European Heart Journal – Cardiovascular Imaging (2013) **14**, 1203–1210
doi:10.1093/ehjci/jet068

Added prognostic value of myocardial blood flow quantitation in rubidium-82 positron emission tomography imaging

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Received 24 February 2013; accepted after revision 1 April 2013; online publish-ahead-of-print 9 May 2013

Aims We studied the respective added value of the quantitative myocardial blood flow (MBF) and the myocardial flow reserve (MFR) as assessed with ^{82}Rb positron emission tomography (PET)/CT in predicting major adverse cardiovascular events (MACEs) in patients with suspected myocardial ischaemia.

Methods and results Myocardial perfusion images were analysed semi-quantitatively (SDS, summed difference score) and quantitatively (MBF, MFR) in 351 patients. Follow-up was completed in 335 patients and annualized MACE (cardiac death, myocardial infarction, revascularization, or hospitalization for congestive heart failure or de novo stable angor) rates were analysed with the Kaplan–Meier method in 318 patients after excluding 17 patients with early revascularizations (<60 days). Independent predictors of MACEs were identified by multivariate analysis. During a median follow-up of 624 days (inter-quartile range 540–697), 35 MACEs occurred. An annualized MACE rate was higher in patients with ischaemia (SDS >2) ($n = 105$) than those without [14% (95% CI = 9.1–22%) vs. 4.5% (2.7–7.4%), $P < 0.0001$]. The lowest MFR tertile group (MFR <1.8) had the highest MACE rate [16% (11–25%) vs. 2.9% (1.2–7.0%) and 4.3% (2.1–9.0%), $P < 0.0001$]. Similarly, the lowest stress MBF tertile group (MBF <1.8 mL/min/g) had the highest MACE rate [14% (9.2–22%) vs. 7.3% (4.2–13%) and 1.8% (0.6–5.5%), $P = 0.0005$]. Quantitation with stress MBF or MFR had a significant independent prognostic power in addition to semi-quantitative findings. The largest added value was conferred by combining stress MBF to SDS. This holds true even for patients without ischaemia.

Conclusion Perfusion findings in ^{82}Rb PET/CT are strong MACE outcome predictors. MBF quantification has an added value allowing further risk stratification in patients with normal and abnormal perfusion images.

Keywords Myocardial perfusion imaging • Positron emission tomography • Rubidium-82 • Coronary artery disease • Major adverse cardiovascular events • Outcome

Introduction

Myocardial perfusion imaging (MPI) is of prognostic value for predicting major adverse cardiac events (MACEs), and allows monitoring of the effectiveness of risk reduction strategies.[1,2] Positron emission tomography (PET) has been widely used for coronary artery disease (CAD) assessment and can provide quantitative myocardial perfusion measurement in absolute units, hence offering information on both macro- and microcirculation, leading to more accurate detection of early and advanced CAD.[3,4] Recent data have documented the added value of quantitative myocardial perfusion for the evaluation of CAD severity.[5]

While the prognostic value of quantitative MPI with ^{13}N-ammonia and PET has been documented,[6] few retrospective data exist regarding the long-term prognostic value of PET/CT with ^{82}Rb,[7,8] a generator-produced MPI agent with the highest potential for a wide clinical use. Recently, one prospective study by Ziadi *et al.*[9] showed a predictive value of the ^{82}Rb-measured decreased

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myocardial flow reserve (MFR) for an adverse outcome. However, no prospective study with ^{82}Rb PET/CT has compared so far the respective additive prognostic value of the quantitation of the hyperaemic myocardial blood flow (MBF) and MFR over semi-quantitative perfusion in the prediction of MACEs, which was our aim.

Methods

Study population

We prospectively enrolled 351 subsequent patients (36% women) with known or suspected CAD to undergo ^{82}Rb cardiac PET/CT between December 2008 and September 2009 at the Lausanne University Hospital. Cardiovascular risk factors (hypertension, smoking, hypercholesterolaemia, and diabetes) were assessed at the time of the PET/CT scanning, as well as patient's medications and the Framingham 10-year coronary heart disease (CHD) risk in patients without known CAD.[10] The Local Ethics Committee approved this study protocol and all patients gave written informed consent prior to inclusion.

Imaging protocol with ^{82}Rb PET/CT

Patients were instructed to fast for 6 h and avoid caffeine-containing food or beverages 24 h prior to the test. Furthermore, they were advised not to take their usual anti-ischaemic medication on the day of the test. For each patient, a rest and adenosine stress PET/CT scan (Discovery LS, GE Healthcare, Milwaukee, WI, USA) was performed. At rest, a 10–20 s i.v. infusion of 1480–2200 MBq of ^{82}Rb (CardioGen-82, Bracco Diagnostics, Inc., Princeton, NJ, USA) was administered with an automatic infusion system and 2D dynamic PET images were acquired starting at the beginning of the infusion over 6.1 min (12 × 8, 5 × 12, 1 × 30, 1 × 60, and 1 × 120 s).

Ten minutes later, a second acquisition was started following the same protocol with similar activity 2 min into an adenosine infusion (140 μg/kg/min over 6 min). A low-dose CT (140 keV, 10 mA) transmission scan was used for attenuation correction. Images were reconstructed by ordered subsets expectation maximization algorithms (2 iterations, 28 subsets, 3.27 mm FWHM post-filter, 2.34 mm loop-filter 128 × 128-pixel matrix size). Blood pressure, heart rate, and a 12-lead ECG were recorded throughout the procedure. The radiation dose for each patient was estimated to be 2 × 1.85 mSv for rest and stress ^{82}Rb,[11] and 2 × 0.2 mSv for the low-dose attenuation correction CT, resulting in a total dose of 4.1 mSv.

Myocardial perfusion analysis

Before any analysis, the alignment between PET and low-dose CT was checked for possible misalignment to avoid artefacts induced by attenuation correction. Cardiac perfusion was assessed and analysed in a semi-quantitative manner using summed rest (SRS) as well as summed stress (SSS), and summed difference scores (SDS)[7] applying the 17-segment model of the American Heart Association.[12] Two experienced nuclear medicine physicians interpreted the semi-quantitative images in consensus. Patients were subdivided in those with ischaemia (SDS >2) and those without ischaemia (SDS ≤ 2). Patients were also stratified according to tertiles of SSS, SRS, and SDS.

Perfusion was also assessed quantitatively measuring the MBF in millilitre per gram per minute at rest and stress, the MFR was calculated (MFR = stress MBF/rest MBF). The dynamic acquisitions were processed with the fully automated FlowQuant 2.1.3 software (Ottawa Heart Institute, Ottawa, Canada) using 1-tissue compartment model with correction for ^{82}Rb flow-dependant extraction and constant ^{82}Rb distribution volume.[4,13,14] Quantitative (MBF, MFR) values were also reported using the 17-segment AHA model. Patients were assigned into tertiles according to MBF at stress and MFR.

Both semi-quantitative and quantitative perfusion criteria were analysed and compared with the follow-up outcome for each patient in order to assess their prediction potential.

Follow-up

By consenting to participate in this study, patients accepted to be contacted for follow-up. Questionnaires inquiring about cardiac events, cardiac symptoms, or any medical procedure occurring after the ^{82}Rb cardiac PET/CT were sent after a minimum of 6-month after enrolment. For patients whose answers were not obtained by mail return of the questionnaire, information was sought using a pre-scripted telephone interview with the patients, and in case of failure, with their general practitioner or from their medical history available in the hospital information system.

Outcome

Events were classified into MACEs, which included cardiac death, myocardial infarction, revascularization (stent, angioplasty, and CABG), and hospitalization for congestive heart failure or de novo stable angina (defined as angor or chest pain consistent with cardiac origin and requiring further investigations and hospitalization). In patients with multiple events, only the first one was considered for survival analysis. Early revascularizations observed within the first 60 days of post-PET/CT were considered to have been triggered by the myocardial perfusion study and were excluded.[6,15]

Analysis and statistics

Continuous variables are presented as mean ± standard deviation unless noted otherwise and compared using the non-parametrical Wilcoxon rank-sum test and categorical variables using the Fischer test. According to the ^{82}Rb PET/CT results, patients were classified into tertiles based on SSS, SDS, SRS, stress MBF, and MFR. For each tertile, annualized event rates were computed by dividing the number of MACEs by the sum of individual follow-up periods in years. Outcome was analysed for each tertile using Kaplan–Meier event-free survival curves and compared using the log-rank test. Multivariate analysis was performed to identify independent predictors of future cardiac events with a stepwise forward selection of variables among myocardial perfusion, age, gender, and cardiovascular risk factors identified as significant on univariate analyses ($P < 0.05$) using Cox proportional-hazards regression models. In all Cox regressions, the proportional-hazards assumption was tested using Schoenfeld residuals.[16] To determine the additive value of quantitative perfusion variables over semi-quantitative assessment, nested model statistics of Cox proportional hazard regression with Wald testing of the added variable were used. Statistical significance was considered for two-sided P-values <0.05. Analyses were performed using the Stata 11.1 software (Stata Corporation, College Station, TX, USA).

Results

Follow-up and cardiovascular events

Cardiac PET/CT was successfully performed in all 351 enrolled patients. Follow-up was obtained in 335 patients (95%) and 52 MACEs were recorded, out of whom 17 were excluded due to early revascularization (2 CABG and 15 stents/angioplasties <60 days after PET/CT). In the remaining 318 patients, 35 MACEs (11%) were reported during a median event-free follow-up of 624 days (range 210–990, inter-quartile range 540–697). MACEs included 9

myocardial infarction (1 with subsequent cardiac death), 5 cardiac deaths, 15 late ≥60-day revascularization (9 stents/angioplasty, 6 CABG), and hospitalization for 4 congestive heart failures and 2 de novo stable angors. Patient characteristics and medication use at the time of PET/CT are listed in *Table 1*. Patients with MACEs were slightly older ($P = 0.030$) and more often treated with aspirin, beta-blockers, nitroglycerine, or lipid-lowering agents than those without MACEs (all $P < 0.008$).

Cardiac PET/CT MPI

Myocardial ^{82}Rb uptake was normal in 213 and abnormal in 105 patients. All semi-quantitative and quantitative ^{82}Rb PET/CT measurements were significantly worse in patients presenting with MACEs when compared with patients without, except for rest MBF that were similar (*Table 1*). The annualized MACE rate was found to be higher in the ischaemic vs. non-ischaemic group [14% (95% CI: 9.1–22%) vs. 4.5% (2.7–7.4%), $P < 0.0001$] (*Figure 1*).

Predictive value of semi-quantitative analysis

Patients were grouped according to tertiles of an abnormal myocardium (corresponding to the following SSS thresholds: <3, 3–8, and ≥9), tertiles of ischaemic burden (SDS thresholds: 0, 1, and ≥2), and tertiles of scarred myocardium (SRS thresholds: <3, 3–7, and ≥8). An increase in an ischaemic burden was accompanied by an increase in the MACE rate as presented in *Table 2*. MACE incidence was found to be increasing with higher hyperaemic perfusion defect (SSS). This difference among tertiles was significant ($P < 0.0001$) for patients with the highest SSS (Tertile 3) having the lowest survival rates. Patients' allocation into tertiles according to SDS also provides information on MACE occurrence (*Table 2*). These observations were statistically significant ($P = 0.0001$), with patients with the highest SDS having the lowest survival rate. Finally, as regard to SRS, an association existed between increasing rest score defect and MACE incidence ($P = 0.002$; *Table 2*).

Predictive value of quantitative analysis

Patients were allocated into tertiles using lower and upper end values at 1.8 and 2.6 for stress MBF and 1.8 and 2.4 mL/g/min for the MFR. Tertiles of the MFR provides incremental information regarding MACE occurrence (*Table 2*). The difference among tertiles was significant ($P < 0.0001$) for patients with the lowest MFR (Tertile 1) having the lowest survival rate compared with Tertiles 2 and 3 (*Figure 2A*).

Table 1 Population characteristics and MPI results ($n = 318$)

Characteristics	No MACE ($n = 283$)	MACE ($n = 35$)	*P*-value
Age (years)	64 ± 11	69 ± 10	0.030
Male (%)	62	77	0.10
Body mass index (kg/m^2)	29 ± 5	28 ± 5	0.25
Hypertension (%)	64	74	0.26
Diabetes (%)	33	46	0.14
Dyslipidaemia (%)	55	60	0.59
Current smoking (%)	35	34	0.90
Family history of early CAD (%)	13	17	0.43
Known CAD (%)	31	63	<0.001
History of myocardial infarction (%)	18	40	0.006
Framingham 10-year CHD risk (%)	17	26	0.03
Medication use at time of PET (%)			
Aspirin	58	82	0.008
Beta-blockers	42	73	0.005
Angiotensin-converting enzyme inhibitors	52	58	0.58
Diuretic	25	39	0.10
Nitroglycerine therapy	11	36	<0.001
Lipid-lowering agent	57	82	0.005
^{82}Rb semi-quantitative imaging			
Summed stress score	6.3 ± 6.9	13.3 ± 9.0	<0.001
Summed difference score	0.24 ± 4.0	3.5 ± 4.9	<0.001
Abnormal perfusion (SSS ≥4; %)	55	89	<0.001
Presence of ischaemia (SDS >2; %)	21	51	<0.001
^{82}Rb quantitative imaging			
Rest MBF (mL/min/g)	1.13 ± 0.47	1.02 ± 0.26	0.17
Stress MBF (mL/min/g)	2.35 ± 0.88	1.67 ± 0.63	<0.0001
Myocardial flow reserve	2.16 ± 0.67	1.66 ± 0.65	<0.0001

MACE, major acute coronary events; MBF, myocardial blood flow.

For each tertile of stress MBF, the MACE incidence rate was found to be decreasing for higher perfusion values, as shown in *Table 2* and *Figure 2B* ($P = 0.0005$).

Univariate analysis

Among baseline demographics and MBF parameters, we found a significant association of MACE with SDS, SSS, and SRS as well as with MFR and stress MBF (*Table 3*). However, there was a MACE dependency regarding age ($P = 0.016$) without the significant predictive value for gender ($P = 0.081$), hypertension ($P = 0.24$), dyslipidaemia ($P = 0.59$), diabetes ($P = 0.15$), smoking ($P = 0.98$), family history of early CAD ($P = 0.53$), and Framingham 10-year CHD risk ($P = 0.62$).

Concerning medication, the use of aspirin [hazard ratio HR = 3.1 (1.3–7.4), $P = 0.013$], beta-blockers [HR = 2.9 (1.4–5.9), $P = 0.003$], nitroglycerine [HR = 4.0 (2.0–8.2), $P < 0.001$], and lipid-lowering agent [HR = 3.2 (1.3–7.8), $P = 0.010$] were associated with an increased MACE incidence, but not angiotensin-converting enzyme inhibitors ($P = 0.57$) or diuretics ($P = 0.060$).

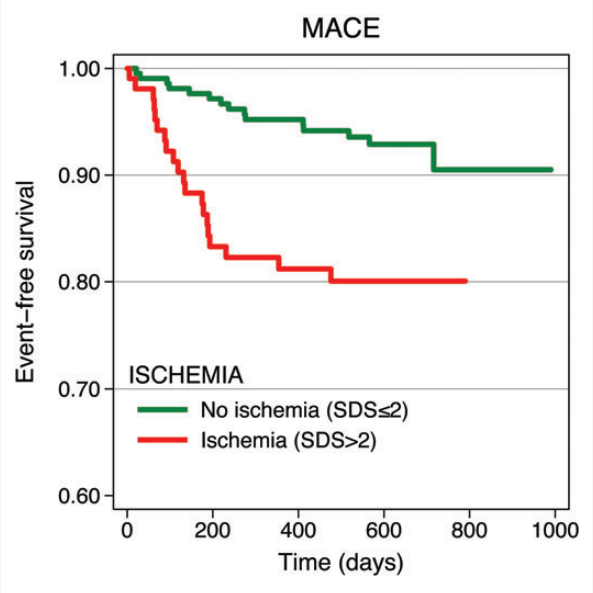

Figure 1 MACE-free survival curves according to the presence or absence of ischaemia ($n = 318$).

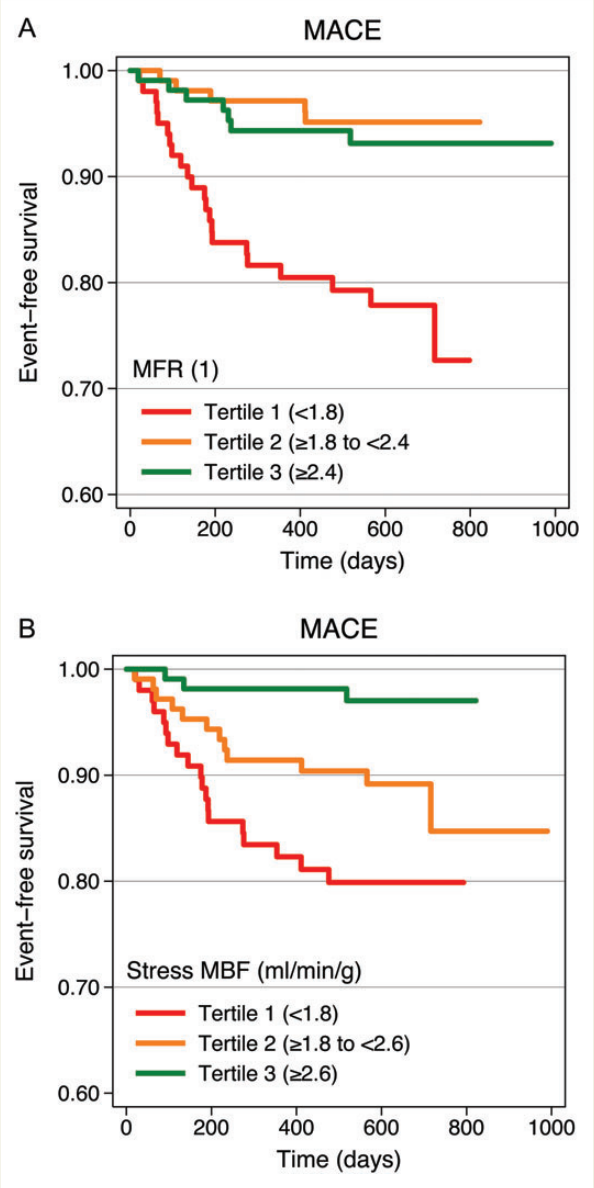

Figure 2 MACE-free survival curves ($n = 318$) according to tertiles of (*A*) MFR and (*B*) hyperaemic MBF (stress MBF).

Table 2 MACE annualized rates according to tertiles of semi-quantitative and quantitative variables

Variable	Tertile 1	Tertile 2	Tertile 3	*P*-value
^{82}Rb semi-quantitative imaging				
Summed stress score	2.3 (0.9–6.2)	4.8 (2.5–9.3)	18 (12–28)	<0.0001
Summed difference score	3.5 (1.9–6.5)	7.8 (3.7–16)	17 (10–27)	0.0001
Summed rest score	5.4 (2.8–10)	3.1 (1.3–7.4)	14 (8.8–21)	0.002
^{82}Rb quantitative imaging				
Myocardial flow reserve	16 (11–25)	2.9 (1.2–7.0)	4.3 (2.1–9.0)	<0.0001
Stress myocardial blood flow	14 (9.2–22)	7.3 (4.2–13)	1.8 (0.6–5.5)	0.0005

Table 3 Significant variables for MACE prediction on univariate and multivariate analyses.

Variable[a]	Univariate hazard ratio	*P*-value	Multivariate hazard ratio	*P*-value
Known CAD (%)	3.50 (1.76–6.95)	<0.001	—	0.55
History of myocardial infarction (%)	2.89 (1.46–5.68)	0.002	—	0.15
Summed difference score	1.17 (1.10–1.26)	<0.001	1.12 (1.05–1.21)	0.001
Summed stress score	1.09 (1.05–1.12)	<0.001	—	0.83
Summed rest score	1.06 (1.03–1.10)	0.001	—	0.20
Age	1.04 (1.01–1.07)	0.016	—	0.37
Stress myocardial blood flow	0.35 (0.22–0.56)	<0.001	0.41 (0.25–0.67)	0.007
Myocardial flow reserve	0.27 (0.15–0.50)	<0.001	—	0.064

[a]Gender, hypertension, dyslipidaemia, diabetes, smoking, family history of early CAD, and Framingham 10-year CHD risk were not significant on univariate analysis. Values are given as mean (95% confidence interval).

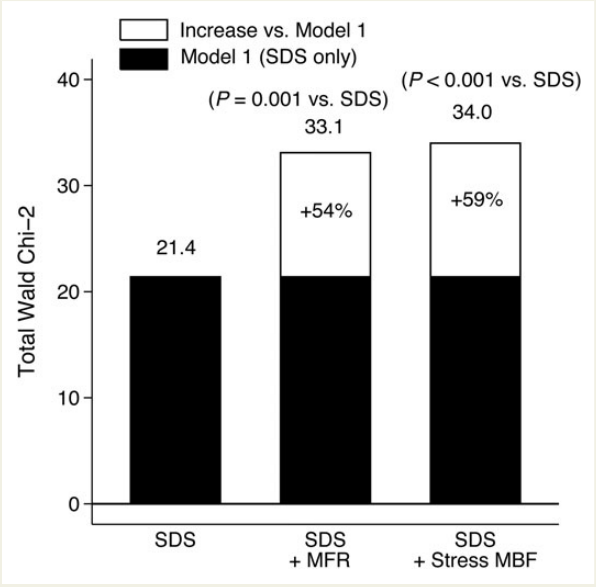

Figure 3 Added value for MACE prediction of quantitative imaging of MFR and hyperaemic MBF (stress MBF) over semi-quantitative perfusion imaging (Model 1: SDS only).

Multivariate analysis

MACEs were only independently predicted by stress MBF and SDS (*Table 3*). The addition of quantitative perfusion results to the semi-quantitative results significantly increased the prediction on nested Cox regressions. Indeed, adding MFR and stress MBF to SDS, χ^2 increased from 21.4 to 34.0 and 33.1, respectively (*Figure 3*). Interestingly, when adding both quantitative variables MFR and stress MBF to semi-quantitative SDS, stress MBF was statistically significant ($P = 0.045$) but not MFR ($P = 0.064$). Thus, risk stratification was most enhanced by the use of SDS combined with stress MBF allowing significant MACE prediction improvement.

Predictive value of quantitative analysis in patients without ischaemia (SDS ≤2)

Importantly, we tested whether the added value of quantitative analysis was retained in patients without ischaemia (SDS ≤2, $n = 241$). This held true, as MFR allowed stratifying for MACE in patients without ischaemia (*Figure 4A*), with annualized MACE rates of 10 (5.7–18%), 1.6 (0.4–6.3%), and 2.4% (0.8–7.3%) in the first, second, and third tertiles, respectively, which were significantly different ($P = 0.003$). Similarly, stress MBF allowed stratifying for MACE in patients without ischaemia (*Figure 4B*), with annualized MACE incidence rates of 8.8 (4.8–16%), 4.6 (2.1–10%), and 0.77% (0.1–5.4%) in the first, second, and third tertiles, respectively, which were significantly different ($P = 0.013$).

Discussion

Our results support that quantitative stress MBF and MFR as assessed by PET/CT with ^{82}Rb are independent predictors of MACE and confer an added value over semi-quantitative evaluation, with a preference for the hyperaemic flow being slightly superior to MFR as a prognostic predictor. Furthermore, the present study is the first to demonstrate that impaired MFR or stress MBF are also independent predictors of MACE in patients with presumably normal semi-quantitative MPI (SDS ≤2).

Recently, Herzog *et al.*[6] demonstrated the predictive value of MFR as assessed with ^{13}N-ammonia PET/CT for cardiac events. However, wider clinical application of MFR would require the use of different tracers, since ^{13}N-ammonia relies on cyclotron production and, hence, is of limited availability. In this regards, generator-produced ^{82}Rb is an interesting alternative, particularly, as recent studies indicated that it could be used for accurate MBF quantification.[13,14]

Overall the MACE annualized rate in the present study was 11%, which ranges well within the values reported in prognostic studies using ^{82}Rb by Dorbala *et al.*[17] (5.8%), Fukushima *et al.*[8] (15%), or Ziadi *et al.*[9] (10.4%). Our study population consisted of intermediate-likelihood patients referred to MPI in accordance with the guidelines for best clinical practice of non-invasive imaging. Similar to Herzog *et al.*,[6] we included an unselected study population, which allows extrapolation of the results, whereas most initial quantitative PET studies have been confined to highly selected patients with specific cardiac disease such as dilated[18] and hypertrophic cardiomyopathy.[19] Of note, our study is one of the few prognostic study of MPI published in a European population[6,20] and the first to be performed using ^{82}Rb.

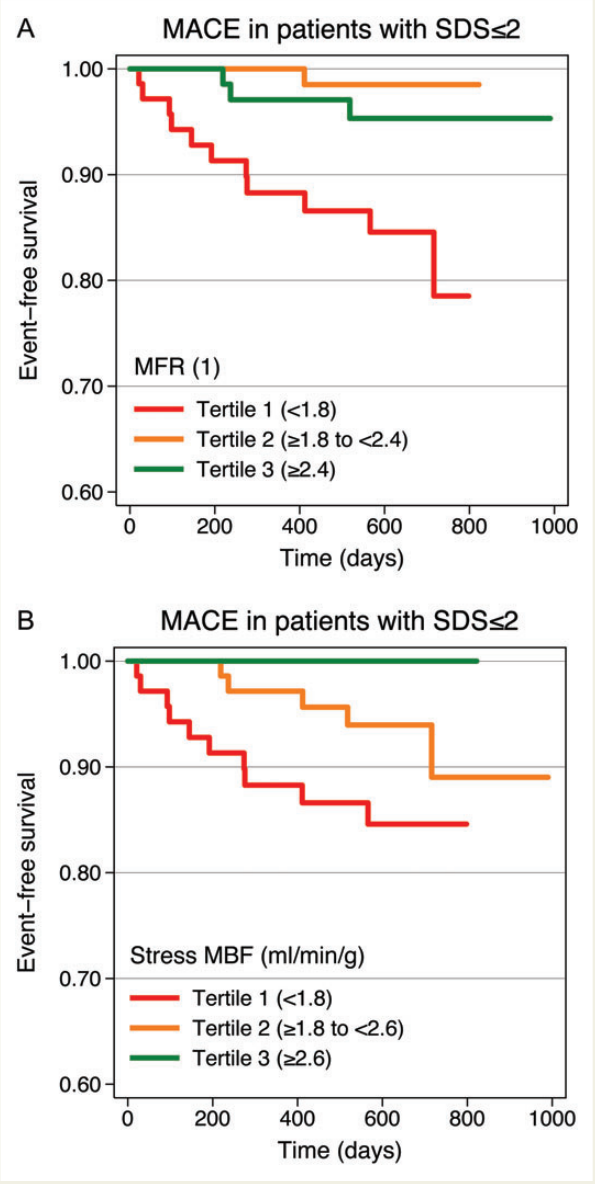

Figure 4 MACE-free survival in patients without ischaemia (SDS ≤2, $n = 241$) according to tertiles of (*A*) MFR and (*B*) stress MBF.

Prognostic value of quantitative perfusion

Univariate analysis highlighted statistical significance in MACE prediction for semi-quantitative and quantitative cardiac PET. It is known that semi-quantitative perfusion data using ^{82}Rb can identify patients at risk for future cardiac events.[7,21] Our study is in agreement, as semi-quantitative perfusion results proved to be useful predictors, and an increase in MACE rate linked to larger perfusion abnormality (SSS), increasing ischaemia (SDS), or scar burden (SRS) was noted, emphasizing the prediction power of semi-quantitative perfusion.

However, this semi-quantitative assessment has limitations and quantitative global MFR has much greater prognostic impact due to the fact that vascular dysfunction extends beyond epicardial coronary lesion into the microcirculation, where 75% of the resistance of the coronary vascular bed lies. As a consequence, quantitative perfusion assessment allows the identification of subtle functional defect that would remain unnoticed otherwise.[22] In our study, patients with the lowest MFR or stress MBF had the highest MACE rate. Our findings document that using stress MBF as an adjunct to semi-quantitative perfusion assessment with SDS provides the most significant added value in MACE prediction. Interestingly, the addition of MFR to stress MBF and SDS only presented a trend for MACE prediction ($P = 0.064$); this could indicate that decreased MFR due to the increase in rest MBF (for instance, due to hypertension or tachycardia) might not have the same predictive value as diminished hyperaemic stress MBF. Conversely, an apparently normal MFR may be the result from contemporary depression of rest MBF and stress MBF, as in cardiomyopathy.[23] Furthermore, forcing stress MBF out of the multivariate analysis also showed an association of MACE with MFR (HR = 0.42, $P = 0.006$) in addition to semi-quantitative SDS.

Prognostic value in patients without ischaemia

Importantly, in patients with normal semi-quantitative perfusion results, impaired stress MBF, and MFR allowed further discrimination into high- vs. low-risk groups for future cardiac events. In patients with normal SDS and stress MBF above the upper tertile limit of 2.6 mL/min/g, outcome was excellent. This is in agreement with a recent study by Sdringola *et al.*[24] defining the value of hyperaemic MBF for ^{82}Rb cardiac PET in a normal population of healthy volunteers (2.7 mL/min/g, $n = 125$) or their subpopulation of true normal individuals (2.9 mL/min/g). The WISE study had already shown that women symptomatic for ischaemia but without obstructive CAD experience more adverse effects than non-symptomatic controls, most likely due to a microvascular dysfunction.[25] This is of potential clinical relevance, as balanced ischaemia due to microvascular disease or three-vessel disease may remain undetected by semi-quantitative assessment, as this relies on heterogeneous myocardial perfusion response to hyperaemic stress.

Comparison with previous quantitative studies

MACE prediction and risk stratification were improved by adding quantitative over semi-quantitative perfusion in cardiac events prediction, as suggested in previous studies.[5,6] Nonetheless, the respective value of hyperaemic MBF vs. MFR was not investigated specifically so far. Indeed, Herzog *et al.*[6] did not include stress MBF in their analysis, which might have been also an independent predictor of MACEs. In the retrospective study by Fukushima *et al.*,[8] the authors showed that impaired MFR or regional perfusion defect predicted short-term (mean follow-up 362 ± 277 days) cardiovascular events, without comparing the respective value of quantitative vs. semi-quantitative MPI assessment, however.

In the study by Murthy *et al.*,[26] the authors showed that decreased flow reserve was a powerful, independent predictor of cardiac mortality, which was 8% over a 3-year period. In contrary to our results, they found that stress MBF was associated with a lesser increase in χ^2 than MFR. This might be due to the chosen fit model properties (rest LVEF and stress-induced LVEF were measured in their study) and

potentially to population differences (48% of men vs. 64% in our study, 11% of smokers vs. 35% in our study, and 27% of family history of CAD vs. 13% in our study, respectively).

In the only prospective study using ^{82}Rb, Ziadi *et al.*[9] have shown an added prognostic value of MFR quantitation over semi-quantitative MPI in a large cohort of patients. However, they did not find that hyperaemic MBF was as valuable. Also here, differences exist when compared with our study. They had a shorter follow-up period [387 (375–416) days vs. 624 (540–697) days], included patients with higher pre-test CAD prevalence (positive family history 50 vs. 13%, smoking 63 vs. 35%) and higher known CAD (56 vs. 31%) or history of myocardial infarction (37 vs. 18%), as well as higher mean SDS in the non-MACE group (2.2 ± 4.0 vs. 0.2 ± 4.0). This may outline different prognostic value of PET-derived indices according to the likelihood and severity of CAD.

Our results extend previous ^{82}Rb studies showing the added value of quantitative over semi-quantitative MPI and show for the first time that stress MBF is slightly better than MFR for MACE prediction. This is in line with the superiority of absolute hyperaemic quantification over relative MFR demonstrated for the diagnosis of significant stenosis.[5]

Clinical implications

These findings are of great potential clinical relevance, as at present, ^{82}Rb is the only widely available myocardial perfusion PET tracer without the need for an onsite cyclotron, not only in the USA where clinical ^{82}Rb PET is already been broadly used, but also in Europe, where initial experience has been very encouraging.[27] Recently, radiation dose of ^{82}Rb has been estimated from human measurements and was shown to be significantly lower than previously thought[11] (3.7 mSv for rest + stress imaging with 1480 MBq each) provided that quality insurance, especially, ^{82}Sr/^{85}Sr maximal breakthrough levels are strictly respected. Our study has two potential clinical implications. First, the fact that hyperaemic MBF only may be of predictive value would important to consider when determining the value of the upcoming ^{18}F-based MPI radiotracers, which are ready to enter the clinical scene. Second, the risk prediction information gained by quantitation in patients with presumably normal, ischaemia-free MPI may be valuable to guide therapy and should be investigated further. Indeed, a proportion of these patients was at risk and finally presented a MACE.

Limitations

It may be perceived as a limitation that the use of cardiac medication was significantly different in patients with vs. without MACEs, as this could act as a confounder. Indeed, more extensive medication was an independent predictor of MACEs; this was unexpected, but most probably simply reflects the fact that patients at a higher risk of CAD were more likely to be pharmacologically treated. However, the fact that despite the higher use of medication these patients had higher MACEs strengthens the validity of our results.

Another limitation would be that our study emanates from a single centre; however, we used the same software as used by Ziadi *et al.*,[9] which can be seen as a way of standardizing ^{82}Rb MBF quantitation and helps comparing results. Even though there was a trend for a higher MACE rate in men when compared with women ($P = 0.081$), it was not significant in univariate or in multivariate analysis, which might be due to the low percentage of women in this study (36%). Also, left ventricular ejection fraction and regional wall motion were not assessed in this study. Finally, coffee abstinence was not verified pharmacologically, but all patients experienced haemodynamic response to adenosine infusion, as seen by an increase $\geq$10% of heart rate frequency or a decrease $\geq$10 mmHg in systolic blood pressure; moreover, a caffeine-induced effect leading to lower hyperaemic MBF would certainly affect MACE and MACE-free patients identically.

Conclusion

Quantification of stress MBF or MFR in ^{82}Rb cardiac PET/CT provides independent and incremental prognostic information over semi-quantitative assessment and is of significant value for risk stratification. Stress MBF associated with SDS provided most prognostic overall MACE information. Importantly, this was also true in patients without ischaemia. This novel prognostic information on MACE and risk stratification may prove useful for monitoring in future trials to guide therapy management, which needs to be confirmed in larger trials.

Acknowlegements

The authors would like to acknowledge the help of Ms Mélanie Recordon and Adriana Goyeneche Achigar, Mr Jérôme Malterre, Martin Pappon, Mikael Buchs for performing the PET/CT studies, as well as Ms Fatima El Hakmaoui and Nathalie Coendoz for data management and M. Fabrice Camus, PhD and M. Kosinski for ^{82}Rb quality control. We, furthermore, are indebted to referring physicians who participated in this study.

Funding

This work was supported by research grants from the Swiss National Science Foundation (grant numbers 320000–109986, 320030–127604); the Michel Tossizza Foundation (Lausanne, Switzerland); The Faculty of Biology and Medicine of the University of Lausanne (Lausanne, Switzerland); and the Société AcadémiqueVaudoise (Lausanne, Switzerland). J.O.P. was recipient of an Academic Research Award from the Leenaards Foundation (Lausanne, Switzerland).

Conflict of interest: H.F, V.D., K.B., G.A., and P.A.K. have none to declare. J.O.P. has received grant support for another study (doi10.1186/2191-219X-1-27 http://www.ejnmmires.com/content/1/1/27) from Bracco Diagnostics, Inc. (PO Box 5225, Princeton, NJ 08543-5225, USA), manufacturer of the ^{82}Rb generator used in this study.

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