Prognostic utility of splenic response ratio in dipyridamole PET myocardial perfusion imaging

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Background. **Cardiac magnetic resonance perfusion studies with adenosine stress have shown that splenic response can identify patients with inadequate pharmacologic stress. We investigate the incremental prognostic impact of splenic response ratio (SRR) in patients with normal Rubidium (Rb)-82 PET myocardial perfusion imaging (MPI).**

Methods. **Consecutive patients undergoing dipyridamole Rb-82 PET MPI for the evaluation of coronary artery disease were screened. Spleen and liver Rb-82 activity was measured and the SRR was calculated: SRR = (Spleen stress/Liver stress)/(Spleen rest/Liver rest). Major adverse cardiac events (MACE) were determined at 1 year of follow-up in patients with normal summed stress score and normal summed difference score.**

Results. **Of the 839 patients screened, the spleen was visualized in 703 (84%) of scans. There was significantly higher MACE observed in splenic non-responders vs splenic responders in both the normal SSS (7.8% vs 2.9%, *P* = .027) and the normal SDS groups (7.4% vs 2.2%, *P* = .014). In multivariate analysis in patients with normal SDS, splenic response was a significant, independent predictor of MACE (HR 2.97, 95% CI 1.10 to 8.04, *P* = .033).**

Conclusions. **SRR is a novel imaging metric to identify patients with sub-maximal vasodilator stress and an incremental prognostic marker in patients with normal SDS and SSS** (Clinical Trial Registration**: https://clinicaltrials.gov/ct2/show/NCT01128023**). **(J Nucl Cardiol 2019;26:1888–97.)**

Key Words: Major adverse cardiac events • myocardial perfusion imaging • positron emission tomography • prognosis • summed difference score • splenic response ratio

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Abbreviations	
HD	Hemodynamic
CT	Computed tomography
MACE	Major adverse cardiac events
MFR	Myocardial blood flow reserve
MPI	Myocardial perfusion imaging
PET	Positron emission tomography
Rb	Rubidium
SDS	Summed difference score
SRR	Splenic response ratio
SSS	Summed stress score

See related editorial, pp. 1898–1900

INTRODUCTION

Myocardial perfusion imaging (MPI) relies on adequate pharmacologic stress to detect myocardial ischemia. Dipyridamole stress rubidium (Rb)-82 positron emission tomography (PET) MPI is a well-established, safe, and effective functional imaging modality to assess myocardial ischemia.[1] However, PET MPI is still subject to a 10% rate of false-negative results.[1,2] Reportedly, up to 34% of false-negative scans in MPI may be secondary to inadequate pharmacologic stress.[3]

Decreased splenic radioactivity was demonstrated initially during exercise stress in radionuclide ventriculography.[4,5] In recent dosimetry studies for Rb-82 PET MPI, the spleen had decreased tracer activity at peak stress compared to rest.[5] This phenomenon of splenic response (e.g., decreased flow to the spleen during stress) is a physiologic response to dipyridamole infusion and likely indicates adequate chemical stress. Consequently, a failure of this response may be an indicator of insufficient pharmacologic stress.

Splenic switch-off (decreased splenic tracer uptake at stress compared to rest) has been identified as a method of identifying true pharmacologic stress in adenosine stress. This technique has recently shown strong correlation with hemodynamic (HD) and symptomatic response in adenosine perfusion cardiovascular magnetic resonance imaging.[6] Failed splenic switch-off also appears to be more common in patients with false-negative than true-negative cardiovascular magnetic resonance MPI findings, further highlighting splenic response as a potential tool to identify inadequate pharmacologic stress.[7] These findings suggest the hypothesis that in patients with normal myocardial perfusion, splenic response may have incremental prognostic value by identifying patients at higher risk for false-negative results.

The role and prognostic value of splenic response has not been previously investigated in dipyridamole stress Rb-82 PET MPI. The objective of this study is to investigate the incremental prognostic impact of splenic response ratio (SRR) in patients with normal Rb-82 PET MPI results.

METHODS

Patient Population

Consecutive patients undergoing dipyridamole Rb-82 PET MPI for the evaluation of coronary artery disease from July 2009 to September 2010 were screened. Patients were at least 18 years of age and had a clinically indicated PET MPI as part of the Rubidium-ARMI trial (NCT01128023). Institutional review board permission was obtained for the present study. If patients had multiple PET MPI studies during this time period, only the first scan was included in our analysis. The first fifty consecutive patients with normal scan results (defined as no perfusion defects, normal wall motion, normal chamber volumes, no visible calcium on computed tomography (CT) attenuation scan, and normal myocardial flow reserve (MFR) of ≥ 2 on blood flow quantification) were used to calculate the normal range of SRR to simulate healthy controls (derivation cohort). The remaining patients comprised the validation cohort for analysis.

PET Image Acquisition and Analysis

Patients underwent standard PET MPI imaging protocol at our center.[8] In brief, they were instructed to abstain from eating or drinking for 6 hours prior to the test ($\geq$ 12 hour for caffeine) and to avoid theophyllines for $>$ 48 hour prior to their MPI. All antianginal medications were held on the morning of the PET scan. Images were acquired using a hybrid PET-CT system (Discovery 690/VCT-64, GE Healthcare, Milwaukee, Wisconsin). First, a fast helical (1.5 second) low-dose ($\sim$ 0.25 mSv) X-ray CT scan was obtained for attenuation correction (120 kVp with axial and angular mA modulation). Patients were then injected with 10 MBq/kg Rb-82 chloride into an antecubital vein using a custom elution system to limit dead-time losses to less than 35%. Parallel list-mode acquisition was then used to acquire rest images (dynamic, 10 minutes Rb-82 scan). After rest image collection, dipyridamole was administered at 140 μg/kg/min for 5 minutes followed by a second infusion of Rb-82 at 8 minutes for PET imaging during hyperemic stress. Static images of Rb-82 uptake were reconstructed from the 2 to 10 min list-mode data, using the vendor iterative reconstruction (VuePoint HD) with 12 mm Hann post-filter. The PET MPI scans were analyzed using HybridViewer Version 4.4 (HERMES Medical Solutions AB, Sweden).

Splenic Response Ratio (SRR) Calculation

Stress and rest PET images were individually superimposed on the patient's rest CT scan using the PET-CTAC (PET-CT Attenuation Correction) HybridViewer fusion display function. Radiotracer activity concentrations (Bq/cm^3) were measured in regions of interest, including the spleen (Figure 1) and the liver at stress and rest. Each region of interest was measured twice and then averaged. The size of the ROIs was predetermined (i.e., spleen: 20 mm diameter and liver: 50 mm diameter) and not changed throughout the study. Spherical volumes of interest (VOI) were sampled in the spleen (20 mm diameter) and liver (50 mm diameter). The VOIs were placed manually near the center of each organ, with a margin at least the same distance (diameter) away from the visible edge of each organ. Patient scans were excluded if both VOIs could not be placed with this margin from the edge of both spleen and liver. SRR was calculated using the liver radioactivity concentrations as a control organ: SRR = (spleen stress/liver stress)/(spleen rest/liver rest). Patients with SRR $\leq$ 0.71 were classified as splenic responders (normal SRR) and those above this value as non-responders (abnormal SRR). The SRR value in the derivation cohort (N = 50) with normal global MFR and normal PET interpretation was 0.54 ± 0.17 (Mean ± SD). A cutoff value of mean + 1 standard deviation (SRR < 0.71) was chosen to increase the sensitivity of SRR as a marker of adequate stress. Splenic non-responders are thus unlikely to be classified as splenic responders, which minimizes the chance of an inadequate stress and enhances the

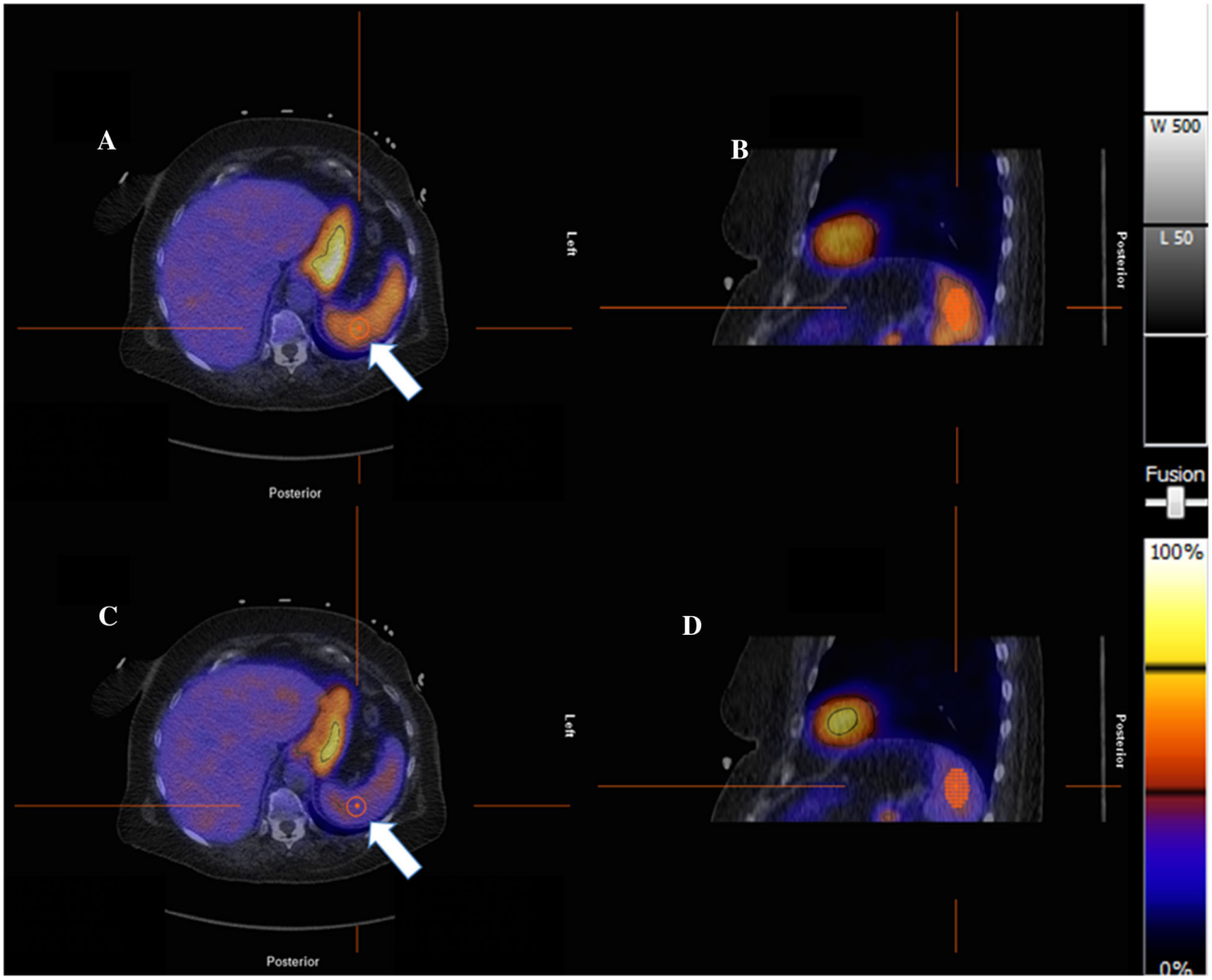

Figure 1. Fused ^{82}Rb stress PET-CT MPI images with crosshairs showing the method of measurement of splenic radiotracer activity concentration (white arrow in panels 1A and 1C) in the regions of interest at rest (panels 1A and 1B) and following stress (panels 1C and 1D). Although only transverse (1A and 1C) and sagittal (1B and 1D) slices are shown in the figure, coronal slice was also used to obtain a mean 3D activity concentration value. A clear reduction in splenic radiotracer activity with stress (normal splenic response) is seen in the figure. *PET*, positron emission tomography; *CT*, computed tomography; *MPI*, myocardial perfusion imaging.

test's ability to rule out disease. A random subset of 20 patients was used to measure inter- and intra-rater reproducibility. There was strong inter-rater reliability in SRR measurements with a Pearson R coefficient of 0.97 for absolute SRR values and a kappa of 0.86 for binary splenic response. Similarly, the intra-class coefficient was 0.98 for intra-rater reproducibility.

Study Data

Splenic response was compared to HD response as a measure of adequate pharmacologic stress. Patients were classified as HD responders if they had both heart rate (increase of $\geq$ 10 bpm) and systolic blood pressure (decrease of $\geq$ 10 mmHg) responses at peak stress. Partial HD responders had only one of these two responses. The cohort was then grouped into those with normal summed stress score (normal SSS $<$ 4) and/or summed difference score (normal SDS $<$ 2). Accepted cutoff values for SSS (SSS $<$ 4, 4 to 7, $\geq$ 8) as well as for global MFR (normal $\geq$ 2) were also used to create additional subgroups of interest.[9,10]

Major adverse cardiac events (MACE) were determined at 1 year of follow-up, which included a composite endpoint of cardiac death, non-fatal acute coronary syndrome or late revascularization (defined as percutaneous coronary intervention or coronary artery bypass surgery $\geq$ 3 months from PET MPI). Patients were followed for cardiac events using telephone follow-up as well as a review of our online electronic medical records.

Statistical Analysis

Data were quantified using SPSS Statistics (Version 21.0, Armonk, NY, IBM Corp) and MedCalc for Windows version 12.0 (MedCalc Software, Ostend, Belgium). For descriptive analysis, we used mean ± standard deviation for continuous variables as appropriate. Categorical variables were compared using a Chi-square test and continuous variables with a Wilcoxon rank sum test. Kaplan–Meier curve estimates for MACE-free survival in splenic response vs non-response used the log-rank test. Two-tailed P values are reported and values of less than .05 were considered statistically significant. Univariate analysis was done to determine relevant variables and only those with $P < .1$ were included in the proportional hazards model to prevent overfitting. Analysis was focused on population of interest, specifically those with SDS $<$ 2. Multivariate analysis was performed using a Cox proportional hazards model to further assess the independent prognostic impact of SRR. Proportional hazards assumption was tested and satisfied in the Cox model using estimated Kaplan–Meier survival curves. Based on clinically important factors, typical variables were chosen to include in the multivariate analysis. As MFR and SRR were correlated, MFR was excluded from the final multivariate analysis. A categorical variable was created for SRR with accepted cutoff values to create variables of interest and for simplicity in creating hazard ratios and survival curves.

RESULTS

Validation of SRR

Within the 1046 patients in our database, 839 had 1-year clinical follow-up data available and were screened. Of these patients, 703 (84%) of scans had adequate visualization of the spleen within the reconstructed imaging field-of-view to quantify SRR, and were included in the study. The first 50 consecutive normal scan result patients were used in the SRR derivation cohort. In this group, there was no significant difference in mean liver responses at stress vs rest (31.9 ± 2.4 vs 28.8 ± 2.0 kBq/cm^3, P = NS).

In the validation cohort of 653 patients, 476 (72.9%) were classified as splenic responders and 177 (27.1%) as splenic non-responders. Baseline characteristics and comorbidities were similar across both groups (Table 1).

Hemodynamic Response and SRR

Full HD response was exhibited in 94 (14.3%) patients, whereas 395 (60.5%) were partial responders and 164 (25.1%) were non-responders (Table 2). Full responders were more likely to experience splenic response whereas patients with no HD response less likely (83.0% vs 57.9%, $P < .0001$). Of the 489 patients that were either partial or full HD responders, 381 (77.9%) had adequate splenic switch-off. Even among patients exhibiting full HD response, 17% of patients were splenic non-responders.

Clinical Outcomes of Splenic Response

Within the validation cohort, 422 had SSS $<$ 4 and 433 had SDS $<$ 2. In the normal SSS group, 307 (73%) were splenic responders, similar to the 312 (72%) in the normal SDS group. There was significantly higher MACE observed in splenic non-responders vs splenic responders in the normal SSS (7.8% vs 2.9%, P = .027) and the normal SDS groups (7.4% vs 2.2%, P = .014) (Table 3, also see Supplementary Table 1). There was no significant difference in the proportion of MACE at 1 year in patients with abnormal SSS = 4 to 7 or SSS $\geq$ 8 (Figure 2).

In patients with a normal SDS, lack of HD response was associated with greater MACE than partial or full HD response (9.6% vs 1.8%, P = <.001). Among those with no HD response, splenic non-responders had higher MACE than splenic responders (16.3% vs 3.6%, P = .028). In patients with normal SDS and abnormal

Table 1. Baseline characteristics

	Splenic non-responder (*n* = 177)	Splenic responder (*n* = 476)	*P* value
Age	65.9 ± 11.8	63.5 ± 10.2	.009
Male	96 (54.2)	267 (56.1)	.723
Smoker	113 (63.8)	276 (58)	.175
Hypertension	137 (77.4)	342 (71.8)	.154
Dyslipidemia	138 (78.0)	359 (75.4)	.498
Diabetes mellitus	57 (32.2)	140 (29.4)	.490
Family history	83 (46.9)	232 (48.7)	.675
BMI (kg/m^2)	31.1 ± 7.2	32.0 ± 7.2	.124
Previous CAD	87 (49.2)	229 (48.1)	.813
Rb-82 PET imaging parameters:			
Rest LVEF	53.2 ± 12.5	52.4 ± 13.6	.467
Stress LVEF	57.9 ± 14.5	58.0 ± 14.8	.921
Rest LVEF < 40%	25 (14.1)	72 (15.1)	.687
Positive ECG	11 (6.2)	44 (9.2)	.215
MFR	2.0 ± 0.8	2.4 ± 0.8	< .001
SSS	3.3 ± 4.7	4.7 ± 7.2	.019
SDS	1.5 ± 2.9	2.4 ± 4.5	.014

BMI, body mass index; *CAD*, coronary artery disease; *LVEF*, left ventricular ejection fraction; *ECG*, electrocardiogram; *MFR*, myocardial flow reserve; *SSS*, summed stress score; *SDS*, summed difference score

Table 2. Hemodynamic response to dipyridamole

	Splenic non-responder	Splenic responder	Total *N* (%)	P value
HD non-responders	69 (42.1)	95 (57.9)	164 (100)	< .0001
HD partial responders	92 (23.2)	303 (76.7)	395 (100)	< .0001
HD full responders	16 (17.0)	78 (83.0)	94 (100)	< .0001
Total	177 (27.1%)	476 (72.9%)	653 (100)	

HD, hemodynamic

MFR, splenic non-responders still had a significantly higher rate of MACE compared to responders (14.8% vs 1.4%, $P = .004$). In patients with normal SSS, there was also a significantly higher rate of MACE in splenic non-responders when stratifying by MFR (Table 3).

Univariate and Multivariable Cox Hazard Models

Only significant univariate predictors of MACE were included in our analysis (Table 4). Although both MFR and SRR emerged as significant univariate predictors of MACE, as they were correlated, MFR was excluded from the final multivariate model. On multivariable analysis in patients with normal SDS, SRR was a significant independent predictor of MACE (hazard ratio: 2.97, 95% CI 1.09 to 8.04, $P = .033$). Age and diabetes mellitus were also significant predictors in the model (Table 5). Multivariate analysis in patients with normal SSS had similar results.

Finally, the log-rank test showed that MACE-free survival at 1 year was significantly lower in splenic non-responders compared to non-responders in the normal SSS group (Figure 3). There was no significant difference in MACE-free survival in patients with SSS ≥ 4. The log-rank test showed similar results in patients with normal SDS as well.

DISCUSSION

To our knowledge, this is the first study to create an objective, quantifiable method of determining splenic

Table 3. MACE in normal SDS and SSS by MFR and HD response

	Splenic non-responder (*n* = 121 in SDS < 2, *n* = 115 in SSS < 4)	Splenic responder (*n* = 312 in SDS < 2, *n* = 307 in SSS < 4)	Total	*P* value
SDS < 2 (*n* = 433)	9 (7.4)	7 (2.2)	16 (3.7)	.014
MFR				
Abnormal	9 (14.8)	1 (1.4)	10 (7.7)	.004
Normal	0 (0)	6 (2.5)	6 (2.0)	.222
HD response				
No HD response	8 (16.3)	2 (3.6)	10 (9.6)	.028
Partial or full HD response	1 (1.3)	5 (1.9)	6 (1.8)	.755
SSS < 4 (*n* = 422)	9 (7.8)	9 (2.9)	18 (4.3)	.027
MFR				
Abnormal	8 (15.1)	3 (4.5)	11 (9.2)	.048
Normal	1 (1.6)	6 (2.5)	7 (2.4)	.679
HD response				
No HD response	7 (17.1)	3 (6.3)	10 (11.2)	.107
Partial or full HD response	2 (2.7)	6 (2.3)	8 (2.4)	.848

SSS, summed stress score; *SDS*, summed difference score; *MFR*, myocardial flow reserve; *HD*, hemodynamic

response in Rb-82 PET MPI. We identify SRR as a potential marker of adequate pharmacologic response with dipyridamole stress. It is also the first study to demonstrate the incremental and independent prognostic value of SRR in patients with normal perfusion in a large cohort of patients being evaluated for coronary artery disease.

SRR in PET MPI vs Splenic "Switch-off" in Perfusion Cardiovascular Magnetic Resonance

Splenic contraction during stress was first described in animal models in the setting of both exercise and chemical stress.[11] Possible physiologic mechanisms for splenic response include active splenic contraction during stress as well as passive flow out of the spleen in the setting of decreased splanchnic flow from stress.[4] Adenosine exerts its effect on splenic vasculature through the A1 and A2B adenosine receptors but mediates coronary vasodilation by acting primarily on the A2A adenosine receptor.[12,13] Dipyridamole increases endogenous adenosine concentrations by inhibiting cellular reuptake of adenosine, and thus likely causes decreased splenic perfusion via the same mechanism.[14,15] Regadenoson, however, is a predominately A2A receptor agonist that is selective for the coronary vasculature, and thus does not exhibit the same splenic response as adenosine or dipyridamole.[7]

Previous studies have evaluated splenic ''switch-off'' in perfusion cardiovascular magnetic resonance by comparing it to HD response[6] as well as to coronary angiogram results to determine that failed ''switch-off'' is associated with higher rates of false-negative results.[7] However, splenic ''switch-off'' remains a subjective visual assessment within the realm of perfusion cardiovascular magnetic resonance, which is susceptible to bias among interpreting clinicians. In our study, we have developed a more standardized method of mapping out splenic response to create an SRR, with a cutoff value to determine splenic response derived from a cohort with normal PET MPI scan. We also include liver stress and rest radiotracer concentrations as a correction for the SRR. A control region of interest is necessary to ensure accuracy because of the precise timing required to map the interest given Rb-82's short half life and to correct for blood pool given the difference in kinetics in flow and dose delivery during stress and rest.[16] The liver was chosen because it is a large, easily measurable organ with constant blood supply and no partial volume effect. This was confirmed with similar liver radiotracer uptake noted on stress and rest images in the derivation cohort.

Studies investigating splenic ''switch-off'' as a marker of adequate stress have been limited to adenosine stress thus far. Dobutamine and regadenoson do not show similar splenic contraction at stress in perfusion cardiovascular magnetic resonance[7] Dipyridamole, however, is another widely used, low-cost alternative

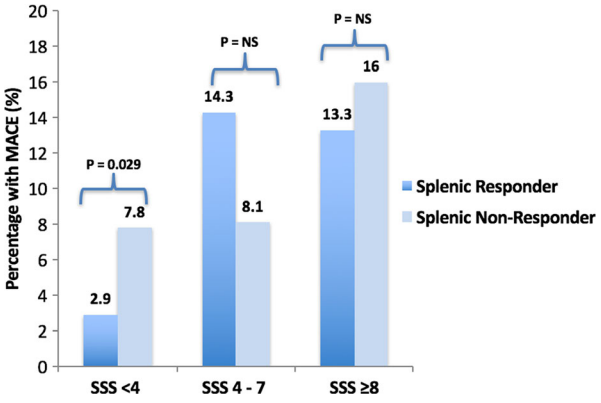

Figure 2. 1-year MACE of SRR across SSS cutoffs. *MACE*, major adverse cardiac events; *SRR*, splenic response ratio; *SSS*, summed stress score. For SSS < 4: splenic responders n = 307, splenic non-responder = 115. For SSS 4–7: splenic responders n = 68, splenic non-responder = 39. For SSS ≥ 8: splenic responders n = 101, splenic non-responder = 23.

stress agent to adenosine in MPI.[17] Our study is the first to investigate splenic response as a marker of adequate pharmacologic stress using dipyridamole stress, which has important implications given its widespread use in nuclear MPI.

Furthermore, the few studies in splenic ''switch-off'' thus far have been limited to the diagnostic utility of splenic response and have been conducted with small sample sizes. We describe the prognostic impact of splenic response in a large cohort of patients with our novel and easily reproducible SRR tool, enhancing its clinical utility.

Clinical Implications of SRR

Splenic response correlated well to HD response in PET MPI, similar to adenosine perfusion MR. Importantly, 17% of patients with full HD response were splenic non-responders, which suggests that splenic switch-off may provide incremental information to aid the interpretation of negative dipyridamole PET MPI.

In patients with normal SSS and SDS, SRR emerged as a potential method of identifying patients who are at increased risk of cardiac events. This is likely due to identification of patients who are inadequately stressed with dipyridamole and are thus at higher risk of a false-negative result. There was a similar rate of MACE across splenic responders and non-responders in patients with abnormal SSS and SDS. This is expected and in fact supports our proposed mechanism as the benefit of splenic response is derived in its ability to identify patients at increased risk of false-negative results, which is less relevant in those with abnormal SSS and SDS.

MFR is an important independent prognostic variable that has been well studied in PET MPI, and abnormal MFR is associated with an increased risk of cardiac events.[8] In our study, a significant correlation

Table 4. Univariate analysis of variables for MACE in SDS < 2

Variable	Chi-Square test	*P* value	HR	CI
Age	**4.66**	**.031**	**1.05**	**1.01–1.101**
Male	0.32	.571	0.87	0.53–1.42
Smoker	1.63	.192	2.09	0.67–6.48
Hypertension	2.12	.126	3.01	0.68–13.23
Dyslipidemia	0.91	.332	1.84	0.53–6.47
Diabetes mellitus	**6.20**	**.013**	**1.87**	**1.14–3.07**
Family history	0.68	.406	1.53	0.56–4.21
BMI (kg/m^2)	1.94	.162	0.95	0.88–1.02
Previous CAD*	0.00	.999	1.00	0.36–2.75
Rb-82 PET imaging parameters				
Rest LVEF	1.86	.171	0.98	0.94–1.01
Stress LVEF	1.29	.257	0.98	0.95–1.01
Rest LVEF < 40%	1.94	.135	1.17	0.94–1.46
Abnormal MFR	**7.04**	**.004**	**3.94**	**1.43–10.38**
Abnormal SRR	**6.04**	**.009**	**3.45**	**1.29–9.26**

Bold values indicate statistically significant univariate variables
SDS, summed difference score; *BMI*, body mass index; *CAD*, coronary artery disease; *LVEF*, left ventricular ejection fraction; *MFR*, myocardial blood flow reserve; *SRR*, splenic response ratio
*Previous CAD includes previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft

Table 5. Multivariate Cox models of MACE for prognostic value of SRR in SDS < 2

Variable	Chi-Square test	*P* value	HR	CI
Age	5.18	.023	1.06	1.01–1.11
Diabetes mellitus	6.91	.009	1.95	1.19–3.21
Abnormal SRR	4.57	.033	2.97	1.10–8.04

SRR, splenic response ratio

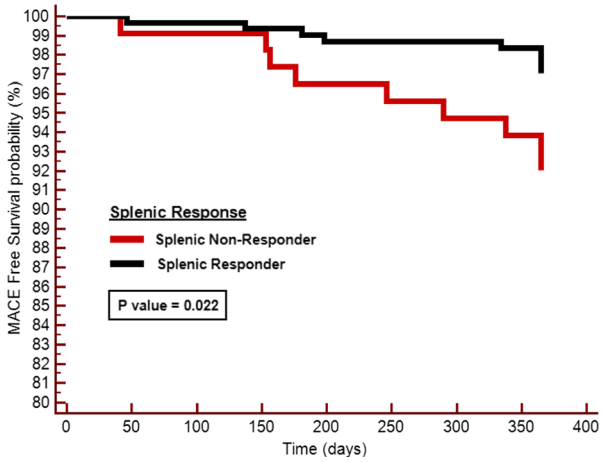

Figure 3. Kaplan–Meier curve comparing MACE-free survival of patients with SSS < 4 based on splenic response. *MACE*, major adverse cardiac events; *SSS*, summed stress score.

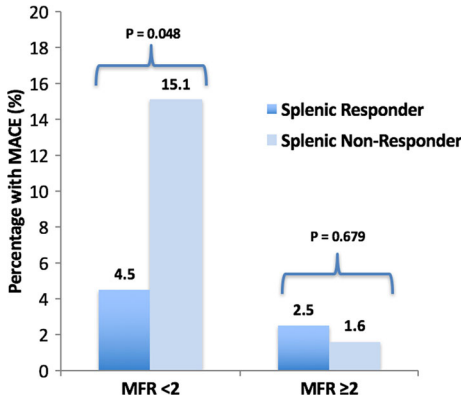

Figure 4. 1-year MACE of SRR across MFR cutoffs. *MACE*, major adverse cardiac events; *SRR*, splenic response ratio; *MFR*, myocardial flow reserve. MFR < 2: splenic responders $n = 158$, splenic non-responders $n = 95$. MFR ≥ 2: splenic responders $n = 311$, splenic non-responder = 80.

was observed between MFR and SRR as prognostic markers. In patients with normal perfusion but abnormal MFR, abnormal SRR was associated with a significantly increased risk of MACE (15.1% vs 4.5%) which further suggests that SRR may offer additional prognostic information in patients with normal perfusion but abnormal MFR. Of note, no difference was noted in MACE rates between splenic responder and splenic non-responders in patients with normal perfusion with normal MFR (Figure 4). In conjunction with MFR, SRR represents a simple adjunctive measure with a clinical role in highlighting high-risk patients.

Importantly, SRR had significant prognostic value in patients with no HD response. This group is the ideal target for SRR as it highlights prognostic implications of a group who may have been inadequately stressed but can still be identified as a high-risk group (for example, no HD response but abnormal SRR) and may warrant further investigation. Used in conjunction with MFR and HD response, SRR thus represents an additional tool to identify high-risk patients with potential false-negative scans in the setting of inadequate pharmacologic stress.

We limited our multivariable analysis using the Cox model to patients with normal SDS (or normal SSS which showed similar results) given that this is the population of interest with this tool. SRR was a statistically significant, independent, and incremental predictor of cardiac events. While MFR remains a valid prognostic marker, SRR represents an alternative prognostic tool that is particularly relevant for centers that are not able to measure MFR, or for studies where an adequate hemodynamic or flow response is questionable. This also has important implications for single-photon emission computed tomography MPI that is unable to measure MFR but could potentially use SRR as an adjunctive measure of adequate stress. Further studies are needed to investigate the role of SRR in single-photon emission computed tomography MPI.

STUDY LIMITATIONS

Although our patient data were collected prospectively, SRR was retrospectively obtained. Thus, not all splenic images were adequate for SRR calculation, which may introduce an element of selection bias. However, we did find that the majority of scans in our

large cohort had adequate splenic images, which limits this potential bias. Furthermore, prognostic data were collected prospectively, which mitigates any potential recall bias. Additionally, this was supplemented by electronic health records search to ensure adequate follow-up. This is a single center study and is thus subject to local referral patterns and patient population. These findings should be confirmed in a large, multicenter, prospective study. We recognize limitations of comparing splenic response to hemodynamic response as a marker of adequate stress, particularly given the possible prognostic implications of a blunted hemodynamic response. Ideally, SRR should be compared with angiography in dipyridamole stress to obtain a more accurate assessment of its ability to identify false-negative results, which would be an interesting adjunct to our work. However, this is logistically difficult since the prognostic ability of SRR is within the normal perfusion scans, and there would be an inherent selection bias in the population undergoing coronary angiograms. Furthermore, we did not explore the possibility of subdiaphragmatic or splenic vascular calcifications on the impact of SRR calculations, which could be investigated in future studies. Nonetheless, we do provide important prognostic data that make SRR a powerful and relevant tool to recognize high-risk patients with normal MPI.

NEW KNOWLEDGE GAINED

Splenic response has been shown to identify true pharmacologic stress in adenosine perfusion imaging, and this study expands on this tool by demonstrating its utility in dipyridamole stress. Our findings support splenic response as an adjunctive tool to identify those inadequately stressed in Rb-82 PET MPI. Those with an abnormal SRR may need further evaluation given the possibility of false-negative results and increased MACE in these patients.

CONCLUSIONS

Splenic response represents a simple and reproducible marker of adequate pharmacologic stress in Rb-82 PET MPI to identify patients at risk of false-negative results. SRR had a prognostic impact in patients with normal Rb-82 PET MPI results in a large cohort of patients referred for assessment of coronary artery disease. Assessment of SRR may represent a novel tool to identify patients at increased risk of cardiac events in this patient population.

Disclosures

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