Original Article

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Inadequate Response to Adenosine Infusion During Cardiac Stress Magnetic Resonance Imaging

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ABSTRACT

Aim: To determine the factors associated with an inadequate response to adenosine infusion during cardiac stress magnetic resonance imaging (MRI).

Study Design: It is a retrospective cohort study.

Introduction: Stress cardiac MRI is a highly accurate and non-invasive method to diagnose coronary artery disease (CAD). Stress MRI is performed by inducing stress with adenosine infusion. There is an increase in systemic and myocardial blood flow (MBF) with vasodilator agents. Capillaries are maximally dilated in a diseased artery and cannot sustain increased myocardial oxygen demand. It results in delayed delivery of contrast, which leads to an area of perfusion defect in the myocardium. These perfusion defects can be accurately seen by cardiovascular magnetic resonance (CMR) and help in the prognosis of patients.

Methods: A retrospective study on patients subjected to cardiac stress MRI was conducted in a Tertiary Care Cardiac Center from January 2019 to January 2022. In total, 99 patients underwent adenosine stress perfusion cardiac MRI. All patients received an adenosine infusion of 140 mcg/kg/min for 2 min. Subsequently, the dosage was increased by 20 mcg/kg/min every 2 min to a maximum of 210 mcg/kg/min until an adequate stress response was achieved. Adequate stress was defined as two or more of the following criteria: 1) Increase in heart rate >/= 10 beats per minute. 2) Decrease in systolic blood pressure SBP by >/= 10 mm Hg Symptoms like chest discomfort, breathlessness, and headache. Patients who satisfied two or more of the above criteria were labeled as responders and the patients who did not satisfy the above criteria with the maximum dose of 210 mcg/kg/min of adenosine infusion were labeled as non-responders. Multivariable logistic regression analysis with forward and backward stepwise selection was used to identify predictors in non-responders. Basic demographic variables with *P* value </= 0.2 were examined for inclusion in the model. A *P* value </= 0.05 was considered significant.

Results: Nine patients (9.1%) showed inadequate stress response to adenosine infusion even with a maximum dose of 210 mcg/kg/min. Multivariate logistic regression analysis showed that left ventricular end-diastolic volume (LVEDV) was a predictor of inadequate response to adenosine infusion.

Conclusion: Inadequate stress response to adenosine occurred in 9.1% of subjects with an infusion of 140–210 ug/kg/min. LVEDV is an independent and strong predictor in non-responders.

Keywords: Adenosine, cardiac stress MRI, left ventricular end-diastolic volume

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INTRODUCTION

Ischemic heart disease remains one of the leading causes of death, accounting for over 9 million deaths per year worldwide.[1,2]

According to the American Heart Association, the annual incidence of new coronary events is approximately 720 000 cases per year, and the current prevalence of ischemic heart disease is approximately 18.2 million cases in the United States alone.[2]

Invasive coronary angiography is considered the standard for detecting epicardial coronary artery stenosis, but it is expensive, carries some risk, and cannot assess the physiologic impact of stenosis.

Of the non-invasive imaging methods, stress perfusion imaging methods magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have become the most widely used which help assess myocardial viability to varying degrees.

Indications of stress perfusion imaging include known or possible stable angina and assessing the physiologic significance of known coronary artery stenosis.[3,4]

Two sets of myocardial perfusion images of the heart are obtained during stress perfusion imaging: stress and rest. Stress images are obtained during the administration of a vasodilator medication (or at peak exercise stress), coordinated with an injection of contrast or radionuclide material.

Stress cardiac MRI is a highly accurate and non-invasive method to diagnose coronary artery disease (CAD). Stress MRI is performed by inducing stress with adenosine infusion. There is an increase in systemic and myocardial blood flow (MBF) with vasodilator agents. Capillaries are maximally dilated in a diseased artery and cannot sustain increased myocardial oxygen demand. It results in delayed delivery of contrast, which leads to an area of perfusion defect in the myocardium. These perfusion defects can be accurately seen by cardiovascular magnetic resonance (CMR) and help in the prognosis of patients.[5-9]

Suboptimal physiological stress can be seen in patients who do not show adequate hemodynamic changes that is increased heart rate and decrease in blood pressure. Thus false-negative findings on stress CMR perfusion can be seen in patients with inadequate stress response, which further leads to suboptimal clinical management. AIM of the present study is to determine the factors associated with an inadequate response to adenosine infusion during cardiac stress MRI.

METHODS

This was a retrospective analysis from January 2019 to January 2022. Patients undergoing adenosine stress perfusion CMR were included. The inclusion criteria were patients with known or suspected CAD. Exclusion criteria were patients with asthma, unstable angina, acute myocardial infarction within two weeks of the study, and second or third-degree atrioventricular block. A 12-lead electrocardiogram (MR Philips System Ingenia CX) was performed before the CMR scan. All patients were asked to abstain from caffeine for 24 h before the scan. Beta-blockers, calcium channel blockers, and any drug known to decrease heart rate were stopped 24 h before the CMR scan. (Ethical committe approval was obtained from Institutional Ethical Committe Board).

All patients received an adenosine infusion rate of 140 ug/kg/min for 2 min. Heart rate (HR), blood pressure (BP), and symptoms were determined after adenosine infusion. If there was an inadequate response for the next 2 min, the dosage was increased by 20 ug/kg/min after 2 min to a maximum of 210 mcg/kg/min until adequate stress response was achieved. Adequate stress was defined as two or more of the following criteria: An increase in HR >/= 10 bpm, a decrease in systolic blood pressure (SBP) by >/= 10 mm Hg, and symptoms like chest discomfort, breathlessness, and headache. Patients who satisfied two or more of the above criteria were labeled as responders and the patients who did not satisfy the above criteria with the maximum dose of 210 mcg/kg/min of adenosine infusion were labeled as non-responders.

Once the patient is labeled as a responder, the infusion is continued for the next 2 min and stress perfusion imaging with a gadolinium dose of 0.1 mmol/kg was performed during the last minute of the adenosine infusion. Rest perfusion imaging was then performed after an appropriate delay using an additional gadolinium dose of 0.1 mmol/kg. Cine white blood imaging including short axis and two, three, and four-chamber long-axis views were performed using a steady-state free precession (SSFP) sequence to evaluate cardiac morphology and function. Delayed enhanced imaging was performed using a phase-sensitive inversion recovery (PSIR) sequence. Images were post-processed on a computer workstation to assess cardiac anatomy and ventricular function.

Field strength - 1.5 T

Patient parameters of age, height, weight, body surface area (BSA), gender, diabetes mellitus (DM), hypertension (HTN), hypothyroid, smoker, left ventricle ejection fraction, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic diameter (LVEDD), left ventricular systolic volume index (LVSVI), left atrial (LA) diameter, regional wall motion abnormality (RWMA), atrial fibrillation, heart rate, SBP, diastolic blood pressure (DBP) were recorded during rest and stress.

Splenic switch off sign was negative for non-responders.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and were assessed by an independent student t-test. Categorical variables were expressed as count and percentage. A comparison of categorical variables between groups was performed with Pearson's Chi-square test. Multivariable logistic regression analysis was performed for variables with *P* value </= 0.2. Multivariable logistic regression analysis with forward and backward stepwise selection and 95% confidence intervals to identify potential predictors of inadequate response were used. A *P* value </= 0.05 was considered significant and two-tailed *P* values were used for all statistics.

RESULTS

Data were collected from 99 consecutive subjects. Ninety of 99 patients (90.90%) were responders. Nine of 99 (9.1%) patients were non-responders.

Predictors of inadequate stress from adenosine infusion of 210 ug/kg/min (non-responders)

Demographic variables that showed a trend towards significance ($p < 0.2$) and which are potential predictors of inadequate stress included male gender, smoker, higher BSA, and height.

Non-responders had significantly higher LVESV, LVEDV, LVEDD, LVSVI, and low left ventricular ejection fraction (LVEF), increased left atrial diameter, presence of RWMA, lower SBP at rest as tabulated in Table 1.

There was a significant increase in HR, SBP, DBP in responder group after adenosine infusion whereas in non responders there was no significant increase in SBP and DBP [Table 2].

By multivariable logistic regression analysis, the predictors of inadequate stress were found to be only LVEDV [Table 3].

Table 1: Patient characteristics of the study population

Parameter	Responders *n*=90	Non-responders *n*=9	*P* value
Age	56.04±14	53.11±18.34	0.574
Height	161.52±9.95	166.56±5.81	0.140
Weight	68.28±12.90	73.48±6.37	0.236
BSA	1.73±0.21	1.83±0.08	0.160
Male	62 (68.8)	9 (1)	0.048
DM	29 (32.2)	2 (22.2)	0.537
HTN	35 (38.8)	2 (22.2)	0.324
Hypothyroid	3 (3.33)	0	0.578
Smoker	1 (1.1)	1 (11.1)	0.042
EF	55.04±10.67	48.67±10.57	0.091
LVESV	60.70±35.46	99.67±42.10	0.003
LVEDV	127.49±39.69	181.11±50.123	0.00
LVEDD	50.28±6.442	55.67±7.64	0.021
LVSVI	35.01±19.85	54.52±23.137	0.007
LA DIAMETER	39.79±5.78	44.11±5.32	0.034
RWMA	25 (27.7)	5 (55.5)	0.084
AF	3 (3.33)	0	0.578
HR REST	80.25±14.09	75.79±17.76	0.378
SBP REST	148.32±23.52	135.67±20.61	0.123
DBP REST	89.53±18.17	81.89±12.30	0.221

DISCUSSION

Adenosine is a powerful vasoactive substance. There occurs dilatation of coronary and peripheral arterial beds, increase in myocardial blood flow, and sympatho-excitation upon activation of cardiac A2A and A2B adenosine receptors.[10] As a result, there occurs a mild decrease in blood pressure and baroreceptor-mediated reflex tachycardia.[11,12] Most of the patients show signs of sufficient peripheral vasodilatory response after 2–3 min of adenosine infusion at the standard dose of 140 ug/kg/min. However, some patients show a reduced response to the standard dose according to prior studies.[10,13,14]

In the present study, 9 of 99 patients (9.1%) were non-responders.

In a study conducted by Cheng *et al.*,[15] 56 of 150 patients (37%) did not show adequate stress response with an adenosine triphosphate (ATP) infusion rate of 140 mcg/kg/min. Karamitsos *et al.*[16] demonstrated that 18% of patients did not achieve adequate hemodynamic stress under the standard dose of 140 ug/kg/min.

Since the dosage in the above studies was limited to 140 ug/kg/min, more patients were non-responders. The lower percentage of non-responders in the present study is due to an increased dosage of adenosine with a maximum of 210 mcg/kg/min.

In the present study, no significant decrease in systolic and diastolic blood pressure [Table 2] was seen in the non-responder group only. But there was a significant

Table 2: Hemodynamic parameters at rest and during adenosine stress

	Responders rest	Responders *n*=90 Peak	*P* value	Non-responders rest	Non-responders *n*=9 Peak	*P* value
HR bpm	80.25±14.09	107.89±18.29	<0.0001	75.78±17.76	88.67±16.89	0.0068
SBP	148.45±23.62	140.17±26.04	0.0001	135.67±20.61	131.11±18.54	0.1324
DBP	89.53±18.18	83.43±15.28	0.0006	81.89±12.30	80.44±9.07	0.46

Table 3: Multivariate logistic regression model for predictors in non-responders

Variable	Coefficient	Standard Error	Significant	Odds Ratio	95% CI	
					Lower	Upper
Height	-0.098	0.127	0.438	0.906	0.707	1.162
BSA	3.509	5.651	0.535	33.412	0.001	2158165.416
Preop EF	-0.010	0.070	0.887	0.990	0.863	1.136
LVESV	-0.113	0.107	0.291	0.893	0.724	1.102
LVEDV	0.077	0.038	0.043*	1.080	1.002	1.164
LVEDD	-0.009	0.132	0.943	0.991	0.765	1.283
LVSVI	0.111	0.181	0.538	1.118	0.784	1.592
LA DIA	0.018	0.105	0.862	1.018	0.829	1.250
SBP rest	-0.028	0.022	0.213	0.973	0.931	1.016
Gender	-20.755	5996.727	0.997	0.000	0.000	0.000
Smoker	1.669	1.819	0.359	5.309	0.150	187.474
RWMA	-0.974	1.190	0.413	0.378	0.037	3.891
Constant	25.364	5996.762	0.997	103614267538.269		

*$P<0.05$

increase in heart rate in both groups. Seventeen percent of patients in the non-responder and 35% of patients in the responder group had a significant increase in heart rate.

In a study by Brown *et al*.,[17] it was shown that there is no significant relationship between a rise in HR at standard dose adenosine (140 mcg/kg/min) and an increase in stress MBF with high dose adenosine which indicates that in patients with low HR response at standard dose adenosine, a higher dose does not increase myocardial perfusion. Also, no significant difference in SBP change was seen between the group of patients or adenosine doses.

In a study by Karamitsos *et al*.,[16] 18% of patients had an inadequate peripheral hemodynamic response to the standard infusion dose of adenosine. Impairment of the baroreceptor reflex, resulting in decreased vascular reactivity in response to vasodilator stimuli is a possible cause of reduced heart rate response. Diabetic or elderly patients have attenuated reflex tachycardia in response to vasodilator-induced decreased blood pressure, possibly attributable to autonomic dysfunction.[13]

In the present study, the majority of patients in the responder group had chest discomfort ($n = 62$) as compared to non-responders ($p < 0.01$).

Among the non-responder group, one patient had CAD by coronary angiogram. Other patients were diagnosed with dilated cardiomyopathy, left ventricular non-compaction, and amyloidosis who had increased LVEDV.

In the present study, many factors like higher LVEDV, LVESV, LVEDD, LA diameter, low EF <40%, smokers, male gender, higher BSA, and height were found to be significant for non-responders ($p < 0.2$). But only high LVEDV was found to be statistically significant ($p < 0.05$).

The mechanism of lower adenosine response is the downregulation of gene expression of both adenosine receptors and adenosine deaminase in impaired myocardium, together with a decrease in the activity of adenosine deaminase.[18,19]

In chronic heart failure patients, increased levels of cardiac adenosine have been measured and this higher endogenous level explains the requirement for higher exogenous doses to achieve vasodilatation required in stress testing.[18,19]

Karamitsos *et al*.[16] found a LVEF of less than 57% was associated with an inadequate peripheral hemodynamic response which can be due to an already increased sympathetic nervous activity known to be present in heart failure. Patients with heart failure have high resting peripheral vasomotor tone, which makes them less responsive to the vasodilator effect of adenosine. Also high catecholamine levels and endogenous adenosine formation act as a negative feedback system in patients with heart failure.

Cheng *et al*.[15] found that low body weight and male gender were independent predictors of an inadequate stress response.

In the present study, a splenic switch-off sign was performed in non-responders and was found to be negative. If the patient is labeled as a non-responder, he is reviewed after ten days post-optimization.

Limitation of the study was that it was single centre and retrospective in nature.

CONCLUSION

LVEDV is an independent predictor of inadequate response to adenosine infusion during cardiac stress MRI.

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Conflicts of interest
There are no conflicts of interest.

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