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Cardiac resynchronization therapy evaluated by myocardial scintigraphy with ^{99m}Tc-MIBI: changes in left ventricular uptake, dyssynchrony, and function

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Abstract

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Purpose— ^{99m}Tc -MIBI gated myocardial scintigraphy (GMS) evaluates myocyte integrity and perfusion, left ventricular (LV) dyssynchrony and function. Cardiac resynchronization therapy (CRT) may improve the clinical symptoms of heart failure (HF), but its benefits for LV function are less pronounced. We assessed whether changes in myocardial ^{99m}Tc -MIBI uptake after CRT are related to improvement in clinical symptoms, LV synchrony and performance, and whether HMS adds information for patient selection for CRT.

Methods—A group of 30 patients with severe HF were prospectively studied before and 3 months after CRT. Variables analysed were HF functional class, QRS duration, LV ejection fraction (LVEF) by echocardiography, myocardial ^{99m}Tc -MIBI uptake, LV end-diastolic volume (EDV) and end-systolic volume (ESV), phase analysis LV dyssynchrony indices, and regional motion by HMS. After CRT, patients were divided into two groups according to improvement in LVEF: group 1 (12 patients) with increase in LVEF of 5 or more points, and group 2 (18 patients) without a significant increase.

Results—After CRT, both groups showed a significant improvement in HF functional class, reduced QRS width and increased septal wall ^{99m}Tc -MIBI uptake. Only group 1 showed favourable changes in EDV, ESV, LV dyssynchrony indices, and regional motion. Before CRT, EDV, and ESV were lower in group 1 than in group 2. Anterior and inferior wall ^{99m}Tc -MIBI uptakes were higher in group 1 than in group 2 ($p < 0.05$). EDV was the only independent predictor of an increase in LVEF ($p = 0.01$). The optimal EDV cut-off point was 315 ml (sensitivity 89%, specificity 94%).

Conclusion—The evaluation of EDV by HMS added information on patient selection for CRT. After CRT, LVEF increase occurred in hearts less dilated and with more normal ^{99m}Tc -MIBI uptake.

Keywords

Cardiology ventricular function; Gated SPECT; Myocardial perfusion SPECT; Nuclear medicine SPECT MIBI myocardium; Pacing

Introduction

Left bundle-branch block is frequent in patients with dilated cardiomyopathy [1]. This electric conduction disturbance can worsen left ventricular (LV) function because it leads to wall motion dyssynchrony [2]. It is well known that LV ejection fraction (LVEF) is an independent predictor of mortality and that cardiac performance and LV remodelling improvement are associated with a better prognosis [3, 4].

Cardiac resynchronization therapy (CRT) is considered an important adjunctive treatment for patients with dilated cardiomyopathy, QRS duration > 120 ms, especially in the presence of left bundle-branch block, and severe heart failure (HF) refractory to optimized medical therapy [5, 6]. CRT improves clinical symptoms in the majority of patients [7–9], but its benefits on LV function seem to be less pronounced [10, 11]. The mechanisms involved in this phenomenon are not completely understood. Studies have shown that the clinical improvement promoted by CRT in some patients might be just a placebo effect and that about 30% of the patients do not respond to this therapy [7, 12]. Therefore, more refined parameters are needed to better select these patients and to show objectively the benefits promoted by this costly therapy. Experimental studies in dogs have demonstrated changes in myocardial structure [13] and regional activation of stress-response kinases and globally cell-survival signalling [14] that could be related to an improvement in previously abnormal myocyte function after correction of LV dyssynchrony.

Nuclear medicine imaging is a functional method that allows the noninvasive evaluation of several pathophysiological mechanisms involved in HF [15–17]. The tracer technetium-99m 2-methoxy-2-isobutyl-isonitrile (^{99m}Tc -MIBI) is a lipophilic cationic molecule that was synthesized as a myocardial perfusion imaging agent. Its cellular uptake and retention are responsive to changes in cellular integrity, and mitochondrial and plasma membrane potentials [18]. Moreover, gated myocardial single-photon emission computed tomography (GMS) with ^{99m}Tc -MIBI allows the evaluation of regional and global LV function [19–21]. In addition, a method has recently been developed to measure LV dyssynchrony from GMS [22, 23].

The presence of transmural or intramural LV dyssynchrony could lead to impairment in perfusion and progressive deterioration of myocyte structure and function [13, 14]. Thus, the aims of this study were to assess whether changes in myocardial ^{99m}Tc -MIBI uptake induced by CRT are related to the improvement in clinical symptoms, and LV synchrony, remodelling and function, and whether GMS with ^{99m}Tc -MIBI can add information to selection and follow-up of patients undergoing CRT.

Materials and methods

Patients

A group of 30 patients with dilated cardiomyopathy, chronic HF in New York Heart Association functional class III or IV, LVEF <35%, and left bundle-branch block (QRS ≥ 120 ms) referred for implantation of a CRT device were prospectively included in the present study after providing written informed consent. The ethics committee of our institution approved the study protocol.

These patients were rigorously selected from our Arrhythmia and Pacing Department at InCor between May 2005 and December 2007. Of the 30 patients, 19 (63%) had coronary angiography excluding coronary artery disease and 11 (37%) had previous imaging which did not show myocardial ischaemia. All of them had negative Chagas' disease serology; therefore they were classified by their doctors as nonischaemic and nonchagasic dilated cardiomyopathy.

The mean age of the patients was 59 ± 11 years (range 37 to 79 years); 14 patients (47%) were men. Cardiac medications for HF at baseline and during follow-up included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in all 30 patients (100%), beta-blockers in 29 (97%), spironolactone in 27 (90%), diuretics in 30 (100%), and digoxin in 22 (73%). The pharmacological therapy was the same at least in the previous 1 month and was unchanged during follow-up. Patients were excluded from the study if they had atrial fibrillation, atrioventricular block, or a permanent pacemaker.

Study protocol

Before and at least 3 months after CRT, patients underwent functional class assessment, electrocardiogram, echocardiography, and GMS with ^{99m}Tc -MIBI at rest. After CRT, patients were divided into two groups according to LVEF improvement measured by 2-D echocardiography (Simpson's rule): group 1 with an increase in LVEF of 5 or more points, and group 2 without a significant increase in LVEF.

Atrioventricular device implantation

Commercially available pacemakers with an atrioventricular system were used in all patients (Insync III 8042/Medtronic, Minneapolis, MN; Stratos LV/Biotronik, Berlin, Germany; and Frontier II/St. Jude Medical, Memphis, TN). The right atrial lead was

positioned in the right atrial appendix and the ventricular lead in the right ventricular outflow. In 23 patients (77%), the LV pacing lead was implanted in a posterior or lateral branch of the coronary sinus (transvenous implant). LV lateral wall epicardial lead implantation using limited thoracotomy was performed in 7 patients (23%) because of coronary sinus approach failure.

Electrocardiography

Surface 12-lead electrocardiograms were recorded at a 25 mm/s speed and were evaluated by two observers without knowledge of the clinical status of the patient. QRS duration was measured on the electrocardiogram using the widest QRS complex from the DII lead.

Echocardiography

Transthoracic bidimensional echocardiographic studies were performed with a Philips HDI-5000 model (Philips, Andover, MA) equipped with a 2–4-MHz transducer, following American Society of Echocardiography recommendations [24]. Two experienced independent observers, who had no knowledge of the clinical data, measured LVEF using the biplane method (Simpson's rule).

GMS with ^{99m}Tc -MIBI imaging protocol

GMS acquisition began 45 to 60 min after tracer injection (370 MBq) at rest using a dual-detector 90° Cardio MD system (Philips Medical Systems, Bothell, WA) equipped with low-energy high-resolution collimators. All studies used the following parameters: 64 projections; 180° noncircular orbit, right anterior oblique to left posterior oblique angles; 64×64 matrix; 6.7-mm pixel size; eight frames per cardiac cycle; and 30 s per stop. GSM projection was reconstructed by an iterative method (OSEM) using five subsets and Butterworth filter (order 5, cut-off frequency 0.6 Nyquist). No attenuation correction was applied to the images.

LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using the quantitative GSM program (Cedars-Sinai Medical Center, Los Angeles, CA) [20]. This program evaluates the regional myocardial wall motion using the following scores in a 20-segment model: 0 normal, 1 mild hypokinesis, 2 moderate hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis [21]. The ^{99m}Tc -MIBI myocardial uptake defect size at rest was automatically calculated from the measurements of both severity (depth below the normal curve) and extent (width under the normal curve) of the myocardial perfusion abnormalities. The integrated measurement is expressed as percent LV defect size. Cardiac uptake was also quantified as a percentage of myocardial counts per segment according to a normal default and displayed as bull's eye maps [19]. Wall motion scores and ^{99m}Tc -MIBI myocardial uptake values in 20 segments of LV were then grouped into six major regions: anterior (segments 1, 7 and 13), anteroseptal (segments 2, 8 and 14), inferoseptal (segments 3, 9 and 15), inferior (segments 4, 10 and 16), inferolateral (segments 5, 11 and 17) and anterolateral (segments 6, 12 and 18; Fig. 1). Both segments corresponding to the apical region (19 and 20) were excluded from the analysis. The mean segment value represented the myocardial wall motion score and ^{99m}Tc -MIBI myocardial uptake of each region.

Assessment of LV dyssynchrony by phase analysis of GSM images

Phase analysis of the GSM images of 22 patients in this study was performed in the Department of Radiology of Emory University School of Medicine by investigators (J.C. and E.V.G.) who were blinded to the patients' electrocardiographic, echocardiographic, and clinical data. Once GSM data were acquired, reconstructed, and reoriented, gated short-axis

images were obtained and converted to gated polar maps. Because each pixel in the polar map represented the local maximum count (that is proportional to the wall thickness), a wall-thickening curve over the cardiac cycle was generated for each pixel of the polar map. Afterwards, phase distribution was obtained for the entire LV. The following two quantitative indexes were calculated from the phase analysis: (1) phase standard deviation, which is the standard deviation of the phase distribution; and (2) phase histogram bandwidth, which includes 95% of the elements in the phase distribution. This tool has been implemented in the Emory Cardiac Toolbox, and it is a totally automatic process [22, 23].

Statistical analysis

Data are expressed as means±standard deviation. The categorical and proportional data were analysed using the chi-squared test, the likelihood ratio test, or Fisher's exact test. For comparison of parametric variables before and after CRT, the paired Student's *t* test was used. The data were compared between groups using the unpaired *t*-test, and a stepwise logistic model was used to identify predictive parameters. The sensitivity and specificity of the EDV before therapy for predicting LVEF improvement after CRT was determined by receiver-operating characteristic curves. Statistical significance was defined at $p < 0.05$.

Results

The baseline characteristics of the two groups of patients are shown in Table 1. The medical treatment of both groups of patients was optimized. However, it was observed that a higher percentage of group 2 patients used digoxin (89%) compared with group 1 patients (50%, $p = 0.018$). After CRT, there were no significant changes in medical treatment or in the patients' weight (Table 2) in either group.

Effects of CRT on functional class and QRS width in accordance with changes in LVEF

Three months after CRT, 12 patients (40%, group 1) showed an improvement in LVEF of ≥ 5 points on 2-D echocardiography and 18 patients (60%, group 2) did not (Fig. 2). Mean LVEF increased from $22 \pm 4\%$ to $35 \pm 7\%$ in group 1 and did not significantly change in group 2 (from $21 \pm 3\%$ to $21 \pm 3\%$). After CRT, both groups showed an improvement in HF functional class ($p < 0.001$), and these changes were significantly different between groups ($p = 0.005$): nine group 1 patients (75%) were in functional class I and three (25%) were in functional class II, whereas 5 group 2 patients (28%) were in functional class I, six (33%) were in functional class II and 7 (39%) remained in functional class III. Both groups showed a significant reduction in QRS width, and this reduction was more significant in group 1 than in group 2 (Table 2).

Effects of CRT on LV volumes and regional wall motion

After CRT, group 1 patients showed a significant reduction in EDV (from 276 ± 94 ml to 183 ± 87 ml, $p < 0.001$) and in ESV (from 220 ± 85 ml to 129 ± 82 ml, $p < 0.001$). The changes seen in LV volumes in group 2 patients were not significant (EDV changed from 477 ± 168 ml to 456 ± 161 ml, $p = 0.107$, and ESV changed from 401 ± 154 ml to 395 ± 160 ml, $p = 0.759$; Fig. 2, Table 2). In group 1 patients the wall motion score showed statistically significant increase in the anterior, anteroseptal, inferoseptal and inferior regions, whereas in group 2 patients no increase was seen. Furthermore, in group 2 patients the wall motion score decreased in the anterolateral region (Table 3, Fig. 3).

Effects of CRT on ^{99m}Tc -MIBI myocardial uptake

After CRT, the total extension of the defect as shown by ^{99m}Tc -MIBI myocardial uptake at rest decreased from $14 \pm 5\%$ to $7 \pm 5\%$ in group 1 ($p = 0.003$) but did not show a significant

change in group 2 (from $17\pm 10\%$ to $15\pm 10\%$, $p=0.249$). Regional ^{99m}Tc -MIBI myocardial uptake increased significantly in the anterior, anteroseptal and inferoseptal LV walls in group 1 patients ($p<0.05$). Group 2 patients also showed ^{99m}Tc -MIBI myocardial uptake increase in the anteroseptal, inferoseptal, and inferior LV walls and showed a decrease in ^{99m}Tc -MIBI myocardial uptake in the anterolateral wall ($p=0.003$; Table 4, Fig. 3). Figures 4 and 5 show the changes in myocardial ^{99m}Tc -MIBI uptake and motion (polar map) before and after CRT in one patient of each group.

Effects of CRT on LV dyssynchrony evaluated by phase analysis of GMS images

LV dyssynchrony indices by phase analysis of GMS images was performed in 10 group 1 patients and in 12 group 2 patients before and after CRT. The phase standard deviation declined significantly in group 1 patients (from $52^\circ\pm 24^\circ$ to $24^\circ\pm 12^\circ$, $p=0.016$) and tended to decline in group 2 patients (from $62^\circ\pm 15^\circ$ to $52^\circ\pm 22^\circ$, $p=0.051$). The phase histogram bandwidth decreased significantly in group 1 patients (from $163^\circ\pm 71^\circ$ to $78^\circ\pm 42^\circ$, $p=0.017$) but the decrease was not significant in group 2 patients (from $215^\circ\pm 66^\circ$ to $179^\circ\pm 87^\circ$, $p=0.075$).

Predictors of improvement in LVEF after CRT

By univariate analysis, EDV, ESV, anterior and inferior myocardial wall ^{99m}Tc -MIBI uptake variables were significantly different between the groups before CRT. The EDV and ESV were higher in group 2 than in group 1 (EDV 477 ± 168 ml vs. 276 ± 94 ml, $p<0.001$; ESV 401 ± 154 ml vs. 220 ± 85 ml, $p<0.001$, group 2 and group 1, respectively), whereas ^{99m}Tc -MIBI uptake in the anterior and inferior myocardial wall was lower in group 2 than in group 1 (anterior $60\pm 10\%$ vs. $67\pm 7\%$, $p=0.049$; inferior $48\pm 10\%$ vs. $59\pm 11\%$, $p=0.001$, group 2 and group 1, respectively). By stepwise logistic regression analysis, EDV was the only independent predictor of LVEF improvement after CRT ($p=0.011$). The receiver-operating characteristic curve for prediction of LVEF increase after CRT showed the greatest area under the curve for EDV before CRT (area of 0.94, IC95% 0.85–1). The optimal cut-off point for EDV was 315 ml with 89% sensitivity and 92% specificity (Fig. 6).

Discussion

The main results of this study show that (1) there was significant LV remodelling in group 1 patients demonstrated by an important decrease in LV diastolic and systolic volumes; (2) the probability of LVEF improvement and LV reverse remodelling after CRT was higher in patients who had lower LV volumes and more normal regional ^{99m}Tc -MIBI uptake, especially in the inferior myocardial wall before CRT; (3) independently of LVEF increase, LV remodelling and dyssynchrony improvement, CRT promoted significant increases in anteroseptal and inferoseptal myocardial wall ^{99m}Tc -MIBI uptake, and improved HF functional class in the majority of the patients. Moreover, GMS allowed direct LV dyssynchrony evaluation and follow-up by means of phase standard deviation and histogram bandwidth indices.

LVEF significantly improved in 40% of patients, which is in accordance with the findings of other studies [10, 11]. More importantly, since GMS is a tridimensional method, it was possible to discriminate the LV regions that recovered their function. CRT improved the anterior, anteroseptal, inferoseptal and inferior wall motion in group 1 patients but not in group 2 patients.

Multivariate analysis showed that EDV obtained before CRT by GMS was an independent predictor of LVEF increase after CRT. Massive LV dilation is considered an independent contributor to poor outcome in patients with advanced HF [25]. Possibly, the more dilated

hearts of group 2 patients represented a more advanced stage of the disease with no potential to increase their performance after therapy. Our results also show that the percentage of digoxin use was higher in group 2 patients than in group 1 patients, suggesting more severe HF. Recently, we have shown that patients with lower cardiac ^{123}I -MIBG uptake, a marker of cardiac sympathetic activity, have a low probability of clinical improvement after CRT [15]. These findings reinforce the notion that to achieve measurable benefits from CRT, patients should be treated at an earlier stage of the disease. The EDV cut-off point found in this study could be used to refine the selection of patients for this therapy.

To the best of our knowledge, this is the first study to evaluate the differences in regional myocardial $^{99\text{m}}\text{Tc}$ -MIBI uptake according to changes in LVEF after CRT. The benefit of CRT is greater in patients with smaller fibrotic regions, in those with nonischemic cardiomyopathy, and if the paced zone does not involve fibrosis [26, 27]. The quantitation of $^{99\text{m}}\text{Tc}$ -MIBI myocardial uptake defect size is a parameter of myocardial fibrosis [17]. Sciagra et al. [26] have shown that the presence of severe rest defects on myocardial scintigraphy is associated with a nonsignificant improvement in LVEF or reduction in LV volumes after CRT. In this study, we also analysed the total extent and severity of the defect at rest, and we did not observe significant differences in this parameter before CRT between the groups. However, we found using univariate analysis that group 2 patients had lower $^{99\text{m}}\text{Tc}$ -MIBI uptake in the anterior and inferior walls than did group 1 patients. Thus, in patients with nonischemic cardiomyopathy, the location of fibrosis seems to be more important than the total amount of myocardial scar burden, since the presence of fibrosis may prevent the electric stimuli passing properly through these walls.

Myocardial perfusion impairment, mitochondrial dysfunction and specialized Purkinje cell derangement may reflect the progression of myocardial damage in chronic HF. A recent study [14] has demonstrated that CRT reverses regional and global molecular remodelling, generating more homogeneous activation stress kinesis and reducing apoptosis. Functional imaging methods that noninvasively assess cellular perfusion and integrity can provide information about the effects of CRT on myocyte performance. Some studies have shown that CRT improves myocardial tracer uptake in the septum and decreases uptake in the lateral wall, suggesting a reverse remodelling of regional myocardial functional status [28–30].

We observed that despite the lack of increase in LVEF after therapy group 2 patients had an increase in LV anteroseptal, inferoseptal and inferior wall $^{99\text{m}}\text{Tc}$ -MIBI uptake, and about 60% of them had improvement in functional class. Chiu et al. [18] showed that cellular $^{99\text{m}}\text{Tc}$ -MIBI uptake and retention are dependent on both mitochondrial and plasma membrane potentials. Matsuo et al. [31] showed that the myocardial washout rate of $^{99\text{m}}\text{Tc}$ -MIBI provides prognostic information in patients with congestive HF. Thus, it seems that the increase in myocardial $^{99\text{m}}\text{Tc}$ -MIBI uptake, as shown in this study, is indicative of improvement in cellular perfusion and mitochondrial function. These favourable cellular effects could explain why this therapy improved functional class even in patients who did not show LVEF increase and LV reverse remodelling.

Study limitations

The most significant limitation of this study was that we did not directly measure mitochondrial function, and for this reason we could not establish a direct correlation between myocardial $^{99\text{m}}\text{Tc}$ -MIBI uptake and mitochondrial function. But this measurement can be quite difficult in vivo and needs myocardial biopsy. The small number of patients studied limited the power of our results, and further studies are needed to confirm them.

The myocardial ^{99m}Tc -MIBI uptake results before and after CRT could be partially due to a decreased septal wall thickness relative to other segments of the cardiac wall, leading to an apparent relative decrease in counts per unit volume (an artefactual decrease in counts due to a partial-volume effect). However, we observed that in group 2 patients no improvement occurred in any LV regional wall motion score after CRT. Nevertheless, myocardial ^{99m}Tc -MIBI uptake increased significantly in the antero-septal, infero-septal, and inferior walls. In group 1 patients, we also observed that the wall motion score improved in the inferior wall but no significant change occurred in ^{99m}Tc -MIBI uptake in this region (Fig. 3).

The lack of use of attenuation correction in the images may also have been a limitation of this study. Therefore, the myocardial ^{99m}Tc -MIBI measurement could be underestimated, especially in the inferior wall, in the larger LV, and in the more obese patients. But we emphasize that we used the same measurement method before and after CRT and the patients' weight did not change significantly between before and after therapy. Therefore, the changes observed in ^{99m}Tc -MIBI myocardial uptake after CRT probably were not influenced by this factor.

Conclusion

LV volumes, regional ^{99m}Tc -MIBI uptake, and LV dyssynchrony phase analysis indices assessed by GMS may add information for the selection and follow-up of potential candidates for CRT. Our data show that the probability of an improvement in LVEF after CRT was higher in patients with lower EDV. Furthermore, because ^{99m}Tc -MIBI uptake depends on cellular perfusion and mitochondrial integrity, the monitoring of changes in myocardial ^{99m}Tc -MIBI uptake before and after CRT may improve our understanding of the importance of cellular derangement in defining the response to this therapy. Independently of LVEF increase, LV remodelling and dyssynchrony improvement, CRT promoted a significant increase in ^{99m}Tc -MIBI uptake in some LV myocardial regions. These favourable modifications may have been related to the clinical improvement observed in the majority of these patients.

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References

1. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J*. 2002; 143(3):398–405. [PubMed: 11868043]
2. Prinzen FW, Augustijn CH, Arts T, Alessie MA, Reneman RS. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. *Am J Physiol*. 1990; 259(2 Pt 2):H300–H308. [PubMed: 2386214]
3. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993; 87(6 Suppl):VI17–VI23. [PubMed: 8500235]
4. Nicod P, Gilpin E, Dittrich H, Chappuis F, Ahnve S, Engler R, et al. Influence on prognosis and morbidity of left ventricular ejection fraction with and without signs of left ventricular failure after acute myocardial infarction. *Am J Cardiol*. 1988; 61(15):1165–1171. [PubMed: 3376878]
5. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005; 26(11):1115–1140. [PubMed: 15901669]

6. Hunt SA. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol*. 2005; 46(6):e1–e82. [PubMed: 16168273]
7. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. MIRACLE Study Group. Multicenter Insync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002; 346:1845–1853. [PubMed: 12063368]
8. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, et al. Cardiac resynchronization and death from progressive heart failure – a meta-analysis of randomized controlled trials. *JAMA*. 2003; 289(6):730–740. [PubMed: 12585952]
9. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF study). *N Engl J Med*. 2005; 352:1539–1549. [PubMed: 15753115]
10. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation*. 2002; 105(4):438–445. [PubMed: 11815425]
11. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003; 107(15):1985–1990. [PubMed: 12668512]
12. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med*. 2004; 141:381–390. [PubMed: 15353430]
13. Nishijima Y, Sridhar A, Viatchenko-Karpinski S, Shaw C, Bonagura JD, Abraham WT. Chronic cardiac resynchronization therapy and reverse ventricular remodeling in a model of nonischemic cardiomyopathy. *Life Sci*. 2007; 81(14):1152–1159. [PubMed: 17884106]
14. Chakir K, Daya SK, Tunin RS, Helm RH, Byrne MJ, Dimaano VL. Reversal of global apoptosis and regional stress kinase activation by cardiac resynchronization. *Circulation*. 2008; 117(11):1369–1377. [PubMed: 18316490]
15. Nishioka SAD, Martinelli Filho M, Brandão SCS, Giorgi MC, Vieira MLC, Costa R, et al. Cardiac sympathetic activity pre- and post-resynchronization therapy evaluated by 123I-MIBG myocardial scintigraphy. *J Nucl Cardiol*. 2007; 14(6):852–859. [PubMed: 18022112]
16. Brandão SC, Giorgi MC, de Míche RT, Nishioka SD, Lopes RW, Izaki M, et al. Ventricular synchrony in patients with dilated cardiomyopathy and normal individuals: assessment by radionuclide ventriculography. *Arq Bras Cardiol*. 2007; 88:596–601. [PubMed: 17589637]
17. Brandao S, Cagnac R, Roncalli J, Lotterie JA, Elbaz M, Richez F, et al. Identification of viable myocardium in ischemic heart disease with severe left ventricular contractile dysfunction: comparison of myocardial scintigraphy with 99mTc-sestamibi and with 201-thallium. *Arch Mal Coeur Vaiss*. 2005; 98(6):620–627. [PubMed: 16007815]
18. Chiu ML, Kronauge JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2-methoxyisobutylisonitrile) technetium(I) in cultured mouse fibroblasts. *J Nucl Med*. 1990; 31(10):1646–1653. [PubMed: 2213187]
19. Van Train KF, Areeda J, Garcia EV, Cooke CD, Maddahi J, Kiat H, et al. Quantitative same-day rest-stress technetium-99m-sestamibi SPECT: definition and validation of stress normal limits and criteria for abnormality. *J Nucl Med*. 1993; 34(9):1494–1502. [PubMed: 8355069]
20. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med*. 1995; 36(11):2138–2147. [PubMed: 7472611]
21. Sharir T, Berman DS, Waechter PB, Areeda J, Kavanagh PB, Gerlach J, et al. Quantitative analysis of regional motion and thickening by gated myocardial perfusion SPECT: normal heterogeneity and criteria for abnormality. *J Nucl Med*. 2001; 42(11):1630–1638. [PubMed: 11696631]

22. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL, et al. Onset of left ventricular contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. *J Nucl Cardiol*. 2005; 6:687–695. [PubMed: 16344231]
23. Henneman MM, Chen J, Ypenburg C, Dibbets P, Bleeker GB, Boersma E, et al. Phase analysis of gated myocardial perfusion single-photon emission computed tomography compared with tissue Doppler imaging for the assessment of left ventricular dyssynchrony. *J Am Coll Cardiol*. 2007; 49:1708–1714. [PubMed: 17448373]
24. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on quantification of Two-Dimension Echocardiograms. *J Am Soc Echocardiogr*. 1989; 2:358–367. [PubMed: 2698218]
25. Lee TH, Hamilton MA, Stevenson LW, Moriguchi JD, Fonarow GC, Child JS, et al. Impact of left ventricular cavity size on survival in advanced heart failure. *Am J Cardiol*. 1993; 72(9):672–676. [PubMed: 8249843]
26. Sciagrà R, Giaccardi M, Porciani MC, Colella A, Michelucci A, Pieragnoli P, et al. Myocardial perfusion imaging using gated SPECT in heart failure patients undergoing cardiac resynchronization therapy. *J Nucl Med*. 2004; 45(2):164–168. [PubMed: 14960631]
27. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, et al. Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation*. 2001; 104(25):3026–3029. [PubMed: 11748094]
28. Lindner O, Vogt J, Kammeier A, Wielepp P, Holzinger J, Baller D, et al. Effect of cardiac resynchronization therapy on global and regional oxygen consumption and myocardial blood flow in patients with non-ischaemic and ischaemic cardiomyopathy. *Eur Heart J*. 2005; 26(1):70–76. [PubMed: 15615802]
29. Ukkonen H, Beanlands RS, Burwash IG, de Kemp RA, Nahmias C, Fallen E, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. *Circulation*. 2003; 107(1):28–31. [PubMed: 12515738]
30. Nowak B, Stellbrink C, Sinha AM, Kaiser HJ, Reinartz P, Koos R, et al. Effects of cardiac resynchronization therapy on myocardial blood flow measured by oxygen-15 water positron emission tomography in idiopathic-dilated cardiomyopathy and left bundle branch block. *Am J Cardiol*. 2004; 93(4):496–499. [PubMed: 14969635]
31. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol*. 2007; 14(2):215–220. [PubMed: 17386384]

Fig. 1. Segmental myocardial display for LV $^{99\text{m}}\text{Tc}$ -MIBI uptake and motion analysis in a 20-segment model

Fig. 2.
Effects of CRT on LVEF, LV EDV and ESV in group 1 (G1) and group 2 (G2)

Fig. 3. Schematic showing changes in regional myocardial ^{99m}Tc -MIBI uptake and wall motion score following CRT in the two groups

Fig. 4. GMS with ^{99m}Tc -MIBI images obtained before (a) and after (b) CRT in a patient of group 1. After CRT regional ^{99m}Tc -MIBI myocardial uptake shows an increase in the anterior and septal LV walls. The motion score (SMo) also shows an improvement after CRT, especially in the anterior and septal walls

Fig. 5. GMS with ^{99m}Tc -MIBI images obtained before (a) and after (b) CRT in a patient of group 2. After CRT regional ^{99m}Tc -MIBI myocardial uptake shows an increase in the septal and inferior LV walls. The motion score (SMo) does not show an improvement after therapy

Fig. 6. Receiver operating characteristic curve for the prediction of LVEF improvement after CRT. The receiver operating characteristic curve showed the greatest area under the curves for the LV EDV. The optimal cut-off point of the EDV was 315 ml (sensitivity 89%, specificity 92%)

Table 1

Baseline characteristics of the patients in each group before CRT

Variable	Group 1 (n=12)	Group 2 (n=18)	p value
Age (years)	62±9	57±12	NS
Weight (kg)	70.4±12.0	73.4±17.8	NS
Male, n (%)	4 (33%)	10 (56%)	NS
QRS (ms)	167±16	169±24	NS
Functional class, n (%) ^a			NS
III	11 (92)	17 (94)	
IV	1 (8)	1 (6)	
Medication, n (%)			
ACEI/ARB	12 (100)	18 (100)	NS
Beta-blockers	12 (100)	17 (94)	NS
Spironolactone	10 (83)	17 (94)	NS
Diuretics	12 (100)	18 (100)	NS
Digoxin	6 (50)	16 (89)	0.018

ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, NS not significant.

^aNew York Heart Association.

Table 2

Characteristics of group 1 and group 2 patients before and after CRT

Variable	Group 1		Group 2		p value
	Before CRT	After CRT	Before CRT	After CRT	
Weight (kg)	70.4±12.0	70.7±13.2	73.4±17.8	73.8±16.9	NS
QRS (ms)	167±16	131±14	169±24	156±22	0.012
Functional class, n (%) ^a					<0.001
I-II	0 (0)	12 (100)	0	11 (61)	
III-IV	12 (100)	0 (0)	18 (100)	7 (39)	
LVEF (%) ^b	22±4	35±7	21±3	21±3	NS
EDV (ml) ^c	276±94	183±87	477±168	456±161	NS
ESV (ml) ^c	220±85	129±82	401±154	395±160	NS

NS not significant.

^aNew York Heart Association.^bBy echocardiography.^cBy GMS.

Table 3

Semiquantitative LV regional wall motion evaluation by GMS with $^{99m}\text{Tc-MIBI}$ in the two groups before and after CRT

LV region	Group 1		Group 2		<i>p</i> value
	Before CRT	After CRT	Before CRT	After CRT	
Anterior	2.4±1.0	1.1±0.9	2.9±0.7	3.0±0.9	0.321
Anteroseptal	3.1±0.8	1.3±0.9	2.7±1.3	2.8±1.1	0.868
Inferoseptal	3.0±0.8	1.3±1.1	2.8±1.3	2.6±0.8	0.679
Inferior	2.6±1.2	1.7±1.0	3.3±0.6	3.0±0.9	0.148
Inferolateral	2.3±1.1	2.0±1.2	2.8±0.7	2.9±0.6	0.641
Anterolateral	2.2±1.0	2.1±1.2	2.6±0.7	3.0±0.7	0.042

^{99m}Tc-MIBI myocardial uptake in groups 1 and 2 as assessed by GMS in accordance with the improvement in LVEF after CRT. Group 1 showed an increase of ≥ 5 points by 2-D echocardiography; group 2 showed no significant change

Table 4

LV wall	Group 1			Group 2		
	Before CRT (%)	After CRT (%)	p value	Before CRT (%)	After CRT (%)	p value
Anterior	67 $\pm$ 7	72 $\pm$ 6	0.017	60 $\pm$ 10	61 $\pm$ 9	0.269
Anteroseptal	54 $\pm$ 5	61 $\pm$ 6	<0.001	55 $\pm$ 10	60 $\pm$ 10	0.001
Inferoseptal	57 $\pm$ 7	61 $\pm$ 8	0.047	55 $\pm$ 7	62 $\pm$ 7	<0.001
Inferior	59 $\pm$ 11	62 $\pm$ 10	0.193	48 $\pm$ 10	51 $\pm$ 12	0.044
Inferolateral	72 $\pm$ 7	68 $\pm$ 9	0.174	68 $\pm$ 9	68 $\pm$ 8	0.958
Anterolateral	78 $\pm$ 3	76 $\pm$ 6	0.185	77 $\pm$ 7	73 $\pm$ 7	0.003