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Sharma, R., O'Driscoll, J., Saha, A., Sritharan, M., Sutton, R. and Rosen, S. (2015) Differing autonomic responses to dobutamine stress in the presence and absence of myocardial ischaemia. *The Journal of Physiology*, 593 (9). pp. 2171-2184. ISSN 1469-7793.

Link to official URL (if available):

<http://dx.doi.org/10.1113/JP270063>

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**DIFFERING AUTONOMIC RESPONSES TO DOBUTAMINE STRESS IN THE PRESENCE AND ABSENCE OF MYOCARDIAL ISCHAEMIA.**

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**RUNNING TITLE:** Autonomic function during dobutamine stress.

**KEY WORDS:** Autonomic Function, Ischaemia, Stress Echocardiography

**TABLE OF CONTENTS CATEGORY:** Cardiovascular.

**WORD COUNT:** 6733.

## **KEY POINTS SUMMARY:**

- Dobutamine stress echocardiography (DSE) is a validated tool for the non-invasive evaluation of myocardial ischaemia and makes feasible the recording of heart rate variability in non-resting conditions.
- In this study we determined whether individuals with transient myocardial ischaemia had different autonomic responses to the stress of dobutamine infusion compared to non-ischaemic (normal) responders.
- Non-ischaemic responders had a residual predominance of parasympathetic over sympathetic activity. However, under conditions of myocardial ischaemia, there was a directionally opposite cardiac autonomic response with a residual increase of sympathetic over parasympathetic modulation.
- The sympathetic response to dobutamine stress is augmented as the burden of myocardial ischaemia is increased.

**ABSTRACT:** Cardiac autonomic dysfunction has prognostic significance in patients with coronary artery disease. This investigation aimed to assess changes in autonomic modulation induced by dobutamine stress in the presence and absence of myocardial ischaemia. Three hundred and fourteen individuals underwent dobutamine stress echocardiography to detect or exclude myocardial ischaemia. Simultaneous autonomic and haemodynamic data were obtained using a plethysmographic device. Total power spectral density and associated low frequency (LF) and high frequency (HF) power spectral components in absolute ( $\text{ms}^2$ ) and normalised units (nu) were determined. Participants were categorised as non-ischaemic (NI) or ischaemic (IS) responders. There were no significant differences in LFnu or HFnu between groups at baseline. At peak stress, LFnu decreased from baseline in NI ( $43\pm 1.8$  to  $40\pm 1.8\%$ ), but increased from baseline in IS responders ( $39.5\pm 2$  to  $56\pm 2\%$ ,  $p<0.05$ ). In contrast, HFnu increased in NI patients ( $57\pm 1.8$  to  $60\pm 1.8\%$ ) but decreased in IS responders ( $60.5\pm 2$  to  $44\pm 2\%$ ,  $p<0.05$ ). Those with a high ischaemic burden ( $>3$  ischaemic left ventricular [LV] segments) had a greater increase in LFnu ( $41\pm 4.8$  to  $65\pm 3.2\%$  vs  $44.8\pm 3.8$  to  $57.7\pm 3.1\%$ ,  $p<0.05$ ) and greater decrease in HFnu ( $59\pm 4.8$  to  $35\pm 3.2\%$  vs  $55.2\pm 3.8$  to  $42.3\pm 3.1\%$ ,  $p<0.05$ ) compared to patients with a low ischaemic burden (1-3 ischaemic LV segments) respectively, at peak stress. In the absence of myocardial ischaemia, dobutamine stress is associated with a residual predominance of parasympathetic over sympathetic activity. Under conditions of ischaemia, there is a directionally opposite autonomic response with a significant residual increase of sympathetic over parasympathetic modulation. This response is augmented as the burden of ischaemia is increased.

**ABBREVIATIONS:** ANS, autonomic nervous system; BRS, baroreceptor reflex sensitivity; BSA, body surface area; BP, blood pressure; CAD, coronary artery disease; dBP, diastolic blood pressure; DSE, dobutamine stress echocardiography; E, early transmitral filling velocity; Ea, early transmitral tissue Doppler velocity; HF, high frequency; HR, heart rate; HRV, heart rate variability; IS, ischaemic; LF, low frequency; LV, left ventricle; LVEF, left ventricular ejection fraction; NI, non-ischaemic; NU, normalised unit; PSD, power spectral density; sBP, systolic blood pressure; TFM, task force monitor; V<sub>p</sub>, flow propagation velocity; WMSI, wall motion score index.

## INTRODUCTION

The autonomic nervous system (ANS) modulates depolarization of the sino-atrial node, inducing cyclical variations in R-R intervals. Heart rate variability (HRV), a marker of neural outflow modulation, is a valuable non-invasive tool for examining autonomic cardiovascular control (Floras, 2009). High-frequency (HF) oscillation (0.15 to 0.4 Hz) of R-R intervals is regarded as a marker of parasympathetic modulation and, although contentious, low-frequency (LF) oscillation (0.04 to 0.15 Hz) of R-R intervals is considered a marker of cardiac sympathetic activity (Akselrod *et al.*, 1981; Malliani *et al.*, 1991).

A reduced HRV predicts morbidity and mortality in healthy populations (Tsuji *et al.*, 1994; Dekker *et al.*, 1997) and in patients with coronary artery disease (CAD) (Hayano *et al.*, 1990; van Boven *et al.*, 1998). These studies have been conducted under resting conditions. There are few data on changes in autonomic modulation during functional myocardial stress in humans. Small sample size observational studies have indicated that during myocardial ischaemia there is an increase in LF oscillations of HRV (Yoshio *et al.*, 1993; Binkley *et al.*, 1995; Lanza *et al.*, 1996; Joho *et al.*, 1999) and LF/HF ratio (Petrucci *et al.*, 1996; Manfrini *et al.*, 2004), suggesting a predominance of sympathetic activity. However, the results are inconclusive due to significant differences in the nature of the stressor and haemodynamic workloads between patient groups. Petrucci *et al.* (1996) analysed differences in autonomic function between myocardial ischaemic and non-ischaemic patients, in response to microcirculatory vasodilator challenge with dipyridamole. Binkley *et al.* (1995) used dobutamine infusion to test for differences in autonomic function between ischaemic and non-ischaemic patients. Within this study, ischaemic responders

had a significantly higher heart rate response (haemodynamic workload) compared to non-ischaemic patients. It is therefore unclear if the reported differences in autonomic modulation are due to myocardial ischaemia. Research in canine models demonstrated that the ANS plays an important role in modulating the cardiovascular effects of dobutamine, buffering the chronotropic and pressor responses via reductions in systemic vascular resistance (Liang & Hood, 1979).

We present a large observational study, the aim of which was to assess the cardiac autonomic response to myocardial stress and to determine whether differences exist in ischaemic and non-ischaemic responders at comparable external, haemodynamic and myocardial workloads. We postulated that any differences may, in part, provide another mechanism for increased myocardial vulnerability during ischaemia.

Dobutamine stress echocardiography (DSE) was the model we selected, as it is a functional test validated for the diagnosis of CAD and it can differentiate low and high-risk patients according to the presence or absence of myocardial ischaemia (Sicari *et al.*, 2003).

## **METHODS**

### **Ethical Approval**

All procedures for this investigation conformed to Declaration of Helsinki principles and the National Research Ethics Service Committee for London-Harrow approved the study (09/H0710/37). Signed informed written consent was obtained from all participants.

### **Study Design and Patients**

We prospectively recruited 314 patients undergoing clinically indicated DSE for the evaluation of angina pectoris. All patients underwent DSE with simultaneous autonomic and haemodynamic monitoring. Exclusion criteria included unstable angina, severe aortic stenosis, age <18 years, inability to consent, patients not in sinus rhythm and a left ventricular ejection fraction (LVEF) <40% (due to the confounding influence impaired LV function has on measures of HRV). In addition, patients who developed extra-systoles and those who required atropine to achieve target HR were excluded. The DSE results were interpreted by 2 or more experienced readers (>5 years experience), who were blinded to the results of all other tests.



## **Echocardiographic Image Acquisition**

All image acquisitions and measurements were performed as recommended by the American Society of Echocardiography (Schiller *et al.*, 1989). LVEF was determined by the modified biplane Simpson's rule, with measurements averaged over three cardiac cycles. Pulsed Doppler was used to record transmitral flow in the apical four-chamber view. Flow propagation velocity ( $V_p$ ) was calculated from colour M mode in the apical four chamber view. Tissue Doppler velocities were acquired at the lateral mitral annulus. LV filling pressure was estimated from the mitral E/Ea and E/ $V_p$  ratios (Ommen *et al.*, 2000). Measured values were indexed to body surface area (BSA).

## **Dobutamine Stress Challenge**

Patients underwent a standard DSE protocol (Pellikka *et al.*, 1995) with stepwise infusion of dobutamine in 3-minute stages of 10, 20, 30, 40  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .  $\beta$ -blocker therapy was stopped 72-hours before DSE. Images were acquired in standard parasternal long- and short-axis and apical two, three, and four chamber views at baseline, during infusion of dobutamine and in recovery. Baseline, low-dose (HR 10–15 beats above baseline), peak, and recovery (10-minutes after infusion terminated) images were stored in digital quad screen format for off-line analysis. A 12-lead electrocardiogram (ECG) and blood pressure (BP) were recorded at each infusion stage. Criteria for terminating the test were achievement of target HR of  $(220-\text{age}) \times 0.85 \text{ b}\cdot\text{min}^{-1}$ , development or deterioration of wall motion abnormalities, angina, ST depression  $>2 \text{ mm}$ , systolic blood pressure (sBP) increase to  $>240 \text{ mmHg}$  or decrease to  $<100 \text{ mmHg}$ , diastolic

blood pressure (dBP) increase >140 mmHg, and if severe ventricular or supraventricular arrhythmias developed. The LV was divided into a 17-segment model for qualitative analysis (Cerqueira *et al.*, 2002). Regional myocardial wall motion was described as normal, hyperkinetic, hypokinetic, akinetic, or dyskinetic. In the non-*ischaemic* (normal) response, a segment is normokinetic or hypokinetic at rest with an overall increase in wall motion during stress. In the *ischaemic* response, a segment worsens its function during stress from normokinesis to hypokinesis, akinesis, or dyskinesis (Armstrong, 1991). Based on the myocardial response to dobutamine during stress echocardiography, patients were categorised as non-*ischaemic* or *ischaemic*. The resting and peak wall motion score index (WMSI) was calculated. Patients were further categorised with low (1-3 *ischaemic* LV segments) or high (>3 *ischaemic* LV segments) *ischaemic* burden as per European Society of Cardiology guidelines (Sicari *et al.*, 2008). For patients with poor endocardial border definition in 2 or more contiguous LV segments, the intravenous LV contrast agent SonoVue<sup>®</sup> was used to ensure optimal LV border definition.

### **Autonomic and Haemodynamic Assessment**

The Task Force<sup>®</sup> Monitor (TFM) (CNSystems, Graz, Austria) is a validated non-invasive monitoring system (Fortin *et al.*, 2001), which was used for the continuous beat-to-beat monitoring and real-time calculation of all autonomic and haemodynamic parameters. HR was calculated from the ECG, beat-to-beat stroke index by impedance cardiography (Fortin *et al.*, 2006a), and beat-to-beat BP by the vascular unloading technique (Fortin *et al.*, 2006b). Beat-to-beat BP was automatically corrected to oscillometric BP values obtained from the brachial artery

of the contralateral arm. Baroreceptor reflex sensitivity (BRS) was automatically calculated using the sequence method (Bertinieri *et al.*, 1985), which is based on computer identification of a series of successive increases or decreases in sBP (3 beats) and assessment of the effect on pulse interval. The slope of the regression line between the sBP and pulse interval in each sequence is taken as an index of the BRS control of the heart (Di Rienzo *et al.*, 2001; Valipour *et al.*, 2005). Total peripheral vascular resistance was calculated according to Ohm's law and indexed to BSA.

HRV was calculated using power spectral analysis and applying an autoregressive model (Fortin, 1998). Specific frequencies within the power spectrum of HRV have been previously used to quantify autonomic nervous control of the cardiovascular system. LF-HRV is considered a marker of sympathetic efferent drive to the heart (Akselrod *et al.*, 1981; Pomeranz *et al.*, 1985; Montano *et al.*, 1994) and HF-HRV is an indicator of parasympathetic cardiac modulation (Akselrod *et al.*, 1981; Pomeranz *et al.*, 1985). Parameters of HRV were automatically calculated by the TFM and expressed in absolute ( $\text{ms}^2$ ) and normalised units (nu). The normalisation of the frequency components of HRV has proven crucial to the interpretation of data (Malliani *et al.*, 1994) and the ratio of LF-to-HF for HRV is an accepted index of cardiac sympathovagal balance (Ditor *et al.*, 2005).

### **Heart Rate Variability Data Analysis**

The TFM records HRV data continuously and intervention marks enable the separation of the cumulative HRV data into independent stages during DSE. Intervention marks were set at

baseline, at each incremental dose of dobutamine infusion (10, 20, 30, and 40  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), and at 3 and 10-minutes into recovery. Fifteen minutes of supine resting HRV data was obtained, in line with current short-term HRV recording recommendations (Marek *et al.*, 1996). During DSE, the intervention marks allowed independent HRV sampling for each 3-minute incremental dose of dobutamine as well as sampling at 3 and 10-minutes into recovery. All biological signals were recorded with a sample frequency of 1000 Hz and 16-bit resolution.

## **Statistics**

Unless otherwise stated, continuous variables were expressed as mean $\pm$ SD. All data were analysed using the statistical package for social sciences (SPSS 19 release version for Windows; SPSS Inc., Chicago IL, USA). Differences between and within groups were determined by 2-way repeated measures ANOVA and Chi-square test was used to compare categorical data. The C statistic (area under the receiver operator curve [AUC]) was computed as a measure of the ability for HRV to discriminate non-ischaemic and ischaemic patients. A *p* value <0.05 was regarded as statistically significant.

## RESULTS

### General

Of the 379 patients referred for DSE, 65 were excluded from our final analyses (Figure 1). Table 1 shows the demographic characteristics. The DSE examination result was interpreted as positive for inducible myocardial ischaemia in 62 (19.7%) patients and negative in 252 (80.3%). There were no significant differences between non-ischaemic (NI) and ischaemic (IS) patients with respect to age, sex, BSA, smoking history, hypertension, hypercholesterolemia, diabetes, previous percutaneous coronary intervention, previous myocardial infarction, left ventricular hypertrophy and anti-ischaemic drugs (Table 1). Family history of cardiovascular disease was more common in IS responders ( $p<0.001$ ). In addition, IS responders were more likely to have undergone coronary artery bypass graft surgery and be on aspirin (all  $p<0.05$ ).

When IS patients were further evaluated (Table 2), patients with greater LV ischaemic burden (>3 ischaemic LV segments) were older and more likely to be on aspirin compared to patients with low ischaemic burden (1-3 ischaemic LV segments) (all  $p<0.05$ ).

### Dobutamine stress response and echocardiographic classification

No adverse events occurred during the DSE procedure and the dobutamine dose was comparable between groups ( $32.4\pm 6$  and  $34.9\pm 4$   $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , IS and NI group respectively). Significant differences (all  $p<0.05$ ) were seen between IS and NI patient groups with LV end systolic

diameter, LV end diastolic diameter, LVEF, WMSI, mitral E/Ea, and mitral E/Vp at baseline and peak dose dobutamine (Table 3). LV maximal wall thickness was similar in the 2 groups.

### **Haemodynamic response to dobutamine stress**

Table 4 shows the haemodynamic response to dobutamine stress in IS and NI responders. At baseline, only dBp differed between groups. In NI responder's dobutamine stress produced a significant increase in HR ( $p<0.001$ ), sBP ( $p<0.05$ ), rate pressure product ( $p<0.001$ ), and cardiac index (defined as cardiac output/body surface area) ( $p<0.05$ ), and a significant decrease in stroke index ( $p<0.05$ ), and total peripheral resistance index ( $p<0.001$ ). In IS responder's dobutamine stress produced a significant increase in HR ( $p<0.001$ ), rate pressure product ( $p<0.001$ ), and cardiac index ( $p<0.05$ ), and a significant decrease in stroke index ( $p<0.05$ ), and total peripheral resistance index ( $p<0.001$ ). At peak dose dobutamine significant differences between IS and NI responders were seen in sBP, dBp, and cardiac index (all  $p<0.05$ ).

### **Autonomic response to dobutamine stress**

Autonomic responses to dobutamine stress in IS and NI patients are shown in figure 2 and table 4. Dobutamine infusion produced a significant reduction in R-R power spectral density (PSD) and associated R-RLFms<sup>2</sup> and R-RHFms<sup>2</sup> oscillations in both IS and NI responders from baseline to peak dose dobutamine (all  $p<0.001$ ). At baseline, IS patients had significantly lower PSD and R-RLFms<sup>2</sup> (both  $p<0.05$ ) compared to NI patients. At peak dose dobutamine IS patients had significantly lower R-RLFms<sup>2</sup> and R-RHFms<sup>2</sup> (both  $p<0.05$ ) compared to NI patients. When

analyzing HRV in normalised units (nu), R-RHFnu ( $44\pm 2\%$  vs  $60\pm 1.8\%$ ) and R-RLFnu ( $56\pm 2\%$  vs  $40\pm 1.8\%$ ) differed significantly (all  $p<0.05$ ) between IS and NI responders respectively, at peak dose dobutamine. From baseline to peak dose dobutamine R-RHFnu tended to increase ( $57\pm 1.8\%$  to  $60\pm 1.8\%$ ) in NI responders, but significantly decreased ( $p<0.05$ ) in IS responders ( $60.5\pm 2\%$  to  $44\pm 2\%$ ). In contrast, from baseline to peak dose dobutamine R-RLFnu tended to decrease ( $43\pm 1.8\%$  to  $40\pm 1.8\%$ ) in NI responders, but significantly increased ( $p<0.05$ ) in IS responders ( $39.5\pm 2\%$  to  $56\pm 2\%$ ). From baseline to peak dose dobutamine, the R-RLF/HF ratio tended to increase in IS responders ( $1.32\pm 0.12$  to  $1.7\pm 0.09$ ) and tended to decrease in NI responders ( $1.6\pm 0.21$  to  $1.3\pm 0.09$ ). There was a significant group by time interaction for R-RLFnu and R-RHFnu ( $F(4,26) = 4.33, p<0.05$ ) and the LF/HF ratio ( $F(4,18) = 3.65, p<0.05$ ).

Of note, there were no significant differences in BRS between groups during dobutamine infusion and no significant differences were seen in autonomic function according to ischaemic territory (anterior versus posterior myocardial ischaemic regions). Furthermore, baseline total power spectral density of HRV was a poor indicator of the development of myocardial ischaemia during DSE (AUC = 0.56, 95% CI 0.48 – 0.64,  $p=0.17$ ).

### **Ischaemic Burden**

When IS responders were further evaluated, patients with greater ischaemic burden ( $>3$  ischaemic LV segments) had a significantly higher pulse pressure, and significantly lower R-PSD and R-RLFms<sup>2</sup> (all  $p<0.05$ ) compared to low ischaemic burden (1-3 ischaemic LV segments) patients at baseline (Table 5). Patients with the greatest ischaemic burden

demonstrated a significantly greater increase in R-RLFnu oscillations ( $41\pm 4.8$  to  $65\pm 3.2\%$  vs  $44\pm 3.8$  to  $57.7\pm 3.1\%$ ,  $p<0.05$ ) and greater decrease in R-RHFnu ( $59\pm 4.8$  to  $35\pm 3.2\%$  vs  $55.2\pm 3.8$  to  $42.3\pm 3.1\%$ ,  $p<0.05$ ) compared to patients with low ischaemic burden, from baseline to peak dose dobutamine. Significant differences between ischaemic groups were also seen in recovery (Figure 3).



## DISCUSSION

Our study has shown that autonomic modulation during dobutamine infusion is significantly different between IS and NI responders at comparable external, haemodynamic and myocardial workloads. In the absence of myocardial ischaemia, dobutamine stress is associated with a residual predominance of parasympathetic over sympathetic activity. Vagal activation promotes vasodilatation (Kovach *et al.*, 1995) and may exert anti-fibrillatory effects (Myers *et al.*, 1974; La Rovere *et al.*, 2002). In contrast, under conditions of ischaemia, there is a reverse alteration of autonomic balance with greater residual sympathetic over parasympathetic activity.

Patients with highest ischaemic burden (>3 ischaemic LV segments) demonstrated a significantly greater move towards a residual predominance of sympathetic over parasympathetic activity compared to patients with low ischaemic burden (1-3 ischaemic LV segments). This suggests that the shift in residual autonomic balance is related to the magnitude of the ischaemic response. Importantly, significant differences were also seen at rest in PSD and absolute measures of R-RLFms<sup>2</sup> between IS and NI groups and between those with high versus low ischaemic burden. A low HRV is associated with increased risk of death and a reduced LF has been associated with greater sympathetic activity in high-risk cardiac patients (Kotecha *et al.*, 2011).

### *Comparison with previous studies*

There are few studies that have assessed autonomic function during myocardial ischaemia and all had small sample sizes. Lanza *et al.* (1996) and Yoshio *et al.* (1993) analysed changes in HRV during episodes of spontaneous ST segment elevation detected on Holter monitor. However, it is

difficult to ascertain if all ST segment changes were due to ischaemia. Joho et al. (1999) used balloon coronary occlusion, which is non-physiological with the potential for infarction as well as ischaemia. Manfrini et al. (2004) compared balloon inflation with spontaneous ischaemia but the mean duration of HRV analysis was more than double for spontaneous ischaemia, which would influence HRV data. Petrucci et al. (1996) assessed changes in HRV in IS and NI patients during dipyridamole infusion; however IS patients had lower doses of the drug than NI, which may have caused the differences reported. In addition, dipyridamole itself has direct effects on sympathetic outflow from the central nervous system (Lucarini *et al.*, 1992). Binkley et al. (1995) used dobutamine stress to ascertain differences in HRV response in 16-patients. However IS patients had a significantly greater haemodynamic response, which may, in part, have accounted for the results. In addition, ischaemic burden, BRS, and recovery were not assessed.

#### *Possible explanations for the autonomic responses*

Several possible mechanisms could be suggested to explain the autonomic responses that we found, but most are problematic. (a) Haemodynamic workload cannot be the cause of the differences, since there were no significant differences with respect to HR or BRS from baseline to peak dose dobutamine. (b) Altered reflexes associated with LV hypertrophy are unlikely to account for our findings since LV wall thickness was similar in those with and without ischaemia. (c) Dobutamine dose was comparable between groups; and (d) the medications of the two groups of patients were comparable. (e) The autonomic dysfunction known to be associated with impaired systolic function does not fully explain our data since mean LVEF was within normal limits in both IS and NI groups; and (f) similarly, although differences in diastolic function existed between IS and NI groups, there was no significant difference in diastolic

function between patients with low vs high ischaemic burden (data not shown). This would suggest diastolic function contributes to the observed difference between IS and NI groups, but cannot be the sole cause. (g) The absence of differences in BRS is a significant negative result bearing in mind the known reduction in BRS in some post-MI patients who have an associated increased arrhythmic risk. However, in the best known of these studies, that of La Rovere et al. (1998), the increased risk in post-MI patients was significant only when HRV and BRS ( $<3.0 \text{ ms}\cdot\text{mmHg}^{-1}$ ) were depressed and risk was greatest in patients with a LVEF  $<35\%$ . In patients with a BRS  $>6.1 \text{ ms}\cdot\text{mmHg}^{-1}$  there was a 2-year mortality rate of just 2%. At baseline in our study, mean BRS was  $\geq 11 \text{ ms}\cdot\text{mmHg}^{-1}$  for NI, IS, and low and high ischaemic burden patients. In addition, no significant differences in autonomic modulation were seen in our IS patients according to ischaemic territory. This contrasts with typical clinical findings in post-MI patients with anterior versus posterior infarction, in whom differences in the reflex response to myocardial injury are observed according to anatomical region of injury, characteristically with posterior MI resulting in bradycardia and hypotension (Bezold-Jarisch effect) and anterior MI more frequently evoking tachycardia and hypertension (Bainbridge reflex) (Webb *et al.*, 1972; Zipes, 1990). The differences observed in our study may be due to our subjects experiencing transient ischaemia compared to myocyte injury tissue necrosis.

We recognise that IS patients had a significantly lower LVEF and significantly higher estimated LV filling pressure than NI responders. These differences may have contributed to the observed differing autonomic responses of the 2 groups during stress. This may also be true for the greater number of patients in the IS group who underwent previous coronary intervention. In addition, although not significantly different, IS patients and those with a higher ischaemic response had a

higher percentage of patients with diabetes. It is well known that pre-clinical cardiomyopathy is associated with cardiac autonomic neuropathy in patients with diabetes and as well as being at higher risk of presenting with myocardial ischaemia, these patients also have a higher prevalence of autonomic neuropathy (Dinh *et al.*, 2011). However, although these differences likely impact cardiac autonomic modulation between the two groups, myocardial ischaemia also appears to play a significant role. This is particularly evident when IS patients were divided according to the degree of myocardial ischaemia. We found that a dose-response relationship exists, such that patients with greater myocardial ischaemia demonstrate a greater increase in residual sympathetic over parasympathetic modulation compared to low ischaemic burden patients.

In NI responders, the Bezold-Jarisch reflex (Mark, 1983) may explain the autonomic response seen. Stimulation of inhibitory cardiac receptors by stretch (mechanoreceptor stimulation) and chemoreceptor stimulation due to acidosis and reactive oxygen species (Huang *et al.*, 1995; Longhurst *et al.*, 2001) augments parasympathetic modulation and inhibits sympathetic activity, governed by vagal reflexes. In the IS group, this response may have been delayed, potentially due to diminished sympathoinhibitory reflexes. Myocardial ischaemia is capable of producing transient dysfunction of autonomic cardiac modulation, which can extend into the reperfusion period (Malliani *et al.*, 1969; Abe *et al.*, 1997). Indeed, loss of vagal reflex has been shown with coronary occlusion (Zipes, 1990). A cardiac sympathetic reflex response may be activated by metabolic mediators (Malliani *et al.*, 1983; Longhurst *et al.*, 2001), such as adenosine, which may affect neurotransmission in the ischaemic area and acts as a biochemical stimulus in the ischaemic cascade. This functional neural impairment may have important clinical implications, since it may contribute to ventricular tachyarrhythmias (Abe *et al.*, 1997). Dysfunction of

sympathoinhibitory reflexes has been demonstrated through a reduction in sBP, reduced inotropy, and through altered ventricular dilation (Floras, 1993). Indeed, IS patients had significantly greater LV dilatation and a significantly reduced CI, sBP, and LVEF at peak dose dobutamine, which supports this concept.

The coronary circulation is dynamic, responding to changes in metabolic tissue demand via arterial vasodilatation and vasoconstriction and therefore controlling blood flow and oxygen delivery to the myocardium. Neural and endocrine stimuli including cardiac adrenergic signals are important mediators in regulating myocardial blood flow (Di Carli *et al.*, 1997). An increase in sympathetic nerve activity causes coronary artery dilatation and thus increases myocardial blood flow (Zeiber *et al.*, 1989), and atherosclerosis is associated with an impairment in the capability of the coronary arteries to dilate (Zeiber & Drexler, 1991; Zeiber *et al.*, 1991). In addition, ischaemia and the metabolic process itself may directly promote an increase in sympathetic nerve activity as described above.

Patient follow-up was too short to derive any prognostic significant of the autonomic response seen. However, a reduced HRV and sympathetic activation is associated with CAD, hypertension, heart failure and a poorer prognosis (Marek *et al.*, 1996). Indeed, a recent angiographic study demonstrated a high inverse correlation with LF power and severity of CAD (Kotecha *et al.*, 2011). Furthermore, sympathetic drive and parasympathetic withdrawal reflected by changes in HRV has been demonstrated in ambulatory human subjects with ischaemic episodes (Bernardi *et al.*, 1988) and before the onset of major arrhythmic events in patients with implantable cardioverter defibrillators (Guzzetti *et al.*, 2005). Therefore, the results of this study

may have many clinical implications for patients with ischemic heart disease and explain, in part, a potential cause of increased mortality seen in this group.

To our knowledge this is the first human functional myocardial stress study to compare differences in autonomic modulation between IS and NI responders at comparable external, haemodynamic and myocardial workloads as well as evaluating differences in the magnitude of ischaemia. The findings are consistent with results of previous research, however, a potential association of this response with the generation of arrhythmia and increased mortality, requires further research.

#### *Clinical Perspective*

Cardiac autonomic dysfunction, specifically a decrease in parasympathetic activity and the presence of myocardial ischaemia are associated with an increased risk of mortality. It may be suggested that patients who exhibit such responses are candidates for closer surveillance, which may include early revascularization and/or more aggressive pharmacological and/or device therapy to protect against premature mortality.

#### *Study Limitations*

The interplay between the ANS and myocardial ischaemia are complex and difficult to study in humans. In this study we used DSE since it is a reproducible, standardized, non-invasive clinical technique used to analyze transient myocardial ischemia. In addition, it enables stationary recording, which is essential for HRV recording. However, although DSE has high sensitivity and specificity, it is operator dependent and subjective in detection of inducible myocardial

ischemia. In order to reduce subjectivity two experienced independent observers reported images off line.

It may not be possible to differentiate endogenous autonomic modulation from direct myocardial stimulation from dobutamine on HRV. However, persistent beta stimulation produced by a steady-state infusion of dobutamine may not itself be expected to directly alter the dynamic phasic changes associated with HRV (Binkley *et al.*, 1995). Therefore, the differences observed in HRV are probably induced by reflexive autonomic modulation in response to the changes in chemical and mechanical milieu of the myocardium during dobutamine administration.

We recognise that sampling HRV data for only 3-minutes at each stage of dobutamine infusion is a limitation. However, we felt it would have been inappropriate to modify a routine standardised clinical investigation in order to obtain longer periods of recording at each incremental dose. In addition, although non-ischaemic patients within the study cannot be regarded as normal subjects, the absence of inducible myocardial ischaemia makes them an appropriate control group for the study.

The Bezold-Jarisch reflex might, at least in the case of the NI patients, explain the findings; to pursue this, one could conduct a microneurographic study during DSE to look at sympathetic efferent activity with greater precision and temporal resolution, but it would not be a very easy or tolerable study in practice. A further limitation is that we did not control for respiratory rate at rest or during dobutamine infusion. However, metronome-guided respiration is not necessarily required for HRV measurement if subjects avoid irregular respiration (Kobayashi, 2009).

Furthermore, previous research has demonstrated that dobutamine infusion does not significantly alter breathing rate (van de Borne *et al.*, 1999).

## **CONCLUSION**

Our findings suggest that in the absence of myocardial ischaemia, dobutamine stress is associated with a significant increase in residual parasympathetic over sympathetic modulation. However, during ischaemia, there is a directionally opposite response in residual autonomic tone, with greater sympathetic compared to parasympathetic activity. This response is augmented as the burden of ischaemia is increased.

**ACKNOWLEDGEMENTS:** None

**FUNDING:** None

**CONFLICTS OF INTEREST:** None



## REFERENCES

- Abe T, Morgan DA & Gutterman DD. (1997). Protective role of nerve growth factor against postischemic dysfunction of sympathetic coronary innervation. *Circulation* **95**, 213-220.
- Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC & Cohen RJ. (1981). Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* **213**, 220-222.
- Armstrong WF. (1991). Stress echocardiography for detection of coronary artery disease. *Circulation* **84**, 143-49.
- Bernardi L, Lumina C, Ferrari MR, Ricordi L, Vandeia I, Fratino P, Piva M & Finardi G. (1988). Relationship between fluctuations in heart rate and asymptomatic nocturnal ischaemia. *Int J Cardiol* **20**, 39-51.
- Bertinieri G, di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A & Mancia G. (1985). A new approach to analysis of the arterial baroreflex. *J Hypertens Suppl* **3**, S79-81.
- Binkley PF, Orsinelli DA, Nunziata E, Patterson SP, Khot UN, Puri R, Latcham AP & Pearson AC. (1995). Differing autonomic response to dobutamine in the presence and absence of ischemia: implications for the autonomic contribution to positive inotropic intervention. *Am Heart J* **130**, 1054-1061.

- Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T & Verani MS. (2002). Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* **105**, 539-542.
- Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA & Kromhout D. (1997). Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol* **145**, 899-908.
- Di Carli MF, Tobes MC, Mangner T, Levine AB, Muzik O, Chakroborty P & Levine TB. (1997). Effects of cardiac sympathetic innervation on coronary blood flow. *N Engl J Med* **336**, 1208-1215.
- Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G & Pedotti A. (2001). Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. *Am J Physiol Regul Integr Comp Physiol* **280**, R744-751.
- Dinh W, Futh R, Lankisch M, Bansemir L, Nickl W, Scheffold T, Bufe A, Krahn T & Ziegler D. (2011). Cardiovascular autonomic neuropathy contributes to left ventricular diastolic dysfunction in subjects with Type 2 diabetes and impaired glucose tolerance undergoing coronary angiography. *Diabet Med* **28**, 311-318.

- Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N & Hicks AL. (2005). Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. *J Appl Physiol* **98**, 1519-1525.
- Floras JS. (1993). Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* **22**, 72A-84A.
- Floras JS. (2009). Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* **54**, 375-385.
- Fortin J, Habenbacher W, Heller A, Hacker A, Grullenberger R, Innerhofer J, Passath H, Wagner C, Haitchi G, Flotzinger D, Pacher R & Wach P. (2006a). Non-invasive beat-to-beat cardiac output monitoring by an improved method of transthoracic bioimpedance measurement. *Comput Biol Med* **36**, 1185-1203.
- Fortin J, Haitchi G, Bojic A, Habenbacher W, Grullenberger R, Heller A, Pacher R, Wach P & Skrabal F. (2001). Validation and verification of the Task Force® Monitor.
- Fortin J, Marte W, Grullenberger R, Hacker A, Habenbacher W, Heller A, Wagner C, Wach P & Skrabal F. (2006b). Continuous non-invasive blood pressure monitoring using concentrically interlocking control loops. *Comput Biol Med* **36**, 941-957.

- Fortin JH, W. Gruellenberger, R. Wach, P. Skrabal, F. (1998). Real-time monitor for hemodynamic beat-to-beat parameters and powerspectra analysis of the biosignals. *Engineering in Medicine and Biology Society, 1998 Proceedings of the 20th Annual International Conference of the IEEE vol.1*, 360-363
- Guzzetti S, Borroni E, Garbelli PE, Ceriani E, Della Bella P, Montano N, Cogliati C, Somers VK, Malliani A & Porta A. (2005). Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation. *Circulation* **112**, 465-470.
- Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K, Watanabe Y & Takata K. (1990). Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. *Circulation* **81**, 1217-1224.
- Huang HS, Pan HL, Stahl GL & Longhurst JC. (1995). Ischemia- and reperfusion-sensitive cardiac sympathetic afferents: influence of H<sub>2</sub>O<sub>2</sub> and hydroxyl radicals. *Am J Physiol* **269**, H888-901.
- Joho S, Asanoi H, Remah HA, Igawa A, Kameyama T, Nozawa T, Umeno K & Inoue H. (1999). Time-varying spectral analysis of heart rate and left ventricular pressure variability during balloon coronary occlusion in humans: a sympathoexcitatory response to myocardial ischemia. *J Am Coll Cardiol* **34**, 1924-1931.

- Kobayashi H. (2009). Does paced breathing improve the reproducibility of heart rate variability measurements? *J Physiol Anthropol* **28**, 225-230.
- Kotecha D, New G, Flather MD, Eccleston D, Pepper J & Krum H. (2011). Five-minute heart rate variability can predict obstructive angiographic coronary disease. *Heart* **98**, 395-401.
- Kovach JA, Gottdiener JS & Verrier RL. (1995). Vagal modulation of epicardial coronary artery size in dogs. A two-dimensional intravascular ultrasound study. *Circulation* **92**, 2291-2298.
- La Rovere MT, Bersano C, Gnemmi M, Specchia G & Schwartz PJ. (2002). Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. *Circulation* **106**, 945-949.
- La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A & Schwartz PJ. (1998). Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* **351**, 478-484.
- Lanza GA, Pedrotti P, Pasceri V, Lucente M, Crea F & Maseri A. (1996). Autonomic changes associated with spontaneous coronary spasm in patients with variant angina. *J Am Coll Cardiol* **28**, 1249-1256.

- Liang CS & Hood WB, Jr. (1979). Dobutamine infusion in conscious dogs with and without autonomic nervous system inhibition: effects on systemic hemodynamics, regional blood flows and cardiac metabolism. *J Pharmacol Exp Ther* **211**, 698-705.
- Longhurst JC, Tjen ALSC & Fu LW. (2001). Cardiac sympathetic afferent activation provoked by myocardial ischemia and reperfusion. Mechanisms and reflexes. *Ann N Y Acad Sci* **940**, 74-95.
- Lucarini AR, Picano E, Marini C, Favilla S, Salvetti A & Distante A. (1992). Activation of sympathetic tone during dipyridamole test. *Chest* **102**, 444-447.
- Malliani A, Lombardi F & Pagani M. (1994). Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* **71**, 1-2.
- Malliani A, Pagani M, Lombardi F & Cerutti S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation* **84**, 482-492.
- Malliani A, Pagani M, Pizzinelli P, Furlan R & Guzzetti S. (1983). Cardiovascular reflexes mediated by sympathetic afferent fibers. *J Auton Nerv Syst* **7**, 295-301.
- Malliani A, Schwartz PJ & Zanchetti A. (1969). A sympathetic reflex elicited by experimental coronary occlusion. *Am J Physiol* **217**, 703-709.

- Manfrini O, Morgagni G, Pizzi C, Fontana F & Bugiardini R. (2004). Changes in autonomic nervous system activity: spontaneous versus balloon-induced myocardial ischaemia. *Eur Heart J* **25**, 1502-1508.
- Marek M, Bigger T, Camm JA, Kleiger RE, Malliani A, Moss AJ & Schwartz PJ. (1996). Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* **93**, 1043-1065.
- Mark AL. (1983). The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* **1**, 90-102.
- Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M & Malliani A. (1994). Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation* **90**, 1826-1831.
- Myers RW, Pearlman AS, Hyman RM, Goldstein RA, Kent KM, Goldstein RE & Epstein SE. (1974). Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. *Circulation* **49**, 943-947.
- Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM & Tajik AJ. (2000). Clinical utility of Doppler echocardiography and tissue Doppler imaging in the

estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation* **102**, 1788-1794.

Pellikka PA, Roger VL, Oh JK, Miller FA, Seward JB & Tajik AJ. (1995). Stress echocardiography. Part II. Dobutamine stress echocardiography: techniques, implementation, clinical applications, and correlations. *Mayo Clin Proc* **70**, 16-27.

Petrucci E, Mainardi LT, Balian V, Ghiringhelli S, Bianchi AM, Bertinelli M, Mainardi M & Cerutti S. (1996). Assessment of heart rate variability changes during dipyridamole infusion and dipyridamole-induced myocardial ischemia: a time variant spectral approach. *J Am Coll Cardiol* **28**, 924-934.

Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ & et al. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* **248**, H151-153.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I & et al. (1989). Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* **2**, 358-367.



- Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL & European Association of E. (2008). Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* **9**, 415-437.
- Sicari R, Pasanisi E, Venneri L, Landi P, Cortigiani L & Picano E. (2003). Stress echo results predict mortality: a large-scale multicenter prospective international study. *J Am Coll Cardiol* **41**, 589-595.
- Tsuji H, Venditti FJ, Jr., Manders ES, Evans JC, Larson MG, Feldman CL & Levy D. (1994). Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* **90**, 878-883.
- Valipour A, Schneider F, Kossler W, Saliba S & Burghuber OC. (2005). Heart rate variability and spontaneous baroreflex sequences in supine healthy volunteers subjected to nasal positive airway pressure. *J Appl Physiol* **99**, 2137-2143.
- van Boven AJ, Jukema JW, Haaksma J, Zwinderman AH, Crijns HJ & Lie KI. (1998). Depressed heart rate variability is associated with events in patients with stable coronary artery disease and preserved left ventricular function. REGRESS Study Group. *Am Heart J* **135**, 571-576.

van de Borne P, Heron S, Nguyen H, Unger P, Leeman M, Vincent JL & Degaute JP. (1999).

Arterial baroreflex control of the sinus node during dobutamine exercise stress testing.

*Hypertension* **33**, 987-991.

Webb SW, Adgey AA & Pantridge JF. (1972). Autonomic disturbance at onset of acute

myocardial infarction. *Br Med J* **3**, 89-92.

Yoshio H, Shimizu M, Sugihara N, Kita Y, Shimizu K, Minagawa F, Nakabayashi H & Takeda

R. (1993). Assessment of autonomic nervous activity by heart rate spectral analysis in

patients with variant angina. *Am Heart J* **125**, 324-329.

Zeiber AM & Drexler H. (1991). Coronary hemodynamic determinants of epicardial artery

vasomotor responses during sympathetic stimulation in humans. *Basic Res Cardiol* **86**

**Suppl 2**, 203-213.

Zeiber AM, Drexler H, Wollschlaeger H, Saurbier B & Just H. (1989). Coronary vasomotion in

response to sympathetic stimulation in humans: importance of the functional integrity of

the endothelium. *J Am Coll Cardiol* **14**, 1181-1190.

Zeiber AM, Drexler H, Wollschlager H & Just H. (1991). Endothelial dysfunction of the

coronary microvasculature is associated with coronary blood flow regulation in patients

with early atherosclerosis. *Circulation* **84**, 1984-1992.

Zipes DP. (1990). Influence of myocardial ischemia and infarction on autonomic innervation of heart. *Circulation* **82**, 1095-1105.

## Figure legends

Figure 1: DSE=dobutamine stress echocardiography.

Figure 2: Autonomic response to dobutamine stress in ischaemic and non-ischaemic patient groups (mean [SEM]). Note: A=R-R Power spectral density (HRV) response; B=R-R normalised units low frequency response; C=R-R normalised units high frequency response; D=R-R LF/HF Ratio;  $*$ = $p<0.05$  between groups;  $\dagger$ = $p<0.05$  and  $\ddagger$ = $p<0.001$  within groups from baseline to peak dose dobutamine;  $\S$ = $p<0.05$  and  $\parallel$ = $p<0.001$  within groups from peak dose dobutamine to recovery.

Figure 3: Autonomic response to dobutamine stress in patients with low and high ischaemic burden (mean [SEM]). Note: A=R-R Power spectral density (HRV) response; B=R-R normalised units low frequency response; C=R-R normalised units high frequency response; D=R-R LF/HF Ratio;  $*$ = $p<0.05$  between groups;  $\dagger$ = $p<0.05$  and  $\ddagger$ = $p<0.001$  within groups from baseline to peak dose dobutamine;  $\S$ = $p<0.05$  and  $\parallel$ = $p<0.001$  within groups from peak dose dobutamine to recovery.

Table 1. Baseline Characteristics of Ischaemic and Non-Ischaemic Patient Groups.

Characteristics	Non-Ischaemic (n=252)	Ischaemic (n=62)
<b>Demographics</b>		
Age (yrs)	64±11.2	66.9±11.9
Male	128 (50.8%)	36 (58.1%)
Height (cm)	174.4±9.9	174.8±8.8
Weight (kg)	78.6±18.5	75.2±14.5
BSA (m <sup>2</sup> )	1.85±0.23	1.85±0.18
<b>History</b>		
Hypertension	107 (42.5%)	32 (51.6%)
Hypercholesterolemia	63 (25%)	21 (33.9%)
Diabetic	42 (16.6%)	17 (27.4%)
Family Hx of CVD	10 (4%)	14 (22.6%) <sup>†</sup>
Previous PCI	47 (18.7%)	17 (27.4%)
Previous CABGS	30 (11.9%)	13 (21%)*
Previous MI	16 (6.3%)	7 (11.3)
LVH	50 (19.8%)	13 (21%)
Current smoker	6 (2.4%)	3 (4.8%)
Previous smoker	1 (0.4%)	1 (1.6%)
<b>Cardiac Medication</b>		
ACE	107 (42.5%)	22 (35.5%)
Angiotensin II receptor antagonist	50 (19.8%)	14 (22.6%)

Table 1. Baseline Characteristics of Ischaemic and Non-Ischaemic Patient Groups (cont).

Aspirin	162 (64.3%)	53 (85.5%)*
Beta blockers	111 (44%)	31 (50%)
Calcium antagonists	108 (42.9%)	29 (46.8%)
Diuretic	93 (36.9%)	28 (45.2%)
Lipid-lowering agents	40 (15.9%)	19 (30.6%)
Nitrates	62 (24.6%)	23 (37.1%)
Warfarin	16 (6.3%)	3 (4.8%)

Values are mean±SD, n (%).

BSA=Body surface area; Family Hx of CVD=Family history of cardiovascular disease; PCI=Percutaneous coronary intervention; CABGS=Coronary artery bypass graft surgery; MI=Myocardial infarction; LVH=Left ventricular hypertrophy; ACE=Angiotensin converting enzyme inhibitor; \*= $p < 0.05$ ; †= $p < 0.001$  between groups.

Table 2. Baseline Characteristics of Patients with Low and High Ischaemic Burden.

Characteristics	Low (n=44)	High (n=18)
<b>Demographics</b>		
Age (yrs)	64.6±12.9	72.5±8*
Male	28 (63.6%)	8 (44.4%)
Height (cm)	176.6±9.9	174.5±8.5
Weight (kg)	76.2±16.9	74.8±12.3
BSA (m <sup>2</sup> )	1.84±0.21	1.85±0.27
<b>History</b>		
Hypertension	24 (54.5%)	8 (44.4%)
Hypercholesterolemia	12 (27.3%)	9 (50%)
Diabetic	9 (20.5%)	8 (44.4%)
Family Hx of CVD	9 (20.5%)	5 (27.8%)
Previous PCI	11 (25%)	6 (33.3%)
Previous CABGS	8 (18.2%)	5 (27.8%)
Previous MI	5 (11.4%)	2 (11.1%)
LVH	8 (18.2%)	5 (27.8%)
Current smoker	1 (2.3%)	2 (11.1%)
Previous smoker	0 (0%)	1 (5.6%)
<b>Cardiac Medication</b>		
ACE	14 (31.8%)	8 (44.4%)
Angiotensin II receptor antagonist	11 (25%)	3 (16.7%)

Table 2. Baseline Characteristics of Patients with Low and High Ischaemic Burden (cont).

Aspirin	35 (79.5%)	18 (100%)*
Beta blockers	22 (50%)	9 (50%)
Calcium antagonists	22 (50%)	7 (38.9%)
Diuretic	20 (45.5%)	8 (44.4%)
Lipid-lowering agents	11 (25%)	8 (44.4%)
Nitrates	15 (34.1%)	8 (44.4%)
Warfarin	1 (2.3%)	2 (11.1%)

Values are mean±SD, n (%).

BSA=Body surface area; Family Hx of CVD=Family history of cardiovascular disease; PCI=Percutaneous coronary intervention; CABGS=Coronary artery bypass graft surgery; MI=Myocardial infarction; LVH=Left ventricular hypertrophy; ACE=Angiotensin converting enzyme inhibitor; \*= $p<0.05$  between groups.



*Table 3. Comparison of Echocardiography Results Between Ischaemic and Non-Ischaemic Patient Groups.*

Parameter	Non-Ischaemic (n=252)	Ischaemic (n=62)
<b>Baseline</b>		
LVEDD (mm)	32±12	38±16*
LVEDD (mm)	64±33	69±22*
LVEF (%)	64±17	55±15*
WMSI	1.0±0.2	1.2±0.5*
Maximal LVEDD Wall Thickness (cm)	1.16±0.32	1.13±0.71
LA size (mm)	43±11	45±16
E/A ratio	1.29±0.8	1.31±0.5
Mitral E Deceleration Time (ms)	214±115	226±103*
E/Ea ratio	8±3	12±5*
E/Vp ratio	1.36±0.89	1.54±0.63*
<b>Peak Dose Dobutamine</b>		
LVEDD (mm)	21±12	34±16*
LVEDD (mm)	48±26	67±36*
LVEF (%)	76±33	62±18*
WMSI	1.0±0.1	1.4±0.2*
LA size (mm)	44±15	45±18
E/A ratio	1.18±0.4	1.22±0.6
Mitral E Deceleration Time (ms)	316±153	196±64*

Table 3. Comparison of Echocardiography Results Between Ischaemic and Non-Ischaemic Patient

Groups (cont).

E/Ea ratio	11.3±7.6	14.1±8.2*
E/Vp ratio	1.56±0.69	1.89±0.84*

Values are mean±SD.

LVEDS=Left ventricular end systolic diameter; LVEDD=Left ventricular end diastolic diameter; LVEF=Left ventricular ejection fraction; WMSI=Wall motion score index; LA=Left atrium; E/A=Ratio of peak velocity of early filling to peak velocity of atrial filling; Mitral E/Ea=Ratio of transmitral blood flow velocity to tissue Doppler velocity; E/Vp=Ratio of peak velocity of early filling to flow propagation velocity; \*= $p < 0.05$  between groups.