行政院國家科學委員會補助專題研究計畫成果報告

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※ 在 Dobutamine 催迫性檢查時的心臟整合逆散射超音波組織特性之分析 ※
※ **Ultrasonic Tissue Characterization with Integrated Backscatter during** ※
※ **Inotropi Stimulation** ※
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中文摘要

關鍵詞：心肌超音波組織特性變化、催迫性超音波心圖、心肌缺氧、心肌存活度。

利用心臟整合逆散射超音波組織特性 (Integrated Backscatter Tissue Characterization)，**可以定量分析心肌的生物物理狀態，進而加強雙面超音波心圖在解剖及功能學上的診斷能力。我們過去的研究已顯示此超音波組織特性在心肌梗塞或缺氧時有顯著之變化。近年來利用** Dobutamine **催迫性超音波心圖來診斷心肌缺氧或存活度已被廣泛在臨床上使用，而在此催迫狀態下的的超音波組織特性變化亦引起廣泛之注意。然而在催迫狀態下的局部心肌超音波組織特性變化則仍未明瞭。本研究發現以心臟週期的整合逆散射超音波組織持性變化來觀察原來平坦無變化之機械功能失全的心肌，在接受** Dobutamine **催迫後，其組織特性之變化能否重新表現週期性之線形變化，端視心肌之存活度及缺氧度。有病灶之心肌組織在** Dobutamine **催迫前。均顯示有平坦化的現象，但若以低劑量** Dobutamine **催迫之仍具存活組織之心肌則趨向正常若為壞死之結痂組織則無法回復。此方法較傳統催迫性超音波更為客觀，值得臨床應用之推廣。**

ABSTRACT

Ultrasonic tissue characterization with integrated backscatter is an objective method to quantitatively define the physical state of the myocardium. To investigate whether backscatter imaging during inotropic stimulation could be used objectively to determine the myocardial viability and ischemia in patients with ischemic heart disease, the backscatter changes were examined in 23 patients with myocardial infarction during dobutamine stress two-dimentional echocardiography. Coronary angiography was performed within 1 to 2 days after the stress test. The results of this study demonstrated that changes in backscatter variability correlated significantly with the wall motion changes in stress echocardiography during dobutamine infusion ($p<0.0001$). In addition, it was shown that the backscatter changes were significantly different in various types of myocardial tissue. In 23 normal control segments, the ultrasonic backscatter variability was preserved and unchanged during inotropic stimulation (p=NS). In 15 viable infarct zones, restoration or an increase in backscatter variability during low-dose dobutamine infusion was noted, this being lost when ischemia developing during high-dose dobutamine infusion ($p<0.01$). In 9 non-viable infarct zones, the phase-weighted variation was usually ≤ 0 and did not change significantly during inotropic stimulation, regardless of the patency of the infarct-related arteries. In 15 remote ischemic myocardial zones, the backscatter variability was preserved at the baseline level, did not changed during low-dose dobutamine infusion, but decreased significantly during high-dose dobutamine stress ($p<0.01$). In conclusion, dobutamine stress tissue characterization could offer an objective approach for the detection of myocardial viability and ischemia, and might be a useful adjunct to the conventional stress echocardiography.

Key words: Ultrasonic backscatter, tissue characterization, inotropic stimulation, and ischemic heart disease.

Introduction

The purpose of ultrasonic tissue characterization using integrated backscatter is to quantitatively define the physical state of the myocardium and to complement the anatomic and functional information obtained by two-dimensional echocardiography. Alterations in ultrasonic backscatter parameters are seen with myocardial infarction (MI) or ischemia (Fitzgerald et al. 1987; Milunski et al. 1989; Vered et al. 1989; Vitale et al. 1995). Cyclic variations in myocardial integrated backscatter (CVIBS) are blunted during experimental myocardial ischemia and recover after reperfusion (Glueck et al. 1985; Barzilai et al. 1990). Furthermore, the restoration of CVIBS early after revascularization is an indicator of viability that allows accurate discrimination between reversible (stunned) and irreversible (scarred) tissue injury (Sagar et al. 1987; Lin et al. 1998a; Lin et al. 1998b). Recently, there had been considerable interest in using inotropic stimulation in combination with echocardiography to identify the type of myocardial tissue (Previtali et al. 1993; Salustri et al. 1994; Smart et al. 1994; Smart et al. 1997). However, the changes occurring in regional acoustic properties during inotropic stimulation had not been well defined. Natio et al. observed that the CVIBS increased during dobutamine infusion in normal subjects (Natio et al.1996). In contrast, Feinberg et al. reported a dissociation between wall thickening and CVIBS during inotropic stimulation in the normal myocardium, with the mean value of the CVIBS remaining unchanged despite the progressive dobutamine-induced increase in wall thickening (Feinberg et al. 1996). Changes in backscatter variability during inotropic stimulation in myocardium with a wall motion abnormality were not described. Studies directed at assessing whether inotropic stimulation can restore CVIBS in mechanically dysfunctional segments with an initially blunted CVIBS may be important as an objective approach to detect viable (stunned or hibernating) myocardium. Accordingly, the aims of this study were to determine the changes in regional ultrasonic backscatter occurring during inotropic stimulation in the normal and diseased myocardium, and to evaluate whether backscatter imaging combined with inotropic stimulation could be useful in determining myocardial viability and detecting ischemia in patients with ischemic heart disease.

METHODS

Patients

Twenty-three patients, 21 men and 2 women, mean age 55 ± 12 years, were admitted to our hospital with the diagnosis of myocardial infarction (MI). Eighteen were in the acute stage of MI. Patients who had undergone previous coronary artery bypass surgery and patients with unsatisfactory precordial echocardiographic imaging were excluded. No patients had a history of cardiomyopathy or presented atrial fibrillation/frequent premature beats on examination. Of the patients with acute MI, 6 underwent thrombolytic therapy and 6 had primary angioplasty.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed using a commercially available real-time

two-dimensional (2-D) imaging system (SONOS 2500, Hewlett Packard, Andover, MA) and an image storage system (P90, Tomtec). Dobutamine was initially administered intravenously at consecutive dosages of 10 and 20 ug/kg/min, each for 3 min (low-dose testing) (Afridi et al. 1995). The dosage was then increased by 10 ug/kg/min every 3 min up to a maximal dose of 40 ug/kg/min. If there were no significant side effects due to dobutamine administration and if the heart rate response was inadequate, 0.5 mg of atropine was given twice at 1 min intervals to achieve a peak heart rate of > 120 bpm (Ling et al. 1996). The examination was terminated prematurely if severe angina, >2 mm ST-segment depression or elevation, marked wall motion deterioration, systemic hypertension (blood pressure > 220/120 mmHg) or hypotension (a decrease in systolic pressure > 20 mmHg), major ventricular arrhythmia, or obvious adverse effects appeared. Four standard views of the left ventricle (parasternal long- and short-axis, apical 4-and 2-chamber views) were recorded at baseline and during dobutamine infusion. Wall motion was graded as: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. Coronary lesions were predicted using conventionally defined wall segments (Schiller et al. 1989) and a schema correlating segmental wall motion abnormalities with coronary artery distribution (Sawada et al. 1991; Segar et al. 1992). The infarct-related artery (IRA) territories were recognized by correlating wall motion abnormalities with the evolutional changes in electrocardiography. An IRA territory was considered to be viable when there was an improvement in contractility of >= 1 grade in at least 2 contiguous segments or of >= 2 grades in 1 segment. Myocardial ischemia in the infarct zone (residual ischemia) was considered positive when deterioration of wall thickening and motion were seen at higher doses with, or without, an initial improvement at the lower dose. Myocardial ischemia in the non-infract zone (remote ischemia) was considered positive when a new wall motion abnormality occurred in an initially normal contractile segment. When there was no improvement in wall thickening or motion in an akinetic or dyskinetic segment during low-dose dobutamine infusion, the myocardium was considered to be non-viable. Any disagreement between the 2 reviewers (LCL and YBL) was resolved through discussion.

Backscatter data acquisition and analysis

The backscatter data was collected as previously described (Lin et al. 1998b; Liu et al. 1999), using a real-time (2.0/2.5 MHz), 2-D imaging system (Acoustic Densitometry, Hewlett Packard, Andover, Massachusetts, U.S.A.). Briefly, the imaging frame rate was automatically set to 30 Hz and the dynamic range of the integrated backscatter signal was approximately 44 decibels (dB). The parasternal short-axis view at the papillary muscle level was used to obtain the 2-D image of the integrated backscatter. Backscatter images were acquired at baseline and during inotropic stimulation with low-dose (10 and 20 ug/kg/min) and high-dose (30 and 40 g/kg/min) dobutamine infusion. Data acquisition was performed simultaneously with dobutamine stress echocardiography. The integrated backscatter was quantified by placing a region of interest in the myocardium on the frozen image. The location of the region of interest was adjusted frame-by-frame to keep it well within the subendocardial myocardium

(Wickline et al. 1986). As in our previous studies, three regions of interest were chosen (Lin et al. 1998b; Liu et al. 1999). One was in the mid-anteroseptal area and represented the myocardium perfused by the left anterior descending coronary artery, another was at the junction of the mid-posterior and mid-lateral area and represented the myocardium perfused by the left circumflex artery, and the other was in the mid-inferior area and represented the myocardium perfused by the right coronary artery. Using the electrocardiographic (ECG) R wave as a trigger reference, serial changes with time in the magnitude of the integrated backscatter (in decibels) were displayed throughout the cardiac cycle. The images and data sets were stored on an optical disc for off-line analysis. After first harmonic Fourier curve fitting, two parameters, the amplitude and the phase of the curve, were obtained. Figure 1 shows a typical integrated backscatter power curve and its first harmonic Fourier fitting overlay. We designated the variation, by doubling the amplitude, to represent the difference between maximal and minimal values of integrated backscatter after Fourier curve fitting. Using the ECG R wave as the trigger reference, the phase-weighted variation (PWV) was derived from the variation multiplied by a phase-weighting factor (Wickline et al. 1986; Lin et al. 1998b; Liu et al. 1999). The following criteria were used to determine the phase-weighting factor derived from the phase angle:

$$\text{Factor} = \begin{cases} -1 & \text{if } (0^0 \leqq \text{phase} < 45^0) \\ -\cos[2(\text{phase}-45^0)] & \text{if } (45^0 \leqq \text{phase} < 135^0) \\ 1 & \text{if } (135^0 \leqq \text{phase} < 225^0) \\ \cos[2(\text{phase}-45^0)] & \text{if } (225^0 \leqq \text{phase} < 315^0) \\ -1 & \text{if } (315^0 \leqq \text{phase} < 360^0) \end{cases}$$

Data reproducibility

All the data sets stored on the optical disc were reviewed by another examiner who independently performed the backscatter data acquisition and analysis. The reproducibility of the measurements was calculated from the standard error of the estimate. In our laboratory, the inter-observer variations for the amplitude and phase are 8% and 7%, respectively (Lin et al. 1998b; Liu et al.1999).

Coronary angiography

After giving their written informed consent, 23 patients underwent coronary angiography within 2 days after the dobutamine stress echocardiography. A computer-aided quantitative angiographic analysis system (DCI-S Automated Coronary Analysis System, Philips Medical Systems, Eindhoven, The Netherlands) was used. The patency and severity of stenosis of coronary arteries were assessed by 2 observers who had no knowledge of the stress echocardiography results.

Statistical analysis

Continuous variables were expressed as the mean $\pm$ SD. We categorized the segments into 3

groups according to the changes in wall motion scores during dobutamine stress echocardiography (increase, decrease, or no change). Differences in the changes in CVIBS of the segments between these 3 groups were also analyzed by ANOVA. The baseline CVIBS values were compared with those obtained during low-dose (10 and 20 ug/kg/min) and high-dose (30 and 40 ug/kg/min) dobutamine infusion in the same segment. Analysis of variance for repeated measurements (ANOVARM) using the Bonferroni adjustment was used to determinate whether there were any significant changes in backscatter variability during dobutamine infusion. The ANOVA test and the least significant difference multiple comparison procedure were used to analyze the differences in CVIBS in various types of myocardial tissue. A p value of <0.05 was considered as statistically significant.

RESULTS

Correlation between backscatter changes and dobutamine stress echocardiography

In these 23 patients, 65 segments were well visualized in backscatter imaging during dobutamine infusion and were used for analysis. The myocardial segments were categorized into 3 groups according to the change in wall motion scores seen during dobutamine infusion: decrease (-1), no change (0), and increase (1). It could be shown that the changes of various backscatter parameters among the 3 different categories of myocardium during dobutamine infusion. The PWV was significantly different in these 3 groups ($p<0.0001$). In addition, the PWV increased significantly when the wall motion improved (i.e. a reduction in wall motion score) and decreased significantly when ischemia developed (i.e. an increase in wall motion score) during dobutamine infusion. The phase showed a slight, but insignificant, increase while ischemia developed. No significant change in variation was noted in these 3 groups.

Altered backscatter during different doses of dobutamine infusion in various types of myocardial tissue

In order to evaluate the backscatter changes in various types of myocardial tissue, we classified the myocardial segments into 4 groups. Group I (control segments) consisted of the territories supplied by patent coronary arteries in which no ischemia was induced during dobutamine stress echocardiography. Group II (viable infarct zones) consisted of those IRA territories showing a dobutamine-responsive contractile improvement. Group III (non-viable infarct zones) consisted of those IRA territories which did not show a dobutamine-responsive contractile improvement. Group IV (remote ischemic segments) consisted of those vessel territories supplied by remote-diseased coronary arteries with lesions of more than 50% stenosis. We further divided groups II and III into subgroups A and B on the basis of IRA patency. In control segments, inotropic stimulation did not significantly alter the PWV, despite the progressive increase in wall thickening during dobutamine infusion in these segments. In viable infarct zones, the PWV increased significantly during low-dose dobutamine infusion ($p<0.01$), then either remained at this level (subgroup without IRA stenosis) or decreased significantly (subgroup with IRA stenosis) ($p<0.01$) during high-dose

dobutamine infusion. In non-viable infarct zones, there was no significant change in PWV during dobutamine infusion and no difference between the subgroups with and without IRA stenosis. In remote ischemic segments, the PWV decreased significantly during high-dose dobutamine infusion ($p<0.01$). Table 1 summarized the PWV values under baseline conditions and during inotropic stimulation for all 4 groups. In the baseline condition, the PWV in infarct zones (groups II and III) was significantly lower than those in the control and remote ischemic segments (groups I and IV) ($p<0.001$). During low-dose dobutamine infusion, the PWV in viable infarct zones (group II) increased and approached those in groups I and IV. The PWV in non-viable infarct zones (group III) was still significantly lower than that in the other 3 groups ($p<0.001$). During high-dose dobutamine stress, the PWV in control segments was significant higher than that in the other 3 groups ($p<0.01$). The PWV in remote ischemic segments was also higher than that in non-viable infarct zones ($p<0.05$). Moreover, different PWV changes during dobutamine infusion were found in group IIA and IIB. In group IIA, the PWV increased during low-dose dobutamine infusion, then decreased with subsequent high-dose stress, whereas, in group IIB, the PWV was higher in the baseline condition, increased during low-dose infusion, but did not decrease during high-dose stress.

Comparison of dobutamine stress echocardiography and dobutamine stress backscatter imaging for the detection of myocardial ischemia

We used a perfusing artery with more than 50% stenosis on the coronary angiogram as the gold standard for myocardial ischemia. In this study, there were 12 segments of viable infarct zones with residual ischemia and 15 segments of non-infarct zones with remote ischemia. Myocardial ischemia was defined as an increase in wall motion score using dobutamine stress echocardiography or a decrease in PWV of more than 50% using dobutamine stress backscatter imaging. Table 2 shows that the backscatter imaging detected more ischemic segments than did conventional stress echocardiography. This difference was more significant for the detection of remote ischemia in the patients with MI and multivessel coronary artery disease (10 detected by stress backscatter image vs. 5 by stress 2-D echocardiography).

DISCUSSION

In this study, we performed combined dobutamine stress echocardiography simultaneously with backscatter imaging in order to define myocardial viability and ischemia in the patients with myocardial infarction. Firstly, we demonstrated that the changes in backscatter variability correlated significantly with the changes in wall motion during dobutamine infusion. Secondly, the changes in backscatter were significantly different in various types of myocardial tissue. In normal myocardium, ultrasonic backscatter variability was preserved and unchanged during inotropic stimulation. In viable infarct zones, restoration or an increase in backscatter variability was seen during low-dose dobutamine infusion, while loss of variability reappeared when ischemia was induced during high-dose infusion. In non-viable infarct zones, the PWV was usually ≤ 0 and did not change significantly during

inotropic stimulation, regardless of the patency of IRA. In remote ischemic myocardium, backscatter variability was preserved at baseline and decreased significantly during high-dose dobutamine stress. Thirdly, dobutamine stress tissue characterization could offer an objective and adjunctive measure for the detection of myocardial ischemia during the stress echocardiographic test, and especially good in the case of remote ischemia.

Previous studies on changes in ultrasonic backscatter parameters during inotropic stimulation have given conflicting results. Sagar et al. found that, in normal experimental animals, dobutamine produced a significant increase in the Fourier coefficient of amplitude modulation, an index of cardiac CVIBS (Sagar et al. 1988). Natio et al. reported that the magnitude of the CVIBS increased in normal human subjects during dobutamine infusion (Natio et al. 1996). However, using experimental animals, Wickline et al. observed that the magnitude of the CVIBS did not change under different heart rate by using paired ventricular pacing or under condition of an altered contractile state by using full-dose β-adrenergic blockade in experimental animals (Wickline et al. 1985a). Feinberg et al. reported that, in patients with normal resting and dobutamine stress echocardiographic results, the mean value of the CVIBS remained unchanged, despite a progressive increase in wall thickening during dobutamine infusion (Feinberg et al. 1996). Our findings are consistent with those in the studies of Wickline and Feinberg in so far as the ultrasonic backscatter variability of normal myocardium did not change significantly during inotropic stimulation. The apparent differences between the results of the present study and those obtained in other investigations might be explained on the basis of the different methods used for determination of myocardial acoustic properties.

One of the aims of this study was to clarify whether the combination of dobutamine stress testing and backscatter image provided more information than just using the resting ultrasonic backscatter image in the patients with ischemic heart disease. Previous studies have shown that the magnitude of the resting CVIBS reflects the severity of ischemia (Fitzgerald et al. 1987; Milunski et al. 1989; Wickline et al. 1986). The CVIBS of scar tissue has been described as a normal magnitude of backscatter cyclic variation with a reversal phase, i.e. a 180^{o} delay (Wickline et al. 1985b). In the present study, we demonstrated that the PWV in the resting condition was significantly lower in infarct zones than in normal or remote ischemic segments. Moreover, low-dose dobutamine stimulation was able to restore the CVIBS in mechanical dysfunctional segments with an initially blunted CVIBS in viable infarct zones, but not in non-viable infarct zones. Thus, an increase in PWV during low-dose dobutamine stress could be a sign of viable myocardium. In this study, we also demonstrated that the increase in PWV correlated well with the improvement of wall motion in dobutamine stress echocardiography. When using a PWV > 0 as a criterion for viable myocardium, viable segments could be detected in only 8 of the 15 viable infarct zones in resting backscatter imaging (data not shown). However, combining the low-dose dobutamine with resting backscatter imaging increased the sensitivity for detecting viable myocardium by 47%.

From the point of view for revascularization, being able to differentiate between the viable

myocardium with and without residual ischemia is important for the detection of potentially salvageable myocardium after infarction. In viable segments with residual ischemia, the PWV changes showed a biphasic response (an increase, followed by a decrease) during dobutamine infusion, similar to the changes in wall motion during traditional dobutamine stress echocardiography. Our previous study has demonstrated that the viable myocardium without residual ischemia gave a similar result as the healthy control group at rest on ultrasonic tissue characterization (Lin et al. 1998a). In that study, the PWV of the viable segments in infarct zones without residual ischemia (group IIB) was significantly higher than that of the segments with residual ischemia (group IIA) or that of the non-viable infarct zones (group III). However, the resting PWV in ischemic viable infarct zones (group IIA) could not be clearly differentiated from that in non-viable infarcted myocardium (group III). The myocardium represented by group IIA is what will benefit most from revascularization and needs most to be detected. In this study, we have shown that the increase of PWV during low-dose dobutamine infusion could clearly differentiate the ischemic viable myocardium from the non-viable infarct zones (Table 1). Thus, taking into account the resting and low-dose dobutamine backscatter images together, the ischemic viable myocardium could be differentiated well from not only the normal and non-ischemic viable myocardium, but also the scarred tissue, even without the help of high-dose dobutamine stress.

Stress echocardiography has recently become a cost-effective alternative for the diagnosis of coronary artery disease. However, the Achilles' heel of the stress echocardiography is that the conventional clinical assessment of endocardial wall motion and myocardial thickening is based on visual interpretation, which is subjective, qualitative and experience dependent (Preda I. 1999). It has been demonstrated that the diagnostic accuracy of stress echocardiography is highly dependent on the experience of the interpreting physician. The sensitivity, specificity and accuracy of the interpretations made by inexperienced reviewers were lower than those by experienced readers (Picano et al. 1991). Furthermore, it has recently been shown that, even among experienced observers working in an institution with an undisputed reputation in stress echocardiography, interinstitutional variability can be substantial (Hoffmann et al. 1996). Thus, the need for an objective technique to evaluate regional left ventricular function has become more obvious with the growing popularity of stress testing in echocardiography. Regarding the detection of ischemic myocardium, Gibson et al. stated that the sensitivity for detecting remote ischemia using dobutamine stress echocardiography in patients with acute MI is 58% (Gibson et al. 1982), which is much lower than that of 90% for the detection of myocardial ischemia in patients with stable angina (Ho et al. 1997). This low sensitivity may result from the lower dosage of dobutamine infusion used in patients with acute coronary syndrome or from the premature termination of the test because of the demonstration of low-threshold asynergies. Some investigators discovered that alterations in backscatter parameters during ischemia might precede the regional dyssynergy (Vitale et al. 1995; Lin et al. 1998b). In this study, the backscatter imaging seemed to detect more ischemic segments than did conventional stress echocardiography (Table 2). This

difference was more significant for remote ischemia in the patients with MI and multivessel coronary artery disease (10 vs. 5). These findings suggested that backscatter images might provide an objective and independent contribution to the detection of ischemic myocardium. We did not calculate the sensitivity, specificity and accuracy of this new technique because a larger patient population would be required. However, our results proved the feasibility of applying this new technique to the patients referred for pharmacological stress echocardiography and as an objective and adjunctive measure for the detection of dobutamine-induced regional wall motion abnormalities.

The mechanisms underlying the alterations in CVIBS during inotropic stimulation could still not be clarified from the results of this study. In general, the PWV changes were directly correlated with the wall thickening, i.e. contractile performance, during dobutamine infusion. However, increases in wall thickening were seen both in the normal and viable myocardium during low-dose dobutamine infusion, whereas PWV increases could be demonstrated only in the viable myocardium. One possibility could be that the presence of recruitable contractile elements in the viable myocardium during low-dose dobutamine stress resulted in the PWV increases, whereas there might be no recruitable elements in normal myocardium. Thus, ultrasonic tissue characterization provides a measure of intramural contractile function that is relatively independent of wall motion or thickening and parallels the contractile reserve (Pasquet et al.1998).

This study has several limitations. Firstly, ultrasonic backscatter imaging could not provide a comprehensive view of the whole ventricle because of anisotropy. However, in spite of substantial anisotropy in parasternal short axis view, the differences in the changes of backscatter during inotropic stimulation among various types of myocardial tissue were still evident in our study after using optimal lateral gain compensation (Recchia et al. 1993). Secondly, we only obtained the parasternal short-axis view in backscatter imaging, which could lower the detection rate for myocardial ischemia resulting from a distal coronary lesion. Thirdly, when the heart rate exceeded 140/min during high-dose dobutamine infusion, the fixed sampling rate of the integrated backscatter would limit the sampling number for each cardiac cycle, which might result in some measurement errors in the CVIBS.

In conclusion, this study has shown that backscatter changes during inotropic stimulation were different in the normal and diseased myocardium. Subtle changes in myocardial acoustic properties could be demonstrated by the use of not only resting but also dobutamine stress backscatter parameters. Dobutamine backscatter imaging could offer an objective and useful adjunct for the delineation of myocardial viability and ischemia in the patients with ischemic heart disease.

REFERENCES

Afridi I, Kleiman NS, Raizner AE, Zoghbi WA. Dobutamine echocardiography in myocardial hibernation: optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty. *Circulation* 1995; 91:663-670.

Barzilai B, Vered Z, Mohr GA, Wear KA, Courtois M, Sobel BE, Miller JG, Perez JE. Myocardial ultrasonic backscatter for characterization of ischemia and reperfusion: relationship to wall motion. *Ultrasound in Med & Biol.* 1990;16:391-398.

Feinberg MS, Gussak HM, Davila-Roman VG, Baumann CM, Miller JG, Perez JE. Dissociation between wall thickening of normal myocardium and cyclic variation of backscatter during inotropic stimulation. *Am J Cardiol* 1996;77:515-520.

Fitzgerald PJ, McDaniel MD, Rolett FL, Strohbehn JW, James DH. Two-dimensional ultrasonic tissue characterization: backscatter power, endocardial wall motion, and their phase relationship for normal, ischemic and infarcted myocardium. *Circulation.* 1987; 76:850-869.

Gibson RS, Bishop HL, Stamm RB, Crampton RS, Beller GA, Martin RP. Value of early two dimensional echocardiography in patients with acute myocaridal infarction. *Am J Cardiol* 1982; 49:1110-1119.

Glueck RM, Mottley JG, Miller JG, Sobel BE, Perez JE. Effects of coronary artery occlusion and reperfusion on cardiac cycle-dependent variation of myocardial ultrasonic backscatter. *Circ Res*. 1985;56:683-689.

Ho YL, Wu CC, Chao CL, Lin LC, Tseng WK, Chen WJ, Huang PJ, Lee YT. Localizing Individual Coronary Artery Obstructions with the Dobutamine Stress Echocardiography. *Cardiology* 1997;88:197-202.

Hoffmann R, Lethen H, Marwick T, Arnese M, Fioretti P, Pingitore A, Picano E, Buck T, Erbel R, Flachskampf FA, Hanrath P. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. *J Am Coll Cardiol* 1996;27:330-336.

Lin LC, Wu CC, Ho YL, Lin CW, Chen WJ, Chen MF, Liau CS, Lee YT. Ultrasonic tissue characterization for coronary care unit patients with acute myocardial infarction. *Ultrasound Med Biol* 1998a;24:187-196.

Lin LC, Wu CC, Ho YL, Chen MF, Liau CS, Lee YT. Ultrasonic tissue characterization in pedicting residual ischemia and myocardial viability for patients with acute myocardial infaction. *Ultrasound in Med. & Biol* 1998b;24:1107-1120.

Ling LH, Pellikka PA, Mahoney DW, Oh JK, McCully RB, Roger VL, Seward JB. Atropine augmentation in dobutamine stress echocardiography: role and incremental value in a clinical practice setting. *J Am Coll Cardiol* 1996;28:551-557.

Liu YB, Wu CC, Lin LC, Ho YL, Kao HL, Lee YT. Alterations in ultrasonic backscatter during intra-aortic balloon counterpulsation support in patients with acute myocardial infarction. *Ultrasound Med Biol* 1999; 25:1185-1193.

Milunski MR, Mohr GA, Perez JE, Vered Z, Wear KA, Gessler CJ, Sobel BE, Miller JG, Wickline SA. Ultrasonic tissue characterization with integrated backscatter. Acute myocardial ischemia, reperfusion, and stunned myocardium in patients. *Circulation.* 1989;80:491-503.

Natio J, Masuyama T, Mano T, Kondo H, Doi Y, Yamamoto K, Nagano R, Hori M, Inoue M, Kamada T. Dobutamine stress ultrasonic myocardial tissue characterization in patients with dilated cardiomyopathy. *J Am Soc Echocardiogr* 1996;9:470-479.

Pasquet A, D'Hondt AM, Melin JA, Vanoverschelde JLJ. Relation of ultrasonic tissue characterization with integrated backscatter to contractile reserve in chronic left ventricular ischemic dysfunction. *Am J Cardiol* 1998;81:68-74.

Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. *J Am Coll Cardiol* 1991;17:666-669.

Preda I. Stress echo: more method than madness. *Eur Heart J* 1999;20:1216-1217.

Previtali M, Poli A, Lanzarini L, Fetiveau R, Mussini A, Ferrario M. Dobutamine stress echocardiography for assessment of myocardial viability and ischemia in acute myocardial infarction treated with thrombolysis. *Am J Cardiol* 1993;72:124G-130G.

Recchia D, Miller JG, Wickline SA. Quantification of ultrasonic anisotrophy in normal myocardium with lateral gain compensation of two-dimensional integrated backscatter images. *Ultrasound in Med. & Biol* 1993;19:497-505.

Sagar KB, Rhyne TL, Warltier DC, Pelc L. Wann LS. Intramyocardial variability in integrated backscatter: effect of coronary occlusion and reperfusion. *Circulation.* 1987;75:436-442.

Sagar KB, Pelc LE, Rhyne TL, Wann LS, Waltier DC. Influence of heart rate, preload, afterload, and inotropic state on myocardial ultrasonic backscatter. *Circulation* 1988, 77(2): 478-483.

Salustri A, Elhendy A, Garyfallydis P, Ciavatti M, Cornel JH, ten Cate FJ, Boersma E, Gemelli A, Roelandt JR, Fioretti PM. Prediction of improvement of ventricular function after first acute myocardial infarction using low-dose dobutamine stress echocardiography. *Am J Cardiol* 1994;74:853-856.

Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Willianms R, Fineberg NS, Armstrong WF, Feigenbaum H. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991;83:1605-1614.

Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. *J Am Coll Cardiol* 1992;19:1197-1202.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendation for the quantification of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;5:358-367.

Smart SC, Sawada S, Ryan T, Segar D, Atherton L, Berkovitz K, Bourdillon PD, Feigenbaum H. Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infaction. *Circulation* 1993;88:405-415.

Smart SC, Knickelbine T, Stoiber TR, Carlos M, Wynsen JC, Sagar KB. Safety and accuracy of dobutamine-atropine stress echocardiography for the detection of residual stenosis of the infarct-related artery and multivessel disease during the first week after acute myocardial infarction. *Circulation* 1997;95:1394-1401.

Vered Z, Mohr GA, Barzilai B, Gessler CJ, Wickline SA, Wear KA, Shoup TA, Weiss AN, Sobel BE, Miller JG, Perez JE. Ultrasound integrated backscatter tissue characterization of remote myocardial infarction in human subjects. *J Am Coll Cardiol.* 1989;13:84-91.

Vitale DF, Bonow RO, Gerundo G, Pelaggi N, Lauria G, Leosco D, Coltorti F, Bordini C, Rengo C, Rengo F. Alterations in ultrasonic backscatter during exercise-induced myocardial ischemia in Humans. *Circulation*. 1995;92:1452-1457.

Wickline SA, Thomas LJ, Miller JG, Sobel BE, Perez JE. The dependence of myocardial ultrasonic integrated backscatter on contractile performance. *Circulation* 1985a; 72(1):183-192.

Wickline SA, Thomas III LJ, Miller JG, Sobel BE, Perez JE. A relationship between ultrasonic integrated backscatter and myocardial contractile function. *J Clin Invest* 1985b;76:2151-2160.

Wickline SA, Thomas III LJ, Miller JG, Sobel BE, Perez JE. Sensitive detection of the effects of reperfusion on myocardium by ultrasonic tissue characterization with integrated backscatter. *Circulation* 1986;74:389-400.

FIGURE LEGENDS

Fig. 1. Integrated backscatter power curve versus time for one cardiac cycle. Frame #0 is the beginning of electrocardiographic R wave. The solid curve represents the result of the first Fourier harmonic fitting. The phase and doubling amplitude of the first Fourier harmonic fitting are indicated.

Fig. 2. The changes of various backscatter parameters in the 3 categories of myocardium with different changes in wall motion score [decreased (-1), no change (0), and increased (1)] during dobutamine infusion. Significant differences in the phase-weighted variation were demonstrated among these 3 groups.

Fig. 3. The changes of phase-weighted variation in the control (left upper), viable infarct (right upper), non-viable infarct (left lower), and remote ischemic segments (right lower) before and during dobutamine infusion [baseline (B), low-dose (L), and high-dose (H)]. The mean values are represented by solid circles or squares, and the standard deviations are shown by error bars. The changing patterns were significantly different among the myocardium with viable infarction and remote ischemia during dobutamine infusion. IRA: infarct-related artery.

TABLES

Table 1. Changes in phase-weighted variations during dobutamine infusion

Group	Baseline	Low-dose dobutamine	High-dose dobutamine
Group I (n=23)	6.6 ± 2.1	6.3 ± 1.9	5.8 ± 2.7 §
Group II (n=15)	1.5 ± 4.5†	5.8 ± 2.1	0.8 ± 4.8
IIA with stenotic IRA (n=12)	0.8 ± 4.5	5.4 ± 1.9	-0.8 ± 3.8
IIB without stenotic IRA (n=3)	4.1 ± 3.6	7.4 ± 2.1	7.2 ± 2.1
Group III (n=9)	-2.0 ± 2.7†	-3.2 ± 2.1‡	-3.9 ± 1.9
IIIA with stenotic IRA (n=6)	-1.8 ± 3.0	-3.2 ± 2.5	-3.7 ± 2.2
IIIB without stenotic IRA (n=3)	-2.2 ± 2.5	-3.1 ± 1.1	-4.4 ± 1.2
Group IV (n=15)	5.0 ± 3.2	5.1 ± 3.9	1.4 ± 5.5

Group I: control segments; group II: viable infarct zones; group III: non-viable infarct zones; group IV remote ischemic segments; DSE: dobutamine stress echocardiography; n= number of vessel territories; IRA: infarct-related artery; † $p<0.001$ compared with groups I and IV; ‡ $p<0.001$ compared with groups I, II, and IV; § $p< 0.01$ compared with groups II, III, and IV; $p<0.05$ compared with group IV.

Table 2. Detection of ischemic vessel territories by dobutamine stress echocardiography and dobutamine stress integrated backscatter imaging

	Coronary angiogram	DSE	DS-IBS
Residual ischemia	12	10 *	11 *
Remote ischemia	15	5 *	10 *

DSE: dobutamine stress echocardiography; DS-IBS: dobutamine stress integrated backscatter imaging; *number of ischemic vessel territories demonstrated by DSE or DS-IBS; ischemia was defined as an increase in wall motion score using DSE or a decrease in phase-weighted variation (>50%) using DS-IBS.