; interslice gap, 3 mm) were acquired in the 3 long-axis views (ie, horizontal and vertical long-axis and the left ventricular outflow tract views) using prospective ECG gating. A short-axis stack was then acquired, parallel to the atrioventricular groove to obtain coverage of the entire left ventricle.

For perfusion imaging, a 0.04-mmol/kg bolus of a gadolinium-based contrast agent (Gadodiamide, Omniscan, GE Healthcare) was injected, followed by a 15-mL bolus of normal saline. During the first pass of the contrast, 3 short-axis images (representing basal, midventricular, and apical segments) were acquired every cardiac cycle using an ECG-gated T1-weighted fast gradient echo sequence with generalized autocalibrating partially parallel acquisition reconstruction (echo time, 1.04 ms; repetition time, 2 ms; saturation recovery time, 100 ms; voxel size, 2.1×2.6×8 mm\(^3\); flip angle, 17°).

For late gadolinium enhancement (LGE) imaging, after a further bolus of Gadodiamide (total dose, 0.125 mmol/kg), images were acquired in the 3 long axes and all short axes to obtain coverage of the entire left ventricle, using a T1-weighted segmented inversion-recovery turbo fast low-angle shot sequence (echo time, 4.8 ms; voxel size, 1.4×2.4×8 mm\(^3\); flip angle, 20°).

CMR Image Analysis
CMR image analysis was performed blinded to patient data, study time point, and angiographic data. For analysis of left ventricular function, short-axis steady-state free-precession images were analyzed using customized software (Syngo, Siemens Medical Solutions, Erlangen, Germany). Epicardial and endocardial borders were traced manually in successive short-axis slices at end-diastole and endocardial borders at end-systole. The basal slice for the left ventricle was defined as the most basal slice with at least 50% of the blood pool being surrounded by myocardium. From these data, the following left ventricular parameters were determined: end-diastolic volume, end-systolic volume, stroke volume, ejection fraction, and myocardial mass.

For perfusion analysis, endocardial and epicardial contours were traced (MASS, Medis Medical Imaging Solutions, Leiden, The Netherlands) and manually corrected for cardiac displacement. In accordance with the American Heart Association segmentation model, the myocardium was divided into 6 equiangular segments (for basal and midventricular slices and 4 for apical slices), and a region of interest was placed in the center of the left ventricular cavity. Time-signal intensity curves were then generated for all segments. Quantitative perfusion analysis was performed for each myocardial segment using model-independent deconvolution of myocardial signal intensity curves with the arterial input signal intensity curve as previously described.\(^18\) For LGE imaging, images were assessed visually, and segments were graded according to the presence or absence of LGE.

Angiographic Analysis
Coronary angiography was performed at baseline, before CABG, using standard techniques. Images of the coronary arteries were obtained in multiple projections, with avoidance of overlap of side branches and foreshortening of relevant coronary stenoses.

Angiographic data analysis was performed blinded to all CMR data. Diameters of reference and stenotic coronary arteries were measured using a computer-assisted quantitative method (Siemens
Axiom Artis QCA Software). The contrast-filled catheter was used for image magnification calibration. Angiographic images were scored according to the SYNTAX (synergy between PCI with TAXUS and cardiac surgery) score algorithm as previously described.19 On the basis of angiographic appearances, each myocardial segment was ascribed a supplying coronary artery using standardized criteria, taking into account which coronary artery was dominant.20 Segments were further subdivided according to the severity of coronary stenosis in the subending artery, using a 50% threshold to define diseased segments and an 85% threshold to define critical stenosis. Using the surgeon’s operative report in conjunction with the baseline angiogram, segments were further characterized as to whether they had been revascularized.

Statistical Analysis
Analyses were limited to myocardial segments with <85% stenosis in the subtending coronary artery at baseline. For the analysis of pre-CABG MBF, using the angiographic appearance of their subtending arteries, myocardial segments were categorized as diseased or nondiseased (subtended by 50% to 84% stenosis or <50% stenosis, respectively). For the analysis of post-CABG MBF, myocardial segments were categorized as those revascularized by a CABG graft and those that remained ungrafted.

At each time point, within-patient averages of MBFs for the 2 segment types were compared by paired t test. For the comparison of grafted versus ungrafted segments, statistical power or the probability of a type II (β) error was estimated with α=0.05 and using the observed sample standard deviation. The null hypothesis was of a 10% or larger difference in resting MBF between grafted and ungrafted segments.

In addition to the paired t test, linear mixed effects (LME) models were used to account for the within-patient correlation of segmental blood flows. Regression analysis of MBF measurements was performed using the NLME software package (nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1 to 92).21 In the LME models, 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. At the patient level, any regression coefficient other than the intercept and the treatment effect was fixed across the cohort. For the pre-CABG measurements, a categorical variable for the presence of significant disease was used as a dependent variable to test whether there was any difference of rest MBF between diseased and nondiseased segments. For post-CABG MBF, a categorical variable encoding for the presence or absence of a graft was used as an independent variable to test whether rest MBF was significantly different in grafted versus ungrafted segments. Approximate confidence intervals for the parameters in the linear mixed-effects model were obtained in the R statistical analysis environment with the “intervals.lme” routine of “nlme,” using a normal approximation to the distribution of the (restricted) maximum likelihood estimators.


Other statistical analyses were carried out with Medcalc 9.1.0.1 (Mariakerke, Belgium). Statistical significance was assumed for probability values <0.05. Unless otherwise stated, all measurements are summarized as mean±SD.

Results
Patients
Twenty-eight patients undergoing elective CABG were prospectively recruited. Clinical characteristics of these patients are outlined in the Table. Nineteen patients had 3-vessel disease, and 9 had 2-vessel disease. At baseline, LGE was present in 16 patients.

| Table. Baseline Clinical Characteristics |
|-----------------|-----------|
| Age, y          | 63.0±8.8  |
| Male            | 22 (79%)  |
| Risk factors    |           |
| Diabetes mellitus| 4 (14%)  |
| Prior myocardial infarction| 8 (29%)  |
| Family history of coronary disease| 15 (54%)  |
| Hypertension    | 18 (64%)  |
| Drug history    |           |
| Aspirin         | 26 (93%)  |
| Clopidogrel     | 4 (14%)   |
| Statin          | 25 (89%)  |
| β-blocker       | 21 (75%)  |
| ACE inhibitor or ARA | 18 (64%) |
| Calcium channel blocker | 5 (18%) |
| SYNTAX score    | 22.8±6.05 |
| LGE as % of LV mass | 10.9±13.9 |
| EDV, mL         | 152±40.2  |
| EF, %           | 66.9±10.9 |
| Myocardial mass index, g/m² | 61.8±11.3 |

ACE indicates angiotensin-converting enzyme; ARA, angiotensin receptor antagonist; SYNTAX, synergy between PCI with TAXUS and cardiac surgery; LGE, late gadolinium enhancement; LV, left ventricular; EDV, end-diastolic volume; and EF, ejection fraction.

Revascularization Procedure
In the 28 patients, on-pump CABG was performed using 67 grafts (2.39 grafts per patient). Conduit material used for grafting comprised 28 pedicle left internal mammary grafts, 37 saphenous vein grafts, and 2 free arterial grafts. The average time on bypass was 55.9±19.0 minutes, with cross-clamp time of 34.3±10.3 minutes.

Baseline MBF in Diseased Versus Nondiseased Segments
From a total of 448 segments, 249 were subtended by coronary arteries with <85% stenosis at baseline. Of these, 164 of 249 segments were diseased (subtended by 50% to 84% stenosis) and 85 of 249 segments were nondiseased (subtended by <50% stenosis). At baseline, resting MBF in the 164 diseased segments was 0.85±0.22 mL/min/g and in the 85 nondiseased segments, 0.87±0.19 mL/min/g (P=0.95, LME model, Figure 1). The 95% confidence interval for the effect of disease in this linear mixed effects model ranged from −0.052 to 0.048 mL/min/g, and the effect of disease was estimated by the model to be −0.0017 mL/min/g (P=0.95). With simultaneous adjustment of baseline resting MBF for the presence of LGE (P=0.15), the rate-pressure product (P<0.0001), sex (P=0.45), and age (P=0.49), the presence of disease continued to show no significant effect on resting MBF (P=0.86).

At baseline, 13 patients had both diseased and nondiseased segments, allowing a paired comparison of resting MBF in these 2 types of segments in each patient. In these patients, baseline MBF averaged 0.81±0.16 mL/min/g in nondiseased
segments and $0.82 \pm 0.11$ mL/min/g in diseased segments ($P=0.78$, paired $t$ test).

Therefore, both paired $t$ test and LME model analysis revealed no significant difference in resting MBF between diseased and nondiseased myocardial segments. This supports the main assumption on which this study was based, namely that with noncritical coronary stenoses ($<85\%$), resting MBF remains unchanged.

**Postrevascularization MBF in Grafted Versus Ungrafted Segments**

For segmental MBF measurements after revascularization, we again evaluated the 249 segments with $<85\%$ stenosis in the subtending coronary arteries at baseline. After the revascularization procedure, 153 of 249 segments received bypass grafting and 96 of 249 remained ungrafted. Resting MBF in grafted segments ($0.82 \pm 0.15$ mL/min/g) did not differ significantly from MBF in ungrafted segments ($0.82 \pm 0.19$ mL/min/g) ($P=0.87$, LME model; Figure 2). The lower and upper 95% confidence interval limits for the effect of a CABG graft in the linear mixed effects model were $-0.09$ and $0.04$ mL/min/g, respectively. If the comparison was limited to the 164 of 249 segments with a stenosis in the range between 50% to 85%, then resting MBF after revascularization was not significantly different between grafted ($0.82 \pm 0.15$ mL/min/g; $n=142$) and ungrafted segments ($0.85 \pm 0.11$ mL/min/g; $n=22$) segments ($P=0.98$, LME model), with a 95% confidence interval for the effect of a CABG graft ranging from $-0.06$ to $0.06$ mL/min/g.

In the CABG cohort, 21 of 28 patients had at least 1 ungrafted segment, enabling comparison of the within patient means of resting MBF in grafted and ungrafted segments. A paired 2-sample $t$ test for per-patient averages of MBF in grafted ($0.86 \pm 0.15$ mL/min/g) and ungrafted segments ($0.83 \pm 0.16$ mL/min/g) in these 15 patients showed no significant difference ($P=0.60$, paired $t$ test).

Therefore, both paired $t$ test and LME model analysis revealed no significant difference in resting MBF in grafted versus ungrafted segments. This argues against the systematic underestimation of MBF in graft-subtended myocardium, relative to segments perfused by native coronary arteries, even when the analysis is limited to an intermediate range of stenosis (50% to 85%).

**Baseline and Postrevascularization MBF in Segments Treated With Bypass Grafting**

Of the 249 myocardial segments subtended by noncritical stenoses ($<85\%$) at baseline, 153 were subsequently revascularized by CABG. After revascularization, in these segments, MBF did not change significantly from baseline ($0.86 \pm 0.20$ mL/min/g to $0.82 \pm 0.15$ mL/min/g, $P=0.82$, LME model). Similarly, in the 96 segments that remained ungrafted, MBF did not change significantly from baseline ($0.86 \pm 0.21$ mL/min/g to $0.82 \pm 0.19$ mL/min/g, $P=0.23$, LME model).

For the baseline measurements, the mean of the within-patient differences of rest MBF ($n=13$) in normal and diseased with $<85\%$ stenosis averaged $-0.016 \pm 0.11$, and the 95% confidence limits of agreement for the MBF differences ranged from $-0.24$ to $0.21$ mL/min/g ($n=13$). After CABG, the mean of the within-patient differ-
these "noncritical" segments is normal at baseline. This was based on the assumption that MBF in segments with bypass grafting) in this study, analyses were limited to the overall dispersion of the contrast bolus. Our findings indicate that dispersion is actually more pronounced at rest than at stress. However, a recent study examining bolus dispersion in constricted vessels, the same may not necessarily apply at stress. In the absence of experimental measurements of bolus dispersion, we cannot exclude the possibility that dispersion is greater during hyperemia than at rest. However, a recent study examining bolus dispersion in constricted vessels indicates that dispersion is actually more pronounced at rest than at stress. The degree of dispersion of a contrast bolus during transit through a nonstenotic vascular segment is indeed normal at baseline (ie, not significantly different from flow in segments subtended by unstenosed, normal coronary arteries) and does not increase further with revascularization. Therefore, the approach of confining analyses to segments with <85% stenosis at baseline ensures that the potential confounding effect of treatment is removed and that resting blood flow is indeed normal at baseline.

Previous studies involving CMR assessment of blood flow after CABG have used velocity mapping within bypass grafts as well as visual and semiquantitative assessment of myocardial perfusion. However, in the literature, absolute quantification of myocardial perfusion with CMR in patients after CABG has not previously been attempted, and the potential problem associated with contrast dispersion in grafts has not specifically been addressed. A study by Campisi et al used PET to examine blood flow in myocardium subtended by bypass grafts: MBF and flow reserve were evaluated in 15 CABG patients. However, the authors did not address the issue of dispersion in graft-subtended segments, even though this may potentially confound PET-derived estimates of MBF. Nonetheless, in this study, the investigators found no significant difference in resting MBF between patients and control subjects, which is consistent with the findings of our study.

**Limitations**

A significant limitation in our study is that no invasive measurement of MBF was undertaken to corroborate our findings. Furthermore, angiographic verification of the success of CABG was not undertaken. Although the results of our study strongly suggest that conventional model-independent deconvolution analysis does not render systematic error in the calculation of resting myocardial blood flow, the same may not necessarily apply at stress. In the absence of experimental measurements of bolus dispersion, we cannot exclude the possibility that dispersion is greater during hyperemia than at rest. However, a recent study examining bolus dispersion in constricted vessels indicates that dispersion is actually more pronounced at rest than at stress. The degree of dispersion of a contrast bolus during transit through a nonstenotic vascular segment, such as a CABG graft, increases in proportion to the variance of the mean transit times. Assuming nonturbulent flows, simulations have shown that the variance of the
mean transit times decreases as the flow rate is increased, indicating that bolus dispersion may be most noticeable during resting conditions rather than hyperemia. Therefore, it is likely that any underestimation of blood flow, resulting from any (unaccounted) bolus dispersion, is less pronounced during hyperemia than at rest. Nonetheless, to definitively address all these limitations requires an animal model of CABG, with validation of CMR-derived perfusion against microsphere determination of MBF in graft-subtended segments.

**Conclusion**

In conclusion, the present study demonstrates that the use of absolute quantification with CMR model-independent deconvolution analysis does not give rise to systematic underestimation of MBF in graft-subtended territories. Therefore, for the purpose of quantitative assessment of myocardial perfusion after CABG using tracer-based imaging methods, defining the arterial input function within the left ventricular blood pool is justified.

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**Disclosures**

None.

**References**

In the noninvasive assessment of coronary artery disease, though the diagnostic performance of qualitative methods is well established, quantitative measures potentially offer improved accuracy and greater objectivity in the serial assessment of myocardial perfusion. Most tracer-based imaging methods used for quantification of myocardial blood flow (MBF) use an arterial input function that is conventionally approximated by tracer changes within the left ventricular blood pool. In patients with coronary artery bypass grafting, this approach may prove problematic as dispersion of tracer in the bypass graft may result in significant modification of the arterial input function and lead to systematic underestimation of MBF.

Such a possibility was investigated in this study, using cardiovascular magnetic resonance to test for bias in the measurement of resting MBF. The analyses revealed that in myocardial segments subtended by bypass grafts, there is no evidence of systematic underestimation of MBF by cardiovascular magnetic resonance. These findings can be extrapolated to other quantitative imaging techniques (such as positron emission tomography and contrast echocardiography) that use an arterial input function defined within the left ventricular blood pool. Therefore, the use of these quantitative methods for the evaluation of myocardial perfusion after coronary artery bypass grafting is justified. In the clinical setting, these techniques may facilitate improved serial assessment and identification of hypoperfusion after bypass grafting.
Myocardial Perfusion Imaging After Coronary Artery Bypass Surgery Using Cardiovascular Magnetic Resonance: A Validation Study

J. Ranjit Arnold, Jane M. Francis, Theodoros D. Karamitsos, Chris C. Lim, William J. van Gaal, Luca Testa, Paul Bhamra-Ariza, Joseph B. Selvanayagam, Rana Sayeed, Stephen Westaby, Adrian P. Banning, Stefan Neubauer and Michael Jerosch-Herold

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