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The relationship between functional capacity and ultrasonic tissue characterization in patients with idiopathic dilated cardiomyopathy

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Abstract

Background: *Ultrasonic tissue characterization (UTC) has been widely used to investigate left ventricular (LV) dysfunction in various cardiac disorders. The aim of this study was to investigate the correlation between functional capacity and UTC in patients with idiopathic dilated cardiomyopathy (IDCM).*

Methods and Results: *Treadmill test according to modified-Bruce protocol was performed in 48 patients with IDCM to assess their functional capacity. Baseline clinical and echocardiographic variables were obtained and UTC was performed on images obtained from septum and posterior wall (PW). Cyclic variation (CV) index of mean gray level (MGL) was calculated according to the formula:* $[(\mathit{MGLdiastole} - \mathit{MGLsystole}) \div \mathit{MGLdiastole}] \times 100$. *PW and septum CV indices were correlated with exercise duration (*$r = 0.63$, $p = 0.001$ *and* $r = 0.67$, $p = 0.0001$*, respectively) and "MET" level (*$r = 0.80$, $p = 0.0001$ *and* $r = 0.83$, $p = 0.0001$*, respectively). The ROC curve analysis revealed that the PW CV index was a strong indicator of good exercise capacity (> 8 METs) with an AUC of 0.97 (95% CI 0.90–1.0), as the interventricular septum (IVS) CV index (AUC = 0.97, 95% CI 0.89–1.0). Sensitivity, specificity, positive predictive value, and negative predictive value to identify good exercise capacity for IVS CV index were 90%, 88%, 82%, and 94%, respectively and for the PW CV index, 90%, 88%, 82%, and 94%, respectively.*

Conclusions: *In this particular study, we found out that in patients with severe LV dysfunction good exercise capacity was related to septum and PW CV indices measured by UTC, and these indices may be used as an indirect prognostic marker in heart failure.* (Cardiol J 2013; 20, 6: 626–632)

Key words: exercise capacity, functional capacity, idiopathic dilated cardiomyopathy, ultrasonic tissue characterization, videodensitometry

Introduction

Heart failure (HF), a frequently encountered public health problem in clinical practice, still has high morbidity and mortality rates despite developments in pharmacologic and device treatment modalities. Idiopathic dilated cardiomyopathy (IDCM), a common cause of HF, has a variable natural history. Clinical presentation may range from asymptomatic left ventricular (LV) dysfunction to severe congestive HF [1]. In daily clinical practice, the 2 most important and widely used prognostic

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markers are the LV ejection fraction (EF) and the functional capacity [2]. Functional capacity, classified according to the New York Heart Association (NYHA), was shown to be an independent predictor for mortality [2]. Cardiopulmonary exercise testing has recently been accepted as the gold standard for assessing the functional capacity of the patient and provides valuable prognostic data in terms of mortality [3, 4]. Impaired functional capacity may be a consequence of increased myocardial fibrosis. However, in patients with HF, we frequently observe a discrepancy between functional capacity and conventional echocardiographic parameters [5]. Ultrasonic tissue characterization has been proposed as a method defining the physical state of the myocardium beyond the chamber dimensions and functional indices assessed by conventional 2-dimensional echocardiography [6, 7]. Ultrasonic tissue characterization (UTC) has been used to document the cyclic variation (CV) of myocardial acoustic properties in various cardiac disorders, including those of ischemic and non-ischemic origin [7–12]. This study was designed to assess whether an alternative non-conventional echocardiographic method by means of videodensitometric analysis could predict functional capacity in patients with IDCM.

Methods

Patients

A total of 48 patients (18 women, mean age 47 ± 11 years) with IDCM who met the following inclusion criteria were enrolled in the study: (a) dilated LV (left ventricular end-diastolic diameter [LVEDD] > 60 mm and left ventricular end-systolic diameter [LVESD] > 45 mm); (b) EF < 40%; (c) normal coronary angiographic evaluation. Patients with atrial fibrillation, primary valvular disease, serious ventricular arrhythmias, severe chronic obstructive pulmonary disease and biventricular pacemaker, and patients with moderate to severe mitral regurgitation were excluded. All medications that the patients were taking were recorded. Echocardiography examination was performed in all patients, and records were transferred to the digital archive. Then, to determine functional capacity symptom limited exercise test was performed according to modified Bruce protocol. Informed consent was obtained from all patients.

Doppler echocardiography

The examinations were performed using a commercially available ultrasound system (VIVID 7, GE Vingmed Ultrasound, Horten, Norway) with a 3.5-MHz phased-array transducer. LV dimensions and wall thickness were measured from M-mode tracings in accordance with the recommendations of the American Society of Echocardiography on parasternal long axis view [13]. LV volumes and EF were measured using the modified Simpson method on apical 4- and 2-chamber images. The measurements represented the mean of 3 consecutive cardiac cycles. Pulmonary artery pressure (PAP) was measured from apical 4 chamber view, right ventricular (RV) inflow or parasternal short axis view and was derived from the tricuspid regurgitant and inferior vena cava plethora [14].

Videodensitometric myocardial texture analysis

The same gain settings and compensation profiles were used for all participants to achieve approximately uniform brightness of the interventricular septum (IVS) and posterior wall (PW) throughout all the echocardiography examinations. Harmonic imaging was not used, and the gray-scale transfer function was adjusted to be linear at a depth of 16 cm to 18 cm. Dynamic range, emission power, focal plane, filters, and overall gain were adjusted to fixed settings so as to minimize noise on the images. To avoid bias in data analysis, the manual adjustment for depth gain compensation (linear curve) was kept at zero.

For each subject, the optimal ECG-guided end-diastolic and end-systolic 2-dimensional echocardiographic images of 3 consecutive beats in the cine loop were transferred directly from the screen to the digital archive of the echocardiography system. This was done using an image format of 24-bit intensity range and resolution of 800 × 564 pixels. End-diastole was defined as the point in the cardiac cycle marked by the beginning of the R wave on ECG. End-systole was defined as the time of minimal LV chamber size, marked by the peak of the T wave on ECG. The digitized images were transferred from the echocardiography system to a personal computer for UTC.

The same observer analyzed the data. By using a dedicated software (NIH-ImageJ-1.43u, National Institutes of Health, USA), the images were converted to a format of 8-bit intensity range and 800 × 564 resolution, with each pixel featuring 256 gray levels (0 = black, 255 = white). The same software allows the examiner to generate a histogram that depicts echocardiography gray level distribution across each image. Plotting gray-level distribution on the abscissa and frequency on the ordinate generated a histogram. For images captured in the parasternal long axis view, a trackball-controlled

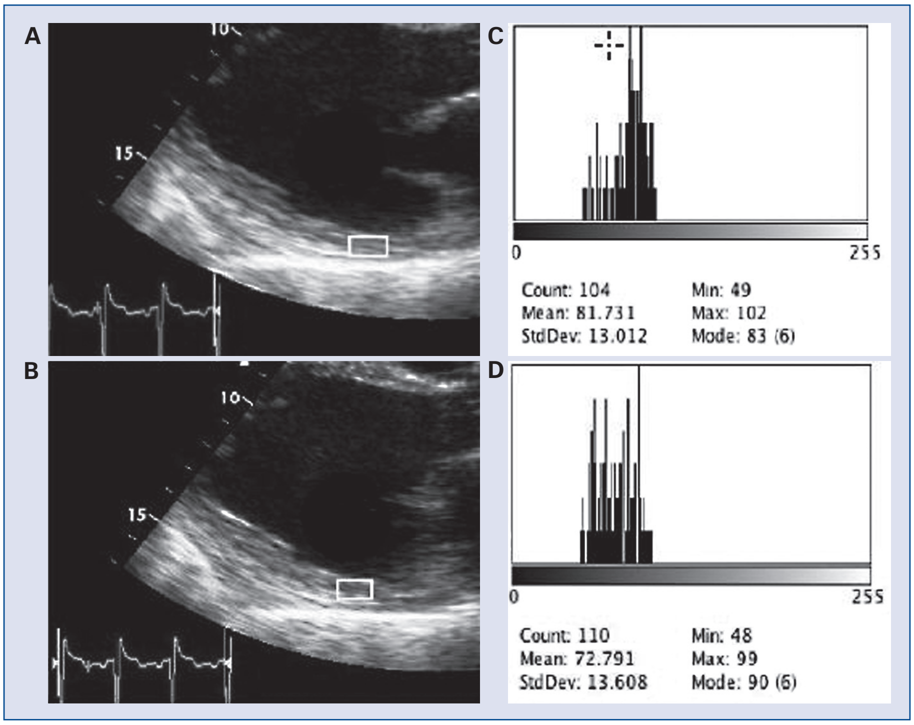

Figure 1. Digitized images from a subject show the position of the region of interest on the posterior wall of the left ventricle in (**A**) end-diastole and (**B**) end-systole (cycle phases determined from electrocardiography). A histogram was generated (the gray-level distribution on abscissa, frequency on the ordinate) for each region of interest at (**C**) end-diastole and (**D**) end-systole.

cursor was used to outline and highlight the region of interest (ROI) on each image. An effort was made to position each ROI at the same location, near the tips of the mitral leaflets, on the IVS and on the PW (Fig. 1) [15–19]. Special attention was paid to including only the myocardium and excluding the endocardial and epicardial specular echoes to avoid areas of echo dropouts and obvious artifacts. For each ROI in each wall region (IVS and PW), the background signal was subtracted from the mean gray level (MGL) to obtain background-corrected MGL (BC-MGL). The CV index of the gray-level amplitude for each ROI was calculated according to the formula [20]:

$$\text{CV index (\%)} = ([\text{BC-MGL}_{\text{End-diastole}} - \text{BC-MGL}_{\text{End-systole}}]/\text{BC-MGL}_{\text{End-diastole}}) \times 100.$$

To assess the variability of these measures, 3 consecutive cycles were analyzed.

Statistical analysis

Data analysis was performed by SPSS 17 (SPSS Inc., Chicago, Illinois, USA) package software. Continuous variables were expressed as mean ± standard deviation and nominal variables were expressed as percentages. After employing normality tests for understanding the distribution characteristics of the data, Pearson test for correlation analysis and one-way ANOVA with *post hoc* Tukey's test for the comparison between groups were used. Intraobserver variability for echocardiographic parameters was done by Bland-Altman analysis. An exploratory evaluation of additional cut-points was performed using the receiver-operating characteristics (ROC) curve analysis. A p-value < 0.05 was considered statistically significant. All p values were two sided.

Results

Three groups were generated according to the exercise capacities: high risk (≤ 5 METs), moderate risk (5–8 METs) and low risk (≥ 8 METs) for cardiovascular mortality [21]. Baseline clinical characteristics and the conventional echocardiographic indices of groups are presented in Table 1. Forty of 48 patients were taking angiotensin converting enzyme inhibitors and 8 patients were taking angiotensin receptor blockers. Twenty five patients were taking beta-blockers and 10 patients were taking

Table 1. Baseline characteristics of the groups.

	≤ 5 METs (n = 14)	5–8 METs (n = 17)	≥ 8 METs (n = 17)	P
Clinical characteristics				
Age [years]	46.2 ± 13.1	47.1 ± 14.1	45.1 ± 13.1	0.93
Gender (male/female)	9/5	10/7	11/6	0.45
Hypertension	4 (22%)	3 (37.5%)	4 (20%)	0.69
Diabetes mellitus	2 (22%)	1 (12.5%)	2 (20%)	0.88
Body mass index	23.2 ± 3.2	26.6 ± 4.6	25.2 ± 4.8	0.056
Hemoglobin [g/dL]	12.5 ± 1.6	13.3 ± 1.3	13.9 ± 0.7	0.12
Metabolic equivalents	3.8 ± 0.6	6.3 ± 0.4	10.9 ± 1.3	< 0.001
Exercise duration [s]	209 ± 79	477 ± 250	751 ± 158	< 0.001
Echocardiographic data				
LVEDD [mm]	67.3 ± 7.4	66.2 ± 5.1	65.1 ± 4.3	0.501
LVESD [mm]	60.9 ± 8.3	61.3 ± 5.7	58.6 ± 7.1	0.449
LVEDV [mL]	238.9 ± 57.3	231.1 ± 40.9	212.2 ±2 9.2	0.208
LVESV [mL]	117.1 ± 53.0	171.8 ± 35.6	150.1 ± 33.5	0.149
IVS [mm]	9.3 ± 1.1	10.3 ± 1.3	9.2 ± 1.8	0.179
PW [mm]	9.3 ± 1.2	10.3 ± 1.6	9.7 ± 1.1	0.170
LVEF [%]	26.8 ± 6.2	26.2 ± 6.4	28.3 ± 7.2	0.498
SPAP [mm Hg]	48.3 ± 15.6	44.7 ± 9.4	39.8 ± 11.8	0.318

Data presented are mean values ± standard deviation. Significance was set at $p < 0.05$; IVS — interventricular septum; LVEF — left ventricular ejection fraction; LVEDD/LVEDV — left ventricular end-diastolic diameter/volume; LVESD/LVESV — left ventricular end-systolic diameter/volume; PW — posterior wall; SPAP — systolic pulmonary artery pressure.

asetylsalicylic acid treatment. However, there was no difference between groups regarding their medication. One-way ANOVA analysis revealed that there was no significant difference between the groups in terms of conventional echocardiographic parameters such as LVEF, LV diameters, LV volumes, PAP. We analyzed the correlation between exercise time (and therefore maximum "METs" achieved by the patients) and conventional and videodensitometric echocardiography parameters by Pearson test (Table 2). According to the Pearson test, exercise duration and the maximum "METs" achieved were correlated with CV indices of IVS and PW ($r = 0.67$, $p = 0.001$ and $r = 0.83$, $p = 0.0001$ for IVS CV index and $r = 0.63$, $p = 0.0001$ and $r = 0.80$, $p = 0.0001$ for PW CV index). However, there was no correlation between exercise duration, METs and LV dimensions, LV volumes and LVEF (Table 2). Although IVS CV index was found to be correlated with LVEDD, LVESD, LVESV and LVEF ($r = –0.42$, $p = 0.024$; $r = –0.48$, $p = 0.019$; $r = –0.411$, $p = 0.004$; $r = 0.37$, $p = 0.041$, respectively), there was no correlation between PW CV index and LV dimensions, LV volumes and LVEF (Table 2). The CV indices of IVS and PW were found to be well correlated with each other ($r = 0.84$, $p < 0.001$).

The videodensitometric variables are shown in Table 3. There was no significant difference between groups in terms of IVS and PW end-systolic and end-diastolic mean gray levels according to the data obtained from myocardial tissue analysis. On the other hand, mean CV indices of both IVS and PW were different between groups ($p < 0.001$). The *post-hoc* analysis with Tukey's test revealed that IVS CV index values were not different between the "≤ 5 METs" group and the "5–8 METs" group ($p = 0.036$), but the " ≥ 8 METs" group was different from the "≤ 5 METs" group and the "5–8 METs" group ($p < 0.0001$ and $p = 0.001$, respectively). The results were similar for PW CV index (no difference between the "≤ 5 METs" and the "5–8 METs" groups ($p = 0.025$), whereas the "≥ 8 METs" group was different from the other groups ($p < 0.0001$ and $p = 0.001$, respectively).

The ROC curve analysis further revealed that the PW CV index was a strong indicator of good exercise capacity (> 8 METs) with an AUC of 0.97 (95% CI 0.90–1.0) and the IVS CV index (AUC = 0.97, 95% CI 0.89–1.0). The optimal threshold of IVS CV index that maximized the combined specificity and sensitivity to predict good exercise capacity was 18% and the optimal threshold of PW CV index was 20%. Sensiti-

Table 2. The correlation analysis between exercise and echocardiographic parameters.

	LVEDD	LVESD	LVEDV	LVESV	LVEF	METs	Exercise duration
CV index IVS							
r	**–0.42**	**–0.48**	–0.368	**–0.411**	**0.37**	**0.83**	**0.67**
p	0.024	0.019	0.010	**0.004**	0.041	0.0001	0.001
CV index PW							
r	–0.28	–0.27	–0.234	–0.245	0.10	**0.80**	**0.63**
p	0.22	0.19	0.11	0.093	0.57	0.0001	0.0001
Exercise duration							
r	–0.23	–0.72	–0.34	–0.27	–0.46		
p	0.90	0.72	0.82	0.85	0.82		
METs							
r	–0.24	–0.26	–0.255	–0.249	0.15		
p	0.22	0.19	0.80	0.88	0.45		

The correlation analysis was conducted by Pearson test. Significance was set at $p < 0.05$; CV — cyclic variation; IVS — interventricular septum; LVEDD/LVEDV — left ventricular end-diastolic diameter/volume; LVEF — left ventricular ejection fraction; LVESD/LVESV — left ventricular end-systolic diameter/volume; MET — metabolic equivalent; PW — posterior wall; r — correlation coefficient.

Table 3. The results of the videodensitometric myocardial texture analysis.

	≤ 5METs (n = 14)	5–8 METs (n = 17)	≥ 8 METs (n = 17)	P
IVS				
C-MGL-ED	75.4 ± 26.8	83.3 ± 24.9	73.9 ± 23.1	0.513
C-MGL-ES	70.1 ± 23.3	72.3 ± 26.2	57.7 ± 17.6	0.436
CV index [%]	6.5 ± 3.2	13.5 ± 5.2	26.9 ± 8.3	**< 0.001**
PW				
C-MGL-ED	62.1 ± 19.8	83.0 ± 2640	92.1 ± 43.9	0.356
C-MGL-ES	59.9 ± 15.4	71.3 ± 21.4	65.5 ± 32.3	0.511
CV index [%]	7.5 ± 4.4	17.3 ± 7.2	31.1 ± 8.8	**< 0.001**

Data presented are mean values ± standard deviation. Significance was set at $p < 0.05$. All groups were compared with ANOVA. *Post-hoc* Tukey's test were performed thereafter; C-MGL — corrected mean gray level; CV — cyclic variation; ED — end-diastole; ES — end systole

vity, specificity, positive predictive value, and negative predictive value to identify good exercise capacity for IVS CV index were 90%, 88%, 82%, and 94%, respectively, and for the PW CV index, 90%, 88%, 82%, and 94%, respectively. A Bland-Altman analysis was performed and the intraobserver variability was found to be < 6% for videodensitometric myocardial texture analysis parameters.

Discussion

In this particular study, we found a good correlation between the exercise capacity of patients with IDCM and CV index which is a non-conventional echocardiographic parameter. In the management of patients with HF, the two most important and widely used prognostic markers are the LVEF and the functional capacity [2]. In daily clinical practice, functional capacity is frequently classified according to NYHA classification [22]. However, cardiopulmonary exercise testing has recently been accepted as the gold standard for assessing the functional capacity of the patient and it provides valuable prognostic data in terms of mortality [3, 4]. During cardiopulmonary exercise testing, exercise capacity is measured indirectly and it is expressed as metabolic equivalent (MET). The exercise capacity given as METs is a strong predictor for cardiovascular mortality [21, 23, 24]. Exercise capacity is dependent on the ability to increase cardiac output and to use oxygen in peripheral tissues, as well as on muscle condition, age, motivation and pulmonary status. Myers et al. [21] showed that, in terms of cardiovascular mortality, the risk was twice higher in the patients with poor exercise capacity (< 5 METs) when compared to the patients with good exercise capacity (> 8 METs). It was also reported that every 1 min decrement in the exercise time (approximayely 0.5 MET) leads to a 7% increment in mortality [24]. In another study it was shown that every 1 MET increment in the exercise capacity is associated with a 10–25% decrement in mortality [21, 25–28]. Based on these facts, we grouped our patients as the "< 5 METs" group, the "5–8 METs" group and the "8 METs" group.

Early detection and evaluation of quantitative changes in the tissues of a disease process is one of the important difficulties of the non-invasive imaging techniques. Therefore, to determine the onset and progression of myocardial disease, a noninvasive imaging modality must make distinction between normal and abnormal tissue. However, in patients with HF, we frequently observe a discrepancy between functional capacity and conventional echocardiographic parameters [5]. In previous studies there was no correlation found between exercise capacity and LV systolic function [5, 29, 30]. Therefore, with this study we aimed to find an alternative echocardiographic parameter associated with functional capacity. Tissue characterization by echocardiography uses information that is formed by interaction of sound waves with tissues. Myocardial tissue characterization by ultrasound was first used in 1957 in differentiation of infarcted hearts from normal hearts [31]. This technique is complementary to the conventional echocardiographic method in evaluating the myocardium [7, 16, 18, 32–35]. Previous studies showed that CV index enables us to discriminate ischemic [36], hypertensive [9, 17], and diabetic [37] hearts from normal myocardium. In the videodensitometric studies conducted on the patients with ischemic and dilated cardiomyopathy, diminished CV index values were detected for the PW and the IVS [11, 35]. In addition, Dagdeviren et al. [11] found a relationship between contractile reserve index and prognosis in IDCM patients. In this study, the group with PW CV index < 11% had less contractile reserve, therefore, they had higher 1-year cardiac event and mortality than the group with PW CV index ≥ 11% at a significant level.

In our study, although we found no relationship between conventional echocardiographic parameters and functional capacity, CV index, an alternative echocardiographic parameter was strongly correlated with both exercise duration and METs regardless of LV dimensions and EF for the posterior wall and the IVS. As mentioned above, the exercise capacity is associated with many conditions, such as: the ability to increase cardiac output, use of oxygen in the peripheral tissues, pulmonary status and, regarding the fact that the good exercise capacity (> 8 METs) is related to better survival, to detect early structural changes that eventually lead to a decrement in the exercise capacity (therefore survival). This unconventional echocardiography is about discriminating the abnormal myocardial texture which is responsible for the deterioration of the exercise capacity and may be of clinical importance. Another remarkable finding of the current study is that CV values of IVS and PW were well correlated with each other, but when compared to LV dimensions, LV volumes and LVEF individually, the results of individual correlation analyses were not in concordance, which may be the result of assymetrical involvement in the remodeling process which effects the whole dilated myocardium. Assymetrical involvement of the LV may lead to impairment in the LV systolic synchrony. LV dyssynchrony is known to contribute to decreased functional capacity and cardiovascular mortality [38, 39].

Limitations of the study

The main limitation of our study is the number of patients included. Besides, exercise capacity was used as a prognostic measure in our study, long term follow up would be more appropriate for the real prognostic information. Although symptom limited treadmill test is a practical and accepted method evaluating the functional capacity, it would be more appropriate to make a quantitative analysis of oxygen consumption.

Despite these limitations, in patients with IDCM, CV index can give us clinically important data about the myocardial texture which is associated with good exercise capacity, even though the conventional echocardiographic parameters are not distinctive.

Conclusions

In this particular study, we found out that in the patients with severe LV dysfunction, good exercise capacity was related to septum and PW CV indices measured by UTC, and these indices may be used as an indirect prognostic marker in heart failure.

Conflict of interest: none declared

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