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THE VALUE OF GLOBAL MYOCARDIAL INDEX TO DETECT CARDIAC DYSSYNCHRONY IN PATIENTS WITH NON-ISCHEMIC DILATED CARDIOMYOPATHY

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ABSTRACT. A variety of parameters has been proposed in left ventricular (LV) asynchrony evaluation. Echocardiography was performed in 95 patients with non-ischemic dilated cardiomyopathy (DCM). Global myocardial index (GMI) and time to peak systolic velocity (Ts) was measured from the beginning of the QRS complex to the peak myocardial systolic velocity. Absolute difference in Ts between any two of the four basal LV segments, absolute difference in Ts between any two of the six basal LV segments, absolute difference in Ts between any 2 of the 12 (6 basal and 6 mid) LV segments, and standard deviation of Ts of the 12 (6 basal and 6 mid) LV segments were derived. A composite score was calculated combining the above four dyssynchrony parameters. All GMI differed significantly among dyssynchrony groups. The area under ROC-curve to detect patients with all four criteria of dyssynchrony was 0.94 for GMI (100% sensitivity, 90% specificity). In conclusion, GMI could be used as simple index to detect LV desynchronization in DCM.

Keywords: Cardiac dyssynchrony, Global myocardial index, Tissue Doppler Imaging

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a validated tool in the management of patients with advanced heart failure (Cazeau et al., 2001; Abraham et al., 2002). Although the selection of patients is highly debated and the selection of patients is mainly based on QRS duration (Kass, 2003; Dickstein et al., 2010) there is an important trend toward using echocardiography as ideal technique to identify responders. A wide variety of parameters has been proposed in left ventricular (LV) asynchrony evaluation(Bax et al., 2004; Mollema et al., 2007; Yu et al., 2002; Yu et al., 2003; Notabartolo et al., 2004; Poerner et al., 2005; Lafitte et al., 2006; Suffoletto et al., 2006; Bax et al., 2003). Tisue Doppler imaging (TDI) is validated and considered the golden standard of regional motion quantification as it seems to be sensitive enough to determine the LV systolic desynchronization and to predict benefit of CRT (Yu et al., 2002; Yu et al., 2003; Notabartolo et al., 2004; Poerner et al., 2005). Lafitte et al (Lafitte et al., 2006) showed that 49% of heart failure patients had both positive and negative criteria for LV dyssynchrony during echocardiography. In the same time there is a need for simplier echocardiographic parameteres to validate desynchronization as TDI is time consuming and requires high qualification and is not available in screening patients for CRT indication. Global myocardial index (GMI) is a sensitive indicator of overall cardiac function (Tei, 1995; Tei et al., 1995). The GMI or Tei-index has already been applied clinically in patients with dilated cardiomyopathy (Dujardin, et al., 1998) and predictive discrimination of the GMI for congestive heart failure has shown a qualitative assessment of dP/dt and it has been significantly related to left ventricular filling pressure (Su et al., 2007). The primary objective of this study is to verify the hypothesis that GMI might be a qualitative parameter to detect of ventricular desynchronization in patients with non-ischemic dilated cardiomyopathy (DCM) in sinusal rhythm; secondary is to verify the accuracy of GMI to detect patients with cardiac dyssynchrony definited by currently used echocardiographic parameters of asynchrony.

MATERIALS AND METHODS

Patient Selection

Consecutive patients presenting non-ischemic DCM referred for echocardiography were considered for the study. The exclusion criteria were: PR interval >200 ms, persistent/permanent atrial fibrillation and the refuse of patients to enter this study. The study protocol was approved by the locally appointed ethic committee. Initial assessment included history, physical examination, 12-lead surface ECG, chest radiography and transthoracic echocardiography.

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Echocardiographic examination

Trans-thoracic echocardiography was performed with the subjects at rest in the left lateral decubitus position with commercially available ultrasound transducer and equipment (M3S probe, Vivid 7, GE-Vingmed, Horten, Norway). Images were digitally stored on hard disks for offline analysis (EchoPAC version BT06, GE-Vingmed). All tissue Doppler imaging and spectral Doppler analysis were taken as averages of at least three representative cycles. Complete two-dimensional, colour, pulsed- and continuous-wave Doppler examination were performed according to standard techniques. The echo-cardiographic examination for GMI measurements (Dujardin et al., 1998; Su et al., 2006) was performed; Doppler time intervals were measured from mitral inflow and left ventricular outflow tracings: "a" interval was measured from the cessation to onset of mitral inflow is the sum of isovolumic contraction time, ejection time and isovolumic relaxation time. Ejection time "b" is derived from the duration of the left ventricular outflow Doppler velocity profile; the sum of isovolumic contraction and relaxation time was obtained by subtracting b from a. The GMI was calculated as (a-b)/b as showed in figure 1.

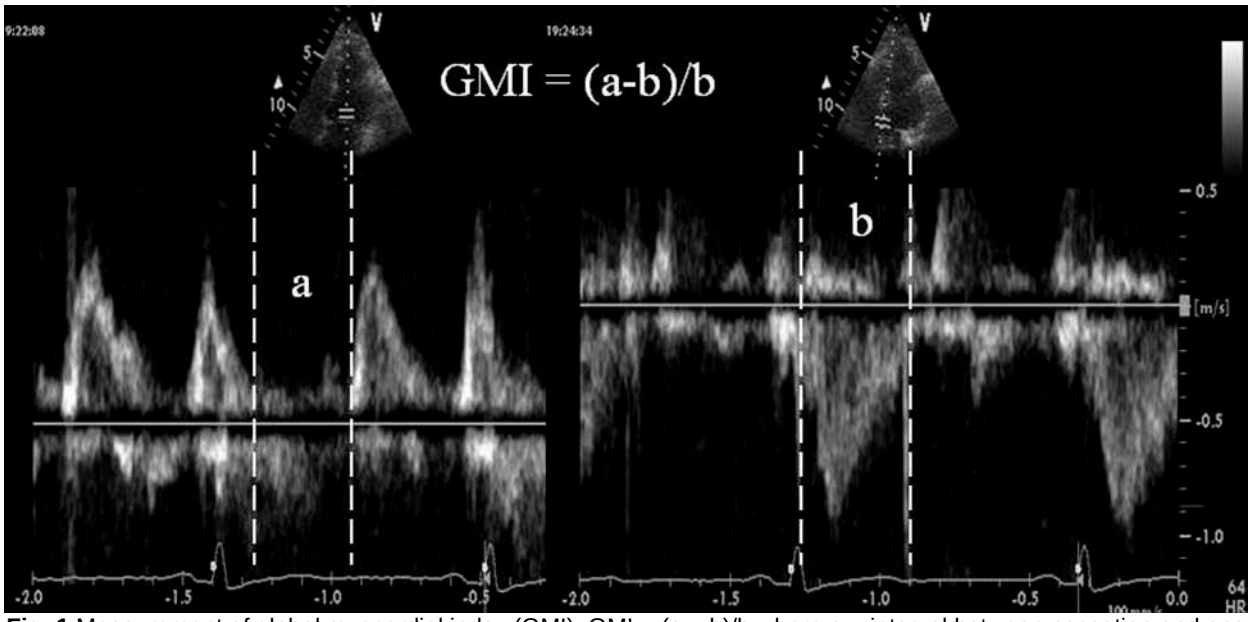

Fig. 1 Measurement of global myocardial index (GMI): GMI = (a – b)/b where a = interval between cessation and onset of mitral flow and b = aortic ejection time.

Left ventricular dyssynchrony

Long-axis tissue Doppler velocities were assessed from six basal and six mid-segments in the septal, anteroseptal, anterior, lateral, posterior, and inferior walls for a total of 12 segments. Time to peak systolic velocity (Ts) was measured from the beginning of the QRS complex to the peak myocardial systolic velocity within the ejection period, with care taken not to include isovolumic contraction velocity. From the colour tissue Doppler images, the following LV dyssynchrony parameters were derived using cut-off values previously published:

(i) absolute difference in Ts between any two of the four basal septal, lateral, inferior, and anterior LV segments (ΔTs - 4), with significant dyssynchrony defined as ≥65 ms (Bax et al., 2004);

(ii) absolute difference in Ts between any two of the six basal LV segments (ΔTs - 6), with significant dyssynchrony defined as ≥110 ms (Notabartolo et al., 2004);

(iii) absolute difference in Ts between any 2 of the 12 LV (6 basal and 6 mid) segments (ΔTs - 12), with significant dyssynchrony defined as ≥100 ms (Yu et al., 2003);

(iv) standard deviation of Ts of the 12 (6 basal and 6 mid) LV segments (Ts - SD), with significant dyssynchrony defined as ≥32.6 ms (Yu et al., 2003; Yu et al., 2004).

As studies had previously shown the presence of both positive and negative criteria for LV dyssynchrony within the same individual depending on the type of parameter used (Lafitte et al., 2006), we derived a composite dyssynchrony score ranging from 0 to 4 to determine the value of combining the above four different dyssynchrony parameters, with a value of 1 or 0 given to each positive or negative parameter. Thus, a dyssynchrony score of 0 means all four parameters were negative (group 0), and a dyssynchrony score of 4 means all four dyssynchrony parameters were positive (group 4).

Statistical analysis

Numeric variables are presented as mean value ± standard variation (SD) and compared using Student's t-tests or analysis of variance, as appropriate.

Categorical variables as absolute values and frequency percentages and compared with chi-square tests. Receiver operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity. All statistical analyses used the software package SPSS version 11.5 (SPSS Inc, Chicago, IL). A p value of <0.05 was accepted as statistically significant.

RESULTS AND DISCUSSION

The study included 95 consecutive patients with non-ischemic DCM, in sinus rhythm whit a mean age of our patients with HF was 58 ± 15 years, 58 patients were man (62%), the mean NYHA functional class was 2.6 ± 0.6, LVEF was 31 ± 13% and the mean QRS duration was 135 ± 32 ms. Of our patients 21 presented a severe functional mitral regurgitation (22%). The characteristics of the study population are presented in Table 1.

Table 1

Baseline characteristics of the study population

Characteristics	Values
Age, years	58 ± 15
Men/women, n	58 / 37
Body surface area, m^2	1.8 ± 0.6
Heart rate, beats/min	80 ± 13
New York Heart Association class	2.6 ± 0.6
QRS duration, ms	135 ± 32
LV diastolic volume, ml	178 ± 31
LV systolic volume, ml	122 ± 26
LV ejection fraction (%)	31 ± 13
Severe functional MR, n (%)	21 (22%)
Global myocardial index	0.57 ± 0.25
ΔTs – 4, ms	79.9 ± 48.3
ΔTs – 6, ms	92.4 ± 44.8
ΔTs – 12, ms	115.7 ± 41.8
Ts – SD, ms	38.3 ± 19.3
Medication	
Beta-blockers, n (%)	85 (89%)
ACEI/ARB, n (%)	90 (94%)
Diuretics, n (%)	93 (97%)
Digitalis, n (%)	36 (37%)

Legend: data are presented as mean ± SD or absolute values (%); ACEI/ARB = angiotensin conversion enzime inhibitor/ angiotensin receptor blocker; MR = mitral regurgitation; Ts = time to peak systolic velocity; ΔTs – 4 = absolute difference in Ts between any two of the four basal septal, lateral, inferior, and anterior LV segments; ΔTs – 6 = absolute difference in Ts between any two of the six basal LV segments; ΔTs – 12 = absolute difference in Ts between any 2 of the 12 LV (6 basal and 6 mid) segments; Ts – SD = standard deviation of Ts of the 12 LV segments

A minimum one ecocardiographic sign for cardiac dyssynchrony was found in 64 patients (67%) of our patients with DCM in sinusal rhythm, but only 12 patients with asincronism presented all four criteria of mecanical dyssynchrony (19%). Seventeen patients presented 2 of 4 echocardiographic signs of cardiac dyssynchrony (27%) and 18 patients presented 3 signs. The mean value of GMI was 0.57 ± 0.25. All GMI differed significantly among groups in overall test (score 0: 0.31 ± 0.08, score 1: 0.46 ± 0.09, score 2: 0.65 ± 0.10, score 3: 0.82 ± 0.18, score 4: 1.06 ± 0.27, each $p < 0.01$). Comparisons of each GMI ratio among groups are shown in Figure 2.

Using the ROC analysis for GMI accuracy for prediction of patients with dyssynchrony score of 4, the area under ROC-curve (AUC) was 0.94, $p < 0.001$; the cut-off value for GMI to predict the presence of all four echocardiographical criteria of dyssynchrony was 0.75 with a sensitivity of 100% and a specificity of 90% (figure 3).

If we considered together the patients with dyssynchrony score 3 and 4 the AUC was 0.95 with an optimal cut-off at 0.58 and 97% sensitivity and 85% specificity (figure 4).

Our results suggest in patients with non-ischemic DCM in sinusal rhythm, GMI could be used as qualitative and simple echocardiographic parameter to detect ventricular desynchronization.GMI has a good accuracy to detect patients with cardiac dyssynchrony definited by currently used echocardiographic parameters of asynchrony.

Tissue Doppler imaging parameters of ventricular dysynchrony were introduced and validated. A wide variety of parameters has been proposed in left ventricular (LV) asynchrony evaluation (Bax et al., 2004; Mollema et al., 2007; Yu et al., 2002; Yu et al., 2003; Notabartolo et al., 2004; Poerner et al., 2005; Lafitte et al., 2006; Suffoletto et al., 2006; Bax et al., 2003). Timing and peak velocities systolic and diastolic E wave, from QRS onset to peak (time to peak) to measure the standard deviation was done to assess the longitudinal synchronicity (Yu et al., 2002; Yu et al., 2003). But Tissue Doppler Imaging assessment is time consuming and requires new echocardiographic techniques which are not available

in all hospitals. Another difficulty with any time measurement using tissue Doppler imaging is the relatively high intra- and interobserver variability as is reflected in our study. Consistent with this observation, a recent multicentre study on echocardiographic quantifications of intraventricular dyssynchrony in predicting response to cardiac resynchronization therapy (PROSPECT study) revealed similar high intra- and interobserver variability (Chung et al., 2008). The authors and the editorial reviewer concluded that the sensitivities and specificities of individual echocardiographic dyssynchrony parameters were too low to be clinically useful for predicting patients' response to cardiac resynchronization therapy (Chung et al., 2008; Marwick, 2008). On the other hand, Lafitte et al (Lafitte et al., 2006) showed that 49% of heart failure patients had both positive and negative criteria for LV dyssynchrony during echocardiography.

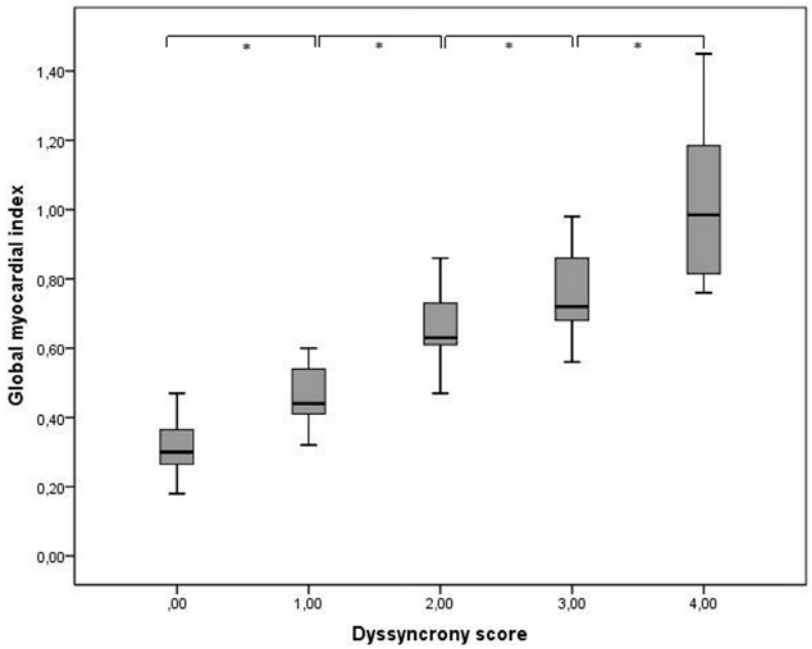

Fig. 2 Comparison of mean global myocardial indexes among dyssynchrony score groups. See text for a definition of groups. * p < 0.01

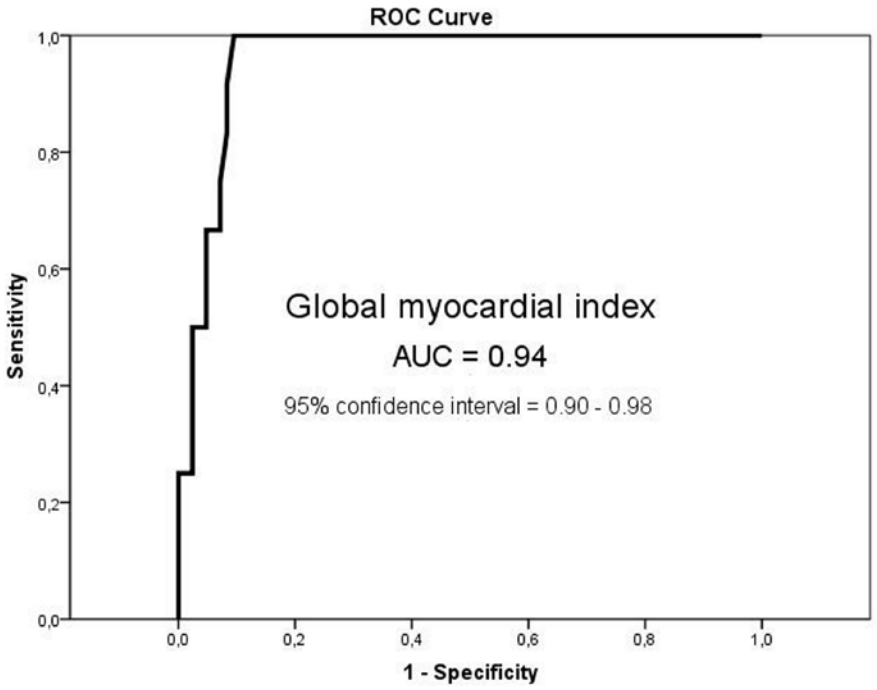

Fig. 3 Receiver operating characteristic (ROC) curve for global myocardial index to predict patients with dyssynchrony score of 4. AUC = area under ROC curve

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GMI is a sensitive and independent indicator of cardiac function witch can predict congestive heart failure (Xiao et al., 1994) using a cut point of 0.47. This index, which is defined as the sum of isovolumic contraction and relaxation time divided by the ejection time, was reported to be simple, reproducible and independent of heart rate and blood pressure (Tei, 1995; Tei et al., 1995). GMI index is significantly correlated with left ventricular end diastolic pressure and has a significantly better predictive discrimination for separating with versus those without congestive heart failure than left ventricular ejection fraction witch underline the potential clinical utility of this index (Bruch et al., 2000). In the presence of congestive heart failure, systolic and diastolic dysfunction frequently coexists. Tei and coworkers (Tei et al., 1995) showed that GMI was significantly higher in patients with dilated cardiomyopathy than in healthy subjects while Bruch and coworkers (Bruch et al., 2000) assessed the clinical utility of GMI in congestive heart failure and proved that GMI is a sensitive and reproducible indicator of overall cardiac dysfunction. Dysynergic ventricular contraction alters regional workload and stress (Xiao et al., 1994). The region of early activation works against minimal load; this kind of contraction is ineffective and does not contribute at pressure development because the rest of myocardium is still inactive. Late activated region work against high load and stress, while contraction is wasted without contribution to ejection flow. Regional ventricular delayed activation results in an uncoordinated and prolonged ventricular contraction with lengthening of the isovolumetric contraction and relaxation time and decrease of the time available for filling and ejection.

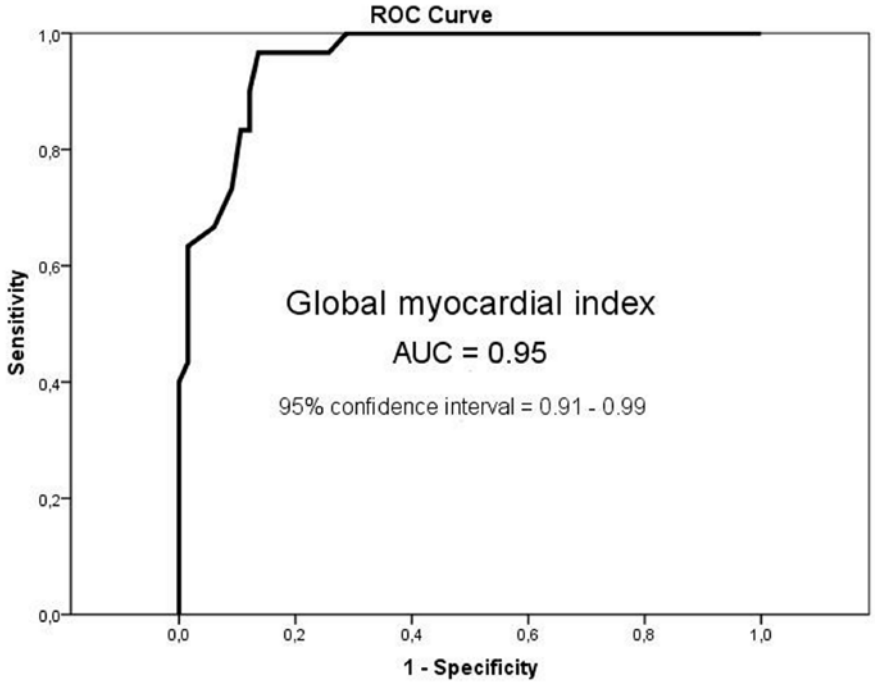

Fig. 4 Receiver operating characteristic (ROC) curve for global myocardial index to predict patients with dyssynchrony score of 3 and 4. AUC = area under ROC curve

Previously, several indexes derived from timing of peak systolic tissue velocities were proposed as predictors of CRT response. Several cut-off values of differences in timing of peak systolic velocities from various segments have been derived from patients with heart failure. Pacing of the late-activated ventricular regions could restore both interventricular and intraventricular synchronism prolongs diastolic filling and the time of ejection. GMI explore all this major parameters and it is ameliorated by multisite pacing (diminution of its value). The baseline data concerning GMI are consistent with those of previous authors (Xiao et al., 1994; Hochleiter et al., 1990; Nishimura et al., 1996).

Our results showed that only 19% of patients with mecanical dyssynchrony had concordance in all four LV tissue Doppler dyssynchrony parameters, and 49% of analysed patients exhibited combinations of both positive and negative criteria for LV dyssynchrony. In this study GMI showed a good accuracy to detect patients with dyssynchrony score of 4 (AUC = 0.94, $p < 0.001$) with a cut-off value of 0.75 (sensitivity of 100% and a specificity of 90%). All GMI ratios differed significantly among groups in overall test. Some authors reported a similar result; Su et al demonstrated that Tei index increased progressively with an increasing severity of LV diastolic dysfunction and can be used to effectively differentiate the pseudonormal/restrictive from normal mitral inflow

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pattern in a large, heterogenous group of patients with various cardiac disorders (Su et al., 2006; Dandel et al., 2004). In a recent study the baseline LV Tei index was significantly higher in CRT responders and exhibited an acute and sustained improvement after CRT (Toshinori et al., 2009). The Tei index was significantly correlated with NYHA class, EF and ventricular volumes, while values >0.77 were associated with higher 1-, 3- and 5-year mortality (Lakoumentas et al., 2005). GMI is reproducible and independent of blood pressure, heart rate, and age. Although this index is not a gold standard method in detecting myocardial dysfunction, it appears to be reliable for the evaluation of the severity of myocardial dysfunction. Measurement of the Tei index is non-invasive and easily obtained, it does not require the presence of an echocardiographer with great experience and it does not materially prolong the time required for the examination.

Our results should be considered in the context of several limitations. The number of patients in this study was relatively small; however, we were able to reach several significant observations. Selection bias is possible since our study was performed in a tertiary centre where evaluations were performed in a referral base. Patients PR interval >200 ms, persistent/permanent atrial fibrillation, ischemic heart failure were not included. Our results must be taken with caution in these subsets of patients. Larger studies with clinical endpoints are required to examine the ability of measures of early LV dyssynchrony and to predict clinical outcome.

CONCLUSIONS

Our results show that GMI could be used as qualitative and simple echocardiographic parameter to detect ventricular desynchronization in patients with non-ischemic DCM, in sinusal rhythm. GMI has a good accuracy to detect patients with cardiac dyssynchrony definited by currently used echocardiographic parameters of asynchrony.

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