Association of hemodynamic response during dipyridamole stress testing with ^{99m}Tc-MIBI SPET myocardial perfusion image findings

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Abstract

The aim of this study was to assess whether there is an association between changes in the heart rate and blood pressure after dipyridamole stress and abnormal scan findings detected with gated technetium-99m methoxy isobutylisonitrile (^{99m}Tc-MIBI) myocardial perfusion imaging (MPI). *A total of 200 consecutive patients* with known or suspected coronary artery disease underwent MPI using a 2 days stress/rest protocol. Heart rate (HR), blood pressure and electrocardiogram were monitored during the stress study. Dipyridamole-induced increase in HR ratio (peak HR/baseline HR) of more than 1.20 and decrease in systolic blood pressure (SBP) of 10mmHg or more were defined as a normal response. Low ejection fraction (EF) was defined as EF less than 45%. Semi-quantitative measures used include summed stress score (SSS), summed difference score (SDS), end systolic volume (ESV) and left ventricular ejection fraction (LVEF). Chi-square-and regression analysis was used to assess associations between the various hemodynamic parameters and MPI abnormalities. *Our results showed* that 75% of patients had abnormal scans. Statistically significant associations were observed between each of the following factors and abnormal scan findings: abnormal SBP response to dipyridamole (P=0.011), increased SSS (P=0.040) and low LVEF (P=0.012). A significant association was also observed between decreased HR response and low LVEF (P=0.012). *In conclusion*, **t**his study demonstrated that an abnormal hemodynamic response during dipyridamole stress test was associated with abnormal myocardial perfusion imaging scan findings, low LVEF and SSS.

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Introduction

Pharmacological stress testing is a commonly used alternative to exercise stress used with both single photon emission tomography (SPET) and positron emission tomography (PET) myocardial perfusion imaging (MPI). This plays an important role in the diagnosis and risk stratification of patients with coronary artery disease for [1]. Vasodilators, such as adenosine and dipyridamole, are frequently used in patients who cannot exercise adequately for a variety of reasons [2]. The afore-mentioned vasodilators augment coronary myocardial blood flow indirectly via inhibition of deaminase, relaxation of vascular smooth muscles and endothelial release of nitric oxide. This is contrary to the effect seen with exercise where increase in heart rate (HR) and blood pressure (BP) are directly proportional to myocardial oxygen demand, [3, 4].

When intravenously (i.v.) infused, dipyridamole increases endogenous adenosine by blocking its cellular uptake and by inhibiting its enzymatic degradation by adenosine deaminase [5]. Subsequently, adenosine interacts with cardiac and peripheral adrenergic A2a receptors to mediate vasodilatation of coronary and systemic arteries [6]. The systemic vasodilatory effects result in a fall in systolic BP (SBP) of at least 10mmHg and a concomitant reflex tachycardia, which increase the heart rate by about 10 beats/min [2, 6]. The clinical significance of these hemodynamic responses is debatable, [7-9] but it may provide useful predictive information on imaging abnormalities [10]. This may prove especially helpful in cases where MPI results are equivocal and a repeat study may not be feasible due to technical or logistic reasons.

Therefore, we sought to evaluate whether there is an association between hemodynamic responses and scan findings during dipyridamole stress gated technetium-99m methoxy isobutylisonitrile (^{99m}Tc-MIBI) MPI.

Materials and methods

Study population

We performed a prospective study of consecutive patients who were routinely referred for myocardial perfusion imaging to the department of Nuclear Medicine at the Steve Biko Academic Hospital and University of Pretoria. The following patients were excluded: patients who were inadequately prepared, who received nitrates for the rest study or had a SBP of less than 90mmHg. Written informed consent was obtained from all participants.

Dipyridamole stress protocol

Patients were instructed to fast for a minimum of 4h and to withhold beta-blockers, calcium channel blockers, nitrates, methyl-xanthenes containing drugs and caffeinated food and beverages for at least 24-48h prior to the study. Dipyridamole 0.142mg/kg/min was administered intravenously (i.v.) over 4min while the patient was in an upright position and performed low level exercise. To patients who experienced severe dipyridamole side effects aminophylline 50-75mg was i.v. administered.

Myocardial perfusion imaging protocol

All patients underwent a two days imaging protocol with a dipyridamole stress test. Technetium-99m-MIBI 555MBq was administered i.v. 4min after dipyridamole infusion for the stress study, and also prior to the rest study. Patients were imaged 60min after the ^{99m}Tc-MIBI injection for both the stress and the rest part of the study. Imaging was performed by SPET with a Siemens ECAM dual-head gamma camera and low energy high resolution collimator. Images were acquired using a 64x64 matrix and 20% window centred at 140kev. Both stress and rest studies were ECG gated and consisted of eight frames per cardiac cycle. Sixty four projections, of 25 seconds/projection, were acquired over a 180^0 orbit at 3^0 angular increments in a step and shoot acquisition. Images were processed using standard quantitative software (4DMSPET). No scatter or attenuation correction was applied.

Table 1. *Clinical variables in normal and abnormal scan findings*

Variable	MPI scan findings		
	Normal (n = 50)	Abnormal (n =150)	P value
Male	23 (46%)	89 (59%)	0.10
Female	27 (54%)	61 (41%)	0.10
Hypertension	44 (88%)	130 (87%)	0.80
Diabetes	20(40%)	49 (33%)	0.35
Hyperlipidaemia	31 (62%)	97(65%)	0.73
Smoking	13 (26%)	24 (16%)	0.12
Previous MI	7 (14%)	40 (27%)	0.07

Table 2. *Hemodynamic changes with dipyridamole stress*

		Mean HR (beats/min)		Mean SBP (mmHg)		Mean DBP (mmHg)	
Para-meter	Category	Before	After	Before	After	Before	After
Scan Findings	Normal (n=50)	76±15	92±12	158±38	144±33	94±17	87±17
	Abnormal (n=150)	73±14	91±17	148±30	139±55	89±16	85±15
P value		0.47	0.29	<0.001	0.80	0.09	0.92

Table 3. *Hemodynamic changes with dipyridamole stress*

		HRR		Decrease in SBP (mmHg)	
Parameter	Category	Normal ≥1.2	Abnormal <1.2	Normal ≥10	Abnormal <10
Scan Findings	Normal (n=50)	26(52%)	24(48%)	18(36%)	32(64%)
	Abnormal (n=150)	89(59%)	61(41%)	85(57%)	65(43%)
P value		<0.001	0.97	<0.001	0.12

Measurements

Baseline electrocardiogram (ECG), heart rate (HR) and blood pressure (BP) measurements were recorded for each patient and monitored every 2min following dipyridamole infusion.

Peak HR and SBP measured after dipyridamole infusion were the highest and lowest values, respectively. Heart rate ratio (HRR) was calculated as the ratio of the highest HR measured over the baseline HR and was used as an index for HR response. A HRR of more than 1.20 was defined as normal response whereas a HRR of less than 1.20 was considered an abnormal HR response. A reduction in SBP

of more than 10mmHg from baseline to peak SBP was defined as a normal response wheras a reduction of less than 10mmHg from baseline was considered as an abnormal SBP response. Depression of the ST of more than 1mm on the ECG was considered significant. The presence of left bundle branch block, pacemaker rhythm or ST depression on baseline ECG were evaluated as stress-induced ST changes.

Myocardial perfusion images were visually assessed in the short, vertical and horizontal long axes. Abnormal scans findings included reversible defects, fixed defects or both. A polar map of 17 segments was used to assess tracer uptake in each segment using the following 5-point score scale: 0=normal; 1=mild; 2=moderate, 3=severe and 4=absent uptake. The summed stress score (SSS), which represents the extent and severity of a perfusion abnormalities was obtained by adding the score of the 17 segments representing the stress study. A SSS of less than 4 was interpreted as normal, 4-8 as mild, 9-12 as moderate and more than 12 as severe vascular involvement. The summed difference score (SDS), which reflects the amount of ischemia, when less than 2 was considered as normal, 2-3 as mild, 4-7 as moderate and ≥8 as severe ischemia. End systolic volume of less than 70mL was considered normal, whereas 70mL or more was considered abnormal. Vascular territory involvement of the left anterior descending artery (LAD), the right coronary artery (RCA) and the left circumflex artery (LCx) was recorded.

Statistical analysis

Descriptive statistics was used to report patients' clinical characteristics. Semi-quantitative MPI indices of SSS, SDS, ESV and LVEF were related to HR and BP changes. Chi-square analysis testing, Students t test and logistic regression were used to assess associations between the various hemodynamic parameters and MPI abnormalities.

Results

This study included 200 consecutive patients and consisted of 112 males and 88 females who had a mean age of 57±11 years. Normal myocardial perfusion imaging results were present in 50 patients, with abnormal MPI findings noted in 150 patients. No statistically significant differences with regards to gender, co-morbidities or risk factors were detected between these two groups (see Table 1).

Dipyridamole infusion increased the heart rate and decreased SBP and DBP in patients with both normal and abnormal MPI findings. Baseline and lowest SBP and DBP measurements were slightly higher in patients with normal MPI compared to those with abnormal MPI findings, although this was not statistically significant (see Table 2).

Abnormal scans findings based on the presence of reversible, fixed perfusion defects or both were present in 150 (75%) patients. The majority of these patients 122 (81%) had fixed defects. An abnormal Heart rate ratio (HRR) of <1.2, was observed in 85 (42.5%) patients (see Table 3) for which a statistically significant association with low LVEF was found (P=0.012). The mean post-stress left ventricle EF (LVEF) was normal in patients with abnormal scan findings. However, LVEF in patients with abnormal MPI results was significantly lower than in patients with normal scans 53±17% vs 73±9%.(P<0.0001). The abnormal SBP response which was present in 97 (48.5%) patients, was significantly associated with abnormal scan findings (P=0.011), SSS (P=0.040) and low LVEF (P=0.012).

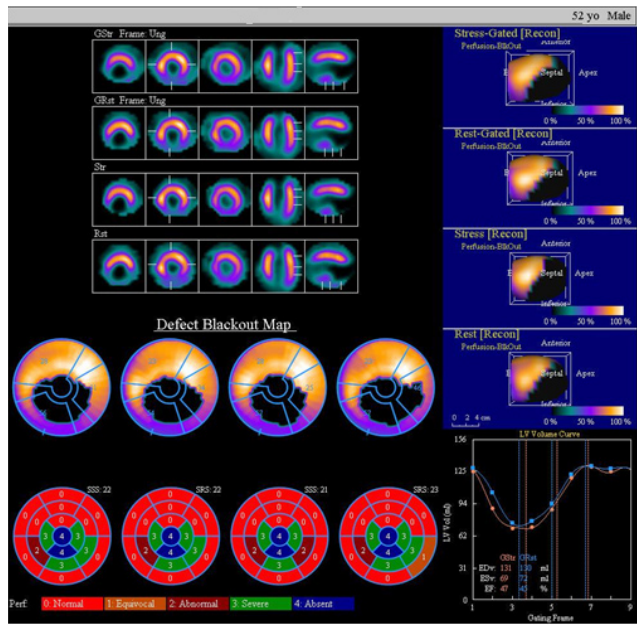

Figure 1. A 52 years old male with STEMI and progressive chest discomfort. During stress testing, his diastolic pressure raised >10mmHg, and heart rate ratio less than <1.20.

Discussion

Dipyridamole causes flow heterogeneity in coronary arteries, which, in the presence of CAD, becomes evident as myocardial perfusion defects on myocardial perfusion imaging [6, 11, 12]. The vasodilatory effect on the coronary arteries is not influenced by peripheral hemodynamic responses in HR or BP; therefore, the diagnostic accuracy of gated SPET MPI for the detection of CAD is not compromised [9, 10]. Hemodynamic responses may however, enhance detection of CAD and identify patients with high-risk disease.

This study demonstrated that patients with an abnormal hemodynamic response (an attenuated drop in SBP and/or HR response) after dipyridamole infusion are more likely to have abnormal scan findings (reversible defects, fixed or both) (Fig. 1). These patients also have an increase in LV dysfunction when compared to patients with normal scan findings. A previous study observed similar results in 2000 patients who underwent adenosine gated ^{99m}Tc-MIBI MPI [13]. The clinical and prognostic significance of a decreased HR response to dipyridamole in relation to myocardial perfusion and ventricular function has been confirmed and highlighted by various other studies [14, 15].

One of these studies (done on post-myocardial infarction patients after adenosine infusion SPET MPI) demonstrated a correlation between a decreased HR response and LVEF and SSS [14]. This finding is similar to ours. An increased cardiac-related mortality has been documented in patients with a low HR response, low LVEF and SSS >8 compared to those with normal parameters [16]. It has also been shown that in subgroups of elderly patients, those with diabetes, renal failure, non-ischemic cardiomyopathy and with normal scan findings, low HR response may be attributed to cardiovascu-

lar autonomic dysfunction and cardiac autonomic neuropathy [17-20].

Very few studies have looked at the implication of an abnormal SBP response to vasodilators [21, 22]. Contrary to the findings of another group [21], we found that an abnormal SBP response to dipyridamole was significantly associated with abnormal scan findings, low EF and SSS. Recent studies indicate that increases in HR could be due to a direct adenosine-induced stimulation of sympathetic nervous system which may be independent of the BP [23]. Another group reported myocardial ischemia more frequently in patients whose SBP was decreased compared to patients with no change or even an increment in SBP [22]. This apparent paradox was also demonstrated in our study where we found a significant association with abnormal MPI findings in patients who had a decrease in SBP ≥10mmHg. However, no significant association was present in those whose SBP decreased less than 10mmHg. We also demonstrated that there was a significant association between the scan findings and HR for patients who showed a normal response but not those who showed an abnormal response. Our results are original and also show some apparent contradictions that must be further investigated in a larger study. No significant association, however, was found between hemodynamic responses and SDS in this study. A SBP response may, therefore, be considered as a significant hemodynamic response during dipyridamole stress, although its prognostic value needs further investigation.

The mechanism of interaction between dipyridamole-induced peripheral hemodynamic changes and ventricular function is more likely to be multifactorial and is not entirely clear. However, extensive and severe myocardial perfusion defects, previous myocardial infarction with remodelling or both may lead to persistent LV dysfunction which may be compensated by activating the sympathetic nervous system and inhibitory effect on the baro-receptor reflex. Abnormal hemodynamic responses have been attributed to imbalances in cardiac autonomic control, increased catecholamine levels and alteration in adrenergic receptor G related protein [24].

In conclusion, this study showed that an abnormal hemodynamic response detected during dipyridamole stress test, is associated with abnormal MPI scan findings, low LVEF and increased SSS. This hemodynamic response is useful during MPI as it may provide useful information for study interpretation and for management of the patients studied. However, a study with a large number of patients is needed to fully implement these findings.

The authors declare that they have no conflicts of interest.

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