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Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease?

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Objectives We compared the accuracy of quantified myocardial flow reserve and absolute stress myocardial blood flow (MBF) alone in the detection of coronary artery disease (CAD).

Background Myocardial flow reserve, i.e. ratio of stress and rest flow, has been commonly used to detect CAD with many imaging modalities. However, it is not known whether absolute stress flow alone is sufficient for detection of significant CAD.

Methods We enrolled 104 patients with moderate (30–70%) pre-test likelihood of CAD without previous myocardial infarction. MBF was measured by positron emission tomography and O-15-water at rest and during the adenosine stress in the regions of the left anterior descending, left circumflex, and right coronary artery. All the patients underwent invasive coronary angiography including the measurement of fractional flow reserve when appropriate.

Results Quantified myocardial flow reserve (optimal cut-off value 2.5) detected significant coronary stenosis with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 81, 87, 66 and 94%, respectively. When compared with flow reserve, absolute MBF at stress (optimal cut-off value of 2.4 mL/min/g) was more accurate in detecting significant coronary stenosis [area under the curve (AUC) 0.94 vs. 0.90, $P = 0.02$] with sensitivity, specificity, PPV, and NPV of 95% ($P = 0.03$ vs. flow reserve), 90, 73, and 98%, respectively. An absolute increase of MBF from rest to stress by <1.5 mL/g/min had also similar accuracy in detecting CAD (AUC: 0.95). The results were comparable in patients who did and did not receive i.v. beta-blockers prior imaging.

Conclusions Absolute stress perfusion alone was superior to perfusion reserve in the detection of haemodynamically significant CAD and allows shorter imaging protocols with smaller radiation dose.

Keywords Positron emission tomography • Coronary artery disease • Myocardial perfusion imaging • Myocardial blood flow • Myocardial perfusion reserve

Introduction

Assessment of stress-induced myocardial perfusion defects with either single photon emission computed tomography or positron emission tomography (PET) plays an important role in the evaluation of coronary artery disease (CAD). It is possible to make quantitative measurements of myocardial blood flow (MBF, mL/g/min) and myocardial flow reserve (MFR) with the use of PET.[1] The quantification of MBF with PET flow tracers ^{15}O-water and ^{13}N-ammonia and tracer kinetic modelling has been validated for over a wide range of blood flows both experimentally and in human subjects.[2,3] Recently, quantification using ^{82}Rb has also been shown to be feasible.[4–8] Compared with conventional relative evaluation of regional differences in tracer uptake, quantitative assessment of MBF can provide additional information on microvascular function and haemodynamic significance of stenosis in each of the coronary arteries.[1,9] Quantitative analysis has been shown to improve diagnostic accuracy[10–13] and provide incremental prognostic information[9,14,15] over traditional semi-quantitative measures of myocardial ischaemia. However, optimization of quantitative MBF analysis methodology is required in order to achieve feasible clinical applications.

Reduced MFR, defined as the ratio of maximal MBF at stress-to-basal MBF at rest, is an established marker of the haemodynamically significant coronary stenosis.[2,14,16] Recently, it has been proposed

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that stress MBF alone may be accurate and sufficient for the detection of CAD in patients without previous myocardial infarction.[13] Compared with MFR, the assessment of stress MBF alone would simplify and shorten the imaging protocols and reduce the radiation dose to the patient. Furthermore, it is not affected by large variability in the measured resting MBF between individuals.[17–20] However, the hypothesis that quantification of MBF during stress alone is sufficient for the detection of CAD has not been prospectively validated in the clinical setting.

We prospectively evaluated whether the quantification of MBF using ^{15}O-water PET during the stress alone is sufficient for localization and detection of haemodynamically significant CAD in patients with intermediate likelihood of CAD. We measured regional MBF using ^{15}O-water PET during rest and stress and evaluated optimal threshold values for MFR, absolute stress MBF, and absolute increase of MBF from rest to stress as well as compared diagnostic performance of each parameter in the localization and detection of haemodynamically significant coronary stenosis as determined using invasive coronary angiography including the measurement of fractional flow reserve (FFR) when appropriate.

Methods

Patient population and study protocol

We prospectively enrolled 107 consecutive out-patients (66 males and 41 females) with a history of stable chest pain and 30–70% pre-test likelihood of CAD after the analysis of the risk factors and the exercise test.[21] Exclusion criteria were atrial fibrillation, iodine allergy, unstable angina, severe loss of renal function, second or third degree AV-block, severe congestive heart failure (NYHA IV), symptomatic asthma, and pregnancy. Patients with angiographically proven CAD or clinical history of previous myocardial infarction were not eligible. No cardiac events took place during the study. However, complete PET images of three patients were not available for analysis due to technical reasons and these patients were excluded. Thus, the final study population consisted of 104 patients whose characteristics are shown in *Table 1*.

Table 1 Characteristics of study patients

Gender (male/female)	64/40
Age (years)	64 (50–80)
Weight (kg)	78 (50–116)
Body mass index	26.6 (18.0–39.1)
Risk factors (%)	
Family history of CAD	42 (40.4)
Diabetes	13 (13.0)
Impaired glucose tolerance	9 (8.7)
Hypertension	39 (37.5)
Hypercholesterolaemia	53 (51.0)
Current or previous smoker	24 (23.1)
Medication (%)	
Statin	49 (48.5)
Beta-blocker	56 (53.8)
Aspirin	70 (67.3)
Long-acting nitrate	7 (6.7)

CAD, coronary artery disease.

The study was conducted according to the guidelines of Declaration of Helsinki and the study protocol was approved by the ethics committee of the Hospital District of Southwest Finland. All the patients gave their informed consent. All the patients underwent myocardial PET perfusion imaging at rest and during adenosine stress using hybrid scanner of PET and computed tomography (CT). Before perfusion imaging all patients had coronary CT angiography. Within 2 weeks of PET, all the patients underwent invasive coronary angiography. Measurement of FFR was performed for stenoses of intermediate severity when feasible. The decision for further therapy was based only on clinical information and coronary angiography with FFR.

PET image acquisition

Rest-stress perfusion cardiac PET was performed immediately after CT angiography with a 64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems, WI, USA). Prior to CT angiography, patients received up to 20 mg of metoprolol i.v. to reach target heart rate of $<$60 bpm. After CT angiography, dynamic PET scans at rest and during the pharmacologic stress were performed. ^{15}O-labelled water (900–1100 MBq) was injected (Radiowater Generator, Hidex Oy, Turku, Finland) as an i.v. bolus over 15 s at an infusion rate of 10 mL/min. A dynamic acquisition of 4 min 40 s was performed (14 $\times$ 5 s, 3 $\times$ 10 s, 3 $\times$ 20 s, and 4 $\times$ 30 s). After a 10 min decay of the ^{15}O radioactivity, a stress scan was performed during adenosine-induced hyperaemia. Adenosine was started 2 min before the scan start and infused to the end of the scan at 140 μg/kg body weight/min. Alignment of PET images and CT images used for attenuation correction was adjusted and confirmed visually for all rest and stress studies immediately after imaging. Images were reconstructed using two-dimensional OSEM algorithm.

PET image analysis

Images were quantitatively analysed using validated Carimas™ software described earlier.[22] An experienced observer (M.M.) analysed the images blinded to other results and clinical data as described earlier.[22] Volume view and reorientation were done manually. Definition of regions of interest in the myocardium and blood pool inside the left ventricular cavity, though performed automatically, was usually accompanied by visual confirmation and appropriate manual adjustment. Modelling and reporting of results were automatic. The reproducibility of the analysis has been reported previously.[22] Average MBF values were measured for regions of the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) using individual known coronary anatomy both at rest and during stress. Overall, 312 regions were analysed. Average MFR was calculated as the ratio of stress-to-rest MBF in each region. The absolute increase was calculated as the absolute difference between stress and rest MBF. Optimal threshold values of absolute stress MBF, absolute increase of MBF, and MFR for the detection of significant coronary stenosis were defined by receiver operating characteristic (ROC) analysis. Furthermore, we tested 2.0 as the pre-defined cut-off value of MFR[2] and 2.4 mL/g/min as the pre-defined cut-off value of absolute stress MBF.[22] Stenosis in the left main (LM) coronary artery was considered to affect perfusion in both the LAD and LCX areas.

Coronary angiography and FFR

All coronary angiographies were performed on Siemens Axiom Artis coronary angiography system (Siemens, Munich, Germany). In a total of 23 vessels with intermediate stenoses (30–80% luminal narrowing), FFR measurement was performed using ComboMap® pressure/flow

instrument and a 0.014-inch BrightWire® pressure guidewires (Volcano Corp., Rancho Cordova, CA, USA). Haemodynamically significant stenosis was detected based on FFR value <0.8 in 14 of these vessels. The pressure was measured distally to the lesion during maximal hyperaemia induced by 18 μg intracoronary boluses of adenosine with simultaneous measurement of aortic pressure through the coronary catheter. FFR was calculated as the ratio between mean distal pressure and mean aortic pressure.

Quantitative analysis of coronary angiograms (QCA) was performed using software with automated edge detection system (Quantcore, Siemens, Munich, Germany) by an experienced reader (MP) blinded to the results of PET, CTA and FFR.

Significant stenosis was defined as luminal diameter narrowing >50% by QCA. When FFR was available, stenoses with FFR ≥0.8 were classified as non-significant, regardless of the degree of narrowing.

Statistical methods

Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each imaging method (PET, CT, and PET/CT). A ROC analysis curve was used to reconfirm the best cut-off points of MBF stress, MFR, absolute increase of MBF at stress in the current population. Area under the curve (AUC) values were compared using the Chi-square test. McNemar's test was performed to compare the accuracy of stress MBF, increase of MBF and MFR cut-offs <2.0 and <2.5 against golden standard (i.e. ICA with FFR). The effect of beta-blocker therapy was tested using Fisher's exact test. The analyses were performed both per main vessel and per patient (correctly classified as either with or without significant coronary artery stenosis). A *P*-value of <0.05 was considered statistically significant. The statistical tests were performed with SAS version 9.1.

Results

Patients

Based on combined invasive coronary angiography and FFR measurements, significant stenoses were found in 35 patients. Of these, 12 patients had single-vessel disease, 11 patients two-vessel disease, and 12 patients multi-vessel disease. Two patients had significant LM disease. There were 73 significant coronary artery stenoses in the three main coronary branches. Of these, 33 were in the LAD, 23 in the LCX, and 17 in the RCA. Among these were six total occlusions (four in the middle LAD and two in the middle RCA). None of the patients had a history of myocardial infarction based on symptoms, ECG, and echocardiography.

Threshold values of absolute MBF and MFR for detection of stenosis

Example polar maps of absolute MBF at rest and stress in a patient with significant coronary stenosis are shown in *Figure 1*. The average rest MBF was comparable in the myocardial regions subtended by significantly stenosed coronary arteries and non-stenosed arteries (0.96 ± 0.27 vs. 1.0 ± 0.25 mL/g/min, $P = 0.04$), but absolute MBF during adenosine stress was significantly lower in the regions subtended by significantly stenosed coronary arteries (1.77 ± 0.59 vs. 3.53 ± 1.0 mL/g/min, $P < 0.0001$). The absolute increase of MBF was significantly lower in the stenosed regions than in non-stenosed regions (0.81 ± 0.59 vs. 2.49 ± 0.95 mL/g/min, $P < 0.0001$). Thus, average MFR was lower in the presence of

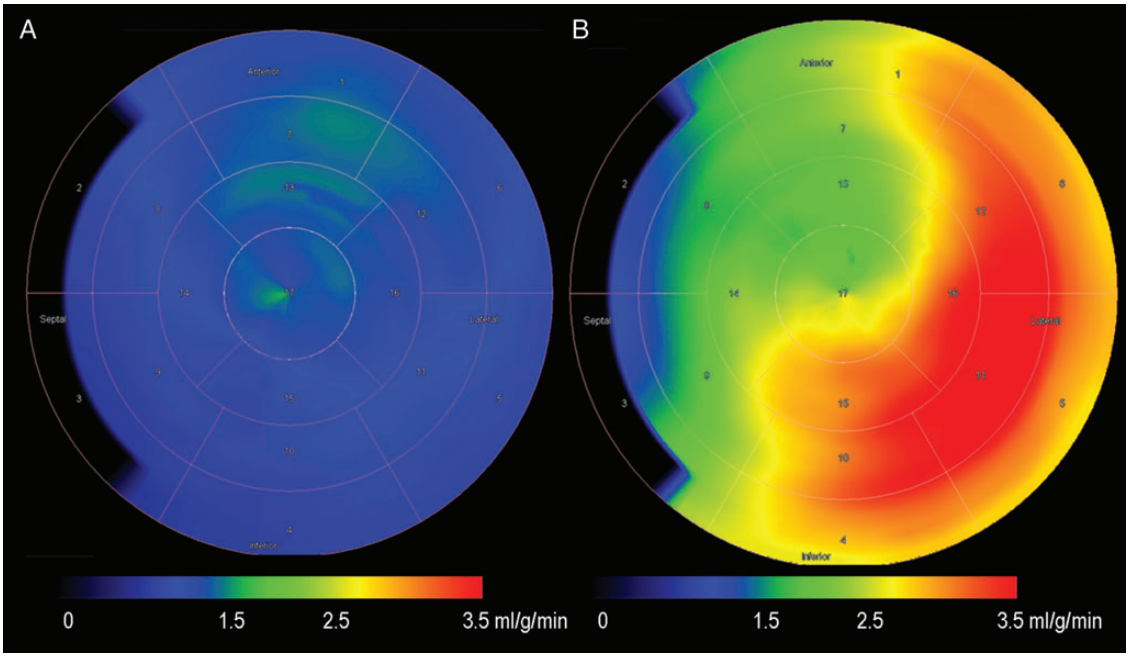

Figure 1 Figure shows examples of polar maps of MBF as assessed by ^{15}O-water PET and analysed using the CARIMAS™-software at rest (*A*) and during adenosine stress (*B*) in a patient with significant coronary stenosis in the LAD. The average rest MBF is 1.0, 1.2, and 1.4 mL/g/min in the RCA, LCX, and LAD regions, respectively. The average stress MBF was lower in the region of LAD vessel (2.1 mL/g/min) than other regions (LCX 3.7 mL/g/min, RCA 2.9 mL/g/min) resulting in lower MFR (1.5) in the LAD region than LCX (3.1) or RCA (2.9) regions.

haemodynamically significant stenosis than in the absence of stenosis (1.94 ± 0.79 vs. 3.5 ± 1.0, $P < 0.001$).

The ROC curves of rest and stress MBF alone, increase of MBF from rest to stress, and MFR for detection of significant coronary stenosis are shown in *Figure 2*. For the detection of significant coronary stenosis, the optimal cut-off value of absolute stress (AUC: 0.95) MBF was 2.4 mL/g/min, absolute increase of MBF from rest to stress was 1.5 mL/g/min (AUC: 0.95) and MFR 2.5 (AUC: 0.90).

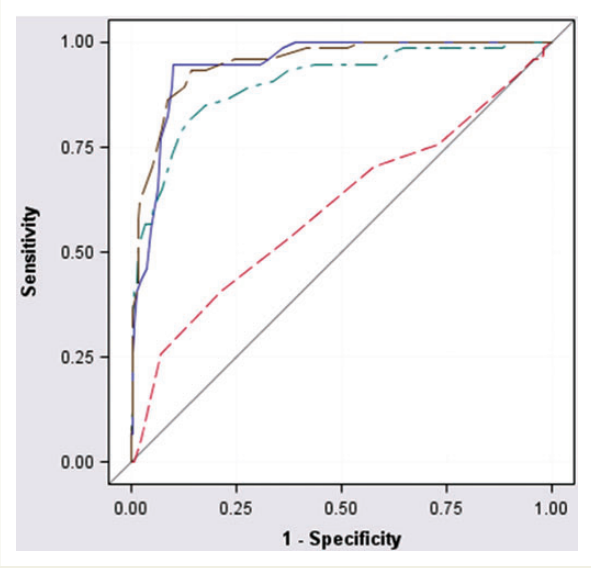

Figure 2 The ROC curves comparing diagnostic accuracy of MFR (green, dotted line), stress MBF alone (blue continuous line), absolute increase of MBF from rest to stress (brown, cut line), and rest MBF alone (red, cut line) for haemodynamically significant coronary stenosis. The optimal cut-off value for MFR was 2.5 that resulted in AUC of 0.90. Optimal cut-off value of absolute stress MBF alone was 2.4 mL/g/min that resulted AUC 0.94 that was significantly higher than that of MFR ($P = 0.02$). The absolute increase of MBF from rest to stress resulted in AUC of 0.95 with optimal cut-off value of 1.5 mL/g/min that was comparable with stress MBF alone ($P = 0.52$).

Comparison of diagnostic accuracy

Based on ROC curve analysis (*Figure 2*), absolute stress MBF alone performed better than MFR in the detection of significant coronary stenosis (area under the ROC curve 0.95 vs. 0.90, $P = 0.02$). The performance of absolute stress MBF and increase of MBF (area under the ROC curve 0.95) was comparable ($P = 0.52$).

The diagnostic accuracies of MFR, absolute stress MBF alone, and absolute increase of MBF from rest to stress are shown in *Table 2*. Stress MBF alone resulted in better sensitivity ($P = 0.035$) than MFR with cut-off 2.5 without compromising specificity ($P = 0.27$). Similarly, sensitivity of absolute increase of MBF from rest to stress by adenosine was better than that of MFR with 2.5 cut-off ($P = 0.003$) while specificity remained comparable ($P = 0.08$). The stress MBF alone had better accuracy than MFR with cut-off 2.5 ($P = 0.04$), whereas absolute increase of MBF and MFR had comparable accuracy.

On patient-based analysis, diagnostic accuracies, sensitivities and specificities of MFR, stress MBF alone, and absolute increase of MBF from rest to stress were comparable as shown in *Table 2*. The number of patients with all regions correctly classified by stress MBF alone was 88 (accuracy 84%) and MFR 75 (accuracy 74%).

We compared diagnostic accuracies of MFR with the cut-off value of 2.5 or 2.0. On vessel-based analysis, the accuracy, sensitivity, specificity, PPV, NPV, and of MFR with cut-off value of 2.0 were 87, 57, 95, 84, and 88% (for both sensitivity and specificity $P < 0.0001$ vs. 2.5 cut-off). The corresponding values on patient-based analysis were 85, 66, 95, 89 ($P = 0.005$ vs. 2.5 cut-off), and 83% ($P = 0.03$ vs. 2.5 cut-off). *Table 2* shows the results with MFR cut-off value of 2.5.

Effect of beta-blocker therapy

Since this study included CT angiography with i.v. beta-blockers before the PET scans, diagnostic accuracy of MFR and absolute stress MBF were studied separately in patients who received ($n = 79$) or did not receive ($n = 25$) i.v. beta-blocker therapy prior to perfusion imaging. In the regions that were subtended by non-stenosed coronary arteries, rest MBF was comparable in patients who received or did not receive beta-blocker prior to imaging (1.0 ± 0.2 vs. 1.0 ± 0.3 mL/min/g, $P = 0.60$). Although stress MBF was slightly higher in

Table 2 Diagnostic accuracy of myocardial flow reserve (stress MFR <2.5), absolute stress MBF and absolute increase of (increase MBF) for the detection of significant stenosis in the whole patient group

	Accuracy	Sensitivity	Specificity	PPV	NPV
Vessel-based analysis ($n = 312$)					
MFR	86	80	87	66	93
Stress MBF	90*	89*	90	73	96
Increase MBF	88	92	87	69	97
Patient-based analysis ($n = 104$)					
MFR	88	87	88	80	92
Stress MBF	91	95	89	84	97
Increase MBF	89	95	86	80	97

PPV, positive predictive value; NPV, negative predictive value.
*$P < 0.05$ vs. MFR

Table 3 Diagnostic accuracy of myocardial flow reserve (stress MFR), absolute stress MBF, and absolute increase of (increase MBF) for the detection of significant stenosis in patients who received or did not receive intravenous beta-blocker prior to imaging (vessel-based analysis)

	Accuracy	Sensitivity	Specificity	PPV	NPV
Beta-blocker ($n = 237$)					
MFR	87	83	88	63	95
Stress MBF	91	96	90	69	99
Increase MBF	88	91	87	64	98
No beta-blocker ($n = 75$)					
MFR	80	78	81	70	87
Stress MBF	91	93	90	83	96
Increase MBF	88	93	85	78	95

PPV, positive predictive value; NPV, negative predictive value.

patients who received beta-blocker (3.5 ± 1.0 vs. 3.0 ± 0.9 mL/min/g, $P = 0.04$), MFR was not different (3.5 ± 1.0 vs. 3.1 ± 0.9 mL/min/g, $P = 0.10$).

Diagnostic accuracy of absolute stress flow, MFR, and absolute increase of MBF during adenosine stress were comparable in patients who received or did not receive beta-blocker therapy as shown in *Table 3*.

Discussion

Our results show that absolute stress MBF alone, absolute increase of MBF from rest to stress and quantified MFR using ^{15}O-water PET during the adenosine stress have high accuracy in the detection of haemodynamically significant CAD in symptomatic patients with intermediate likelihood of disease and no previous myocardial infarction. Importantly, absolute MBF during stress was more accurate than MFR in the detection of haemodynamically significant coronary artery stenosis. These results indicate that a single measurement of MBF during the vasodilator stress is sufficient to detect significant coronary stenosis allowing shorter imaging protocols with lower radiation dose to the patient.

This study is the first prospective study to show in a relatively large number of patients that absolute stress MBF alone is sufficient to detect CAD and confirms the results of a previous retrospective analysis of Hajjiri *et al.*,[12] using different flow tracer (^{13}N-ammonia) in a small number of patients ($n = 27$). Furthermore, our study provides the first data indicating the stress MBF actually performs better than MFR in detection of CAD.

The finding that stress MBF alone may perform better than MFR in the detection may be explained by several factors. First, the quantification of MBF involves dynamic data acquisition and complex data processing and therefore, a single measurement is likely to be less affected by statistical noise compared with repeated measurements. Second, reduced MFR does not necessarily reflect a change of maximum flow, but may as well be caused by changes in resting flow. This could happen in several conditions associated with high cardiac workload at rest, such as hypertension, dilated cardiomyopathy, or hypertrophic cardiomyopathy.[23,24] Our findings and those of Hajjiri *et al.* indicate that sensitivity of stress MBF is better than that of MFR for detection of CAD and suggest that indeed this may have been the case in some patients.[13] However, it is important to recognize that both rest and stress flow are essential for interpretation of flow results in many patient groups, such as those with previous myocardial infarction in whom irreversible injury and reversible ischaemia can be distinguished.[25] Neither stress MBF nor MFR likely can differentiate, whether reduced maximal flow is caused by microvascular dysfunction or a coronary stenosis. This may explain the somewhat lower PPVs of all quantitative parameters applied in the present study as compared with earlier PET studies without quantification. In a standard relative image analysis, these patients are not classified as abnormal since the reduction of flow is global in microvascular disease. However, this is not a problem when hybrid or combined imaging with coronary anatomy by CT angiography is used as reported earlier.[26]

According to the study of Hajjiri *et al.* the best threshold value of stress MBF for the detection of >70% flow-limiting coronary stenosis with ^{13}N-ammonia PET was 1.85 mL/g/min.[13] In our study, the optimal threshold value with ^{15}O-water PET was 2.4 mL/g/min. This is in line with our previous observation (2.5 mL/g/min) in a pilot study in a smaller patient population.[22] Potential explanations for different optimal cut-off values could be related to differences in the gold standard that was >70% stenosis in the study of Hajiri and >50% together with FFR confirmation in our study. There could also be due to differences in characteristics of the tracers used. ^{15}O-water is a freely diffusible tracer that has a linear relationship with perfusion even at high flow rates. In contrast, the fraction of ^{13}N-ammonia retained in the myocardium during its first pass is linear for values of blood flow up to 2.5 mL/g/min, but shows decrease at higher flow rates.[27] However, this phenomenon is accounted for in the model and is not likely the explanation. It is also likely that the characteristics of patient populations have impact on the absolute flow and thereby the cut-off values. In the present study, the patients were those with intermediate pre-test likelihood of CAD and did not have previous myocardial infarctions, heart failure and most did not have advanced CAD. These conditions are known to have reduced global stress MBF.

Values of MFR <2.0 are usually considered abnormal, but we found that optimal threshold for detection of haemodynamically significant coronary stenosis was 2.5 instead of 2.0 leading to a better

specificity, but sensitivity was not significantly affected. It remains to be studied how use of ^{15}O-water PET with the MFR threshold of 2.5 performs in comparison with the standard evaluation of myocardial perfusion imaging.

Our study protocol included coronary CT angiography in the same imaging session as PET and the comparison of these two methods has been reported earlier.[26] Therefore, most of our patients received i.v. beta-blocking therapy to reduce heart rate <60 bpm before imaging. Although patients receiving beta-blockers had modestly higher stress flow, rest flow, and MFR were comparable with patients who did not receive beta-blockers in the regions that were not subtended by significantly stenosed coronary artery. Consistently, we found no difference in diagnostic accuracy between patients receiving or not receiving beta-blockers. Haijiri *et al.* [12] observed no effect on stress MBF in patients receiving long-term beta-blocker therapy, while a modest increase in stress flow was detected in healthy subjects in another study.[28] It has been demonstrated that beta-blocker therapy does not affect invasive measurements of FFR.[29] A limitation of our study is that we did not measure FFR for all of the stenoses. This is due to the anatomy of some vessels and lesions, but also to logistics of the busy invasive laboratory. Because it is unrealistic to obtain FFR from 100% of lesions our goal was to evaluate stenoses with borderline significance with FFR that was possible in most of such patients.

The simplified perfusion imaging protocol using only stress imaging may become especially valuable in the future when novel ^{18}F-fluorine labelled flow tracers become available for the evaluation of CAD, because these tracers cause higher radiation exposure to the patient than ^{15}O-water and since the longer half-life of ^{18}F[30] requires longer interval between the repeated scans.

Conclusions

Absolute quantification of MBF is an excellent diagnostic tool for evaluation symptomatic patients with intermediate likelihood of CAD. Single measurement of absolute MBF during the vasodilator stress is sufficient to identify non-infarcted myocardium that is subtended by haemodynamically significant coronary stenosis allowing shorter imaging protocols with lower radiation dose to the patient than the measurement of perfusion reserve.

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Conflict of interest: none declared.

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IMAGE FOCUS

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Cor triatriatum sinister

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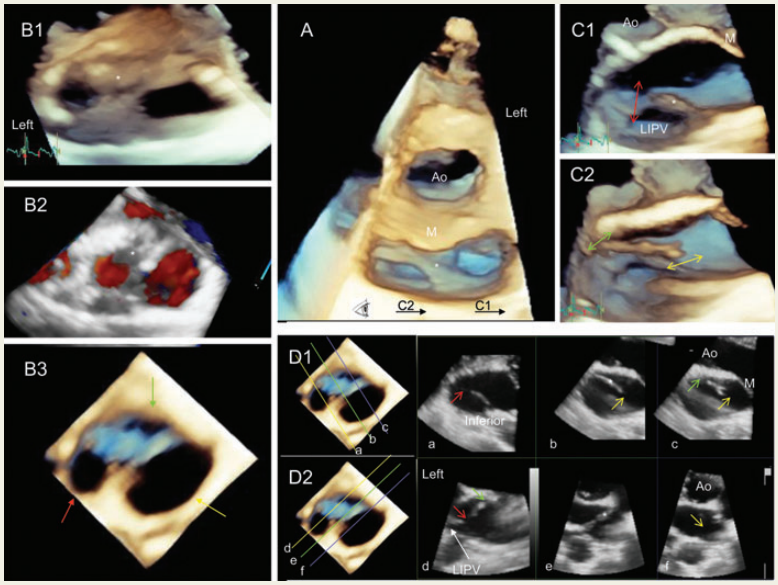

A 25-year-old asymptomatic woman showed, in two-dimensional (2D) transthoracic echocardiogram (TTE), a membrane in the left atrium (LA) diagnostic of cor triatriatum sinister. A three-dimensional (3D) TTE (view from the left ventricle; *Panel A* and Supplementary data online, *Video S1*) and from LA's posterior wall (*Panels B1–B3*) showed the membrane (asterisk) with three orifices [superior-left: red arrow (1.2 cm^2); inferior-right: yellow arrow (3.9 cm^2), and superior-medial: green arrow (0.4 cm^2)] with non-restrictive flow (*Panel B2*). The membrane originated from the left inferior pulmonary vein [LIPV; lateral view from the interatrial septum (*Panels C1* and *C2*)] rising from the antero-inferior part of the LA to the postero-superior region. A lateral and axial multislice study (*Panels D1–D2*) confirmed these findings. Surgery was not considered. The 3D TTE defines the anatomy and functionality of the membrane (location, number, and size of the orifices) and has the advantage, over transoesophageal echocardiography, of being able to analyse all the LA in a single volume.

M, mitral; Ao, aorta.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.