Myocardial Perfusion Imaging Following Coronary Artery Bypass Surgery Using Cardiovascular Magnetic Resonance: A Validation Study

Running Title: Arnold et al: CMR Perfusion Imaging Following CABG

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Abstract

**Background**—Absolute quantification of perfusion with cardiovascular magnetic resonance (CMR) 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 non-critical 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 CMR systematically underestimates MBF in segments subtended by bypass grafts.

**Methods and Results**—The study population comprised 28 patients undergoing elective CABG for treatment of multi-vessel coronary artery disease. Eligible patients had angiographic evidence of at least one myocardial segment subtended by a non-critically stenosed coronary artery (<85%). Subjects were studied at 1.5T, 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. Following 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 following revascularization did not change significantly from baseline (0.86±0.20ml/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.

**Key Words:** coronary artery bypass grafting, myocardial blood flow, cardiovascular imaging
In the non-invasive 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 multi-vessel disease, and greater objectivity in the serial assessment of myocardial perfusion.\(^2-5\)

All tracer-based imaging methods used for quantification of myocardial blood flow (MBF) utilize 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 following coronary artery bypass grafting (CABG).\(^4,7,8\) Accurate assessment of MBF is critically dependent on the fidelity of the AIF: post-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 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 which 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, in this study using cardiovascular magnetic resonance (CMR).

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.\textsuperscript{10-13} Although quantitative assessment of perfusion by CMR has been applied in patients undergoing percutaneous coronary intervention, it has not been attempted following CABG, and the validity of the latter remains undetermined.\textsuperscript{7, 8}

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

Patient population

The study population comprised patients with multi-vessel or left main coronary artery disease who had been referred for elective CABG. In a recently published study involving 80 patients with multi-vessel coronary disease, we compared peri-procedural myocardial injury in subjects randomized to percutaneous coronary intervention or CABG (randomization ratio 1:1). 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 one myocardial segment subtended by a non-critically stenosed coronary artery (<85%). Exclusion criteria were: severe claustrophobia, metallic implants or foreign bodies, and contraindications to gadolinium (anaphylaxis, estimated glomerular filtration rate <60ml/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, as according to standard practice. General anesthesia was administered according to usual care, with coronary artery bypass using non-pulsatile flow and a membrane oxygenator. Core patient temperature was allowed to drift down to a minimum of 32 degrees Celsius. 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 following revascularization.
CMR Procedures

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

After piloting, left ventricular functional imaging was performed using a steady-state free-precession (SSFP) sequence. Cine images (TE/TR 1.5/3.0 ms, flip angle 60°, in-plane resolution 1.5×1.5mm, slice thickness 7mm, inter-slice gap 3mm) were acquired in the 3 long-axis views (i.e. 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 0.04mmol/kg bolus of a gadolinium-based contrast agent (Gadodiamide, Omniscan™, GE Healthcare) was injected, followed by a 15ml bolus of normal saline. During the first pass of the contrast, 3 short-axis images (representing basal, mid-ventricular and apical segments) were acquired every cardiac cycle using an ECG-gated T1-weighted fast gradient echo sequence with generalized autocalibrating partially parallel acquisitions (GRAPPA) reconstruction (echo time 1.04ms, repetition time 2ms, saturation recovery time 100ms, voxel size 2.1×2.6×8mm³, flip angle 17°).

For late gadolinium enhancement (LGE) imaging, following a further bolus of Gadodiamide (total dose 0.125mmol/kg), images were acquired in the three 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 (FLASH) sequence (echo time 4.8ms, voxel size 1.4 ×2.4×8 mm, flip angle 20°).

**CMR image analysis**

CMR image analysis was performed blinded to patient data, study timepoint and angiographic data. For analysis of left ventricular function, short-axis SSFP 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 (ROI) 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. For LGE assessment, images were assessed visually, and segments were graded according to the presence or absence of LGE.
**Angiographic analysis**

Coronary angiography was performed at baseline, prior to 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 score algorithm as previously described. Based on angiographic appearances, each myocardial segment was ascribed a supplying coronary artery using standardized criteria, taking into account which coronary artery was dominant. Segments were further subdivided according to the severity of coronary stenosis in the subtending 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 non-diseased (subtended by 50-84% 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 which remained ungrafted.

At each timepoint, within-patient averages of MBF’s for the two 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 (\( \beta \)) error was estimated with \( \alpha = 0.05 \), 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 in order 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 3.1-92). In the LME models, two 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 non-diseased 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. LME model analysis was performed in the R-environment (R version 2.10.0, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Other statistical analyses were carried out with Medcalc 9.1.0.1 (Mariakerke, Belgium). Statistical significance was assumed for p-values less than 0.05. Unless otherwise stated all measurements are summarized as means ± standard deviation.
Results

Patients

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

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 non-diseased segments

From a total of 448 segments, 249 were subtended by coronary arteries with <85% stenosis at baseline. Of these, 164/249 segments were diseased (subtended by 50-84% stenosis) and 85/249 segments were non-diseased (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 non-diseased 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), gender (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 non-diseased segments, allowing a
paired comparison of resting MBF in these two types of segments in each patient. In
these patients, baseline MBF averaged 0.81±0.16ml/min/g in non-diseased segments
and 0.82±0.11ml/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 non-diseased myocardial segments.
This supports the main assumption on which this study was based, namely that with
non-critical coronary stenoses (<85%), resting MBF remains unchanged.

Post-revascularization MBF in grafted versus ungrafted segments
For segmental MBF measurements post revascularization, we again evaluated the 249
segments with <85% stenosis in the subtending coronary arteries at baseline.
Following the revascularization procedure, 153/249 segments received bypass
grafting and 96/249 remained ungrafted. Resting MBF in grafted segments
(0.82±0.15ml/min/g) did not differ significantly from MBF in ungrafted segments
(0.82±0.19ml/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 -0.032 and 0.038 ml/min/g, respectively. If the comparison was limited to
the 164/249 segments with a stenosis in the range between 50-85%, then resting MBF
after revascularization was not significantly different between grafted (0.82±0.15
ml/min/g; n=142) and ungrafted segments (0.85±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 -0.061 to 0.060 ml/min/g.
In the CABG cohort, 21/28 patients had at least one ungrafted segment, enabling comparison of the within patient means of resting MBF in grafted and ungrafted segments. A paired two-sample t-test for per-patient averages of MBF in grafted (0.86±0.15 ml/min/g) and ungrafted segments (0.83±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 post-revascularization MBF in segments treated with bypass grafting**

Of the 249 myocardial segments subtended by non-critical stenoses (<85%) at baseline, 153 were subsequently revascularized by CABG. Following revascularization, in these segments, MBF did not change significantly from baseline (from 0.86±0.20ml/min/g to 0.82±0.15ml/min/g, p=0.82, LME model). Similarly, in the 96 segments which remained ungrafted, MBF did not change significantly from baseline (from 0.86±0.21 ml/min/g to 0.82±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 segments with <85% stenosis averaged -0.016±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). Post-CABG, the mean of the within patient differences of rest MBF (n=21) in ungrafted and grafted segments averaged -
0.025±0.062, and the 95% confidence limits of agreement for the MBF differences ranged from -0.15 to 0.10 ml/min/g (Figure 3).
Discussion

The principal finding in this study is that for the absolute quantification of perfusion using CMR, the use of an arterial input function up-stream from any CABG graft does not cause systematic error in the calculation of MBF. Specifically, defining the arterial input within the left ventricular blood pool does not lead to underestimation of MBF in grafted segments relative to segments perfused by native coronary arteries. Although this finding does not contradict the notion that the transit of the contrast through the CABG grafts causes some dispersion of the contrast bolus, the net effect of such dispersion on the estimation of blood flow was not detectable, presumably in part because of the peripheral venous injection of contrast. In the setting of a venous injection of contrast, the dispersion of contrast in the CABG graft makes a relatively weak contribution to the overall dispersion of the contrast bolus. Our findings have implications for the clinical assessment of MBF post-CABG using not only CMR but also other imaging modalities such as positron emission tomography (PET), whose estimation of MBF requires an arterial input function.

In order to avoid the potential confounding influence of revascularization (i.e. improved resting MBF due to bypass grafting) in this study, analyses were limited to segments with less than 85% stenosis in the subtending artery at baseline. This was based on the assumption that MBF in these ‘non-critical’ segments is normal at baseline, and does not increase with revascularization. This rationale is supported by several lines of evidence which demonstrate that resting MBF remains unchanged in segments with non-critical stenosis. A study by Gould and colleagues involving open-chest anesthetized dogs demonstrated that a reduction in diameter of greater than 85% was necessary to reduce resting MBF. A similar result was found in a human study.
using intraoperative $^{133}$Xenon clearance to estimate resting MBF in patients undergoing CABG. The landmark study by Uren and colleagues, involving the use of PET to measure absolute MBF, showed that in coronary stenoses up to 87%, there was no significant reduction in resting MBF. The results of the present CMR study also indicate that resting MBF in ‘non-critical’ segments is normal at baseline (i.e. 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 less than 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 following CABG have utilized velocity mapping within bypass grafts as well as visual and semi-quantitative assessment of myocardial perfusion. However, in the literature, absolute quantification of myocardial perfusion with CMR in patients following 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 and colleagues 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 controls, 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.\(^{29}\) The degree of dispersion of a contrast bolus during transit through a non-stenotic vascular segment, such as a CABG graft, increases in proportion to the variance of the mean transit times. Assuming non-turbulent 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.\(^{29}\) 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, this 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 following CABG using tracer-based
imaging methods, defining the arterial input function within the left ventricular blood pool is justified.
Sources of Funding

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Disclosures

None.
References


Table. Baseline clinical characteristics

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Abbreviations: ACE=angiotensin-converting enzyme, ARA=angiotensin receptor antagonist, LGE=late gadolinium enhancement, EDV=end-diastolic volume, EF=ejection fraction
Figure Legends

**Figure 1.** Boxplot of rest MBF in myocardial segments with and without disease proven by QCA in 28 patients before CABG (p=0.95).

**Figure 2.** Boxplot of rest MBF post-revascularization in segments without a graft and those supplied by a CABG graft (p=0.87).

**Figure 3.** Bland-Altman plot showing within patient differences of rest MBF (n=21) for ungrafted and grafted segments post-CABG. In the CABG cohort, 21/28 patients had at least one ungrafted segment, enabling comparison of the within patient means of resting MBF in grafted and ungrafted segments. The results of this analysis are consistent with the more comprehensive analysis of segmental blood flows in grafted and ungrafted segments, using mixed effects analysis.
Ungrafted vs. Grafted Segment MBF post CABG

Mean difference = -0.025
95% CI: [-0.054, 0.003]
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