



# Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study

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(Myocardial Doppler in Stress Echocardiography)

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Received 10 October 2002; received in revised form 2 December 2002; accepted 11 December 2002

## KEYWORDS

Stress echocardiography;  
Tissue Doppler;  
Dobutamine

**Aims** To develop optimal methods for the objective non-invasive diagnosis of coronary artery disease, using myocardial Doppler velocities during dobutamine stress echocardiography.

**Methods and results** We acquired tissue Doppler digital data during dobutamine stress in 289 subjects, and measured myocardial responses by off-line analysis of 11 left ventricular segments. Diagnostic criteria developed by comparing 92 normal subjects with 48 patients with coronary disease were refined in a prospective series of 149 patients referred with chest pain. Optimal diagnostic accuracy was achieved by logistic regression models, using systolic velocities at maximal stress in 7 myocardial segments, adjusting for independent correlations directly with heart rate and inversely with age and female gender (all  $p < 0.001$ ). Best cut-points from receiver-operator curves diagnosed left anterior descending, circumflex and right coronary disease with sensitivities and specificities of 80% and 80%, 91% and 80%, and 93% and 82%, respectively. All models performed better than velocity cut-offs alone ( $p < 0.001$ ).  
**Conclusion** Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography is best performed using diagnostic models based on segmental velocities at peak stress and adjusting for heart rate, and gender or age.

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## Introduction

Stress echocardiography has become a common non-invasive test in patients with chest pain, but like exercise electrocardiography<sup>1</sup> it has major limitations. Analysis of grey-scale images based on subjective visual interpretation of wall motion and thickening has considerable

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**Table 1** Baseline characteristics of study groups

	Normals Group 1 (n=92)	Known CAD Group 2 (n=48)	Unselected patients, Group 3		
			<50% (n=59)	>50% (n=90)	Total (n=149)
Male (%)	55.4	68.8	42.4	74.4***	61.7
Age (years)	50.8 (15.4)	62.4 (10.0)***	56.6 (10.1)	60.6 (9.0)*	59.0 (9.6)
Height (cm)	171.2 (9.2)	168.4 (8.3)	165.9 (7.7)	169.3 (9.5)*	168.0 (9.0)
Weight (kg)	77.5 (12.7)	77.5 (14.1)	76.1 (14.6)	79.5 (14.6)	79.3 (14.6)
Body mass index (kg/m <sup>2</sup> )	26.5 (4.5)	27.4 (5.1)	28.7 (5.2)	27.7 (4.5)	28.1 (4.8)
Cholesterol (mmol/l)	5.3 (1.1)	5.6 (1.4)	5.4 (1.1)	5.4 (1.2)	5.4 (1.1)
HDL-Cholesterol (mmol/l)	1.3 (0.4)	1.1 (0.4)*	1.4 (0.5)	1.3 (0.8)	1.3 (0.7)
Triglycerides (mmol/l)	2.0 (1.6)	2.9 (2.0)*	2.1 (1.6)	1.9 (0.9)	2.0 (1.2)
Current smokers (%)	16.3	18.8	30.5	28.9	29.6
Ex-smokers (%)	20.7	45.8**	33.9	38.9	36.9
Diabetes mellitus (%)	6.5	22.9**	8.5	21.1*	16.1
History of hypertension (%)	26.1	58.3***	33.9	43.3	39.6
Family history of CAD (%)	32.6	29.2	54.2	53.3	53.7

Mean (SD).

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  for Group 2 vs. Group 1; or for Group 3 >50% vs <50%.

HDL high density lipoprotein; CAD coronary artery disease.

variability even among experts.<sup>2</sup> Useful performance is achieved in research studies,<sup>3</sup> but the value of conventional stress echocardiography should be questioned when it is performed in centres with limited experience.

Regional myocardial function can be quantified by tissue Doppler echocardiography. In experiments, myocardial velocity falls progressively from 5 s after the onset of ischaemia,<sup>4</sup> and so its measurement has been proposed as an objective marker of dysfunction during stress. Early clinical investigations were based on decoding the velocity of a segment from the colour flow map,<sup>5</sup> or on recording velocity in real-time using a pulsed Doppler technique.<sup>6</sup> Ischaemia has also been detected by measuring a reduced transmural myocardial velocity gradient.<sup>7</sup>

Tissue Doppler data can be stored as digital images of the left ventricle, which are then available for post-processing after a stress study has been completed.<sup>8–10</sup> We have demonstrated high feasibility and reproducibility for off-line measurements of myocardial systolic velocities obtained during dobutamine stress.<sup>11</sup> Other investigators used myocardial velocities with cut-points, and reported that these were as accurate in diagnosing coronary disease as wall motion scoring by an expert.<sup>12</sup> To date, however, there is no agreement on methods or diagnostic criteria. We tested the hypothesis that tissue Doppler diagnosis of coronary disease will be optimised by taking account of factors that influence myocardial responses in normal subjects.

## Patients and Methods

### Study design

The MYDISE Study (Myocardial Doppler in Stress Echocardiography) was a collaboration between eight European centres (Appendix A), all experienced in performing stress echocardiography. The study was coordinated and the statistical analyses were performed in a core laboratory (in Cardiff). Ethical ap-

proval was given by the Ethics Committee of each institution, and each subject gave written informed consent.

Regional myocardial velocity responses to dobutamine were compared firstly in two selected groups – normal subjects (Group 1) and patients with known coronary artery disease (Group 2) – to identify the best method of discriminating between normal and ischaemic responses. The criteria were tested in a third, unselected group of patients who were studied prospectively after referral for the diagnosis of chest pain (Group 3), in order to develop the final diagnostic models.

### Patients

A total of 289 subjects aged >20 years were studied. Patients were included even if grey-scale images were suboptimal or incomplete. Exclusion criteria were atrial fibrillation, previous myocardial infarction (Q waves on the electrocardiogram, or akinetic segments on the resting echocardiographic images), previous revascularisation, unstable angina, complete bundle branch block, significant heart valve disease, contraindication to dobutamine or atropine, and possible pregnancy. Normal subjects were excluded if they had echocardiographic evidence of left ventricular hypertrophy, and patients were excluded if they had uncontrolled hypertension. The groups are described in Table 1.

**Group 1 (normal):** 92 subjects aged 20–83 years, with similar numbers of men and women. The age distribution was gaussian, with >10 subjects per decade and with 40% aged 50–69 years. Normal subjects were recruited from two sources. Sixty were patients referred for assessment of atypical chest pain; all had normal coronary arteriography within 3 months of the stress echocardiogram. All but six had a normal exercise electrocardiogram (ECG) prior to arteriography, and those with mild ST-segment abnormalities all had a normal perfusion scintigram. Perfusion scintigraphy was performed in 22% of subjects and was normal in all cases. The second group of normal subjects comprised 32 healthy volunteers, all of whom had a normal exercise ECG and a low pre-test probability of developing coronary disease (on average,  $8.9 \pm 8.0\%$  over 10 years).<sup>13</sup> All volunteers aged >70 years (19%) had a normal perfusion scintigram. No healthy volunteer had coronary arteriography.

**Group 2 (known coronary disease):** 48 patients selected because recent coronary arteriography demonstrated significant epicardial coronary disease. Their ages ranged from 44 to 80 years, and 69% were men. There were 19 with single vessel, 15 with double vessel, and 14 with triple vessel disease. The totals with disease in each territory were: 38 left anterior descending artery (LAD), 31 left circumflex artery (Cx), and 22 right coronary artery (RCA). Patients in Group 2 were on average 12 years older than subjects in Group 1.

**Group 3 (prospective study):** 149 unselected patients referred with chest pain. All had exercise ECG and then dobutamine stress echocardiography, before elective coronary arteriography. The investigations were performed and interpreted by different observers, who were unaware of the results of the other tests. This group included 59 patients with normal coronary arteriography (i.e. no angiographic diameter stenosis >50%) and 90 with coronary disease (36 patients with single vessel, 27 with double vessel, and 27 with triple vessel disease). The totals with disease in each territory were 70 LAD, 53 Cx, and 48 RCA. Patients with and those without significant coronary disease had similar age distributions, but there was a higher proportion of women among the patients without significant disease.

## Stress protocol

Cardiovascular drugs were stopped 48 h before the study, apart from short-acting nitrates which patients could continue until the morning of the investigation. No patient was taking a beta-receptor antagonist at the time of the study.

Dobutamine was infused intravenously for 3-minute stages at 5, 10, 20, 30 and 40  $\mu\text{g}/\text{kg}/\text{min}$ . In patients who had not reached their target heart rate [ $>85\%$  of  $(220 - \text{age in years})$ ] or another end-point, the last dose was continued while atropine 0.25 mg was given by intravenous bolus every minute up to a total of 1 mg. Heart rate and rhythm were monitored from a precordial modified lead I or II, and blood pressure and the 12-lead ECG were recorded every 3 min. Symptoms were documented.

Pre-defined end-points were intolerable symptoms (such as chest pain),  $\geq 2$  mm of horizontal or downsloping ST-segment depression on any ECG lead, persistent arrhythmias such as ventricular tachycardia or new atrial fibrillation, systemic hypotension (fall of systolic pressure  $>30$  mmHg), or bradycardia.

## Echocardiographic acquisition

Patients were studied in the left lateral decubitus position, using a Vingmed System V (GE Vingmed Ultrasound, Horten, Norway) with a 1.5–2.5 MHz transducer. After 10 min of rest (baseline), and during the last 90 s of each stage of the infusion, digital images were acquired during passively held end-expiration, from 4 standard imaging planes: parasternal long-axis (PLAX), parasternal short-axis, apical four-chamber (A4C), and apical two-chamber (A2C) views. In each view, a 2-beat loop was edited to start before one QRS complex and to end after the third QRS complex. This loop was reviewed to ensure that there was no significant translation of the heart on the image, and then transferred to a Macintosh computer for storage in the Echopac programme (GE Vingmed) and on magneto-optical disk.

Grey-scale studies were performed with harmonic imaging, but digital loops were acquired while displaying superimposed colour tissue Doppler. To avoid aliasing during stress, the Nyquist limit was increased to 25 cm/sec. Sector angles were adjusted with the aim to obtain frame rates for colour tissue Doppler of  $>100/\text{s}$ .

## Off-line analysis

Investigators who performed echocardiographic studies and off-line analyses were unaware of the findings of coronary arteriography. The protocol for measuring myocardial velocities has been described in detail elsewhere.<sup>11</sup> Digital loops were retrieved and 11 segments were analysed at each stage, by one of three observers. Velocities of radial function were recorded in three segments, from the PLAX image: basal posterior (BP), mid posterior (MP), and mid-anterior septum (MAS). Velocities of longitudinal shortening were measured from the A4C and A2C, in four basal [basal septal (BS), basal anterior (BA), basal lateral (BL) and basal inferior (BI)] and four mid-ventricular [mid septal (MS), mid anterior (MA), mid lateral (ML) and mid inferior (MI)] segments. Five segments normally included in an analysis of wall motion<sup>14</sup> were not used (apical segments and basal anterior septum) because off-line velocities in these segments are unreliable.<sup>11</sup>

In parasternal views, the cursor was positioned in the posterior wall so that it did not encompass the pericardium at any time during the cardiac cycle. In apical views, each left ventricular "wall" was divided into thirds and the cursor was placed within the basal portion of each segment during systole; in the basal segments it never encompassed the mitral annulus. No angle corrections were used. Velocities were measured using customised software (Echopac TVI, GE Vingmed).

Inter-observer agreement in the MYDISE study has been reported.<sup>11</sup> Ten randomly selected studies were each analysed by nine observers. The most reproducible parameter was peak systolic velocity (PSV), defined as the maximal velocity (in cm/s) during ejection. Pooled standard deviations for its measurement in the four basal segments from apical windows at peak stress ranged from 1.4 to 2.1 cm/s, giving coefficients of variation between 11% (BS) and 18% (BA); for mid-ventricular segments in the same views, coefficients of variation were between 17% (MI) and 26% (ML). In the PLAX view, the coefficient of variation for PSV at maximal stress in the BP segment was 16%. Although the coefficients of variation at peak stress ranged from 11 to 26%, most were closer to the lower boundary. The median and mean coefficients of variation for measurements of PSV in all segments, were 12% at rest and 16% at peak stress.

## Coronary arteriography

Patients underwent elective coronary arteriography using standard projections. Significant disease was coded if there was a diameter stenosis  $\geq 50\%$  in a vessel or its major branch (e.g. first diagonal of LAD or obtuse marginal of Cx). Left main stenosis was coded as both LAD and Cx disease. Segments judged to be supplied by the LAD were MAS, BA, MA, and MS. The Cx segments were BP and MP, and BL and ML. The BI, MI, and BS segments were supplied by the RCA when it was dominant, and the BS the by Cx when it was dominant.<sup>15</sup> Arteriograms were interpreted by observers blinded to the results of stress echocardiography, using quantitative coronary arteriography where available (in 12%) or visual analysis with calipers. The arteriograms of 63 patients were reported independently by two observers, who agreed on the presence or absence of significant coronary disease in 96% of arterial territories.

## Statistical methods

Analyses were performed using commercially available software (SPSS Inc, Chicago, Illinois). Continuous variables were described by means and standard deviations and categorical data were described by percentages. In each subject, the peak

**Table 2** Haemodynamic measurements, end-points, and symptoms during dobutamine, in the three study groups

	Normals Group 1	Known CAD Group 2	Unselected patients, Group 3		
			<50%	>50%	Total
Heart rate (min <sup>-1</sup> )					
Rest	70.4 (11.2)	70.0 (13.9)	71.5 (11.7)	68.1 (11.7)	69.5 (11.8)
Peak	132.4 (18.7)	120.5 (23.2)**	137.2 (15.0)	126.8 (18.8)*	130.9 (18.1)
Resting blood pressure (mmHg)					
Systolic	134.2 (19.4)	143.0 (21.1)***	140.6 (22.2)	143.9 (20.2)	142.6 (21.0)
Diastolic	78.5 (11.2)	78.0 (11.4)	82.2 (13.5)	81.2 (14.8)	81.6 (14.3)
Peak blood pressure (mmHg)					
Systolic	150.8 (30.0)	149.5 (26.1)	143.2 (28.7)	150.2 (31.7)	147.4 (30.6)
Resting double product	9467 (2204)	10056 (2754)	10094 (2531)	9913 (2230)	9986 (2349)
Peak double product	19745 (4238)	18019 (4022)***	19683 (4649)	19539 (5054)	19596 (4879)
Dobutamine maximal dose given					
20/30/40 µg/kg/min (%)	10/20/30	10/34/27	5/24/27	6/19/28	6/21/27
40 µg/kg/min and atropine (%)	40	29	44	47	46
End-points for stopping test					
Achieved target HR, no symptoms (%)	60	56	63	38**	47
Completed protocol, no symptoms (%)	12	7	5	10	8
ECG changes, akinesia, ischaemia (%)	0	2	3	3	4
Chest pain (%)	11	25***	22	39***	32
Fatigue, sickness, dizziness (%)	4	0	3	2	3
Hypotension (%)	3	0	2	8	5
Hypertension (%)	5	4	0	0	0
Arrhythmias (%)	5	6	2	0	1

Mean (SD).

\**p*<0.001, \*\**p*<0.01, \*\*\**p*<0.05 for Group 2 vs. Group 1; or for Group 3 >50% vs. <50% HR heart rate.

response was taken at the maximal dose of dobutamine which was attained, or at the penultimate stage if the patient had developed hypotension or bradycardia.

Peak systolic velocity data from Groups 1 and 2 were first assessed by analysis of variance to determine the between-subject effects (group, age, and gender) and the within-subject effects (dobutamine dose and heart rate). To determine the best discriminators of normal status and disease, univariate and multiple stepwise logistic regressions were performed including factors for velocity data, age, gender and heart rate. The logistic regression models from the multivariate analysis gave an outcome *y*, which was used to generate a predicted probability of disease *p*, using the formula  $p = e^y / (1 + e^y)$ . One model was developed for each coronary territory (Cx, RCA, LAD). There was insufficient evidence to suggest that the relationships between the continuous covariates (PSV measurements, age and heart rate) and the endpoint (disease status) were non-linear. A *p*-value <0.05 was considered significant.

Receiver-operator curves were used to determine a cut-point for *p* that gave optimal sensitivity and specificity, with the aim of maximising sensitivity without significantly compromising specificity. A minimum level of specificity of >80% was accepted, in order to optimise sensitivity, since the most important clinical objective was considered to be a high negative predictive value. A patient with a probability that was lower than the cut-point was classified as normal, and a patient with a probability that was higher was classified as diseased. In the models, male sex was coded as '1' and female sex was coded as '2'.

A new variable ('any disease') was calculated for each patient using the results of the three separate models. Subjects predicted to have coronary disease in any of the three territories

were coded with 1, and subjects predicted to have no coronary disease at all were coded with 0. A receiver-operator curve was used to determine the diagnostic accuracy of the new variable.

The distribution of coronary disease in the selected subjects was bimodal, with patients either having no angiographic disease at all (Group 1) or flow limiting coronary disease (Group 2) whereas the unselected patients recruited prospectively (Group 3) demonstrated a more normal distribution of angiographic severity. The logistic formulae from Groups 1 and 2 were therefore refined using the data from Group 3.

Reproducibility of velocity data, as assessed by pooled standard deviations and coefficients of variation, has been reported elsewhere.<sup>11</sup>

## Results

### End-points of stress tests

Clinical and haemodynamic end-points are summarized in Table 2. There were no serious adverse effects, and only a few studies were stopped because of hypotension or bradycardia. There were differences between diseased and normal subjects in workload and symptoms, as expected.

The proportion of the segments that were interpretable at rest ranged from 100% in the basal septal segment to 90% in the basal anterior segment. At peak stress, the proportion of segments that were interpretable ranged from 100% in the basal inferior, mid inferior, and basal septal segments, to 87% in the basal anterior segment.



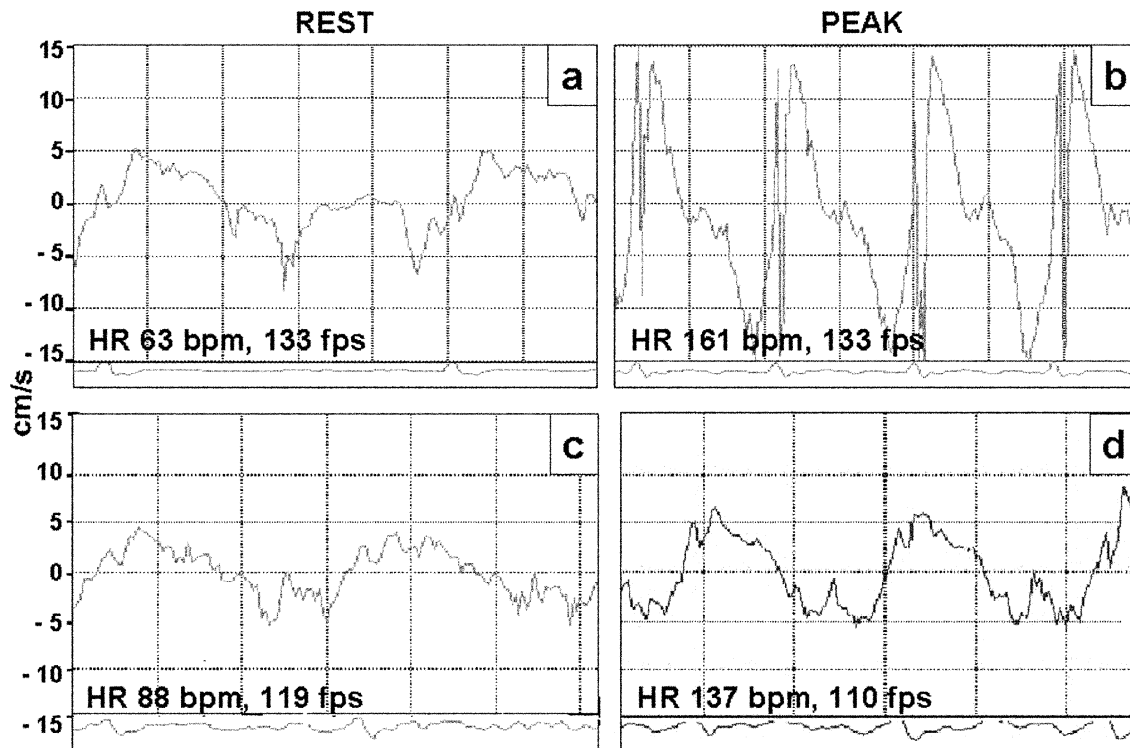


Fig. 1 Myocardial velocity traces obtained at off-line analysis in a 48-year old man with normal coronary arteriography (panels a and b) and in a 45-year old man with triple vessel coronary artery disease (panels c and d). Panels a and c show similar velocities at rest, but peak systolic velocity more than doubles at peak dose of dobutamine in the normal subject (panel b) whereas there is no significant change in the patient with coronary artery disease (panel d). HR heart rate, bpm beats per minute, fps frames per second. All traces were obtained from the same myocardial segment (basal septum, apical 4-chamber view).

Both at rest and at peak stress, tissue Doppler traces could be interpreted and measured in 97% of all the segments that were selected in the diagnostic models.

### Discrimination between normal and ischaemic responses (Groups 1 and 2)

At peak stress, patients with coronary disease reached a lower peak systolic velocity than did normal subjects. Representative traces are shown in Fig. 1.

Logistic regression models selected peak systolic velocity at peak stress in 7 myocardial segments, for discrimination between normal and diseased subjects. All segments were entered into the analysis, but the segments selected by the models were supplied by the corresponding artery (LAD: BA and MS; Cx: BL and BP; RCA: BI, MI and BS). Additional factors were age and peak heart rate. The models for diagnosing LAD and Cx disease also selected gender. In each coronary territory, the diagnostic accuracy of the model was superior to that obtained using peak systolic velocity as the sole discriminator ( $p < 0.001$ ).

### Diagnosis of coronary artery disease (Group 3)

#### Diagnostic models

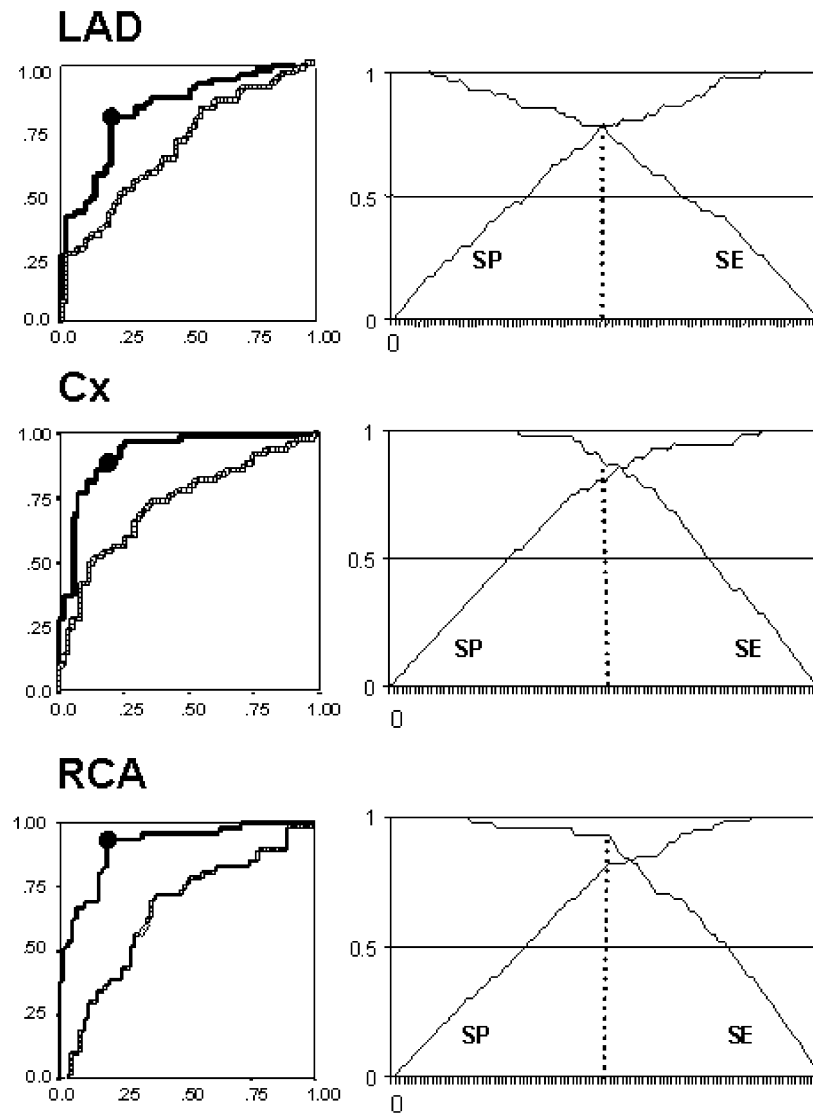
Refined models developed to diagnose significant coronary disease in patients in Group 3 selected the same

segments and factors as for the analysis of Groups 1 and 2, apart from one: for the diagnosis of LAD disease, the model selected one segment supplied by the LAD (basal anterior) but also one supplied by the Cx artery (mid lateral). There was high concordance between velocities in the ML and MA segments ( $r = 0.6$ ,  $P < 0.001$ ), which are contiguous, and the feasibility of obtaining data was higher in the ML segment (92% compared with 82% in the MA<sup>11</sup>).

The regression models were:

- LAD disease:  $y = 12.905 - (0.053 \times \text{Peak heart rate}) - (1.384 \times \text{Sex}) - (0.168 \times \text{BA PSV}) - (0.205 \times \text{ML PSV})$ ;
- Cx disease:  $y = 23.375 - (0.095 \times \text{Peak heart rate}) - (2.349 \times \text{Sex}) - (0.196 \times \text{BL PSV}) - (0.229 \times \text{BP PSV}) - (0.335 \times \text{ML PSV})$ ;
- RCA disease:  $y = 21.361 - (0.085 \times \text{Peak heart rate}) - (3.849 \times \text{Sex}) - (0.309 \times \text{BI PSV}) + (0.171 \times \text{MI}) - (0.257 \times \text{BS PSV})$ .

These models gave sensitivities and specificities of 80% and 80% for LAD disease (cut-point of probability score 0.53), 91% and 80% for Cx disease (cut-point 0.37), and 93% and 82% for RCA disease (cut-point 0.37). The areas under the receiver-operator curves were 0.84, 0.92, and 0.91 respectively (Fig. 2). The models gave high negative predictive values, especially for excluding Cx or RCA disease (91% and 94% respectively, Fig. 3). When the three models were combined to diagnose significant



**Fig. 2** Receiver-operator characteristic curves showing performance of diagnostic methods in the unselected population (Group 3). In the left-hand panels, the solid lines represent the logistic regression models, while the dotted lines display the performance of peak systolic velocity in a single segment; x axes=1-specificity, and y axes=sensitivity. The optimal points selected from the diagnostic models are indicated by the superimposed bullets (●). The right-hand panels display specificity (SP) and sensitivity (SE) values for probabilities obtained using the three models; x axes=probability, and y axes=%. The vertical dotted lines represent the probability cut-points selected for optimal diagnostic performance, but note that the probabilities on the x axis are not plotted using a uniform scale. LAD left anterior descending, Cx circumflex, RCA right coronary artery.

stenosis in any coronary territory, compared with no disease, the overall sensitivity was 87% and specificity 75%.

The discriminant power of the models was achieved by adjusting for gender and peak heart rate. We studied these factors in all normal subjects in Group 1 combined with patients with no significant disease from Group 3. Velocities in the four basal myocardial segments were averaged, to give a mean velocity of systolic longitudinal shortening of the left ventricle. In these 151 subjects, there was an inverse relationship between age and systolic velocity at peak dose of dobutamine, in both men and women ( $r=-0.36$ ,  $p<0.001$ ; Fig. 4). At all ages, the mean velocity was less in women than in men.

This difference was unrelated to body mass index, but systolic velocity at peak stress correlated with height and on average women were shorter than men (1.64 (SD 0.7) compared with 1.75 (0.7) metres,  $p<0.001$ ). The association between heart rate at peak stress and velocities in normal subjects is shown in Fig. 5 ( $r=0.42$ ,  $p<0.001$ ).

#### Velocity cut-points

On average, PSV increased  $\geq 100\%$  in healthy subjects compared with 50–75% in patients with coronary disease (Table 3). Receiver-operator curves for PSV as the only discriminator between patients with normal and stenosed coronary arteries are shown in Fig. 2. The

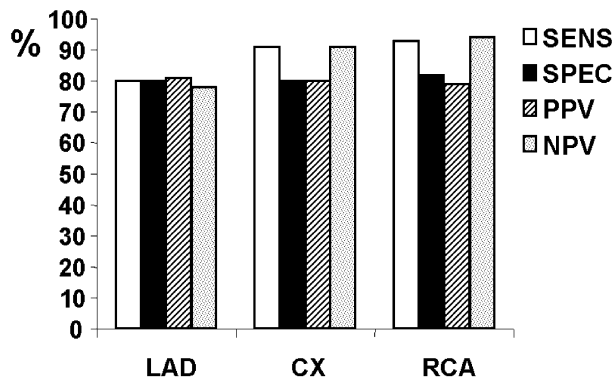


Fig. 3 Summary of the diagnostic performance of multiple logistic regression equations in subjects in Group 3. SENS sensitivity, SPEC specificity, PPV positive predictive value, NPV negative predictive value.

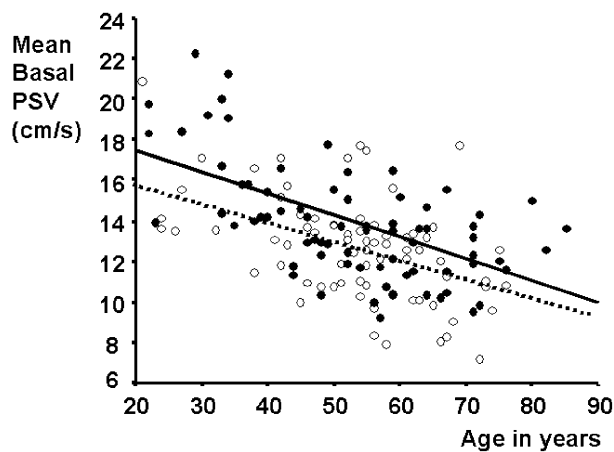


Fig. 4 Relationships between myocardial velocity at peak dose of dobutamine and age, in men (●) and in women (○). Velocity calculated as the mean peak systolic velocity in four basal segments (BS and BL in A4C, and BA and BI in A2C) at peak pharmacological stress.

highest sensitivities and specificities that could be obtained were 63% and 60% for LAD disease (cut-off velocity 10.3 cm/s in BA segment), 69% and 67% for Cx disease (cut-off velocity 10.8 cm/s in BL segment), and 69% and 67% for RCA disease (cut-off velocity 12.8 cm/s in BI segment). These values were all less than those obtained using the logistic regression models ( $p < 0.001$ ).

Peak systolic velocity (PSV) at peak stress was found to be a better discriminator of disease, than was change in PSV from baseline to maximal stress with dobutamine. At rest, there were only small differences in PSV between segments in patients with significant coronary disease and the same segments in those without, and there was a very strong correlation between change in velocity and measurements at peak stress ( $r > 0.9$ ,  $p < 0.0001$  for most segments). Measurement of baseline velocities doubles the time required for off-line tissue Doppler analysis, and increases the potential for observer variability without increasing diagnostic accuracy.

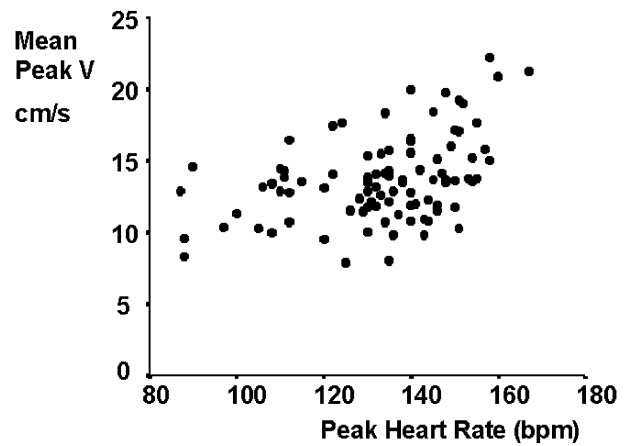


Fig. 5 Relationship between myocardial velocity at peak dose of dobutamine and peak heart rate. Mean velocity calculated as in Fig. 4. Bpm beats per minute.

## Discussion

In the MYDISE study we have demonstrated that coronary artery disease can be diagnosed accurately and objectively, from off-line measurements of myocardial velocities recorded non-invasively by tissue Doppler echocardiography during dobutamine stress. Excellent diagnostic performance is achieved by simple models that incorporate peak systolic velocity and adjust for maximal heart rate, and age or gender.

## Limitations of standard stress echocardiography

An objective method of quantifying myocardial function during stress echocardiography is needed because the reproducibility of conventional methods is disappointing. Agreement is increased by applying protocols for interpretation,<sup>16</sup> but recognition of wall motion abnormalities on grey-scale images remains difficult particularly in patients with single vessel disease, and uncertain when images are incomplete.<sup>2</sup> Overall, sensitivities and specificities are not more than 80–85%,<sup>3</sup> and accuracy is less when the test is performed by inexperienced observers.<sup>17</sup>

Image quality and inter-observer agreement in the interpretation of wall motion are improved by using harmonic imaging and by injecting echocardiographic contrast agents that cross the pulmonary circulation and outline the endocardial border of the left ventricle,<sup>18,19</sup> but interpretation remains subjective. Colour kinesis displays endocardial motion objectively,<sup>20</sup> but its resolution is relatively low. Our objectives therefore were to develop new methods for quantifying dobutamine stress echocardiography and diagnosing coronary disease that would be feasible in most subjects, highly reproducible, accurate, and easily applied by inexperienced as well as expert observers.

It would be useful to determine the incremental diagnostic value in the same population of using tissue Doppler quantification, compared with grey-scale wall motion abnormalities. This could not be tested in the

**Table 3** Resting myocardial velocities and responses to dobutamine

Territory and Segments	Unselected patients, Group 3								
	<50% stenosis				≥50% stenosis				
	Rest		Peak		Rest		Peak		
	Male	Female	Male	Female	Male	Female	Male	Female	
LAD	BA	6.0 (2.4)	5.8 (2.1)	11.8 (2.9)	11.8 (4.0)	5.5 (1.6)	4.1 (1.6)	9.9 (3.4)***	8.3 (2.5)**
	MA	4.1 (2.5)	4.0 (1.4)	8.9 (2.5)	9.4 (3.4)	3.9 (1.5)	2.7 (0.5)	7.5 (4.2)	7.4 (2.6)***
	MS	4.8 (1.3)	4.8 (1.1)	10.4 (2.5)	9.3 (2.1)	5.0 (1.1)	5.0 (0.8)	8.7 (2.7)***	9.5 (2.9)
	<b>MAS</b>	-2.7 (1.6)	-3.1 (1.5)	-9.4 (3.4)	-7.8 (5.2)	-3.4 (1.4)	-3.9 (1.6)	-7.6 (4.4)	-7.8 (4.6)
Cx	BL	6.2 (2.3)	6.1 (1.9)	13.1 (4.4)	12.8 (4.4)	5.9 (2.2)	4.3 (2.2)	10.4 (4.4)***	6.0 (2.4)*
	ML	4.3 (1.7)	4.6 (1.9)	11.4 (5.1)	12.6 (4.4)	3.9 (2.0)	2.8 (1.5)	8.0 (3.8)**	6.5 (2.8)*
	<b>BP</b>	5.5 (1.5)	4.4 (2.0)	13.3 (3.4)	10.0 (2.4)	5.3 (1.2)	4.5 (1.2)	11.0 (3.2)**	9.6 (2.8)
	<b>MP</b>	4.4 (1.1)	3.8 (1.3)	10.4 (4.1)	8.1 (2.5)	4.1 (1.2)	3.1 (0.8)	7.3 (4.0)**	6.8 (2.0)
RCA	BI	7.2 (1.7)	6.8 (1.0)	15.6 (4.2)	12.9 (3.9)	6.9 (1.5)	5.7 (1.6)	12.5 (4.3)**	8.6 (2.2)***
	MI	5.4 (1.9)	5.1 (1.3)	11.7 (4.5)	9.4 (2.9)	5.1 (1.0)	4.0 (1.8)	9.8 (4.5)	6.7 (2.1)***
	BS	6.4 (1.8)	6.1 (1.7)	13.9 (2.9)	12.1 (2.9)	6.5 (1.3)	6.1 (1.8)	11.2 (2.8)*	9.6 (4.2)

Mean (SD) in cm/s.

\* $P < 0.001$ , \*\* $P < 0.01$ , \*\*\* $P < 0.05$  for comparisons of velocities at peak stress between patients with insignificant disease (<50%) or significant disease (>50%), analysed for men and women separately.

Peak systolic velocities, not adjusted for heart rate or age; abbreviations as in text. The segments identified in bold italics were assessed from parasternal windows (radial function); all others were assessed from the apex (long-axis function).

current study because digital data could only be collected with colour Doppler superimposed on the grey-scale images, which therefore were not optimised.

### Tissue Doppler echocardiography in ischaemia

Tissue Doppler echocardiography (also called Doppler myocardial imaging)<sup>21</sup> has major advantages for quantifying regional function during stress. Data are acquired digitally at high frame rates, so function can be measured after the test with good temporal resolution in each segment. Changes that have been documented during ischaemia include reduced and delayed peak systolic velocities,<sup>4</sup> reduced myocardial velocity gradients,<sup>7</sup> and impaired diastolic relaxation.<sup>22</sup> We studied systolic velocity because it is the most reproducible tissue Doppler parameter,<sup>11</sup> and because it is very sensitive to ischaemia. We measured the velocities of longitudinal shortening of the left ventricle, in basal myocardial segments studied from apical windows, because these reflect subendocardial function and this is linearly related to myocardial perfusion.<sup>23</sup>

Myocardial functional reserve has been studied by tissue Doppler during pharmacological stress<sup>5,24</sup> and dynamic exercise.<sup>25</sup> An early limiting factor was the impracticality of recording spectral pulsed Doppler from each segment every 3 min, but this was overcome by storing images digitally.<sup>8,9</sup> The feasibility of measuring velocities off-line was confirmed for dynamic stress on a semi-supine bicycle,<sup>10</sup> and we reported feasibilities of at least 90% when it is applied to dobutamine stress.<sup>11</sup>

### Study design

The MYDISE study was designed in two stages. Firstly, since it was not known what factors might discriminate between populations, we selected two groups that would

be as different from each other as possible: Group 1 subjects were healthy volunteers or else patients with no disease (normal coronary arteriography), whereas Group 2 consisted of patients with angiographically proven severe disease. These groups gave good power for the identification of criteria that could distinguish normal from diseased responses, but differences between the groups were exaggerated by the selection criteria. The regression analysis of stress responses in Groups 1 and 2 identified that peak systolic velocity was the most useful parameter for discriminating between normal subjects and patients with severe coronary artery disease, and it also demonstrated that heart rate and gender were significant covariates. Comparison of these groups also selected age as an important factor that influences the peak myocardial response to dobutamine, irrespective of the presence of coronary artery disease, but this is not surprising since the groups had not been matched for age: subjects in Group 1 were aged 20–80 years, whereas most patients in Group 2 were aged 50–70 years.

Having first identified the variables that differentiated between normal subjects and patients with coronary disease, we then studied prospectively a group of unselected patients (Group 3) who had been referred for the diagnosis of chest pain. These results are presented in greatest detail because this group most accurately reflects the distribution of normal or insignificant disease (<50% stenosis) and severe coronary artery disease (>50%) that is present in a population referred for stress echocardiography in clinical practice. Regression analysis in this group confirmed the findings of the study of Groups 1 and 2, namely that peak systolic velocity, heart rate and gender, best predict the presence of coronary artery disease. In Group 3, age was not a discriminating variable in the model, since patients with and those without significant coronary disease had similar mean ages.



When implementing quantitative stress echocardiography in clinical practice, whether to diagnose myocardial ischaemia or to detect reduced regional functional reserve from any other cause, peak responses will need to be compared to those of age-matched controls, or else adjustments for age will need to be made in a diagnostic model.

### Tissue Doppler stress echocardiography

The most important new finding of the MYDISE study is that tissue Doppler diagnosis of coronary artery disease is much more accurate using logistic regression models rather than myocardial velocities alone. The accuracy achieved exceeds that which can be obtained by conventional analysis of wall motion abnormalities.<sup>3</sup>

Cain and colleagues used systolic velocities without any adjustment, and reported that these gave diagnostic accuracy equivalent to expert interpretation of regional wall motion.<sup>12</sup> They selected the lower 20th centiles of the distributions of velocities at peak stress in a normal population as their cut-off values, whereas we selected cut-points from receiver-operator curves. Applied to the MYDISE groups, their velocity cut-points give poor overall diagnostic performance (with specificities of about 95% but sensitivities of less than 25%). These differences may be explained at least in part by varying selection criteria and methods. Cain and colleagues defined controls by the presence of normal wall motion at peak stress,<sup>12</sup> but given the suboptimal sensitivity of conventional stress echocardiography to diagnose single vessel disease<sup>3</sup> they may have included some diseased subjects among their controls. They did not exclude patients receiving beta blockers which lower velocities.<sup>26</sup> There may also have been differences in the proportions of patients with left ventricular hypertrophy<sup>27</sup> or chronic volume overload,<sup>28</sup> both of which are associated with reduced longitudinal velocities perhaps as a non-specific effect of subendocardial fibrosis. In apical views they measured velocities in the middle of each segment, which would give lower values than we obtained in the basal parts of each segment, since there is a gradient of velocity from base to apex.

The alternative approach adopted in the MYDISE study was designed to control for any factors that influence myocardial velocities in normal subjects independently of the effects of coronary disease. Patients should be compared with age-matched controls (as occurred in Group 3) or else an adjustment for age is required (as the models for Groups 1 and 2 demonstrated). The difference between men and women at peak stress was related to height, suggesting that it may be a consequence of increased systolic augmentation of central arterial pressure in subjects with shorter aortas and earlier wave reflections. The independent association of maximal velocity with heart rate needs to be considered, as subjects can reach very different heart rates at their maximal tolerated dose of dobutamine. Ignoring these factors reduces both sensitivity and specificity.

A notable feature of the MYDISE study is that the results were achieved using only velocities in seven segments at peak stress, and without considering wall motion. The high negative predictive values suggest that no other investigation is required to 'rule out' coronary disease with considerable confidence. The selected segments make intuitive sense since they are supplied by the relevant coronary artery, with the exception of the mid-lateral segment in the model of LAD disease in Group 3. This is probably due to the reduced feasibility of obtaining velocities from the anterior wall and to tethering effects in adjacent segments, and it may account for the overall accuracy of the models when applied together to diagnose any coronary disease.

We measured velocities in basal segments but changes there can reflect ischaemia at the apex,<sup>29</sup> because ischaemia within any segment in the same 'wall' on a longitudinal image will reduce the amplitude and velocity of motion of the basal segment. Once a diagnosis of ischaemia within a myocardial wall has been made, the site of ischaemia can be determined more precisely by studying apical grey-scale images if they are of good quality, or by assessing regional strain rate.<sup>30</sup> Another approach could be to use a composite mean velocity derived from measurements of both radial and longitudinal function,<sup>31</sup> but it would first be necessary to demonstrate that myocardial ischaemia affects radial and longitudinal function similarly.

### Limitations of the study

The current results may be biased due to over-fitting, and they should be confirmed on new prospective series. Ideally, data are needed from very large populations to generate definitive normal values, and robust models. Our models may not perform equally well in populations of patients with different distributions of disease. We used coronary arteriography as the criterion standard for diagnosing coronary disease, but performed quantitative analysis (QCA) in a minority of patients. Inter-observer reproducibility of visual grading of stenoses was good, however, and QCA is unreliable because disease in reference segments is usually underestimated.<sup>32</sup> Tissue Doppler echocardiography may be a better test than angiography for assessing if there is significant ischaemia, since it is an objective test of function rather than anatomy.

The results of this study cannot be extrapolated directly to myocardial velocities measured by pulsed tissue Doppler *during* stress, since such velocities are about 20% higher than 'off-line' measurements.<sup>33</sup> Velocities are reduced in patients with impaired resting left ventricular function<sup>34</sup> or left ventricular hypertrophy,<sup>27</sup> and after myocardial infarction,<sup>25</sup> and so separate studies are needed in such patients. Finally, our results were obtained in patients in sinus rhythm, and they will need to be tested separately in patients with atrial fibrillation. Other tissue Doppler methods may be needed in patients who have a significant resting conduction defect such as complete bundle branch block.

## Acknowledgements

The MYDISE study was supported by Project Grants 98/070 and 99/162 from the British Heart Foundation (London, UK) and by a technical grant from GE Vingmed (Horten, Norway).

## Appendix A

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