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The shape of the aortic outflow velocity profile revisited. Is there a relation between its asymmetry and ventricular function in coronary artery disease?

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ABSTRACT

Background: Myocardium contracts in the beginning of ejection causing outflow acceleration, resulting in asymmetric outflow velocity profiles peaking around 1/3 of ejection and declining when force development declines.

Aims: To demonstrate that decreased contractility in coronary artery disease (CAD) changes outflow timing and profile symmetry.

Methods and results: 79 patients undergoing routine full dose dobutamine stress-echo (DSE) were divided into 2 groups based on resting wall-motion and DSE-response: DSE negative (DSE_{neg}) (35/79) and positive (DSE_{pos}) (44/79) which were compared to 32 healthy volunteers. Aortic CW-Doppler traces at rest were analyzed semi-automatically; time-to-peak (T_{mod}), ejection-time (ET_{mod}), rise- (t_{rise}) and fall-time (t_{fall}) were quantified. Asymmetry (asymm) was calculated as the normalized difference of left and right half of the spectrum. Normal curves were triangular, early-peaking, while patients showed more rounded shapes and later peaks. T_{rise} was longest in DSE_{pos}. T_{fall} was shortest in DSE_{pos}, followed by controls and DSE_{neg}. Asymm was lowest in DSE_{pos}, followed by controls and DSE_{neg}.
Abnormally symmetric profiles (asymm<0.25) were found in none of the controls, 2.9% DSE_{neg} and 27.3% DSE_{pos}. A good correlation was found between assym and ejection fraction (EF) and T_{mod}/ET_{mod} and EF.
Notably, an LV dynamic gradient was induced in 71.4% DSE_{neg} and in 18.2% DSE_{pos}, associated with LV hypertrophy and supernormal (very asymmetric) traces.

Conclusions: Decreased myocardial function results in a more symmetrical outflow, while very asymmetrical traces suggest increased contractility, potentially inducing intra-cavity gradients during DSE. Therefore, including outflow symmetry as a clinical measurement provides additional information on patients with CAD.

KEY WORDS: Left ventricular outflow trace, Doppler echocardiography, dobutamine stress echocardiography, left ventricular function, haemodynamics.

INTRODUCTION

Blood pool Doppler echocardiography provides a method to measure blood velocities within the ventricles and blood vessels [1]. By measuring velocities through the cardiac valves, the amount of flow (cardiac output, filling) and the driving pressure gradient, causing the flow, can be quantified [1-9], which can be clinically used to assess hemodynamic parameters and ventricular function [1-6].

The profile of the aortic flow velocity curves can be described by the rate of increase (acceleration) in velocity, the peak and the time of peak velocity, the mean velocity during systole and the ejection duration [1]. Normal outflow shows an asymmetric, triangular shaped profile with a fast rise in velocities, peaking around 1/3 of the ejection duration [1]. Animal studies have shown that the flow acceleration is a sensitive indicator of the inotropic state [10], which was confirmed by clinical research [5,11]. In LV failure, both a lower and a slower increase in velocities (a more rounded Doppler profile with a later peak velocity) was observed [1]. Similar changes can be present in normal function but decreased filling (i.e. severe mitral stenosis, atrial septal defect, pulmonary hypertension) [1]. Changes in aortic velocity curves have been reported in other conditions such as hypertrophic cardiomyopathy [12], mitral regurgitation [13] and shock [14]. Furthermore, flow remodelling is regularly seen in aortic stenosis where, besides an increasing gradient, the profile changes from a triangular shape with an early peak, to a much more rounded form with a later peak in higher grade stenoses [1, 8].

Additionally, it is known that active force development in the myocytes peaks around 1/3 of the ejection, after which it decreases rapidly [15]. This implies that the early flow acceleration is caused by the active contraction, while flow decelerates when force development declines. This explains why flow acceleration increases with increased contractility. Additionally, research on isolated myocytes suggested that chronic ischaemia decreases, but prolongs contraction [16].

From this, we hypothesize that in the presence of coronary artery disease, in a subset of patients, the overall decrease in contractility caused by regional ischaemia and a slower contraction of chronic ischaemic myocytes, might be reflected in the aortic outflow profile, particularly in the timing and shape of the LV outflow curve and that these changes are related to the severity of contractile dysfunction. In order to study this relation and its usefulness in providing diagnostic clinical information, we propose a novel method for Doppler signal analysis where various properties of the envelope of the aortic outflow are quantified.

MATERIALS AND METHODS

Patients

From a retrospective series of 109 patients which were referred for a routine dobutamine stress echo (DSE) at St. George's hospital (London, UK), 79 (37 male, 42 female, mean age 62.7±9.4 years) had sufficient visualization of all myocardial walls and interpretable continuous Doppler (CW) LV outflow traces and did not have increased outflow velocities at rest (baseline) due to either aortic stenosis or the presence of an intra-cavity gradient. Furthermore, none of these patients had significant valve disease or left bundle branch block. In patients prescribed with beta blocker therapy, it was discontinued three days prior to the study.

Based on the resting wall motion and the response to the dobutamine challenge, the patients were divided in 2 subgroups.

The **DSE negative group (DSE_{neg})** consisted of 35 patients without resting wall motion abnormalities and a (quantitative) DSE study without signs of inducible ischaemia (9 male, 26 female, 60.3±8.4 years).

The **DSE positive group (DSE_{pos})** consisted of 44 patients with a DSE study showing signs of ischaemic heart disease, either at baseline or during any of the stress levels (28 male, 16 female, 64.7±9.7 years).

Additionally, 32 healthy volunteers with no signs or symptoms of cardiovascular disease or arterial hypertension were studied at baseline (not undergoing an DSE study) and served as a **control group** (15 male, 17 female, 59.1±11.5 years). The investigation conforms with the principles outlined in the Declaration of Helsinki.

Echocardiographic imaging

Standard cardiac ultrasound data (including Doppler myocardial imaging (DMI)) at baseline (healthy volunteers and patients) and during the DSE (patients) were acquired with a Vivid Seven ultrasound scanner equipped with a 2.5-MHz transducer (GE, Horten, Norway). Data were obtained from the parasternal and apical views. For the 2D studies, parasternal long and short axis as well as apical two-, three-, four- and five-chamber views were used. Aortic outflow CW Doppler traces were acquired from the apical five-chamber view. The echocardiographic data were obtained for three complete cardiac cycles during a single end-expiratory breath hold.

For the DSE study, dobutamine was infused at rates of 5, 10, 15, 20, 30 and 40 mcg/kg/min and increased with 3 min steps until reaching 85% of age-predicted heart rate (HR) (target HR). The study was interrupted earlier in the presence of induced ischaemia, occurrence of severe symptoms, raised blood pressure (BP) or upon reaching target HR.

Echocardiographic data, together with BP and a 12-lead ECG, were acquired at low (5 mcg/kg/min), intermediate (20 mcg/kg/min), peak dose (40 mcg/kg/min) and recovery. DMI data were simultaneously acquired for post-processing. At each stage, CW Doppler traces of aortic flow were additionally acquired.

The presence of echocardiographic signs of ongoing ischaemic heart disease was evaluated by two experienced cardiologists, both by assessment of regional wall motion abnormalities [17], as well as by analysis of the underlying DMI data [18].

Offline analysis was performed using dedicated software (Echopac, GE, Horten, Norway). Ejection fraction (EF) was measured by the Simpson biplane method [17]. LV size and mass (LVM) were measured [17, 19]; relative wall thickness (RWT) (the sum of posterior and septal wall thickness divided by the internal diameter) was calculated as an index of LV concentric remodelling [20]. 2D measurements of the basal interventricular septum as well as the basal lateral wall were obtained as an additional measure of LV hypertrophy in hypertensive heart disease [21].

Doppler outflow analysis

The baseline CW outflow Doppler traces were analyzed for the purpose of this study, both manually and semi-automatically. For the manual analysis, the time from onset of aortic flow to peak flow (T_{man}), as well as the ejection time (ET_{man}) and HR were measured. The ratio T_{man}/ ET_{man} (indicating the position of the peak within the ejection period), as well as the ratio ET_{man}/HR (indicating the duration of ejection within the heart cycle), were calculated. The manual analysis was blinded to the DSE results as well as to the automatic analysis.

The automated quantification of the CW outflow Doppler traces was previously described [22]. Doppler traces were not calculated, but rather extracted from the ultrasound image. This was done using an image segmentation method. In the first step, the image is converted and pre-processed to obtain only the forward velocities. On these images, the velocity envelope is detected automatically using thresholding. Next, the onset and the end of the aortic flow were manually indicated, thus isolating the outflow profile. Since the Doppler trace has to be continuous and smooth the constraint was implemented forcing the trace to be piecewise polynomial. This was done using two cubic polynomial (i.e functions of the form $f(x) = ax^3 + bx^2 + c + d$) with demands for the first derivatives to be zero at the beginning and end of the signal, as well as in the adjacent points where also the second derivative was forced to be equal for both of the adjacent polynomials to satisfy the smoothness criteria (Figure 1, right). From the modelled signals, several parameters describing their shape were extracted. Time to peak (T_{mod}), ejection time (ET_{mod}), rise time (t_{rise}) and fall time (t_{fall}) were quantified. Rise

and fall times were defined from 10% to 90% of the peak (Figure 1, bottom). The ratio T_{mod}/ET_{mod} as well as the ratio ET_{mod}/HR were calculated. Additionally, an asymmetry factor (asymm) was calculated as the difference of the area under the curve of left and right half of the spectrum normalized by the overall area. A value for asymm lower than 0.25 was considered an indicator of an abnormally symmetrical trace.

Additionally, the development of an intra-ventricular gradient during DSE was defined as a late-peaking LV Doppler velocity profile that exceeded the basal maximum velocity by at least 1 m/sec [23].

Statistical analysis

Continuous variables' data are expressed as mean value ± SD and the unpaired two-tailed Student t-test was performed for comparative analysis. Categorical variables are expressed as a percentage. For categorical variables, comparisons between groups were made using the chi-square test. Results were considered significant at $P<0.05$. A linear correlation was used to test the similarity between the manual and automated analysis.

RESULTS

Patient group characteristics and basic echocardiography data

The basic patient characteristics as well as coronary artery disease severity are provided in table 1. The values of both systolic and diastolic blood pressure (BP) were significantly lower in controls while the values of systolic BP exceeded normal values in 66% of patients in DSE_{neg} and 71% of patients in DSE_{pos}. The heart rate was significantly higher in DSE_{pos}, compared to controls.

In 15/35 DSE_{neg} patients, a coronary angiogram was performed (which was diagnostically inconclusive, or performed due to recurrent chest pain symptoms after previous treatment). Five of the DSE_{neg} patients had undergone successful coronary revascularization (one by

coronary artery bypass grafting - CABG), five had a (remaining) insignificant stenosis. Although they had normal rest and stress studies, in six patients, a significant stenosis was present at the time of the DSE study (single vessel disease in 1, double in 2, triple in 2 and multivessel in 1 patient).

In DSE_{pos}, significant, non revascularized, coronary artery stenoses were present in 16/44 patients (6 single vessel disease, 5 double vessel disease, while triple and multivessel disease were present in 3 and 2 patients, respectively). Overall, 27/44 patients had previous coronary revascularization (14/27 CABG), of these, 9 had a stenosis at time of investigation (2 in-stent restenoses and 2 bypass stenoses). 5/44 had an insignificant coronary artery stenosis and no angiography data were available for the remaining 5/44 patients.

The basic echocardiographic measurements are given in table 2. LV mass (ASE formula), was significantly higher in DSE_{pos} compared to DSE_{neg} and controls ($p=0.01$ and $p<0.00001$, respectively) mostly due to larger LV cavity measures. The size of the LV cavity was significantly smaller in DSE_{neg}, both in end systole as well as in end diastole. RWT, an indicator of concentric hypertrophy, was significantly larger in DSE_{neg}. Patients in DSE_{neg} and DSE_{pos} had a notable basal septal thickening/bulge, measuring in average 1.3±0.3 cm, while it was significantly smaller in the controls. Furthermore, EF was significantly higher in DSE_{neg} compared to the other two groups ($p<0.000001$ vs. controls and DSE_{pos}). Ejection fraction was preserved in all healthy volunteers and patients in DSE_{neg}, while it was reduced in 39% of the DSE_{pos} patients.

Notably, an LV dynamic intracavitary gradient was induced by DSE in 71.4% of DSE_{neg} patients and 18.2% of DSE_{pos}. In patients developing an intracavitary gradient, RWT ($p<0.004$ vs. no gradient, $p<0.000001$ vs. controls) and EF ($p<0.0001$ vs. controls, $p<0.00001$ vs. no gradient) were significantly larger than in patients who did not develop an intracavitary gradient during DSE, or controls.

Doppler outflow analysis

Figure 2 shows typical examples (both the raw Doppler trace and the extracted profile) from the 3 subgroups. The properties extracted from the aortic flow are shown in table 3. Figure 3 shows the correlation between the manual and automated measurements of ejection time (ET_{man} versus ET_{mod}; r=0.69) and time to peak velocity (T_{man} versus T_{mod}; r=0.56).

Ejection time corrected by heart rate (ET_{man} or ET_{mod}) was not different among the three groups. The absolute time to peak (T_{mod}) was significantly higher in DSE_{pos}, followed by DSE_{neg} and the controls.

The relative time to peak T_{mod}/ET_{mod} was the longest in DSE_{pos}; notably, it was found to be shorter in DSE_{neg} compared to controls.

Rise time t_{rise} was longest in DSE_{pos} compared to DSE_{neg} (p=0.01) and controls (p=0.02). Fall time t_{fall} was shortest in DSE_{pos}, though it was the longest in DSE_{neg} (p<0.005 vs. controls and DSE_{pos}). Furthermore, t_{fall} was notably prolonged in the patients who developed an intracavitary gradient during DSE (0.17±0.03), compared to the ones without an inducible gradient (0.15±0.03, p<0.01) and controls (0.15±0.01, p<0.03).

Asymm was the lowest in DSE_{pos}, followed by controls and DSE_{neg} (Table 3). An abnormally symmetric profile (asymm<0.25) was found in 1/35 (2.9%) of the DSE_{neg} patients and in 12/44 (27.3%) of the DSE_{pos} patients, while in none of the controls.

The relations between the EF and asymm, T_{mod}/ET_{mod}, t_{rise} and t_{fall}, as well as LVIDd vs. asymm, T_{mod}/ET_{mod}, t_{rise} are shown in figure 4 and figure 5, respectively. No significant correlation was found between t_{rise} and t_{fall} (r=0.19). Moreover, neither asymm, nor t_{rise} or t_{fall} seemed to be influenced by systolic blood pressure (r=0.08).

The difference in values of asymm, T_{mod}/ET_{mod}, t_{rise} and t_{fall} among the three patient groups are shown in figure 6.

In the patients who developed an intracavitary gradient during DSE, t_{fall} was significantly prolonged while T_{mod}/ET_{mod} was significantly shorter compared to the group of patients without an inducible intracavitary gradient by DSE (figure 7).

In the subgroup of patients who underwent coronary angiography, the sensitivity of the DSE study in detecting CAD was 76%, while its specificity was 31%. In the same subgroup of patients, the sensitivity of the semi-automated method (using the asymmetry factor) was 35%, while its specificity was 88%. A combined sensitivity of DSE and the semi-automated method (using the asymmetry factor) was 58%, while the specificity was 67%. Within the DSE_{pos} and DSE_{neg} groups, the sensitivity of the asymmetry factor in detecting the DSE study outcome was 27%, while the specificity was 97%.

DISCUSSION

In this study, we have observed that the aortic outflow velocity profile is altered in the presence of coronary artery disease where in an import portion of patients the flow profile becomes much more symmetrical and rounded, whereas it is clearly asymmetrical and triangular in normal subjects. On average, in CAD, the rise time prolongs, the time to peak velocity is delayed and the fall time shortens.

Aortic outflow is the result of pressure development and deformation of the LV. Generation of pressure within the cavity of the LV is a direct consequence of active force development within the myofibres. Once initial force is developed by the contractile elements, the ventricle can increase its internal pressure up to the point high enough to open the aortic valve. From this moment, the shortening of the contractile elements will decrease the cavity size so that its internal blood content is ejected [18, 24]. The velocities with which the blood is ejected through the aortic valve depend on the pressure gradient. In the absence of an aortic stenosis, this gradient is determined by the developed LV pressure and the pressure in the aorta, which depends on the peripheral circulation and the aortic stiffness. In the absence of afterload changes, aortic outflow should directly reflect active force development and the resulting myocardial deformation. Sabbah et al. have shown that the peak acceleration of aortic blood flow assessed non-invasively in patients with a CW Doppler velocity meter is a

useful indicator of global LV performance, as assessed by EF, while neither peak velocity nor the systolic velocity integral related as closely to EF [11]. This was also shown in experimental setups [10]. An analysis of aortic wave intensity and aortic velocities during a dobutamine infusion showed the increased acceleration of the velocity and a more asymmetrical profile with faster deceleration, mainly due to the interaction of the forward and backward waves in the aorta [25]. It was also shown that dobutamine provokes an increase in aortic acceleration, although the increase was significantly lower in patients with CAD. However, no difference in aortic acceleration was found between patients and controls at baseline [26].

Additionally, in a pig model of myocardial hibernation, Bito and co-authors demonstrated that isolated chronically ischaemic myocytes show a reduced and slowed contraction when compared to normal myocytes and that they show a significant reduction in active force development [16, 27]. Furthermore, several studies on long axis function have demonstrated that, in areas affected by CAD, the onset of contraction is delayed, the overall amplitude and velocity of contraction may be reduced and its duration prolonged [28, 29, 30]. Hatle and co-authors showed that the relative timing of the maximal aortic flow occurred later in LV heart failure [8]. The same study showed the lowest values of time to peak velocity in patients with hyperkinetic heart syndrome or with considerable aortic regurgitation.

In this study, we hypothesize that the presence of coronary artery disease can result in a global decrease in contractility such that the LV is not able to generate the required stroke volume anymore when developing (normal) short-lived active contraction force. In order to generate enough stroke volume the whole LV will prolong the development of contractile force, which, besides a slower increase in the blood velocities through the aortic valve, will also result in a longer duration of aortic acceleration and a more symmetrical profile of which the bulk of the flow shifts towards the later part of the ejection period.

This remodelling of the aortic velocity profile can be quantified based on the timing and the overall shape of the LV outflow curve. In this study we have analyzed CW Doppler traces in patients with and without signs of ischaemic heart disease, as assessed by quantitative DSE.

We have implemented an automated analysis tool, using modelling of the velocity envelope, to measure the time intervals relevant for determining later peaking of the outflow traces in CAD.

Our results show that the shape of the aortic outflow trace may reflect decreased contractility: the traces of patients within DSE_{pos} show a tendency towards a more symmetrical, later peaking and faster falling curve than in DSE_{neg} patients and normals. There was a clearly positive correlation of the relative timing of the peak velocity (T_{mod}/ET_{mod}) with EF and a negative one with LVIDd, as a marker of LV dilatation. Furthermore, we observed that an asymm<0.25, indicating a markedly more symmetrical trace, was present in only 2.9% patients in DSE_{neg} and 27.3% of patients in DSE_{pos} while it was greater than 0.25 in all controls. Moreover, asymm proved to be a valid indicator of contractility: it correlated well with EF and had a somewhat weaker, negative correlation with LVIDd.

Although the acceleration of the aortic outflow was previously suggested as a marker of contractility [11], the aortic rise time t_{rise} showed a weaker correlation both with EF and LVIDd, compared to T_{mod}/ET_{mod} and our measure of curve symmetry (asymm), suggesting that not only the initial acceleration, but the whole velocity profile has to be considered to describe LV function.

While we hypothesize that a more symmetrical aortic outflow profile indicates decreased global contractility, surprisingly, we found that the patients within the DSE_{neg} group, on average, showed a more asymmetrical aortic flow pattern with a shorter T_{mod}/ET_{mod} and prolonged t_{fall} when compared to controls. This group of patients also had a significantly higher RWT and EF, as well as higher values of SBP and DBP, compared to the other two groups. Additionally, in this DSE_{neg} group, an LV dynamic intracavitary gradient was induced by DSE in as much as 71% of the patients while this was observed in only 18% in the DSE_{pos} group. This characteristic late and large increase in outflow velocities reflects the dynamic nature of an additional pressure gradient developed within the LV when the cavity size decreases during ejection [31, 32]. This gradient was previously noted in 21% of patients in a series of 57 patients undergoing DSE and was associated with a significantly higher resting

EF but no evidence of a significant difference in history of hypertension, LV hypertrophy, or signs of CAD was present [23]. In another series, the late increase in outflow tract velocities was associated with signs of basal septal hypertrophy and smaller LV cavities [33]. In a series of 394 patients, 17.5% developed a significant LV outflow gradient, which was associated with asymmetrical septal hypertrophy and a lower frequency of wall motion abnormalities [34]. Overall, in our group of patients, a significant prolongation of the duration of t_{fall} was present in patients who developed an intracavitary gradient compared to the ones which had no inducible gradient or controls. This, together with the increased hypertrophy and EF, would let us hypothesize that the patients who develop a dynamic gradient during the DSE have actually increased contractility at baseline and thus indeed show a more asymmetric outflow profile with an earlier peak. The hypertrophy and associated increased contractility in these patients might be caused by the transient, exercise induced, increased pressure overload due to the development of the gradient. The potential to develop a dynamic gradient might be triggered by the localized basal septal hypertrophy, induced by the presence of hypertension [21].

Clinical perspective

The goal of this study was not to present another non-invasive parameter to be used in discrimination CAD patients, but rather to address flow remodelling as a consequence of cellular and force remodelling which occurs in ischaemic heart disease. We have shown that decreased overall contractility results in a more symmetrical outflow velocity profile. In clinical practice, the presence of an abnormally symmetrical profile in an individual patient would thus suggest that the global development of contractile force has been remodelled to cope with the decreased output resulting from decreased contractility. On the other hand, a very asymmetrical and early peaking profile implies increased contractility, which, in the presence of (regional) hypertrophy, might induce a dynamic intracavitary gradient. Additionally, these patients are prone to Tako-Tsubo cardiomyopathy [35].

Incorporating parameters describing the profile of the outflow trace, in the clinical echocardiographic measurements thus provides additional information on myocardial function.

LIMITATIONS

Left ventricular outflow velocities represent the pressure gradient between the LV and aorta and are thus influenced by either of them. This implies that changes in the peripheral vessel tree could influence the flow profile. However, a dynamically increasing resistance in the vessel tree, associated with decreased compliance, as expected in CAD, would reduce late velocities while the presence of high late velocities should thus be related to prolonged LV pressure development. Changes in the isometric contraction duration in itself, would not change the measurements since we start quantifying from the opening of the valve. However, a lengthening of the isometric contraction time would also be expected with a decreased contractility, which would be reflected again in a slower rise time and later peaking, as we observe.

Although contractility was not measured directly, there is a strong body of evidence proving that DSE testing, especially including information on changes in local deformation, is indicative of increase in contractility. Furthermore, as this was a retrospective study on routine clinical data, catheterisation measurements of LV contractility were not available, nor was sufficient mitral regurgitation present in most of the patients in order to measure Dp/dt. Therefore, we have chosen to subgroup the patients based on the DSE response rather than angiographically proven CAD, which then served as an adjunctive marker of LV contractility, Moreover, the current study was performed using CW Doppler, which is also influenced by velocities in the LV cavity (such as the development of a dynamic gradient). Finally, although dobutamine mimics exercise, its effects are quite different in terms of loading as it decreases preload and afterload. Therefore, identical effects should not be assumed for exercise echocardiography.

CONFLICTS OF AND COMPETING INTERESTS: The authors report no conflicts of or competing interests with regard to this study.

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FIGURE LEGENDS:

Figure 1. Raw aortic outflow continuous wave Doppler trace (top). The piecewise cubic model fitted on the original trace and the properties extracted from it (bottom). P - area

Figure 2. Raw continuous wave Doppler trace and extracted profile from the control group (left), DSE negative group (middle) and DSE positive group (right). DSE – dobutamine stress echocardiography; t_r – rise time (dashed line); t_f – fall time (dashed line); asymm – asymmetry factor.

Figure 3. The correlation between the manual and automated measurements of ejection time and time to peak velocity. ET_{man} – ejection time by manual analysis of the Doppler signal, ET_{mod} - ejection time by analysis of the modelled signal, T_{man} - time from onset of aortic flow to peak flow by manual analysis of the Doppler signal, T_{mod} **-** time from onset of aortic flow to peak flow by analysis of the modelled signal.

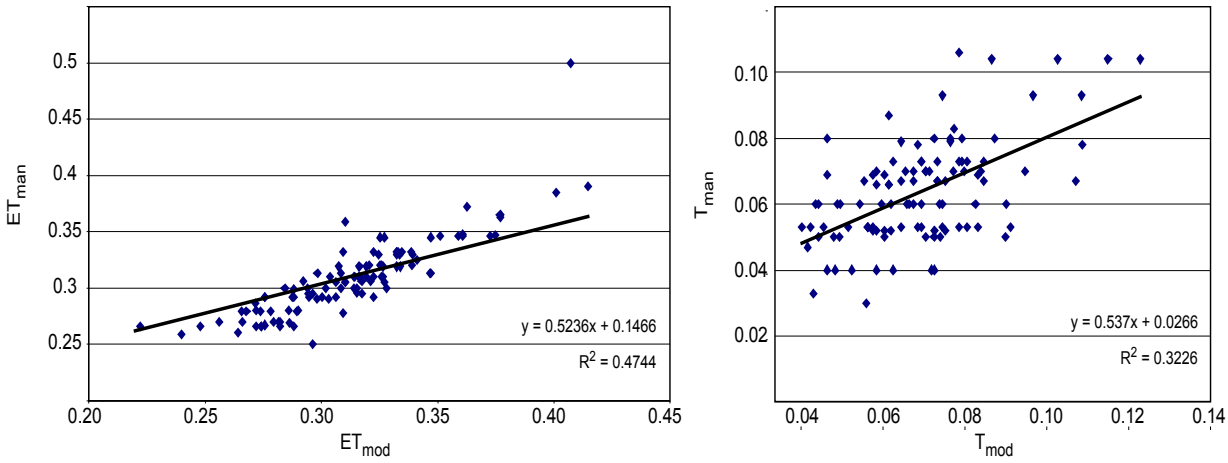


Figure 4. The correlation between EF and asymm, T_{mod}/ET_{mod}, t_{rise} and t_{fall}. EF – ejection fraction, asymm – asymmetry factor, T_{mod}/ET_{mod} – ratio of time to peak and ejection time flow by analysis of the modelled signal, t_{rise} – rise time, t_{fall} – fall time, DSE_{neg} – dobutamine stress echocardiography negative group, DSE_{pos} - dobutamine stress echocardiography positive group.

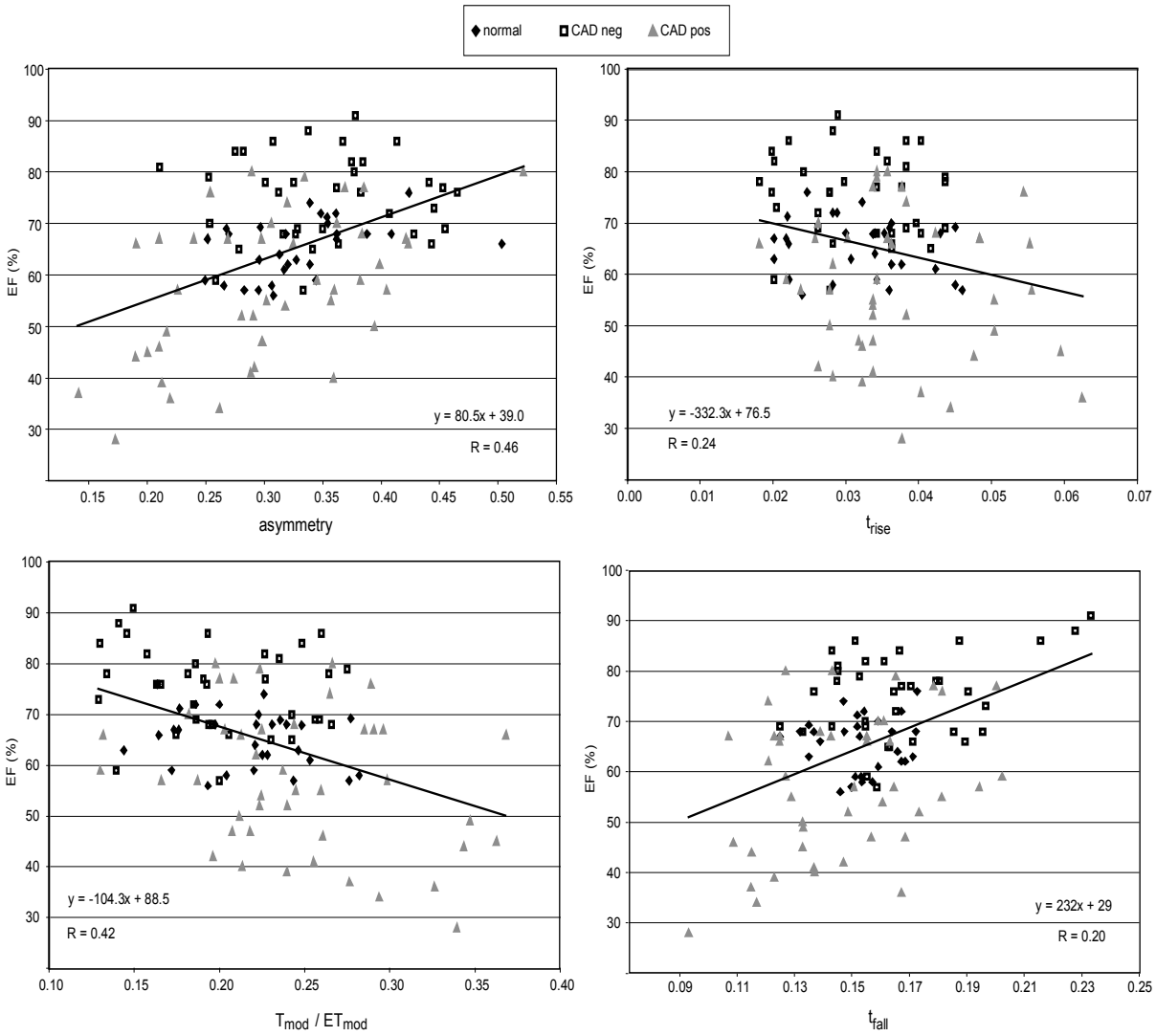
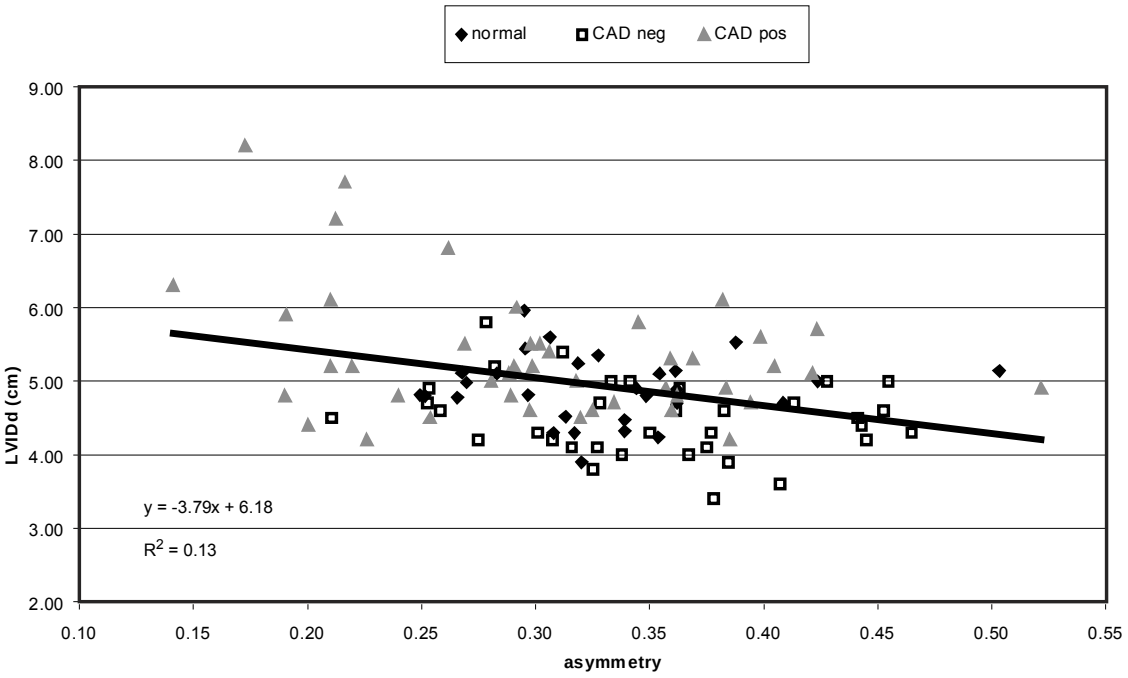
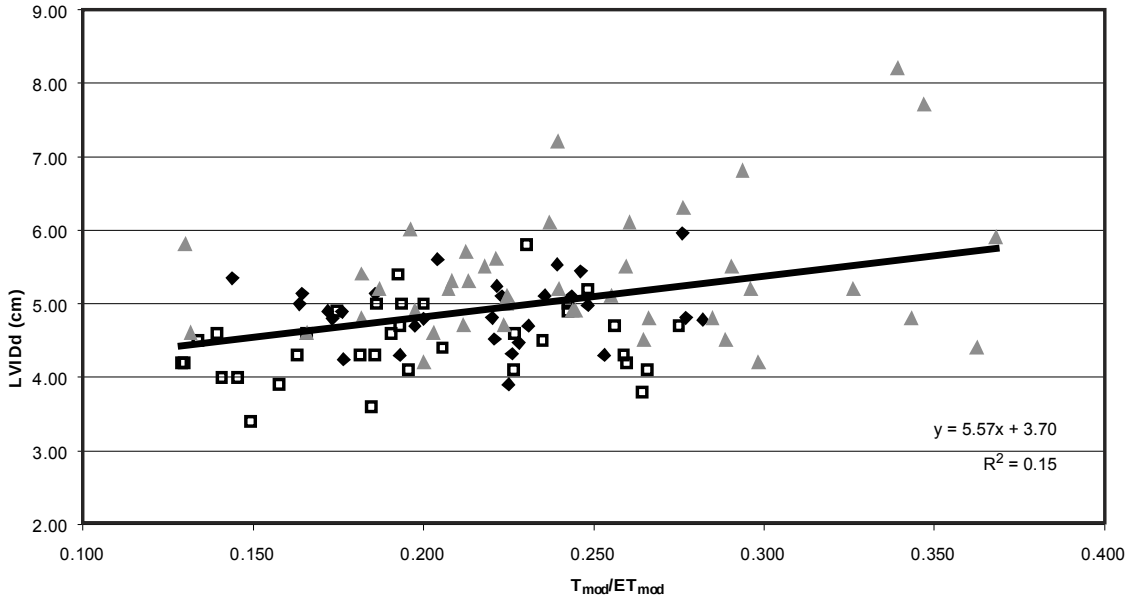


Figure 5. The correlation between LVIDd and asymm, T_{mod}/ET_{mod}, t_{rise}. LVIDd – left ventricular internal dimension at end diastole, asymm – asymmetry factor, T_{mod}/ET_{mod} – ratio of time to peak and ejection time flow by analysis of the modelled signal, t_{rise} – rise time, t_{fall} – fall time, DSE_{neg} – dobutamine stress echocardiography negative group, DSE_{pos} - dobutamine stress echocardiography group.


normal
CAD neg
CAD pos
LVIDd (cm)
asymmetry
y = -3.79x + 6.18
R2 = 0.13


LVIDd (cm)
Tmod/ETmod
y = 5.57x + 3.70
R2 = 0.15

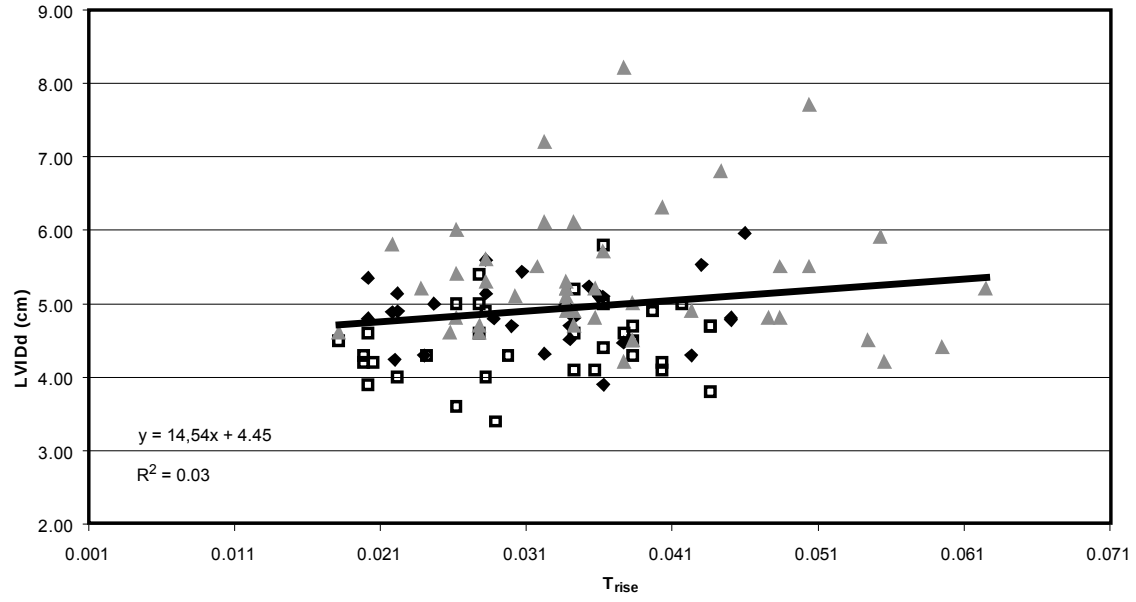
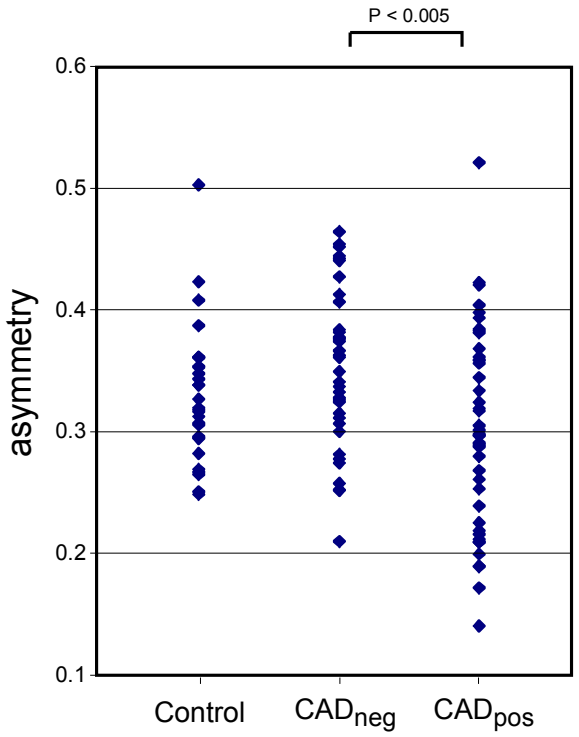
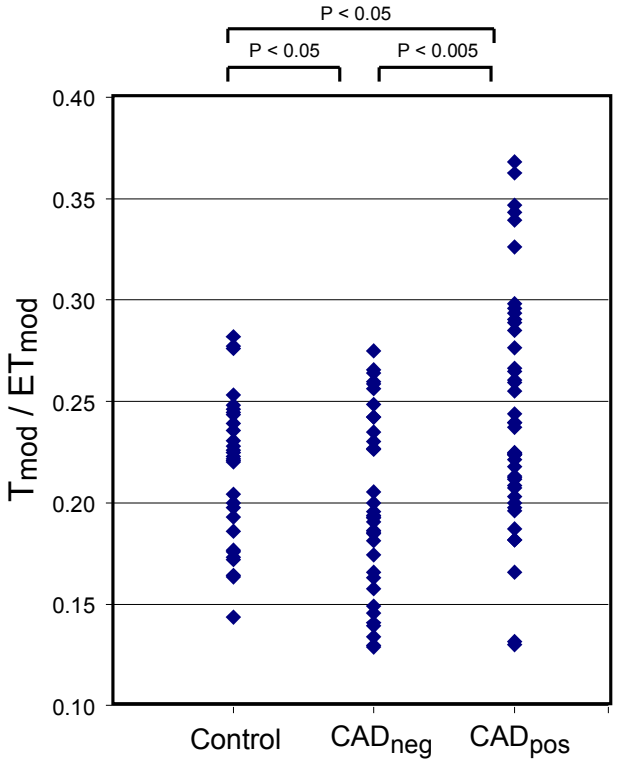
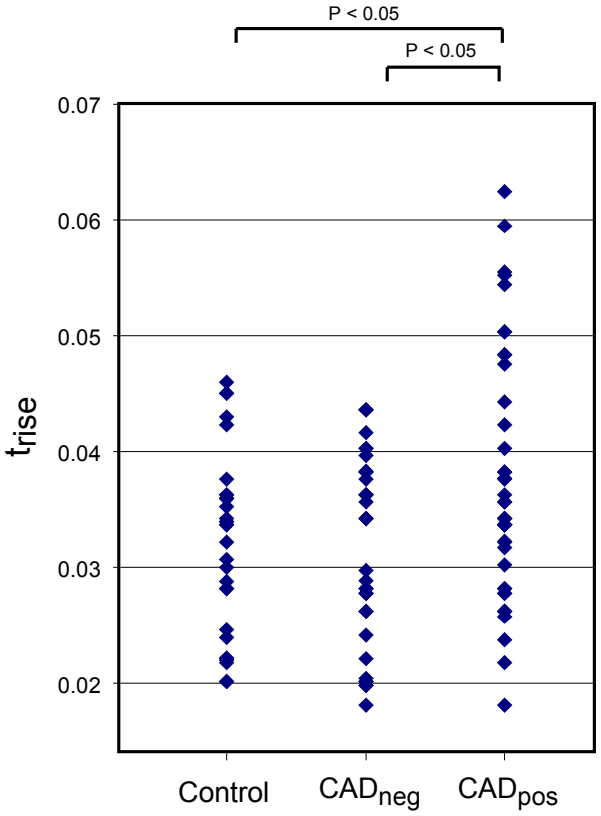

LVIDd (cm)
Trise
y = 14,54x + 4.45
R2 = 0.03

Figure 6. The values of asymm, T_{mod}/ET_{mod}, t_{rise} and t_{fall} among the three patient groups. asymm – asymmetry factor, T_{mod}/ET_{mod} – ratio of time to peak and ejection time flow by analysis of the modelled signal, t_{rise} – rise time, t_{fall} – fall time, DSE_{neg} – dobutamine stress echocardiography negative group, DSE_{pos} - dobutamine stress echocardiography positive group.


P < 0.005
asymmetry
0.6
0.5
0.4
0.3
0.2
0.1
Control
CADneg
CADpos


P < 0.05
P < 0.05
P < 0.005
Tmod / ETmod
0.40
0.35
0.30
0.25
0.20
0.15
0.10
Control
CADneg
CADpos


P < 0.05
P < 0.05
trise
0.07
0.06
0.05
0.04
0.03
0.02
Control
CADneg
CADpos

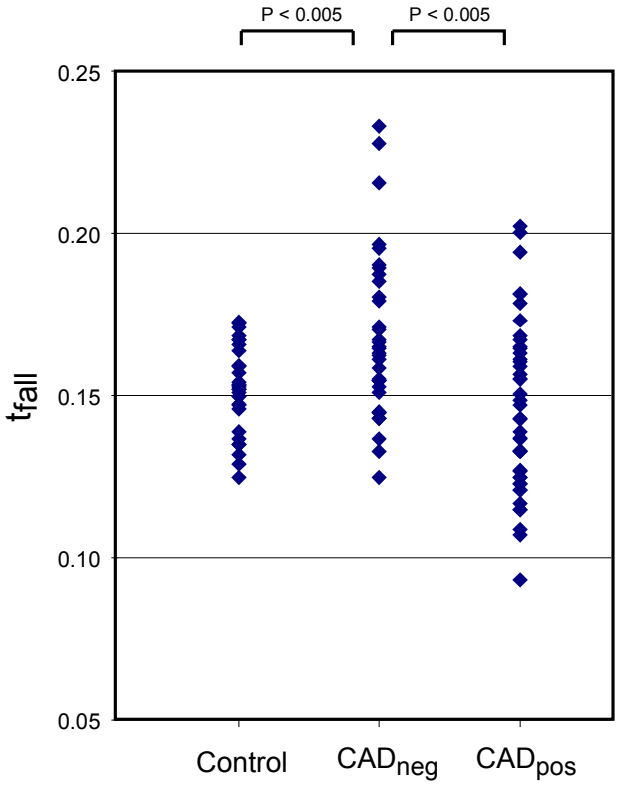

P < 0.005
P < 0.005
tfall
0.25
0.20
0.15
0.10
0.05
Control
CADneg
CADpos

Figure 7. The values of EF, RWT, t_{fall} and T_{mod}/ET_{mod} among the patients grouped in regard to inducible intracavity gradient. EF – ejection fraction, RWT – regional wall thickness, t_{fall} – fall time, T_{mod}/ET_{mod} – ratio of time to peak and ejection time flow by analysis of the modelled signal, $GRAD_{neg}$ – patients without an inducible intracavitary gradient by dobutamine stress echocardiography, $GRAD_{pos}$ - patients with an inducible intracavitary gradient by dobutamine stress echocardiography.

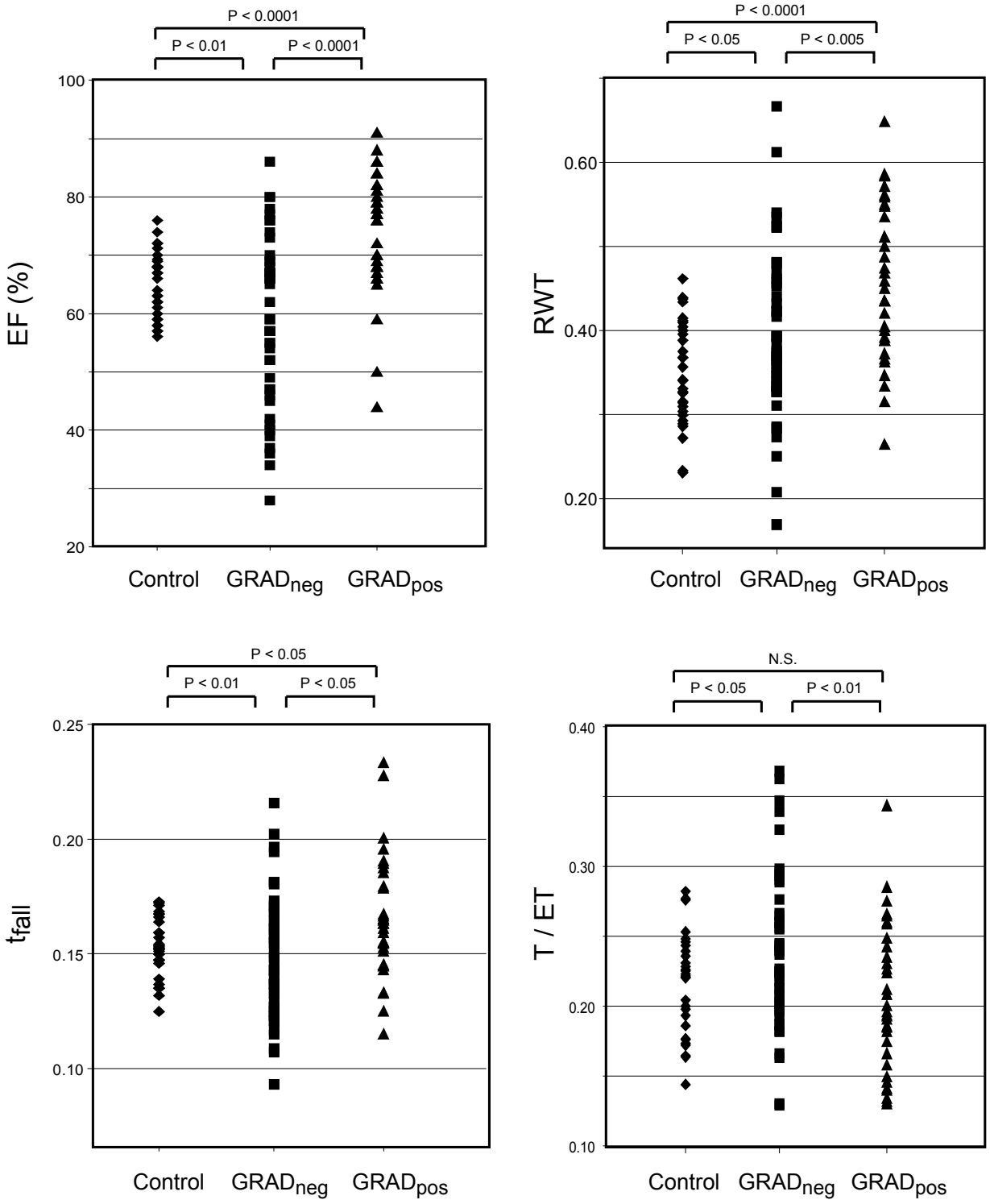

P < 0.0001
P < 0.01
P < 0.0001
EF (%)
100
80
60
40
20
Control
GRADneg
GRADpos
P < 0.0001
P < 0.05
P < 0.005
RWT
0.60
0.40
0.20
Control
GRADneg
GRADpos
P < 0.05
P < 0.01
P < 0.05
tfall
0.25
0.20
0.15
0.10
Control
GRADneg
GRADpos
N.S.
P < 0.05
P < 0.01
T / ET
0.40
0.30
0.20
0.10
Control
GRADneg
GRADpos

Table 1. Basic patient characteristics

	control group (n=31)	DSE_{neg} (n=35)	DSE_{pos} (n=44)
Age (years)	59.0±11.5	60.3±8.4	64.7±9.7*
male/female	15/17	9/26	28/16
SBP rest (mmHg)	119.7±13.2	154.1±22.3†	146.3±16.7†
DBP rest (mmHg)	73.3±6.8	82.2±10.9‡	79.6±11.0§
HR rest (/min)	62.9±10.8	67.5±11.2	70.9±10.7§
CABG (pts)	-	1	14
PCI (pts)	-	4	15
Insignificant stenosis (pts)	-	5	5
single vessel (pts)	-	1	6
double vessel (pts)	-	2	5
triple vessel (pts)	-	2	3
multi vessel (pts)		1	2

DSE: dobutamine stress echocardiography; DSE_{neg}: patients without resting wall motion abnormalities or signs of inducible ischaemia on DSE; DSE_{pos}: patients with resting wall motion abnormalities or a positive DSE; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CABG: coronary artery bypass grafting; pts: patients; PCI: percutaneous coronary intervention.

* $P<0.05$ vs. DSE_{neg}; †$P<0.0001$ vs. control, ‡ $P<0.001$ vs. control, § $P<0.05$ vs. control.

Table 2. Echocardiographic measurements

	control group (n=31)	DSE_{neg} (n=35)	DSE_{pos} (n=44)
LVIDd (cm)	4.9±0.5	4.5±0.5*	5.3±0.9†‡
LVIDs (cm)	3.0±0.5	2.7±0.6§	3.5±0.9§‡
IVSd (cm)	0.9±0.2	1.1±0.2†	1.1±0.3†
LVPWd (cm)	0.8±0.2	1.0±0.3†	0.9±0.2†
IVS bulge (cm)	1.1±0.2	1.3±0.3†	1.2±0.3§
lateral wall (cm)	0.9±0.1	1.0±0.2§	0.9±0.2
RWT	0.35±0.06	0.47±0.08*	0.38±0.10‡
EF (%)	65.4±5.6	75.6±7.9*	57.5±13.9†‡
LV mass (g)	167.1±53.3	177.8±58.3	241.8±89.5*‖
LV mass ASE (g)	145.2±42.7	158.1±46.3	204.4±72,1*‖
inducible gradient (pts)	-	25	8

DSE: dobutamine stress echocardiography; DSE_{neg}: patients without resting wall motion abnormalities or signs of inducible ischaemia on DSE; DSE_{pos}: patients with resting wall motion abnormalities or a positive DSE; LVIDd: left ventricular internal diastolic dimension at end-diastole; LVIDs: left ventricular internal diastolic dimension at end-systole; IVSd: interventricular septum thickness at end-diastole LVPWd: left ventricular posterior wall thickness at end-diastole; IVS: interventricular septum; RWT: regional wall thickness; EF: ejection fraction; LV: left ventricular; ASE: American Society of Echocardiography; pts: patients.

* P<0.0001 vs. control, † P<0.005 vs. control, ‡P<0.0001 vs. DSE_{neg}, § P<0.05 vs. control, ‖P<0.001 vs. DSE_{neg}

Table 3. Properties extracted from aortic Doppler traces

	control group (n=31)	DSE_{neg} (n=35)	DSE_{pos} (n=44)
asymm	0.33±0.06	0.35±0.07	0.30±0.08*
asymm < 0.25 (%)	0.0	2.9	27.3
ET_{mod}	293.4±59.3	329.4±33.6†	305.3±37.7*
ET_{man}	296.0±19.4	324.8±40.5†	304.8±33.5‡
ET_{mod}/HR	4.55±1.30	5.12±1.11	4.62±1.22
ET_{man}/HR	4.59±0.90	5.06±1.27	4.60±1.16
T_{mod}	65.66±13.50	65.16±13.81	74.50±18.93 §‡
T_{man}	55.33±10.42	64.49±16.03§	68.73±15.97‖
T_{mod}/ET_{mod}	0.215±0.036	0.199±0.046§	0.244±0.055§*
T_{man}/ET_{man}	0.187±0.036	0.201±0.055	0.228±0.057†‡
t_{rise}	0.032±0.008	0.032±0.008	0.037±0.010§‡
t_{fall}	0.153±0.013	0.168±0.025†	0.146±0.026*

DSE: dobutamine stress echocardiography; DSE_{neg}: patients without resting wall motion abnormalities or signs of inducible ischaemia on DSE; DSE_{pos}: patients with resting wall motion abnormalities or a positive DSE; asymm: asymmetry factor; ET_{mod}: ejection time derived by mathematical modelling; ET_{man}: ejection time measured manually; HR: heart rate; T_{mod}: time from onset of aortic flow to peak aortic flow derived by mathematical modelling; T_{man}: time from onset of aortic flow to peak aortic flow measured manually; t_{rise}: rise time; t_{fall}: fall time.

* P<0.005 vs. DSE_{neg}, † P<0.005 vs. control, ‡ P<0.05 vs. DSE_{neg}, § P<0.05 vs. control, ‖ P<0.0001 vs. control.