Left ventricular ejection fraction, myocardial blood flow and hemodynamic variables in adenosine and regadenoson vasodilator 82-Rubidium PET

Simon M. Frey, MD,[a,b] Ursina Honegger, MSc,[b] Olivier F. Clerc, MD,[a,b] Federico Caobelli, MD,[c] Philip Haaf, MD,[a,b] and Michael J. Zellweger, MD[a,b]

[a] Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland
[b] Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland
[c] Department of Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland

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Aims. **In most Rubidium-(Rb)-positron emission tomography (PET) studies, dipyridamole was used as vasodilator. The aim was to evaluate vasodilator PET left ventricular ejection fraction (LVEF), myocardial blood flow (MBF), hemodynamics, and the influence of adenosine and regadenoson on these variables.**

Methods and results. **Consecutive patients (N = 2299) with prior coronary artery disease (CAD) or no prior CAD undergoing adenosine/regadenoson ^{82}Rb-PET were studied and compared according to CAD status and normal/abnormal PET (summed stress score 0-3 vs. ≥4). Rest and stress LVEF differed significantly depending on CAD status and scan results. In patients with no prior CAD, rest/stress LVEF were 68% and 72%, in patients with prior CAD 60% and 63%. LVEF during stress increased 5 ± 6% in normal compared to 1 ± 8% in abnormal PET (*P*<0.001). Global rest myocardial blood flow(rMBF), stress MBF(sMBF) and myocardial flow reserve (sMBF/rMBF) were significantly higher in no prior CAD patients compared to prior CAD patients(1.3 ± 0.5, 3.3 ± 0.9, 2.6 ± 0.8 and 1.2 ± 0.4, 2.6 ± 0.8, 2.4 ± 0.8 ml/g/min, respectively, *P*<0.001) and in normal versus abnormal scans, irrespective of CAD status(no prior CAD: 1.4 ± 0.5, 3.5 ± 0.8, 2.8 ± 0.8 and 1.2 ± 0.8, 2.5 ± 0.8, 2.2 ± 0.7; prior CAD: 1.3 ± 0.4, 3.1 ± 0.8, 2.7 ± 0.8 and 1.1 ± 0.4, 2.3 ± 0.7, 2.2 ± 0.7 ml/g/min, respectively, *P*<0.001). LVEF and hemodynamic values were similar for adenosine and regadenoson stress. Stress LVEF ≥70% excluded relevant ischemia (≥10%) with a negative predictive value (NPV) of 94% (CI 92-95%).**

Conclusions. **Rest/stress LVEF, LVEF reserve and MBF values are lower in abnormal compared to normal scans. Adenosine and regadenoson seem to have similar effect on stress LVEF, MBF and hemodynamics. A stress LVEF ≥70% has a high NPV to exclude relevant ischemia. (J Nucl Cardiol 2022;29:921–33.)**

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The authors have also provided an audio summary of the article, which is available to download as ESM, or to listen to via the JNC/ASNC Podcast.

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Reprint requests: Ursina Honegger, MSc, Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland; *honegger.ursina@bluewin.ch*

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Chinese Abstract

背景. 在大多数铷-正电子断层扫描 (Rb-PET)中,双嘧达莫是常见的血管扩张剂。本研究目的是评估血管扩张剂腺苷和瑞加德松PET扫描时对左心室射血分数 (LVEF)、心肌血流量(MBF)、血流动力学这些变量的影响。

方法与结果. 对接受腺苷/瑞加德松进行 ^{82}Rb-PET 的 2299 名连续就诊的疑似或已知冠状动脉疾病 (CAD)患者进行研究,并根据 CAD 状态和PET正常/异常(总负荷积分 0-3 与 ≥ 4)进行分组比较。 对CAD患者的状态和扫描结果分析可以发现静息和负荷状态下的LVEF显著不同。在疑似CAD患者中,静息/负荷状态下的LVEF分别为 68% 和73%,在既往CAD患者中静息/负荷状态下的LVEF分别为 60%和63%。PET正常组负荷LVEF增加5±6%,PET异常组LVEF增加 1±8% (p < 0.001)。疑似CAD组的整体静息心肌血流量(rest myocardial blood flow, rMBF)、负荷MBF(stress myocardial blood flow, sMBF)和心肌血流储备(sMBF/rMBF)显著高于既往CAD组(分别为 1.3±0.5、3.3±0.9、2.6±0.8和1.2±0.4、2.6±0.8、2.4±0.8 ml/g/min,p<0.001);与PET异常组比较,PET正常组的rMBF、sMBF和MFR明显增高,并且与CAD状态无关(无 CAD: 1.4±0.5、3.5±0.8、2.5±0.8和1.2±0.8, 2.5±0.8, 2.2±0.7 ml/g/min;确诊 CAD: 1.3±0.4,3.1±0.8,2.7±0.8和1.1±0.4,2.3±0.7,2.2 ±0.7ml/g/min, p<0.001)。腺苷和瑞加德松负荷的LVEF和血液动力学参数相似。负荷LVEF ≥70%排除相对缺血(面积≥10%)的阴性预测值(NPV)为94%(置信区间92-95%)。

结论. 与正常的PET扫描相比,LVEF、LVEF储备和MBF值在PET异常情况下降低。腺苷和瑞加德松对负荷 LVEF、MBF和血流动力学有相似的作用。负荷 LVEF ≥70% 对排除相对缺血具有高 NPV 。 **(J Nucl Cardiol 2022;29:921–33.)**

Key Words: Nuclear imaging · ^{82}Rubdium positron emission tomography · PET · Coronary artery disease · Left ventricular ejection fraction · Myocardial blood flow · Adenosine · Regadenoson

Abbreviations

MPI	Myocardial perfusion imaging
PET	Positron emission tomography
SPECT	Single photon emission computed tomography
CT	Computed tomography
Rb	Rubidium
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
CABG	Coronary artery bypass graft
PCI	Percutaneous coronary intervention
LVEF	Left ventricular ejection fraction
BP	Blood pressure
HR	Heart rate
ECG	Electrocardiogram
SRS	Summed rest score
SSS	Summed stress score
SDS	Summed difference score
BMI	Body mass index
LV	Left ventricle
ESV	End systolic volume
EDV	End diastolic volume
SD	Standard deviation
IQR	Interquartile range

See related editorial, pp. 934–937

INTRODUCTION

Myocardial perfusion imaging (MPI) is widely used and well-studied for the non-invasive diagnosis and management of patients with prior or suspected coronary artery disease (CAD).[1,2]

As the extent and severity of ischemia is inversely correlated with left ventricular ejection fraction (LVEF) and reserve (stress LVEF–rest LVEF),[3-6] LVEF is an important element of MPI interpretation. LVEF and LVEF reserve have independent and incremental prognostic value above clinical variables for cardiac events and all-cause death.[6,7]

Most studies focusing on LVEF in PET used dipyridamole as stressor. Adenosine and regadenoson were less frequently used and studied.

Adenosine, the non-selective A_{2A}, A_1, A_{2B}, and A_3 receptor agonist, is an established pharmacologic vasodilator stress agent.[8] The activation of A_{2A} receptors leads to coronary vasodilation and results in an increased myocardial blood flow (MBF).[8] Besides the vasodilation, an activation of A_1, A_{2B}, and A_3 receptors can cause short term undesirable side effects such as chest pain, flushing, and bronchospasm.[8,9] Adenosine needs to be administered as a continuous intravenous infusion because of the very short half-life. In contrast,

the new vasodilator regadenoson is a selective and more potent A_{2A} receptor agonist causing less side effects and can be used even in patients with asthma.[9-11] Regadenoson can be administered as a single fixed-dose bolus. In contrast, dipyridamole does not act directly but indirectly by inhibiting adenosine reuptake. Therefore, it has a relatively long half-life with the corresponding side effects.

The aims of this large single center ^{82}Rb-PET study were (1) to describe adenosine/regadenoson PET LVEF characteristics and hemodynamics for patients with or without prior CAD and normal or abnormal PET (2) to compare the influence of adenosine and regadenoson on these before mentioned variables (3) to evaluate stress LVEF and LVEF reserve as predictors of ischemia.

METHODS

Study Design and Patient Selection

All consecutive patients undergoing an ^{82}Rb-PET scan at the University Hospital Basel from 2016 until January 2020 were identified (N = 2496) and included for the analysis if the PET scan was complete, had adequate gating, and if LVEF values were available for rest and stress images (Figure S1). Patients were stratified into groups of suspected, but no history of prior CAD and history of prior CAD. Prior CAD means that patients either had suffered a myocardial infarction in the past or had undergone an intervention such as PTCA or CABG.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee (Req-2020-00283).

Imaging and Stress Protocol

Patients were instructed to withhold caffeine-containing beverages and foods for 24h before the test. Patients were scanned using a whole-body 3D-PET/CT scanner (Biograph mCT, Siemens Healthineers, Erlangen, Germany). A non-enhanced low-dose CT scan was obtained for attenuation correction (increment 0.6 mm, soft-tissue reconstruction kernel, 120 keV, CAREDOSE 4D). Thereafter ^{82}Rb-chloride was intravenously injected in a weight-adjusted manner for rest and stress images (<100kg: 30 mCI - 1110 MBq, ≥100kg 40mCI-1480). After resting imaging acquisition, patients were generally stressed with adenosine (140 µg/kg/min for 6 minutes). If contraindications or personal preferences were present (mostly allergic asthma, severe COPD), regadenoson was used (400 µg single-dose). ^{82}Rb infusion started 3 minutes after the start of the adenosine infusion or 10 seconds after application of regadenoson. Patients were monitored according to the guidelines.

ECG-gated PET images were recorded for rest and stress over 7 minutes in list mode starting with the tracer injection. Reconstruction details are described in the supplementary material document online. ECG-gated images were analyzed using QGS-QPS software included in the SyngoVia package, with 8 gated-frames for cardiac cycle. Left ventricular (LV) end-diastolic volume (EDV), LV end-systolic volume (ESV), and LVEF were calculated based on automated contour detection.

Images Interpretation

Images were analyzed and interpreted by an experienced board-certified nuclear medicine physician and cardiologist as a joint read reaching consensus. LVEF, volumes and MBF were automatically calculated with SyngoVia (Siemens Healthineers, Erlangen, Germany) and approved by the readers. A visual semi-quantitative 17-segment model with a 5-point scale (0: normal tracer uptake, 4: no tracer uptake) was used to calculate summed stress (SSS), rest (SRS) and difference score (SDS = SSS-SRS). Rest, stress MBF (rMBF, sMBF) and myocardial flow reserve (MFR) were calculated. The arterial input function was derived from the dynamic PET data. A single tissue compartment model was used to calculate myocardial perfusion in ml/g/min as described previously.[12]

The changes in hemodynamics were calculated subtracting the value during rest from the maximum value for heart rate (HR), systolic blood pressure (sBP), diastolic blood pressure (dBP) and LVEF. A SSS ≥4 was considered as abnormal. Derived from a theoretical "maximal ischemia" (17 segments x 4 points = 68), an SDS ≥7 was considered a relevant ischemia (≥10% ischemic myocardium = ≥ 6.8) as described in the current guidelines.[1] As described by other authors, an LVEF increase of +5% or decline of -5% could exclude/include severe ischemia, similar cut-offs were defined.[3,13,14]

Statistical Analysis

Normally distributed continuous variables are reported as mean ± standard deviation (SD), non-normally distributed continuous variables as median ± interquartile range. Unpaired T-test or Mann-Whitney-U test were used as appropriate. Categorical variables are displayed using frequencies and percentages and compared using the Chi-squared or ANOVA test. A *P*-value <0.05 was considered as statistically significant.

To estimate the value of LVEF increase by +5%, LVEF decline by -5% and LVEF peak stress as a

predictor for relevant ischemia (≥10%) we used a multivariable binary logistic regression model adjusted for age, sex and body mass index (BMI), symptoms as well as known clinical and biologically plausible factors (CAD risk factors, presence of non-reversible segments, HR at rest and stress, sBP and dBP at rest and stress). A stepwise selection process with a stay and entry criteria of P <0.2 was used.

Diagnostic accuracy of stress LVEF and LVEF reserve was assessed by the area under the receiver-operating characteristic curve. The optimal cut-off thresholds were calculated with the Youden Index. Statistical analyses were performed using SPSS™ (version 22) and R (version 3.6.3).

RESULTS

Patient Population

A total of 2299 patients were enrolled. The mean age was 65 ± 11 years and 36% were female, and 1424 (62%) patients had no prior CAD. In patients without prior CAD, PET was normal in 1087 (76%) patients. In patients with prior CAD PET was normal in 298 (34%) patients.

Baseline Characteristics

A baseline comparison between patients with and without prior CAD and between patients with normal and abnormal PET is summarized in Table 1. Men more often had prior CAD and an abnormal PET. Patients with prior CAD or abnormal PET were older and had more risk factors (diabetes, hypercholesteremia, hypertension and smoking).

LVEF and Myocardial Blood Flow

Patients were stratified by CAD status and PET result. PET variables differed across all compared groups (Figure 1; Figure S2). LVEF and MBF were higher during stress than at rest in all groups (no prior CAD + SSS ≥4: P <0.05, for all other groups: P <0.001). SSS values were significantly higher in patients with prior CAD (median (IQR) 6 (0-13) vs. 0 (0-2), P <0.001). Rest, stress LVEF and LVEF reserve differed between the no prior CAD and prior CAD groups (68 ± 12% vs. 60 ± 14%, 72 ± 12% vs. 63 ± 15%, 4 ± 7% vs. 3 ± 7%, respectively, for all P <0.001). Furthermore, different rest and stress LVEF and LVEF reserve values were observed when comparing normal and abnormal scans in both groups.

In addition, global rMBF, sMBF and MFR were higher in patients with normal scans compared to patients with abnormal scans, irrespective of CAD status. rMBF and sMBF were significantly higher in patients without prior CAD (Figure 1; Figure S2).

Rest and Stress Hemodynamics

Hemodynamics are summarized in Figure S3. Within all subgroups, HR and sBP increased, and dBP decreased significantly (P <0.001) from rest to stress, except for no decrease in dBP in patients with abnormal scans and no prior CAD.

Adenosine vs. Regadenoson

Regadenoson was used as stressor in 277 (12%) patients. Baseline characteristics of adenosine and regadenoson patients were similar and are summarized in Table S1. Dyspnea and female gender were more frequent in the regadenoson group. More normal PET scans were seen in the regadenoson group (14 vs. 10%, P = 0.003). PET and hemodynamic values were similar in patients undergoing adenosine or regadenoson stress across all patient groups, except for rest LVEF in one and sBP in two subgroups (Table 2). Patients without prior CAD and normal scans had a higher sBP and delta sBP using adenosine. Rest LVEF and delta sBP were higher in the group with no prior CAD and an SSS ≥4 using adenosine.

LVEF, LVEF Reserve and Ischemia

Overall, stress LVEF and LVEF reserve inversely correlated with the severity and extent of ischemia (measured by SDS), however the relationship was weak (Figure 2).

Regarding relevant ischemia, multivariable analysis (Table S2) showed an inverse correlation of stress LVEF and ischemia. Furthermore, an LVEF reserve of ≥+5% was associated with a lower odds ratio (OR 0.62, CI 0.46-0.84) of relevant ischemia. In contrast, male gender, age, prior CAD, diabetes, higher resting sBP and typical angina were associated with higher odds of relevant ischemia.

Diagnostic Accuracy and Performance of Stress LVEF and LVEF Reserve to Exclude/Diagnose Relevant Ischemia (≥10%)

The diagnostic accuracy of stress LVEF, rest LVEF, and LVEF reserve to exclude relevant ischemia was moderate in the overall cohort as well as in the gender subgroups (Figure 1, Panel D; Figure 3). Overall, stress LVEF ≥70% allowed to exclude relevant ischemia with a negative predictive value (NPV) of 94% (CI 92-95%).

Table 1. Baseline characteristics of patients studied with ^{82}Rb-PET in our cohort stratified by prior coronary artery disease and normal/abnormal scan (normal scan: SSS 0-3, abnormal scan: SSS ≥ 4)

	Overall N = 2299	No prior CAD N = 1424	Prior CAD N = 875	*P* value	SSS < 4 N = 1385	SSS ≥ 4 N = 914	*P* value
Male gender	1479 (64)	795 (56)	684 (78)	<0.001	741 (54)	738 (81)	<0.001
Age [years]	65 ± 11	64 ± 11	67 ± 11	<0.001	64 ± 11	67 ± 10	<0.001
BMI [kg/m^2]	28 ± 6	29 ± 6	28 ± 5	0.012	29 ± 6	28 ± 5	0.127
Prior myocardial infarction	458 (20)	0 (0)	458 (52)	<0.001	298 (22)	577 (63)	<0.001
Prior revascularization				<0.001			<0.001
PCI	579 (25)	0 (0)	579 (66)		223 (16)	356 (39)	
CABG	254 (11)	0 (0)	254 (29)		64 (5)	190 (21)	
Angina pectoris				0.042			<0.001
Atypical	655 (29)	430 (30)	225 (26)		456 (33)	199 (22)	
Typical	498 (22)	291 (20)	207 (24)		264 (19)	234 (26)	
Dyspnea*	942 (41)	572 (40)	370 (42)	0.278	579 (42)	363 (40)	0.45
Diabetes	617 (27)	353 (25)	264 (30)	0.005	310 (22)	307 (34)	<0.001
Hypercholesteremia	1436 (63)	746 (52)	690 (79)	<0.001	777 (56)	659 (72)	<0.001
Hypertension	1684 (73)	974 (68)	710 (81)	<0.001	947 (68)	737 (81)	<0.001
Family history for CAD	670 (29)	379 (27)	291 (33)	0.001	387 (28)	283 (31)	0.13
Smoker (current or former)	1255 (55)	707 (50)	548 (63)	<0.001	689 (50)	566 (62)	<0.001
Regadenoson used	277 (12)	177 (12)	100 (11)	0.516	190 (14)	87 (10)	0.003
Rest heart rate [bpm]	71 ± 12	72 ± 13	68 ± 11	<0.001	72 ± 12	69 ± 12	<0.001
sBP rest [mmHg]	126 ± 20	127 ± 20	124 ± 20	0.002	126 ± 20	126 ± 21	0.307
dBP rest [mmHg]	70 ± 12	72 ± 12	69 ± 11	<0.001	71 ± 12	69 ± 12	<0.001

CAD, coronary artery disease; *SSS*, summed stress score; *BMI*, Body mass index; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *sBP*, systolic blood pressure; *dBP*, diastolic blood pressure
*Missing values in 350 (15%) patients. Values are expressed as mean (standard deviation) or number (percentage)

Rest and stress LVEF, but not LVEF reserve, differed significantly between female and male patients (Table S3). Therefore, a sex specific analysis was performed, which is displayed in Table 3. A cut-off of ≥70% in male and ≥75% in female patients excluded a relevant ischemia with an NPV of 91% (CI 88-93%) and 98% (CI 97-99%), respectively. A LVEF reserve ≥5% had also a NPV 90% (CI 88-92%) in the overall cohort.

The predefined cut-off LVEF decrease ≥5% achieved a specificity of >90% for indicating relevant ischemia, however the positive predictive value (PPV) was poor with ≤51% across all groups, which can partly be explained by the low prevalence of LVEF decrease ≥5% in our cohort.

Comparison Between SSS = 0 and SSS 0-3

There was no relevant difference between the SSS = 0 and SSS 0-3 group (Table S4), except for a by definition expected difference in the number of non-reversible segments.

DISCUSSION

The main findings of the current study are: (1) LVEF and MBF values are lower in patients with prior CAD and in patients with abnormal PET irrespective of CAD status. (2) In patients with normal scans, mean LVEF increase during stress was 5% compared to 1%-2% in abnormal scans irrespective of CAD status. (3) Stress LVEF, LVEF reserve and all MBF values were similar in patients who underwent adenosine and regadenoson stress. (4) Stress LVEF and LVEF reserve showed a high negative predictive value and high specificity to exclude relevant ischemia. (5) Rest and stress LVEF were higher in women.

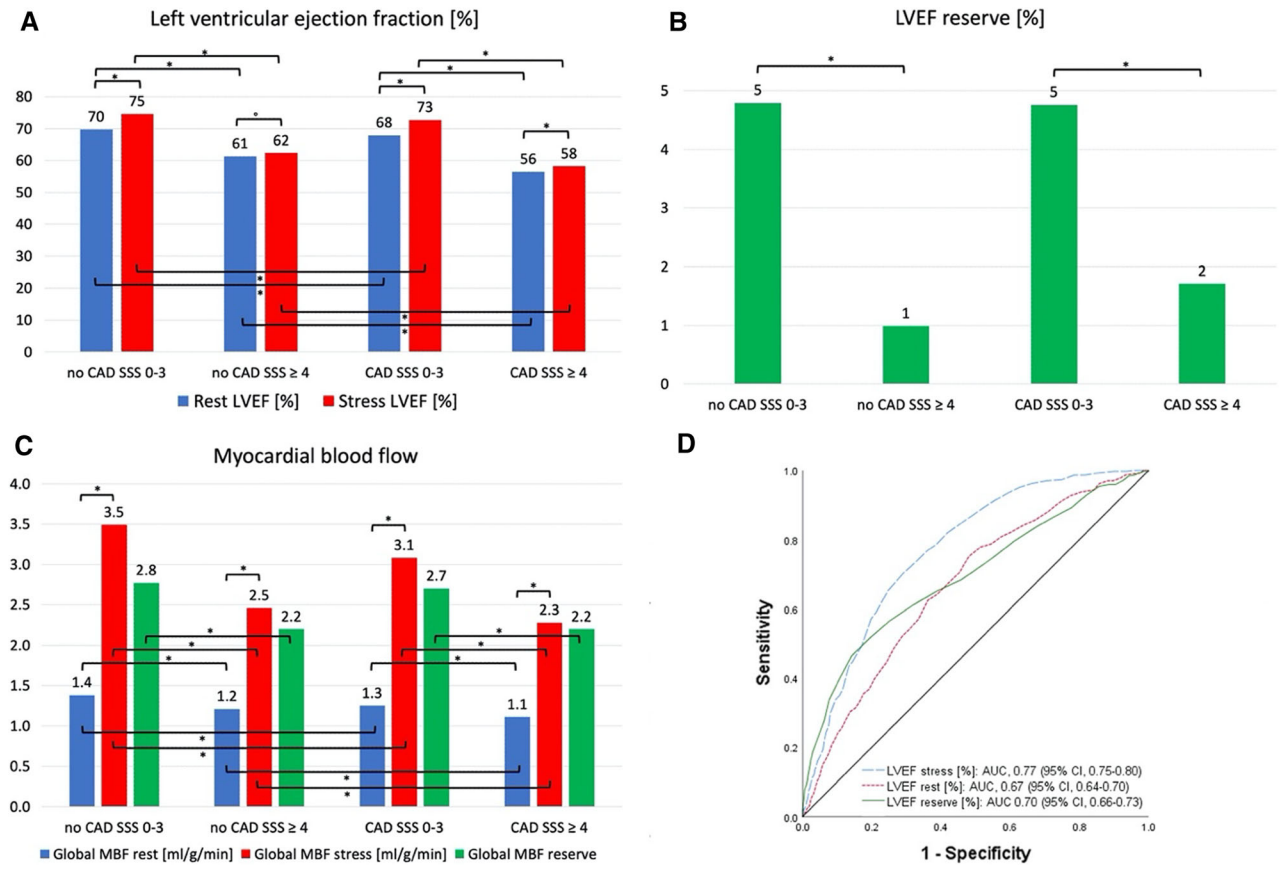

Figure 1. Overview of left ventricular ejection fraction and myocardial blood flow values. **A** Rest and stress left ventricular ejection fraction (LVEF) stratified by subgroups. LVEF values significantly increased from rest to stress in all groups. LVEF values differed significantly between normal and abnormal scans as well as depending on CAD status. **B** LVEF reserve stratified by subgroup. LVEF reserve was significantly higher in patients with normal scans. **C** Myocardial blood flow (MBF) stratified by subgroup. MBF stress increased significantly from rest to stress in all subgroups. MBF values were significantly higher in normal scans and in patients without CAD. **D** Receiver operating characteristics (ROC) for LVEF rest, stress and reserve in the overall cohort to exclude a prognostically relevant ischemia (≥10% of myocardium ischemic). Statistically significant results are marked with * ($P < 0.001$) and ° ($P < 0.05$). CAD: coronary artery disease. No CAD: suspected, but no prior known CAD. CAD: prior known CAD.MBF: myocardial blood flow. SSS: summed stress score.

LVEF and LVEF Reserve

The functional values (LVEF and MBF) differed significantly between patients without prior CAD and prior CAD and between patients with normal and abnormal scans. Stress LVEF and LVEF reserve correlated inversely with the extent and severity of ischemia. Hence, the current study confirms the findings of smaller studies.[3-5,15,16] As LVEF values differ between software packages, they cannot be readily compared between different studies if different tools were used .[17,18]

Overall, LVEF reserve in our cohort is similar to the results published in smaller studies using Rb-PET and generally dipyridamole:

Dorbala[3] (N = 510, 81% dipyridamole, 19% adenosine, ECTB software) reported a slightly higher LVEF reserve of 7 ± 7% in patients without CAD risk factors and similar 5 ± 6% in patients with CAD risk factors and normal scans. LVEF reserve was, as in our cohort, lower in patients with abnormal scans (3 ± 7%). Brown[4] (N = 110, dipyridamole, QGS software) published comparable results with a lower LVEF reserve in patients with perfusion defects (SDS ≥4) compared to

Table 2. Scan derived values and hemodynamic values in different subgroups stratified by vasodilator used

	no CAD + SSS 0-3			**no CAD + SSS ≥ 4**		
	Adenosine N = 939	**Regadenoson N = 148**	***P*-value**	**Adenosine N = 308**	**Regadenoson N = 29**	***P* value**
Rest LVEF [%]	70 ± 11	70 ± 12	0.501	62 ± 13	58 ± 12	**0.047**
Stress LVEF [%]	75 ± 10	75 ± 10	0.961	63 ± 13	59 ± 13	0.206
LVEF reserve [%]	5 ± 6	4 ± 5	0.184	1 ± ± 8	3 ± 7	0.252
Global MBF rest	1.4 ± 0.5	1.4 ± 0.4	0.236	1.2 ± 0.4	1.2 ± 0.4	0.401
Global MBF stress	3.5 ± 0.8	3.6 ± 0.7	0.070	2.5 ± 0.8	2.3 ± 0.7	0.326
Global MBF reserve	2.8 ± 0.8	2.7 ± 0.7	0.531	2.2 ± 0.8	2.1 ± 0.6	0.543
Number of NRS	0 (0-0)	0 (0-0)	0.208	0 (0-2)	1 (0-2)	0.275
Rest heart rate [bpm]	72 ± 12	74 ± 13	0.107	70 ± 13	70 ± 14	0.840
Maximum heart rate [bpm]	100 ± 18	101 ± 16	0.432	94 ± 16	93 ± 16	0.765
Δ heart rate [bpm]	27 ± 15	27 ± 14	0.851	23 ± 12	22 ± 10	0.692
sBP rest [mmHg]	127 ± 20	125 ± 19	0.288	127 ± 21	129 ± 24	0.633
sBP stress [mmHg]	136 ± 23	130 ± 21	**0.004**	136 ± 24	131 ± 26	0.277
Δ sBP [mmHg]	9 ± 19	5 ± 20	**0.026**	8 ± 18	1 ± 19	**0.038**
dBP rest [mmHg]	72 ± 12	72 ± 10	0.955	70 ± 13	67 ± 13	0.229
dBP stress [mmHg]	71 ± 14	69 ± 12	0.201	70 ± 15	67 ± 12	0.332
Δ dBP [mmHg]	− 1 ± 12	− 3 ± 10	0.174	− 1 ± 12	0 ± 9	0.829
	CAD + SSS 0-3			**CAD + SSS ≥ 4**		
	Adenosine N = 256	**Regadenoson N = 42**	***P* value**	**Adenosine N = 519**	**Regadenoson N = 58**	***P* value**
Rest LVEF [%]	68 ± 10	68 ± 12	0.896	56 ± 14	56 ± 15	0.963
Stress LVEF [%]	73 ± 9	73 ± 11	0.991	58 ± 15	60 ± 13	0.874
LVEF reserve [%]	5 ± 6	5 ± 7	0.813	2 ± 7	2 ± 7	0.816
Global MBF rest	1.2 ± 0.4	1.3 ± 0.4	0.250	1.1 ± 0.4	1.2 ± 0.4	0.341
Global MBF stress	3.1 ± 0.8	3.3 ± 0.7	0.112	2.3 ± 0.7	2.4 ± 0.7	0.246
Global MBF reserve	2.7 ± 0.8	2.6 ± 0.5	0.571	2.2 ± 0.7	2.2 ± 0.7	0.909
Number of NRS	0 (0-0)	0 (0-0)	0.109	2 (0-3)	2 (1-4)	0.193
Rest heart rate [bpm]	67 ± 10	69 ± 11	0.372	68 ± 12	70 ± 12	0.382
Maximum heart rate [bpm]	91 ± 15	94 ± 16	0.313	90 ± 16	93 ± 18	0.181
Δ heart rate [bpm]	24 ± 11	25 ± 10	0.619	21 ± 14	23 ± 13	0.376
sBP rest [mmHg]	124 ± 19	124 ± 18	0.929	124 ± 21	124 ± 22	0.940
sBP stress [mmHg]	130 ± 21	126 ± 22	0.310	128 ± 24	127 ± 24	0.898
Δ sBP [mmHg]	6 ± 16	2 ± 15	0.177	4 ± 19	3 ± 17	0.909
dBP rest [mmHg]	69 ± 11	68 ± 11	0.579	68 ± 1	68 ± 13	0.614
dBP stress [mmHg]	66 ± 13	63 ± 11	0.226	66 ± 13	66 ± 11	0.743
Δ dBP [mmHg]	− 3 ± 12	− 4 ± 9	0.346	− 2 ± 11	− 1 ± 11	0.422

Table illustrating values derived from PET with 82Rb stratified by subgroup and vasodilator
Values are expressed as mean (standard deviation) or median [interquartile range]
CAD, coronary artery disease; *No CAD*, suspected, but no prior known CAD; *CAD* prior known CAD; *SSS*, summed stress score; *MBF* myocardial blood flow; *LVEF*, left ventricular ejection fraction; *LVEF*, reserve: stress LVEF - rest LVEF; *NRS*, non-reversible segment, *sBP*, systolic blood pressure; *dBD*, diastolic blood pressure

patients without (3 ± 7% vs. 7 ± 7%). Overall, the LVEF response in Brown's study was higher compared to our results, but rest and stress LVEF were lower (47 vs. 65% and 53 vs. 68%, respectively), even though the percentage of CAD patients was higher in our cohort (38% vs. 15%). Van Tosh (N = 205, regadenoson, ECTB

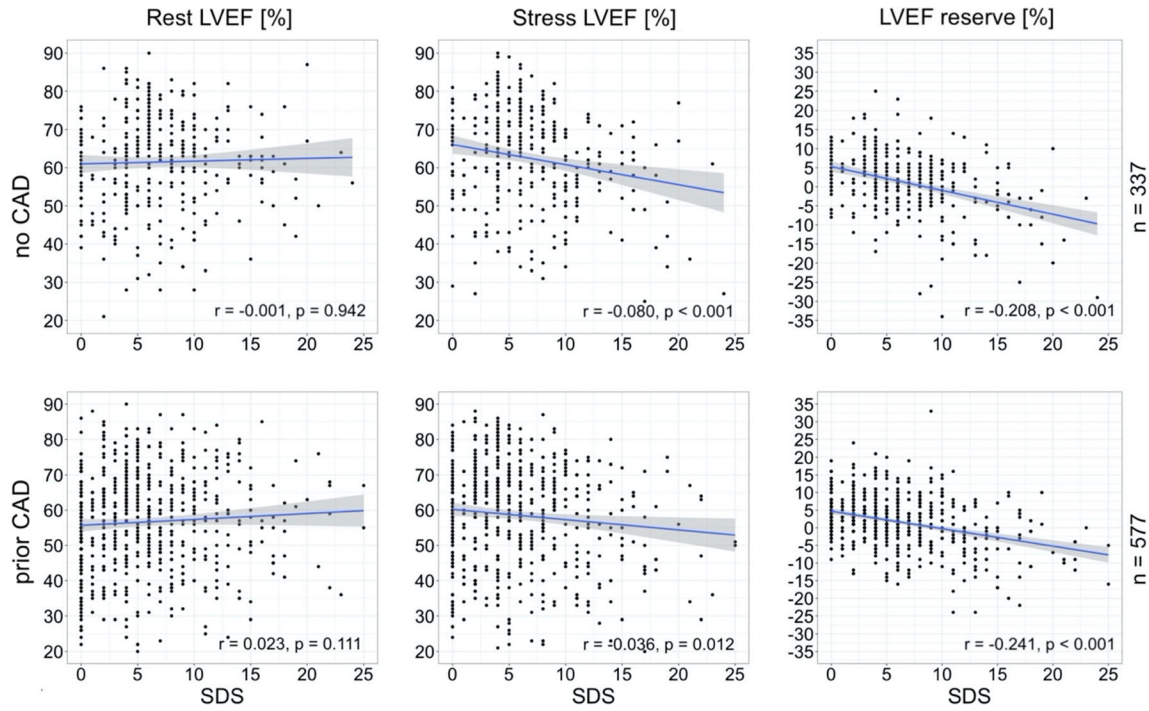

Figure 2. Rest LVEF, stress LVEF and LVEF reserve correlated with SDS in patients with abnormal scan stratified according to CAD. The graphs show the values for rest LVEF, stress LVEF and LVEF reserve with corresponding SDS value in patients without CAD or prior CAD. *LVEF*, Left ventricular ejection fraction; *SDS*, Summed difference score; *CAD*, Coronary artery disease.

software) communicated similar results in a rather small cohort[13]: Overall, LVEF increased during stress by 4 ± 9%, and even more in patients without stress induced left ventricular dysfunction (6 ± 7%). As the mean SSS was higher (9.8) in this cohort, comparability to our data might be limited (mean SSS = 4.5). Similar results were published by Hsiao (N = 134, regadenoson, 4DM SPECT software).[5]: they found a LVEF reserve of 6.5 ± 5.4% compared to − 0.2 ± 8.4% in moderate to severe ischemia. Although the authors used a different definition of a normal scan (SSS = 0), results were comparable to our findings. Nakazato (N = 125, adenosine, Syngo 6.0)[19] found a slightly higher LVEF reserve (7 ± 6% vs. 5 ± 6%). The values for overall rest and stress LVEF are similar to the values in our subgroup of patients without prior CAD and normal scan (rest LVEF 67 ± 10% vs. 70 ± 11%, stress LVEF 75 ± 9% vs. 75 ± 10%), which is likely due to the fact that these values are derived from patients with a low likelihood of CAD.

Slightly different results were presented from a larger cohort by Letsburapa (N =1441, dipyridamole, Autoquant).[7] They reported an overall decrease in stress LVEF compared to rest (60%, 58%, -1.9 ± 5.1%); this difference may result due to the fact that more patients in Letsburapa's study had an SDS >2 than in the current study (58.2% vs. 35.8%). In addition, prior CAD was present more frequently in the former than in the latter (58 vs. 38%).

Myocardial Blood Flow

Concordance and agreement between MBF and MFR derived from ^{15}O-water[20] and ^{13}N-ammonia[21] with ^{82}Rb was very good as shown in previously published studies. However, direct comparability for MBF values between studies might be limited as quantitative assessment of MBF depends on the software packages used.

However, there is no large study assessing MBF values with an ^{82}Rb PET protocol and the SyngoMBF software (Siemens Healthineers, Erlangen, Germany) in a comparable patient cohort.[19,22-12] Nevertheless, there are different, mostly smaller ^{82}Rb studies assessing MBF values in patients with suspected CAD using different software and radiotracers:

In a cohort by Van Tosh[13] including patients with suspected or known prior CAD (N = 205, regadenoson, ECTB software) mean global rMBF and sMBF were

Table 3. Performance of stress LVEF /LVEF reserve ≥+5%/LVEF reserve ≥-5% in excluding the presence of relevant ischemia (≥10%)

Cut-off	Sensitivity (95% CI), %	Specificity (95% CI), %	NPV (95% CI), %	PPV (95% CI), %
Overall (N=2299)				
prevalence ischemia ≥ 10% = 16%				
Stress LVEF ≥ 70%	79 (74-83)	61 (59-63)	94 (92-95)	28 (25-31)
LVEF reserve ≥ +5%	74 (70-79)	46 (43-48)	90 (88-92)	21 (19-23)
LVEF reserve ≤ -5%	28 (24-33)	94 (93-95)	87 (86-89)	46 (40-53)
Women (N=820)				
prevalence ischemia ≥ 10% = 8%				
Stress LVEF ≥ 75%	86 (75-92)	69 (66-72)	98 (97-99)	20 (16-25)
LVEF reserve ≥ +5%	87 (77-93)	42 (38-45)	97 (95-99)	12 (10-15)
LVEF reserve ≤ -5%	42 (31-54)	93 (92-95)	95 (93-96)	37 (27-48)
Men (N=1479)				
prevalence ischemia ≥10% = 20%				
Stress LVEF ≥ 70%	80 (76-85)	49 (46-52)	91 (88-93)	29 (26-32)
LVEF reserve ≥ +5%	71 (66-76)	48 (45-51)	87 (84-89)	26 (23-29)
LVEF reserve ≤ -5%	25 (20-30)	94 (92-95)	83 (81-85)	51 (43-59)

Prevalence of LVEF reserve ≥+5% was 42% in the overall cohort, 39% in women, 44% in men. Prevalence of LVEF reserve ≥-5% was 10% in all groups. Prevalence of stress LVEF ≥70% was 55% in the overall cohort. Prevalence of stress LVEF ≥75% was 65% in women. Prevalence of stress LVEF ≥70% in men was 43%.
LVEF, reserve: stress LVEF − rest LVEF; *NPV*, Negative predictive value; *PPV*, Positive predictive value

0.80 ± 0.56 and 1.65 ± 0.95, respectively. The rMBF and sMBF values in the current cohort were 1.3 ± 0.4 and 3.0 ± 0.9, respectively. This difference could be due to the higher overall mean SSS (9.8 vs 4.5) in Van Tosh's cohort and/or because of the different software used. However, reported mean MFR values were 2.1 ± 1.0 compared to 2.5 ± 0.8 in the current cohort.[13] Goudarzi[24] (N = 104, 50% regadenoson/dipyridamole, CardIQ physio) found no significant difference in MBF between dipyridamole and regadenoson in a cohort of patients with no prior CAD, normal perfusion and left ventricular function. Values for rMBF, sMBF and MFR were 0.8 ± 0.2, 2.2 ± 0.6, 2.9 ± 0.8 and 0.8 ± 0.2, 2.1 ± 0.6, 2.8 ± 0.7 for regadenoson and dipyridamole, respectively. Compared to patients without known CAD in our cohort, rMBF and sMBF were lower, whereas MFR was comparable (1.3 ± 0.5, 3.3 ± 0.9, 2.6 ± 0.8). Similarly, there was no difference between the vasodilators used.

Another small study (N = 33, adenosine, PMOD)[20] comparing MBF values assessed by ^{82}Rb and ^{15}O-water in a control group with a low likelihood of CAD (N = 22) and a CAD group (N = 11) found rMBF, sMBF, and MFR values of 1.03 ± 0.42, 3.82 ± 1.21, 3.88 ± 0.91 and 0.88 ± 0.21, 2.53 ± 1.01, 2.85 ± 0.86, respectively. The sMBF and MFR values in patients with CAD seem to be similar to CAD patients in our study despite the different software used, which is in concordance with the results from Slomka et al.[12], showing no difference between the two softwares used. As in the current study, sMBF and MFR values were different in patients without CAD and with CAD. Higher global sMBF and MFR values in patients with normal scan compared to patients with abnormal scan can be expected as it is the expression of the vasodilator effect of the stress agent used.[9,10]

Another small study[23] (N = 55, adenosine or regadenoson, Corridor4DM vs. QPET vs. SyngoMBF) assessed MBF values with SyngoMBF, which were lower compared to our cohort: rMBF: 1.1 ± 03 vs. 1.3 ± 0.4, sMBF: 2.4 ± 0.9 vs. 3.0 ± 0.9, MFR: 2.2 ± 0.7 vs. 2.5 ± 0.8. Due to lack of information about baseline and clinical characteristics in these patients, interpretation of the measured values is difficult.

Comparison of Adenosine and Regadenoson

So far, there is no other publication directly comparing adenosine and regadenoson.

There was no relevant difference in scan results between the two vasodilators, similar to smaller ^{82}Rb-PET studies with dipyridamole and regadenoson (N=32, N=104)[24,25] or a ^{13}N-PET study with adenosine and regadenoson (N=12).[26]

In the current study, there was no difference between the functional and hemodynamic variables between patients stressed with adenosine or regadenoson. Particularly, LVEF and MBF values were similar, except for a slightly lower rest LVEF with regadenoson in the group with no prior CAD and abnormal scan. This difference is probably due to the higher number of non-reversible segments in the regadenoson group and the small group size (N = 29). Myocardial blood flow appears to be influenced rather by history of prior CAD and extent of ischemia than by any relevant differences caused by the different vasodilators.

In contrast to Goudarzi[24], who demonstrated a significantly higher increase in heart rate in regadenoson compared to dipyridamole, there was no difference between adenosine and regadenoson in our cohort, but we observed a slight trend towards higher systolic blood pressure values in the adenosine group.

However, one has to consider, that this analysis was done in an unpaired study design instead of a paired design as Johnson et al.[27] used to compare dipyridamole and regadenoson.

The incidence of abnormal scans was lower in the regadenoson group. We assume this difference to be due to the higher percentage of women who have by gender a lower prevalence of CAD.

Gender Differences in LVEF

Similar to results from SPECT studies, rest and stress LVEF values are higher in females.[19] This study confirms this finding in a larger cohort, although absolute LVEF values were lower. Whereas contradictory to another PET study,[3] LVEF reserve was similar in men and women.

Predictors of Relevant Ischemia

A stress LVEF ≥70% allowed to exclude relevant ischemia with an NPV of 94% in the overall cohort. Overall, a LVEF reserve ≥5% had also a NPV 90%. In a previous study's small subgroup, in which patients underwent coronary angiography following PET, this predefined cut-off allowed the exclusion of severe left-main/3-vessel CAD with a sensitivity and a NPV of both >90%.[3] These mostly comparable results indicate that an LVEF reserve increase by ≥5% may be an additional diagnostic tool to make severe CAD less likely, especially in women as shown in our cohort. The lower mean stress LVEF in men compared to women.[28-31] or the higher scar burden might be a reason for this gender difference.

The predefined cut-off LVEF decrease ≥5% from rest to stress was used in SPECT-MPI studies as a hint for severe ischemia, however the value of this cut-off in

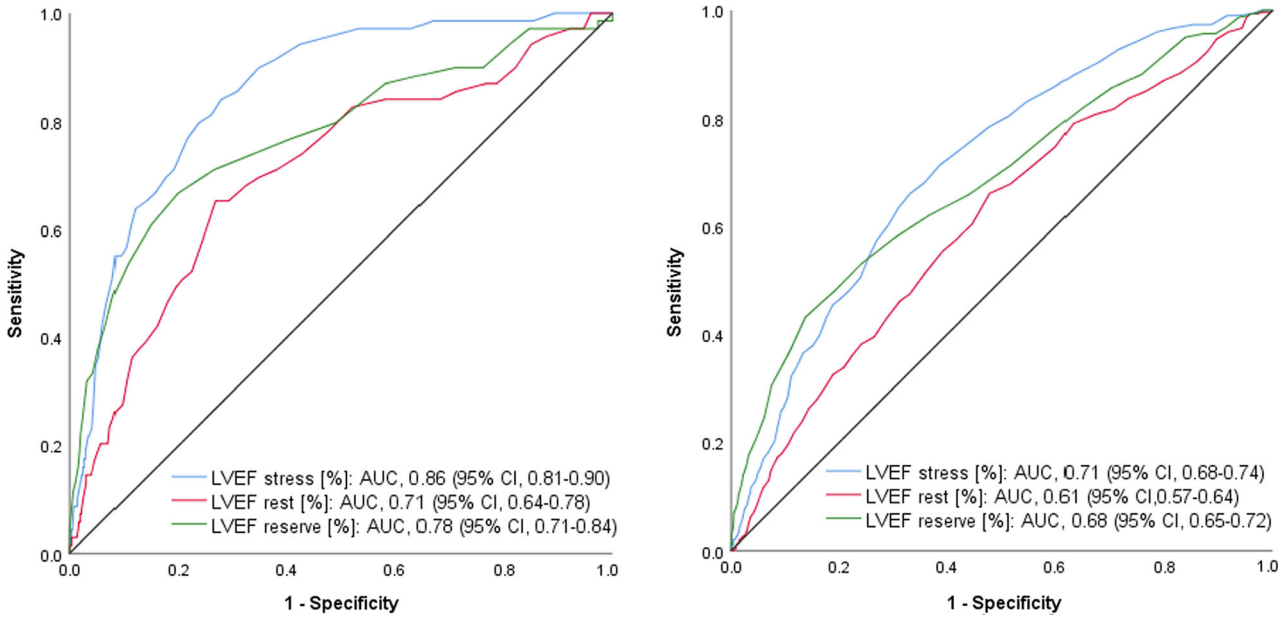

Figure 3. Receiver operating characteristics (ROC) curve of stress LVEF, rest LVEF and LVEF reserve with relevant ischemia (≥10%) as outcome in women and men. ROC curve in women (left) and men (right). *AUC*, Area under the receiver-operating characteristic curve; *LVEF*, Left ventricular ejection fraction; *LVEF reserve*, stress LVEF–rest LVEF.

PET-MPI studies is unclear. A previous ^{82}Rb-PET study[13] reported that an LVEF decrease ≥5% was associated with multivessel CAD. In our cohort, LVEF decrease ≥5% had a specificity of >90% for indicating relevant ischemia, although PPV was poor (≤51%). The previously mentioned study[3] reported a similar specificity, but a higher PPV for LVEF decrease ≥5% in this selected subgroup of patients with coronary angiography after PET . Therefore, LVEF decrease ≥5% seems not to be a useful diagnostic tool for indicating relevant ischemia in a general unselected patient population undergoing PET.

Limitations

Regarding the use of either adenosine or regadenoson vasodilator stress was up to the discretion of the treating physician. This might have influenced the results. However, there was no relevant difference in baseline characteristics between the two vasodilator groups (Table S1). Regadenoson was used in patients with (relative) contraindications to adenosine, such as allergic asthma or COPD. Still, there might be a residual risk of confounding as some relevant comorbidities for the decision to use regadenoson are not recorded in the report. No clinically relevant adverse event associated with both vasodilators occurred during this observation period. In addition, the regadenoson group accounts for a rather small percentage (12%) of our cohort, but compared to previously published studies with regadenoson, the study size of 277 patients is still considerable (van Tosh N = 205[13], Hsiao N = 134[5], Naya, N = 141[32]).

With our definition of normal scan (SSS 0-3) there might be some slightly pathological scans included in the normal group and therefore falsify the values. In an additional analysis we compared SSS 0 with SSS 0-3 scans and found no statistically significant difference except for a slight, clinically non-relevant difference in rest and stress LVEF in CAD patients (Table S4). Furthermore, stratifying patients according to SSS, which is a mixed marker of ischemia and scar, can label patients with an old scar but without ischemia as abnormal and information about ischemia is not purely available. Therefore, we re-analyzed the data stratified by ischemia only (normal: SDS 0-1, abnormal: SDS >2). Results were comparable to the previous analysis with SSS ≥ 4 as cut-off as displayed in tables S5/S6 and figures S4/S5. As expected, values for LVEF and MBF were higher compared to SSS ≥4, but the same patterns of difference were observed. When using SDS ≥2 as cut-off, the difference between MFR in patients with SDS 0-1 depends significantly on CAD status (figure S4) and family history of CAD is more prevalent in patient with SDS ≥ 2 (Table S5).

MBF and MFR values can differ significantly depending on software packages and compartment models used[33]. We used the syngoMBF package, which uses the one-tissue compartment model which agreed best with other software packages, we expect our results to be widely applicable.

CONCLUSION

Normal values for rest and stress LVEF, LVEF reserve and MBF in daily practice have been defined in a large, unselected patient cohort, in several subgroups undergoing adenosine or regadenoson ^{82}Rb-PET. Rest and stress LVEF, LVEF reserve as well as MBF values are considerably lower in patients with abnormal PET compared to patients with normal scans.

Adenosine and regadenoson vasodilator stress seem to result in similar stress LVEF and MBF responses. A stress LVEF ≥70% or LVEF increase ≥5% from rest to stress have a high negative predictive value to exclude relevant ischemia.

As stress LVEF and LVEF reserve are easily available during PET interpretation, the knowledge of their reaction to vasodilator stress and their predictive value can help to exclude relevant ischemia with even more diagnostic accuracy and certainty.

NEW KNOWLEDGE GAINED

In ^{82}Rb-PET, adenosine and regadenoson seem to have similar effect on stress LVEF, MBF and hemodynamics. Rest/stress LVEF, LVEF reserve and MBF values differ significantly between normal and abnormal scans as well as depending on CAD status. A stress LVEF ≥70% has a high NPV to exclude relevant ischemia.

Author contributions

SMF: data collection, statistical analysis, data interpretation, draft of manuscript, approval of final manuscript version. UH: data collection, statistical analysis, data interpretation, draft of manuscript, approval of final manuscript version. OFC: assistance with statistical analysis, critical revision, approval of final manuscript version. FC: critical revision, approval of final manuscript version. PH: critical revision, approval of final manuscript version. MJZ: senior author, concept and study design, data interpretation, critical revision, approval of final manuscript version

Disclosures

Simon M. Frey, Ursina Honegger, Olivier F. Clerc, Federico Caobelli, Philip Haaf, and Michael J. Zellweger declares that they have no conflict of interest.

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