Quantitative Myocardial Perfusion Predicts Outcomes in Patients with Prior Surgical Revascularization

Short title:
Quantitative myocardial perfusion predicts outcomes post CABG

Andreas Seraphim MD[a,b], Benjamin Dowsing MD[b], Krishnaraj S Rathod PhD[b], Hunain Shiwani MD[a,b], Kush Patel MD[a,b], Kristopher D Knott MD[a], Sameer Zaman MD[c], Ieuan Johns MD[c], Yousuf Razvi MD[d], Rishi Patel MD[d], Hui Xue PhD[e], Daniel A Jones PhD[b], Marianna Fontana PhD[a,d], Graham Cole PhD[d], Rakesh Uppal MD[b,f], Rhodri Davies PhD[a,b], James C Moon MD[a,b], Peter Kellman PhD[e], Charlotte Manisty PhD[a,b]

a. Institute of Cardiovascular Science, University College London, Gower Street, London, UK
b. Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, UK
c. Imperial College London, Imperial College, Healthcare NHS Trust, South Kensington, London SW7 2BX, UK.
d. Royal Free Hospital, Pond Street, London, UK
e. National Heart, Lung, and Blood Institute, National Institutes of Health, DHHS, Bethesda, MD, USA
f. William Harvey Research Institute, Queen Mary University of London, United Kingdom

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Address for correspondence:
Dr Charlotte Manisty, Barts Heart Centre, West Smithfield, London, UK. E-mail: c.manisty@ucl.ac.uk. Telephone: +44 2034656336.

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Abbreviations list:

AHA: American Heart Association
CABG: Coronary Artery Bypass Graft
FWHM: Full-Width Half Maximum
LIMA: Left Internal Mammary Artery
LGE: Late Gadolinium Enhancement
MACE: Major adverse cardiovascular events
MBF: Myocardial Blood Flow
MPR: Myocardial Perfusion Reserve
PCI: Percutaneous Coronary Intervention
PET: Positron Emission Tomography

Background: Patients with prior coronary artery bypass graft (CABG) surgery typically have complex coronary disease and remain at high risk of adverse events. Quantitative myocardial perfusion indices predict outcomes in native vessel disease, but their prognostic performance in patients with prior CABG is unknown.

Objectives: To evaluate whether global stress myocardial blood flow (MBF) and perfusion reserve (MPR) derived from perfusion mapping cardiac magnetic resonance (CMR) independently predict adverse outcomes in patients with prior CABG.

Methods: Retrospective analysis of consecutive patients with prior CABG referred for adenosine stress perfusion CMR. Perfusion mapping was performed in-line with automated quantification of myocardial blood flow. Primary outcome was a composite of all-cause mortality and major adverse cardiovascular events defined as non-fatal myocardial infarction and unplanned revascularization. Associations were evaluated using Cox proportional hazards models after adjusting for comorbidities and CMR parameters.

Results: 341 patients (median age 67 years, 86% male) were included. Over a median follow up of 638 days (IQR 367, 976), 81 (24%) patients reached the primary outcome. Both stress MBF and MPR independently predicted outcomes after adjusting for known prognostic factors (regional ischaemia, infarction). The adjusted hazard ratio (HR) for 1ml/g/min decrease in stress MBF was 2.56 (95%CI, 1.45-4.35) and for 1unit decrease in MPR the adjusted HR was 1.61 (95%CI, 1.08-2.38).

Conclusions

Global stress MBF and MPR derived from perfusion CMR, independently predict adverse outcomes in patients with prior CABG. This effect is independent of the presence of regional ischemia on visual assessment and the extent of previous infarction.

Abstract word count: 250

Key words: Mapping, blood flow, perfusion reserve, CABG

Condensed Abstract:

Understanding the pathophysiological processes that determine outcomes in patients with prior surgical revascularization may allow improved risk stratification and identification of novel therapeutic targets. Stress myocardial blood flow (MBF) and perfusion reserve (MPR) independently predict adverse outcomes in patients with prior CABG after adjusting for conventional prognostic factors, including age and diabetes. This association remains independent of the presence of regional ischemia on visual assessment and the extent of infarction. Quantitative perfusion offers enhanced pathophysiological assessment in such patients, likely by incorporating additional, prognostically important processes such as the presence of microvascular coronary disease and incomplete revascularization.

Introduction

Patients with prior coronary artery bypass graft (CABG) surgery typically have advanced coronary atherosclerotic disease and remain at high risk for symptom recurrence and adverse events (1). Surgical revascularization is primarily aimed towards treatment of epicardial coronary artery disease, but incomplete revascularization and co-existent microvascular disease may also impact on patient outcomes. Improved understanding of the pathophysiological parameters that determine prognosis, particularly the impact of myocardial blood flow post-surgical revascularization, may facilitate risk stratification and offer novel therapeutic targets.

Stress perfusion cardiac magnetic resonance imaging (CMR) imaging has high diagnostic accuracy for the detection and characterisation of myocardial ischemia in native vessel disease (2) and predicts adverse cardiovascular outcomes (3). Recently, qualitative (visual) assessment of first pass perfusion with CMR was shown to predict outcomes in patients post CABG (4), however the diagnostic accuracy of qualitative (visual) assessment was previously shown to be reduced in this patient population (5). Importantly, conventional methods of ischaemia assessment primarily focus on the detection of obstructive epicardial disease and may not adequately capture additional processes that predict prognosis in this patient population.

Myocardial perfusion mapping permits the fully quantitative evaluation of myocardial blood flow (MBF in mls/g/min), and is increasingly deployed for detection of both epicardial and microvascular coronary disease (6). It has demonstrated superior diagnostic performance compared to qualitative assessment (7), enabling global and segmental MBF evaluation even in the presence of multivessel coronary artery disease (8). Importantly, quantitative perfusion with CMR (9) and Positron Emission Tomography (PET) (10) has also been shown to

independently predict outcomes in native coronary artery disease, with a prognostic benefit incremental to established imaging biomarkers. In these studies patients with prior CABG were either excluded or poorly-represented, with no specific analysis related to this subgroup of patients.

The prognostic utility of quantitative perfusion mapping in patients post CABG, a technically complex disease model for perfusion assessment, has not been previously tested. We therefore aimed to investigate whether evaluation of stress myocardial blood flow using perfusion mapping CMR in patients with prior CABG would be independently associated with adverse outcomes.

Methods

Patients and study design

A single centre retrospective cohort study of consecutive patients with prior CABG surgery, clinically referred for an adenosine stress myocardial perfusion cardiac MRI scan at Barts Heart Centre, London, between September 2016 and December 2020. Patients with underlying cardiomyopathies known to affect myocardial perfusion (cardiac amyloidosis, hypertrophic cardiomyopathy) and patients with implanted devices a were excluded. Comorbidities and clinical events were retrieved from electronic patient records and the National Health Service Spine portal. Data collected included cardiovascular risk factors and co-morbidities, prior percutaneous coronary intervention (PCI, any time prior to the CMR study), and surgical information including timing of surgery and presence of left internal mammary artery (LIMA) grafts.

The primary outcome was a composite of death and major adverse cardiovascular events (MACE) that included non-fatal myocardial infarction and unplanned (late) coronary revascularization (>90 days post CMR). Patients undergoing early revascularization within

90 days after CMR were excluded from the analysis to prevent the inclusion of revascularization events driven by the results of the perfusion CMR study. Time-to-MACE was defined as the period from the CMR study date to the occurrence of the first MACE, death or censorship at the end of the follow-up period. Data was collected as part of the Barts Revascularisation Registry with prior approval from the Barts Health NHS Trust Institutional Review Board (Study ID: 142567). In view of the study design, informed consent was not required. Ethical approval is also in place from East of England (Cambridge Central) National Research Ethics Service Committee (21/EE/0037) for collection and use of de-identified CMR and outcome data from clinical patients for research.

The CMR perfusion research sequence and image reconstruction software used in these studies was provided by the National Institutes for Health (NIH) under a core-competency partnership (C2P) agreement with Siemens. Local Institutional approval is in place for their use in diagnostic clinical studies at Barts Heart Centre. This is an established process which ensures that patient safety guidelines are met and that the use of research tools is in the best interest of the patient as determined by the responsible clinician

Cardiovascular magnetic resonance scans

Patients underwent adenosine stress myocardial perfusion CMR at 1.5T (Aera) or 3.0T (Prisma, Siemens Healthineers, Erlangen, Germany). The imaging protocol included cine imaging, stress and rest perfusion followed by late gadolinium enhancement (LGE) imaging. First pass myocardial perfusion was performed post administration of adenosine and at rest, according to standard protocols (140mcg/kg/min adenosine infused for 4 minutes) (11). The myocardial perfusion sequence is a single-bolus, dual sequence previously described (12). Basal, mid-ventricular, and apical short-axis perfusion images were acquired at both stress and rest. Image acquisition was performed over 60-90 heartbeats. A bolus of 0.05 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Paris, France) was administered at 4 ml/s during

both maximal hyperemia and at rest. Perfusion maps were generated automatically, in-line with each pixel of myocardium encoding MBF expressed in ml/g/min. The quantitative perfusion technique incorporates a machine learning approach for myocardial segmentation (13), allowing derivation of both global and segmental MBF based on the 16-segment AHA model with no manual input.

CMR image analysis

Scans were analysed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Myocardial volume and mass analysis were derived from short axis stack cine images. For regional perfusion defects, conventional first pass perfusion images were analysed visually by CMR operators (attending cardiovascular imaging consultants with >5years CMR experience) blinded to the study outcome results. A visual perfusion defect was defined as an inducible defect (reduced relative signal intensity) in at least one myocardial segment, that extended beyond any area of LGE uptake. Both stress and rest perfusion imaging were used for the interpretation of an inducible perfusion defect in line with consensus recommendations (11). Quantitative analysis of myocardial perfusion was performed automatically in-line with no manual operator adjustment. Global MBF was derived as the average of all myocardial pixels, with global MPR representing the ratio of stress MBF/rest MBF (Figure 1). In view of the high infarct burden in the cohort and the known association between MBF and infarct scar, a further sensitivity analysis of global MBF and MPR was performed by excluding myocardial segments with evidence of LGE (Online Figure S1, Data supplement). Similarly, given the expected association between LGE and prognosis, qualitative and semi-quantitative LGE analysis was performed. The latter was analysed from the LV short-axis stack LGE (phase-sensitive inversion) images, using two different signal intensity thresholding methods (full-width half maximum (FWHM) and 5xSD above remote myocardium) as previously described (14). LGE was expressed as a percentage of total LV

mass. Myocardial segments with artefacts were manually excluded from the quantitative LGE analysis.

Statistical analysis

Continuous variables were reported as mean±SD or median (interquartile range (IQR)) depending on normality. Normality was assessed using a Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using a student's t-test, Mann-Whitney U test, and with a χ^2 test or Fisher's exact test for categorical variables. Multivariate linear regression models were used to evaluate predictors of stress MBF and MPR. Unstandardized beta coefficients were obtained. Variables significantly associated with MBF and MPR in univariate analysis as well as pre-specified clinical and imaging variables regardless of strength of univariable associations were included in the models (15). Cox proportional hazard regression analyses were performed with adjustment for a number of covariates, with additional models presented in the Data Supplement. Stress MBF and MPR were not included in the same models. The proportional hazards assumption was checked using Schoenfeld residuals (Online Figure S2, Data supplement). A sensitivity analysis was also performed to obtain Firth's bias-adjusted estimates to ensure there was no bias in the estimated coefficients due to the relatively low event rates (Online Table S1). Results were similar to the original models. Kaplan-Meier survival curves were constructed and compared using log-rank tests based on stress MBF and MPR value cut offs derived from receiver operating characteristics (ROC) curve analysis. A p-value<0.05 was considered significant. Analysis was performed using SPSS software package (IBM SPSS Statistics, version 27.0).

Data access statement

All data and metadata included in this study are available from the corresponding author upon reasonable request.

Results

Cohort description and characteristics

Perfusion mapping in 390 patients with previous CABG was available. 13 patients were excluded due to lack of follow up data, 17 were excluded due to erroneous quantitative perfusion data (inappropriate slice planning, timing of contrast injection, perfusion map quality). 3 patients were excluded due to a diagnosis of hypertrophic cardiomyopathy. 16 patients underwent revascularization within 90 days of perfusion CMR and were therefore censored. A total of 341 patients were included in the final analysis.

Mean age was 67 ± 10 years, 86% were male. The clinical indications for the perfusion scan included: presence of typical angina symptoms in 164 (48%) patients, dyspnoea in 54 (16%), atypical symptoms in 29 (9%) and in 94 cases (28%) patients were referred for risk stratification (asymptomatic from cardiac perspective). Median time interval from CABG surgery to CMR study was 9 years (3-15). Comorbidities and cardiovascular risk factors were reflective of the population studied, with 190 (56%) patients having a history of diabetes mellitus and 173 (51%) patients having undergone previous PCI. The median LVEF across the cohort was 61% (50-68%) and 256 (75%) had infarction (infarct-like LGE in at least one myocardial segment). Baseline characteristics, including additional details of CMR parameters are summarized in Table 1.

Predictors of stress myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) in patients post CABG

Median stress myocardial blood flow was 1.49 (1.18-1.90) ml/g/min, and median myocardial perfusion reserve (MPR) was 2.03 (1.63-2.57). Both stress MBF and MPR were lower in those patients with an inducible visual perfusion defect compared to those without (stress MBF 1.44 ml/g/min, IQR 1.13-1.77 versus 1.73 ml/g/min, IQR 1.29-2.06 $p<0.001$), (MPR 1.99, IQR 1.59-2.41 versus 2.21, IQR 1.70-2.77, $p=0.007$). These differences remained even when only LGE-free segments were included ($p<0.001$ and $p=0.007$ respectively) (Online Figure S1, Data supplement).

In a multivariate regression analysis (Table 2), stress MBF was independently associated with age ($\beta=-0.013$, $p<0.001$), sex (female sex, $\beta=0.149$, $p=0.045$) and the percentage of global LGE ($\beta=-0.008$, $p=0.003$), whilst MPR was associated with age ($\beta=-0.019$, $p<0.001$) and the presence of diabetes mellitus ($\beta=-0.241$, $p<0.001$), (Online Table S2, Data supplement).

Predictors of MACE and all-cause mortality

Over a median follow up period of 638 days (IQR 367, 976) there were 85 events, in 81 (24%) patients. These included 24 (7%) myocardial infarctions, 36 (11%) unplanned revascularizations and 25 deaths (7%). Patients with events (death or MACE) had lower stress MBF (1.30ml/g/min; IQR 1.05-1.73; versus 1.54ml/g/min; IQR 1.26-1.96; $p< 0.001$) and lower MPR (MPR 1.96, IQR 1.56-2.33 versus 2.09, IQR 1.67-2.61; $p=0.038$) compared to those without events. Similar differences were observed when stress MBF was estimated after excluding segments with LGE ($p=0.002$). Patients who reached the primary end-point were more likely to have a visual perfusion defect (83% vs 66%, $p<0.001$), a longer period since CABG surgery ($p=0.037$) and a history of previous PCI ($p=0.003$). Detailed comparison between the groups is shown in Table 3. Univariate associations between parameters and the primary end-point are shown in the Data Supplement, Online Table S3.

Multivariate cox proportional hazard analysis demonstrated that both stress MBF and MPR (in separate models), independently predicted death or MACE, even after adjusting for a number of parameters including age, sex, extent of LGE (using either FWHM or 5xSD method), left ventricular ejection fraction, diabetes, history of previous PCI and the presence of regional ischemia on visual assessment (additional models are shown in Online Tables S4 and S5 in Data Supplement).

The adjusted hazard ratio (HR) for 1 ml/g/min decrease in stress MBF was 2.56 (95% CI, 1.45-4.35) and for 1 unit decrease in MPR the adjusted hazard ratio (HR) was 1.61 (95% CI, 1.08-2.38). In a standardised hazard model, the effect of stress MBF was found to be greater than MPR for death or MACE (standardized HR for a 1 SD decrease in stress MBF and MPR, 1.59 versus 1.35 respectively) (Table 4). Kaplan Meier event-free survival estimates by stress MBF and MPR are shown in Figure 2.

To assess whether stress MBF and MPR outcome associations are driven by the presence of previous infarction, we repeated the analysis using global stress MBF and global MPR derived only from segments without infarction (segments with infarct-pattern LGE). After the same adjustments (age, diabetes etc), both remained predictive (HR for 1 ml/g/min decrease in stress MBF was 2.22 (95% CI, 1.35-3.70; p =0.002) and for 1 unit decrease in MPR the HR was 1.49 (95% CI, 1.03-2.13; p=0.032)). Similarly, to evaluate whether early revascularization had an impact on the prognostic power of stress MBF and MPR, we performed a further analysis using early revascularization (<90 days from CMR) as a covariate. In this model, stress MBF and MPR remained independently predictive of death and MACE, whereas early revascularization itself did not have an impact on subsequent patient outcomes (Online Tables S6, S7).

Discussion

In patients with prior surgical revascularization, global stress myocardial blood flow and perfusion reserve are shown to independently predict adverse outcomes. This is independent of other known predictors (age, diabetes, prior PCI, infarction, cardiac function and measured regional ischaemia).

Factors affecting myocardial blood flow post-surgical revascularization

Patients with prior CABG generally have advanced, focally obstructive epicardial coronary disease, but they also commonly have diffuse small vessel atherosclerosis and microvascular disease. Consequently, even with anatomical bypassing of obstructive epicardial coronary lesions, myocardial blood flow is not necessarily restored to normal levels (16). It is therefore unsurprising that patients in our cohort had lower global stress MBF and MPR compared to previously reported values of healthy controls (6), and patients with similar clinical presentations but with un-grafted native vessels (8).

Data on perfusion indices post CABG are scarce. Although few studies have previously evaluated myocardial perfusion in these patients, our results are comparable to the limited data available, despite differences in imaging modalities and quantification techniques, (16,17). Using ^{15}O-water PET, Aikawa et al (17) reported a median stress MBF of 1.49ml/g/min in patients assessed 6-months post CABG. Similarly, Driessen et al (18) evaluated myocardial perfusion within 3 months of CABG surgery and reported a mean stress MBF of 2.05ml/g/min, however patients with low LVEF or prior infarction were excluded.

The significantly reduced myocardial perfusion parameters post CABG cannot solely be explained by native epicardial coronary disease. Coronary disease beyond the main epicardial

vessels, including diffuse branch vessel and microvascular disease, are almost universal in patients post CABG, and these are associated with a reduction in stress MBF and MPR (19). In our study, the presence of diabetes and increasing age, parameters also closely associated with the development of microvascular disease (20), were independently associated with myocardial blood flow indices (Online Table S2). Beyond this, our study also includes a large proportion of patients with prior infarction, with 203 (73%) patients having evidence of LGE. The extent of LGE, was shown to be an independent predictor of stress MBF in our analysis, which is in agreement with previous studies demonstrating reduced MBF in areas of infarction (21). Furthermore, it is recognised that graft failure is not uncommon post CABG, and considering the interval between surgery and perfusion assessment in this study, it is likely that a significant rate of graft failure would have been encountered in our cohort (22). Similarly, accelerated progression of native vessel disease post CABG (23) was recently shown to contribute to the reduction of stress MBF irrespective of graft patency (15). In our study, longer time from surgery was also associated with both reduced global stress MBF and MPR in univariate analysis, but the association was not maintained in multivariate modelling (Table 2, Online Table S2).

Association of quantitative perfusion indices with adverse clinical events

Despite the favourable impact of surgical revascularization on patient outcomes (24), patients with prior CABG remain at high risk for symptom recurrence and adverse events. Up to 30% are expected to undergo clinically-driven angiography within 10-years (1), and up to 13% of patients post CABG will undergo repeat revascularization during the same period (25). Given the different mechanisms leading to reduced myocardial perfusion post revascularization, determining their contribution on outcomes may inform the methods by which we measure the success of revascularization and improve risk stratification post procedure.

Several studies across different imaging modalities including nuclear (26), echocardiography (27) and more recently CMR (4), have demonstrated a prognostic role for qualitative ischemia detection in patients with prior CABG. Pen et al (26) evaluated 953 patients with prior CABG using Rb-82 MPI or hybrid PET/computed tomography and reported that visual estimation of summed stress score (SSS) independently predicted all-cause mortality and cardiac death. Kinnel et al (4) recently demonstrated that detection of ischaemia using stress CMR predicted cardiovascular death or non-fatal myocardial infarction post CABG, although most patients were asymptomatic (67%) and ischaemia was determined qualitatively from visual analysis. Irrespective of the imaging modality used, visual assessment relies on the discrimination of regional differences within myocardial territories, and is primarily geared towards the detection of focal epicardial disease. Indeed, visual analysis was previously shown to have reduced diagnostic accuracy in advanced coronary disease models, including multivessel disease (8) and post-surgical revascularization (5), and major studies evaluating the prognostic impact of visual detection of ischemia with CMR have excluded patients with prior CABG (2,3).

It is however likely that prognosis post CABG will also be influenced by many of the factors beyond epicardial coronary disease that impact myocardial blood flow (28). We propose that quantitative perfusion can interrogate these processes (including atherosclerotic burden (29), microvascular function (19), and the presence of scar (21)), and may better predict outcome than qualitative or visual assessment alone.

To our knowledge, no previous study specifically evaluated the prognostic value of quantitative MBF estimation in patients with prior CABG. Quantitative perfusion assessment offers a reproducible method of MBF quantification irrespective of the imaging modality used (30),

providing incremental diagnostic value even in complex disease models, including multivessel epicardial (8) and microvascular coronary disease (31). Large studies deploying quantitative perfusion with either PET or CMR have either excluded (10) patients with prior CABG or these patients were poorly represented (32,33). Importantly, both stress MBF and MPR were shown to independently predict outcomes in the context of native coronary artery disease using CMR (9,32) and PET (10,33) and the current study suggests that a similar prognostic value is maintained in patients with prior CABG.

These data highlight both the complexity of myocardial perfusion in patients post CABG and the challenges of evaluating the effects of revascularization. Incorporating quantitative perfusion into future interventional studies post CABG may provide incremental insights into the relationship between restoration of myocardial blood flow and outcomes.

Limitations

The study is limited by the sample size and its retrospective single-centre design. Data on the cause of death was not available for the majority of patients, therefore associations with cardiovascular mortality could not be assessed. This is however the largest cohort focusing exclusively on patients with prior CABG undergoing quantitative perfusion imaging across all imaging modalities, and provides novel data on the prognostic role of quantitative perfusion indices in this population. This was a single timepoint study without contemporary coronary anatomical information, making drawing conclusions about the distinct pathophysiological mechanisms of reduced MBF in this cohort challenging. Future prospective studies with paired information on coronary anatomy and quantitative perfusion imaging could provide insights into these mechanisms. However, our findings are reflective of real-world clinical practice in broadly unselected patients, with significant variability between the original surgery and the

time of perfusion evaluation. This cohort included a subset of asymptomatic patients (n=94, 28%). A sub-analysis of these patients shown in Data Supplement Table S8, suggests that stress MBF and MPR remain predictive of outcome. However, in view of the small sample size and event rate, the prognostic value of routine use of quantitative perfusion imaging in asymptomatic patients post CABG cannot be supported by this data.

Furthermore, the availability of perfusion mapping data in addition to the first pass perfusion imaging at the time of clinical reporting may have introduced bias in the interpretation of an inducible perfusion defect, at least in some cases. However, clinical reporting of an inducible perfusion defect is based on the interpretation of stress and rest first pass perfusion imaging, in conjunction with evaluation of LGE imaging and no absolute cut offs for normal stress MBF or MPR are used in our centre. Indeed, the primary purpose of this study was not a comparison in the diagnostic performance of visual interpretation of ischemia against quantitative perfusion mapping, but rather the assessment of the prognostic importance of myocardial perfusion indices in this population.

Finally, there are technical challenges related to the use of first pass perfusion in patients with prior CABG (contrast dispersion and delay, vasomotor differences between grafts) that may have an impact on absolute MBF quantification. Previous studies however examined the performance of quantitative perfusion in the context of CABG and have provided reassuring results (15,34).

Conclusion

In this cohort of consecutive, clinically referred patients with prior CABG, both global stress MBF and MPR independently predicted all-cause mortality and adverse cardiovascular events.

Their prognostic effect is independent of the presence of ischemia on visual assessment, cardiac function or the extent of myocardial scar. These results suggest that quantitative perfusion may offer additional insights into the pathophysiological processes that determine outcomes post CABG, and should be further evaluated in prospective studies.

Clinical Perspective**:**

Competency in patient Care and Procedure Skills:

In patients who have undergone coronary artery bypass graft surgery (CABG), quantitative perfusion indices, stress myocardial blood flow, and perfusion reserve predict adverse events independent of clinical features or imaging evidence of ischemia or infarct size.

Translational outlook:

Prospective studies are needed to assess the utility of quantitative myocardial perfusion for risk stratification before and after CABG.

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Figure legends:

Figure 1. Inducible ischaemia interpretation and analysis of stress myocardial blood flow (MBF).

A: First pass perfusion imaging of basal, mid and apical short axis slices. B: Quantitative perfusion mapping with estimation of global and segmental MBF (C). D: LGE imaging at the corresponding short axis slice positions shows segments with previous infarction that correlate with the stress perfusion defects shown in A and B. In this patient, no inducible perfusion defect was demonstrated."

Figure 2. **Kaplan-Meier event-free survival curves for stress myocardial blood flow (MBF) and myocardial perfusion reserve (MPR)**

Event-free survival curves for death and major adverse cardiovascular events (non-fatal myocardial infarction and unplanned revascularization) according to (A) stress MBF and (B) MPR. Lower stress MBF and MPR were associated with higher rates of events (log-rank $p<0.001$ and $p=0.041$ respectively).

Central illustration. **Quantitative myocardial perfusion predicts outcomes in patients with prior surgical revascularization**

Top: Perfusion mapping permits the fully quantitative estimation of global and regional stress myocardial blood flow (MBF) and perfusion reserve (MPR). Bottom: Event-free survival curve for death and major adverse cardiovascular events (non-fatal myocardial infarction and unplanned revascularization) according to stress myocardial blood flow.

Tables

Table 1. Baseline demographics and characteristics of patients with prior coronary artery bypass graft (CABG) surgery

	Patients with previous CABG (n=341)
Demographics	
Age, years	67 ± 10
Male, n	294 (86)
BSA, m^2	1.9 (1.8-2.1)
BMI, kg/m^2	28 (25-31)
Co-morbidities/ Risk factors, n (%)	
Diabetes mellitus	190 (56)
Hypertension	307 (90)
Hypercholesterolaemia	301 (88)
Smoking	105 (31)
Previous stroke / TIA	21 (6)
Atrial fibrillation	37 (11)
Previous PCI	173 (51)
Coronary artery bypass graft surgery	
Interval between CABG and CMR study (years)	9 (3-15)
LIMA to LAD graft, n (%)	264 (90)[a]
Indication for stress CMR, n (%)	
Typical chest pain	164 (48)
Dyspnoea	54 (16)

Atypical symptoms	29 (9)
Risk stratification (asymptomatic)	94 (28)
CMR parameters	
LVEDVi, ml/m^2	75 (65 – 92)
LVMi, g/m^2	57 (48 – 66)
LVEF, %	61 (50 - 68)
Visual perfusion defect (qualitative), %	240 (70)
Stress MBF, ml/g/min	1.49 (1.18 - 1.90)
Rest MBF, ml/g/min	0.74 (0.60 - 0.88)
Myocardial perfusion reserve (MPR)	2.03 (1.63 - 2.57)
Stress MBF with LGE segments excluded	1.51(1.22-1.93)
Rest MBF with LGE segments excluded	0.74 (0.60-0.90)
MPR with LGE segments excluded	2.05 (1.63 - 2.62)
LGE analysis	
LGE present at least in 1 segment (n, %)	256 (75)
LGE as % of global myocardium (FWHM)	9.3 (0 - 17)
LGE as % of global myocardium (5x +SD)	8.6 (0 – 18.7)

BSA, body surface area; BMI, body mass index; TIA, transient ischemic attack; PCI percutaneous coronary intervention LIMA, left internal mammary artery; LAD, left anterior descending artery; CABG, coronary artery bypass graft surgery; LVEDVi, left ventricular end-diastolic volume index, LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; LGE late gadolinium enhancement. Results shown as mean ± SD or median (IQR). [a] LIMA data available for 292 patients

Table 2. Multivariable regression model of predictors of stress MBF in patients with prior CABG

Independent variables	Standardized B	β (unstandardized)	95% CI of β	*P* value
Age (years)	-0.245	-0.013	-0.018 to -0.007	<0.001
Female sex	0.104	0.149	0.003 to 0.295	0.045
Global LGE (%)[a]	-0.191	-0.008	-0.013 to -0.006	0.003
Diabetes Mellitus	-0.095	-0.094	-0.195 to 0.010	0.066
Time since CABG surgery (years)	-0.079	-0.005	-0.012 to 0.002	0.174
Previous PCI	-0.028	0.027	-0.129 to 0.075	0.599
LVEF (%)	0.109	0.004	-0.002 to 0.010	0.179
LVEDVi (ml/m^2)	0.060	0.001	-0.002 to 0.004	0.413

[a]5x SD thresholding method; *LVEF* left ventricular ejection fraction; *CABG* Coronary artery bypass graft surgery; *LVEDVi,* left ventricular end-diastolic volume index; *LGE,* late gadolinium enhancement; *PCI,* percutaneous coronary intervention

Table 3. Characteristics of patients during follow-up period in relation to the primary outcome

Characteristics	**Death or MACE (n=81)**	**No death or MACE (n=260)**	***P* Value**
Demographics			
Age, years,	68 ± 10	67 ± 10	0.165
Male sex, n (%)	76 (94)	218 (84)	**0.023**
BSA, kg/m^2	1.9 (1.8-2.1)	1.9 (1.7-2.1)	0.269
Time since CABG surgery (years)	10 (6-17)	8 (3-15)	**0.037**
Comorbidities			
Diabetes	41 (51)	149 (57)	0.290
Hypertension	71 (88)	236 (91)	0.414
Dyslipidaemia	73 (90)	228 (88)	0.553
Previous PCI	53 (65)	120 (46)	**0.003**
Atrial fibrillation	7 (9)	30 (12)	0.464
Stroke or TIA	2 (2)	19 (7)	0.182
Smoking history	30 (37)	75 (29)	0.163
Cardiovascular Magnetic Resonance parameters			
LVEDVi, ml/m^2	75 (65-94)	75 (65-91)	0.743
LVEF, %	60 (43-67)	61 (50-68)	0.383
LVMi, g/m^2	61 (52-68)	56 (48-66)	0.051
Any late gadolinium enhancement, n (%)	67 (83)	189 (73)	0.069
Myocardial segments with LGE, n	3 (1-5)	3 (0-5)	0.445

Global LGE (%, 5xSD)	9.6 (2.4-17.3)	7.9 (0-19.3)	0.319
Global LGE (%, FWHM)	10.3 (3.5-17.7)	9.2 (0-16.85)	0.202
Global Stress MBF, ml/g/min	1.30 (1.05-1.73)	1.54 (1.26-1.96)	**<0.001**
Global MPR	1.96 (1.56-2.33)	2.09 (1.67-2.61)	**0.038**
Stress MBF of segments without LGE	1.39 (1.07-1.79)	1.57 (1.26-1.98)	**0.002**
MPR of segments without LGE	2.02 (1.60-2.44)	2.07 (1.68-2.71)	0.086
Visual perfusion defect	69 (83)	171 (66)	**<0.001**

MACE - defined as myocardial infarction or unplanned coronary revascularization. BSA, body surface area; BMI, body mass index; TIA, transient ischemic attack; PCI percutaneous coronary intervention CABG, coronary artery bypass graft surgery; LVEDVi, left ventricular end-diastolic volume index, LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; LGE late gadolinium enhancement. Results presented as medians (IQR), means (± SD) or n (%). p-values <0.05 shown in bold.

Table 4. Cox Proportional Hazard Models for stress MBF and MPR as predictors of death or MACE

Predictors	Death or MACE
Stress myocardial blood flow (MBF)	
Unadjusted	
Hazard ratio (95% CI) per 1x SD decrease	1.49 (1.18-1.92)
P value	<0.001
Adjusted*	
Hazard ratio (95% CI) per 1x SD decrease	1.59 (1.20-2.08)
P value	<0.001
Model *Chi-square* value	26.25
Myocardial Perfusion Reserve (MPR)	
Unadjusted	
Hazard ratio (95% CI) per 1x SD decrease	1.33 (1.04-1.69)
P value	0.021
Adjusted	
Hazard ratio (95% CI) per 1x SD decrease	1.35 (1.05-1.75)
P value	0.020
Model *Chi-square* value	20.9
MACE (myocardial infarction and coronary revascularization). Model for was adjusted for age, sex, left ventricular ejection fraction (LVEF), diabetes, history of previous PCI and global LGE (5x SD method used in this model).	

Figures:

Figure 1. Analysis of stress myocardial blood flow (MBF) with perfusion mapping

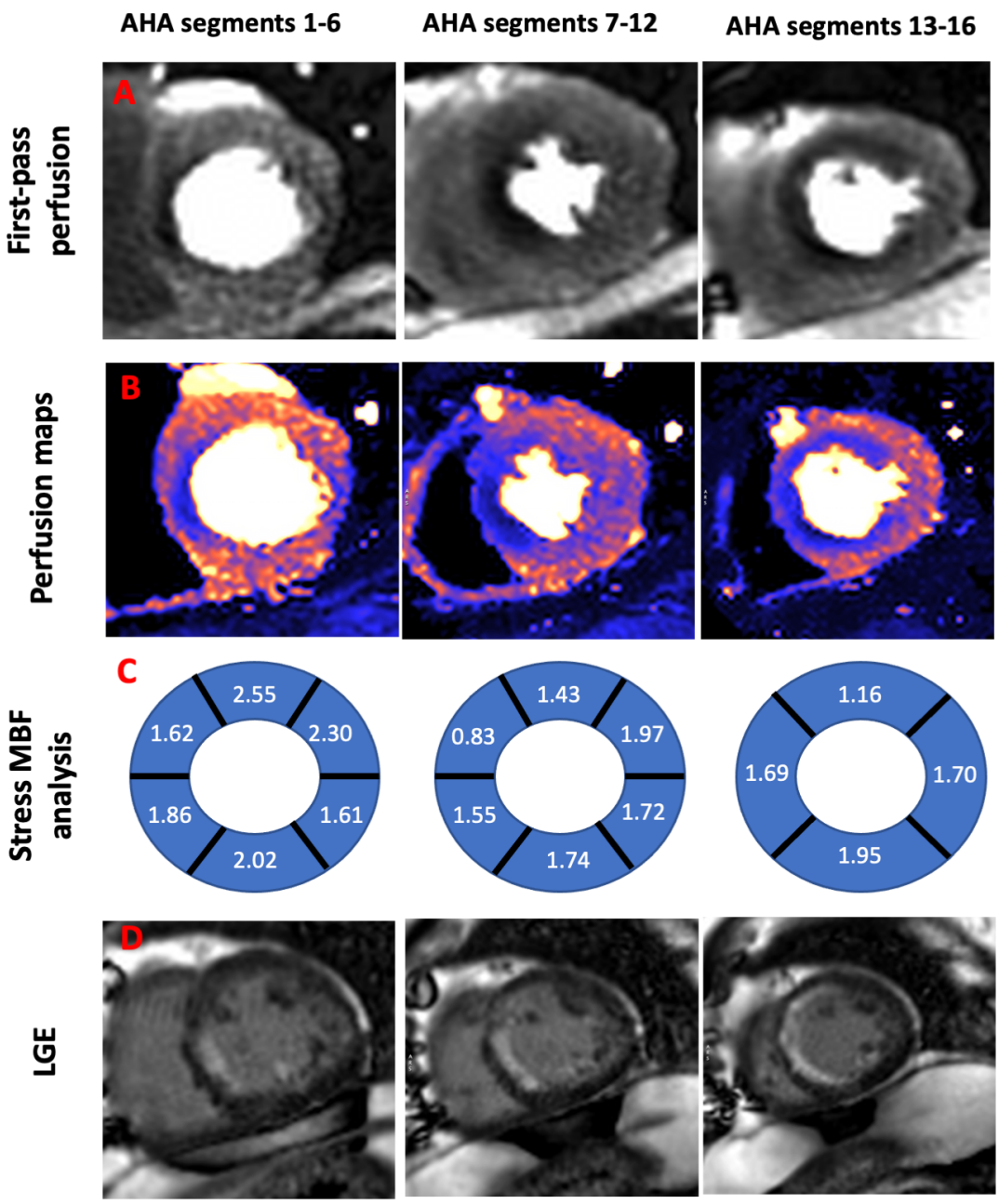
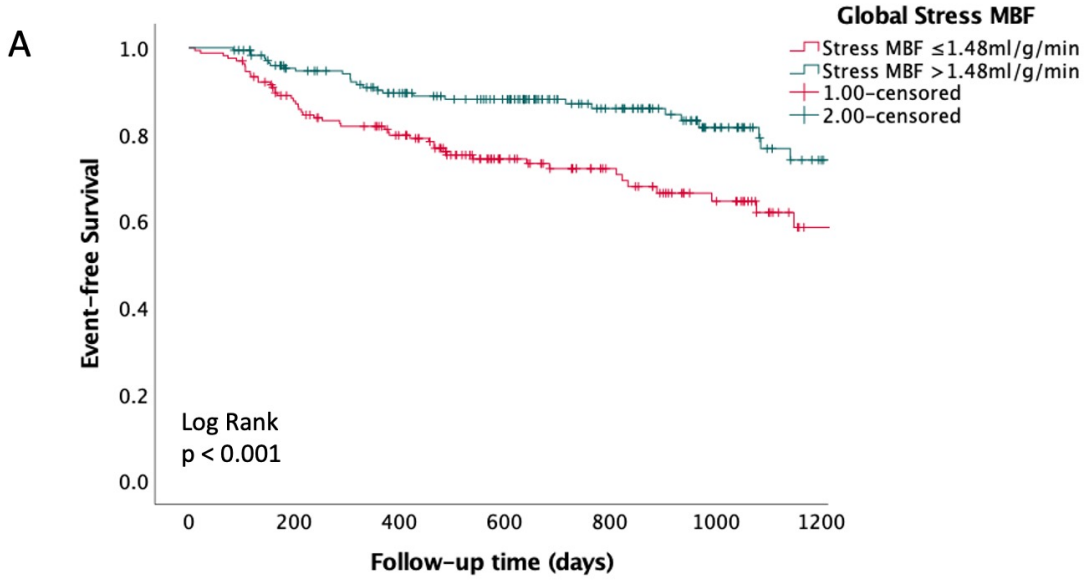
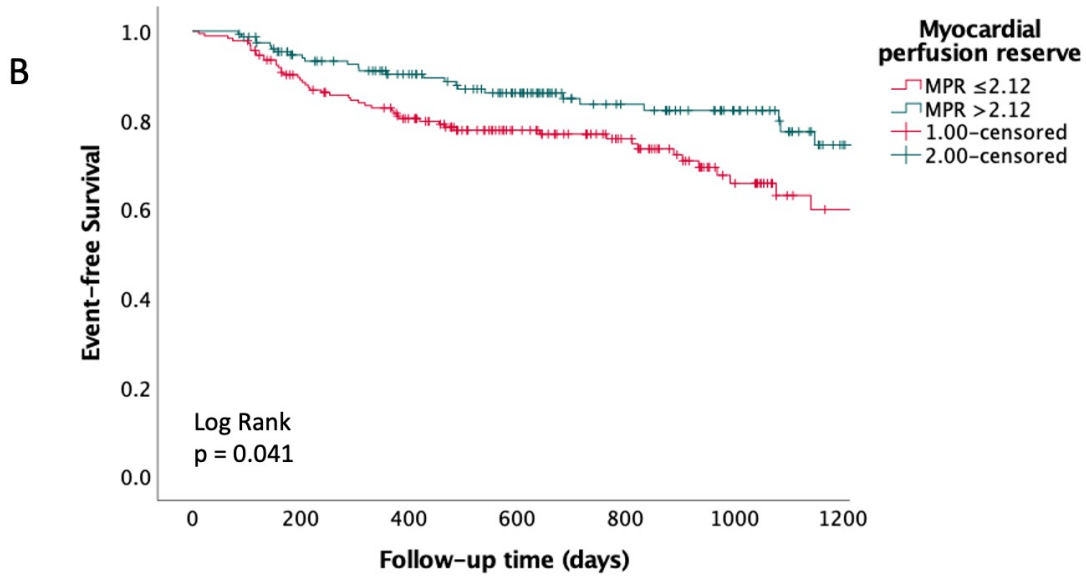


Figure 2. Kaplan-Meier event-free survival curves for stress MBF and MPR



Time (days)								
	0	200	400	600	800	1000	1200	Number at risk
Stress MBF ≤ 1.48	165	137	113	72	52	34	14	
Stress MBF > 1.48	176	154	132	112	76	46	24	



Time (days)								
	0	200	400	600	800	1000	1200	Number at risk
MPR ≤ 2.12	186	157	131	94	68	36	18	
MPR > 2.12	155	134	114	90	60	44	20	

Central illustration