Acute Modifications of Left Ventricular Torsional Mechanics Induced by Cardiac Resynchronization Therapy Affect Short-Term Reverse Remodeling

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Background: Left ventricular (LV) torsion is an important aspect of cardiac mechanics and is altered in heart failure patients. Cardiac resynchronization therapy (CRT) has a positive effect on LV function, but the exact mechanisms through which it works are not completely depicted. Our aim was to investigate (1) the acute CRT effect on LV torsional mechanics in heart failure patients using 3D speckle tracking echocardiography (3DSTE) and (2) its effect on short-term LV remodeling.

Methods and Results: We considered 48 patients (age 72±11 years, 35 men) who received CRT. They underwent 3DSTE during CRT-on (biventricular stimulation) vs. CRT-off (intrinsic conduction/right atrial/ventricular stimulation alone), in a random fashion. Patients were classified as CRT responders based on LV systolic volume reduction ≥15% at 6 months (final population: 31 responders, 17 non-responders). Acute CRT positively affected responders in terms of LV torsion (from 0.32±0.06°/cm CRT-off to 0.41±0.06°/cm CRT-on), but adversely affected non-responders (from 0.54±0.08°/cm CRT-off to 0.28±0.08°/cm CRT-on, interaction P=0.02). A similar trend was confirmed for apical (interaction P<0.04), but not for basal torsion (interaction P=0.351).

Conclusions: CRT has a positive role in acute recovery of LV torsion (particularly in its apical component) in responders, likely modulating the improvement in LV remodeling at early follow-up.

Key Words: 3-dimensional echocardiography; Cardiac resynchronization therapy; Systolic heart failure; Ventricular torsion

LEFT ventricular (LV) torsion is an important component of cardiac mechanics, both in systole and diastole (de-torsion phase).1 The helical myocardial fiber arrangement leads to opposing systolic rotation between the base and LV apex around its longitudinal axis.2,3 In particular, the base rotates clockwise and the apex counterclockwise, leading to a rotational gradient along the long axis that reflects a type of ventricular wringing directly contributing to LV systolic function.4,5 Potential energy is stored during the twisting phase and released in early diastole, thus facilitating the subsequent filling process.6,8 LV torsion is known to be impaired in heart failure (HF) patients,9,10 and in the past few years it has gained increasing interest for its possible role in predicting the response to cardiac resynchronization therapy (CRT).11 The short-term positive effect of CRT on LV function is, in fact, well established, but the exact mechanisms through which it works are not completely depicted.12,13 In this regard it is plausible that an improvement in CRT-induced torsion could be a potential contributor. Thus, this study’s purpose was to assess whether and to what extent the potential acute gain in LV torsion is affecting short-term LV remodeling in recently implanted CRT patients.

Methods
After appropriate informed consent, in agreement with institutional human review studies committee guidelines and local IRB approval, 77 consecutive HF patients scheduled for CRT were prospectively considered. All patients, who had received at least 3 months’ optimal medical therapy before device implantation, underwent CRT according to the NICE guidelines (QRS duration threshold ≥120ms in case of or >150ms in absence of left bundle branch block in minimally symptomatic patients).15 Ejection fraction (EF) had to be ≤35% at time of admission to the CRT clinic. Responders were defined as ≥15% LV end-systolic volume reduction at 6-month follow-up.16 Etiology of HF was considered ischemic in the presence of significant coronary artery disease (≥75% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or...
Full-volume datasets (mean volume sampling $35.4\pm 22.6$ frames/s) were analyzed with the integrated quantification software 4D Auto LVQ by manually selecting the apex and the mitral plane in both end-diastole and end-systole. The software automatically detects endocardial borders and a manual adjustment can be applied to follow the endocardial and epicardial limits throughout the cardiac cycle. The tracking algorithm is based on the identification of speckles within the 3DSTE volume and the detection of position changes in consecutive images. Distance between identified structures can then be calculated and parameters such as strain, rotation and torsion can be provided.

Briefly, the ventricle is divided by the software into basal level (mitral annulus), mid-level (across the papillary muscles) and apical level (placed beyond the implantation of the papillary muscles). Rotation is computed for each level and LV torsion is calculated by the software as the absolute apex-to-base difference in LV rotation, indexed for LV length. Further, regional torsion is calculated as the absolute difference in LV rotation between the most apical and most basal rings of the corresponding segment, indexed for the length of that segment, as explained by the following equations:

- **Global torsion** = (rotation of the apex – rotation of the base)/LV length
- **Apical torsion** = (rotation of the most apical ring of the apical segment – rotation of the most basal ring of the apical segment)/length of the apical segment
- **Basal torsion** = (rotation of the most apical ring of the basal segment – rotation of the most basal ring of the basal segment)/length of the basal segment

**Echocardiographic Measurements**

Standard and 3D (3DSTE) echocardiographic examinations were performed in all patients using a Vivid E9 digital ultrasound system equipped with 4V-D probe (GE Medical Systems, Horten, Norway). After optimization of the atrioventricular interval, we acquired, in a random fashion, 2 series of datasets: (1) during CRT-on (i.e., biventricular stimulation) and (2) during CRT-off (i.e., during spontaneous rhythm in those patients with adequate intrinsic rhythm or during right atrial stimulation in those with preserved atrioventricular conduction but insufficient sinus activity or, finally, during right ventricular stimulation in pacemaker-dependent patients). For each dataset we obtained transmural and LV outflow tract pulsed Doppler flow velocities, triplane volumetric acquisitions (gray-scale, color and tissue color Doppler) and a pyramidal 3DSTE full-volume dataset acquired from the apex using a 3V transducer. Full-volume datasets were recorded over 6 beats, with a frame rate $\geq 20$ frame/s and during breath-holding. In the only non-pacemaker-dependent patient in atrial fibrillation (AF), with irregular RR intervals at CRT-off, datasets were recorded over 2 beats, trying to avoid stitching artifacts. Biventricular stimulation at CRT-on and right ventricular stimulation during CRT-off in pacemaker-dependent patients assured the presence of regular RR intervals in all the remaining cases of AF. Cardiac cycles were stored in digital, cineloop format for off-line analysis performed with a dedicated software package (EchoPac PC, v. 201, GE Healthcare, WI, USA).
Optimized Lead Position Identification

Using the same data set, a 3DSTE circumferential strain tracking technique was also performed and integrated as the last step in the “ventricular quantification tool”, which includes volume and mass measurements. The meshes so created were re-used for the LV 3DSTE circumferential strains computation generated for individual segments (n=17) obtained from 3 short-axis slices (apical, mid- and basal level). For the purposes of this study apical strains (5 segments) were excluded from the final analysis, while strains in the circumferential orientation (6 segments each) were computed, with time from QRS to maximal segmental deformation quantified and the corresponding lastly activated segment identified at the basal or midventricular level slice using custom software.

Optimized LV lead placement was then searched for and defined, post-implant, as concordance of the ventricular segment with the latest circumferential systolic strain prior to CRT and the segment with assumed LV lead position, irrespective of basal or midventricular location. Assumed LV lead position was defined from 2 orthogonal chest X-ray views (anteroposterior and lateral) obtained the day after CRT implantation. LV lead position was scored as anterior, lateral, posterior or inferior at the basal or midventricular level. Detailed analysis of the myocardial contraction sequence using strain imaging to assess if the

Results can be exported in .csv extension (comma separated values) and analyzed with MS Excel spreadsheet (Microsoft Corp., WA, USA).

It has to be said that, over time, different definitions of LV torsion have been given in the literature, so there is a risk of misinterpreting the related studies. The terminology we used conformed to the definitions described in the ASE/EAE Consensus Statement.17 Thus, the term “rotation” refers to rotation around the LV long axis and is expressed in degrees. The absolute apex-to-base difference in LV rotation is referred to as the “net LV twist angle” (also expressed in degrees). The term “torsion” refers to the base-to-apex gradient in the rotation angle along the LV long axis, expressed in degrees per centimeter.

Through a dedicated Visual Basic macro we computed the systolic global and regional (basal and apical) peak torsion values (Figure 1). We also measured the torsion delay index (TDI), which was defined as the sum of the differences between peak and end-systolic regional torsion across 16 segments, such as the strain delay index. The TDI is considered to represent the amount of rotational energy lost by dyssynchrony.18 Finally, LV torsion curves were filtered by polynomial interpolation and analytically derived to measure the untwisting rate (UTR) value and recoil rate (i.e., the slope of the linear regression of recoil (i.e., untwisting) vs. time in early diastole).18
Receiver-operating curves (ROC) were used to assess the capacity of a given measurement to assess the presence/absence of the LV remodeling response at follow-up. Interobserver variability, expressed as absolute mean difference ± the percentage coefficient of variation (SD/mean), was assessed by analyzing 3D volumes, LV torsion, TDI and UTR during CRT-off/on using the same clips for 16 patients randomly chosen by a 2nd investigator on a different occasion. LV torsion variability was also calculated by averaging differences between 2 readings and displaying them as an absolute difference divided by the average of 2 observations. Analyses were performed using Sigmaplot v.12.5 (Systat Software, CA, USA) statistical software.

Results

From the initial 77 patients, we excluded 8 who were lost at 6-month follow-up (unable to be classified as responders or non-responders) and 21 whose torsion curves were not obtainable because of poor imaging quality. The final study population thus comprised 48 subjects: 31 responders and 17 non-responders. Their baseline clinical characteristics are summarized in Table 1. AF was present in 23% of the population.

Echocardiographic characteristics obtained in each group during CRT-on/off are summarized in Table 2 and Table 3. The LV and apical torsional behaviors differed significantly site of latest mechanical activation, as assessed in the short-axis echocardiographic views, is coincident with LV lead position, determined radiographically, has been reported to result in greater improvement in LV function after CRT than a non-optimal position.20,21

Statistical Analysis

Data are expressed as mean±standard deviation or mean±standard error where explicitly defined. Differences between mean values were assessed using t-tests for paired data. Signed-rank tests (Mann-Whitney test) were used when data were not normally distributed. Data normality was assessed using the Shapiro-Wilk test. Differences in percentages were assessed using the Fisher exact test or the chi-square test. Regression analysis (least-squares method) was used as necessary.

A two-way analysis of variance (2-ANOVA) was used to look for any interaction of LV volume and EF, LV filling characteristics, TDI, torsion and UTR vs. CRT-off/on by using the attribution to responder vs. non-responder group as a between-patient factor. Concordance or discordance of the ventricular segment with assumed lead position with the segment with the latest circumferential peak strain prior to CRT at the basal or midventricular level was also used as a further between-patient factor in a three-way analysis of variance (3-ANOVA). In the case of missing values, results were computed using a general linear model.
between the 2 groups, given that they both improved in responders during CRT-on and worsened in non-responders (interaction $P=0.020$ and $P=0.038$, respectively, Figure 2, Table 2). The same trend was observed for basal torsion, but it did not reach statistical significance (interaction $P=0.351$, Figure 2, Table 2). TDI showed an overall significant improvement with CRT-on ($P=0.001$, Table 2), not different, however, between responders and non-responders (interaction $P=0.204$, Table 2). UTR values did not change (interaction $P=0.877$, Table 2).

There were no LV volume differences during the experiment, although responders had LV cavities that were significantly smaller as compared with non-responders (Table 3). However, even when corrected for diastolic volumes at CRT-off according to a general linear model, the difference in LV torsion at CRT-on between responders and non-responders persisted as significant (+0.10±5.56°/cm vs. −0.25±4.12°/cm, $P=0.005$). Stroke volumes and EF did not behave differently in the 2 groups (Table 3).

We did not find any significant differences as far as E, DT and the E/DT ratio (an index of diastolic function) were concerned (Table 3). Only the A wave averaged higher and the E' later in responders ($P=0.029$ and $P=0.004$, respectively, Table 3), but the interaction was not significant ($P=0.943$ and $P=0.174$, respectively, Table 3). Similarly, the interaction was insignificant for E/E' ($P=0.253$, Table 3), in contrast with what has been observed in previous studies and with what we had expected. However, changes in the recoil rate, measured from the LV torsion curves (obtainable in 15/48 patients, at both steps, as the slope of a significant linear regression line fitted over 60 ms [minimum of 3 time points, average 6±4] immediately after peak torsion) linearly correlated with changes in LV torsion between CRT-on and CRT-off ($r=0.59$, $P=0.02$, Figure 3). This finding suggested that, in our study population, acute improvement in torsion during CRT-on could likely modulate some improvement in the relaxation phase as well.

Concordance Between Late Systolic Contraction, Assumed Lead Position and LV Torsion Response

Overall, in 33% of the population (n=16) the inferoposterior region was the site of latest mechanical activation, whereas this was true for the anterolateral wall in 60% of the patients (n=29); 3 patients could not be assigned because of overriding distribution. In the group of “concordant” patients (n=12), responders (n=9) demonstrated a significant increase in LV torsion at CRT-on as compared with non-responders (interaction $P=0.047$, Figure 4). In the “discordant” subjects (n=33) group torsion decreased in non-responders (n=12) at CRT-on as compared with responders, but the difference did not reach statistical significance (interaction $P=0.082$, Figure 4).
Torsion and CRT

ROC curve analysis demonstrated that an improvement in LV torsion >0.035°/cm during CRT-on had good specificity (83%), although poor sensitivity (64%), in identifying concordance vs. discordance between late systolic contraction segment and assumed lead position (ROC curve area 0.76, P=0.008). On the other hand, the exact same increment in torsion during CRT-on demonstrated high sensitivity (88%), but limited specificity (68%), in predicting reverse remodeling at 6-month follow-up (ROC curve area 0.80, P=0.0005).

Reproducibility
Mean absolute difference (±% coefficient of variation) between 2 measurements of LV volumes (performed 7

months apart by a 2nd operator) averaged 3.3 mL±1.0%, 2.6 mL±1.3% and 3.1 mL±1.1% for diastolic, systolic and stroke volume, respectively. Equivalent values for TDI and UTR were 1.11°/cm±1.06% and 1.79°/cm/s±0.88%. For LV torsion, values were 0.25°/cm±0.89%. For basal and apical torsion the values were 0.84°/cm±20.20% and 0.61°/cm±5.47%, respectively. Furthermore, the correlation coefficient between the 2 measurements was 0.53 for LV torsion (P<0.01), 0.37 for basal (P<0.05) and 0.73 (P<0.001) for apical torsion, respectively. Plots of the average between 2 readings against their difference demonstrated no over- or underestimation at either the basal or apical level, but the data dispersion was larger for torsion at the basal as compared with the apical level (Figure 5).
**Discussion**

To our knowledge, this is the first study to use 3DSTE echocardiography for an analysis of torsional mechanics in CRT patients, to compare differences obtainable in an acute setting between biventricular vs. intrinsic conduction and their influences on reverse remodeling in a short-term follow-up.

Previous studies mainly focused on analyzing LV twist with 2D speckle tracking echocardiography.\(^{24-26}\) This technique is limited because it considers only the basal and apical planes. Indeed, short-axis acquisitions must be obtained with cut-planes perpendicular to the LV long axis and they should contain the true LV apex. Unfortunately, oblique planes, together with out-of-plane motion, can highly influence LV twist assessment.\(^{27}\)

The newer 3DSTE technique evaluates the full volume of the LV, assuring a more accurate analysis and precisely identifying the correct cut-planes and the true apex, while looking at different planes during the same heartbeat.\(^{28}\) It enables computation of not only the twisting motion, but also the true LV torsion, allowing a direct comparison between hearts of different dimensions and providing a complete picture of LV rotational mechanics. Unfortunately, because of its dependency on acoustic window quality, 3DSTE is not obtainable in all patients, but it has an acceptable feasibility (78% in our study, calculated as 108 analyzable out of 138 acquired datasets in 69 patients). Image acquisition times are relatively short (=30 s), even if presently 3DSTE is limited by the considerable time devoted to post-processing and, and, as such, is not amenable to everyday use in clinical practice. However, this limitation will be easily overcome with the implementation of machine-integrated software.

According to our data, CRT seems to have a beneficial role in the acute recovery of LV torsion in responder patients, whereas in non-responders we observed a worsening of torsion during biventricular stimulation. In particular, this trend seems to be related, in responders, to an improvement in the apical component (Figure 2), although we did not find any significant difference for basal torsion between the 2 groups of patients. Previous studies have demonstrated that the apical component is the main determinant of LV torsion.\(^{29,30}\) A loss of function in the true apex, with a consequent reduction in LV torsion, strongly influences LV remodeling after an acute myocardial infarction.\(^{31}\)

**Torsion in Reduced Ejection Fraction Heart Failure (HFrEF) Patients**

Various authors have observed that in some HF patients the basal and apical rotations follow the same direction, resulting in a loss of opposite rotation.\(^{9,32}\) This phenomenon is called “rigid body rotation” and can be found in up to 60% of HFrEF patients. An interesting nuclear magnetic study conducted in 34 CRT patients found that rigid body rotation was related to the acute hemodynamic response during biventricular stimulation and was a highly sensitive and specific predictor of an acute response,\(^{33}\) while being associated with LV reverse remodeling at long-term follow-up.

What we found in the acute setting, switching from CRT-off to CRT-on, indicated that patients who acutely recruit a higher reserve of torsion are those who will get more benefit, in the near future, in terms of LV reverse remodeling. LV torsion modifies acutely and its changes can be observed earlier than congruent variations in LV volumes, which take place later in the disease course. In our study population, in fact, we did not find any statistically significant interaction at 2-ANOVA regarding ventricular volumes and EF with CRT-on/off, although we could demonstrate some linear relationship (r=0.20, P=0.05) between apical torsion and LV stroke volume after the latter had been corrected for end-diastolic volume according to a general linear model.\(^{34}\)

We hypothesize that increased LV torsion during ejection could be an expression of higher potential energy that results, during the relaxation phase, in improved suction forces. This hypothesis, already considered by our group in a previous study focused on CRT effects on diastolic function,\(^{35}\) was tested in the present study where we analyzed the CRT-off/on variations in untwisting and filling parameters, with results, however, that did not reach any significant conclusion. It must be noted, however, that UTR is a time-derived value from torsion. Thus, it is not unexpected that such a parameter did not change during CRT-off/on, given the relatively low frame rate of the 3DSTE technique used for the study. In any case, the discrepancy with what was expected could also have been partially related to the small sample size and should be re-evaluated in further studies with a larger patient population.

Another potential explanation, however, might be gained from the results of a study performed by Dong et al in 2001.\(^{18}\) They analyzed 10 dogs at baseline and after dobutamine, saline, esmolol, and methoxamine treatments, obtaining an invasive measurement of the relaxation time constant (r) and a nuclear magnetic quantification of the recoil rate (i.e., the slope of the linear regression of recoil (untwisting) vs. time in early diastole). Those authors showed that the recoil rate was inversely and significantly correlated with r, better than echocardiographic parameters such as the isovolumetric relaxation time, concluding that such measurement could be viewed as a non-invasive preload-independent assessment of LV relaxation.\(^{18}\) The significant positive correlation obtainable between variations in the recoil rate and torsion at CRT-off/on in our patients (Figure 3) suggested that the acute LV torsion improvement detected with CRT-on in our study could be associated with some improvement in the LV relaxation phase as well.

**Torsion, TDI and Site of Stimulation**

Another interesting aspect to this study is the relation between torsional regional mechanics and the degree of dysynchrony of dysfunctional ventricles. Retracing Lee et al’s study,\(^{10}\) we analyzed the TDI and its variations in our population with CRT-off/on. Unfortunately, we did not find any significant interaction for this parameter between the 2 patients’ groups, although we could detect an overall significant reduction in dysynchrony with CRT-on as compared with CRT-off (P=0.001, Table 2). Furthermore, we were able to demonstrate that patients with concordance between the site of latest mechanical activation and presumed LV lead position did respond better, in terms of LV torsion at post-implantation CRT-on, as compared with “discordant” patients (Figure 4). These findings reinforce the concept that CRT is beneficial for the dyssynchronous ventricle but, most importantly, that the LV lead should be placed in the area of greatest delay in electrical activation and mechanical contraction, in order to achieve optimal
torsional effects.\textsuperscript{25,36}

**Study Limitations**

The main limitation of our study is the small sample size. This can be overcome by persevering in data collection, given that such a limit is partially related to the dependency of 3DSTE on acoustic window quality, which forced us to exclude a non-negligible proportion of subjects.

LV volumes were smaller in responders at the time of the experiment. This discrepancy might be related to some random difference in the time interval between CRT implantation and test execution between the 2 groups (78 [16–124] days in responders vs. 54 [25–125] days in non-responders, P=0.77). However, as reported above, changes in torsion obtained from activation of CRT persisted significantly, even after correction for immediately pre-test LV diastolic volumes.

Another limitation to be taken into account is the lack of prognostic clinical data at follow-up. Even if mean persistency significantly, even after correction for immediately mediated by an associated acute improvement in LV relaxation, is particularly evident in those patients who exhibit LV reverse remodeling. This effect, which could be partly part of the earliest positive effects of CRT on LV mechanics, hypothesize that acute recovery in torsion in responders is the main limitation of our study is the small sample size.

Our study demonstrated that CRT had a positive role in acute LV torsion recovery in responder patients, likely modulating subsequent improvement in LV systolic performance at early follow-up. At the opposite end, non-responder patients showed an average worsening of LV torsion during biventricular stimulation. We can thus hypothesize that acute recovery in torsion in responders is part of the earliest positive effects of CRT on LV mechanics, which subsequently can result, at 6-month follow-up, in LV reverse remodeling. This effect, which could be partly mediated by an associated acute improvement in LV relaxation, is particularly evident in those patients who exhibit concordance between the site of latest mechanical activation and presumed LV lead position at the time of implantation.

**Conclusions**

Our study demonstrated that CRT had a positive role in acute LV torsion recovery in responder patients, likely modulating subsequent improvement in LV systolic performance at early follow-up. At the opposite end, non-responder patients showed an average worsening of LV torsion during biventricular stimulation. We can thus hypothesize that acute recovery in torsion in responders is part of the earliest positive effects of CRT on LV mechanics, which subsequently can result, at 6-month follow-up, in LV reverse remodeling. This effect, which could be partly mediated by an associated acute improvement in LV relaxation, is particularly evident in those patients who exhibit concordance between the site of latest mechanical activation and presumed LV lead position at the time of implantation.

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