

Synchronization Parameters and Perfusion Improvement after Cardiac Resynchronization Therapy

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Citation

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Abstract

To evaluate the modification of hemodynamic parameters and of synchrony using radionuclide angiography (RNA), as well as the effect on myocardial perfusion, 20 patients with dilated cardiomyopathy (DCM) were studied before and five months after cardiac resynchronization therapy (CRT). Inter- and intraventricular synchronization was assessed by phase analysis. After CRT, left ventricular ejection fraction improved from $22 \pm 5\%$ to $29 \pm 13\%$, $p=0.04$. There was a significant reduction of intraventricular asynchrony in ischemic patients. There was no difference between inter- and intraventricular asynchrony measured by RNA and echocardiography at baseline nor for the improvement after CRT. The summed rest score (SRS) decreased from 33 ± 14 to 21 ± 12 ($p=0.004$). SRS reduced from 35 ± 12 to 27 ± 9 (p NS) among ischemic patients, and from 31 ± 17 to 17 ± 11 ($p=0.02$) among non-ischemic. Radionuclide angiography is a useful method to assess heart failure patients before and after CRT. CRT improves myocardial perfusion mainly in non-ischemic patients.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has shown hemodynamic [1,2,3] and clinical [2,3,4,5] improvement, as well as a reduction of electrical asynchrony [6,7,8] in patients with dilated cardiomyopathy (DCM) and intra- and/or interventricular asynchrony.

Although mostly echocardiography (and especially tissue Doppler imaging) is used to assess the degree of intra- and interventricular asynchrony [9], other noninvasive techniques such as radionuclide angiography (RNA) and magnetic resonance tagging provide indirect information about cardiac conduction pathways through contractility parameters.

RNA allows not only global left ventricular function assessment with more reproducibility than echocardiography, but also the measurement of ventricular volumes and mitral regurgitation index. Furthermore, using phase analysis in RNA, a colour scale-coded image of the regional phase angles can be obtained as a map of sequential contraction, which is related to the depolarization wave. Therefore, cardiac conduction and synchronization parameters can also be evaluated by RNA [6,7,10].

Ischemic heart disease and old age have been found to be

significant predictors of a poor response to CRT [11]. Duncan et al demonstrated that patients with idiopathic DCM show significantly more extensive left ventricle (LV) remodelling than do those with ischemic DCM [3], and Sciagrà et al found that, despite clinical improvement, patients with severe resting perfusion defects do not show significant improvement in left ventricular ejection fraction (LVEF) or reduction in LV volumes [12]. The effect of CRT on oxygen consumption and myocardial blood flow has also been studied by PET [13,14], but the combination of data of function, synchronism and perfusion given by nuclear medicine studies could be a good approach for the evaluation of patients before and after CRT, an approach which has not been sufficiently exploited up to now.

Thus, the aim of this prospective study was to evaluate, by means of RNA, the modification of both hemodynamic parameters and synchrony due to CRT, comparing synchrony with echocardiographic data. A second aim was also to evaluate the effect of CRT on myocardial perfusion assessed by SPECT scintigraphy.

METHODS

STUDY POPULATION

Twenty consecutive patients (14 men and 6 women, mean age: 56 ± 11 years) with refractory heart failure (New York Heart Association –NYHA– class III or IV), depressed LVEF ($<35\%$), QRS width >120 ms, and substantial LV dyssynchrony were prospectively included for implantation of a CRT device. Eight of them (40%) had an ischemic DCM (five with a previous myocardial infarction), while the others were idiopathic. Etiology was considered ischemic in the presence of significant coronary artery disease (50% stenosis in one or more of the major epicardial coronary arteries) or a history of myocardial infarction.

The study design was approved by the Review Board of the Institute of Cardiology, and a written informed consent to participate was obtained from all patients before CRT. Patients were studied before (baseline) and on an average of 5.2 months after pacemaker implantation.

The clinical evaluation was performed by an independent cardiologist blinded to all other data. The functional evaluation included a NYHA class and six-minute walking distance [15]. In all cases, QRS duration was measured from the surface electrocardiogram (ECG) using the widest QRS complex from the leads DII, V1, and V6.

RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography was performed using the in vivo method of red blood cells labelling (2 ml Na-pyrophosphate IV; 400 mg K^+ perchlorate per os; 740 MBq of ^{99m}Tc IV). A gated blood-pool equilibrium RNA was acquired in the left anterior oblique projection, with an incidence between 30° and 60° (best septal visualization) and a 10° to 15° caudal tilt, with the patient lying supine. A single-head gamma camera (Siemens Orbiter), equipped with a low energy, all-purpose collimator was used. Twenty-four 64×64 ECG-gated frames per cardiac cycle were acquired with 10×10^6 counts, and a 10% rejection window was set around the average R-R interval. Images were normalized and filtered for space-time high-frequency noise.

Variable left ventricular regions of interest (ROI) were constructed with a semiautomatic edge detection algorithm in each time frame. Scintigrams were encoded for amplitude, setting background pixels below 25% of maximal amplitude to zero, which provided clearer ventricular edges for ROI detection [8]. After background subtraction, LVEF was calculated from the corresponding activity-time curves as: $EF = (\text{end diastolic counts} - \text{end systolic counts}) / (\text{end}$

diastolic counts - background counts). LVEF $>50\%$ was considered normal.

The LV peak filling rate was determined from the activity-time curve as the maximum positive of dV/dt and expressed as end-diastolic volume per second (EDV/s).

For assessment of mitral regurgitation, a two-factor analysis was applied (ventricles and atria plus great vessels) using the DiPaola algorithm [16] after which the regurgitation index (RI) was obtained with the following formula: $RI = \text{Left SV counts} / \text{Right SV counts}$ [17,18]. Values of 1.3 ± 0.8 were considered normal [17].

Phase analysis was performed using a software which performs an independent Fourier assessment [6,10] based on the fact that within the ventricular region, the phase angle of each pixel is proportional to the time of maximal activity change. A colour-coded image of the end-systolic phase angle is generated as a map of sequential contraction after computation of the Fourier transform. ROIs were constructed over LV, RV, LV septum (S), lateral (L), anterior (ANT) and inferior (INF) walls, as well as over base (B) and apex (A).

Interventricular activation time (T_{RV-LV}) was calculated from the difference between RV and LV phase peaks of the phase histogram, with a mean time resolution of ± 5 ms [6].

Intraventricular activation duration was computed from the distribution of phase angles within the LV ROI (T_{S-LW} and $T_{ANT-INF}$). LV and RV contraction onset (T_{0-LV} and T_{0-RV}), as well as S, L, ANT, INF, B and A contraction onset (T_{0-S} , T_{0-L} , T_{0-ANT} ,

T_{0-INF} , T_{0-B} , T_{0-A}) were also measured. Published normal values in milliseconds (ms) are: $T_{RV-LV} = 2 \pm 25$ ms; $T_{S-LW} = 4 \pm 22$ ms [10]; Apex to base delay (T_{A-B}): 2 ± 16 ms [6].

MYOCARDIAL SCINTIGRAPHY

A SPECT ^{99m}Tc -MIBI scintigraphy was performed at rest before (baseline), and three months after pacemaker implantation. Images were acquired 45 minutes to one hour after the intravenous injection of 740 MBq of ^{99m}Tc -MIBI, with a rotating dual-head gamma camera (Sopha SMV) equipped with a low-energy, high-resolution parallel-hole collimator centered on the 140 keV photopeak with a 20% window. Thirty-two projections (25 seconds per projection), with a 64×64 matrix were obtained over an 180 orbit. Filtered back-projection was then made with a low-resolution Butterworth filter with a cutoff frequency of 0.25

cycles per pixel, order 7. No attenuation or scatter correction was applied.

SCINTIGRAPHIC IMAGE INTERPRETATION

The semiquantitative visual interpretation of images employed short-axis and vertical long-axis tomograms divided into 17 segments for each patient [19]. Each segment was scored by the consensus of two expert independent observers who were unaware of the clinical and angiographic data, using a five-point scoring system (from 0 = normal to 4 = absence of myocardial uptake).

Disagreements in image interpretation, including every score in each SPECT segment, were resolved by consensus.

ECHOCARDIOGRAPHY

Echocardiographic analysis was done with high-resolution ultrasound equipment (Philips iE33 2006, version 2.0.1.420) with a S25-1 transducer (from 1.3 to 3.6 MHz). For Doppler Tisular Imaging (DTI), color Doppler frame rates varied between 150 and 400 frames/s depending on the sector width of the range of interest and aliasing velocities between 16 and 32cm/s. The digital cine-loops were analyzed using commercial software (Philips) by offline analysis. The sample volume was placed in basal portions of the septum, lateral, inferior, and anterior walls (using the apical four- and two-chamber images) to derive velocity profiles. Myocardial velocity curves were obtained, and regional systolic velocity (Sm) during ejection phase, early diastolic velocity (Em), as well as the time to peak Sm (Ts) and time to peak Em (Te) were measured. For the measurement of timing, the beginning of the QRS complex was used as the reference point. To assess LV synchronicity, SD of Ts (Ts-SD) and Te (Te-SD) of all the 12 segments were computed. The higher the values, the more severe the LV asynchrony. The cut-off value for asynchrony septum-lateral was 65 ms.

CRT IMPLANTATION

A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead in the coronary sinus, preferably in the lateral or postero-lateral vein. The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber ventricular ICD.

STATISTICAL ANALYSIS

For reasons of uniformity and the reduced number of patients studied, summary statistics for continuous variables obtained from the radionuclide angiography are presented as

medians. The other continuous variables were expressed as mean \pm 1 standard deviation. Each patient was his or her own control at follow-up. Continuous variables were analyzed using the Wilcoxon matched-pair test between baseline and follow-up, and data from ischemic and non-ischemic patients were analyzed by the Mann-Whitney U test. For comparison of asynchrony data obtained by RNA and echocardiography the McNemar test was used. A p value $<$ 0.05 was considered significant.

RESULTS

Patients' characteristics and clinical improvement after CRT

Implantation was successful and without complications in all patients. Due to potentially lethal ventricular arrhythmias, in eight patients (40%) the automatic implantable defibrillation function was also activated.

At baseline, 11 patients (55%) had a NYHA functional class III, and the other nine, a class IV. After a mean of 5.2 months of CRT, four patients improved by one NYHA functional class and 14 patients improved by two. No patients stayed in class IV. Ischemic patients improved more than non-ischemic: 88% achieved a NYHA class I, and only one showed a class II. On the contrary, among the non-ischemic patients, 54% attained a class II and one stayed in class III. Thirty-three percent of patients showed a six-minute walking distance $>$ 300 m at baseline, which in all cases increased after CRT.

Two patients (non-ischemic) died of worsening heart failure before the three-month follow-up evaluation. One patient (of ischemic etiology) died after the evaluation due to an infectious endocarditis on the pacemaker electrodes. At follow-up, QRS width decreased from 171 ± 34 ms to 116 ± 25 ms, and the PR interval also decreased from 179 ± 34 ms to 110 ± 24 ms ($p=0.0001$ in both cases). The mean LVEF at baseline was 22%.

VENTRICULAR FUNCTION

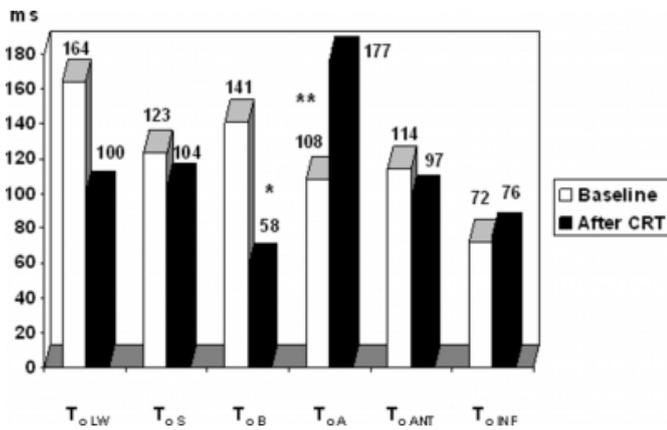
After CRT, there was a significant LVEF improvement (from $22 \pm 5\%$ to $30 \pm 13\%$, $p=0.04$). Diastolic function improved, but not significantly: from 1.39 ± 0.83 to 1.89 ± 0.93 End-Diastolic Volume / second (EDV/s). The regurgitation index showed an important reduction after CRT (from 2.2 ± 0.7 to 1.8 ± 0.5 , $p<0.03$). No significant difference was observed in the ventricular functional improvement according to the etiology of the DCM.

SYNCHRONIZATION PARAMETERS

Mean T_{0-LV} and T_{0-RV} decreased from 111 ms to 105 ms and from 67 ms to 59 ms (p NS), respectively. Regarding interventricular synchronism, mean T_{RV-LV} reduced from 76 to 54 ms, although it was non significant. Mean intraventricular asynchronism (T_{S-LW} and $T_{ANT-INF}$) reduced from 137 to 70 ms and from 67 to 49 ms, respectively. The onset of contraction in the different walls is shown in Figure 1. All walls except the apex and inferior wall started contraction earlier after CRT. In the case of apex – base contraction, CRT reversed the apex-to-base ventricular activation sequence, causing early contraction of the LV base followed by the apex.

Figure 1

Figure 1: Times of onset of contraction in the different walls. White bars represent baseline values and the black ones correspond to the values three months after CRT.



* $p = 0.0009$ ** $p = 0.01$

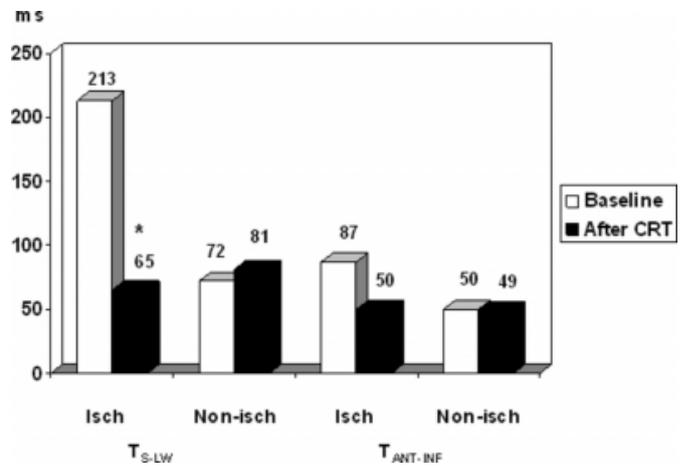
T_{0-S} : septal contraction onset; T_{0-LW} : lateral wall contraction onset; T_{0-B} : basal contraction onset; T_{0-A} : apex contraction onset; T_{0-ANT} : anterior contraction onset; T_{0-INF} : inferior contraction onset; CRT: cardiac resynchronization therapy

Inferior-to-anterior wall ventricular activation sequence was always in the right direction, but with a bigger delay at baseline, which reduced after CRT.

Figure 2 shows the evolution of ventricular asynchrony after CRT according to the etiology of the heart disease. Only in ischemic patients, the reduction of intraventricular dyssynchrony measured by the T_{S-LW} was significant ($p=0.02$). Regarding the intraventricular dyssynchrony measured by the $T_{ANT-INF}$, again the ischemic patients were those who experienced the biggest reduction, although non significant.

Figure 2

Figure 2: Intraventricular synchronism (septal-lateral wall and anterior-inferior). Comparison between ischemic and non-ischemic patients. White bars represent baseline values and the black ones correspond to the values three months after CRT.



* $p = 0.01$

T_{S-LW} : septal – lateral wall contraction time; $T_{ANT-INF}$: anterior – inferior contraction time; CRT: cardiac resynchronization therapy

RADIONUCLIDE ANGIOGRAPHY VS. ECHOCARDIOGRAPHY

There was no difference between inter- and intraventricular dyssynchrony measured by RNA and echocardiography at baseline, nor for the improvement after CRT (see Tables 1 and 2).

Figure 3

Table 1: Interventricular Dyssynchrony. Radionuclide angiography vs. Echocardiography

A) At Baseline

		Dyssynchrony by Echocardiography	
		YES	NO
Dyssynchrony by RNA	YES	16	1
	NO	1	0

A) Improvement Post CRT

		By Echocardiography	
		YES	NO
By RNA	YES	15	0
	NO	2	1

CRT: cardiac resynchronization therapy, RNA: radionuclide angiography

In both cases, p NS

Figure 4

Table 2: Intraventricular Dyssynchrony. Radionuclide angiography vs. Echocardiography

A) At Baseline

		Dyssynchrony by Echocardiography	
		YES	NO
Dyssynchrony by RNA	YES	16	1
	NO	0	1

A) Improvement Post CRT

		By Echocardiography	
		YES	NO
By RNA	YES	12	2
	NO	4	0

CRT: cardiac resynchronization therapy, RNA: radionuclide angiography

In both cases, p NS

MYOCARDIAL PERFUSION

Mean baseline summed rest score (SRS) was 33±14 and the mean number of affected segments per patient was 3. In the whole group of patients, myocardial perfusion significantly improved after CRT: the SRS decreased from 33±14 to 21±12 (p=0.004) and the mean number of affected segments was 2.

SRS reduced from 35±12 to 27±9 (p NS) among ischemic patients, and from 31±17 to 17±11 (p=0.02) among non-ischemic patients.

DISCUSSION

Phase analysis of gated cardiac blood pool is a useful and accepted method for the localization of the contraction (pacemaker) onset and the measurement of the magnitude and characterization of the sequence of regional contraction which reflects electrical conduction [20]. Compared with echocardiography, the technique is independent of the acoustic window and more reproducible. Furthermore, RNA can be applied in the presence of pacemakers, unlike nuclear magnetic resonance cardiac imaging and, as our results prove, constitutes a comparable method with echocardiography to assess the synchronization times both

for deciding whether to implant the biventricular pacing and for follow-up.

Kerwin et al [8] found that changes in LVEF with pacing exceeded the measured interobserver variability, suggesting that interventricular dyssynchrony was a correctable parameter contributing to LV dysfunction. In our cases the T_{RV-LV} , as a manifestation of interventricular dyssynchrony, reduced at five months after CRT, but the reduction was not significant, probably due to the small sample included.

Among our cases, the intraventricular dyssynchrony was present mainly between septal and lateral walls. But it was only in ischemic patients where the reduction of intraventricular dyssynchrony after CRT, measured by the T_{S-LW} , was significant. Inferior-to-anterior wall ventricular activation sequence was always in the right direction, but with a bigger delay at baseline, which reduced after CRT, and again the ischemic patients were those who experienced the biggest reduction, although non significant. We have not found any reference stating differences between synchronization times according to the etiology of the heart failure. Ours were not impressive and, evidently, more patients and further investigation are necessary. Nonetheless, this difference could account for the bigger improvement in clinical status among ischemic patients, taking into account that effective pumping by both ventricles requires this synchronous type of contraction.

Decreased diastolic time is one of the proposed mechanisms to explain cardiac abnormalities found in isolated LBBB [21]. Patients in our study showed a moderate peak filling rate reduction at baseline, which improved at follow-up after a mean of five months of CRT, becoming a minor abnormality.

Functional mitral regurgitation in DCM results from an imbalance between the closing and the tethering forces that act on the mitral valve leaflets [22]. Ventricular dilation and chamber sphericity increase the distance between the papillary muscles and the enlarged mitral annulus, restricting leaflet motion and increasing the force needed for effective mitral valve closure [22,23,24]. Breithardt et al [25] found that LV systolic function improvement after CRT causes an accelerated rise in the transmitral pressure gradient, which effectively counteracts the increased tethering forces that impair mitral valve competence. We considered that the reduction of the regurgitation index, as has been found before in heart failure patients after certain treatments (for example, postcardiomyoplasty) [18], has been the main factor

contributing to the functional improvement in our cases. Also, the reverse remodelling process that occurs chronically in these patients, which was present in 35% of our patients, contributes to a further decrease in functional mitral regurgitation severity [14,26]. This small number could be related to the fact that our patients had only a three-month follow-up, while in other studies the reverse remodelling has been evaluated at a longer interval of time (six months or more after CRT) [14,26].

Although the overall time necessary to activate all ventricular regions is not changed by the CRT, its regional effect on the septum, through less ventricular asynchrony [7], and its restitution of a coordinated base-apex activation [7], as we can see in this study, may also explain the systolic function improvement, mainly in the left ventricle. We did not find significant differences in systolic function improvement according to the etiology of the heart failure, as observed by other authors [27,28].

Echocardiography is mostly used nowadays to assess the intra- and interventricular dyssynchrony before and after CRT, providing useful and practical selection criteria for this therapy. However, it is important to point out that RNA is more reproducible, and offers comparable data. Besides, considering the new possibilities given by phase analysis using gated SPECT [29], which allows for the analysis of both functional and perfusion data with the same study, nuclear medicine techniques should be taken into account for assessment of patients before and after CRT.

It is important to point out that LBBB causes septal hypoperfusion and hypokinesia. Vernooy et al [30], in an experimental study, suggested that this septal hypoperfusion appears to be primarily determined by reduced septal workload. On the other hand, septal glucose metabolism is also reduced and seems to be improved by CRT without significant changes [31] or with only a mild influence on myocardial perfusion [37]. According to Neri [31], CRT not only improves myocardial wall function but could also induce normalization of the myocardial metabolism in the septum, suggesting a better use of glucose as a metabolic substrate without interfering with cellular membrane pumps observed in LBBB [33]. Therefore, resynchronisation of the septum contraction does require this increased energy consumption.

It has been suggested that CRT rebalances the loading conditions of the heart [13]. Knaapen et al have found that resting myocardial blood flow (MBF) is unaltered by CRT

despite an increase in LV function; however, the distribution pattern of resting MBF becomes more homogeneous [13]. There are two explanations for the improved myocardial perfusion. First, congestive heart failure is accompanied by increased LV filling pressure and wall stress, both of which may affect myocardial perfusion through extravascular compression of the coronary vascular bed [34], and which are reduced by CRT [35,36]. Second, myocardial perfusion is predominantly a diastolic process, and dyssynchrony of the heart reduces diastole by shortening the LV filling time [37], which can be increased by CRT. In general, we found a significant reduction of the SRS after CRT, but this difference was more important in non-ischemic patients: from 31 ± 17 to 17 ± 11 ($p=0.02$), compared with the ischemic, where the SRS only reduced from 35 ± 12 to 27 ± 9 (p NS). These results coincide with those of other studies [13,14]. Flow-limited stenoses and the presence of scar tissue in five cases may be responsible for these differences.

Recently, it has been demonstrated by using SPECT imaging with technetium-99m tetrofosmin [38] and by using 18F-FDG SPECT [39], that the extension of scar tissue and viable myocardium are directly related to the response to CRT, and that scar tissue in the LV pacing lead region may prohibit response to CRT. We did not perform viability studies in this group of patients, but the site of lead implantation was the posterolateral wall, where there was no infarction among our cases.

LIMITATIONS OF THE STUDY

1. A small number of patients were included.
2. Gated blood-pool SPECT was not used. Thus, the factor analysis was applied (as an alternative approach) to separate overlapping structures, in order to assess the regurgitation index.
3. A myocardial viability analysis was not performed before CRT implantation.

CONCLUSIONS

Radionuclide angiography is a useful method to assess heart failure patients before and after CRT. CRT improves myocardial perfusion mainly in non-ischemic patients.

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