Factors Determining Inadequate Stress Response to Adenosine Triphosphate in Perfusion Cardiovascular Magnetic Resonance

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Objective: Adenosine triphosphate (ATP) is an established pharmacological agent for stress cardiovascular magnetic resonance (CMR) in the Asia Pacific region. Inadequate cardiac stress in a CMR study may lead to false-negative results. The aim of the present study is to identify the proportion of patients with inadequate stress using a 140 mcg/kg/min protocol and the factors for inadequate stress in ATP stress CMR.

Materials and Methods: A retrospective analysis from January to December 2017 was performed. In total, 150 patients underwent ATP stress perfusion CMR at 1.5 tesla. All patients received ATP infusion of 140 mcg/kg/min for 4 min. Adequate stress was defined as two or more of the following criteria: 1) positive splenic switch off sign, 2) increased heart rate ≥ 10 bpm, and 3) drop in systolic blood pressure ≥ 10 mm Hg. Multivariable logistic regression analysis with forward and backward stepwise selection was used to identify predictors of inadequate response to ATP. Basic demographic variables with p-value ≤ 0.2 were examined for inclusion in the model. A p-value less than 0.05 was considered significant.

Results: Fifty-six (37%) patients did not demonstrate adequate cardiac stress response. Non-responders to ATP more often had atrial fibrillation, higher indexed left ventricular end systolic volume, and lower ejection fraction. Multivariable logistic regression analysis showed that low body weight and male gender were consistent independent predictors of inadequate stress in all models.

Conclusion: Inadequate stress occurred in 37% of subjects with ATP infusion of 140 mcg/kg/min. Low body weight and male gender are independent predictors of inadequate response to ATP. Higher infusion rates of ATP should be considered in patients with inadequate stress.

Key words Magnetic resonance imaging · Adenosine triphosphate · Stress test.

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INTRODUCTION

Stress cardiovascular magnetic resonance (CMR) is a highly accurate, safe, and non-invasive method for diagnosis of coronary artery disease (CAD) and has been incorporated into guidelines for diagnosis of obstructive CAD [1-6]. Stress CMR is commonly performed using vasodilatory pharmacological stress agents such as adenosine or adenosine triphosphate (ATP) [7,8]. These adenosine-based compounds generate systemic vasodilatation and reflex sympatho excitation with a consequent decrease in systolic blood pressure (SBP), increase in heart rate (HR),

and modest increase in rate-pressure product [9,10].

As potent coronary vasodilators, adenosine and ATP cause an up to four-fold increase in myocardial blood flow in areas supplied by normal coronary arteries. With gadolinium-based contrast agents, reduced flow gives rise to regional perfusion defects in the presence of coronary stenosis [7].

However, some patients fail to demonstrate adequate hemodynamic changes (increased HR and decreased SBP), indicating suboptimal physiological stress. These non-responders are at risk of false-negative findings on stress CMR perfusion and suboptimal clinical management.

The splenic switch off (SSO) sign has been recently demonstrated. The short axis image orientation, where most myocardial perfusion magnetic resonance (MR) images are acquired,

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usually includes the spleen. There is marked attenuation of splenic perfusion signal in the stress images compared with the rest of the images. The SSO sign has recently been shown to gauge the adequacy of CMR stress [11].

ATP infusion rates in some centers have been set at 160 mcg/kg/min for 5 min [10,12-20]. The purpose of this retrospective study is to identify the proportion of patients with inadequate stress using a lower dose 140 mcg/kg/min protocol and to determine the factors related to inadequate stress in ATP stress CMR.

MATERIALS AND METHODS

This study was conducted under approval by the Institutional Review Board (UW 18-317). This was a retrospective non-interventional analysis of the database of our institution from 1st January 2017 to 31st December 2017. The inclusion criteria were patients with known or suspected CAD referred for stress CMR imaging for clinical purposes. Exclusion criteria were patients with asthma, unstable angina, or acute myocardial infarction within two weeks of the study or second or third degree atrioventricular block. A 12-lead electrocardiogram was performed before the CMR scan. All patients were asked to abstain from caffeine for 24 hours prior to the scan. However, patients who reported caffeine intake within the last 24 hours were still included in the study. Written consent are obtained from participants.

Adenosine triphosphate infusion protocol

All patients initially had an ATP injection with an infusion rate of 140 mcg/kg/min for 4 min through an antecubital vein using a syringe pump. Hemodynamic status (i.e., HR, BP, and oxygen saturation) was determined at 0, 1, 2, and 3 min after ATP infusion. If, after 4 min of continuous infusion at the rate of 140 mcg/kg/min, the hemodynamic response to ATP was inadequate (increase in HR less than 10 bpm or decrease in systolic BP less than 10 mm Hg), the clinician would decide either to proceed to scan or increase the infusion rate to 170 mcg/kg/min.

CMR protocol

All CMR examinations were performed with subjects in a supine position on a 1.5 MR Tesla instrument (Aera, Siemens AG, Erlangen, Germany) with a 32-element phased array coil. During the last minute of ATP infusion, a gadolinium-based contrast agent was administered intravenously (injection rate of 4 mL/s, followed by a 20 mL saline flush at the same flow rate). Perfusion imaging was performed every cardiac cycle during the first pass, using a T1 weighted fast gradient echo sequence [dynamic trufi echo time (TE) 0.98 ms, repetition time (TR) 177 ms, saturation recovery time 110 ms, voxel size 2.3×2.3×8

mm, flip angle 50°]. Three short axis slices, positioned from the base to the apex of the left ventricle, were obtained. The same imaging sequence was repeated 10 minutes later without ATP to obtain perfusion images at rest. For assessment of left ventricular function, steady-state free precession (SSFP) cine images (TE/TR 1.28/40.17 ms, voxel size 1.2×1.2×6 mm, flip angle 62°) were acquired in three long axis views and a short axis stack to obtain coverage of the entire left ventricle (LV). Analysis of LV function was performed with syngo.via (Siemens AG) using the short axis SSFP images. The following left ventricular parameters were determined: end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF), and LV mass.

Splenic perfusion analysis

A recently proposed marker of adequate stress is splenic blood flow attenuation during stress perfusion (i.e., spleen appears hypointense in signal) [11]. Splenic first-pass perfusion was analyzed by a fellow radiologist using syngo.via (Siemens AG). Splenic regions of interest were placed on stress and rest perfusion images to generate curves showing mean splenic signal intensity (SI, arbitrary units) changes over time. Filling of the LV was defined as time zero to ensure the synchronous comparison of rest and stress scans. Peak splenic perfusion SI was estimated as the numerical difference between baseline SI and maximal SI during the splenic first-pass perfusion. Splenic intensity ratio (SIR) was calculated as peak splenic perfusion SI during stress divided by peak splenic perfusion SI during rest. The SSO sign was defined as positive if SIR was less than 0.4 (Figs. 1, 2, and 3).

Adequate hemodynamic response

Adequate hemodynamic response was defined as an increase in HR ≥ 10 bpm and a decrease in systolic BP ≥ 10 mm Hg during the ATP infusion period.

Adequate stress

Adequate stress was defined as the presence of two or more of the following criteria: 1) positive SSO sign, 2) HR increase ≥ 10 bpm, and 3) systolic BP decrease ≥ 10 mm Hg during ATP infusion. Inadequate stress was defined as ≤ 1 of the above criteria.

Statistical analyses

Continuous variables were expressed as mean $\pm$ standard deviation and were assessed by independent Student's t-test. Categorical variables were expressed as count and percentage. Comparisons of categorical variables between groups were performed with Pearson's chi-square test. Multivariable logistic regression analysis was performed for variables with p-value ≤ 0.2 . We used multivariable logistic regression analysis with forward and backward stepwise selection and 95% confidence intervals to identify potential predictors of inadequate response.

Fig. 1. Representative stress and resting splenic first-pass gadolinium perfusion, showing SI curves with positive SSO sign. SI curves represent splenic perfusion SI (y-axis, arbitrary units) versus time (x-axis). The maximum and minimum spleen SI values are as indicated. Splenic intensity ratio=0.15. (A) Splenic regions of interests on perfusion images are outlined in green during rest. (B) Splenic regions of interests on perfusion images are outlined in red during stress. SSO: splenic switch off, SI: signal intensity.

A p-value less than 0.05 was considered significant, and two-tailed p-values were used for all statistics. Statistical analyses were performed using statistical software (SPSS version 25.0 for Windows, IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Data were collected from 150 consecutive subjects with a mean age of 61 ± 15 years (range: 15–90 years), of whom 81 (54%) were men. See Table 1 for patient characteristics of those with and without adequate stress. See Table 2 for hemodynamic parameters.

Nineteen (12%) of 150 patients showed stress-induced myocardial ischemia on perfusion CMR (Table 3). Of the 131 patients without stress-induced myocardial ischemia, 81 (61%) achieved adequate stress. Of the total 150 patients, eight underwent angiographic coronary angiogram within one year after the CMR study. Of these eight patients, four (50%) were found to have severe CAD ($>70\%$ stenosis). Two of the four patients who were diagnosed angiographically with severe CAD had negative CMR examination. One of the two (50%) of them had inadequate stress.

Fig. 2. Representative stress and resting splenic first-pass gadolinium perfusion, showing SI curves with no SSO sign. SI curves represent splenic perfusion SI (y-axis, arbitrary units) versus time (x-axis). The maximum and minimum spleen SI values are as indicated. Splenic intensity ratio=1.0. (A) Splenic regions of interests on perfusion images are outlined in green during rest. (B) Splenic regions of interests on perfusion images are outlined in red during stress. SSO: splenic switch off, SI: signal intensity.

Fig. 3. A representative example from a CMR perfusion scan during high-dose adenosine stress. The patient was an 88-year-old man with history of dyslipidemia. Note the marked perfusion defect in the septum and anterior wall (arrow) in the left anterior descending artery territory (A). The resting perfusion scan (B) is normal and shows homogenous enhancement in all myocardial regions.

Adequate hemodynamic response and adequate stress

Ninety-four of 150 patients (62%) experienced adequate stress at the ATP infusion rate of 140 mcg/kg/min. In addition, 84 of the 94 (89%) patients had adequate hemodynamic responses (i.e., increase in HR ≥ 10 bpm and decrease in systolic BP ≥ 10 mm Hg).

Five of the 56 patients (9%) with inadequate hemodynamic responses received a higher infusion rate of ATP of 170 mcg/kg/min. Two of these five patients (40%) achieved adequate he-

modynamic response.

Splenic switch off sign

SIR ranged from 0.15 to 1.6; the mean SIR was 0.66 ± 0.29 . The SSO sign was identified in 29 (19%) of 150 patients. Within the adequate stress group, 27 (28%) of the 94 patients demonstrated a positive SSO sign. The mean SIR for the adequate stress

group was 0.59 ± 0.27 . For the inadequate stress group, 2 (3%) of the 56 patients demonstrated a positive SSO sign. The mean SIR for the inadequate stress group was 0.77 ± 0.2 (Table 4).

Hemodynamic response and splenic switch off sign

Seventeen of 84 patients (21%) with adequate hemodynamic response demonstrated the SSO sign. Twelve of 66 patients (18%) without adequate hemodynamic response demonstrated the SSO sign (Table 5).

Adverse events

There were no deaths, myocardial infarctions, or episodes of pulmonary edema as a result of the ATP stress.

Predictors of inadequate stress from ATP infusion of 140 mcg/kg/min

Patients who showed inadequate stress in response to ATP infusion more often had atrial fibrillation, significantly higher indexed left ventricular ESV, and lower EF. Variables that showed a trend toward significance ($p \leq 0.2$) were gender, weight, SBP at rest, HR at rest, atrial fibrillation, aspirin use, indexed EDV, indexed ESV, and LV EF.

CMR volumes and LV EF were not included since they are likely to be unavailable prior to stress. Digoxin and caffeine intake within 24 hours were not included, as only four and eight patients, respectively, had been prescribed digoxin or consumed caffeine. Only six patients had atrial fibrillation and were not included. The potential predictors of inadequate stress included for adjustment were gender, weight, SBP at rest, and HR at rest. By multivariable logistic regression analysis, the predictors of inadequate stress are low body weight ($p=0.02$) and male gender ($p=0.019$) (Table 6).

Table 3. Summarizing the subsequent management for patients diagnosed with ischemia changes

CMR with ischemia	Total=19
With invasive PCI performed within 1 year after CMR	4
Conservative or medical treatment	12
Further work up with CT coronary angiogram	2
Defaulted Follow up	1

CMR: cardiovascular magnetic resonance, PCI: percutaneous coronary intervention

Table 1. Patient characteristics of study population

	Adequate stress group (n=94)	Inadequate stress group (n=56)	p value
Age (yr)	60±15	62±16	0.500
Male	46 (49)	35 (62)	0.100
Height (cm)	161.2±9.7	163±8.9	0.260
Weight (kg)	67±15.8	63.3±12.1	0.130
BSA	1.7±0.2	1.68±0.2	0.280
Caffeine <24 prior to scan	4 (4)	4 (7)	0.450
Hypertension	57 (60)	31 (55)	0.530
Diabetes	28 (29)	16 (28)	0.870
Hyperlipidemia	46 (48)	23 (41)	0.350
Smoking	12 (12)	11 (19)	0.250
End-diastolic volume index (mL)	73±15	81±27	0.050
End-systolic volume index (mL)	27±11	36±26	0.019
Ejection fraction (%)	63±8	57±13	0.008
Mass index (gram/m ²)	69±16	72±23	0.380
Beta-blocker	41 (43)	25 (44)	0.900
Ca-channel blocker	32 (34)	21 (37)	0.660
ACE-inhibitor	23 (24)	15 (26)	0.750
Statin	63 (67)	39 (69)	0.730
Aspirin	47 (50)	22 (39)	0.200
Digoxin	1 (1)	3 (5)	0.100
Glomerular filtration rate	85±20	81±19	0.250
Atrial fibrillation	1 (1)	5 (8)	0.017
Ectopic	6 (6)	6 (10)	0.344
HR at rest (bpm)	67.5±14.1	70.4±12.9	0.200
SBP at rest (mm Hg)	146±19	140±21	0.070
DBP at rest (mm Hg)	84±12	83±11	0.500
ATP infusion time (min)	4.7±0.4	5±0.8	0.020

Data are presented as mean±standard deviation or count (%). BSA: body surface area, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ATP: adenosine triphosphate

Table 2. Hemodynamic parameters at rest and during adenosine stress

	Adequate stress group (n=94)			Inadequate stress group (n=56)		
	Rest	Peak	p value	Rest	Peak	p value
HR (bpm)	67±14	85±14	<0.001	70±12	78±14	0.002
SBP (mm Hg)	146±19	119±17	<0.001	140±21	122±21	<0.001
DBP (mm Hg)	84±12	70±10	<0.001	83±11	72±12	<0.001
Rate pressure product	9928±2644	10233±2512	0.42	9918±2652	9715±2920	0.7

Data are presented as mean±standard deviation. SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

Table 4. Hemodynamic response, SSO, and adequate stress to standard dose adenosine

	Adequate stress group (n= 94)	Inadequate stress group (n=56)	p value	Total (n=150)
Adequate haemodynamic response	84 (89)	0 (0)	<0.001	84 (56)
SIR	0.59±0.27	0.77±0.2	<0.001	0.66±0.29
SSO positive (SIR<0.4)	27 (28)	2 (3)	<0.001	29 (19)

Data are presented as mean±standard deviation or count (%). SSO: splenic switch off, SIR: splenic intensity ratio

Table 5. Comparison of SSO and hemodynamic response rate (p= 0.75)

	Adequate hemodynamic response	Inadequate hemodynamic response	Total
SSO	17	12	29
No SSO	67	54	121
Total	84	66	150

SSO: splenic switch off

Table 6. Logistic regression model with gender, weight, SBP at rest, HR at rest, atrial fibrillation as variables

Variable	Coefficient	Standard error	Sig.	Odds ratio	95% confidence interval
Male	1.016	0.432	0.019	2.762	1.185–6.438
Weight	-0.036	0.016	0.020	0.964	0.935–0.994
SBP at rest	-0.015	0.009	0.096	0.985	0.967–1.003
HR at rest	0.021	0.013	0.104	1.021	0.996–1.048

Predictor for inadequate stress is low body weight (p=0.02) and male gender (p=0.019). SBP: systolic blood pressure, HR: heart rate

DISCUSSION

In our study, 56 of 150 patients (37%) did not demonstrate adequate cardiac stress response with the ATP infusion rate of 140 mcg/kg/min. In addition, we found that low body weight and male gender were independent predictors of inadequate stress response.

ATP is typically infused at a rate of 140 mcg/kg/min [21] or 160 mcg/kg/min [10]. There are currently limited data on their differences in terms of inadequate cardiac stress, adverse reactions, and false-negative rates. To our knowledge, ours is the first study with a lower ATP infusion rate of 140 mcg/kg/min to determine the proportion of inadequate cardiac stress responses and the independent predictors of inadequate cardiac stress. We demonstrated that up to 63% of patients can achieve adequate cardiac stress with the infusion rate of 140 mcg/kg/min.

Without adjustment, the inadequate stress group had significantly higher indexed LV ESV, lower EF, and more atrial fibrillation in our study. Karamitsos et al. [4] used adenosine for perfusion CMR and concurred with our findings that the inadequate stress group had significantly higher indexed LV ESV and lower EF. The proportion of inadequate stress in our study (37%) was higher compared with that reported by Karamitsos et

al. [4], who demonstrated that 18% of patients did not achieve adequate hemodynamic stress. This is probably attributable to our protocol of relatively low ATP infusion rate (140 mcg/kg/min) for 4 min. From the literature, ATP can be infused intravenously at 160 mcg/kg/min for 5 min [10,12-20,22]. Karamitsos et al. [4] found that age and reduced EF were the predictors of inadequate response. We did not replicate this result. These findings may be attributed to different sample sizes, stress agents, ethnic groups, and most importantly, the criteria for defining adequate stress. In contrast to Karamitsos et al. [4], we had a greater sample size of patients, with a total of 150 subjects, which would bring a greater level of confidence. Second, our data are predominantly from a Chinese population, while the study by Karamitsos et al. [4] is based on a Caucasian population. Third, Karamitsos et al. [4] defined inadequate stress solely by hemodynamic response (HR increase <10 bpm or SBP decrease <10 mm Hg).

Hosking et al. [23] demonstrated that lack of SSO is prevalent, easily measurable, and has the potential to improve upon hemodynamic criteria as a marker of adenosine under stress in CMR perfusion scans. Hosking et al. [23] suggested that further work combining SSO with hemodynamic response should be performed to minimize false-negative rates further. In our study, we combined the assessment of hemodynamic response and SSO sign as the criteria of adequate cardiac stress. This combined assessment would be more objective and may minimize false-negative rates.

ATP has been shown to be safe and to elicit adequate stress with effects similar to those of adenosine [13,17, 22]. There are also fewer side effects and lower costs with ATP infusion [14,15,20]. ATP has been documented to demonstrate the SSO sign, which is not present with the use of other pharmacological agents such as regadenoson [12,22]. One disadvantage for ATP infusion is the relatively long infusion time needed to achieve a pharmacological stress response compared with adenosine [22].

Male gender was shown to be an independent predictor of inadequate stress in our models. This phenomenon is supported by Miyagawa et al. [10], who demonstrated that male gender was associated with significantly lower adverse effects of ATP infusion in thallium-201 myocardial tomography. This phenomenon is not well understood, but our postulation is that there could be a gender difference in cardiac adenosine receptors. Low body weight was shown to be another independent

predictor of inadequate stress, which is likely explained by the dose-dependent response to ATP. The total amount of ATP given is dependent on the patient's body weight. This finding is supported by Yildirim Poyraz et al. [24], who demonstrated that obese patients suffered more from the side effects of adenosine during myocardial perfusion SPECT/CT imaging. From our receiver-operative characteristic curve, the cut-off of low body weight was defined as ≤ 65.8 kg with a sensitivity of 51.8% and specificity of 51.1% [area under the curve (AUC): 0.55 ± 0.04].

The SSO is a new sign with a clear potential clinical application for assessment of stress adequacy during adenosine myocardial stress perfusion MR imaging. Manisty et al. [11] demonstrated that failed SSO occurred in more than one-third of proven false-negative adenosine perfusion examinations, almost four times more commonly than in examinations with true negative results. The SSO can either be measured quantitatively or assessed visually. In our study, we quantitatively measured the SIR. The SSO sign is defined as positive if SIR is less than 0.4. This threshold of SIR for the SSO sign is based on Hosking et al. [23] (sensitivity=82.5%, specificity=92.3%, AUC=0.91).

HR and mean arterial pressure changes are known to be poor predictors of myocardial blood flow and coronary vascular resistance changes. It may be misleading to determine stress adequacy from hemodynamic responses alone [25]. Recent studies have shown that the hyperemic and hemodynamic responses to adenosine correlate poorly [25]; therefore, SSO is only weakly associated with hemodynamic response. In our study, we observed a poor correlation between hemodynamic response and the SSO sign ($p=0.75$). From the literature [26], there was a good correlation of myocardial hyperemic response to adenosine with the splanchnic vasoconstrictor response. Therefore, the SSO sign is thought to be a better indicator of adequate adenosine stress than is the hemodynamic response. In our study, the SSO sign was only identified in 29 (19%) of 150 patients. One explanation is the relatively low ATP infusion rate (140 mcg/kg/min for 4 min) in our study compared to Miyagawa et al. [10], where ATP was infused intravenously at 160 mcg/kg/min for 5 min. It may also be explained by the semi-quantitative measure of SIR with the cut-off at 0.4. Indeed, we did demonstrate that the SI ratio was lower in the adequately stressed patients than in those not adequately stressed.

Inadequate stress CMR may lead to false-negative results and suboptimal clinical management. One future strategy is to measure real time splenic flow directly during adenosine-induced stress before contrast administration, which would ensure that perfusion images are acquired only when an adequate stress response is achieved. From Liu et al. [27], the delta T1 of the spleen can facilitate optimization of stress responses before gadolinium first-pass perfusion CMR. This enables prediction of the visual SSO sign without the need for gadolinium. It potentially guides

adenosine dosage up-titrations before contrast injection, thereby improving the quality of stress response before first-pass perfusion imaging [27]. One disadvantage of this methodology is the extra time required for T1-mapping. Further research is warranted to determine whether T1-mapping decreases the number of false-negative perfusion scans.

Stress CMR has a reported false-negative rate of 5–16% [28–30]. In our study, 131 of 150 patients had normal perfusion CMR findings, but 50 of the 131 patients (38%) had inadequate stress (Table 7). This group of patients is subjected to the potential risk of false-negative results. Inadequate adenosine stress response is the most common cause of false-negative perfusion scans [30]. Initiating higher dose adenosine protocols may reduce false-negative rates on myocardial perfusion studies by up to 33%, according to Manisty et al. [11]. In our study, 56 patients (37%) had an inadequate response to the ATP infusion at 140 mcg/kg/min. Of note, only five of these 56 patients received an increased ATP dose of 170 mcg/kg/min for further cardiac stress. Two out of the five patients (40%) who received an increased ATP dose subsequently achieved an adequate hemodynamic stress. The implementation rate of the high dose protocol was conceivably low in our study. Clinicians should vigilantly implement the high dose protocol if they observe an inadequate stress response.

Karamitsos et al. [4] demonstrated that a high dose adenosine protocol (up to 210 mcg/kg/min) is well tolerated, safe, and results in adequate hemodynamic response in nearly all patients. The infusion rate of ATP that causes maximal coronary vasodilation has not been determined [10]. In our study, the high dose ATP protocol was 170 mcg/kg/min, with a maximum of 210 mcg/kg/min. Whether the ATP doses of 170 mcg/kg/min and 210 mcg/kg/min would reduce the rate of inadequate stress warrants further research.

Watkins et al. [31] compared the diagnostic accuracy of perfusion CMR versus fractional flow reserve. In a per-patient analysis, the sensitivity and specificity of perfusion CMR for the detection of functionally significant CAD were 95% and 91%, respectively, with respective positive and negative predictive values of 97% and 84%. Stress perfusion CMR can detect functionally significant CAD with excellent diagnostic accuracy [12].

The strength of our study is the large number of patients involved. We also used a new objective measure of adequate stress, the SSO sign, to help determine stress. Male sex and low body

Table 7. Comparison of CMR results and stress adequacy

	Normal CMR perfusion	CMR with ischemia	Total
Adequate stress	81	13	94
Inadequate stress	50	6	56
Total	131	19	150

CMR: cardiovascular magnetic resonance

weight as independent predictors can routinely be determined prior to stress CMR, allowing one to better identify the potential risk of inadequate stress.

This study has limitations. Our study is a single-center retrospective study; therefore, further research is required to determine if results can be replicated. Second, our study population involved a predominantly Chinese population, which may render our study results less generalizable. Third, ATP-related side effects were not available for review. We believe that our study provides further data on the predictors of inadequate stress in stress CMR. The use of ATP is prevalent in the Asia Pacific region [16-19], and our data are likely relevant and similar to those of other Asia Pacific CMR centers. Further research is required to determine if the same predictors can be replicated in other populations. Correlating the predictors with catheter coronary angiography data and fractional flow reserve would be useful to determine the impact of inadequate stress on false-negative rates in stress CMR.

In conclusion, our study indicates that independent predictors of inadequate ATP stress in stress CMR are low body weight and male sex. In addition, the proportion of inadequate stress was 37% with an ATP infusion rate of 140 mcg/kg/min. Clinicians should consider higher infusion rates in patients with inadequate stress.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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REFERENCES

- Greenwood JP, Maredia N, Younger JE, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;379:453-460.
- Schwiter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettler K, et al. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013;34:775-781.
- Bettencourt N, Chiribiri A, Schuster A, Ferreira N, Sampaio F, Duarte R, et al. Cardiac magnetic resonance myocardial perfusion imaging for detection of functionally significant obstructive coronary artery disease: a prospective study. *Int J Cardiol* 2013;168:765-773.
- Karamitsos TD, Ntusi NA, Francis JM, Holloway CJ, Myerson SG, Neubauer S. Feasibility and safety of high-dose adenosine perfusion cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;12:66.
- Chen J, Einstein AJ, Fazel R, Krumholz HM, Wang Y, Ross JS, et al. Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. *J Am Coll Cardiol* 2010;56:702-711.
- Walker S, Girardin F, McKenna C, Ball SG, Nixon J, Plein S, et al. Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. *Heart* 2013;99:873-881.
- Gerber BL, Raman SV, Nayak K, Epstein FH, Ferreira P, Axel L, et al. Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory, and current state of the art. *J Cardiovasc Magn Reson* 2008;10:18.
- Christiansen JP, Karamitsos TD, Myerson SG, Francis JM, Neubauer S. Stress perfusion imaging using cardiovascular magnetic resonance: a review. *Heart Lung Circ* 2010;19:697-705.
- Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595-1606.
- Miyagawa M, Kumano S, Sekiya M, Watanabe K, Akutzu H, Imachi T, et al. Thallium-201 myocardial tomography with intravenous infusion of adenosine triphosphate in diagnosis of coronary artery disease. *J Am Coll Cardiol* 1995;26:1196-1201.
- Manisty C, Ripley DP, Herrey AS, Captur G, Wong TC, Petersen SE, et al. Splenic switch-off: a tool to assess stress adequacy in adenosine perfusion cardiac MR imaging. *Radiology* 2015;276:732-740.
- Yamada A, Ishida M, Kitagawa K, Sakuma H. Assessment of myocardial ischemia using stress perfusion cardiovascular magnetic resonance. *Cardiovasc Imaging Asia* 2018;2:65-75.
- Belhassen B, Pelleg A. Electrophysiologic effects of adenosine triphosphate and adenosine on the mammalian heart: clinical and experimental aspects. *J Am Coll Cardiol* 1984;4:414-424.
- Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. *J Am Coll Cardiol* 1994;23:384-389.
- Coma-Canella I, Palazuelos J, Bravo N, García Velloso MJ. Myocardial perfusion imaging with adenosine triphosphate predicts the rate of cardiovascular events. *J Nucl Cardiol* 2006;13:316-323.
- Watanabe K, Sekiya M, Ikeda S, Miyagawa M, Kinoshita M, Kumano S. Comparison of adenosine triphosphate and dipyridamole in diagnosis by thallium-201 myocardial scintigraphy. *J Nucl Med* 1997;38:577-581.
- Chun KA, Lee J, Lee SW, Ahn BC, Ha JH, Cho IH, et al. Direct comparison of adenosine and adenosine 5'-triphosphate as pharmacologic stress agents in conjunction with Tl-201 SPECT: Hemodynamic response, myocardial tracer uptake, and size of perfusion defects in the same subjects. *J Nucl Cardiol* 2006;13:621-628.
- Yao Z, Zhu H, Li W, Chen C, Wang H, Shi L, et al. Adenosine triphosphate stress myocardial perfusion imaging for risk stratification of patients aged 70 years and older with suspected coronary artery disease. *J Nucl Cardiol* 2017;24:429-433.
- Tomiyama Y, Manabe O, Oyama-Manabe N, Naya M, Sugimori H, Hirata K, et al. Quantification of myocardial blood flow with dynamic perfusion 3.0 Tesla MRI: Validation with (15) O-water PET. *J Magn Reson Imaging* 2015;42:754-762.
- Bravo N, Giménez M, Mejía S, García-Velloso MJ, Coma-Canella I. Prognostic value of myocardial perfusion imaging with adenosine triphosphate. *J Nucl Cardiol* 2002;9:395-401.
- Kitagawa K, Sakuma H, Nagata M, Okuda S, Hirano M, Tanimoto A, et al. Diagnostic accuracy of stress myocardial perfusion MRI and late gadolinium-enhanced MRI for detecting flow-limiting coronary artery disease: a multicenter study. *Eur Radiol* 2008;18:2808-2816.
- Bartolomé Leal P, Quilez Larragan A, García Baizán A, Millor Muruzábal M, Pueyo Villoslada JC, Bastarrika Alemañ G, Pamplona/ES. Adenosine and adenosine triphosphate (ATP) have a similar stress effect in patients undergoing stress/rest perfusion cardiac magnetic resonance examinations. B-0983. Poster session presented at: European Congress Radiology 2017; 2017 Mar 1-5; Vienna, Austria.
- Hosking A, Koulouroudias M, Zemrak F, Moon JC, Rossi A, Lee A, et al. Evaluation of splenic switch off in a tertiary imaging centre: validation and assessment of utility. *Eur Heart J Cardiovasc Imaging* 2017;18:1216-1221.
- Yıldırım Poyraz N, Özdemir E, Poyraz BM, Kandemir Z, Keskin M, Türkölmez Ş. Predictors and diagnostic significance of the adenosine re-

- lated side effects on myocardial perfusion SPECT/CT imaging. *Mol Imaging Radionucl Ther* 2014;23:89-95.
25. Mishra RK, Dorbala S, Logsetty G, Hassan A, Heinonen T, Schelbert HR, et al. Quantitative relation between hemodynamic changes during intravenous adenosine infusion and the magnitude of coronary hyperemia: implications for myocardial perfusion imaging. *J Am Coll Cardiol* 2005;45:553-558.
 26. Norlén K. Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerin. Studies in the pig. *Br J Anaesth* 1988;61:186-193.
 27. Liu A, Wijesurendra RS, Ariga R, Mahmod M, Levelt E, Greiser A, et al. Splenic T1-mapping: a novel quantitative method for assessing adenosine stress adequacy for cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2017;19:1.
 28. Hamon M, Fau G, Née G, Ehtisham J, Morello R, Hamon M. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson* 2010;12:29.
 29. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2012;59:1719-1728.
 30. Kidambi A, Sourbron S, Maredia N, Motwani M, Brown JM, Nixon J, et al. Factors associated with false-negative cardiovascular magnetic resonance perfusion studies: a clinical evaluation of magnetic resonance imaging in coronary artery disease (CE-MARC) substudy. *J Magn Reson Imaging* 2016;43:566-573.
 31. Watkins S, McGeoch R, Lyne J, Steedman T, Good R, McLaughlin MJ, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009;120:2207-2213.