Original Research

Pre-Ejection Tissue-Doppler Velocity Changes During Low Dose Dobutamine Stress Predict Segmental Myocardial Viability

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Introduction: We tested the hypothesis that low dose dobutamine stress echocardiography (LDDSE) combined with tissue Doppler imaging (TDI) can be used for the quantitative assessment of the content of viable myocardium.

Methods: Forty-one patients with coronary artery disease and left ventricular dysfunction (ejection fraction ≤40%), already scheduled for revascularisation, underwent echocardiographic assessment of viability at rest and during low-dose dobutamine infusion (2.5 μg/kg/min up to 10 μg/kg/min) at two time points, 2 days before and 3 months after revascularisation. Pulsed-wave TDI was performed at rest and during LDDSE; ejection (Ej), pre-ejection (pre-Ej) and diastolic velocities (Ea, Aa) were recorded at rest and at 10 μg/kg/min dobutamine infusion. Recovery of regional function was defined as improvement of one or more grades 3 months post-revascularisation.

Results: A total of 112 vessels were revascularised. Out of 492 segments, 274 segments were characterised as viable and the remaining 218 as non-viable, according to postoperative functional myocardial recovery. Conventional qualitative LDDSE showed a sensitivity of 78% and specificity of 85% in predicting myocardial recovery. Ej, pre-Ej and Ea velocities increased significantly during LDDSE, while Aa velocity did not change significantly. Using ROC curves, the optimal cut-off value for viability assessment was an increase of 0.5 cm/s in Ej during LDDSE (80% sensitivity and 88% specificity, area under the curve 0.801), 0.6 cm/s in pre-Ej (91% sensitivity and 90% specificity, area under the curve 0.890), and 0.44 cm/s in Ea velocity (80% sensitivity and 81% specificity, area under the curve 0.780).

Conclusions: Despite its technical limitations, the measurement of ejection and pre-ejection velocities during dobutamine stimulation appears to be an effective way of predicting myocardial segmental recovery following reperfusion.

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O ver the past few years, it has become evident that, although revascularisation decisions based purely on traditional coronary anatomical indications are justified by existing data, myocardial viability testing may be helpful in efficient patient management, targeting treatment to those who are potentially most likely to benefit from reperfusion.[1,2] Low dose dobutamine stress echocardiography (LDDSE) is a widely used and reliable method for the detection of viable myocardium in patients with coronary artery disease.[3-5] The quantitative assessment of myocardial wall velocities has been made possible by modern echocardiographic techniques,[6-15] such as tissue Doppler imaging (TDI). The changes in these velocities during stress echocardiography represent alterations in myocardial contractility.[6-13]

The usefulness of quantitative measurements of longitudinal systolic velocity by TDI during dobutamine stress, for the evaluation of myocardial viability, has been demonstrated recently. Although regional wall motion abnormalities during ejection have already been studied in ischaemic heart disease, little attention has been paid to the potential changes in myocardial velocities during the pre-ejection period (i.e. the time from the onset of ventricular activation to the end of the isovolumic contraction phase).[5,10] It seems that this short-lasting event can be accurately quantified by TDI.

We hypothesised that changes of pre-ejection inward motion tissue velocity could be proportional to the content of viable myocardium in the corresponding region. The study was designed to investigate whether the quantitative information obtained using TDI during LDDSE would allow the detection of viable segments, providing helpful information for the identification of hibernating myocardium in patients with chronic ischaemic left ventricular dysfunction.

Methods

Forty-three patients with coronary artery disease and left ventricular dysfunction at rest (ejection fraction ≤40%), already scheduled for revascularisation, were screened and prospectively enrolled in the present study, given that their acoustic windows allowed for adequate image acquisition. None of the patients had evidence of acute coronary syndrome, valvular heart disease, primary cardiomyopathy or a history of coronary artery bypass graft surgery. All patients were in sinus rhythm and 34 of them (83%) had a history of previous myocardial infarction. Two patients were withdrawn from the study because of perioperative myocardial infarction. Thus, data from 41 patients were finally analysed. Twenty-three of them had 3-vessel disease and 18 patients had 2-vessel disease. They all underwent complete revascularisation with 2 or 3 grafts each.

The study was approved by the ethics committee of our hospital, and written informed consent was obtained from all participants.

Study protocol

Baseline studies before revascularisation included cross-sectional echocardiography at rest and during dobutamine infusion. Echocardiography at rest was repeated 3 months after revascularisation to determine recovery of function.

Echocardiographic studies

All patients underwent low-dose dobutamine stress echo an average of 2 days before revascularisation. Echocardiographic images were obtained with a Philips ultrasound system (Sonos 5500, Andover, Massachusetts), equipped with the TDI program. Pulsed-wave Doppler tissue sampling was performed during rest and low-dose dobutamine infusion, and ejection, pre-ejection and diastolic velocities were recorded. Dobutamine infusion was initiated at a dose of 2.5 μg/kg/min and increased up to 5 and 10 μg/kg/min after 5 and 10 minutes, respectively. Continuous monitoring of ECG and blood pressure was performed throughout the infusion. Images were recorded both on videotape and in digital format for later analysis. Segments with any improvement of systolic function at low dobutamine doses were considered viable. To match myocardial segments with coronary distribution, the anterior wall, anterior septum, and apex were assigned to the left anterior descending coronary artery (LAD), the lateral wall to the circumflex artery (LCX), and the inferoposterior wall and inferior septum to the right coronary artery (RCA).

Doppler myocardial imaging

By adapting the Doppler settings, pulsed Doppler myocardial mapping traces were recorded at rest, at 5 and 10 μg/kg/min. Gains and filters were adjusted as needed to eliminate background noise and allow for a clear tissue signal. Experience has shown that spectral Doppler curves derived from the left ventricular apex are non-analysable and the sampling gate was moved consecutively to the clearest spectral trace. The peak velocity was determined as the average peak velocity from three consecutive beats, both in the pre-ejection phase and during left ventricular contraction in the ejection period. Cardiac cycles with extrasystolic, post-extrasystolic beats or any rhythm disturbance were excluded.

Pulsed TDI measurements included peak pre-ejection (Pre-Ej), peak ejection (Ej), peak early diastolic (Ea), and peak late diastolic (Aa) velocities. Measurements of these parameters were highly reproducible by the same observer for each patient.

Analysis of echocardiograms

Regional function was graded as 1=normal, 2=hypokinesia, 3=akinesia, and 4=dyskinesia. Segments that

were akinetic at baseline and became dyskinetic on testing were not considered viable. Recovery of regional function was defined as improvement by one or more grades. The response of the dysfunctional segments to dobutamine was classified as previously described: a) worsening, i.e. deterioration of wall motion during low dose infusion of dobutamine; b) improvement, i.e. improvement in function on low dose infusion of dobutamine; and c) no change, i.e. no improvement or worsening during the test. Viable response was defined by echocardiography as the development of a biphasic response, worsening or continuous improvement in dysfunctional segments compared with baseline.

Analysis was performed by 2 observers. Observer A (CA) measured the pre-ejection and ejection velocities at rest and during low-dose dobutamine. Observer B (GR), who was unaware of the TDI data and sequence of studies, interpreted the two-dimensional echocardiograms and the digital pages of each stage of LDDSE.

Left ventricular ejection fraction was calculated with the multiple-disk method both at baseline and during LDDSE (at 10 µg/kg/min) before revascularisation, as well as at rest 3 months after revascularisation.

Coronary angiography

All angiograms were analysed by one of the investigators who had no knowledge of the echocardiographic data. Significant coronary artery disease was defined as >70% stenosis of at least one epicardial artery.

Statistical analysis

Quantitative variables are expressed as mean values ± one standard deviation. Chi-square and non-paired t-tests were used when necessary. The diagnostic accuracy of the noninvasive tests is described in terms of sensitivity and specificity. The optimal ejection and pre-ejection changes for the prediction of myocardial viability were determined by a receiver operator characteristic (ROC) curve constructed for systolic, presystolic and diastolic velocities. Optimal cut-off values of ejection and pre-ejection velocities were obtained from the ROC curves. A p value <0.05 was considered significant to reject the null hypothesis.

Results
Preoperative data

Table 1 gives the baseline data of the study population. A total of 112 vessels were revascularised. Out

Table 1. Baseline data on 41 patients with chronic coronary artery disease and regional myocardial dysfunction who underwent revascularisation.

Age (years), mean ± SD	64 ± 5
Men, n (%)	29 (71%)
History of previous MI, n (%)	37 (90%)
NYHA II/III, mean ± SD	2.4 ± 0.4
LVEF (%), mean ± SD	25 ± 4
Diabetes, n (%)	14 (34%)
Hypertension, n (%)	19 (46%)
Dyslipidaemia, n (%)	21 (51%)
Smoking, n (%)	23 (57%)
Beta-blockers, n (%)	36 (89%)
Calcium-channel blockers, n (%)	9 (22%)
ACE inhibitors, n (%)	36 (89%)
Diuretics, n (%)	26 (63%)
Digitalis, n (%)	10 (24%)
Coronary arteries:	
LAD	41
LCX	34
RCA	39

ACE – angiotensin converting enzyme; LAD – left anterior descending; LCX – left circumflex; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NYHA – New York Heart Association; RCA – right coronary artery.

of a total number of 492 segments, 274 segments were characterised as viable and the remaining 218 as non-viable, according to postoperative functional myocardial recovery. All patients had an improved left ventricular ejection fraction 3 months after revascularisation, from 24 ± 4 to 35 ± 4% (p<0.001).

Neither the severity of stenosis nor the presence of collateral vessels differed between viable and non-viable segments. The mean value of coronary luminal stenosis was 92 ± 8%. Quantitative angiographic parameters were not different between segments with and without recovery of function (mean value of coronary luminal stenosis 91 ± 7% and 93 ± 10%, respectively).

Of the 492 segments, 64 (13%) demonstrated normal regional wall motion/thickening, 162 (33%) had mild to moderate hypokinesia and 266 (54%) had severe dysfunction. Of the latter segments, severe hypokinesia was observed in 152, akinesis in 70, and dyskinesis in 44 segments. Myocardial segments were classified into 2 groups according to low-dose dobutamine stress echo: viable (any response to dobutamine, n=214) and non-viable (no response, n=185).

LDDSE correctly identified 214 myocardial segments as viable (any response to dobutamine) and 185 as non-viable (no response). Sixty segments were erroneously classified as non-viable and 33 segments

as viable. Thus, LDDSE had a sensitivity of 78% (214/274) and a specificity of 85% (185/218) in predicting myocardial recovery. The positive predictive value of LDDSE was 87% (214/247) and the negative predictive value was 76% (185/245).

Pulsed-wave Doppler tissue sampling

Myocardial velocity patterns were assessed at rest and during low-dose dobutamine stress echo (10 μg/kg/min). Table 2 presents the values of pre-ejection and ejection velocities, E and A velocities, at rest and during LDDSE. The pre-ejection, ejection and E velocities increased significantly during LDDSE (10 μg/kg/min), while the A wave velocity did not change.

Using ROC curves, the optimal cut-off value for viability assessment was an increase of 0.5 cm/s in ejection velocity (S wave) during LDDSE (80% sensitivity

Table 2. Comparison of segmental myocardial velocities measured by tissue Doppler imaging at rest and at 10 μg/kg/min dobutamine infusion.

Velocities (cm/s)	Rest	Dobutamine	p
Ej	4.8 ± 1.2	5.9 ± 1.6	<0.001
Pre-Ej	4.9 ± 1.13	6.5 ± 1.95	<0.001
Ea	4.8 ± 0.9	5.6 ± 1.4	<0.001
Aa	6.3 ± 1.4	6.4 ± 1.3	0.163

Aa – late diastolic velocity; Ea – early diastolic velocity; Ej – systolic velocity at rest; Pre-Ej – pre-systolic velocity at rest.

and 88% specificity, area under the curve 0.801, Figure 1). An increment of pre-ejection velocity >0.6 cm/s offered the best accuracy in predicting the segments with functional recovery after revascularisation (91% sensitivity and 90% specificity, area under the curve 0.890, Figure 2). Finally, as far as diastolic TDI velocities were concerned, a cut-off point of 0.44 cm/s for the change in E velocity during LDDSE had high sensitivity (80%) and specificity (81%) in predicting recovery of myocardial function (area under the curve 0.780, Figure 3).
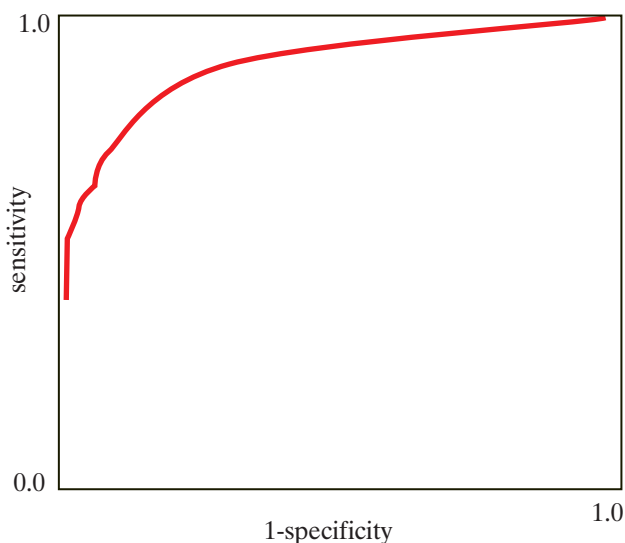
Discussion

Identification of the presence and estimation of the extent of viable myocardium in patients with chronic ischaemic myocardial dysfunction of the left ventricle is important for the management of this group of patients and offers significant prognostic information.[1,2] The present study demonstrates that pre-ejection tissue velocity changes during LDDSE are a reliable index of myocardial viability.

Identification of small changes in myocardial wall velocities during dobutamine challenge has been shown to be feasible with TDI. Hence, the main point of this study was that TDI, as a quantitative technique for the assessment of myocardial velocities, is at least as accurate in identifying viable myocardium in patients with severe left ventricular dysfunction as are traditional qualitative methods. Interestingly, according to our data, an increase in both pre-ejection and ejection velocities was observed during the test. These increases in
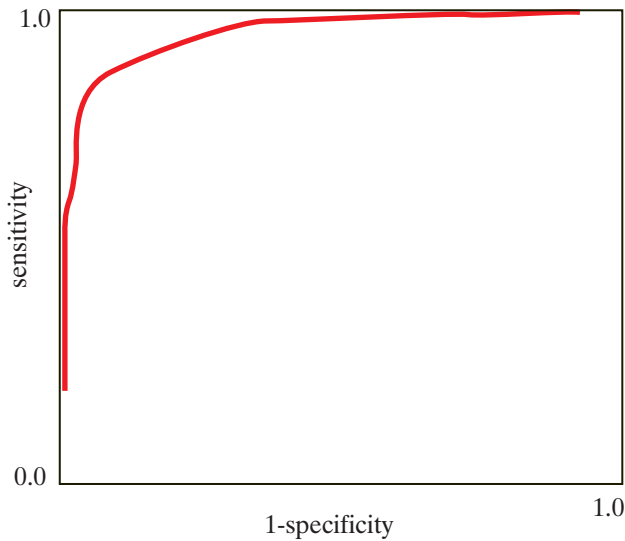

Figure 1. Receiver operator characteristic (ROC) curve constructed for the ability of systolic velocity changes (S wave in tissue Doppler imaging) during low dose dobutamine stress echocardiography to predict segmental myocardial viability.
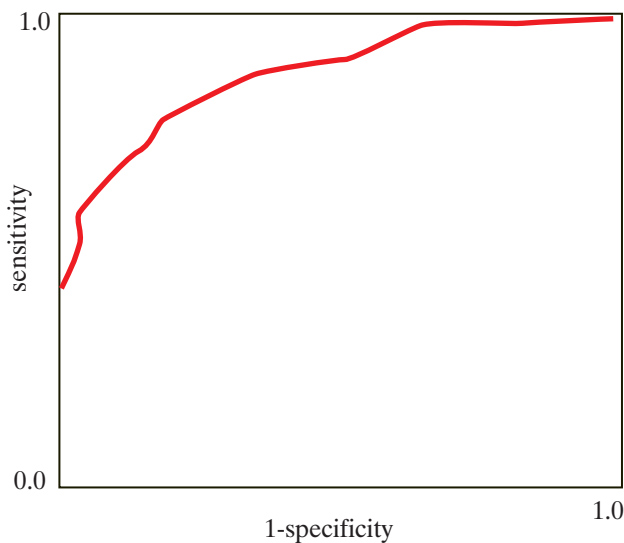
Figure 2. Receiver operator characteristic (ROC) curve constructed for the ability of pre-ejection velocity changes during low dose dobutamine stress echocardiography to predict segmental myocardial viability.

ejection and pre-ejection velocities during LDDSE seem to be a reliable index for the accurate identification of myocardial viability in patients with chronic ischaemic left ventricular dysfunction.

Previous investigators have shown that systolic velocity changes during dobutamine infusion are sensitive indexes of myocardial viability.[9,10] However, segments with predominately scar tissue may show an increase of ejection velocity during LDDSE due to the tethering effect of adjacent viable segments. A possible way to avoid this effect could be the evaluation of pre-ejection velocity changes. During that short period, the left ventricle does not change its shape and the tethering effect is thus minimised.

Moreover, the influence of cardiac rotation is lower during the pre-systolic period than during the ejection period. According to our results, the change of pre-ejection velocities tended to be more specific in identifying myocardial viability compared to systolic velocity changes. Using a cut-off point of 0.5 cm/s for ejection velocity changes during LDDSE gave a sensitivity and specificity of 80% and 88%, respectively. On the other hand, the sensitivity and specificity of pre-ejection velocity changes >0.6 cm/s during LDDSE were 91% and 90%, respectively.

Longitudinal velocity measurements are more reproducible than radial velocities, and are therefore usually preferred. On the other hand, longitudinal ve-

Figure 3. Receiver operator characteristic (ROC) curve constructed for the ability of early diastolic velocity changes (E wave in tissue Doppler imaging) during low dose dobutamine stress echocardiography to predict segmental myocardial viability.

locities show more variability between segments and this complicates their clinical use.

Experimental studies indicate that velocities during isovolumic contraction may serve as a means to determine the degree of myocardial dysfunction during ischaemia. In ventricles with preserved systolic function there is a dominantly positive longitudinal velocity during the pre-ejection period, with only a minor negative velocity component. With progressive ischaemia the positive velocity component diminishes, and the negative component increases. During severe ischaemia the positive component is lost and replaced by a large negative velocity. Penicka et al[7] tested the ability of pre-ejection velocities to predict recovery of myocardial function after coronary revascularisation in myocardial infarction. They showed that a positive pre-ejection velocity after revascularisation predicted recovery of function in the reperfused area. This suggests that measurement of pre-ejection velocities may provide important diagnostic information with regard to myocardial viability after coronary reperfusion.

The increase in wall thickness that occurs in normal myocardium after ventricular activation and before aortic valve opening corresponds to the brief and ample pre-ejection velocity. In our study, the pre-ejection velocities increased during low-dose dobutamine in segments with functional recovery after bypass surgery. This means that viable hibernating myocardium may contract at rest when both left ventricular pressure and wall stress are low (e.g. during pre-ejection), while it cannot sustain the load during ejection. This is consistent with findings that positive pre-ejection velocity wave is a sign of non-transmural necrosis[16] and that increased segmental systolic velocity during LDDSE is associated with viability of these segments.[11]

Penicka et al[7] reported that the resting pattern of myocardial positive pre-ejection velocity, obtained by TDI, accurately predicts the recovery of both the regional and global contractile function after revascularisation in patients with a large myocardial infarction. It seems that, even at rest, the assessment of the positive pre-ejection velocity could characterise a segment as viable in this group of patients. Similarly, we have shown that the assessment of pre-ejection velocities during LDDSE is the best way to assess myocardial viability in patients with left ventricular dysfunction. Furthermore, it is of note that in addition to the changes of ejection and pre-ejection velocities, the change of the early (E) but not the late (A) diastolic velocity during LDDSE was of particular value in de-termining the segmental myocardial recovery after revascularisation.

Regarding E velocity at the mitral annulus, Shan et al[17] demonstrated that it was dependent on receptors that influence the left ventricular lusinotropic state. In contrast, A velocity had no significant relation with the beta-adrenergic receptor density. These observations support the contribution of active ventricular myocardium to S and E and suggest that A perhaps reflects passive ventricular motion, or may be more dependent on atrial myocardium function. As far as we know, there are no data concerning the correlation between pre-systolic velocities and beta-adrenoreceptors.

So far, regional wall motion abnormalities during ejection have been studied, but those during pre-ejection (i.e. the time from the onset of ventricular activation to the end of the isovolumic contraction phase) have received no attention. According to our knowledge, there are a few stress echo studies using TDI that focused on peak systolic velocity changes during the ejection period. The changes in pre-ejection tissue velocities to identify hibernating myocardium and to predict functional recovery after revascularisation have not been previously reported.

It is a fact that the most cost-effective imaging techniques to detect reversible contractile function are, at the moment, stress echocardiography and nuclear perfusion imaging.[2,4] Echocardiography has the advantage of widespread availability, but subjective evaluation remains its main limitation. TDI provides quantitative data and therefore merits clinical evaluation for testing patients for the presence of viable myocardium.

Limitations

Patients in our study population did not undergo repeat coronary arteriography in order to identify restenotic lesions. All patients were asymptomatic during hospitalisation as well as 3 months later. To avoid another limitation of the study, concerning the regional myocardial recovery within 3 months, we scheduled a repeat rest study. We arbitrarily timed the outcome of dysfunctional segments 3 months after surgical revascularisation. However, potential functional improvement after this time point cannot be ruled out.

The measurement of myocardial velocities is affected by the translocation and rotation of the left ventricle throughout the cardiac cycle. These effects were minimised in this study by the intra-individual comparison of resting and stress velocities. The recording of myocardial velocities during dobutamine stress echo was a

time-consuming technique. The need to acquire all values on-line within a limited time margin at peak stress is a limitation of this modality.

Conclusions

Our observations indicate that, in the setting of severe chronic left ventricular dysfunction, longitudinal pulsed-wave Doppler tissue sampling provides quantitative information and is complementary to dobutamine-stress echocardiography for the assessment of myocardial viability. In our study, a change of 0.5 cm/s in ejection or 0.6 cm/s in pre-ejection velocity was a sound predictor of myocardial functional recovery after revascularisation. In conclusion, despite its technical limitations, measurement of ejection and pre-ejection velocities during dobutamine stimulation appears to be an effective way of predicting myocardial segmental recovery following reperfusion.

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