Noninvasive Differentiation of Ischemic Cardiomyopathy From Idiopathic Dilated Cardiomyopathy With Ultrasonic Tissue Characterization Using Integrated Backscatter

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Abstract

Background. The aim of this study was to discriminate ischemic cardiomyopathy (ICM) from dilated cardiomyopathy (DCM) based on inter-segmental and transmural differences in ultrasonic tissue characters.

Methods. The study population consisted of 40 patients with DCM and 40 patients with ICM with ejection fraction of <40%. We recorded short-axis integrated backscatter (IBS) images in each patient. We measured the absolute differences in average IBS values between the anterior septum and posterior wall (|A-P|, dB). We also measured the difference of average IBS in the inner layer minus that in the outer layer in either anterior septum or posterior wall that was more dysfunctional (In-Out, dB).

Results. |A-P| was significantly higher in ICM than DCM (5.3 ± 1.7 vs. 2.7 ± 1.4, p<0.001). Receiver-operating characteristic analysis demonstrated that we can differentiate ICM from DCM with sensitivity of 80 % and specificity of 73 % using |A-P| > 4 dB as a cut-off point. (In-Out) was also significantly higher in ICM than DCM (1.6 ± 1.4 vs. –0.9 ± 1.9, p<0.001). We can also differentiate ICM from DCM with sensitivity of 93 % and specificity of 70 % using (In-Out) >0 dB as a cut-off point. Additionally, all patients with |A-P| > 3 dB and (In-Out) >0 dB belonged to the ICM group except for one patient.

Conclusions. Inter-segmental and transmural differences in myocardial IBS are significantly greater in the ICM than in DCM. Using these particular ultrasonic tissue characters, we can discriminate ICM from DCM with favorable sensitivity and specificity.

Key words: Echocardiography, Myocardial infarction, Cardiomyopathy, Cntractility, Heart failure

Introduction

Idiopathic dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) are characterized by global left ventricular contractile dysfunction, biventricular chamber enlargement, and normal valvular structure. It is often hard to differentiate ICM from DCM based on clinical and/or echocardiographic findings, but this differentiation is clinically important since we could improve the left ventricular function in patients with ICM by coronary intervention and/or coronary bypass surgery. The difference in transmural distribution of myocardial damage and/or fibrosis may help to identify ICM from DCM. According to the ‘wavefront’ phenomenon [1, 2], the myocardial damage would be more severe in the inner layer in the dysfunctional segment in ICM. Additionally, the degree of tissue injury may vary among myocardial segments in ICM depending on the perfusion territory of each coronary artery.

Ultrasonic tissue characterization using integrated backscatter (IBS) is a promising method to assess regional myocardial damage noninvasively. It shows cardiac-cycle dependent variation [3-5] and is blunted during myocardial ischemia and in the zone of myocardial infarction [6-10]. Experimental and clinical studies documented that myocardial IBS, itself, is influenced by tissue damage induced by myocardial ischemia [11], degeneration, and necrosis. It increases with an increase in the extent of myocardial fibrosis [12-15].
Thus, we can compare severity of tissue injury between different myocardial segments by comparing myocardial IBS between them. Using the machine that can display high-resolution IBS images, we can successfully measure IBS variables in the inner or outer layers of the regional myocardium [16-18]. The purpose of this study is to investigate whether we can differentiate ICM from DCM based on inter-segmental and transmural differences in the ultrasonic tissue characters. For this purpose, we assessed the inter-segmental and transmural difference in IBS variables in patients with ICM and DCM and examined their diagnostic potentials.

Methods

Study Population. Eighty patients with acceptable echocardiographic images who met the following criteria of DCM or ICM were enrolled in this study. Eligible criteria of DCM were 1) poor left ventricular function (ejection fraction < 40%); 2) no significant (> 50%) coronary diameter stenosis; 3) possibility of secondary cardiomyopathy was denied; and 4) histological findings of biopsy specimens were compatible with DCM, including myocardial fiber hypertrophy and disarray, myofibrillar lysis, intranuclear alterations, vacuolation of myocardial fibers, and interstitial fibrosis. Eligible criteria of ICM were 1) poor left ventricular function (ejection fraction < 40%), 2) coronary diameter stenosis (> 75%) being present or having been present before coronary interventions in more than one vessel, and 3) interval from the last ischemic episode and echocardiographic examination being > 6 months. DCM and ICM both had 40 patients each. One of the investigators obtained informed consent from each patient. The study protocol was approved by the hospital’s Ethics Committee.

Protocol. We performed two-dimensional echocardiography using a 2.5 or 3.75 MHz transducer with SONOS 2500 or 5500 (Agilent Technologies, Andover) and recorded the images on a 1.25 cm SVHS video tape (AG-MD830, Panasonic, Kadoma). We depicted the short-axis view at the level of mid-papillary muscle using the acoustic densitometry package and recorded it (Figure 1). We transferred the sequential 60 digital images onto a 600 or 1200 megabyte magnetic optical disc. We kept the individual value for time gain compensation constant for each study. We set the same values for time gain compensation in the echo field where the left ventricle is depicted. We also recorded the zoomed image of either anterior septum or posterior wall that showed the worst wall motion.

Data Analysis (Figures 1 and 2). We used digi-
tally stored images for analyzing myocardial IBS. In the short-axis IBS images, a single observer manually moved the ovoid region of interest frame by frame to keep it within the myocardial wall throughout the cardiac cycle in the anterior-septum and in the posterior wall. For analyzing the zoomed images, we placed the region of interest that covers half of the myocardium, in the inner and outer halves of the myocardium (Figure 1) and adjusted it frame by frame to keep it in the same position. After the data acquisition, the package automatically reconstructed a curve of IBS versus time. At the same time, the mean value for IBS throughout the cardiac cycles was automatically measured and displayed. We calculated the absolute difference in average IBS values between the anterior-septum and posterior wall (|A-P|, dB). From the analysis of the zoomed image, we determined the difference of average IBS in the inner layer minus that of the outer layer (In-Out, dB). Intraobserver and interobserver differences were measured in 5 randomly selected patients. Intraobserver and interobserver differences in |A-P| were 5.3±2.1 % and 6.1±2.8 %, respectively. Intraobserver and interobserver absolute differences in (In-Out) were 4.1 ± 2.0 % and 4.1 ± 2.0 %, respectively.

Statistical analysis. All data are expressed as mean ± SD. Multiple comparisons were made by a one-way ANOVA, and individual data were compared by Schef²e’s F test for factor analysis. To analyze predictive value of variables, we constructed receiver operating characteristic curves, a plot of sensitivity against 1-specificity, and determined the suitable cut-off point where the sensitivity is nearly equal to specificity as possible. Differences were considered significant at $P < 0.05$.

Results

Patients’ characteristics. The patients’ characteristics of DCM and ICM groups are summarized in Table 1. Except for age, there were no differences in sex, LV dimensions, wall thickness, fractional shortening, left ventricular ejection fraction, and NYHA class. In the patients with ICM, the distribution of the location of myocardial infarction was the anterior wall in 40 patients, the inferior wall 30 patients, and the posterior wall in 12 patients.

Inter-segmental and transmural differences in IBS values. |A-P| was significantly higher in patients with ICM than in those with DCM (5.5 ± 1.7 vs. 2.7 ± 1.4 dB, $p<0.001$) (Figure 3), implying the inter-segmental differences in average myocardial IBS is greater in ICM than in DCM. Receiver operating characteristic curve analysis demonstrated that |A-P| = 4 dB is the optimal cut-off point to discriminate ICM from DCM with the sensitivity of 80 % and the specificity of 73 %, respectively (Figure 4).

We compared the transmural difference in average IBS between ICM and DCM in either the anterior septum or posterior wall that was dysfunctional. (In-Out) was significantly higher in patients with ICM than in those with DCM (1.6 ± 1.4 dB vs. −0.9 ± 1.9 dB, $P <0.001$) (Figure 3). This indicates that the myocardial IBS was relatively higher in the inner layer in ICM, whereas the transmural difference was vice versa in the patients with DCM. Receiver operating characteristic curve analysis demonstrated that (In-Out) = 0 dB was the most suitable cut-off point to differentiate these diseases (Figure 4). Using (In-Out) > 0 dB, we can predict ICM with the sensitivity of 93 % and the specificity of 70 %.

To compare the quality of various tests, we estimated the sensitivities of tests from receiver operating characteristic curves at the fixed value for specificity of 90 % and compared them. This value for specificity was selected because very high specificity is required to avoid unneeded examination or intervention. The
sensitivity to discriminate ICM from DCM was higher in (In-Out) (72%) than in |A-P| (60%).

**Combination of these two variables.** Figure 5 demonstrated the scatterplot of (In-Out) against |A-P| in patients with ICM and DCM. Plots of DCM are distributed in the left lower fields. In contrast, plots of ICM are located mainly in the right upper field, implying both inter-segmental and transmural differences in myocardial IBS being greater in ICM than in DCM. This figure also demonstrates that all plots in the field of (In-Out) > 0 dB and |A-P| > 4 dB belong to ICM except for one DCM case. The combination of intra-

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Data are presented mean ± SD or number (percent). *p<0.01 vs. DCM

ACE, angiotensin converting enzyme; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; EDPWTh, end-diastolic posterior wall thickness; EDVSTh, end-diastolic ventricular septal wall thickness. 

**Fig. 3.** Scatterplot comparing |A-P| (A) and (In-Out) (B) between DCM and ICM. |A-P| is significantly higher in ICM than in DCM (5.5 ± 1.7 vs. 2.7 ± 1.4 dB). (In-Out) was also significantly higher in ICM than in DCM (1.6 ± 1.4 vs. −0.9 ± 1.9 dB).
mural and inter-segmental differences in myocardial average IBS can identify ICM more accurately compared to each parameter alone.

**Discussion**

ICM and DCM are two major heart diseases that can cause global left ventricular dysfunction without significant valvular disorders. But it has been hard to differentiate these two diseases with conventional echocardiographic techniques. Our data demonstrated that the inter-segmental and transmural differences in myocardial IBS were significantly greater in the patients with ICM than in those with DCM. Based on these inter-segmental and transmural heterogeneity of the myocardial IBS value, we could successfully discriminate ICM from DCM with excellent sensitivity and specificity. Additionally, those with (In-Out) > 0 dB in the dysfunctional segment and |A-P| > 4 dB belonged to the ICM group except for one patient. Therefore, the combination of these parameters augments the specificity to predict ICM. To our knowledge, this is the first report that demonstrates the potential of ultrasonic tissue characterization using IBS to discriminate ICM from DCM with such excellent sensitivity and specificity.

**Inter- and Intra-Segmental Differences in Myocardial IBS.** The infarct tissue is characterized by an increase in the component of connective tissue that is associat-
ed with an increase in average value for myocardial IBS. There is a quantitative relation between the myocardial collagen content and the myocardial IBS [12-14]. In general, IBS for the infarct segment is approximately 5 dB greater than that in normal tissue [19]. The grossly visible scars, however, rarely is present in DCM, that is 7-14% of the patients, and most of these are focal and small in size [20, 21]. In addition to the amount of collagen, the inter-segmental distributions of collagen may be different between ICM and DCM because the degree of myocardial injury and fibrosis should vary among myocardial segments supplied by the different coronary arteries in the patients with ICM. Our study demonstrated that the absolute inter-segmental difference in IBS, that was |A-P|, was significantly greater in ICM than in DCM, implying that the distribution of myocardial damage and/or fibrosis seems to be more heterogeneous in ICM than in DCM. By using the |A-P| > 4 dB as a cut-off point, we can differentiate ICM from DCM with the excellent sensitivity of 80% and specificity of 73%.

The transmural heterogeneity of IBS variables has been reported to be different between myocardial infarction and DCM. Wong et al. [22] compared frequency dependence of IBS of inner, mid, and outer layers of myocardium between the DCM and myocardial infarction. They suggested that the frequency dependence is higher in the outer layer than in the inner layer in DCM but the tendency is vice versa in the infarct zone. Instead of frequency dependence, we measured the difference in myocardial IBS value between the inner and outer layers of dysfunctional myocardial segments. This was due to our hypothesis that myocardial degeneration and/or fibrosis would be greater in the inner layer than in the outer layer after the ischemic injury. Naito et al. [23] documented that IBS value is significantly greater in the inner layer than in the outer layer in the patients with non-Q wave myocardial infarction. But it showed comparable value in the patients with Q-wave myocardial infarction, where transmural damage is speculated. Our data also supported this hypothesis. In the dysfunctional segment, (In-Out) showed positive value in ICM. It implies that the myocardial degeneration or fibrosis would be more severe in the inner layer than in the outer layer in ICM. Thus, we can differentiate ICM from DCM based on (In-Out) > 0 dB as a cut-off point with favorable sensitivity of 93% and specificity of 70%.

However, specificities of these two parameters are not high enough to differentiate ICM from DCM. Therefore, we assessed that the combined use of these parameters may improve the diagnostic potential. The patients with |A-P| > 4 dB and (In-Out) > 0 dB belong to the ICM group except for one patient. In contrast, all patients with |A-P| < 4 dB and (In-Out) < 0 dB belongs to the DCM group. These data indicate that the combination of these criteria augments the specificity to identify ICM or DCM.

**Limitations of the Study.** Myocardial IBS is dependent on the angle between fiber orientation and ultrasonic beam, or anisotropy. In the inferior-septum or lateral wall, the value for myocardial IBS is extremely low and the cyclic variation is hardly demonstrated with imaging along the parasternal short-axis. Data in this study were obtained exclusively from the anterior-septum and/or the posterior wall, in which the myocardial fiber is oriented nearly perpendicular to the ultrasound beam, thereby avoiding problems with anisotropy as possible. Additionally, the analysis is largely dependent on the image quality.

The ability to differentiate DCM from ICM may be limited if hearts with DCM contain confluent transmural scars. However, pathological studies report that the grossly visible ventricular scars is present only in a small population of patients with DCM [20, 21]. The possibility of infarction superimposed on DCM would limit the application of this method. No patient exhibited history of myocardial infarction in this study. The contribution of myocardial stunning and/or hibernation is speculated as an etiology of ICM; changes in myocardial IBS in such pathological states have not been fully elucidated.

**Clinical Implications.** It is generally not possible to delineate the source of systolic dysfunction with conventional echocardiographic data alone, particularly for hearts that manifest global dysfunction. The result of this study suggests that ultrasonic tissue characterization using IBS may provide additional criteria for the noninvasive differential diagnosis between ICM and DCM. Adding the ultrasonic tissue characterization to routine echocardiographic examination requires only a little extra-time (< 2 min) and cost and could provide very important information for the risk stratification of patients.

**References**


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