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Assessment of Splenic Switch-Off With Arterial Spin Labeling in Adenosine Perfusion Cardiac MRI

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Background: In patients with suspected coronary artery disease (CAD), myocardial perfusion is assessed under rest and pharmacological stress to identify ischemia. Splenic switch-off, defined as the stress to rest splenic perfusion attenuation in response to adenosine, has been proposed as an indicator of stress adequacy. Its occurrence has been previously assessed in first-pass perfusion images, but the use of noncontrast techniques would be highly beneficial.
Purpose: To explore the ability of pseudo-continuous arterial spin labeling (PCASL) to identify splenic switch-off in patients with suspected CAD.
Study Type: Prospective.
Population: Five healthy volunteers (age 24.8 ± 3.8 years) and 32 patients (age 66.4 ± 8.2 years) with suspected CAD.
Field strength/Sequence: A 1.5-T/PCASL (spin-echo) and first-pass imaging (gradient-echo).
Assessment: In healthy subjects, multi-delay PCASL data (500–2000 msec) were acquired to quantify splenic blood flow (SBF) and determine the adequate postlabeling delay (PLD) for single-delay acquisitions (PLD > arterial transit time). In patients, single-delay PCASL (1200 msec) and first-pass perfusion images were acquired under rest and adenosine conditions. PCASL data were used to compute SBF maps and SBF stress-to-rest ratios. Three observers classified patients into "switch-off" and "failed switch-off" groups by visually comparing rest-stress perfusion data acquired with PCASL and first-pass, independently. First-pass categories were used as reference to evaluate the accuracy of quantitative classification.
Statistical Tests: Wilcoxon signed-rank, Pearson correlation, kappa, percentage agreement, Generalized Linear Mixed Model, Mann–Whitney, Pearson Chi-squared, receiver operating characteristic, area-under-the-curve (AUC) and confusion matrix. Significance: P value < 0.05.
Results: A total of 27 patients (84.4%) experienced splenic switch-off according to first-pass categories. Comparison of PCASL-derived SBF maps during stress and rest allowed assessment of splenic switch-off, reflected in a reduction of SBF values during stress. SBF stress-to-rest ratios showed a 97% accuracy (sensitivity = 80%, specificity = 100%, AUC = 85.2%).
Data Conclusion: This study could demonstrate the feasibility of PCASL to identify splenic switch-off during adenosine perfusion MRI, both by qualitative and quantitative assessments.
Evidence Level: 2
Technical Efficacy: 2

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Coronary artery disease (CAD), caused by the narrowing or obstruction of the coronary arteries, is a major cause of morbidity and mortality.[1] Cardiac MRI is one of the most comprehensive techniques for its diagnosis, allowing the characterization of several cardiac parameters, such as ventricular volumes, ejection fraction, and myocardial tissue morphology, structure, perfusion, and viability.[2] In patients with suspected CAD, myocardial perfusion is measured under rest and pharmacologically induced stress to identify potential areas of ischemia.[3]

False-negative findings from myocardial perfusion MRI can be up to 10%, and one third of these findings may be due to an inadequate stress level.[4,5] Adenosine is the most frequently used stress agent.[6] Its vasodilator effect is considered adequate when accompanied by a 10-bpm heart rate increase, a 10 mmHg drop in systolic blood pressure, and/or other physical side effects (i.e. chest pain or breathlessness).[7] However, its efficacy seems to be patient dependent, and recent studies suggested that these markers (i.e. 10-bpm heart rate increase) may not be sufficient to reflect a hyperemic state.[8,9]

Splenic switch-off, defined as stress to rest splenic perfusion attenuation in response to A_{2A} A_{2B} receptor-mediated vasoconstriction of the afferent splenic arteries during adenosine infusion,[10] has been proposed as an indicator of stress adequacy in cardiac MRI.[11–15] To date, it has been assessed in first-pass perfusion imaging studies since the spleen is commonly captured by the acquired short-axis slices.[11–15]

The main disadvantage of using first-pass images for the assessment of splenic switch-off is that stress adequacy is usually determined during the study interpretation once the exam has finished.[11–15] Therefore, the utility of the technique seems limited to the detection of false-negative findings. The use of a noncontrast technique would be beneficial for the real-time evaluation of splenic switch-off to objectively determine the vasodilator effect of the drug, thus providing an opportunity for optimizing the stress response by increasing the adenosine dose before gadolinium administration. Previous work has shown that a higher adenosine dose increases the proportion of patients with splenic switch off in comparison to the standard 140 μg/kg/min dose.[15]

In this context, T1 mapping has been previously investigated[16]; however, T1 estimations do not provide a direct measure of splenic perfusion. Arterial spin labeling (ASL) provides noncontrast perfusion measurements by using magnetically labeled arterial blood water spins as endogenous tracers.[17] Previous research has quantified splenic perfusion with ASL,[18–20] reporting a mean splenic blood flow (SBF) of 151 ± 7 mL/min/100 g in healthy subjects,[18] which is lower in comparison to other abdominal organs, such as the kidney.[21] However, to date, ASL has not been used for the assessment of splenic switch-off during adenosine perfusion cardiac MRI studies.

Pseudo-continuous ASL (PCASL) can be employed to selectively label arterial blood in the descending aorta, before it reaches the spleen. Specifically, PCASL is expected to provide higher signal-to-noise ratio (SNR) measurements than pulsed ASL because of its long labeling duration.[22] Multi-delay PCASL, where perfusion measurements are obtained at different delay times after labeling, can allow simultaneous quantification of perfusion and arterial transit time (ATT, the transport time from the labeling position to the tissue).[23] On the other hand, single-delay PCASL has the advantage of shorter scan time. However, the delay time must be longer than ATT for accurate SBF quantification.[24]

The main goal of this study was to evaluate the potential of PCASL to identify splenic switch-off in rest-stress adenosine perfusion studies and to validate the technique against first-pass imaging in patients with suspected CAD. To realize this goal, we first aimed to assess the feasibility of using PCASL to image splenic perfusion in healthy volunteers and to determine the most appropriate postlabeling delay to be used in single-delay measurements.

Materials and Methods

Written informed consent was obtained from all participants (i.e. healthy volunteers and patients) prior to the study, which was approved by the Institutional Ethics Committee.

Subjects

Between October 2021 and April 2022, healthy subjects and patients were prospectively recruited for this study. General inclusion criterion was age greater than 18 years. Additional inclusion criteria for patients were suspicion of CAD (defined as symptoms suggestive of ischemia) and being scheduled for a stress/rest first-pass cardiac MRI examination. General exclusion criteria were contraindications for MRI and splenectomy. Additional exclusion criteria for healthy subjects were clinical history of cardiovascular disease, cardiovascular risk factors (diabetes, obesity, and high blood pressure), hematological disorders, inflammatory conditions and viral infections that could affect the spleen, and unhealthy behaviors (physical inactivity and smoking). Screening was performed by reviewing the medical records of the subjects, prior to inclusion in the study. In addition, images obtained from healthy subjects were reviewed by a radiologist and no incidental findings were found. Patients were asked to refrain from caffeine for 12 hours prior to the MRI scan.

MRI Acquisition

Data acquisition was performed in a 1.5-T Aera scanner (Siemens Healthineers, Erlangen, Germany) using 32-channel spine and 18-channel body array coils.

For healthy subjects, multi-delay PCASL images were acquired in a single axial slice located approximately at the middle section of the spleen. As shown in Fig. 1, the inversion plane was oriented as perpendicularly as possible to the descending aorta and below the heart, in order to avoid labeling of blood inside the left ventricle. The PCASL sequence consisted of six PLDs (500, 700, 1000, 1200, 1500, and 2000 msec), with a labeling duration of 1600 msec, 90% background suppression, and a spin echo–echo planar imaging readout.[25] Further imaging parameters were as follows: matrix

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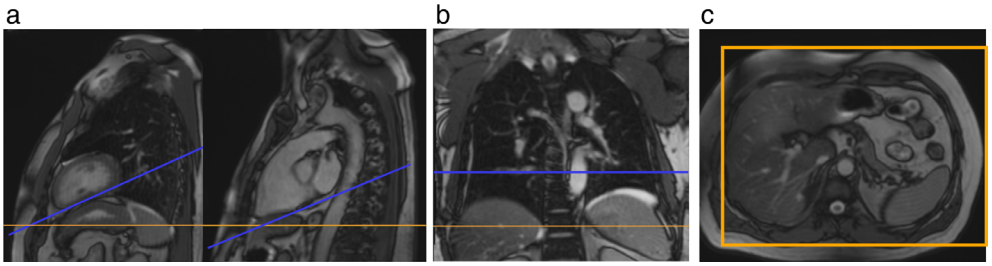

FIGURE 1: Planning of pseudo-continuous arterial spin labeling (PCASL). The labeling plane is shown in blue and the image plane in orange in (a) sagittal, (b) coronal, and (c) axial orientations.

size = 96 × 96, field of view (FOV) = 280 × 280, slice thickness = 10 mm, GRAPP-2, repetition time (TR)/echo time (TE) = 4000/24 msec, flip angle = 90°, and posterior–anterior phase encoding. Fifty label-control images per PLD and a proton density (M_0) image, used for quantification purposes, were acquired. No respiratory triggering was used, but subjects were instructed to synchronize their breathing to the sequence sounds to minimize respiratory motion by acquiring images at the expiratory phase.

For patients, rest-stress single-delay PCASL sequences were added to the clinical protocol prior to the acquisition of first-pass images to avoid the T1 reduction effects caused by gadolinium, as shown in Fig. 2. A PLD of 1200 msec was selected to ensure PLD > ATT, based on the results in healthy subjects. Respiratory triggering was used to minimize motion effects. During rest, M_0 and 30 label-control images were acquired in a scan time of approximately 3 minutes. During stress, the PCASL sequence was initiated with adenosine infusion and stopped before the first-pass sequence. The perfusion protocol included electrocardiogram (ECG)-triggered stress-rest first-pass sequences to acquire basal, mid-ventricular, and apical short-axis images of the heart during free breathing. A gadolinium dose of 0.075 mmol/kg (Gadoterate meglumine, Dotarem 0.5 mmol/mL, Guerbet, Paris, France) was used. The adenosine infusion (Adenoscan 30 mg/10 mL, Sanofi, Barcelona, Spain) was initiated using the standard dosage (140 µg/kg/min) and increased to 180 µg/kg/min whenever there was not a 10-bpm increase in patient heart rate during the subsequent 3–4 minutes. Heart rate and adenosine side effects were recorded during the study. Finally, late gadolinium enhancement (LGE) images were acquired. Imaging parameters and details of the clinical evaluation of myocardial images can be found in Supplementary Material (section S2).

Perfusion Quantification

The PCASL images were preprocessed as described in Supplementary Material (section S1, Figure S1) in less than 1-minute execution time per patient considering both rest and stress sequences.

For healthy volunteers, temporal SNR (tSNR) was computed as the ratio of the mean perfusion-weighted signal to the temporal standard deviation, to assess the temporal fluctuations of the ASL signal. The SBF and ATT were calculated by fitting the data to the Buxton kinetic model[24]:

$$(\mathrm{SI_C}-\mathrm{SI_L}) = \begin{cases} 0 & \text{if } 0 < \tau + \mathrm{PLD} < \mathrm{ATT} \\ \dfrac{2\alpha T1_b}{6000\lambda} M_0 \mathrm{SBF} e^{\frac{-\mathrm{ATT}}{T1_b}} \left(1 - e^{\frac{-(\tau+\mathrm{PLD}-\mathrm{ATT})}{T1_b}}\right) & \text{if } \mathrm{ATT} < \tau + \mathrm{PLD} < \tau + \mathrm{ATT} \\ \dfrac{2\alpha T1_b}{6000\lambda} M_0 \mathrm{SBF} e^{\frac{-\mathrm{PLD}}{T1_b}} \left(1 - e^{\frac{-\tau}{T1_b}}\right) & \text{if } \tau + \mathrm{ATT} < \tau + \mathrm{PLD} \end{cases} \quad (1)$$

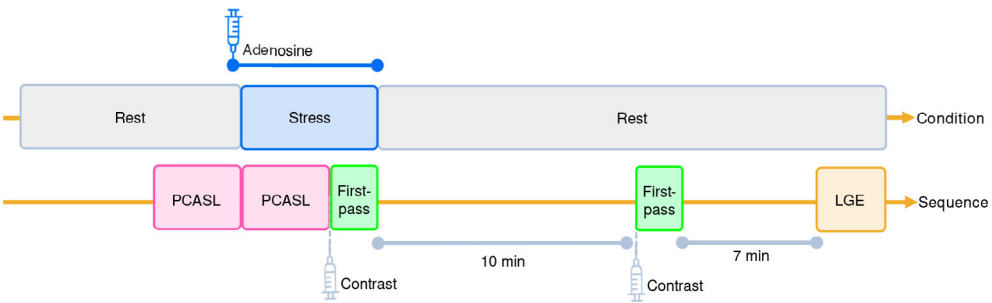

FIGURE 2: Cardiac MRI protocol timeline. Rest-stress PCASL images were acquired followed by stress-rest first-pass images and late gadolinium enhancement (LGE).

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where ($SI_C - SI_L$) is the signal difference between control and label scans for each PLD, $\alpha = 0.6$ is the labeling efficiency, considering a PCASL efficiency of 0.70 and the effect of two background suppression pulses,[25] $\lambda = 0.9$ mL/g is the tissue-blood water partition coefficient, $T1_b = 1480$ msec is the longitudinal relaxation time of blood at 1.5-T,[26] M_0 is the baseline image signal, and $\tau = 1600$ msec is the labeling duration. A single-delay quantification was also performed using the 1200 msec PLD data and equation [1] under the last condition.

For patients, SBF maps were calculated from the single-delay data as previously described for healthy subjects and mean splenic SBF values were obtained. Then, stress-to-rest SBF ratios were computed to evaluate splenic switch-off. In first-pass data, semi-quantitative perfusion quantification was performed in both myocardial and splenic tissue in one short-axis slice where the spleen could be observed. Two regions of interest (ROIs) were manually drawn over a single high-contrast intensity image slice, one over the entire spleen and another covering healthy tissue in the anterolateral myocardial segment (i.e. no ischemic or infarcted tissue was included), to generate time-intensity curves. The ROI delineation was performed by one researcher (S.S-B with 4 years of experience working in cardiac MRI). These curves were filtered with a moving average filter (smoothing factor = 0.05) and the maximum value after contrast administration was selected. This peak value was normalized by subtracting the baseline signal obtained by averaging the intensity values of the images acquired prior to the arrival of contrast to the tissue. The normalized peak values were used as semi-quantitative measurements of cardiac and splenic perfusion. Finally, stress-to-rest intensity ratios were computed as measures of splenic and myocardial perfusion reserve.

Visual Assessment

Three observers (two radiologists: G.B. with 18 years of experience, A.E. with 6 years of experience and 1.5 years of experience in evaluating brain ASL studies; and a cardiologist with special dedication to advanced cardiac imaging: M.P. with 4 years of experience), visually evaluated rest and stress perfusion images obtained with PCASL and first-pass independently to classify patients in "switch-off" or "failed switch-off" categories. Patients with a visual attenuation of splenic perfusion between rest and stress images were classified as having experienced switch-off. In first-pass, this attenuation was evaluated in one short-axis slice, where both myocardium and splenic tissue could be observed. In PCASL images, SBF maps were visually compared using the M_0 image as anatomical reference.

Statistical Analysis

Statistical analyses were performed using Matlab (R2020b, Mathworks, Natick, MA) and RStudio (version 1.4.1106; RStudio Team, Boston, MA). Shapiro–Wilk tests were used to assess data normality. Continuous data were presented as either mean (standard deviation) for normal variables or median (interquartile range) for variables that did not follow a normal distribution. Categorical data were expressed as the number of subjects (percentage). The level of statistical significance was set at $P < 0.05$.

In healthy subjects, differences in multi and single-delay SBF measurements were evaluated using a Wilcoxon signed-rank test. In patient data, correlations between PCASL and first-pass techniques were evaluated using Pearson correlation coefficients for splenic perfusion measurements and stress-to-rest ratios. Analyses of differences between rest and stress splenic and myocardial perfusion measurements were performed using Wilcoxon signed-rank tests. Splenic stress–to-rest ratios were compared to those obtained in the myocardium using a Wilcoxon signed-rank test. Inter-observer and inter-technique agreement in the visual assessment of splenic switch-off was evaluated using Fleiss Kappa (κ) and interpreted according to the following guidelines: <0 = less than chance agreement, 0.01–0.20 = slight agreement, 0.21–0.40 = fair agreement, 0.41–0.60 = moderate agreement, 0.61–0.80 = substantial agreement and 0.81–0.99 = almost perfect agreement.[27] In addition, percentage agreement scores were also computed as (agreements/(agreements + disagreements)) × 100%. Furthermore, to simultaneously study the agreement between ASL and first pass techniques among the three raters, a binomial generalized linear mixed model (GLMM)[28] was implemented with the visual classification (switch off–failed switch off) as dependent variable, three explanatory factors: technique (with two levels), rater (with three levels) and subject (to account for repeated measurements) and an interaction term between method and rater.

The classification obtained from the first-pass visual assessment into patients with "switch-off" or "failed switch-off" categories (using majority voting in the cases of disagreement) was used as reference standard for subsequent analysis. Differences in demographic, clinical, and imaging parameters between both groups were assessed using Mann–Whitney U tests for the continuous variables and Pearson Chi-squared tests for categorical variables. Receiver operating characteristics (ROC) curves were computed together with the area under the curve (AUC) to identify the optimal quantitative threshold for detecting the presence of switch-off using the Youden Index. A confusion matrix was computed to compare the classification performance of PCASL and first-pass using the optimal threshold, and sensitivity, specificity, and accuracy (computed as the ratio of correct predictions to total predictions) were obtained. Splenic switch-off was considered as true positive and failed switch-off as true negative.

Results

Healthy Subjects

Five subjects (1 female, mean age 24.8, SD 3.8, range 21–29 years) were scanned. Multi-delay PCASL yielded perfusion images for each PLD (Fig. 3a), with a group mean splenic perfusion signal of 1.45% for the 500 msec PLD, which increased to a maximum value of 1.59% for the 1000 msec PLD and decreased for longer PLDs (Fig. 3b). Although the group mean maximum perfusion signal was detected for a PLD of 1000 msec, individual curves peaked at other PLDs (from 700 to 1200 msec). Mean tSNR values were 1.65 (PLD = 500 msec), 4.21 (PLD = 700 msec), 2.85 (PLD = 1000 msec), 2.38 (PLD = 1200 msec), 2.68 (PLD = 1500 msec), and 2.33 (PLD = 2000 msec). Fitting the multi-delay data allowed to simultaneously obtain SBF values of 137.6 mL/100 g/min (SD: 26.2, range 98.9–162.7 mL/100 g/min) and ATT values of 735.4 msec (SD: 481.2 msec, range = 0.3–1.2 msec).

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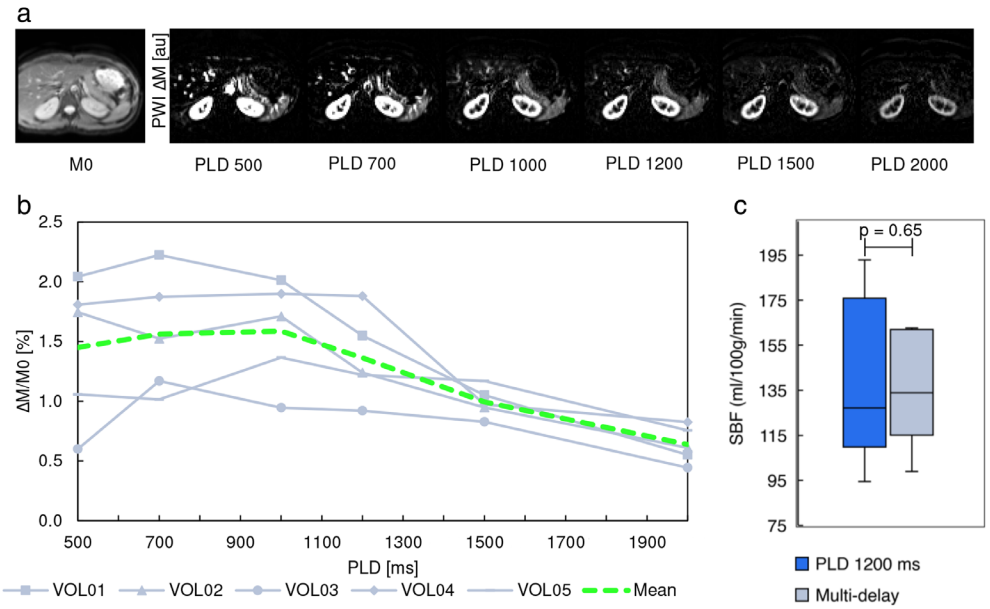

FIGURE 3: Splenic perfusion measurements in healthy subjects. (a) M_0 and perfusion-weighted images (PWI) obtained for each PLD in a representative subject. (b) Perfusion signal (DM) normalized by the M_0 signal per PLD and per subject. (c) Boxplots of SBF computed from the single-delay (PLD of 1200 msec) and multi-delay data.

A PLD of 1200 msec was selected for the single-delay analysis (to ensure PLD > ATT and thus complete delivery of labeled blood to tissue), which yielded SBF values of 139.7 mL/100 g/min (SD: 37.5, range 94.4–192.9 mL/100 g/min). No significant differences were observed between SBF values derived from single and multi-delay data ($P = 0.65$) (Fig. 3c).

Patients

COHORT CHARACTERISTICS. Forty patients were recruited for the study. In three patients, the study was interrupted due to reported discomfort. In one patient, PCASL data were not acquired because it was not possible to position the labeling plane correctly. In two patients, the spleen was not visible in first-pass data. Thus, complete data were obtained in 34 patients. From these, two were removed during preprocessing due to excessive motion during the PCASL acquisitions. In summary, 32 patients were included in the analysis (10 female, mean age 66.4, SD 8.2, range 46–78 years). In two patients, the adenosine dose was increased to 180 µg/kg/min due to the absence of hyperemic effect. Demographic and clinical data are included in Table 1.

PCASL SPLENIC PERFUSION MEASUREMENTS. Adequate SBF maps were obtained for 32 patients. Figure 4 shows quantitative perfusion maps for two representative patients. Group mean SBF values were 105.3 mL/100 g/min (SD: 56.8 mL/100 g/min) at rest and 57.9 mL/100 g/min (SD: 54.2 mL/100 g/min) under stress, a difference that was statistically significant. The mean stress-to-rest SBF ratio was 0.5 (SD: 0.3). Furthermore, tSNR was 1.5 (SD: 1.4) at rest and 0.3 (SD: 0.4) under stress.

FIRST-PASS SPLENIC AND MYOCARDIAL PERFUSION MEASUREMENTS. Figure 5 shows first-pass splenic time-intensity curves together with the images obtained at the peak of the curve for two representative patients with and without splenic switch-off. In the spleen, group peak perfusion was 181.5 [a.u.] (SD: 65.2) at rest and 89.2 [a.u.] (SD: 44.6) under stress, and mean peak intensity stress–to-rest ratio was 0.5 (SD: 0.4). In the myocardium, mean peak perfusion was 115.5 [a.u.] (SD: 32.4) at rest and 158.6 [a.u.] (SD: 60.9) under stress, and mean myocardial perfusion reserve was 1.4 (SD: 0.3).

COMPARISON BETWEEN PCASL AND FIRST PASS. Figure 6a shows boxplots of rest and stress splenic perfusion measurements. No significant differences ($P = 0.58$) were found in the splenic ratios measured by first-pass and PCASL, but these ratios were significantly lower than those obtained in the myocardium (Fig. 6b). Figure S2 shows PCASL and first-pass correlations of perfusion measurements ($r = 0.48$) and stress-to-rest ratios ($r = 0.41$).

ASSESSMENT OF SPLENIC SWITCH-OFF. Splenic switch-off occurred in 84.4% of patients (27/32 patients, included the two patients who received an increased adenosine dose), according to the first-pass visual assessment performed by the radiologists ($\kappa = 0.916$, almost perfect interobserver agreement and 96.9% agreement). Demographic and clinical data per group can be found in Table 1.

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TABLE 1. Demographic and Clinical Data

		All Patients ($n = 32$)	First-Pass Visual Assessment Classification		P Value
			Splenic Switch-Off ($n = 27$)	Failed Switch-Off ($n = 5$)	
Demographic and clinical data					
	Age (years), mean (SD)	66.4 (8.2)	67.2 (7.6)	61.8 (10.8)	0.177
	Male gender, *n* (%)	22 (69)	19 (70.4)	3 (60)	0.646
	Heart rate preadenosine administration (beats per minute), mean (SD)	64.3 (10.1)	64.9 (10.7)	61.4 (6.15)	0.487
	Heart rate postadenosine administration (beats per minute), mean (SD)	81.8 (12.9)	82.2 (12.8)	79.40 (14.8)	0.661
Cardiac MRI findings					
First pass and LGE	Ischemia, *n* (%)	7 (22)	7 (26)	0 (0)	0.198
	Necrosis, *n* (%)	18 (56)	16 (59)	2 (40)	0.425
	Myocardium stress/rest ratio, median [IQR]	1.3 [1.2–1.5]	1.3 [1.2–1.47]	1.26 [1.25–1.41]	0.897
	Spleen stress/rest ratio, median [IQR]	0.48 [0.3–0.7]	0.43 [0.2]	1.04 [1.0–1.1]	**<0.001**
PCASL	Rest SBF (mL/100 g/min), median [IQR]	80.6 [69.9–139.8]	76.6 [67.5–135.7]	100.1 [76.0–147.5]	0.337
	Stress SBF (mL/100 g/min), median [IQR]	47.9 [20.3–63.4]	46.4 [18.3–54.9]	114.9 [74.2–147.7]	**0.015**
	Spleen stress/rest ratio, median [IQR]	0.39 [0.33–0.74]	0.38 [0.3–0.7]	1.03 [1–1.24]	**0.014**

Quantitative variables are reported as mean (SD) or median (interquartile range [IQR]) expressed as [quartile 1 – quartile 3]. Qualitative variables are reported as number of subjects (percentage). Statistically significant P values are indicated in bold (level of statistical significance: $P < 0.05$).
n = number of subjects; PCASL = pseudo-continuous arterial spin labeling; LGE = late gadolinium enhancement; SBF = splenic blood flow.

Visual assessment of splenic switch-off from PCASL data showed a strong interobserver agreement ($\kappa = 0.878$ and 93.8% percentage agreement) with concordance among the three observers in 30 of 32 cases. Results from visual assessment are presented in Fig. 7. Intertechnique agreement was fair ($\kappa = 0.23$ and 78.7% percentage agreement). The results of the GLMM estimation showed that the difference between techniques was nonsignificant (estimate = 1.3261, SE = 0.9800, z-value = 1.253, P value = 0.176), indicating that the two techniques may be used interchangeably.

Figure 8a shows ROC curves for the discrimination between splenic switch-off and failed switch-off for first-pass and PCASL stress-to-rest perfusion ratios. First-pass ROC analysis yielded a cut-off of 0.74. Classification results using this threshold were in full accordance with those obtained by visual assessment (sensitivity = 100%, specificity = 100%, AUC = 100%). For PCASL, the optimal a cut-off was 0.96 (sensitivity = 80%, specificity = 100%, AUC = 85.2%).

Figure 8c shows the confusion matrix obtained comparing PCASL (cut-off = 0.96) with first-pass (cut-off = 0.74) classifications, considering the latter as reference standard, which was in total agreement with first-pass visual assessment, as indicated above. This analysis resulted in a total number of 27 true positives, 4 true negatives, 1 false positive, and 0 false negatives. From this evaluation, PCASL showed a sensitivity of 100%, specificity of 80%, and an accuracy of 97%.

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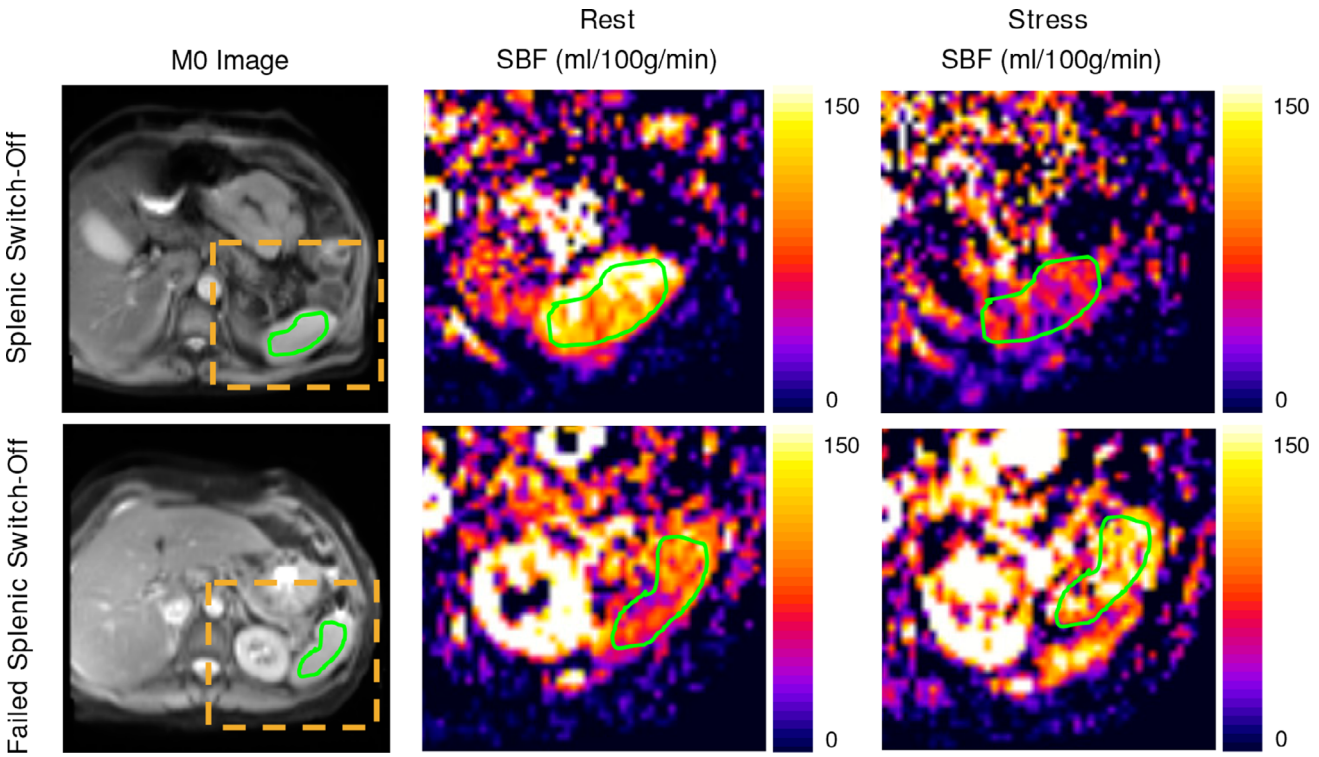

FIGURE 4: PCASL SBF maps obtained during rest and stress in two patients with splenic switch-off (top) and failed switch-off (bottom). M_0 image is presented for anatomical reference. The splenic region of interest is depicted in green.

Discussion

The results of this study could demonstrate the potential of PCASL to quantify splenic perfusion and assess splenic switch-off following adenosine administration in patients with suspected CAD undergoing perfusion cardiac MRI. Classification results obtained with the optimal cut-off in the semi-quantitative first-pass analysis were in full accordance with those achieved by visual assessment. Quantitative PCASL with the optimal threshold showed high agreement with first pass and a diagnostic accuracy of 97%.

Multi-delay PCASL was feasible in healthy subjects, with measured splenic perfusion being in agreement with previously reported values.[18] The achieved tSNR, which is a measure of the signal temporal fluctuations that can be attributed to physiological noise and motion, was in agreement with results obtained in other abdominal organs.[29] In addition, a PLD of 1200 msec appeared to be optimal for quantification of SBF using single-delay data and was thus used for PCASL acquisitions in patients with suspected CAD.

In the patient studies, respiratory triggering was used because of the difficulty of training patients to synchronize their breathing with the sequence sounds, especially in stress conditions. The total number of acquired images was lower than in healthy subjects because the time available for image acquisition after adenosine infusion was limited. The inclusion of rest-stress PCASL sequences in the conventional cardiac MRI perfusion protocol was successful in the majority of patients (only in one patient data could not be acquired due to the difficulty of positioning the labeling plane and two other datasets were discarded due to motion). The acquisition of stress PCASL images was started right after the initiation of adenosine infusion, which might have led to a certain number of images being acquired prior to the hyperemic peak. Thus, PCASL could have underestimated the stress-to-rest perfusion ratio, especially in patients with a late adenosine stress effect. In future studies, the optimal time to start the stress acquisition should be investigated. At rest, tSNR was lower than that measured in the healthy subjects for the same PLD, which might be related to lower perfusion and higher degrees of motion in patient data despite the use of respiratory triggering. Moreover, tSNR further decreased under stress, most probably due to the lower splenic perfusion and increased motion caused by patient discomfort. Rest SBF in patients was lower than in healthy volunteers, which could be attributed to age or health condition.

According to the visual assessment of first-pass perfusion images, the proportion of patients with splenic switch-off was similar to the 90% and 89%,[9,12] but slightly higher than the 72% and 74%[10,11] reported in other studies This higher proportion could be explained because the adenosine dose was increased in case of heart rate increments lower than 10 bpm or no reported symptoms. This is in agreement with a prior study reporting that a 175 μg/kg/min dose of adenosine resulted in a higher proportion of patients with splenic switch-off.[15] Nevertheless, the specific dose to use for stress studies is still controversial. It has been shown that a higher

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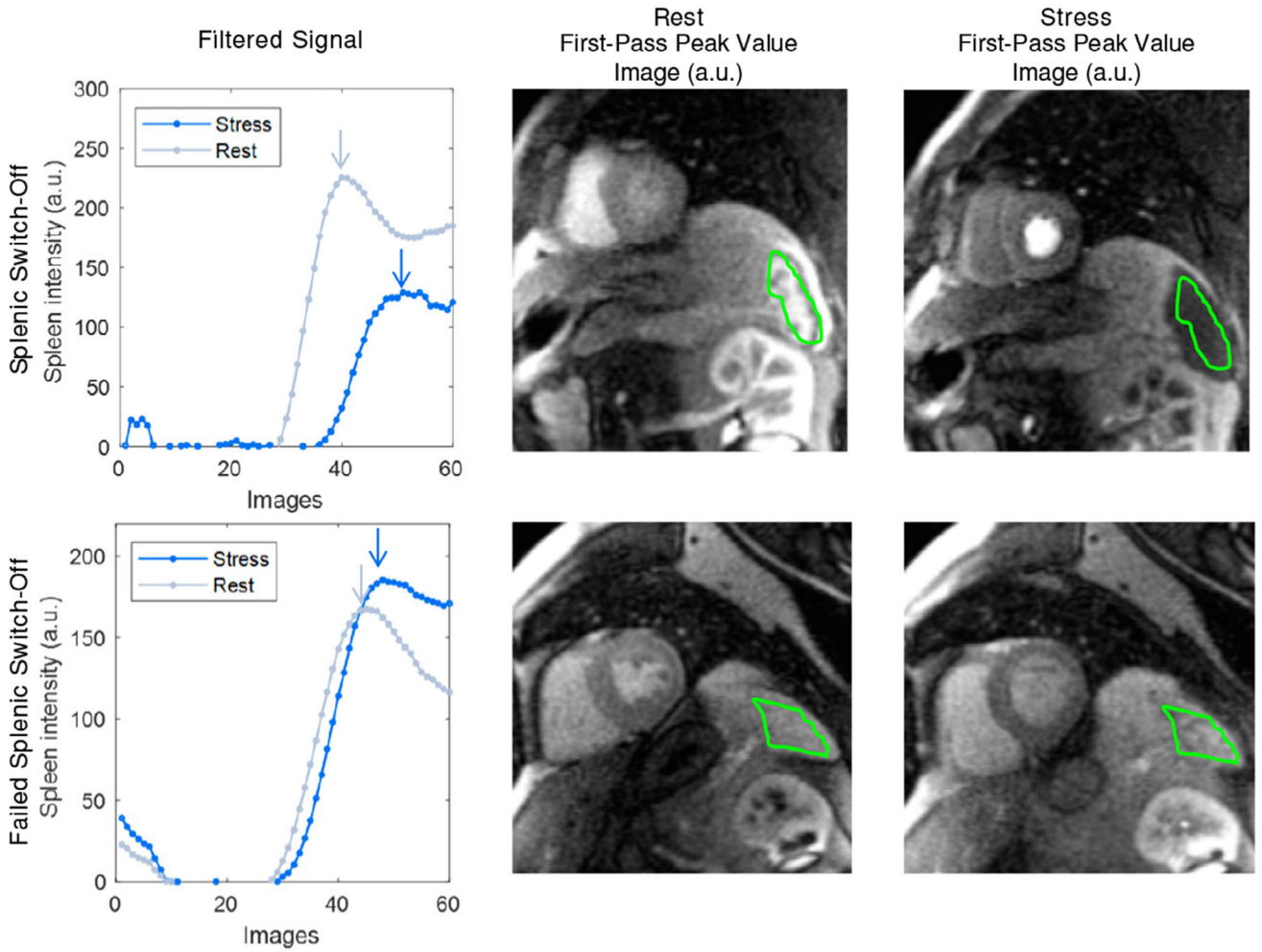

FIGURE 5: Signal intensity time courses obtained from first-pass images during rest (grey) and stress (blue) in two patients with splenic switch-off (top) and failed switch-off (bottom). Arrows indicate the peak value image in rest and stress acquisitions. ROIs used to measure signal intensity values that are shown in green, in the peak value images.

dose improves the peripheral hemodynamic response to adenosine, but it does not induce higher coronary vasodilation.[30] Visual assessment of splenic switch-off from first-pass images yielded higher interobserver agreement than that obtained with PCASL. This could be related to the fact that the PCASL technique is not common practice in the clinical routine. Specific training, such as visualization of a battery of representative SBF maps of splenic switch-off and failed switch-off cases, might further improve the qualitative diagnostic value of PCASL perfusion images.

Stress-to-rest splenic ratios measured with both PCASL and first-pass were significantly lower than those obtained in the myocardium. This supports the idea that splenic perfusion is attenuated with adenosine stress in comparison to myocardial perfusion.[11] Five patients, however, did not experience splenic switch-off. From these, one showed the lowest myocardial perfusion reserve, which could be an indicator of not being properly stressed. Other reasons to explain failed switch-off might include receptor variability.[11] Similar average splenic stress-to-rest ratios were obtained for both PCASL and first-pass images, which were significantly different between patients with and without splenic switch-off. In addition, a moderate but significant correlation was observed between both techniques, which is lower to that found between first-pass and T1 mapping ($r = 0.7$),[16] probably due to the smaller sample size of this study.

The ROC analysis yielded an optimal cut-off value for the detection of splenic switch-off using first-pass stress-to-rest ratio that was similar to the one calculated by Patriki et al (0.71),[12] although lower cut-offs have also been reported in the literature.[13,14] With PCASL, the cut-off that maximized sensibility and specificity was slightly higher than the one obtained for first-pass images. Further studies with a larger number of patients are needed to confirm the specific value. The diagnostic performance of PCASL yielded a sensitivity and accuracy that was superior to the 90% sensitivity and 90% accuracy obtained with T1 mapping.[16] However, lower specificity for PCASL was observed when compared to the reported 88% for T1 mapping.[16] Nevertheless, the high sensitivity of PCASL (no false-negative findings) suggests that it would be optimal to detect all patients with failed switch-off.

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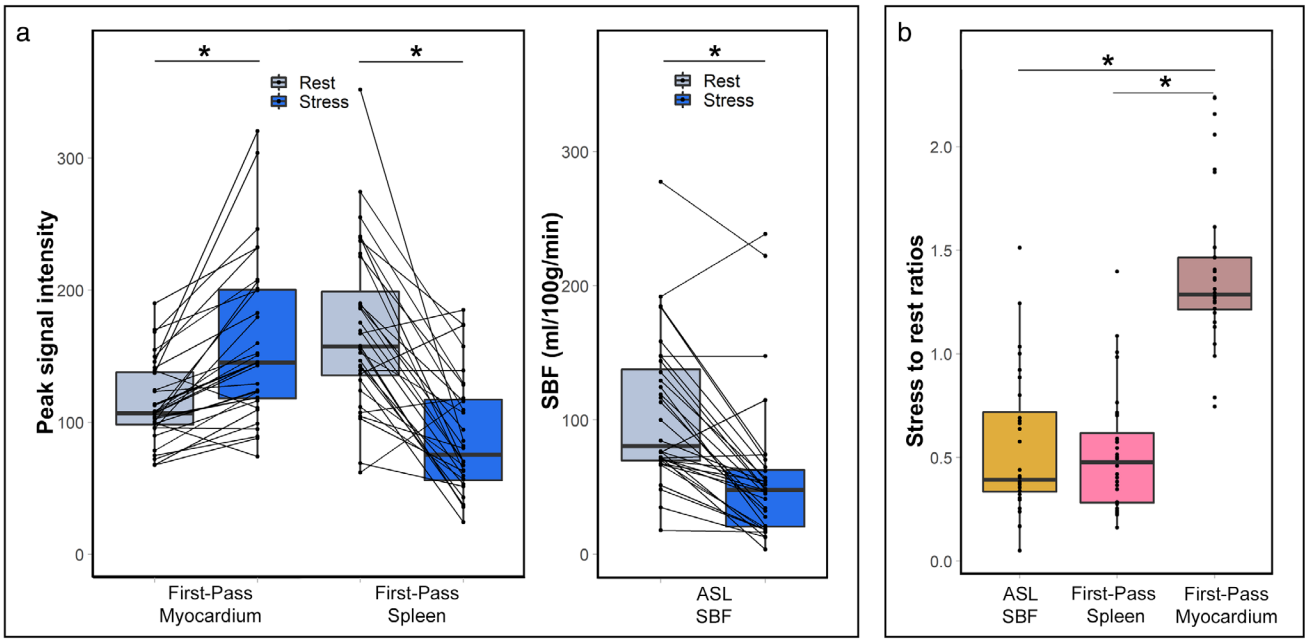

FIGURE 6: Splenic and myocardial perfusion measurements and stress to rest ratios. (a) Boxplots of splenic and myocardial perfusion measurements obtained with first-pass and PCASL. The paired data points are connected with lines. (b) Boxplots of stress to rest ratios. *Denotes statistically significant differences ($P < 0.001$).

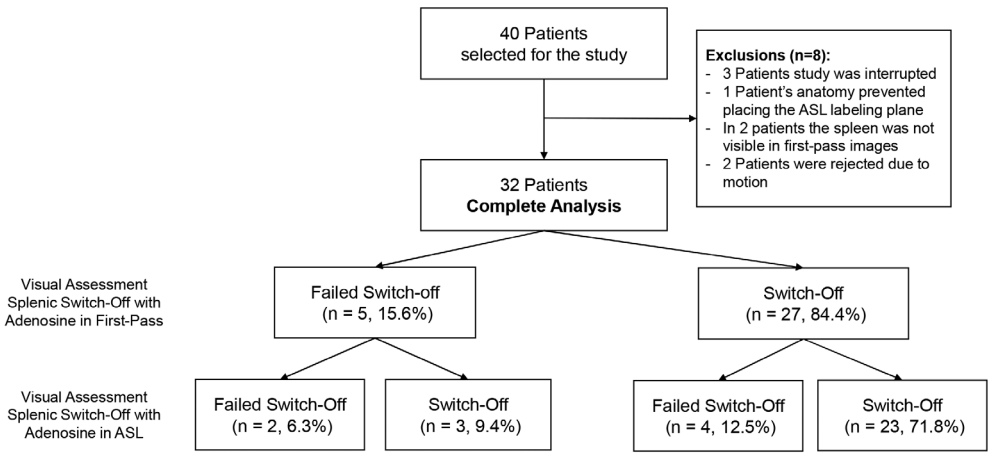

FIGURE 7: Classification results into splenic switch-off and failed switch-off groups obtained from visual assessment.

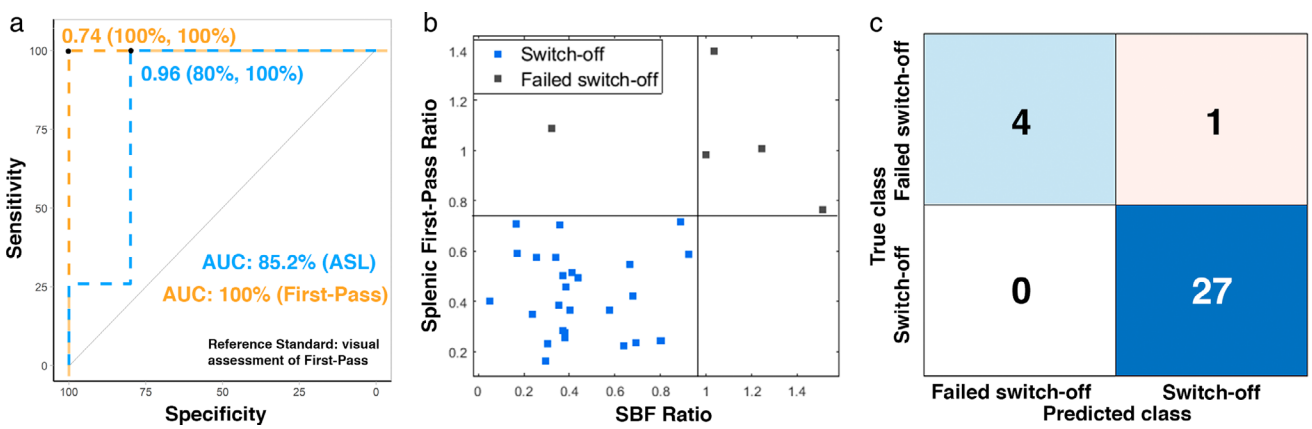

FIGURE 8: Splenic perfusion measurements obtained considering all patients. (a) Receiver-operator characteristic curve curves (in orange for first-pass and in blue for PCASL) for the detection of splenic switch-off. (b) Scatter plot of stress-to-rest ratios, where the vertical and horizontal lines indicate the PCASL and first-pass cut-off values, respectively. (c) Confusion matrix for classification using first-pass as ground truth.

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Limitations

This was a single-center study, with a small number of subjects, performed to evaluate the feasibility of using PCASL to assess splenic switch-off with adenosine. Validation studies should be performed including other pharmacological agents, known not to cause splenic switch-off (such as regadenoson or dobutamine). In addition, larger studies are required to assess the potential of PCASL to detect false-negative myocardial perfusion scans. Patients with ischemia and necrosis were not excluded from the analysis. However, perfusion was quantified from a normally perfused myocardial segment and not from the entire myocardium, to minimize the impact on the results.

Conclusion

This study could demonstrate the feasibility of using PCASL to identify splenic switch-off during adenosine stress cardiac MRI in patients with suspected CAD.

Conflicts of Interest

Marta Vidorreta is an employee of Siemens Healthineers in Spain. The authors have no other conflicts of interest to declare.

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