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ORIGINAL ARTICLE
Vascular and cardiac imaging

Myocardial perfusion imaging by ^{15}O-H_2O positron emission tomography predicts clinical revascularization procedures in symptomatic patients with previous coronary artery bypass graft

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Aims

We wanted to assess if ^{15}O-H_2O myocardial perfusion imaging (MPI) in a clinical setting can predict referral to coronary artery catheterization [coronary angiography (CAG)], execution of percutaneous coronary intervention (PCI), and post-PCI angina relief for patients with angina and previous coronary artery bypass graft (CABG).

Methods and results

We analysed 172 symptomatic CABG patients referred for ^{15}O-H_2O positron emission tomography (PET) MPI at Aarhus University Hospital Department of Nuclear Medicine & PET Centre, of which five did not complete the scan. In total, 145 (87%) enrolled patients had an abnormal MPI. Of these, 86/145 (59%) underwent CAG within 3 months; however, no PET parameters predicted referral to CAG. During the CAG, 25/86 (29%) patients were revascularized by PCI. Relative flow reserve (RFR) (0.49 vs. 0.54 $P = 0.03$), vessel-specific myocardial blood flow (MBF) (1.53 vs. 1.88 mL/g/min, $P < 0.01$), and vessel-specific myocardial flow reserve (MFR) (1.73 vs. 2.13, $P < 0.01$) were significantly lower in patients revascularized by PCI. Receiver operating characteristic analysis of the vessel-specific parameters yielded optimal cutoffs of 1.36 mL/g/min (MBF) and 1.28 (MFR) to predict PCI. Angina relief was experienced by 18/24 (75%) of the patients who underwent PCI. Myocardial blood flow was an excellent predictor of angina relief on both a global [area under the curve (AUC) = 0.85, $P < 0.01$] and vessel-specific (AUC = 0.90, $P < 0.01$) level with optimal cutoff levels of 1.99 mL/g/min and 1.85 mL/g/min, respectively.

Conclusion

For CABG patients, RFR, vessel-specific MBF, and vessel-specific MFR measured by ^{15}O-H_2O PET MPI predict whether subsequent CAG will result in PCI. Additionally, global and vessel-specific MBF values predict post-PCI angina relief.

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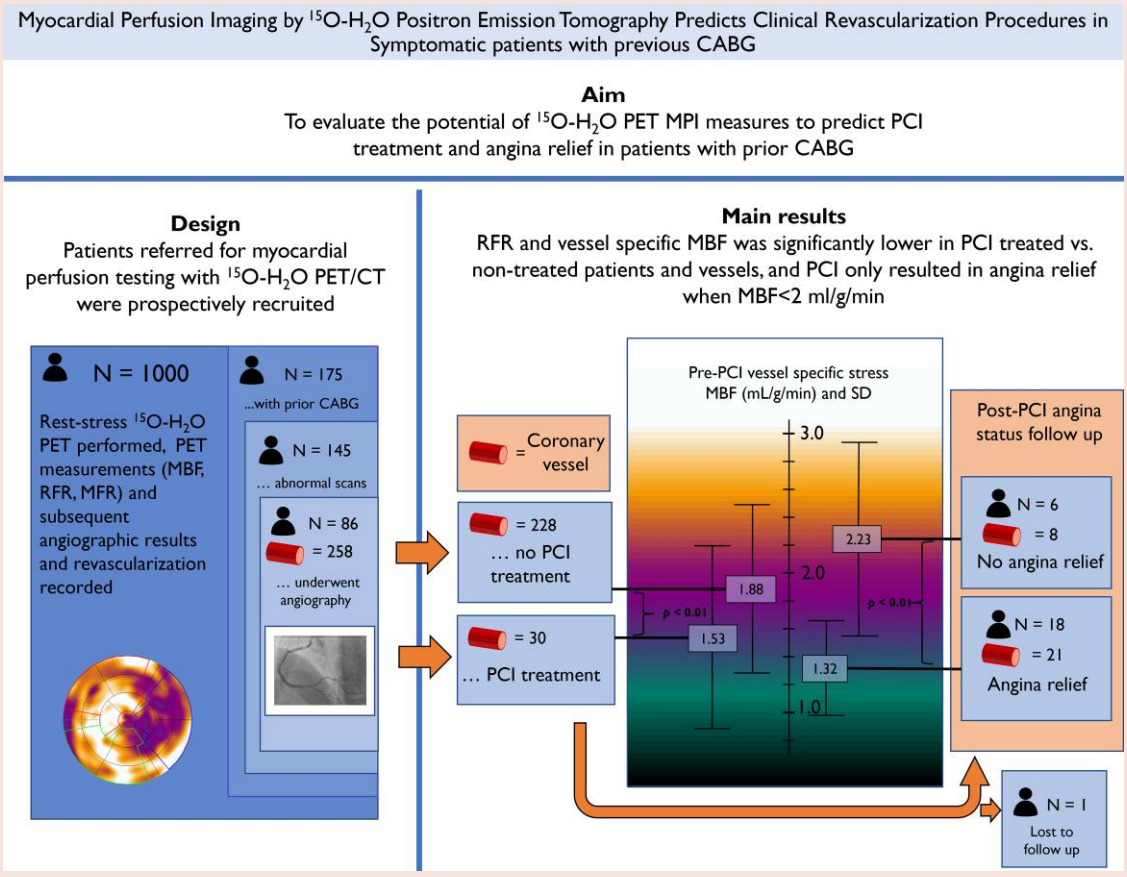
Graphical Abstract



Keywords Coronary artery bypass graft • Percutaneous coronary intervention • Myocardial perfusion imaging

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide,[1] and much effort has therefore been devoted to developing effective and safe diagnostics. The recommended strategy for diagnosis of CAD depends on individual risk assessment based on clinical symptoms and medical history[2] supplemented by an array of tests and procedures such as coronary computed tomography angiography (CCTA), echocardiography, myocardial perfusion imaging (MPI), and invasive coronary angiography (CAG). Ultimately, the goal of these tests is to identify obstructed coronary arteries, which can be targeted for revascularization and restoration of myocardial blood flow (MBF) with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).[3]

Myocardial perfusion imaging by positron emission tomography–computed tomography (PET/CT) can non-invasively evaluate the presence of CAD by detecting areas of hypoperfusion during pharmacologically induced myocardial hyperaemia. Relevant available radiotracers include rubidium-82 (^{82}Rb), ^{13}N-NH_3, and ^{15}O-H_2O.[4–9] ^{82}Rb is the most used PET tracer with a 90% diagnostic accuracy for predicting visual CAD on CAG,[10] whereas ^{15}O-H_2O is less widely used but has been demonstrated to have an excellent diagnostic accuracy. Using a receiver operating characteristic (ROC)-based threshold of 2.3 mL/g/min to discriminate between normal and hypoperfused myocardial segments, ^{15}O-H_2O MPI has an accuracy of 88–92% to detect significant stenoses in patients with no prior ischaemic heart disease (IHD) using fractional flow reserve (FFR)[11–13] as the reference standard. However, that threshold may not be applicable to other patient populations. Thus, patients who have previously undergone CABG surgery often have multivessel CAD in combination with microvascular disease, as reflected by a markedly lower mean MBF compared with patients with no known history of CAD.[3] It is therefore still unclear which MBF threshold should be considered indicative of clinically significant hypoperfusion in patients with previous CABG and which MPI results should result in a subsequent CAG with the aim of revascularization. In addition, it is unknown whether other ^{15}O-H_2O MPI-derived measurements of myocardial perfusion such as myocardial flow reserve (MFR), relative flow reserve (RFR), or regional hypoperfusion can be used to detect coronary stenoses in patients with prior CABG.

At our department, we have prospectively included all symptomatic patients referred for ^{15}O-H_2O MPI into a trial designed to predict outcomes and establish normal values of MBF (the OUTCOME-AARHUS cohort). The OUTCOME-AARHUS cohort includes patients with no known CAD as well as patients with previous CABG, previous PCI, atrial fibrillation, other cardiomyopathies, and diabetes. Given the largely unknown reference values of MBF for CABG patients, it was an aim of

this single-site clinical study to report ^{15}O-H_2O MBF values in the CABG subcohort. In addition, we aimed to determine which ^{15}O-H_2O PET MPI metrics can be used to determine (i) whether a symptomatic patient with previous CABG is offered invasive CAG, (ii) whether CAG results in revascularization by either PCI or repeat CABG, and finally (iii) whether this revascularization results in angina relief.

Methods

Subjects

All patients referred to ^{15}O-H_2O PET for myocardial perfusion assessment were invited to participate in the study and were enrolled into the OUTCOME-AARHUS cohort prospectively. The protocol was approved by the Central Denmark Region Committees on Health Research Ethics in accordance with the Helsinki Declaration, case number 1-10-72-125-20. The storage of data was approved by the regional Data Protection Agency. The cohort is registered at ClinicalTrials.gov as NCT04451551. All participants gave written informed consent before entering the study.

For this paper, the CABG subgroup consisted of 172 CABG patients amongst the initial 1000 participants of the OUTCOME-AARHUS cohort. All patients were above 18 years and were examined at the Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, from July 2020 to June 2021. The inclusion is illustrated in *Figure 1*. Three patients were scanned twice in this period. In these cases, the latest scans were excluded from the study. Five patients did not complete the ^{15}O-H_2O scan and were excluded. Thus, the total cohort consisted of 167 patients with baseline characteristics presented in *Table 1*. The median time from CABG to ^{15}O-H_2O MPI was 7.3 years. Baseline and follow-up medical information (biochemistry, medications, and symptoms) about the participants were gathered from the Electronic Patient Journal (EPJ) system of the Central Denmark Region as well as the Western Danish Heart Database (VDH). Data from the EPJ system were not anonymized during collection, and the data collector was not systematically blinded to the MPI results. Scan data are stored in-house at Aarhus University Hospital.

Scan procedure

Patients were instructed to fast for at least 2 h before the ^{15}O-H_2O PET scan and refrain from caffeine, dipyridamole, and xanthine for 24, 48, and 72 h, respectively. All patients were scanned twice in a GE Discovery MI Digital Ready PET/CT, first during rest and then during pharmacologically induced hyperaemia. The scans were 4 min dynamic acquisitions initiated at the same time as the infusion of an IV bolus of 400 MBq ^{15}O-H_2O. To induce hyperaemia, a 6 min IV infusion of adenosine (0.14 mg/kg/min.) was initiated 2 min prior to the stress scan start. A low-dose CT scan was performed prior to the PET scans to correct for attenuation. Images were reconstructed using the VuePointFX algorithm and a 6 mm Gaussian post-filter in isotropic voxels ($3.27 \times 3.27 \times 3.27$ mm^3).

Positron emission tomography measurements

All PET scans were analysed semi-automatically by aQuant Research (a cardiac research software package developed at Aarhus and Uppsala Universities based on the algorithms described in Harms *et al.*[14]). The left ventricle was divided into 17 distinct segments as recommended by the American Heart Association. The MBF and MFR were determined for each segment individually using a one-tissue compartment model that accounted for partial volume effects using the perfusable tissue index (PTI) as well as luminal activity spill-in.[15] In contrast to the models used for retention tracers, this model estimated MBF per unit mass of perfusable tissue rather than MBF per total volume of the regions of interest (ROI). For vessel-specific analysis, segments were grouped as either left anterior descending artery (LAD), right coronary artery (RCA), or circumflex artery (Cx) based on expected coronary supply and in accordance with present guidelines.[16] An MPI was considered abnormal if the stress MBF was <2.3 mL/g/min in at least two segments or if scar tissue was observed as estimated by PTI < 0.85.[13,17] Scar tissue was considered present if PTI < 0.85 in at least one segment equalling ~5% (1/17 segments) of the left ventricle. The perfusable tissue index is the ratio of the perfusable tissue fraction estimated by PET to the anatomic tissue fraction estimated by CT.[15]

Myocardial blood flow is measured as blood flow per perfusable myocardial tissue in mL/g/min.8 The following parameter definitions are illustrated in *Figure 2*. Myocardial flow reserve is calculated as the ratio of stress MBF to rest MBF.

$$\text{MFR} = \frac{\text{Stress MBF}}{\text{Rest MBF}}$$

Similarly, the vessel-specific flow reserve is calculated as the ratio of stress MBF to rest MBF for the specific vessel.

$$\text{Flow reserve of vessel} = \frac{\text{Vessel stress MBF}}{\text{Vessel rest MBF}}$$

If the stress MBF of an area is lower than 65% of the most perfused myocardial region, the area is considered a *relative defect*. Defect MBF is the stress MBF in that region. The size of the defect is described as a percentage of the total volume of the left ventricle. The RFR is calculated as the ratio of defect MBF to the MBF of the most perfused myocardial region.[18]

$$\text{Stress RFR} = \frac{\text{Defect stress MBF}}{\text{Reference stress MBF}}$$

For a more detailed description, see Supplementary material online, *Parameter definitions*.

Symptomatic relief

The outcome of angina relief was considered present if either partial or complete relief from anginal symptoms was described directly in medical journals within a follow-up period of 9 months after the MPI. If no subjective improvement was present at clinical follow-up, angina relief was not considered present. If no clinical follow-up took place, the patient was not categorized.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD), and categorical variables are presented as the affected number of patients with the percentage of the total cohort in parenthesis. GraphPad Prism 9.4.0 for Mac (GraphPad Software, San Diego, CA, USA, www.graphpad.com) was used for statistical analysis. Continuous and categorical variables were compared between CAG, PCI, and follow-up subgroups with unpaired Student's *t*-test. The independent association between myocardial perfusion and CAG, PCI, and angina relief was further analysed by logistic regression. A ROC curve was produced to demonstrate the performance of a classification model where MPI results were used to predict CAG and PCI procedures within 3 months. The ROC was evaluated using the Wilson/Brown correlation method. With these cutoff values, the positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

^{15}O-H_2O positron emission tomography as a predictor for subsequent coronary angiography

Of the total cohort of 167 patients, the ^{15}O-H_2O PET MPI was reported as normal in 22 patients, whereas 145 patients had abnormal scans. Myocardial perfusion imaging results for the total cohort are summarized in *Table 2*. The mean stress MBF and MFR were substantially lower than what has previously been reported for patients with

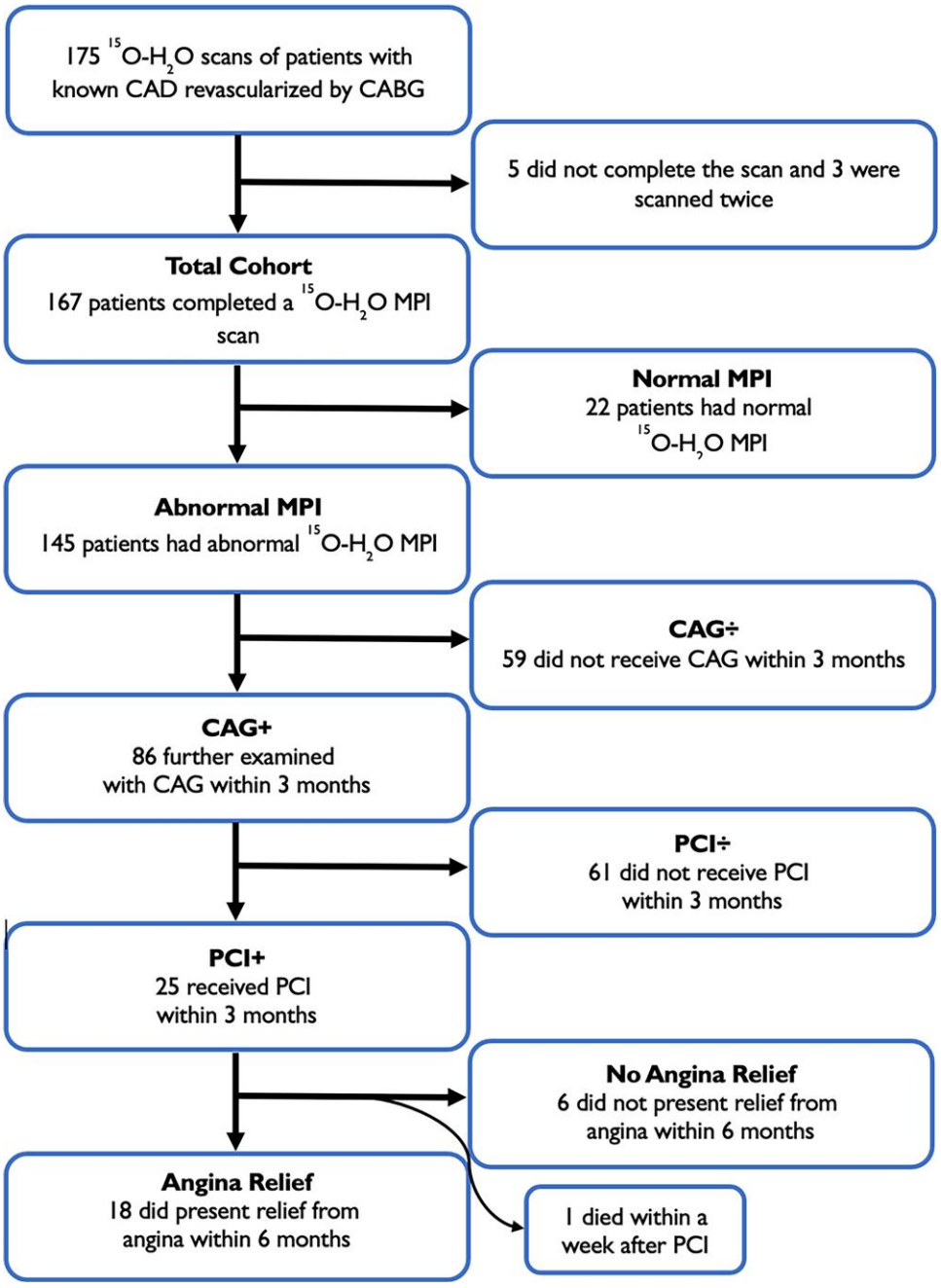


Figure 1 Flow chart of cohort inclusion and exclusion.

no known CAD. Furthermore, 79.6% CABG patients had relative stress perfusion defects as measured by RFR < 0.65.

Of the 145 patients with abnormal MPI, 86 were subsequently referred to CAG within 3 months after the PET scan and 59 were not (*Table 3*). Myocardial perfusion imaging results were not significantly different between patients referred to CAG and those who were not, and these results therefore probably played a minor role in selecting patients for CAG. However, patients referred for CAG were more likely to be female, have hyperlipaemia, and have not been examined with CAG within the last year (see Supplementary material online, *Table S1*). Indeed, logistic regression found sex, hyperlipidaemia, and no recent CAG to be independent factors associated with referral for CAG, while global stress MBF was not (see Supplementary material online, *Table S6*).

Positron emission tomography myocardial perfusion imaging as a predictor of revascularization

Of the 86 patients who underwent CAG, 25 patients were revascularized by PCI while 61 patients were not. Roughly half of the 61 non-revascularized patients turned out to have no visual epicardial stenoses, whereas a smaller fraction was found to have sufficient collaterals or

Table 1 Baseline characteristics

Characteristics, proportion in n (%)	Total cohort n = 167	Normal MPI n = 22	Abnormal MPI n = 145	P-value
Age, mean (SD)	70.6 ± 9.9	67.8 ± 9.69	71.0 ± 10.0	0.16
Female sex	27 (16.2)	8 (36.4)	19 (13.1)	**<0.01**
BMI, mean (SD)	28.7 ± 5.1	29.4 ± 5.0	28.8 ± 4.6	0.56
Previous heart disease				
CTO	98 (58.7)	10 (45.5)	88 (60.7)	0.18
PCI	92 (55.1)	11 (50.0)	80 (55.9)	0.61
Heart failure	45 (26.9)	0	45 (31.0)	**<0.01**
STEMI	25 (15.0)	3 (13.6)	22 (15.2)	0.85
NSTEMI	56 (33.5)	9 (40.9)	47 (32.4)	0.43
LBBB	16 (9.6)	1 (4.5)	15 (10.3)	0.39
AFIB/flutter	41 (24.6)	1 (4.5)	40 (27.6)	**0.02**
Risk factors				
Diabetes mellitus	49 (28.7)	6 (27.3)	43 (29.0)	0.87
Hypertension	143 (85.6)	16 (72.7)	127 (87.6)	0.65
Hyperlipaemia	145 (86.8)	18 (81.8)	127 (87.6)	0.46
Current smoker	14 (8.4)	2 (9.1)	12 (8.3)	0.90
CAD family history	88[1] (56.1)	13[2] (65.0)	74[3] (54.7)	0.39
Symptoms				
Typical angina	69 (41.3)	8 (36.4)	61 (42.1)	0.62
Atypical angina	38 (22.8)	9 (40.9)	29 (20.0)	**0.03**
Dyspnoea	103 (61.7)	13 (59.1)	90 (62.1)	0.79
Medical treatment				
Aspirin	133 (79.6)	22 (100)	111 (76.6)	**0.01**
Beta-blockers	120 (71.9)	7 (31.8)	113 (77.9)	**<0.01**
CCB	85 (50.9)	8 (36.4)	77 (53.1)	0.15
ACE/ARB	111 (66.5)	10 (45.5)	101 (69.7)	**0.03**
Statin	150 (89.8)	19 (86.4)	131 (90.3)	0.57
CABG details[a]				
LAD grafted	166[a] (100)	21[a] (100)	145 (100)	—
Cx grafted	108[a] 65.1	9[a] (42.9)	99 (68.3)	**0.02**
RCA grafted	79[a] 47.6	5[a] (23.8)	74 (51.0)	**0.02**

Missing data for family history of IHD indicates (1) n = 157, (2) n = 20, and (3) n = 137.
CTO, chronic total occlusion; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; LBBB, left bundle branch block; AFIB, atrial fibrillation; CAD, coronary artery disease; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; MPI, myocardial perfusion imaging. Bold *P*-values indicate $P < 0.05$.
[a]Missing data for one participant.

non-accessible stenoses. For a detailed description, please see Supplementary material online. No patients underwent repeat CABG. Global MPI results in patients examined by invasive CAG are presented in *Table 3* (middle bracket), and selected parameters are illustrated in *Figure 3*. Mean stress RFR was lower in revascularized patients compared with patients who were not revascularized, but all other global PET MPI parameters were not significantly different between the two groups. A ROC analysis showed that the overall area under the curve (AUC) for the ability of RFR to predict revascularization was 0.68 ($P = 0.01$) with an optimal threshold of 0.48. However, when analysing vessel-specific MPI parameters, both MBF and MFR of revascularized vessels ($n = 30$) were significantly lower than non-revascularized vessels ($n = 228$). Additionally, logistic regression identified vessel-specific stress MBF to be independently associated with early revascularization with a 9% increase in odds per 0.1 mL/g/min decrease in MBF (see Supplementary material online, *Table S6*). No other characteristics were independently associated with revascularization. A ROC analysis of vessel-specific MBF yielded an AUC of 0.69 ($P < 0.01$), whereas the AUC for MFR was 0.67 ($P < 0.01$). Optimal thresholds for vessel-specific MBF and MFR were 1.36 mL/g/min and 1.28, respectively.

Patients who were revascularized were more likely to have had a previous non-ST-elevation myocardial infarction, family history of CAD, and typical angina pectoris (see Supplementary material online, *Table S2*), but these factors were not independently associated with early revascularization (see Supplementary material online, *Table S6*).

Positron emission tomography myocardial perfusion imaging as a predictor of symptom relief

Angina relief data were available for 116/145 patients with an abnormal MPI. Data were thus not available for 29 patients, of which 23 patients had no follow-up at the hospital, 5 patients had no anginal symptoms at

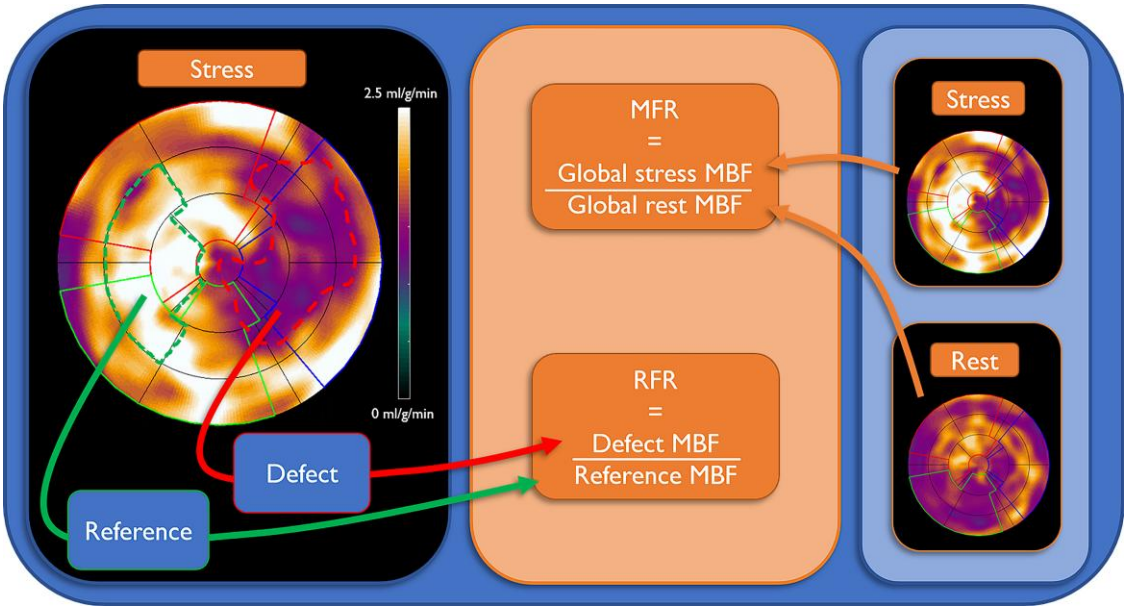


Figure 2 Myocardial blood flow can be estimated by ^{15}O-H_2O positron emission tomography for individual segments of the left ventricle. The average myocardial blood flow of the entire left ventricle during hyperaemia is the global stress myocardial blood flow—similarly, global rest myocardial blood flow during resting conditions. The ratio of global stress myocardial blood flow to global rest myocardial blood flow is termed myocardial flow reserve. An area of reduced myocardial blood flow is termed a defect, the average myocardial blood flow of which is termed the defect myocardial blood flow. The relative flow reserve is the ratio of defect myocardial blood flow to reference myocardial blood flow. The reference myocardial blood flow is the average myocardial blood flow of the most perfused segments of the left ventricle.

Table 2 Baseline perfusion results

Parametric variables, mean (SD)	Total cohort n = 167
Global stress MBF	2.00 ± 0.69
Global MFR	2.16 ± 0.73
Defect MBF	1.40 ± 0.60
Stress RFR	0.56 ± 0.23
Had a relative defect[a]	133 (79.6%)
Relative defect size[b]	21.4 ± 18.7

MBF, myocardial blood flow; MFR, myocardial flow reserve; RFR, relative flow reserve; MPI, myocardial perfusion imaging.
[a]Number (%).
[b]The relative defect size is the mean size including all participants without relative defects.

baseline, and 1 patient died shortly after the MPI. In total, 67/116 patients experienced angina relief while 49 did not. In order to analyse the predictors of angina relief, patient baseline characteristics are reported in Supplementary material online, *Table S3*, while MPI results are presented in *Table 4* (revascularized patients), Supplementary material online, *Table S4* (patients who did not undergo CAG), and Supplementary material online, *Table S5* (non-revascularized patients who underwent CAG). Of interest and as expected, angina relief was more likely in patients presenting with typical angina. In addition, global stress MBF, MFR, defect MBF, vessel-specific MBF, and flow reserve were significantly lower in patients with symptom relief ($n = 18$) after PCI treatment compared with those who did not experience symptom relief ($n = 6$) (an example from such a patient case is presented in *Figure 4*). In contrast, patients *not* referred for CAG with angina relief had significantly higher stress MBF, MFR, and defect MBF compared with patients with no angina relief (see Supplementary material online, *Tables S4 and S5*). Overall, logistic regression revealed that the stress MBF of revascularized vessels was an independent factor associated with angina relief with a 78% increase in odds of angina relief per 0.1 mL/g/min decrease in MBF (see Supplementary material online, *Table S6*), while for patients not revascularized, low MBF was not independently associated to angina relief. Using ROC analysis for revascularized patients, a global MBF threshold of 1.99 mL/g/min yielded an AUC of 0.85 ($P = 0.01$) to predict symptom improvement, whereas the optimal vessel-specific threshold of 1.85 mL/g/min yielded an AUC of 0.90 ($P < 0.01$). Myocardial flow reserve, defect MBF, and RFR yielded comparable results (see *Table 5*, lower bracket). Receiver operating characteristic curves are presented in Supplementary material online, *Figure S1*.

Discussion

Myocardial perfusion imaging is widely used as a gatekeeper examination to select which symptomatic patients with suspected CAD should undergo subsequent CAG and possible revascularization. Amongst PET MPI procedures, ^{15}O-H_2O PET has been proven to have excellent diagnostic accuracy in patients with no known CAD but may be of less value in patients with known CAD who have been revascularized by CABG, as this cohort is characterized by variable degrees of microvascular dysfunction and thus globally and regionally reduced myocardial perfusion not necessarily related to epicardial coronary disease. This clinical study underscores that notion. The vast majority of the included 167 patients with previous CABG who underwent ^{15}O-H_2O PET MPI due to angina

Table 3 Baseline perfusion results of patients with abnormal MPI

CAG follow-up, global variables	No CAG n = 59	CAG n = 86	P-value
Global stress MBF	1.83 ± 0.60	1.82 ± 0.51	0.94
Global MFR	1.99 ± 0.64	2.06 ± 0.64	0.56
Defect MBF	1.26 ± 0.44	1.22 ± 0.37	0.62
Stress RFR	0.56 ± 0.12	0.53 ± 0.11	0.08
Had a relative defect[a]	83.1	86.0	0.62
Relative defect size[b]	20.5 ± 15.9	25.7 ± 19.7	0.10
Had a scar defect[a]	50.8	52.3	0.86
Scar defect size[b]	10.2 ± 12.9	12.4 ± 17.0	0.40
CAG recipients n = 86			
PCI follow-up, global variables	**No PCI n = 61**	**PCI n = 25**	**P-value**
Global stress MBF	1.84 ± 0.47	1.78 ± 0.60	0.59
Global MFR	2.10 ± 0.62	1.96 ± 0.69	0.36
Defect MBF	1.26 ± 0.35	1.13 ± 0.38	0.13
Stress RFR	0.54 ± 0.11	0.49 ± 0.10	**0.03**
Had a relative defect[a]	83.6	92.0	0.31
Relative defect size[b]	23.2 ± 19.9	31.6 ± 18.3	0.07
Had a scar defect[a]	52.5	52.0	0.97
Scar defect size[b]	10.6 ± 14.8	16.7 ± 21.3	0.13
PCI follow-up, vessel-specific variables	**No PCI n = 228**	**PCI n = 30**	**P-value**
Stress MBF of vessels	1.88 ± 0.61	1.53 ± 0.67	**<0.01**
Flow reserve of vessels	2.13 ± 0.75	1.73 ± 0.74	**<0.01**

Continuous variables are presented as means ± SD.
MBF, myocardial blood flow; MFR, myocardial flow reserve; RFR, relative flow reserve; MPI, myocardial perfusion imaging; No CAG, participants with abnormal MPI who did not receive CAG; CAG, participants with abnormal MPI who did receive CAG; No PCI, participants with abnormal MPI who did not receive PCI; PCI, participants with abnormal MPI who did receive PCI. Bold *P*-values indicate $P < 0.05$.
[a]Proportion in %.
[b]The defect size is the mean size including all participants without defects.

had an abnormal MPI as defined by the thresholds validated in patients with no known CAD. Possibly because of this overwhelming number of pathological MPIs, the MPI results apparently did not have a major impact on the decision to refer patients for CAG and possible revascularization. Our study also demonstrates that only vessel-specific hypoperfusion and a low RFR reflecting territorial and relative hypoperfusion could predict revascularization during the CAG. Of interest and in line with the current concept, patients who were revascularized only experienced angina relief if MBF in the revascularized vessel region was impaired.

Average myocardial blood flow is reduced in patients with previous coronary artery bypass graft

Our cohort of CABG patients had a mean global stress MBF of 2.00 ± 0.69 mL/g/min and a mean stress MBF of CABG-treated vessels of 1.62 mL/g/min. This result is in line with *Aikawa et al.*,[19] who found that 13 patients who underwent CABG had a 6-month follow-up post-surgery mean MBF of CABG-treated vessels of 1.61 mL/g/min measured by ^{15}O-H_2O PET. Furthermore, our results are in line with those reported by Driessen *et al.*[3] (global stress MBF of 2.05 mL/g/min), who studied improvement in MBF following revascularization by either PCI or CABG. In any case, it is vital to recognize that ^{15}O-H_2O PET MPIs performed in patients with known CAD and previously revascularized by CABG are characterized by average global MBF values well below the established threshold of 2.3 mL/g/min used to determine whether there are significant stenoses in patients with no known CAD.[13] The reasons are probably multitude and include a larger degree of microvascular dysfunction as well as heart failure.

Selection of patients to undergo coronary angiography is not predicted by the ^{15}O-H_2O positron emission tomography myocardial perfusion imaging

Somewhat to our surprise, an abnormal MPI result appeared to have little impact on the decision to refer patients to a subsequent CAG even though the referring physician is informed about the presence and extent of stress defects, the MFR, and the global and vessel-specific

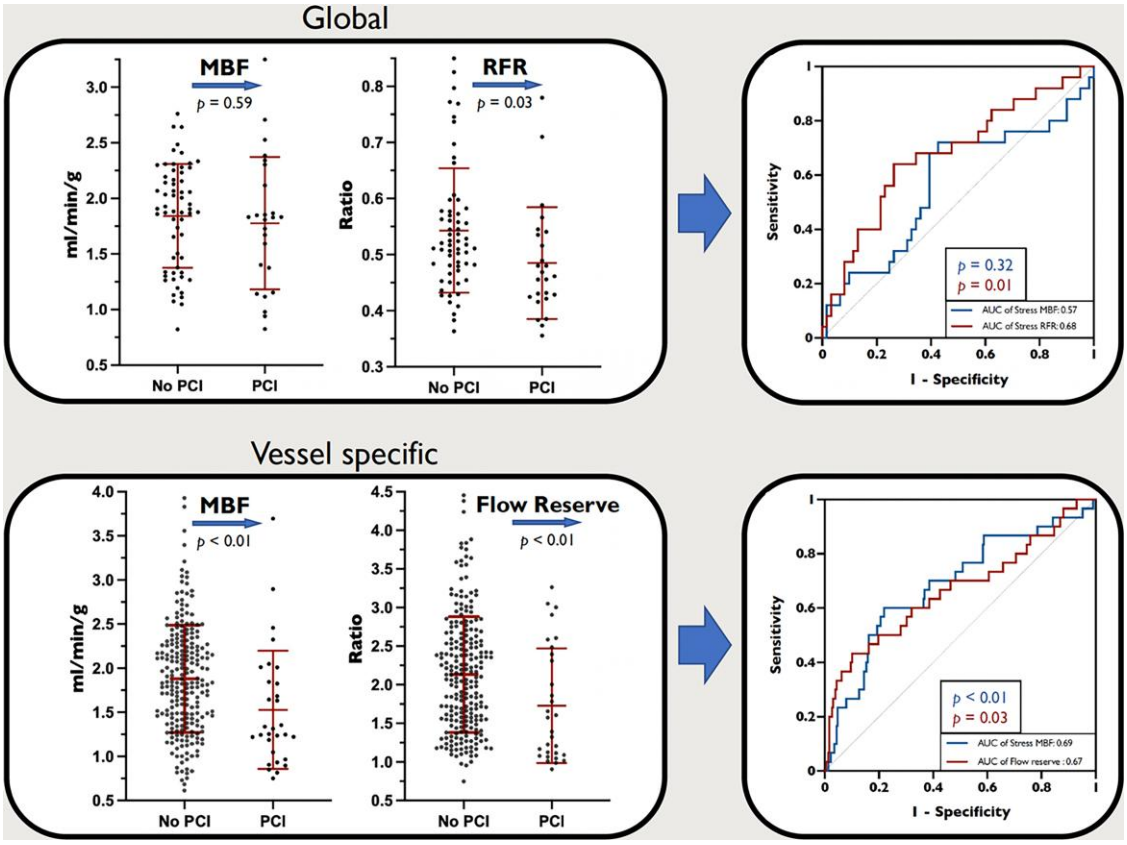


Figure 3 Patients are presented on dot plots based on selected myocardial perfusion imaging parameters and whether they underwent percutaneous coronary intervention treatment (left). Receiver operating characteristic analysis of the same myocardial perfusion imaging parameters (right). Global myocardial perfusion imaging parameters (top). Vessel-specific myocardial perfusion imaging parameters (bottom). Global myocardial blood flow was not significantly lower for patients who underwent percutaneous coronary intervention compared with patients who did not ($P = 0.59$). Global relative flow reserve was significantly lower for patients who underwent percutaneous coronary intervention compared with patients who did not ($P = 0.03$). Vessel-specific myocardial blood flow and myocardial flow reserve were significantly lower for patients who underwent percutaneous coronary intervention compared with patients who did not ($P < 0.01$ in both cases). The accuracy to predict percutaneous coronary intervention treatment was calculated using receiver operating characteristic analysis, which yielded AUC for global myocardial blood flow of 0.57 ($P = 0.32$), AUC for global relative flow reserve of 0.68 ($P = 0.01$), AUC for vessel-specific myocardial blood flow of 0.69 ($P < 0.01$), and AUC for vessel-specific flow reserve of 0.67 ($P < 0.01$).

MBF values. In some patients, this may be explained by the existence of a relatively recent CAG performed prior to the ^{15}O-H_2O PET. Thus, 35% of patients who were *not* referred to a subsequent CAG had a recent CAG vs. 9% in the group referred to CAG. In these patients, hypoperfused areas identified by the MPI are likely to have been subsequently co-localized with areas obviously inaccessible for revascularization identified during the recent CAG. Other patients may have had their anti-anginal medications optimized in the timespan between the ^{15}O-H_2O PET and the decision to perform CAG and may have experienced symptom relief obviating the need for a CAG. Still, others may have experienced spontaneous improvement in symptoms. In addition, it is well known that revascularization is an inappropriate treatment of diffusely affected coronary arteries without targetable obstructive areas. Therefore, global hypoperfusion demonstrated by the MPI will typically not result in a referral to invasive CAG. Finally, cases of severe hypoperfusion are likely to be interpreted as diffuse CAD, in which case referral to CAG is often decided against.

Presence of regional hypoperfusion predicts revascularization

In this study, we chose to evaluate to what extent ^{15}O-H_2O PET MPI can predict revascularization rather than the concordance between ^{15}O-H_2O PET MPI and invasive pressure wire measurements such as FFR. There are several reasons for this. First, in a clinical context, the ultimate aim of performing a ^{15}O-H_2O PET MPI is to identify symptomatic patients subsequently deemed suitable for revascularization and thus angina relief, rather than to predict the result of a different diagnostic test, in this case FFR. Second, it is well known that patients with previous CABG frequently suffer from microvascular disease affecting overall myocardial perfusion, and we therefore find it misleading to use FFR measured in large epicardial arteries as the reference standard. Third, in this cohort, it was not pre-specified to perform FFR during the CAG but to assess the patients as in usual daily practice. Hence, the PCI operators may likely have omitted FFR measurement and applied an integrative approach based on symptoms, CAG, and MPI results.

Table 4 Baseline perfusion results of revascularized patients

Variables, mean (SD)	Angina relief	No angina relief	*P*-value
Global results	***n* = 18**	***n* = 6**	
Global stress MBF	1.59 ± 0.47	2.37 ± 0.61	**<0.01**
Global MFR	1.74 ± 0.57	2.61 ± 0.66	**<0.01**
Defect MBF	1.05 ± 0.29	1.47 ± 0.46	**0.02**
Stress RFR	0.49 ± 0.11	0.47 ± 0.05	0.59
Had a stress defect[a]	89.9	100	0.42
Stress defect size[b]	30.4 ± 19.5	33.5 ± 16.8	0.73
Had a scar defect[a]	50.0	50.0	1.00
Scar defect size[b]	13.4 ± 16.9	15.7. ± 17.3	0.78
Vessel-specific results[c]	***n* = 21**	***n* = 8**	
Stress MBF of vessels	1.32 ± 0.34	2.23 ± 0.69	**<0.01**
Flow reserve of vessels	1.53 ± 0.58	2.43 ± 0.74	**<0.01**

One patient died before follow-up and was therefore excluded.
MBF, myocardial blood flow; MFR, myocardial flow reserve; RFR, relative flow reserve. Bold *P*-values indicate $P < 0.05$.
[a]If a patient was revascularized in multiple coronary arteries, the mean MPI values are inserted for all treated vessels.
[b]The defect size is the mean size including all participants without defects.
[c]Proportion in %.

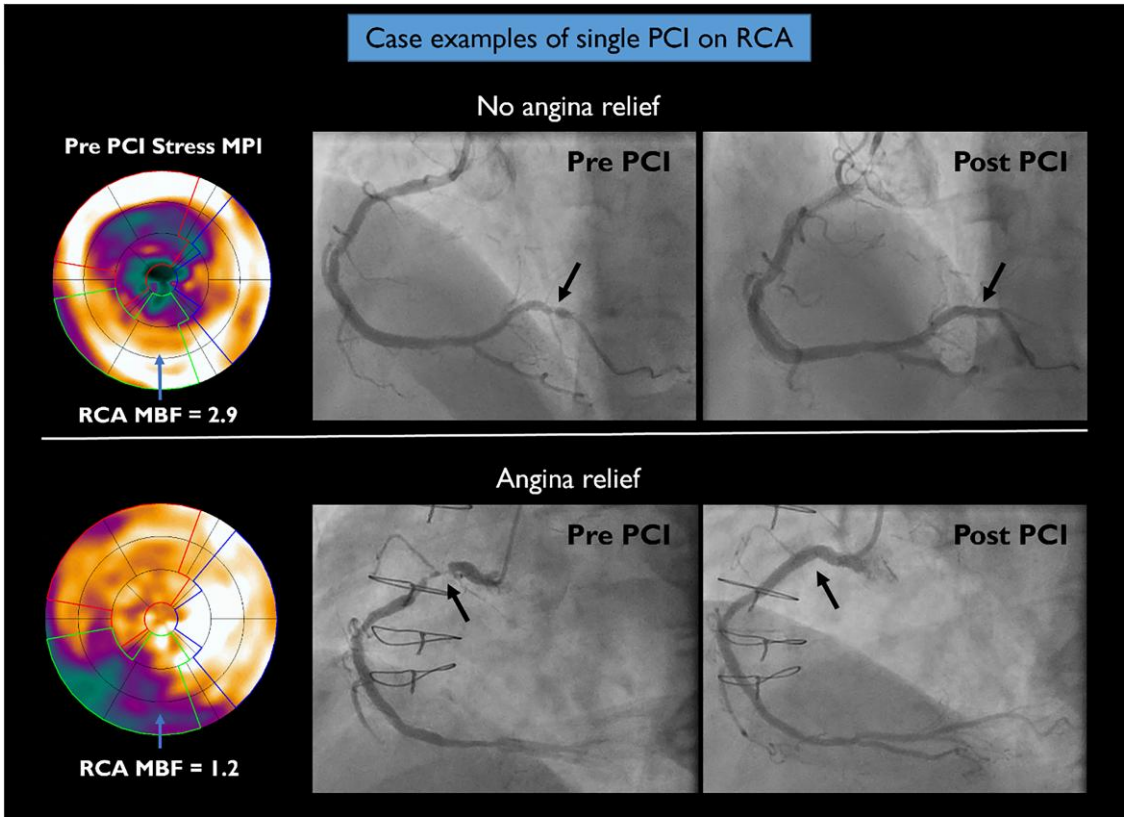


Figure 4 Pre-coronary angiography myocardial perfusion imaging results and coronary angiography results from sample patients who did (lower bracket) and did not (upper bracket) experience angina relief after single percutaneous coronary intervention treatment of the right coronary artery.

Overall, the 167 performed ^{15}O-H_2O PET MPIs led to a total of 25 revascularizations (~15%). For patients selected for CAG, the revascularization percentage was 28%. Compared to the ISCHEMIA trial, where 79% of patients randomized to the invasive arm ultimately had some form of revascularization performed, the revascularization percentage in our study is understandably lower. The difference can

Table 5 Diagnostic value of quantitative MPI on PCI procedure and subsequent angina relief

Parametric variables	AUC	*P*-value	Cutoff	Sensitivity	Specificity	PPV	NPV
PCI procedure							
Global MPI							
Stress MBF	0.57	0.32	1.87	72%	57%	40%	83%
Stress RFR	0.68	**0.01**	0.48	64%	74%	47%	88%
Vessel-specific MPI							
Stress MBF of vessels	0.69	**<0.01**	1.36	60.0%	78.1%	60.0%	78.1%
Flow reserve of vessels	0.67	**<0.01**	1.28	43.3%	89.9%	43.3%	86.4%
Angina relief							
Global MPI							
Stress MBF	0.85	**0.01**	1.99	83%	89%	94%	71%
MFR	0.82	**0.02**	2.35	83%	89%	94%	71%
Defect MBF	0.78	**0.04**	1.31	67%	89%	89%	67%
Vessel-specific MPI							
Stress MBF of treated vessels	0.90	**<0.01**	1.85	83%	95%	89%	67%
Flow reserve of treated vessels	0.80	**0.03**	2.11	83%	83%	94%	63%

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; Cutoff, optimal cutoff value as determined by the Youden index; MBF, myocardial blood flow; MFR, myocardial flow reserve; RFR, relative flow reserve. Bold *P*-values indicate $P < 0.05$.

probably be ascribed to the inclusion criteria employed, since patients were broadly included in our clinical cohort, whereas patients included in the ISCHEMIA trial had some coronary evaluation performed prior to enrolment and were thus purposefully selected to be candidates for revascularization.[20]

We found that regional hypoperfusion as estimated by RFR, vessel-specific MBF, or vessel-specific MFR predicted revascularization with PCI, although only with moderate accuracy (with the area under the ROC curves ~0.7). In contrast, neither global MBF nor MFR predicted PCI, which is uncontroversial given that diffuse microvascular CAD inaccessible for PCI is characterized by global hypoperfusion. These results are in accordance with previous studies that have convincingly found vessel-specific MBF to be associated with obstructive CAD as measured by FFR.[11–13] Likewise, *Kawaguchi et al.*[21] have recently found RFR to be associated with obstructive CAD.

Low pre-revascularization myocardial blood flow predicts angina relief

Although our study was observational and data on angina relief were less than complete, several interesting observations can be made. First, revascularization of the hypoperfused myocardium was more likely to lead to symptom relief than revascularization of areas with normal or near-normal perfusion. Second, patients with the hypoperfused myocardium reported on the MPI but not undergoing subsequent CAG were less likely to experience angina relief than patients with normal or near-normal myocardial perfusion not undergoing CAG after the MPI. Both these observations indicate that there is indeed a correlation between anginal symptoms and myocardial perfusion measured by ^{15}O-H_2O PET MPI, which falls well into line with studies showing that revascularization actually increases myocardial perfusion.[3,22,23] After all, anginal symptoms are most likely caused by transient ischaemia, which is not expected to be present in patients with normal myocardial perfusion during stress conditions. Our results thus suggest that no symptomatic improvement (beyond placebo) can be expected following revascularization of a myocardial region with *a priori* decent perfusion (>2 mL/g/min). In order to further investigate this correlation, we carefully propose to include quantitative MPI in any upcoming randomized study of the effect of revascularization.

Limitations

Some limitations to the study must be acknowledged. First, the study was performed in a public health care system in Scandinavia. Referral of symptomatic CABG patients to MPI is therefore likely less restricted than in a private or semi-private health care system, which may explain the relatively low fraction of revascularization procedures performed. Second, referral of patients to CAG after an abnormal MPI and decisions to perform revascularization naturally reflect local treatment practices, as is the case in observational studies. Thus, the stress MBF cutoff values to predict PCI and angina relief estimated in this study may not be generalizable.

Conclusions

Data from CAD patients with previous CABG included in the single-site OUTCOME-AARHUS ^{15}O-H_2O PET cohort showed that MPI results were not associated with subsequent CAG referral. However, vessel-specific MBF and RFR measured by ^{15}O-H_2O PET predicted subsequent PCI, and pre-CAG vessel-specific MBF predicts post-PCI angina relief. Therefore, ^{15}O-H_2O PET MPI appears to be a promising modality for tailoring treatment in CAD patients with previous CABG suffering from angina.

Lead author biography

Mazen Vester is a recently graduated MD with a particular interest in ischaemic heart disease and cardiac arrhythmias. During his pre-graduate years, he worked on several projects related to the use of myocardial perfusion imaging. He is currently in rotation to obtain his licence to practice as a physician.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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