Assessment of left ventricular long axis contraction can detect early myocardial dysfunction in asymptomatic patients with severe aortic regurgitation

D Vinereanu, A A Ionescu, A G Fraser

Abstract
Objective—To identify variables that could be applied at rest to diagnose subclinical ventricular dysfunction in asymptomatic patients with severe aortic regurgitation.

Design—Cross sectional study.

Patients—Left ventricular long axis contraction was studied using tissue Doppler and M mode echocardiography in 21 patients with no symptoms (New York Heart Association (NYHA) functional class ≤ 2a) but severe aortic regurgitation (jet area/left ventricular outflow tract area > 40%).

Main outcome measures—Left ventricular ejection fraction (LVEF) at baseline and peak exercise (Weber protocol), cardiopulmonary function, and left ventricular long axis function at rest (peak systolic velocity and excursion of the mitral annulus).

Results—In 11 patients, ejection fraction increased or did not change (from mean (SD) 55 (5)% to 58 (4)%, p < 0.05) (group I); in 10 patients it decreased by > 5% (from 54 (4)% to 42 (5)%, p < 0.001) (group II). Exercise ejection fraction was < 50% in all patients in group II. At rest, there were no differences between the groups in ejection fraction, left ventricular diameter indices, wall stress, and short axis contraction. However, patients in group II had reduced long axis contraction compared with group I: peak systolic velocity 8.6 (0.6) v 11.9 (2.2) cm/s (p < 0.001); excursion 11 (2) v 14 (2) mm (p < 0.01). A resting velocity of < 9.5 cm/s was the best indicator of poor exercise tolerance (sensitivity 90%, specificity 100%).

Conclusions—Markers of reduced long axis contraction may provide simple and reliable indices of subclinical left ventricular dysfunction in asymptomatic patients with severe aortic regurgitation.

(Heart 2001;85:30–36)

Keywords: aortic regurgitation; long axis function; tissue Doppler echocardiography; exercise echocardiography

Asymptomatic patients with chronic aortic regurgitation have an excellent prognosis if their resting ejection fraction is greater than 45%. The annual mortality rate is less than 0.5%, but such patients are not a homogeneous group. Thus many remain clinically stable, while 4–6%/year develop left ventricular dysfunction and require surgery. If operation is deferred in all patients until they become symptomatic, a subset may already have irreversible left ventricular dysfunction.

It is a challenge to recognise patients with subclinical myocardial dysfunction in order to operate early enough to prevent postoperative heart failure, but not so early as to subject them to unnecessary operative risks and morbidity related to prosthetic valves. The reported best predictors of subnormal left ventricular performance in asymptomatic patients with severe aortic regurgitation are a decrease in ejection fraction on exercise (by more than 5%) and a low ejection fraction on exercise (less than 50%) coupled with inappropriately high wall stress, assessed by echocardiography or radionuclide ventriculography. Dynamic stress echocardiography with quantification of left ventricular function is difficult and time consuming, however, and so it is not widely used.

An important mechanism of early left ventricular dysfunction in asymptomatic patients with aortic regurgitation may be subendoocardial ischaemia and fibrosis. As the subendoocardial fibres are aligned longitudinally, we speculated that long axis function of the left ventricle would be abnormal in some patients with severe aortic regurgitation but no significant symptoms. We used both M mode echocardiography of mitral annular motion and the new technique of tissue Doppler echocardiography to assess potential echocardiographic indicators of subnormal left ventricular performance related to chronic volume overload, which could be applicable at rest.

Methods

PATIENTS

Asymptomatic patients with chronic aortic regurgitation who were referred for routine clinical assessment of cardiac reserve by stress echocardiography and cardiopulmonary tests were eligible for inclusion. Patients had to be in New York Heart Association (NYHA) functional class I or IIa, to be in sinus rhythm, and to have pure and severe aortic regurgitation by echocardiographic criteria (ratio of jet area to left ventricular outflow tract area > 40%; diameter of the regurgitant jet at origin...
LONG AXIS FUNCTION
Motion of the medial mitral annulus was recorded from the apical four chamber view.

M mode echocardiography
Cross sectional guided M mode of medial mitral annular motion was recorded (fig 1). The systolic amplitude in the long axis was measured from the onset of annular movement towards the apex, on the peak of the QRS complex, to the maximum systolic displacement. This measurement excludes the rapid recoil of the annulus toward the apex during isovolumic contraction.

Tissue Doppler echocardiography
The pulsed sample volume was placed just apical to the medial mitral annulus in systole, identified by colour coded tissue Doppler. A fixed sampling gate of 2.5 mm and minimal optimal gain were used in order to obtain the best signal to noise ratio. Every effort was made to align the pulsed wave cursor so that the Doppler angle of incidence was as close to 0° as possible to the direction of motion of the mitral annulus. Peak systolic velocity was measured excluding the velocities recorded during isovolumic contraction (fig 2).

SHORT AXIS FUNCTION
Pulsed wave tissue Doppler of the left ventricular posterior wall was recorded from the parasternal long axis view. The sample volume was placed inside the myocardium, opposite the tips of the mitral leaflets in diastole and above the insertion of the papillary muscle.

DIASTOLIC FUNCTION
Global diastolic function was assessed by pulsed wave Doppler echocardiography of transmitral flow. The sample volume was placed at the tips of the mitral leaflets in the apical four chamber view. Peak early (E) and atrial velocities (A) were measured, and the E:A ratio was calculated.

Regional diastolic function was assessed using tissue Doppler echocardiography of mitral annular motion for the long axis, and of the left ventricular posterior wall for the short axis. From the spectral traces we measured peak velocities during early filling (E_{TDE}) and atrial contraction (A_{TDE}). The E_{TDE}:A_{TDE} ratio was calculated.

EXERCISE PROTOCOL
Graded treadmill exercise testing was performed using the Weber protocol, until the patient was limited by symptoms. Blood pressure, heart rate, ECG, and cardiopulmonary function were monitored. Immediately after exercise the subjects were placed in the left lateral decubitus position. Recordings of the left ventricle from the apical four chamber view were repeated within one minute of termination of exercise to calculate peak exercise ejection fraction.

ECHOCARDIOGRAPHIC ANALYSIS
Analysis was performed off-line, and all variables were averaged from three consecutive
cardiac cycles. Left ventricular diameters, volumes, and mass were indexed to body surface area. Left ventricular volumes and ejection fraction were calculated using the single plane area–length method.16 End systolic wall stress, in $10^3$ dynes/cm$^2$, was calculated according to the formula described by Grossman.11 12 Left ventricular mass was estimated by the method of Devereux with the application of the Penn convention.13

**CARDIOPULMONARY TESTS**
Oxygen consumption, carbon dioxide production, and minute ventilation were continuously recorded during exercise with a commercially available system (Quinton QMC). Graphs of oxygen consumption against time, carbon dioxide against oxygen consumption, and minute ventilation against carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope) were plotted. Maximum oxygen consumption was defined as the $> 30$ s plateau in oxygen consumption that occurs at peak exercise.14 Anaerobic threshold was calculated non–invasively from the V slope analysis (graph of carbon dioxide production against oxygen consumption), as the point of disproportionate carbon dioxide production relative to oxygen consumption.15 Minute ventilation against carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope) was calculated using commercial software (Quinton, Seattle, USA)

**STATISTICAL ANALYSIS**
Statistical analysis was performed with SPSS software (version 9.0). Results are presented as mean (SD). The change in ejection fraction from baseline to peak exercise was compared by Wilcoxon matched pairs signed ranks test. The characteristics of patients with good and poor exercise responses were compared by the Mann–Whitney U test for independent samples or by Fisher’s exact test for proportions. Pearson bivariate two tailed correlations were obtained between the variables. Sensitivity, specificity, and accuracy analyses were performed to determine the left ventricular volume indices, maximum oxygen consumption, peak systolic amplitude, and velocity of mitral annular motion that would predict a poor exercise response. A probability value of $p < 0.05$ for a two tailed test was considered significant.

Intraobserver variability of measurements of rest and peak exercise ejection fraction, systolic excursion, and peak systolic velocity was determined in eight randomly selected patients. Reproducibility was examined using the Bland–Altman analysis.16 Ninety five per cent confidence limits of a single estimate of the measurements were calculated as $2SD/2$, and reported as absolute values and per cent from the mean value.

**Results**

**PATIENTS**
Twenty one patients (16 men, 5 women) were included, 16 in NYHA functional class I and five in class IIa. All patients completed the protocol apart from one who refused to have cardiopulmonary tests because of claustrophobia. Characteristics of the study group are given in table 1.

Sixteen patients had undergone cardiac catheterisation; each had grade IV aortic regurgitation on aortography but no other valve disease or coronary artery disease. The aetiology of aortic regurgitation had been considered to be rheumatic in 12 patients (none of whom had mitral valve disease), bicuspid aortic valve in six, and previous infective endocarditis (two years before) in one. In two patients no cause could be defined.

Drug treatment was continued at the time of testing in nine patients (42%): seven were on angiotensin converting enzyme inhibitors, five on diuretics, one on sotalol, and one on verapamil.

**EXERCISE RESPONSE**
Exercise response results are shown in fig 3. Ejection fraction increased on exercise, or decreased by less than 5%, in 11 patients: from mean (SD) 55 (5)% to 58 (4)%; $p < 0.05$ (group I; good exercise response). Ejection fraction decreased by more than 5% in 10 patients: from 54 (4)% to 42 (5)%; $p < 0.001$ (group II; poor exercise response). In all patients in the latter group, the ejection fraction on exercise was less than 50% (34–49%).

In these two groups we compared the resting echocardiographic variables, indices of long axis and short axis function, and exercise cardiopulmonary function.

**RESTING ECHOCARDIOGRAPHIC VARIABLES**
Resting echocardiographic variables are given in table 2. There were no significant differences
between the groups in resting ejection fraction, left ventricular diameter indices, end systolic wall stress, and end systolic wall stress to end systolic volume index ratio. Patients with poor exercise responses had a more dilated left ventricle and an increased left ventricular mass index, but resting left ventricular volume indices had low sensitivity and specificity for predicting a poor exercise response: 40% and 80%, respectively, for an end diastolic volume index ratio. Patients with poor exercise responses had long axis diastolic dysfunction, but low sensitivity (44%) for predicting a poor exercise response.

**Diastolic Function**

Seven of the 10 patients with poor exercise responses had global diastolic dysfunction, assessed as an E/A ratio < 1, compared with only one of the 11 patients with good exercise responses (p < 0.01). Sensitivity and specificity of diastolic variables in predicting a poor exercise response were 70% and 64%, respectively, for an E:A ratio < 1, and 80% and 91%, respectively, for an E/ETDE:A/ETDE ratio < 1.

**Cardiopulmonary Function**

There were no significant differences between the two groups in maximum oxygen consumption, exercise duration, workload, anaerobic threshold, and minute ventilation against carbon dioxide production (Ve/VCO₂ slope) (table 2). Maximum oxygen consumption correlated with change in ejection fraction from rest to exercise (r = 0.57, p < 0.01); a value ≤ 20 ml/kg/min had good specificity (91%) but low sensitivity (44%) for predicting a poor exercise response.

**Reproducibility**

Intraobserver variability for the measurement of ejection fraction was ± 3.1% (in absolute terms), or ± 5.6% from the mean value for the resting values, and ± 2.3% (in absolute terms), or ± 4.3% from the mean value for the peak exercise values. Variability of measuring change of the ejection fraction from rest to exercise was ± 3.1% from the mean value (SD 2.2%). Variability of measuring long axis function was ± 0.51 cm/s (± 4.3%) for the peak systolic velocity, and ± 0.75 mm (± 5.8%) for the systolic excursion.
tion have been related to left ventricular functional reserve during exercise, assessed by echocardiography or radionuclide ventriculography. A Borer and colleagues reported that patients whose ejection fraction decreased on exercise by more than 5% had a 12.5%/year risk of developing heart failure or subclinical left ventricular dysfunction, compared with only 1.9%/year if the ejection fraction response was normal; the risk was 8.8%/year if the ejection fraction on exercise was less than 50%. A We applied the same cut off to differentiate between patients with good and poor exercise responses; a fall in ejection fraction on exercise of less than 5% was taken as no change, as this value—used by Borer and colleagues—corresponded to more than 2 SD of our intraobserver variability for this measurement.

Dynamic exercise echocardiography cannot be performed in patients with musculoskeletal problems, and acquiring data within one minute of peak exercise is difficult in patients with poor echocardiographic windows or severe breathlessness. Confidence intervals for detecting changes in individuals by serial echocardiography are disappointing: the reported values are ±15% for end diastolic volume, ±25% for end systolic volume, and ±10% for ejection fraction. A It would therefore be helpful to describe resting variables that can identify left ventricular dysfunction.

Siemienczuk and colleagues showed that progression to surgery was earlier in patients with increased left ventricular volume indices at rest (left ventricular end diastolic index ≥150 ml/m² and end systolic index ≥60 ml/m²). A Although left ventricular volume indices were different in our study between patients with good and poor exercise responses, they had low sensitivity and specificity for predicting the exercise response.

It has been suggested that load adjusted variables should be more reliable for predicting outcome in asymptomatic patients with aortic regurgitation. These include the end systolic wall stress to end systolic volume index and the change in ejection fraction from rest to exercise normalised for change in end systolic wall stress. A We did not find differences between the two groups for either end systolic wall stress or the end systolic wall stress to end systolic volume index. Change of ejection fraction from rest to exercise normalised for the change in end systolic wall stress was shown by Borer and colleagues to be a strong predictor of progression to heart failure in patients with aortic regurgitation. A In our study, peak exercise data were acquired in less than one minute, so there was not enough time also to acquire a good quality M mode recording of the left ventricle from the parasternal view in order to calculate end systolic wall stress on exercise. Moreover, this index is complex, unlikely to be measured accurately or to be used in routine clinical practice, and its reproducibility has not been reported. A

LONG AXIS FUNCTION IN SEVERE AORTIC REGURGITATION

Severe and chronic left ventricular volume overload increases wall stress and may cause subendocardial ischaemia. This is the suggested precursor of deposition of collagen and subendocardial fibrosis, and a mechanism of left ventricular dysfunction in aortic regurgitation. A Thus subendocardial dysfunction might provide a better marker of incipient left ventricular damage than the variables that have already been described. The subendocardial fibres are aligned longitudinally and connected with the mitral annulus. A Long axis contraction results in the apical displacement of the mitral annulus, which can be measured by M mode echocardiography in terms of excursion, or by tissue Doppler echocardiography in terms of velocity. A

DIASTOLIC FUNCTION

Patients with severe aortic regurgitation have diastolic dysfunction, and this correlates with the degree of subendocardial fibrosis. A A ratio of early to late velocity of mitral annular motion < 1, measured by tissue Doppler echocardiography, has good sensitivity and specificity (>70%) for detecting diastolic dysfunction, even in patients with a pseudonormal E:A ratio. A

In our study, patients with poor exercise responses had a higher prevalence of a reversed E:A ratio, but this is difficult to interpret because they were also older than patients with good exercise responses. The changes could be caused by impaired relaxation of the left ventricle in early diastole in subjects with poor exercise responses, related to subendocardial dysfunction. The fact that there were diastolic abnormalities of long axis function but not of short axis function would support this. However, this hypothesis could only be proven by comparison with age matched controls.

CARDIOPULMONARY TESTING IN PATIENTS WITH AORTIC REGURGITATION

Maximum oxygen consumption and anaerobic threshold are relatively direct indices of cardiac functional reserve. A In heart failure, maximum oxygen consumption correlates with symptoms, ejection fraction, and prognosis. A

The ventilatory cost of carbon dioxide elimination, reflected by the minute ventilation against carbon dioxide production (Ve/Co2 slope), is increased in patients with heart failure. A Therefore it is reasonable to suppose that these cardiopulmonary tests reflect left ventricular
function in patients with isolated severe aortic regurgitation who have no respiratory disease.24

We did not find significant differences between patients with aortic regurgitation who had good or poor exercise responses for any of the cardiopulmonary tests investigated. A maximum oxygen consumption of $\leq 20$ ml/kg/min had a good specificity but a low sensitivity for predicting a poor exercise response. Maximum oxygen consumption correlated with change in ejection fraction from rest to exercise, and might be a useful adjunct to conventional exercise testing in asymptomatic patients with severe aortic regurgitation.

STUDY LIMITATIONS

In our study, patients with poor exercise responses were older than patients with good exercise responses. This might affect the comparison of long axis function, but systolic velocities of the myocardium have been reported to be independent of age.73

The single plane area–length method tends to overestimate left ventricular volumes and ejection fraction.50 Its advantages are that it is reliable for assessing ejection fraction even when this is less than 50%, and it has good reproducibility,57–59 as also demonstrated by our study. It is suitable for stress echocardiography, when a short acquisition time is crucial, because it needs only an apical four chamber view.

To assess long axis function we used only the midventral annulus, but in our experience this site gives the best Doppler alignment and has good intraobserver variability.40 It is possible that recording myocardial velocities during stress could add to the prognostic value of resting measurements, but this is hard to assess after dynamic exercise because of the need to record all the data quickly.

This study included a relatively small number of patients, but it is difficult in a single centre to identify many asymptomatic patients with severe aortic regurgitation and normal resting left ventricular function. Nonetheless, long axis function was clearly different between the two groups, and so it may be a powerful predictor.

CONCLUSIONS

Asymptomatic patients with severe aortic regurgitation who have an abnormal ejection fraction response to exercise are accurately identified by measurements of left ventricular long axis contraction at rest. The new echocardiographic technique of tissue Doppler echocardiography may have the potential to reveal subclinical myocardial dysfunction and thereby to improve significantly the timing of aortic valve surgery in such patients. This should now be tested in long term, prospective studies.


12 Percy RJ, Miller AB, Conetta DA. Usefulness of left ventricular wall stress at rest and after exercise for outcome prediction in asymptomatic aortic regurgitation. Am Heart J 1993;125:151–5.


Aneurysms of the left main coronary arteries are found in 0.1% of angiograms. This case involves an athlete with a left main coronary artery aneurysm, which was combined with chronic total occlusion of both left coronary arteries in a young athlete. The ECG showed J point and ST elevation in leads V2–V4, and inverted T waves in leads V5 and V6. Creatine kinase (CK) was raised to 435 U/l (CK-MB 36 U/l), troponin I was 63.4 µg/l, and lactate dehydrogenase was 359 U/l, suggesting cardiac involvement of varicella infection. The left ventricle was globally reduced (ejection fraction 45%). Myocarditis was confirmed by endomyocardial biopsy. The patient was treated with specific varicella hyperimmunoglobulins, aciclovir, and a non-steroidal anti-inflammatory drug. During two months follow up the patient recovered completely. This case report is a reminder that a varicella infection can cause myocarditis in adults. Early diagnosis and appropriate treatment of this rare form of myocarditis may lead to complete recovery.

(Heart 2001;85:e2) www.heartjnl.com/cgi/content/full/85/1/e2

**Varicella myocarditis in an adult**

P Alter, W Grimm, B Maisch

A 24 year old male with varicella myocarditis was admitted with chest pain and fever up to 39°C. The ECG showed J point and ST elevation in leads V2–V4, and inverted T waves in leads V5 and V6. Creatine kinase (CK) was raised to 435 U/l (CK-MB 36 U/l), troponin I was 63.4 µg/l, and lactate dehydrogenase was 359 U/l, suggesting cardiac involvement of varicella infection. The left ventricle was dilated (58 mm) and left ventricular ejection fraction was globally reduced (ejection fraction 45%). Myocarditis was confirmed by endomyocardial biopsy. The patient was treated with specific varicella hyperimmunoglobulins, aciclovir, and a non-steroidal anti-inflammatory drug. During two months follow up the patient recovered completely. This case report is a reminder that a varicella infection can cause myocarditis in adults. Early diagnosis and appropriate treatment of this rare form of myocarditis may lead to complete recovery.

(Heart 2001;85:e3) www.heartjnl.com/cgi/content/full/85/1/e3

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**Left main coronary artery aneurysm with chronic total occlusion of both left coronary arteries in a young athlete**

*S-H Park, S-E Kim, S K Rye*

Aneurysms of the left main coronary arteries are found in 0.1% of angiograms. This case involves an athlete with a left main coronary artery aneurysm, which was combined with chronic total occlusion of the proximal left anterior descending and proximal left circumflex coronary arteries. The extraordinary clinical presentation in this patient may be associated with good coronary collaterals, which may have developed in the patient in response to chronic total occlusion of the coronary artery by the aneurysm, and repeat myocardial hypoxia during high levels of performance as a soccer player.

(Heart 2001;85:e1) www.heartjnl.com/cgi/content/full/85/1/e1

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(Heart 2001;85:e2) www.heartjnl.com/cgi/content/full/85/1/e2

**ST segment elevation in the right precordial leads following administration of class Ic antiarrhythmic drugs**

*M Yashuda, Y Nakazato, H Yamashita, G Sekita, Y Kawano, Y Mineda, K Nakazato, T Tokano, M Sumiyoshi, Y Nakata*

Electrocardiographic changes were evaluated retrospectively in five patients without previous episodes of syncope or ventricular fibrillation who developed abnormal ST segment elevation mimicking the Brugada syndrome in leads V1–V3 after the administration of class Ic antiarrhythmic drugs. Pilsicainide (four patients) or flecainide (one patient) was administered orally for the treatment of symptomatic paroxysmal atrial fibrillation or premature atrial contractions. The QRS duration, QTc, and JT intervals on 12 lead surface ECG before administration of these drugs were all within normal range. After administration of the drugs, coved-type ST segment elevation in the right precordial leads was observed with mild QRS prolongation, but there were no apparent changes in JT intervals. No serious arrhythmias were observed during the follow up periods. Since ST segment elevation with mild QRS prolongation was observed with both pilsicainide and flecainide, strong sodium channel blocking effects in the depolarisation may have been the main factors responsible for the ECG changes. As the relation between ST segment elevation and the incidence of serious arrhythmias has not yet been sufficiently clarified, electrocardiographic changes should be closely monitored whenever class Ic drugs are given.

(Heart 2001;85:e3) www.heartjnl.com/cgi/content/full/85/1/e3
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doi: 10.1136/heart.85.1.30

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