Role of cardiac resynchronization therapy in the development of new-onset atrial fibrillation: A single-center prospective study.

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Albeit several studies examined the association between cardiac resynchronization therapy (CRT) and atrial fibrillation (AF) in heart failure (HF), results are still unclear and quite conflicting. We thereby designed a single-center prospective study to determine whether CRT has a favorable effect on the incidence of new-onset AF in a homogeneous population of patients with non-ischemic idiopathic dilated cardiomyopathy and severe heart failure HF. We enrolled 58 patients, AF naïve when received CRT. After 1 year of follow-up our population was subdivided into responders (72.4%) and non (27.6%), so to compare the incidence of AF after 1, 2 and 3 years of follow-up in these two groups. Already after 1 year, there is a significant ($p<0.05$) difference in new-onset AF in non-responder patients respect to responders (18.2% vs 3.3%). These data are confirmed at 2 year (33.3% vs 12.2%) and 3 year (50.0% vs 15.0%) follow-up. In particular, at 3 year follow-up, non-responders have an increased risk to develop new-onset AF (OR=5.67, 95% confidence interval = 1.36-23.59, $p=0.019$). The present work suggests a possible favorable role of this non-pharmacological therapy, on the prevention of AF.

Keywords Cardiac resynchronization therapy, Atrial fibrillation, Dilated cardiomyopathy, Heart failure, Pacing

Introduction

Several studies have showed the hemodynamic and functional improvement obtained with cardiac resynchronization therapy (CRT) in patients with advanced heart failure (HF) and ventricular conduction delay.(Anand *et al.*, 2009; Cleland *et al.*, 2009; Mullens *et al.*, 2009; Yancy *et al.*, 2009) Nevertheless, despite the positive effects of CRT on hemodynamic, functional status, and mortality in HF, approximately 30% of patients do not respond to this therapy, emphasizing the need for better selection criteria.(Anand *et al.*, 2009; Cleland *et al.*, 2009)

Furthermore, the primary cardiac cause of exacerbation of HF is atrial fibrillation (AF), that is also an independent risk factor for sudden death.(Capucci, 2009) HF and AF often coexist;(Adelstein *et al.*, 2007) both are responsible for increased mortality, more frequent hospitalizations, reduced exercise capacity, and decreased quality-of-life (QoL). Besides, AF and HF are believed to directly predispose to each other.(Larned *et al.*, 2009) In particular, in the setting of advanced HF, 30% to 40% of patients will develop AF during the course of the disease.(Stevenson *et al.*, 1999) So, if CRT influences the occurrence of AF, this might influence patient selection and possibly programming of the device.(Hsia, 2006)

The aims of the present study were: to identify pre-implantation characteristics that best can predict which patients will benefit the most from biventricular pacing, in order to make out suitable candidates for CRT;(Bax *et al.*, 2009) to compare the incidence of new-onset AF(Adelstein *et al.*, 2007) after 1, 2 and 3 years of follow-up in responder and non-responder patients, so to assess a possible favorable role of CRT, through means of an atrial reverse remodeling, on the prevention of this arrhythmia.

Methods

All patients with non-ischemic idiopathic dilated cardiomyopathy had New York Heart Association (NYHA) functional class III or IV symptoms (D'Ascia *et al.*, 2006; Vardas *et al.*, 2007) for at least six months before enrollment, despite optimal pharmacological treatment (including β blockers, loop diuretics,

vasodilators, nitrate, digitalis, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and spironolactone when tolerated), left ventricular ejection fraction (LVEF) ≤ 35%, and QRS duration ≥ 150 ms measured on at least 3 leads on the surface ECG. Exclusion criteria were: recent (previous 3 months) acute coronary syndrome or planned coronary revascularization, previous pacemaker or implantable cardioverter defibrillator (ICD) implantation, requirement of continuous intravenous therapy, a life expectancy of <1 year due to non- cardiac diseases, pre-existent AF, patients whose major echocardiographic parameters could not be obtained cause of poor image quality, systolic blood pressure >170 or <80, heart rate >140, and kidney failure with serum creatinine levels >250 μmol/L.(Vardas *et al.*, 2007)

Detailed clinical and instrumental data (ECG, echocardiogram, QoL evaluation, 6-min walk test, cardiopulmonary exercise test) were collected, with scheduled visits, before implantation and at the 1-, 2- and 3-year follow-up. The detection of AF relied on electrocardiography, 24h Holter examination and strips from continuous telemetric control of implanted devices.(D'Ascia *et al.*, 2009) AF was defined as an episode, with or without symptoms, lasting at least 10 minutes,(Fung *et al.*, 2005; Glotzer *et al.*, 2003) similar to a large sub-study of the CARE-HF trial reported by Hoppe et al.(Hoppe *et al.*, 2006) Patients were also assessed for HF symptoms (NYHA functional class). QoL was evaluated by the Minnesota Living with HF questionnaire (scores range from 0 to 105, with higher scores reflecting a poorer QoL),(Rector *et al.*, 1992) while the 6-min walk test was carried out according to Bittner's recommendations.(Bittner, 1997) Study nurses who had no knowledge of the patients' treatment administered the 6-min walk distance and QoL tests. Coronary angiography was performed prior to implantation in all patients, also to exclude causes of HF amenable to surgery or intervention. This study protocol was designed in compliance with the Helsinki declaration and approved by the local Ethics Committee. Written informed consent was obtained from each participant.

Non-responders were defined after 12 months of follow-up as patients with at least one of the following characteristics: deteriorating function (HF-related death, need for heart transplantation), increase in LVEF ≤ 4 absolute percentage points, worsening in peak oxygen consumption, in QoL score or in the distance walked in 6 min, as previously described.(St John Sutton *et al.*, 2003)

ICD implantation and optimization: Patients were implanted with a biventricular ICD (Contak Renewal 1 or 2, Guidant Inc.). All procedures were performed under local anesthesia. Three transvenous leads were inserted, through the left subclavian vein. The atrial lead was placed in the high right atrium; the right ventricular lead was positioned, in the apex or in the high interventricular septum, as far as possible from the LV lead; LV pacing was obtained after coronary sinus (CS) angiography, advancing a bipolar lead into the lateral or posterolateral cardiac vein. The final lead position was chosen on the basis of visual inspection, assessed by anteroposterior and lateral chest radiography.(D'Ascia *et al.*, 2006; Leon *et al.*, 2005) The atrioventricular interval (electrical delay between atrial and ventricular excitation) was optimized by Doppler echocardiography 1 day after implantation to reach maximal transmitral diastolic filling and maximal biventricular capture,(Jansen *et al.*, 2007) and checked every year. Patients in which transvenous LV lead implantation was acutely unsuccessful (n=5), due to several causes [failure to cannulate the CS (n=2), high threshold to chronic pacing (n=1), CS dissection (n=1) and impossibility to obtain a stable lead placement(n=1)] were obviously excluded from the study.

Echocardiographic evaluation: A trans-thoracic, two-dimensional echocardiogram was serially performed in all patients using a Sonos 5500 ultrasound system (Philips), equipped with a 2.5-MHz transducer. The examination included two-dimensional, M-mode and Doppler data. All recordings were made, as previously described, with the patient in the lateral recumbent position, according to the American Society of Echocardiography recommendations.(Bax *et al.*, 2009) The following parameters were measured using the different axis: LV end-diastolic and end-systolic diameters, LVEF (biplane LV end-systolic and end-diastolic volumes were calculated from apical views according to the modified Simpson's rule), LV end-systolic volume index, left atrial diastolic and systolic areas, amount of mitral regurgitation (calculated as the area of the color-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimeters). All echocardiographic studies were performed and analyzed by the same study-independent physicians, blinded to the study protocol and to the patients' status. Echocardiographic measurements were systematically averaged in five consecutive samples.

Cardiopulmonary exercise test: Symptom-limited cardiopulmonary exercise testing (Treadmills 'Rammill Series', Morgan Italia, Bologna, Italy) was performed, conducted on an upright bicycle ergometer with a 10-W/min step protocol, starting with 2 min of unloaded cycling. Measurements of oxygen consumption (VO_2), were taken at rest and during exercise using a moving average of eight breaths. During each stage of exercise, data on heart rate and rhythm and BP were collected. All patients were encouraged to exercise until they felt unable to continue because of dyspnoea and/or fatigue. The ventilatory threshold was measured by the V-slope method.(Beaver *et al.*, 1986) The maximum VO_2 was defined as the highest VO_2 value measured (peak VO_2).

Statistical analysis: Unless otherwise specified, data are presented as the mean value ± SD or absolute numbers with percentages for categorical variables, unless otherwise specified. Data normality was evaluated through the Kolmogorov-Smirnov test. Comparison of quantitative variables was performed using the Student's t-test for paired and unpaired data when appropriate, with a Bonferroni correction when multiple comparisons were made. Dichotomous or categorical data were assessed with the χ^2 test or Fisher's exact test. The non-normally distributed data within patient groups were compared using the nonparametric Wilcoxon test.(Santulli *et al.*, 2009a; Santulli *et al.*, 2012d) Odds ratios were given with the 95% confidence interval (CI). Differences in event rates (AF, death) over time were calculated according to the Kaplan-Meier method and analyzed with the use of Cox proportional hazard models. To identify predictors of lack of response to CRT, we performed a multivariable Cox regression, using a forward-step model, validated using an 'n-1' strategy. All tests that we performed were two-tailed and a p value <0.05 was considered statistically significant. All statistical tests were performed with the SPSS 16 statistical package (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5.01 (GraphPad software, San Diego, CA, USA).

Results

Baseline characteristics of the patients are reported in Supplementary Table 1. The mean age was 62.5±11.1 years; there was a male predominance (63.8%), with a mean LVEF of 27.57±5.6%. Drug therapy for HF did not change significantly over the follow-up period, and all patients had stable biventricular stimulation.

After 1 year, 42 patients (72.4%) were considered responders to CRT according to the previously defined criteria. There were 16 non-responders (27.6%), with 4 HF-related hospitalizations. Two patients died before the 2-year follow-up visit (1 responder and 1 non); four patients died before the 3-year follow-up visit (1 responder and 3 non).

Our most interesting finding is that, already after 1 year, there is a significant difference in new-onset AF in non-responder patients (18.2%) vs responders (3.3%). These data are confirmed at 2 year (33.3% vs 12.2%) and 3 year (50.0% vs 15.0) follow-up. In particular, at 3 year follow-up, non-responders have a markedly increased risk to develop new-onset AF (odds ratio = 5.67, 95% CI = 1.36-23.59, p=0.019). Thus, this disparity in risk persisted throughout the 3 year follow-up period.

As regards the other purpose of our study, that is the identification of the pre-implantation parameters useful to select responder and non-responder patients, multivariate analysis identified independent predictive factors for non-responder patients. As already shown in previous studies,(Leclercq *et al.*, 2008; Yu *et al.*, 2005) neither age, electrical parameters, NYHA class, nor LVEF appear useful in predicting a response to pacing. Interestingly, we noticed the importance of LV end-diastolic diameter (73.2±9.1 mm in non-responder patients vs 68.1±7.1 mm in responders; $p<0.05$) and the degree of mitral regurgitation (0.28±0.02 in non-responders vs 0.20±0.02 in responders; $p<0.05$).

Moreover, as shown in Supplementary Table 2, there was a favorable improvement of clinical status in the group of CRT responders, evidenced already at 1 year follow-up, and corroborated after 2 and 3 years. Specifically, we evidenced the positive effects of CRT in NYHA functional class, LVEF, reduction of mitral regurgitation, 6-min walk test, Minnesota Living With HF QoL score, oxygen uptake at peak exercise and at anaerobic threshold.

Discussion

The loss of coordination of ventricular contraction contributes to the pathophysiology of HF, reducing the already diminished contractile reserve of the heart.(Kass, 2008) Specifically, dyssynchronous contraction exacerbates inefficient use of energy by the heart (mechano-energetic uncoupling). Indeed, the left lateral wall is activated well after the septum contracts.(Sade *et al.*, 2008) This leads to contraction of the lateral wall during relaxation of the septum resulting in marked mechanical dysfunction. The dyssynchronous failing heart exhibits also deep alterations in protein expression, (Santulli *et al.*, 2011a; Santulli *et al.*, 2009b; Vanderheyden *et al.*, 2009) such as changes in local calcium handling, as exemplified by a strong decrease of phospholamban in the delayed activated myocardium.(Spragg *et al.*, 2003) The purpose of CRT is to restore ventricular relaxation and contraction sequences by simultaneously pacing both ventricles. Numerous studies have reported positive long-term effects in terms of symptoms, exercise tolerance, QoL and HF prognosis after CRT,(Gasparini *et al.*, 2008; Jansen *et al.*, 2007; Leclercq *et al.*, 2008) and our work confirms these findings. A prospective study examining the relation between CRT and AF using as control a HF population that doesn't receive CRT would be neither ethical nor practical, given the proven efficacy of this therapy in treating HF. So, we decide to compare a homogeneous (Lanni *et al.*, 2007; Santulli *et al.*, 2011b) population of CRT recipients, then subdivided in responders and non. One of the most pressing unresolved questions, however, remained how to identify the patients that will not respond to CRT, and how to define response is really central to the entire question,(Bax *et al.*, 2009; Yu *et al.*, 2005) since there is relatively poor correlation between the various measures of CRT response. Thus, as mentioned in methods, we used clear and reproducible criteria for the definition of non-responder patients, also to avoid any case of misinterpretation.

We recruited only patients with non-ischemic dilated cardiomyopathy. In fact, albeit CRT is an effective alternative therapy in patients with dilated heart disease whether of ischemic or non-ischemic origin, the response tends to be slightly lower when the heart disease is ischemic, maybe due to the presence of necrotic tissue. This is the first study that focalizes on this topic, assuring a homogeneous study population. Indeed, heterogeneity may explain controversial results concerning this issue emerged in literature.

Another chief issue to discuss in analyzing the occurrence of AF is how the same AF is detected. We defined AF as an episode, with or without symptoms, lasting 10 minutes or more, identified by electrocardiography, Holter examination and using the continuous monitoring capability offered by implanted devices, that were programmed uniformly to capture AF episodes.(Bottoni *et al.*, 2004; Fuster *et al.*, 2001; Toff *et al.*, 2005) Other studies have used a variety of different definitions for AF, also relied on symptoms, which appear clearly inadequate in assessing overall AF burden.

Despite the extensive evidence of the benefits of CRT on ventricular function, the data about the effects of CRT on atrial function and on the incidence of new-onset AF are conflicting.(Cleland *et al.*, 2009; Fung *et al.*, 2005; Hoppe *et al.*, 2006; Santulli *et al.*, 2012a; Santulli *et al.*, 2012b; Santulli *et al.*, 2012c) The potential mechanisms to take into account for the effect attributed to CRT in the prevention of AF could be related to an improvement in left ventricular systolic function and a decrease of the degree of mitral regurgitation, with a reduction of structural atrial remodeling of the electrophysiological substrate responsible for the initiation/triggers of atrial arrhythmias.(Wijffels *et al.*, 1997) Indeed, the fact that after 3 year follow-up non-responder patients show an increased left atrial diastolic area than responders is a strong evidence for supporting the hypothesis that CRT may prevent AF through atrial reverse remodeling,(Wijffels *et al.*, 1997) probably due to a reduction of the overload in the atria.(Sade *et al.*, 2008) Anyway, atrial function is relatively complex, and more quantitative methods are needed to better explore atrial functional improvement. Moreover, because patients with HF who develop AF have a worse outcome,(Adelstein *et al.*, 2007; Capucci, 2009; Larned *et al.*, 2009; Santulli, 2012a; Santulli, 2012b) it could be interesting to know whether CRT might improve outcome. However, this is only a pilot study, with a small number of subjects, albeit they constitute a remarkable patient population, because of selective inclusion and exclusion criteria. So, the results must be interpreted cautiously, and further studies, pooling data from multiple centers, are needed to confirm our findings and to assess their real clinical impact.

Conclusions

Our study shows that, after a follow-up of 3 years, in CRT non-responder patients there is a significant increased risk to develop new-onset AF. Moreover, we identified two echocardiographic parameters as predictors of lack of response to CRT: the LV end-diastolic diameter and the degree of mitral regurgitation. All these data can be useful in the selection and management of patients with HF.

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