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Haemodynamic effects of pharmacologic stress with adenosine in patients with left ventricular systolic dysfunction☆

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ABSTRACT

Background: In patients with heart failure, downregulation of adenosine receptor gene expression and impaired adenosine-related signal transduction may result in a diminished response to adenosine. This may have implications for cardiac stress testing. We evaluated the haemodynamic response to intravenous adenosine in patients with left ventricular systolic dysfunction (LVSD) undergoing stress cardiovascular magnetic resonance imaging (CMR).

Methods and results: We retrospectively examined 497 consecutive patients referred for clinical stress CMR. Blood pressure and heart rate responses with intravenous adenosine were compared in patients with normal, mild-moderately impaired and severely impaired LV systolic function (ejection fraction [EF] > 55%, 36–55% and < 35%, respectively).

Following 2 min of adenosine infusion, there was a significant difference between the groups in the heart rate change from baseline, with a diminished heart rate response in patients with LVSD ($p < 0.001$). An increase in the dose of adenosine (up to 210 μg/kg/min) was required to achieve a sufficient haemodynamic response in more patients with severe LVSD (41%) than those with mild-moderately impaired and normal LV systolic function (24% and 19%, respectively, $p < 0.001$). Even with increased doses of adenosine in subjects with severe LVSD, peak haemodynamic response remained blunted. With multivariate analysis age ($p < 0.001$) and LVEF ($p = 0.031$) were independent predictors of heart rate response to adenosine.

Conclusion: Patients with reduced LVEF referred for stress CMR may have a blunted heart rate response to adenosine. Further study is warranted to determine whether this may be associated with reduced diagnostic accuracy and also the potential utility of further dose increases or alternative stressors.

1. Introduction

In patients with suspected coronary artery disease (CAD), stress cardiovascular magnetic resonance imaging (CMR) has emerged as a sensitive non-invasive technique for identifying myocardial ischaemia) [1–4]. In clinical practice, the most commonly used vasodilator stress agent is adenosine (almost 80% of stress perfusion CMR studies) [5]. Adenosine is a safe and well-tolerated vasodilator stress agent [6,7]. Coronary vasodilation may lead to a four-fold increase in myocardial blood flow in normally perfused coronary territories, with flow inhomogeneities in diseased segments giving rise to visually detectable perfusion defects [8,9].

The adequacy of vasodilator stress with adenosine is reflected by the extent of systemic vasodilatation, as indicated by decreased blood pressure and reflex tachycardia, typically occurring 2–3 min after commencing adenosine infusion. Conventionally a heart rate increase of ≥10 beats per minute and/or systolic blood pressure fall ≥10 mm Hg is regarded as confirmation of an adequate stress response [9,10]. In patients who fail to demonstrate an adequate initial response to adenosine, dosage can safely be increased from 140 μg/kg/min up to a maximum of 210 μg/kg/min [9].

In patients with heart failure, downregulation of adenosine receptor gene expression [11], impaired adenosine-related signal transduction [12] and altered endothelium-dependent vasodilatory responses [13,14] may result in a diminished haemodynamic response to intravenous adenosine. This may have diagnostic implications for the clinical use of cardiac stress testing with adenosine. Therefore, in this study, we sought to evaluate the impact of left ventricular (LV) systolic dysfunction (LVSD) on the haemodynamic response to intravenous adenosine.

2. Methods

We retrospectively studied consecutive adult patients referred for clinical stress CMR during a 6-month period in our centre (January 2016 to June 2016). The study was presented to and reviewed by our institutional review board (University Hospitals of

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Leicester NHS Trust, Glenfield Hospital Clinical Audit Committee, reference number 8120) and was approved as a clinical audit for which ethical approval was deemed unnecessary.

2.1. CMR image acquisition and adenosine stress testing

Stress CMR studies were undertaken on either a 1.5 Tesla (Siemens Avanto, Erlangen, Germany) or 3 Tesla scanner (Siemens Skyra, Erlangen, Germany). Participants' past medical history, medications, electrocardiographic data, resting pulse and blood pressure were recorded just prior to CMR scanning. Cardiac volumes and function were assessed using standard CMR techniques as previously described by our group [15].

Patients were advised to abstain from caffeine-containing products at least 12 h prior to CMR scanning and to withhold beta-blocker therapy 24 h in advance. For stress testing, adenosine (commencing at 140 μg/kg/min) was infused for 3–5 min. Patients underwent pulse, blood pressure and pulse oximetry monitoring at baseline and at one-minute intervals during adenosine infusion, with documentation of haemodynamic and symptomatic responses at the time of CMR scanning. A heart rate increase of ≥10 beats per minute and/or systolic blood pressure fall ≥10 mm Hg was regarded as an adequate stress response [9,10]. Failure to achieve this at 2 min resulted in a dose increase to 170 μg/kg/min and, if required, to a maximum of 210 μg/kg/min. Peak response to adenosine was defined as the maximal change in heart rate from baseline. Peak rate pressure product calculation was made by multiplying maximal change in heart rate by the systolic blood pressure measured at the same time point.

2.2. Statistical analyses

Statistical tests were performed using the SPSS v24.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA). Normality was assessed using Kolmogorov-Smirnov tests, histograms, and Q-Q plots. Continuous data were expressed as mean ± standard deviation, if normally distributed. Non-normally distributed variables were expressed as median and interquartile range. Patients were separated into three categories on the basis of LV ejection fraction (EF): normal LV systolic function (EF > 55%), mild-moderate LVSD (EF 36–55%) or severe LVSD (EF ≤ 35%) [16]. One-way analysis of variance (ANOVA) was used to compare normal data and the Independent-Samples Kruskal-Wallis test for non-normal data between groups. To determine correlates of haemodynamic response to adenosine, Pearson correlation analysis was performed. Non-normal data were transformed to obtain a sample with normal distribution prior to correlation analysis. Multivariable linear regression was performed to identify independent determinants of haemodynamic response to adenosine infusion. The model contained those covariables which demonstrated significant univariate correlations with haemodynamic response to adenosine.

3. Results

3.1. Baseline characteristics

A total of 497 patients underwent clinical adenosine stress CMR during the consecutive 6-month study period. Demographic characteristics and CMR volumetric and functional data are shown in Table 1. Patients in the severe LVSD group (EF ≤ 35%) were older and had a higher proportion of males than in the other two groups. As expected, indexed LV volumes were significantly greater in the severe and mild-moderate LVSD groups compared to those with normal LV function. There was an appropriately higher proportion of patients on treatment with heart failure medication in the severe LVSD group (Table 1).

3.2. Haemodynamic response to adenosine

At baseline, systolic blood pressure was lower and heart rate higher in patients with severe LVSD than in those with mild-moderate LVSD or normal LV function (Table 2). After 2 min vasodilator stress testing and prior to any adenosine dose increase, however, blood pressure dropped and heart rate increased in all three groups, but less so in those patients with severe LVSD (Table 2). Of the three groups, patients in the severe LVSD group had the lowest overall change in blood pressure, heart rate and rate pressure product with two minutes of intravenous adenosine (Table 2). A lower proportion patients in the severe LVSD group ($n = 26$, 26%) achieved a heart rate increase >10 bpm with 2 min of intravenous adenosine compared to those with mild-moderate ($n = 65$, 55%) and normal LV function ($n = 87$, 68%) (Table 2).

To achieve a satisfactory vasodilator stress response, a greater proportion of patients with severe LVSD (41%) required a dosage increase of intravenous adenosine (up to a maximum of 210 μg/kg/mn) compared to those with mild-moderate LVSD and normal LV function (25% and 19%, respectively, $p < 0.001$) (Table 2). In those patients in whom dose was increased, a smaller proportion of patients with severe LVSD went on to exhibit a heart rate response ≥10 beats/min compared to patients with mild-moderate LVSD or normal LV function (40% vs. 75% vs. 81%, respectively, $p < 0.001$). Despite the dose increase, peak heart rate and rate pressure product were diminished in patients with LVSD, and lowest in those patients with severe LVSD (Table 2).

3.3. Univariable and multivariable predictors of heart rate response to adenosine

Age ($r = -0.219$, $p < 0.001$), LV EF ($r = 0.368$, $p < 0.001$) (Fig. 1) and beta-blocker use ($r = 0.134$, $p = 0.005$) were correlated with change in heart rate > 10 beats per minute, after two minute intravenous adenosine infusion (prior to any dose increase). Other univariable predictors are shown in Table 3. On multivariable regression, only age, LV EDVi and LV EF were independently associated with heart rate response to adenosine infusion (Table 3).

Table 1
Baseline demographic characteristics, medications, and LV volumes and function for study patients.

	Normal LV function (EF > 55%) $n = 128$	Mild-moderate LVSD (EF 36–55%) $n = 118$	Severe LVSD (EF ≤ 35%) $n = 251$	p-Value
Demographic characteristics				
Age (years)	61.3 ± 13.4	63.6 ± 12.4	66.2 ± 10.5	<0.001
Gender (%male)	59	65	79	<0.001
Height (cm)	167.0 ± 10.4	169.6 ± 8.7	168.6 ± 11.5	0.239
Weight (kg)	85.7 ± 25.2	85.2 ± 20.2	80.7 ± 19.9	0.055
Body mass index (kg/m^2)	30.5 ± 7.9	29.2 ± 6.3	28.3 ± 6.6	0.029
Medications				
ACE inhibitor n(%)	36 (28)	55 (47)	158 (63)	<0.001
Angiotensin receptor blocker n(%)	23 (18)	15 (13)	45 (18)	0.401
Beta-blocker n(%)	67 (52)	79 (67)	193 (77)	<0.001
Calcium channel blocker n(%)	23 (18)	17 (14)	13 (5)	<0.001
Loop diuretic n(%)	17 (13)	19 (16)	108 (43)	<0.001
Thiazide diuretic n(%)	5 (4)	1 (1)	8 (3)	0.292
Aldosterone antagonist n(%)	1 (1)	9 (8)	80 (32)	<0.001
Digoxin n(%)	0 (0)	1 (1)	13 (5)	0.005
LV volumes and function				
LV EF (%)	62.3 ± 4.9	47.6 ± 5.7	26.9 ± 6.5	<0.001
LV EDVi (mL/m^2)	75.4 ± 15.8	92.0 ± 24.2	136.7 ± 36.9	<0.001
LV ESVi (mL/m^2)	29.5 ± 8.3	48.9 ± 18.5	101.5 ± 34.6	<0.001

Abbreviations: LV = left ventricle, EF = ejection fraction, EDVi = end-diastolic volume indexed to body surface area, ESVi = end-systolic volume indexed to body surface area.

Table 2
Haemodynamic characteristics at baseline, 2 min and peak stress after commencement of intravenous adenosine infusion.

	Normal LV function	Mild-moderate LVSD	Severe LVSD	*p*-Value
Baseline haemodynamic characteristics				
SBP (mmHg)	145.2 ± 24.3	141.2 ± 23.4	135.6 ± 26.3	0.001
DBP (mmHg)	78.8 ± 12.2	77.9 ± 13.8	79.7 ± 15.4	0.577
HR (beats/min)	67.2 ± 11.9	67.7 ± 13.2	71.0 ± 14.3	0.015
Rate pressure product	9756 ± 2391	9101 ± 2510	9644 ± 2861	0.856
Change in haemodynamic characteristics with 2 minutes adenosine infusion				
SBP (mm Hg)	−7.4 ± 19.9	−5.0 ± 17.7	−2.0 ± 14.2	0.02
DBP (mm Hg)	−4.5 ± 9.5	−3.9 ± 15.1	−3.1 ± 9.9	0.462
HR (beats/min)	15.4 ± 10.3	12.2 ± 10.6	5.6 ± 9.9	<0.001
Rate pressure product	1622 ± 2131	1320 ± 1969	647 ± 1786	<0.001
Change in HR > 10 beats/min achieved n(%)	87 (68)	65 (55)	66 (26)	<0.001
Change in SBP > 10 mm Hg achieved n(%)	42 (33)	37 (31)	61 (24)	0.149
Change in DBP > 10 mm Hg achieved n(%)	29 (23)	32 (27)	43 (17)	0.076
Maximal adenosine dosage and haemodynamic characteristics at peak stress				
Adenosine dose increase required (%)	20 (16)	28 (24)	103 (41)	<0.001
SBP (mm Hg)	−11.4 ± 19.4	−9.6 ± 17.4	−8.4 ± 15.4	0.298
DBP (mm Hg)	−6.3 ± 10.4	−6.7 ± 14.4	−6.8 ± 11.1	0.946
HR (beats/min)	17.1 ± 10.4	14.0 ± 10.1	9.1 ± 11.0	<0.001
Rate pressure product	2108 ± 2365	1628 ± 1915	1116 ± 1874	<0.001

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

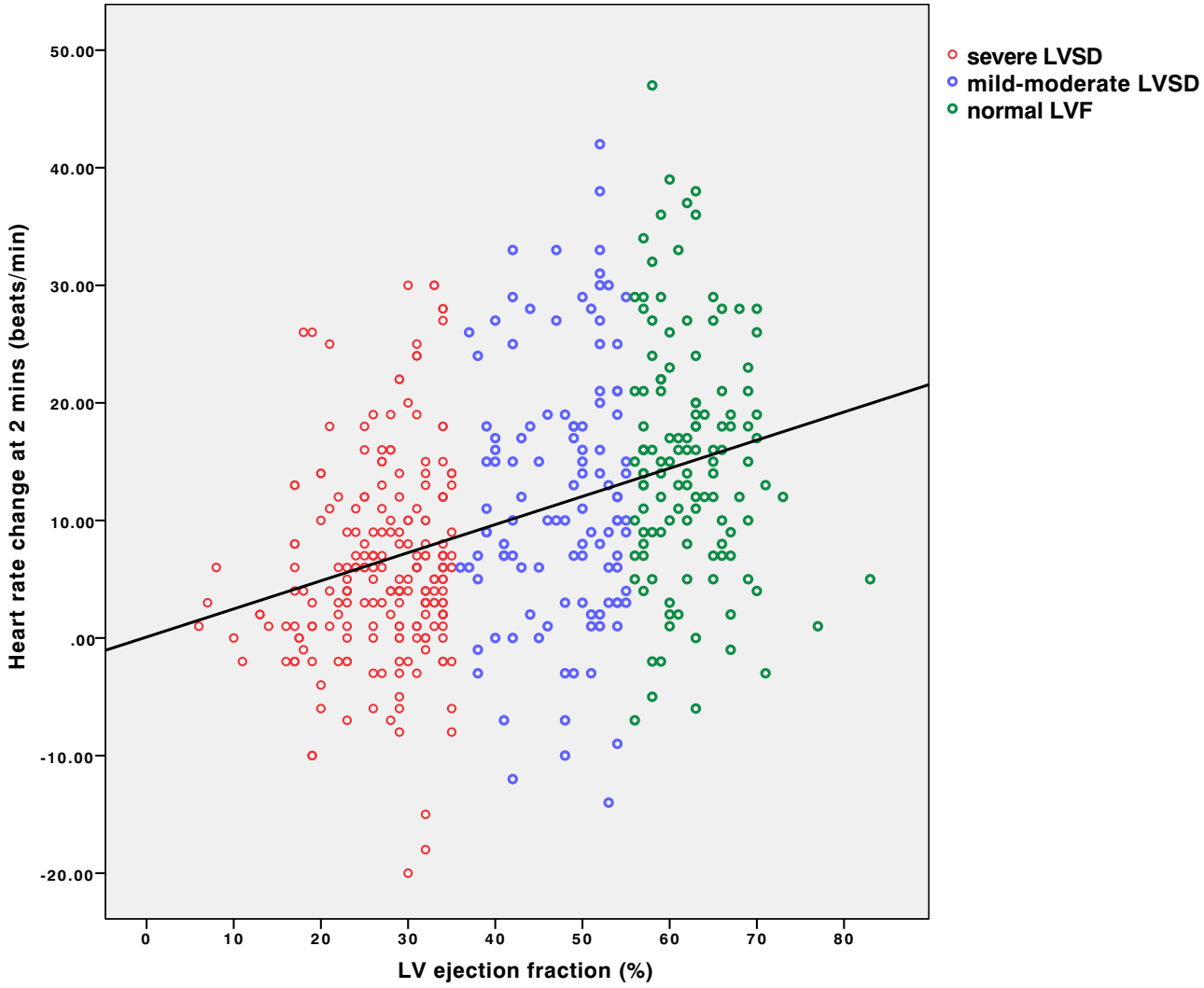

Fig. 1. Relationship between left ventricular ejection fraction (LV EF) and heart rate response to adenosine (140 μg/kg/min) infusion during vasodilator stress testing.

3.4. Response to adenosine in patients not taking beta-blocker therapy

Sub-group analysis was undertaken on patients not on treatment with beta-blockers ($n = 139$). Even when patients taking beta-blockers were excluded from analyses, heart rate increase and blood pressure decrease after 2 min adenosine infusion was lowest in patients with severe LVSD and greatest in patients with normal LV function (Supplementary Table 1).

4. Discussion

This study demonstrates that patients with reduced LV EF referred for stress perfusion CMR have a blunted haemodynamic response to adenosine. This finding may have diagnostic implications not just for CMR but also for other modalities which utilize adenosine stress (such as nuclear imaging), with potential reduction of diagnostic accuracy in patients with LVSD.

CMR is a key imaging modality recommended for identifying the aetiology of heart failure [17,18]. Myocardial tissue characterization with late gadolinium enhancement enables the differentiation of heart failure from ischaemic versus non-ischaemic aetiology [19,20]. CMR first-pass myocardial perfusion imaging has been shown in several large studies to have excellent sensitivity and specificity for detection of CAD [1,2,4]. The EuroCMR registry, which includes data on >27,000 consecutive CMR studies from over 15 European countries, showed that almost one third (29.3%) of CMR studies include adenosine stress perfusion imaging [5]. However, there are no published data pertaining to the diagnostic accuracy of stress CMR in patients with LVSD. Our finding of a diminished haemodynamic response to vasodilator stress with adenosine in patients with LVSD indicates that the diagnostic accuracy of stress perfusion CMR in these patients may be compromised. Importantly, we have demonstrated that the diminished response to adenosine is not attributable to rate controlling medications, being apparent also in beta-blocker naïve individuals. This is consistent with previous reports of downregulated adenosine receptor gene expression, impaired adenosine-related signal transduction and altered endothelium-dependent vasodilatory responses in patients with heart failure [11–14].

In the literature, there are few studies exploring the predictors of the haemodynamic response to adenosine, despite it being the most widely used vasodilator stress agent in CMR [6] and nuclear cardiac stress testing [21]. Increasing age [9,22], male gender [22], diabetes mellitus [9,22] and varying degrees of LV dysfunction [9,22,23] have been associated with an inadequate haemodynamic response to adenosine during stress imaging. However, in these studies only the standard (140 μg/kg/min) dose of adenosine was administered, and the impact of higher doses (up to 210 μg/kg/min) has not been evaluated. Furthermore, LV dysfunction was evaluated as a binary variable and primarily using SPECT; by contrast, our study benefits from CMR volumetric assessment, revealing a graded haemodynamic response with worsening LV systolic dysfunction.

In our cohort, patients received doses up to a maximum of 210 μg/kg/mn as recommended in current guidelines [10]. We found that even an adenosine dose of 210 μg/kg/min failed to bring about an appropriate haemodynamic response in a significant proportion of patients with LVSD. It remains to be established whether the use of adenosine doses higher than 210 mg/kg/min may achieve a sufficient haemodynamic effect in these individuals.

Table 3
Univariate and multivariate predictors of a satisfactory heart rate response (defined as a heart rate increase > 10 beats/min) after 2 min, intravenous adenosine (140 μg/kg/min) infusion in the entire cohort.

	Univariate		Multivariate	
	Pearson's correlation coefficient (r)	*p*-Value	Standardised coefficient (β) ($R^2 = 0.211$)	*p*-Value
Age	−0.219	<0.001	−0.208	<0.001
Gender	−0.153	0.001	−0.061	0.213
Baseline HR	−0.021	0.642	−0.060	0.238
LV EDVi	−0.290	<0.001	−0.182	0.013
LV EF	0.368	<0.001	0.164	0.031
BMI	0.155	0.001	0.053	0.276
Beta-blocker	−0.134	0.005	−0.068	0.238

Abbreviations: HR = heart rate, LV = left ventricle, EDVi = end-diastolic volume indexed to body surface area, EF = ejection fraction, BMI = body mass index.

4.1. Alternative agents for cardiac stress testing

Other coronary vasodilator agents used in stress imaging include dipyridamole and regadenoson [24]. However, as their action is via the adenosine receptor, it is likely that they will yield similar diminished haemodynamic effects in patients with heart failure. An alternative to coronary vasodilator stress tests is the inotropic/chronotropic cardiac stress agent dobutamine, which increases heart rate, blood pressure and myocardial contractility through direct stimulation of β receptors [25]. Therefore, it is possible that it may afford superior diagnostic performance compared with adenosine, though this warrants further testing in future comparative studies. The added advantage with dobutamine is its ability to distinguish viable from non-viable myocardium in patients with heart failure [26].

4.2. Limitations

We did not utilize splenic switch-off as a tool to assess the adequacy of stress testing with adenosine in this study, which may have provided additive value over haemodynamic response for identifying those patients who did not respond to adenosine. Given the complex feedback loops involving blood pressure and heart rate responses to intravenous vasodilators, heart rate change per se may not mirror the adequacy of coronary vasodilatation. Furthermore, we were unable to assess the influence of additional clinical factors that may alter the response to adenosine, such as the presence of known coronary artery disease or chronic kidney disease, haemoglobin levels and thyroid function. Our data are hypothesis generating but further work is required to definitively address this question in subjects with LVSD. Although a potential limitation, the retrospective nature of the study does mitigate against potential subjective bias regarding adenosine dose increase in individual patients, which may confound a prospectively undertaken study. In our study, supervising clinicians were not aware that this subsequent analysis would be undertaken and adenosine dose increases were as per a standardised protocol.

5. Conclusions

Patients referred for stress perfusion CMR with impaired LV systolic function have a diminished haemodynamic response to adenosine. Hence, the use of adenosine as a cardiac stressor in these patients may limit the sensitivity of perfusion imaging, with CMR as well as with alternative non-invasive imaging modalities. Further work is needed to confirm whether the blunted haemodynamic response to adenosine is associated with reduced diagnostic accuracy, and also to determine the potential utility of further dose increases or alternative stressors to achieve a satisfactory haemodynamic response.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.006.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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