Adenosine Triphosphate (ATP)- A Safe and Effective Vasodilator for Stress Perfusion Cardiac Magnetic Resonance

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Research Article

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Abstract

Purpose

The aim of this study was to evaluate the efficiency and safety of adenosine triphosphate (ATP) as a stress agent in a cohort of patients undergoing stress perfusion cardiac magnetic resonance imaging (CMR).

Methods

This retrospective study was conducted between December 2019 and October 2021 at the Beijing Friendship Hospital, Beijing, China. The study included 107 subjects (age range: 53±11 years; male: female, 62%:38%) with suspected non-obstructive coronary artery disease (NOCAD) that underwent stress CMR. These patients showed typical symptoms such as chest pain (stable and unstable angina pectoris) and <50% epicardial coronary artery stenosis based on coronary angiography. Adverse effects and splenic switch-off (SSO) phenomenon was evaluated in the patients undergoing stress CMR. Moreover, qualitative and semi-quantitative analysis of inducible ischemia was performed by using stress CMR data.

Results

The qualitative and semi-quantitative analysis of stress CMR data showed 82 patients with reversible myocardial ischemia. The hemodynamic response was quick and observed within 2 minutes after ATP infusion. Scanning was stopped in three patients because of atrioventricular block. CMR images of seven out of 104 patients were excluded from the final analysis because of inferior quality. During ATP infusion, 31/107 patients (29%) experienced mild adverse effects such as chest pain, flushing, dyspnea, headache, and atrioventricular block. Myocardial infarction and bronchospasms were not observed during ATP infusion. SSO, a marker of adequate stress, was observed in 91% (94/103) of the patients that underwent stress CMR.

Conclusion

ATP is highly effective and safe to use in stress CMR as a coronary vasodilator.The hemodynamic response is observed within 2 minutes after ATP infusion.The adverse effects during ATP infusion were mild. SSO was observed in 91% of the patients undergoing stress CMR.

Introduction

Stress perfusion cardiac magnetic resonance (CMR) is a non-invasive imaging modality that detects coronary stenosis and impaired blood flow reserve in coronary artery disease (CAD)with high sensitivity,

specificity, and accuracy[1–4]. Moreover, stress CMR shows excellent prognostic characteristics and is effective in risk stratification of patients with known or suspected CAD[5–8]. The American College of Cardiology Foundation and the American Heart Association have recommended stress perfusion CMR for evaluation of symptomatic patients that show intermediate or high pre-test probability for CAD [9, 10]. Exercise or pharmacologic drugs are two methods to induce myocardial stress perfusion. Exercise is not clinically used yet for inducing cardiac muscle stress while performing stress perfusion CMR. However, vasodilators and positive inotropic drugs including adenosine are used to induce cardiac stress. Adenosine triphosphate (ATP), a phosphorylation product of adenosine, also demonstrates vasodilatory and hemodynamic properties similar to adenosine[11, 12]. Moreover, it has been commonly used in countries of the Asian Pacific region because of its low cost [12]. However, the safety and stress effects of ATP are not fully known. Therefore, in this study, we evaluated the stress effects and safety of ATP as a cardiac stress agent using stress CMR.

Methods

This study was approved by Ethics committee of the Capital Medical University. All patients signed written informed consent forms at enrollment. Figure 1 shows the study flowchart and exclusion criteria of patients. In this retrospective study, 107 patients were enrolled between December 2019 and August 2021 at the Beijing Friendship Hospital, Beijing, China. The inclusion criteria were (1) patient age ≥18 years and (2) myocardial ischemia was suspected because of chest pain (stable and unstable angina pectoris) and diagnosis of non-obstructive coronary artery disease (NOCAD) according to coronary angiography data (epicardial coronary artery stenosis <50%). The exclusion criteria included acute coronary syndrome, primary cardiomyopathy (hypertrophic, dilated, and restrictive), primary severe valvular heart disease, restrictive pericardial disease, severe arrhythmia, history of allergy to gadolinium contrast agents and ATP, and severe renal dysfunction (glomerular filtration rate 30 mL/min/1.73m^2).

Stress CMR protocol

Stress CMR was performed on a MAGNETOM Prisma 3T MR scanner (Siemens Healthcare, Erlangen, Germany) equipped with an 18-element body matrix coil and a 32-element spine array coil. All images were acquired during breath-holding with mild expiration and electrocardiographic triggering. The S-CMR examination included three components: (1) cine imaging for examining the regional left ventricular (LV) wall motion; (2) stress and rest perfusion imaging for detecting ischemia; and (3) late gadolinium enhancement (LGE) imaging for detecting myocardial infarction and/or scar. The total scan duration was 40 minutes. After locating the heart, patients were infused with ATP at a rate of 0.16 mg/kg/min for approximately 2 min.Observe if the heart rate increased ≥10 beats per minute (bpm) or systolic blood pressure decreased ≥10 mmHg (hemodynamic response). This was followed by an intravenous administration of gadolinium at the rate of 3 to 4 mL/s and subsequent 30 mL saline flush at the same flow rate. Perfusion imaging was performed by T1 weighted fast gradient echo sequence with the following settings: repetition time (TR)/echo time (TE) = 2.1/1.03 ms; inversion time (TI) = 100 msec;

temporal resolution = 155.7 msec; flip angle (FA) = 10°; voxel size = 1.9×1.9×8.0 mm^3. Three short-axis slice images (base, middle, and apex) of the left ventricle were acquired. Then, balanced steady-state free precession (bSSFP) cine images were acquired with the two-, three- and four-chamber long-axis and short-axis views covering the whole left ventricle based on the following settings: TR/TE = 3.3/1.43 msec, temporal resolution = 40 msec, FA = 50°; voxel size = 1.6×1.6×8.0 mm^3. Rest perfusion images were acquired at least 10 min after terminating ATP infusion in the same three short-axis view positions as the stress perfusion images. LGE images were acquired using the phase-sensitive inversion-recovery (PSIR) gradient-echo pulse sequence with the following settings: TR/TE/FA, 5.2 msec/ 1.96 msec/20°; TI = 300 msec; voxel size, 1.4 × 1.4 × 8.0 mm^3.

Stress CMR data analysis

The data variables are represented as mean±standard deviation, median± interquartile range, or percentages.All images were analyzed using the cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). Poor quality images or incomplete data were excluded from the analysis. The presence of ischemia was evaluated by segmental analysis of stress perfusion images, which were recorded in 16 segments (the apical segment is typically not in the field of view) and based on the American Heart Association 17-segment model[13]. Standardized methods were used to analyze myocardial perfusion, left-ventricular volume, function, and mass[14]. The criteria for confirming a stress perfusion defect were as follows: (1) a transmural gradient across the wall thickness of the segment, with the most dense section in the endocardium; (2) defect persisted beyond the peak myocardial enhancement for several R-R intervals; and (3) conformed a coronary arterial distribution. Inducible ischemia was defined as the presence of a stress perfusion defect and absence of matching LGE in≥1 segment that persisted for≥6 beats [15, 16]. Semi-quantitative myocardial perfusion was analyzed by manually tracing contours around the endocardium and epicardium to determine the left ventricular myocardial signal intensity (SI). The myocardial perfusion reserve index（MPRI）was calculated by dividing the results at maximal vasodilation with the results at rest [17].

Splenic switch-off

Splenic perfusion was visually analyzed by comparing the stress and rest perfusion images of each patient. All scans were analyzed by two independent observers for the presence of splenic switch-off (SSO, see Fig 3). In the rest perfusion image, the splanchnic circulation is vasodilated. After injecting ATP, splanchnic vasoconstriction is observed. The spleen shows reduced signal intensity during gadolinium contrast administration compared to the resting perfusion image [18-21]. SSO is a graded and transitory response that can be assessed visually by comparing the rest and stress perfusion images. Therefore, we defined the filling of the left ventricle as time zero to ensure synchronous comparisons between the rest and stress scans[11]. Any disagreements were resolved with the help of a third experienced observer.

Results

Patient characteristics

The clinicopathologic characteristics (demographics and cardiovascular disease risk factors) and stress CMR data analysis of the 107 patients are shown in Table 1. Several patients were associated with one or more cardiovascular risk factors, such as hypertension, smoking history, hypercholesterolemia, and diabetes mellitus.

Table 1. Demographics and stress perfusion CMR data analysis in patients receiving ATP

Patient characteristics of the study population	
Demographics	
Gender (male/female)	66/41
Age (years)	53±11
HR rest (beats/min)	67±9
HR stress (beats/min)	96±16
HR increase (beats/min)	29±13
Height (cm)	167.9±7.2
Weight (kg)	72.5±13.2
Systolic blood pressure (mmHg)	127±16
Diastolic blood pressure (mmHg)	76±11
CVD risk factors	
Hypertension	49/107(46%)
Diabetes	28/107(26%)
Hypercholesterinemia	51/107(48%)
Smoker	37/107(35%)
Drinking	32/107(30%)
CMR Data	
LVEF (%)	62.3±8.2
EDV（ml）	134.9±25.8
ESV（ml）	50.8±15.9
CO(L/min)	6.7±1.5
$MASS_{ED}$（g）	100.4±37.8

The values are expressed as means±standard deviation or percentage (in brackets).HR=heart rate; CVD=cardiovascular disease;CMR=cardiac magnetic resonance;EDV=end diastolic volume;ESV=end systolic volume;LVEF=left ventricular ejection fraction;CO=cardiac output;$MASS_{ED}$=end diastolic myocardial mass.

Adverse effects of ATP infusion

During ATP infusion-induced stress, 31 patients (29%) experienced adverse effects such as chest pain, flushing, dyspnea, headache, and atrioventricular block (Table 2). Chest pain was the most frequently reported adverse effect (Table 2). Symptoms were mild and resolved shortly after receiving ATP. Myocardial infarction, bronchospasms, or other medical complications were not observed. Scanning was stopped in three patients because of atrioventricular block and low baseline heart rates.

Table 2. Frequency of adverse events associated with ATP infusion

Clinical symptoms	Frequency
No symptoms	76
Typical symptoms	
Chest pain	28
Flushing	4
Dyspnea	11
Headache	15
Others	4
Atrioventricular block	3
Supraventricular tachycardia	1

Stress perfusion CMR analysis

Out of 104 patients,we excluded data from 7 patients for the following reasons (1) gadolinium was not injected during scanning in 3 patients, (2) images of 3 patients were not first-pass perfusion, and (3) image quality was poor for 1 patient. Therefore, we performed qualitative analyses was on 97 patients, and semi-quantitative analysis was performed when the results were questionable. The fractional flow reserve (FFR) and index of microvascular resistance (IMR) were examined on 10 patients. Take IMR as a gold standard for identifying impaired myocardial perfusion reserve and MPRI=1.76 as cut off value[22]. Our analysis showed reversible myocardial ischemia in seventy-nine patients.

Splenic switch-off

Adequate splenic tissue for analysis was seen in 96% of the myocardial perfusion examinations(4 patients were excluded due to not scan the spleen).Other situations such as splenectomy should also be taken into account. Interobserver agreement for splenic switch-off was excellent.Splenic switch-off with ATP was present in 91% (91/100) of the ATP perfusion CMR studies as Figure 3.

Discussion

Our study demonstrates that ATP is a safe and potent vasodilator that can be used in stress CMR. ATP infusion was associated with fewer adverse events and demonstrated unique SSO to clearly indicate myocardial stress. Furthermore, stress CMR shows significant clinical value in accurately diagnosing patients with reversible myocardial ischemia by comparing the perfusion images captured during stress and at rest conditions.

Intravenously infused ATP is sequentially metabolized into adenosine diphosphate,adenosine monophosphate, and adenosine. Therefore, the vasodilatory effects of ATP are similar to adenosine, which activates A1 and A2 receptors [23]. Moreover, in our study, the hemodynamic response was observed within 2 minutes after injecting ATP. This was significantly shorter than previously reported for ATP [9].Thus, our research shows that ATP is a valuable stress agent because of its excellent vasodilatory properties and shorter hemodynamic response times after injection.

ATP is readily accessible and economical in China and other countries in the Asia-Pacific region compared withother stress agents. The cost of adenosine is 40 times higher than the cost of ATP. Furthermore, it is difficult to procure adenosine and other stress agents such as regadenoson because of licensing and manufacturing issues. Thus, ATP can be readily used for CMR in China and other countries in the Asia-Pacific region, provided its efficacy and safety are well established. However, compared with other commonly used agents, such as adenosine or dobutamine, the role of ATP as a stress agent in CMR is not well established. The Society for Cardiovascular Magnetic Resonance(SCMR) updated the standardized cardiovascular magnetic resonance imaging (CMR) protocols in 2020 and included ATP as a stress agent along with details regarding the injection dose and contraindications. Our study provides further evidence for using ATP in stress CMR experiments because it is cost-effective, efficient, and safe [24].

Nearly 71% of our study subjects that received ATP infusions at 0.16 mg/kg/min remained asymptomatic during the examination. Shortness of breath, chest pain, and headaches were the most common adverse effects of ATP infusion in our study and were consistent with previously reported data[11, 25]. However, these adverse effects were mild and were resolved within 5 mins after stopping ATP infusion. Previous studies [9, 26] demonstrated the feasibility and safety of increasing ATP infusion rate by 50% in patients that did not respond adequately. However, our study shows that 99% of patients were stressed with an ATP infusion rate of 0.16 mg/kg/min. Thus, our study demonstrates that ATP is a safe and clinically feasible stress agent for CMR.

The “splenic switch-off” phenomenon is used to determine stress adequacy in myocardial adenosine perfusion MR imaging [19]. SSO is a quick marker of stress adequacy and does not require the acquisition of additional measures[21]. In our study, SSO was visually observed in 91% of ATP perfusion examinations. Therefore, SSO can also assess stress adequacy during stress CMR. Splenic blood flow attenuation and SSO have not been observed when using other commonly used stress drugs, such as dobutamine and regadenoson. This provides another advantage of using ATP as a stress agent because visualization of SSO provides a clear analysis of stress adequacy.

Our study has a few limitations. First, this was a retrospective study conducted at a single center. Thus, future multi-center studies with larger cohorts are necessary to confirm our findings.Secondly,we did not follow-up with the patients after conducting stress CMR.Therefore,we did not know if major adverse cardiovascular events (MACE) had occurred in these patients.Thus,we currently lack information regarding the use of ATP as a prognostic marker of stressed patients.Thirdly,we did not compare the efficacy of other widely used vasodilator agents like adenosine or dipyridamole with ATP for stress CMR.Lastly,a few patients did not undergo FFR or IMR to confirm the presence of reversible myocardial ischemia.

In conclusion, our study shows that ATP is a potent coronary vasodilator that is safe for stress CMR. The hyperemic response to ATP is quick and comparable to adenosine. In patients undergoing stress CMR, stress adequacy can be evaluated by SSO. Further research is required to clearly establish the prognostic value of ATP in stress CMR examinations.

Declarations

Declaration of interests

The authors declare no conflict of interest.

Author’s contribution

Xiantao Song, Yi He and Jing An helped to conceive the theme and revise the manuscript. Huihui Kong participated in the research selection, data extraction, analysis, and manuscript drafting. Jiaxin Cao,Zhenchao Tang,Jingwen Yong, and Jinfan Tian contributed data collation and manuscript revision.

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Figures

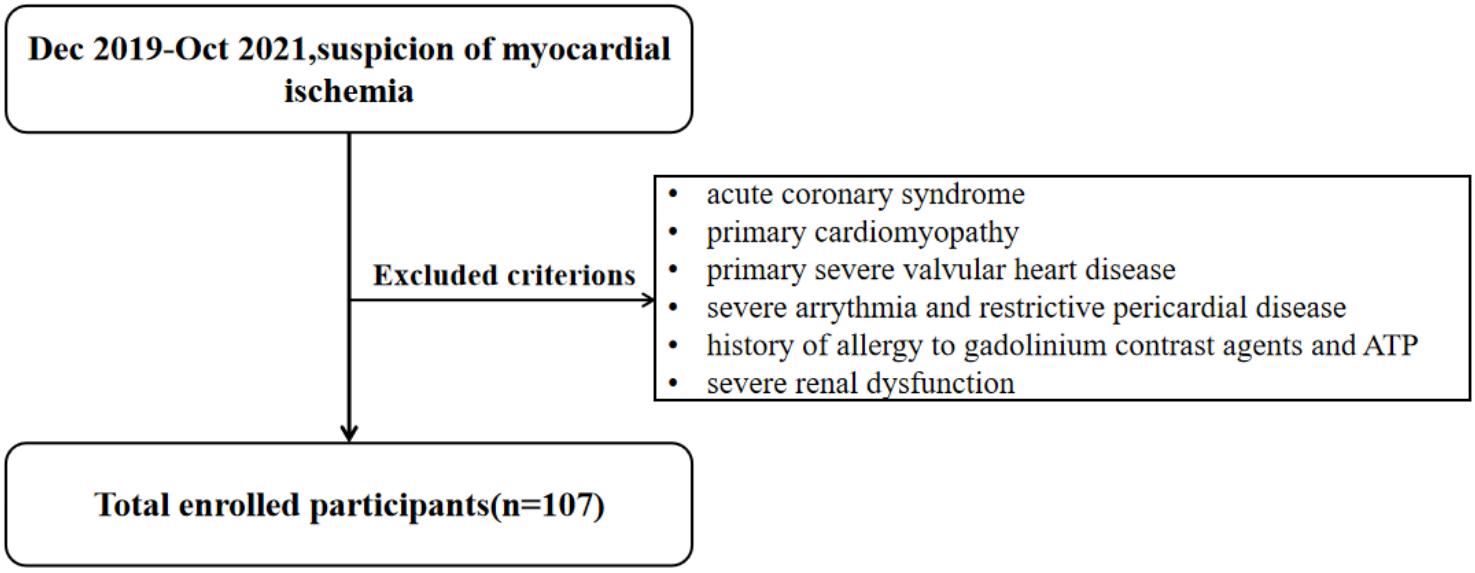

Figure 1

Study flowchart and exclusion criteria of patients.

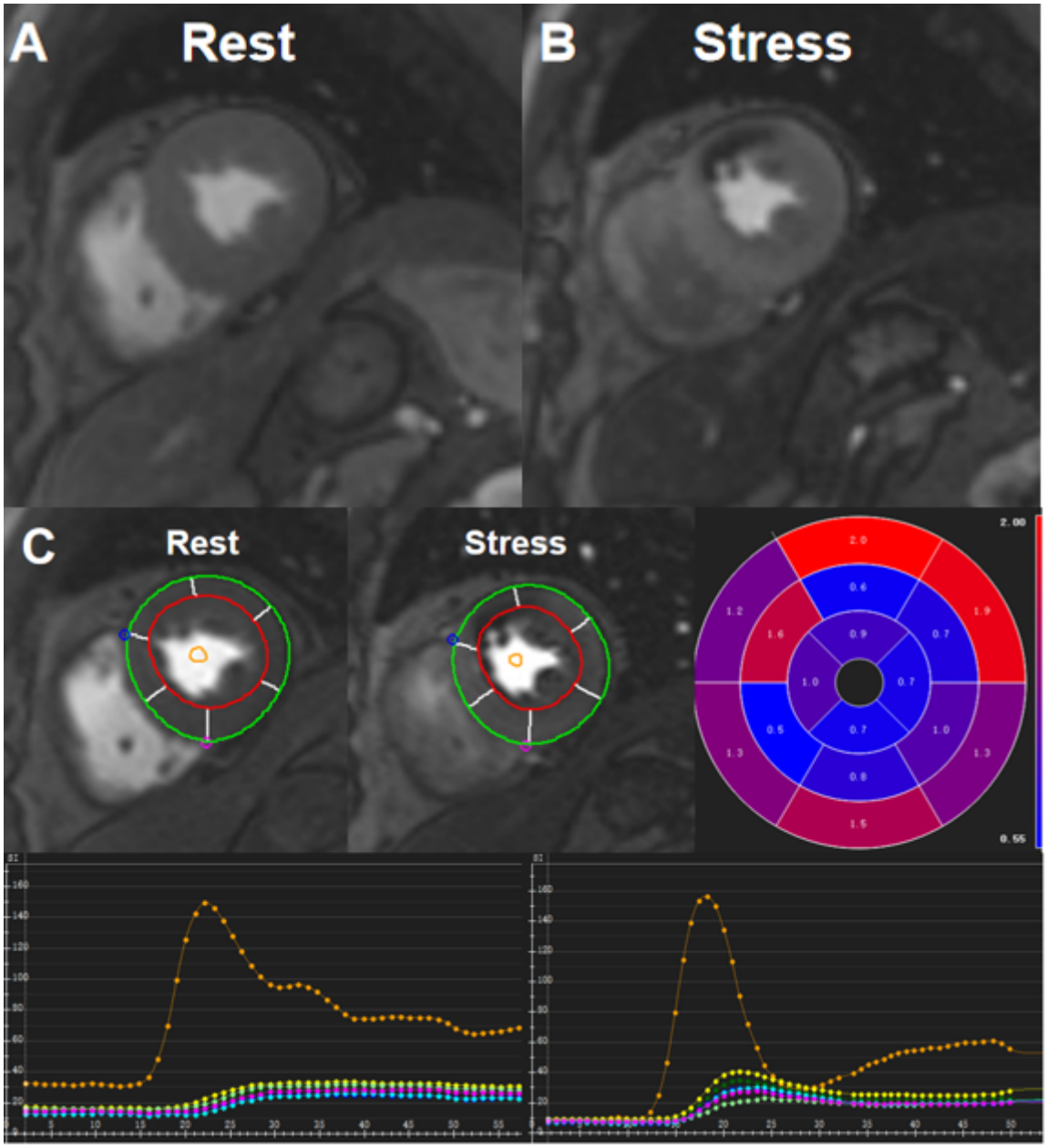

Figure 2

Qualitative and semi-quantitative perfusion analyses of a patient with stress-inducible perfusion defects. A&B shows images of reversible myocardial ischemia in the anterior wall of the left ventricle. C shows the semi-quantitative myocardial perfusion analysis that confirmed the results.The MPRI obtained by the post-processing software was less than 1.76.Semiquantitative results showed reversible myocardial ischemia, consistent with a qualitative diagnosis.

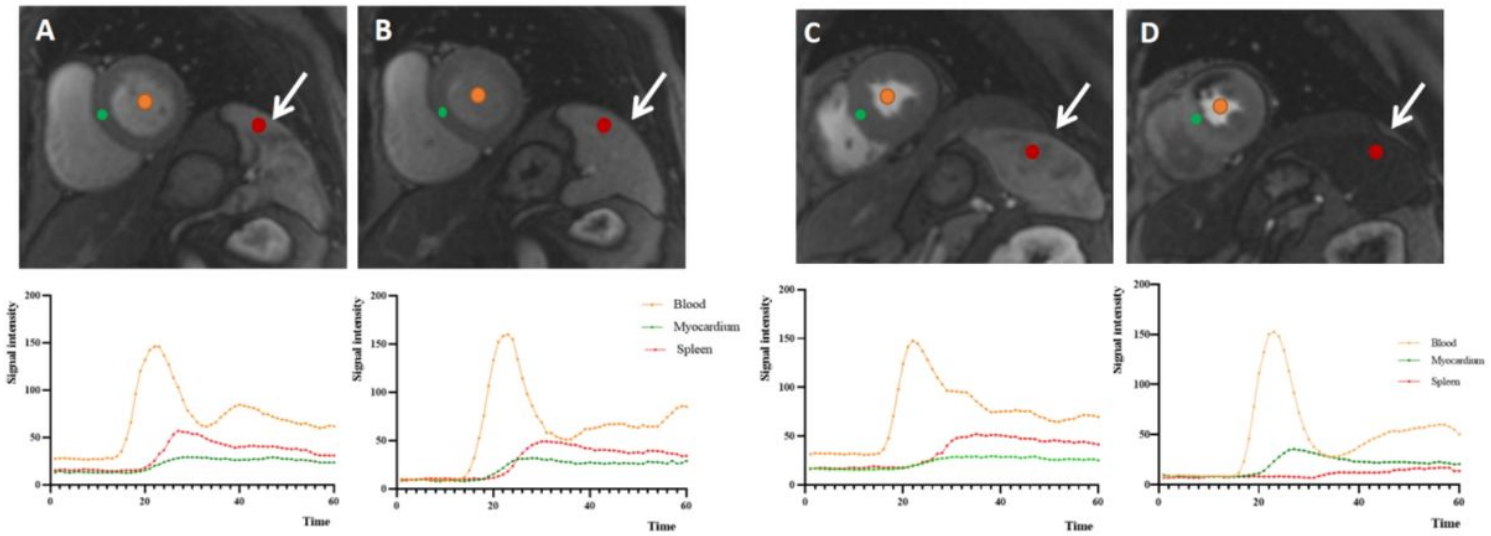

Figure 3

Perfusion images at rest and stress in two patients. The graphs show the time-based signal intensity curves for blood, spleen, and myocardium at rest and stress. (A, B) Perfusion images of the first patient during rest and stress. Both the qualitative and quantitative results suggested the absence of splenic switch-off (SSO). (C, D) Perfusion images of the second patient at rest and stress. Both qualitative and quantitative results suggested the presence of SSO. White arrows indicate the spleen; red dot=spleen, orange dot=blood, and green dot=the left ventricular myocardium.