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以心臟超音波組織特性預測急性心肌梗塞後冠狀動脈阻塞或再灌流  
之研究

The Study of Ultrasonic Tissue Characterization for Evaluating Coronary  
Stenosis or Reperfusion after Acute Myocardial Infarction.

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## 中文摘要:

關鍵詞：超音波組織特性分析、催迫式心臟超音波、心肌梗塞、冠狀動脈心臟病、再灌流治療。

評估急性心肌梗塞病患之預後時，多條血管之冠狀動脈病變是一重要因素。直至今日，冠狀動脈攝影仍被視為標準檢查方式。然而，許多非侵襲性檢查，包括運動心電圖、鉍 201 心肌灌流掃描及催迫式心臟超音波已逐步發展並應用於多血管冠狀動脈心臟病之預測。但以實用觀點而言，仍有許多臨床上的限制。首先，對於心肌梗塞病患，這些催迫式檢查在急性期仍有相當程度的危險性。其次，對於仍需留觀於加護病房之患者，運動心電圖及鉍 201 心肌灌流掃描無法適用。第三，催迫式心臟超音波檢查常於某血管灌流範圍之心肌收縮異常時即停止下一階段之檢查，因此，往往只能偵測到具有最嚴重缺氧程度之單一冠狀動脈，無法同時對三條冠狀動脈進行評估。超音波組織特性分析乃利用心肌組織對於超音波音束之散射作用，將所有逆散射之訊號予以總和，視為反射之能量顯示。於正常心肌組織，此反射能量之大小會隨心臟收縮與舒張，而有週期性之變化，於收縮時達到最小，而於舒張時達到最大。但於心肌缺氧或梗塞時。此週期變化之大小會減少，谷底值出現之時期亦會延後。然而，若即時予以再灌流治療，此變化將比對心肌收縮程度之影響更早恢復。

本計畫乃利用超音波組織特性分析(UTC)及催迫性超音波心圖檢查(DSE)，預測急性心肌梗塞(AMI)病患是否併有多條血管之冠狀動脈病變，並且針對再灌流治療於梗塞血管之成效予以評估。共有三十位病人於 AMI 後之  $8.3 \pm 3$  天內接受 UTC 及 DSE 檢查。在 UTC 檢查中，phase-weighted variation 可分別出一塊心肌組織是否還存有冠狀動脈灌流不足或已結疤 ( $p < 0.001$ )。在存活而不具缺氧狀況的心肌組織其數值則與正常心肌組織類似 ( $p = 0.453$ )。利用 5.8 作分界，用 UTC 之 phase-weighted variation 對存活但仍殘存心肌缺氧組織之判定，其診斷性之靈敏度、特異性及精確度分別是 75%，100% 及 90.2%。而當此心肌接受再灌流治療後其 phase-weighted variation 數值極小，且與冠狀動脈血流是否暢通無關。

因此，吾人發現 UTC 對偵測不具狹窄冠狀動脈的梗塞心肌非常有效，它可用以篩檢急性心肌梗塞後患者是否須接受導管或冠狀動脈穿通術之依據。

## **Abstract:**

**Background** The identification of viable myocardium and residual ischemia in patients with acute myocardial infarction (AMI) has important prognostic implications. The ultrasonic tissue characterization (UTC) with integrated backscatter has been shown to be a sensitive marker of myocardial ischemia and infarction. After reperfusion of occluded coronary artery, the cardiac cyclic-dependent variation of integrated backscatter restores its amplitude modulation before the recovery of myocardial contractility. It implies that the promising method can be used to identify stunning myocardium.

**Methods and Results** UTC and dobutamine-atropine stress echocardiography (DSE) were performed  $8.3 \pm 3$  days after AMI in 30 patients. The DSE was considered as a reference to identify viable myocardium and residual ischemia. After coronary intervention, both modalities were performed to evaluate the influences of residual stenosis. The parameter obtained from UTC, phase-weighted variation, could differentiate the myocardium with residual coronary stenosis or nonviable from the viable myocardium without residual coronary stenosis ( $p < 0.001$ ). The latter has the similar value to that of normal control group ( $p = 0.453$ ). Using the cutoff value of 5.8, the sensitivity, specificity, and accuracy for detecting viable myocardium without residual infarct-related artery stenosis were 75%, 100%, and 90.2%, respectively. The phase-weighted variation of viable infarction zone restored after the coronary stenosis was relieved. Contrarily, the nonviable myocardium had small phase-weighted variation irrelevant to the patency of infarct-related artery.

**Conclusions** The UTC was a very useful method to identify the viable myocardium of which infarct-related artery was free from residual stenosis. It can be used as a predischarge screening tool for risk stratification and is helpful in constructing the intervention strategy.

**Key Words** • myocardial infarction • echocardiography • ischemia • stunning, myocardial

## Background

In patients with acute myocardial infarction (AMI), early thrombolytic therapy can salvage a significant amount of myocardium as well as improve left ventricular function and prognosis.<sup>1-5</sup> However, residual stenosis of the infarct-related artery is common after AMI<sup>6-8</sup> that may further jeopardize viable myocardium in the area at risk.<sup>9-15</sup> The elective revascularization of stenotic coronary arteries with viable myocardium after AMI improved the ventricular function.<sup>15,16</sup> Risk stratification for patients with AMI was based not only on left ventricular function but also on residual ischemia. Dobutamine-atropine stress echocardiography (DSE) can predict the recovery of ventricular function by low-dose testing<sup>13,17-19</sup> as well as detecting the residual coronary artery stenosis during high-dose infusion.<sup>14,20</sup> It may provide an objective evidence in making strategy for further intervention.<sup>20-22</sup> Ultrasonic tissue characterization (UTC) with integrated backscatter has been shown to be valuable in detecting myocardial infarction and ischemia.<sup>23-25</sup> In patients with AMI, the restoration of cyclic variation of integrated backscatter develops before the recovery of wall motion abnormalities and indicates the potentially salutary effects of coronary artery revascularization.<sup>26</sup>

The aims of the present study were to (1) document the reservation of cardiac cyclic-dependent variation of integrated backscatter in the infarct zone that is viable without residual ischemia, (2) show the restoration of cardiac cyclic-dependent variation of integrated backscatter in viable myocardium after relieving residual coronary artery stenosis, (3) verify the accuracy of UTC in identifying the viable myocardium that is free from residual ischemia.

## Methods

### Patient Selection

Thirty consecutive patients fulfilling the following criteria were enrolled in the study: (1) first episode of AMI diagnosed on the basis of ischemic chest pain lasting more than 30 minutes, characteristic electrocardiographic changes and an increase in serum creatine phosphokinase (CK) and CK-MB myocardial enzymes of at least twice above the normal value; (2) a satisfactory precordial echocardiographic window; (3) no contraindication to dobutamine testing, such as unstable angina, major arrhythmia, or severe hypertension. No patients had any of the other criteria of exclusion: atrial fibrillation, multiple ventricular premature contractions, and cardiomyopathy. Fourteen patients received recombinant tissue-type plasminogen activator as the reperfusion therapy. Primary percutaneous transluminal coronary angioplasty was

performed in the other 5 patients, including one patient with primary stenting. When the UTC and DSE were performed, no patient was given any inotropic agent or experienced postinfarction angina. At the discretion of the attending physician, blockers were administered.

### **Backscatter Data Acquisition and Analysis**

The backscatter data was collected by 2 observers within 48 hours before the coronary angiography. UTC examinations were performed with a modified, commercially available, real-time, 2-dimensional imaging system (Acoustic Densitometry in Integrated Backscatter mode, SONOS 2500, Hewlett Packard, Andover, Massachusetts) capable of providing images in which gray levels were displayed proportional to the integrated backscatter amplitude obtained. A 64-element ultrasound transducer operating at a center frequency of 2.5 MHz was used in this study. The imaging frame rate was automatically set to 30 Hz and the dynamic range of the integrated backscatter signal was approximately 44 decibels (dB). In spite of the substantial anisotropy in the parasternal short-axis view, which can be compensated for with lateral gain compensation,<sup>26</sup> we used this view at the papillary muscle level to obtain the two-dimensional image of integrated backscatter for evaluating all the three vessel territories simultaneously. The transmit power, time gain compensation<sup>27</sup> and lateral gain compensation<sup>26</sup> were adjusted to optimize image presentation and remained constant throughout the study for individual patient. Sixty frames were displayed and captured in digital format for each examination period. The integrated backscatter was quantified by placing a region of interest in the myocardium on the frozen image. The region of interest was configured with a different shape, size and orientation to fit within the boundaries of the myocardial wall at end-diastole. For all patients, the  $21 \times 21$  pixel region of interest was used. The location of the region of interest was adjusted frame by frame to keep it well within the subendocardial myocardium<sup>28,29</sup> and to avoid specular endocardial and epicardial echoes throughout the cardiac cycle. For each patient, three regions of interest were chosen in the same parasternal short axis image. One was at the mid-anteroseptal area to represent the myocardium perfused by left anterior descending coronary artery; another was at the junction of mid-posterior with mid-lateral area to stand for the myocardium perfused by left circumflex artery; and the other was at the mid-inferior area for the myocardium perfused by right coronary artery. The serial changes in the magnitude of integrated backscatter (in dBs) within the region of interest were then obtained from each frame and displayed as a curve of integrated backscatter amplitude versus time with electrocardiographic R wave as a reference. The images and data sets were stored in the optic disc for off-line analysis. For most patients, the curve included more than 2 consecutive beats. The amplitude of the integrated backscatter was obtained by

averaging the values corresponding to the same time point in each cardiac cycle. Finally, the integrated backscatter power curve for a full cardiac cycle was plotted as amplitude versus time of 33-millisecond interval. The presence of interpatient acoustic variability (such as miscellaneous attenuation across the chest wall on transthoracic approach) and different gain setting to optimize the image made the standardization of integrated backscatter power difficult. By a dog study, however, Natio et al.<sup>30</sup> disclosed that there was no significant difference in the amplitude of cyclic variation of integrated backscatter between the open chest and closed chest setting. We wrote a program with the MATLAB (the Math Works, Inc.) and the first harmonic Fourier fitting of the power curve was obtained promptly.<sup>23,31</sup>

Two basic measurements were derived from the first harmonic Fourier fitting curve: the amplitude and phase. The amplitude and phase are separate, independent measures of the integrated backscatter power curve that relate to different aspects of myocardial dynamics.<sup>25</sup> The results of UTC can be represented as a vector quantity, with a magnitude (amplitude of cyclic variation) and an orientation (phase).<sup>32</sup> The procedure for phase weighting constitutes a vectorial approach to the determination of changes in dynamic backscatter variables. We designated the variation, by doubling the amplitude, to represent the difference between maximal and minimal values of integrated backscatter. By using the electrocardiographic R wave as the trigger reference, the phase-weight variation was derived from the variation and phase.<sup>23,32</sup> It can be considered as an index of contractile dysfunction and appears to reflect accurately the severity of ischemic injury.<sup>32</sup> The following criteria were used to decide the phase weighting factor:<sup>25</sup>

Factor=	-1	if (0°	phase	45°)
	-cos[2(phase-45°)]	if (45°	phase	135°)
	1	if (135°	phase	225°)
	cos[2(phase-45°)]	if (225°	phase	315°)
	-1	if (315°	phase	360°)

The criteria used in weighting variations were such that the variation with a phase value of approximately 180° (135° to 225°) was normal and had a weight factor of 1. On the contrary, variations with a phase value progressively smaller than 135° or > 225° were reduced by a factor gradually toward -1. The phase-weighted variation represent the alteration in variation and phase simultaneously and was considered as the parameter of UTC in our study. It took about half an hour to acquire the UTC, analyze the backscatter data and arrive at the final parameter for each study.

### **Dobutamine stress echocardiography**

Just after performing UTC, DSE was performed by another 2 observers with the same equipment and an image storage system (P90, Tomtec). Continuous 12-lead

electrocardiographic recording was carried out throughout the test and blood pressure was measured every 3 minutes. The dobutamine was administered intravenously by an infusion pump at the initial dosage of 5, 10, and 20  $\mu\text{g}/\text{kg}/\text{min}$  for a 3-minute duration of low-dose testing.<sup>33</sup> The dosage was then increased by 10  $\mu\text{g}/\text{kg}/\text{min}$  up to a maximum of 40  $\mu\text{g}/\text{kg}/\text{min}$ . If there was no significant side effect and the heart rate response was inadequate, 0.5 mg atropine was given twice with 1-minute interval<sup>34,35</sup> to achieve peak heart rates of  $> 120$  bpm.<sup>36</sup> The test was prematurely terminated if severe angina,  $> 2$  mm ST-segment depression or elevation, marked wall motion deterioration, major ventricular arrhythmia, systemic hypertension (blood pressure  $> 220/120$  mmHg), systolic hypotension (defined as a drop in systolic hypotension  $> 20$  mmHg compared to the previous step), 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.<sup>18,36</sup> The coronary lesions were predicted by using conventionally defined wall segments<sup>37</sup> and a schema correlating the segmental wall motion abnormalities with the coronary artery distribution.<sup>36,38</sup> The echocardiographic site of AMI was recognized by correlating the wall motion abnormalities with the evolutionary electrocardiographic changes. A patient was considered to have significantly viable myocardial segments within the infarction zone when an improvement in contractility

1 grade developed in at least 2 contiguous segments or 2 grades in 1 segment. DSE was considered positive for myocardial ischemia in the infarct zone when a deterioration of its thickening and motion at higher doses occurred after improvement at low doses was noted (biphasic response). A new wall motion abnormality in a basally normal segment or deterioration of a hypokinetic segment belonging to the infarct-related artery territories according to the scheme of coronary perfusion was also considered indicative of ischemia.<sup>14,20,39</sup> When there was no improvement in myocardial thickening or motion during low-dose dobutamine infusion, the akinesic or dyskinetic segments were considered to be nonviable.<sup>40</sup> Changes from dyskinesia to akinesia at low dose were considered to be unchanged.<sup>40</sup> Akinesia deteriorating directly to dyskinesia was not considered indicative of myocardial ischemia.<sup>14,20,40,41</sup>

Agreement among the 2 observers was achieved in 96% (29 of 30) of the studies. Any disagreement among the 2 observers was resolved through discussion.

### **Coronary angiography and angioplasty**

After obtaining the consent forms from the patients, coronary angiography was performed with routine technique at 8.3  $\pm$  3 days after the onset of AMI. A computer-aided quantitative angiographic analysis system (DCI-S Automated Coronary

Analysis System, Philips Medical Systems, Eindhoven, The Netherlands) was used. After identifying the infarct-related artery, the patency was assessed by 2 observers having no knowledge of the result of UTC and DSE. A  $\geq 50\%$  diameter stenosis<sup>42</sup> was considered significant and angioplasty was performed. The success of angioplasty was defined to reduce more than 50% of the diameter stenosis.

### **Follow-up Ultrasonic Tissue Characterization and Dobutamine Stress Echocardiography**

After successful angioplasty, the follow-up UTC and DSE were performed within 24 hours.

#### **Data Reproducibility.**

For each study, the UTC was performed twice to evaluate the intraobserver variability. To evaluate the interobserver variability, the another observer performed the integrated backscatters data acquisition and analysis independently.<sup>43</sup> The mean absolute variabilities for variation were  $0.6 \pm 0.5$  dB (intraobserver) and  $1.0 \pm 0.7$  dB (interobserver). For phase, these were  $5 \pm 7^\circ$  (intraobserver) and  $7 \pm 9^\circ$  (interobserver). Performing correlation analysis of these repeated measurements by linear regression method, the coefficients of correlation for variation were 0.96 (intraobserver) and 0.90 (interobserver). The standard errors of estimate were 0.8 dB (intraobserver) and 1.1 dB (interobserver). As to phase, the coefficients of correlation were 0.90 (intraobserver) and 0.81 (interobserver). The standard errors of estimate were  $8^\circ$  (intraobserver) and  $10^\circ$  (interobserver).

#### **Statistical analysis.**

All results were given as mean  $\pm$  standard deviation. Continuous data were compared using one-way ANOVA test. Duncan's multiple range test was used to find those groups with statistically significant difference. The unpaired t test was used to compare continuous data between 2 different groups. Two-way ANOVA test was used to evaluate the changes of phase-weighted variation after successful angioplasty in different patient groups. McNemar's test was applied to compare the concordance between DSE and UTC. A p value  $<0.01$  (two tailed) was considered statistically significant. The specificity, sensitivity and accuracy for phase-weighted variation in identifying myocardium that was viable without residual ischemia were plotted to determine the cutoff value. Furthermore, the receiver operating characteristics curve analysis was also applied.<sup>44</sup>



## Results

### Patients Data

There were 27 men and 3 women enrolled in this study (mean age, 55 ± 12 years). Thrombolytic therapy was used in 14 patients and 7 patients received primary angioplasty. The reperfusion therapy was given within 4.8 ± 2.6 hours after the onset of AMI.

### Coronary Angiography and Angioplasty

Coronary angiography was performed at 8.3 ± 3 days after AMI. The infarct-related artery was the left anterior descending coronary in 16 patients, the left circumflex in 1, and the right coronary in 13. The residual stenosis of the infarct-related artery was 70±35%. Significant residual stenosis (> 50% luminal diameter stenosis) was found in 73% of the patients (22 of 30), including 4 occluded arteries. Successful angioplasty was done in 15 patients. However, 4 patients refused the follow-up DSE after successful angioplasty. Two patients received coronary artery bypass graft surgery for multivessel disease and complete revascularization.

### Dobutamine-Atropine infusion

For the 30 cases of DSE done before intervention, the peak dobutamine dose was 37 ± 6 g/Kg/min. Atropine (0.5 to 1.0 mg) was used in 16 patients. The peak heart rate and systolic blood pressure were 121 ± 17 bpm and 146 ± 22 mmHg, respectively. End points were heart rate of > 120 bpm in 15 patients, maximal dose in 2, ST depression > 2 mm in 4, angina in 5, vomiting in 1, multiple inducible wall motion deterioration in 1, non-sustained ventricular tachycardia in 1, and hypotension in 1. There were 11 patients receiving DSE after successful angioplasty. All were completed at maximal dose and atropine was used in 5 patients. The peak heart rate and systolic blood pressure were 136 ± 14 bpm and 146 ± 16 mmHg, respectively. No adverse effects were noted.

### Dobutamine-Atropine Stress Echocardiography

Analyzing the wall motion before coronary angiography, the infarction zone showed biphasic in 15 patients and worsened from basally normal or hypokinetic segments in 4. These were defined as viable myocardium with residual ischemia. Five patients have persistently improved wall motion in the infarction zone and were considered to have viable myocardium without residual ischemia. The infarction zone wall motion showed no improvement in 6 patients. That myocardium was considered to be nonviable. According to the inducible ischemic response, the sensitivity, specificity and accuracy for dobutamine-atropine stress echocardiography in detecting residual stenosis of infarct-related artery were 73%(16/22), 63%(5/8) and 70%(21/30),

respectively. Because the nonviable myocardium showed unchanged or worsened from akinesia to dyskinesia in wall motions during dobutamine infusion, even after successful angioplasty, the ability of DSE in detecting residual stenosis in nonviable myocardium was limited.<sup>20</sup> After excluding the nonviable myocardium, the sensitivity, specificity and accuracy had been 94%(16/17), 57%(4/7) and 83%(20/24), respectively. After successful coronary angioplasty, 9 patients whose infarction zone were viable received follow-up DSE. There were no changes in baseline wall motion. The previous inducible ischemia become absence in 6.

### **Ultrasonic Tissue Characterization**

For evaluating the predictability of residual infarct-related artery stenosis on viable myocardium, we classified the results of UTC into 5 groups (Table 1). Group I was those vessel territories supplied by patent coronary arteries and without inducible ischemia in DSE. It was considered as control group. Group IIA was the infarction zone without dobutamine responsive contractile improvement and with residual infarct-related artery stenosis. If there was no residual coronary stenosis of the nonviable myocardium, including the 2 patients after successful angioplasty, the results were designated as group IIB. According to the presence of residual infarct-related artery stenosis of viable infarction zone, the results of UTC were classified into Group IIIA and IIIB, respectively. After relieving the residual coronary stenosis of viable infarction zone by angioplasty, the 9 follow-up studies were also classified into group IIIB. There was significant difference of phase-weighted variation among the 5 groups ( $p < 0.001$ , by one-way ANOVA). The difference existed between group I, IIIB and IIA, IIB, IIIA. It meant that there was no difference of phase-weighted variation between control group and the infarction zone that was viable and without residual coronary stenosis ( $p = 0.453$ ). Contrarily, the phase-weighted variation of nonviable infarction zone, irreverent to the residual infarct-related artery stenosis, was fewer than that of control group (for group IIA and IIB,  $p < 0.001$  and  $p = 0.008$  versus control group, respectively). The phase-weighted variation of the viable infarction zone with residual coronary stenosis was also small ( $p < 0.001$  versus group I and IIIB). To evaluate the influence of residual infarct-related artery stenosis on UTC for infarction zone, two-way ANOVA was performed to compared the change of phase-weighted variation (Table 2, 9 patients with dobutamine responsive contractile reserve on infarction zone and 2 patients with nonviable myocardium). The statistic difference ( $P = 0.0014$ ) was attributed to the restoration of phase-weighted variation of viable infarction zone after relieving residual infarct-related artery stenosis (Fig 4 and 5). To identity the cut-off value of phase-weighted variation in predicting the residual coronary stenosis of viable infarction zone, the curves of sensitivity, specificity and accuracy were plotted. The receiver operating characteristic curve was also drawn.

Using the optimal cut-off value of 5.8, the sensitivity, specificity and accuracy for detecting viable infarction zone without residual infarct-related artery stenosis were 75%(12/16), 100%(25/25), and 90.2%(37/41), respectively. The concordance with DSE was good (McNemar's test,  $\chi^2 = 0$ , after Yate's correction, P=NS). The area under the receiver operating characteristic curve was 0.84.

## Discussion

There were three major findings in this study. First, although the wall motion was dyssynergic, the viable myocardium without residual ischemia had similar result of UTC to the normal control group. Secondly, in viable myocardium, the residual coronary stenosis would hamper the restoration of magnitude in backscatter power curve after AMI. After relieving the residual coronary stenosis, however, the parameter obtained from UTC, phase-weighted variation, would recover before the regional wall motion improved. Finally, the nonviable myocardium had small phase-weighted variation irrelevant to the patency of infarct-related artery. According to these findings, we could differentiate the myocardium with residual coronary stenosis or nonviable from the viable myocardium without residual coronary stenosis.

### Ultrasonic Tissue Characterization of Infarction Zone Myocardium

Previous studies<sup>28,45</sup> have shown a cardiac cycle-dependent variation of integrated backscatter from the myocardium with the highest values recorded at end diastole and the lowest at end systole. According to a physiologically based model for the behavior of ultrasonic backscatter proposed by Wickline et al.<sup>45</sup> the time-varying change in backscattered energy during the cardiac cycle results from a changing acoustic impedance that is caused by variations in tissue elastic modules during sarcomere shorting and is influenced by ischemia. Recently, a "geometric" model has been proposed by O'Brien et al. that is based primarily on changes in the density of scatterers with contraction.<sup>46</sup>

The occurrence of myocardial ischemia or infarction in animals or humans causes a reduction in the cyclic variation and an increase in the phase value obtained by first harmonic Fourier fitting.<sup>23-25,26,32,47,48</sup> The reperfusion after temporary coronary clamping can restore the amplitude of cyclic variation and the phase delay to some extent.<sup>23,26,32,47</sup> However, after prolonged coronary occlusion (>5 hours), the phase delay did not return to normal baseline after reperfusion and was considered useful in distinguishing between ischemic and infarcted myocardium.<sup>23</sup> Because these restorations of cyclic variation and phase develop before the recovery of regional wall motion abnormalities, the ultrasonic tissue characterization has been assumed to be a useful tool in detecting the stunned myocardium.<sup>26,49,50,51</sup> Recently, O'Brien et al.<sup>52</sup>

have verified the acoustic propagation properties capable of identifying stunned and infarcted myocardium.

Milunski and coworkers<sup>26</sup> have performed UTC in patients for detecting AMI and reperfusion. Within the first 24 hours after AMI, the magnitude of cyclic variation of integrated backscatter in infarct regions was lower than that in normal regions. The follow-up study showed that the magnitude increased over time in patients with documented vessel patency, although no recovery of wall thickening was noted. Patients with occluded infarct-related arteries exhibited no significant recovery of cyclic variation. However, no viability assessment or stress test for ischemia was done. In our study, Those myocardium that was viable without significantly residual coronary stenosis (group IIIB) had similar phase-weighted variation to that of control group (group I). Because these viable segments were dyssynergic but free from residual ischemia, it was conceivable that myocardial stunning was responsible for the dysfunction. It was compatible with the findings from animal studies of which the stunning effect was induced by temporary coronary occlusion.<sup>32,48,49</sup> We found that there were two factors limiting the restoration of phase-weight variation: the residual coronary stenosis (Group IIA and IIIA)<sup>26</sup> and nonviability (Group IIA and IIB). The latter has been mentioned in animal studies after prolonged coronary occlusion.<sup>23,32</sup> In our study, almost all the significant residual coronary stenosis of viable myocardium showed ischemic response to dobutamine infusion. It has been reported that the dobutamine stress inducible wall motion deterioration was related to impaired coronary flow reserve.<sup>53</sup> In this study, without the use of dobutamine stress, the diminished functional flow reserve also impaired the recovery of cyclic variation of integrated backscatter in 9 patients with residual stenosis between 50 to 90%. In which range, the coronary lesions were considered not severe enough to decrease resting coronary flow. Because we performed the UTC in the acute stage of AMI, the long-term evolutionary changes of backscatter power curve for viable myocardium could not be well evaluated. The finding needs further investigation.

### **Restoration of Cardiac Cycle-dependent Variation of Integrated Backscatter After Relieving Residual Coronary Stenosis of Viable Myocardium**

Although the terms “hibernation”<sup>54</sup> and “stunning”<sup>50,51</sup> represent uniquely different pathophysiological processes with distinct definitions, in clinical circumstances the boundaries between stunning and hibernation are often indistinct. Both process may occur in the same patient and even coexist in the same myocardial region.<sup>55</sup> The residual ischemia will impair the recovery of dysfunction.<sup>14</sup> It implicates that the viable myocardium will go into hibernation status and the successful revascularization is required for the recovery of regional function.<sup>13,15,56</sup> Our study showed that the residual ischemia also hampered the restoration of cyclic backscatter variation of

viable myocardium (Group IIIA vs IIIB,  $p < 0.001$ ) and the successful revascularization could restore the phase-weighted variation. The restoration developed before the recovery of regional wall motion abnormalities.<sup>47-49</sup> The improvement in function of these segments with low-dose dobutamine indicated their likelihood for eventual recovery,<sup>17-19</sup> especially after successful revascularization and no ischemia induced by follow-up DSE.<sup>13-15</sup> On the contrary, the intervention made no difference on phase-weighted variation of those nonviable myocardium (Table 2). It may be due to the large extent of ischemic injury<sup>23,32</sup> and implicate the irreversible wall motion abnormalities.<sup>39</sup>

### **Risk Stratification After Acute Myocardial Infarction**

Among the multiple factors that govern the risk after an AMI, 3 are recognized as principle: left ventricular function (the single most important variable), residual myocardial ischemia, and cardiac arrhythmia. The first 2 have been the most important in influencing management after AMI because of the available therapeutic modalities.<sup>57</sup> DSE can identify the viable myocardium in infarction zone and predict the recovery of ventricular function by low-dose testing.<sup>13,17-19</sup> If a segment has an inotropic reserve after dobutamine infusion, it is likely to recover and the left ventricular function will improve. The association of viability within the infarction zone with reduction in risk for cardiac events has been verified by DSE.<sup>21</sup> The presence of residual ischemia can further jeopardize viable myocardium in infarction zone, which may act as an unstable substrate for further events<sup>11,12</sup> or show impaired recovery of regional function unless be successfully revascularized.<sup>13-15</sup> Carlos and coworkers<sup>21</sup> provided evidence that supported the use of the noninvasive strategy with DSE for risk stratification of patients surviving an uncomplicated AMI regardless of whether thrombolytic therapy was used. Furthermore, the findings of DSE were better at risk-stratifying patients than was angiographic demonstration of multivessel disease. The widespread application of routine angiography and revascularization dose not improve survival or rates of reinfarction in patients with AMI.<sup>8,58,59</sup> The use of coronary angiography and revascularization should be reserved for patients with angina and/or heart failure symptoms, with demonstrable ischemia by noninvasive stress testing, and patients with depressed left ventricular function in whom multivessel disease is suspected.<sup>21,22,60,61</sup>

In our study, the accuracy of UTC for detecting viable myocardium without residual coronary stenosis was satisfactory (90.2%) and the concordance with DSE was also good. Although the maximal dobutamine stress test is verified safe during the first week after AMI,<sup>20,21</sup> Quinones suggested to wait until the seventh day before submitting a patient to a full dobutamine or exercise protocol. This means that some patients undergo testing as outpatients in today's climate of managed care.<sup>22</sup> In

comparison with DSE, no stress method is needed for UTC. It can be performed in more acute stage after AMI.<sup>23,32,47-49</sup> It means that we can apply the UTC on the patient with AMI after reperfusion therapy. If the phase-weighted variation recovers, the salutary effect of reperfusion therapy has been achieved. The myocardium within the infarction zone can be considered as viable and without residual ischemia. The patient may be classified into low-risk group and will have more preserved ventricular function. Intervention strategy should be held unless other indications are present. If the phase-weighted variation is still low, the infarction zone may become nonviable or the significantly residual infarct-related arterial stenosis may exist. Further evaluation and intervention should be considered.

**Study Limitations** This study has several limitations. Firstly, the myocardial viability was assessed by DSE only. Although it has been assumed to be a valid method, long-term follow-up study is mandatory to verify our observation. Secondly, unlike DSE, the UTC could not afford a comprehensive view of the whole ventricle because of anisotropy and difficult delineation of the endocardium in the apical segments.<sup>24</sup> Only the midventricular myocardium was evaluated. In our study, there was no patient in whom the infarct area was too small to be delineated in this image. Besides, the wall motion response to dobutamine infusion at midventricular segments on which UTC was performed was all compatible with the result of DSE in evaluating the whole left ventricle. Indeed, the most significant wall motion changes developed at midventricle during DSE. However, the difference of myocardial viability between apical and mid-ventricle might influence our interpretation. Thirdly, the magnitude of ultrasonic energy backscattered from myocardial tissue, as well as the attenuation suffered by the ultrasonic waves, depends on the angle of insonification with respect to the predominant orientation of the myofibers at selected intramural levels. Although the property of ultrasonic anisotropy can be compensated by clinically applicable techniques, such as lateral gain compensation and time gain compensation,<sup>26,27</sup> a large-scale study is necessary to disclose the ultrasonic angle dependency of the measurement obtained in the three different areas of the short axis image. Finally, the magnitude of cardiac cycle-dependent variation of integrated backscatter is reduced in the patients with pressure-overload ventricular hypertrophy<sup>62</sup> and diabetes mellitus.<sup>63</sup> The magnitude is also affected by aging.<sup>64</sup> These factors are common in patients with AMI. Our study was too small in scale to reveal the possible effects of these factors. The further investigation is warranted.

### **Conclusion and Clinical Implication**

The UTC was a very useful method to identify the viable myocardium of which the

infarct-related artery was free from residual stenosis. It is safe because no additional stress modalities are needed. It can be used as a pre-discharge screening tool for risk stratification and is helpful in constructing the intervention strategy. The UTC may also be applied to evaluate the beneficial effects of reperfusion if we perform the test promptly after therapy. Could diminished phase-weighted variation predict the restenosis of infarct-related artery of viable myocardium? Could we select the patients for whom reperfusion therapy is really necessary by ruling out the development of spontaneous recanalization of infarct-related arteries after AMI? Further studies are mandatory.

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**TABLE 1. Ultrasonic Tissue Characterization of Infarction Zone in Relation to the Myocardial Viability and Residual Stenosis of the Infarct-related Artery**

Group	Viable myocardium identified by DSE	Residual stenosis of infarct-related artery (coronary lesion severity)	Phase-weighted variation	
I ( control) (n=43)			8.1	2.6
IIA (n=5)	-	+ (98 4%)	3.6	1.4*
IIB (n=3)	-	- (33 21%)	3.5	1.3†
IIIA (n=17)	+	+ (90 8%)	4.2	1.1*
IIIB (n=16)	+	- (10 16%)	7.5	2.7‡

DSE: dobutamine-atropine stress echocardiography; n: number of coronary vessel territory; +: positive finding; -: negative finding; \*: p < 0.001 compared to Group I; †: p < 0.05 compared to Group I; ‡: p < 0.001 compared to Group IIIA

**TABLE 2. Change of Ultrasonic Tissue Characterization of Infarction Zone after Successful Coronary Angioplasty**

DSE results in infarction zone	Patient number	Phase-weighted variation	
		before angioplasty	after angioplasty
Nonviable	2	3.1 0.7	2.7 0.1
Viable	9	4.2 1.2	7.9 2.7

DSE: dob