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The Impact of Cardiac Resynchronization Therapy on the Frequency of Ventricular Arrhythmias

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Abstract

Background: Cardiac resynchronization therapy (CRT) has a proven role in improving mortality in patients with heart failure and ventricular dyssynchrony. However, the effects of biventricular pacing (CRT) on ventricular arrhythmia susceptibility have not been definitely established, and data regarding the risk of ventricular arrhythmias (VA) with CRT has been limited and conflicting.The aim of this study was to compare the burden of VA in the short term before and after an upgrade to a cardiac resynchronization device in order to avoid the long term effects of myocardial remodeling.

Methods: We analyzed 44 consecutive patients with severe LV systolic dysfunction who underwent an upgrade from a single chamber defibrillator to biventricular defibrillator due to worsening heart failure status.

Results: CRT was associated with a decrease in VA in patients with high arrhythmic burden, in women and in patients older than 65.

Conclusion: In this study we provide convincing evidence that in patients with identical electrophysiological substrate, biventricular pacing alone is associated with a decrease in VA burden.

Keywords: Cardiac resynchronization therapy; Ventricular arrhythmias; Myocardial remodeling

Abbreviations: ATP: Antitachycardia Pacing; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter Defibrillator; LV: Left Ventricular; LVEDD: Left Ventricular End Diastolic Diameter; NYHA: New York Heart Association; VA: Ventricular Arrhythmia; VT: Ventricular Tachycardia

Introduction

Cardiac Resynchronization Therapy (CRT) has emerged as a highly effective treatment modality for patients with systolic heart failure and prolonged QRS duration. Meta-analysis has shown that CRT, in addition to optimal medical therapy, reduces mortality in patients with heart failure [1], improves symptoms, exercise tolerance and decreases hospital admissions [2]. However, the effect of CRT on arrhythmia susceptibility has not been definitively established and data regarding the risk of ventricular arrhythmias (VA) with CRT has been limited and conflicting. Case reports have provided anecdotal evidence of CRT precipitating ventricular tachycardia [3,4]; moreover the presence of scarred myocardium has been associated with an increased risk of arrhythmia in CRT [5,6]. Multiple mechanisms have been proposed for this phenomenon. Epicardial pacing results in a reversal of the normal physiologic myocardial activation sequence, which prolongs the QT interval and produces a substrate and the trigger for reentrant arrhythmias in both canine and human subjects [5,7]. The CRT non-responders also experience an increase in ventricular arrhythmia burden [8]. On the other hand,CRT has been shown to reduce the incidence VA, likely by virtue of the reverse remodeling of the myocardium [9,10].

Therefore, the aim of this study was to ascertain the true electrophysiologic effects of CRT on the burden of the VA by comparing frequency of the VA in the short term before and after an upgrade to a cardiac resynchronization therapy in order to avoid the long-term effects of myocardial remodeling.

Methods

We analyzed retrospectively 44-consecutive patients with severe left ventricular (LV) systolic dysfunction who underwent an upgrade from a single chamber defibrillator to biventricular defibrillator in our institution due to worsening heart failure status in the presence of left bundle branch block and with a QRS duration greater than 120 ms. Patients who were implanted for secondary prevention of sudden cardiac death and patients with hereditary arrhythmias were excluded from this analysis. Nearly all left ventricular leads were implanted percutaneously. Lead position was identified through the review of fluoroscopy in left anterior and right anterior oblique projections. Lead position was also identified through the review of posterior-anterior and lateral chest radiograms by an independent reviewer.

Baseline demographic variables, indices of LV size and function, symptomatic status, and pharmacologic therapy were collected from

retrospective chart review. Arrhythmia frequency and characteristics 6 months before and 6 months after an upgrade were determined by the review of routine and unscheduled device interrogation data. Echocardiographic measurements were performed mostly with Phillips Epic ultrasound system. All measurements were done in accordance with ASE guidelines [11].

Classification of events:

All episodes were reviewed by 2 independent electrophysiologists. If disagreement was found, the event was classified by a consensus. Ventricular tachycardia was identified by a rate greater than 170 bpm, regularity of rate and the following:evidence of V-A dissociation and a local electrogram morphology different from baseline. If 1:1 A:V relationship was present, V-V changes had to drive A-A changes. Ventricular fibrillation was identified by rate greater than 210 bpm and disorganized ventricular electrograms. Only the six months preceding and following an upgrade were studied. In that time frame, all ventricular events, which included those that were non-sustained or that required either ATP or shock therapy, were used for analysis.

Statistical analysis

Arrhythmic burden was measured as the sum of ventricular episodes. All data were checked for normalcy. Related samples: Wilcoxon signed rank test was used to compare the differences in cumulative ventricular events in pre-CRT vs. post CRT groups. The Kruskal-Wallis test was used to investigate whether LV lead positioning or polarity was associated with increased or decreased frequency of ventricular arrhythmias. SPSS software was used for statistical analysis. A p-value of <0.05 was considered significant. The study protocol was reviewed and approved by the SUNY Downstate Institutional Review Board.

Results

Baseline characteristics

Demographic and clinical characteristics of the patient cohort are noted in Table 1. Over two-thirds of the patients were males older than 65 years of age. Half of the patients had an ischemic etiology of heart failure and most were in NYHA functional class III at the time of the upgrade. The mean ejection fraction ± SD was 24.6 ± 8.9 and the mean QRS duration was 146.1 ± 25.4 ms. None of the patients had AV nodal conduction disease. The distribution of LV lead location and pacing configurations are shown in Table 2. The post CRT upgrade relation of QRS duration, echocardiographic and device parameters are shown in Table 3.

Clinical and Demographic Features	**Number of patients=25 (Mean ± SD or n (%))**
Age (years)	64.9 ± 11.4
Gender	
Male	20 (80%)
Female	5 (20%)
Race	
White	1 (4%)
Black	23 (92%)
Other/unknown	1 (4%)
Etiology	
Ischemic	17 (68%)
Non-ischemic	8 (32%)
NYHA class	
I	0
II	2 (8%)
III	21 (84%)
IV	2 (8%)
QRS duration prior to implant (ms)	146.3 ± 19.5
LVEF prior to Implant (%)	22.5 ± 7.2
LV pacing (%)	98.2 ± 2.2
Medications	
Beta blockers	24 (96%)
ACEI/ARBS	24 (96%)
Amiodarone	2 (8%)

Table 1: Clinical and demographic characteristics of the cohort

	N (%)
LV Lead placement	
Anterolateral	7 (24%)
Lateral	11 (44%)
Posterolateral	7 (28%)
LV Lead configuration	
True bipolar	18 (72%)
Integrated bipolar	7 (28%)

Table 2: CRT LV Lead placement and configuration

	QRS narrowing	**QRS widening**	**P**
QRS duration (ms)	138.0 ± 11.9	168.1 ± 20.4	0.001
LVEF (%)	31.4 ± 16.2	29.8 ± 12.4	0.93
LVEDD (cm)	6.8 ± 1.0	6.5 ± 1.3	0.52
LVESD (cm)	5.8 ± 1.4	5.5 ± 1.6	0.6
LV sensing (mV)	10.0 ± 6	14.1 ± 7.5	0.08

Table 3: Post CRT upgrade relation of QRS duration, echocardiographic and device parameters

Ventricular events

The mean (SD) cumulative ventricular events in the entire cohort before and after CRT implantation were 7.4 ± 21.6 and 5.6 ± 11.6 episodes per patient p=0.52. When individual change in the number of events (ΔVA) in each patient was analyzed in relation to the frequency of pre-upgrade events, it was shown that patients with the highest number of pre-upgrade events had the biggest reduction in VT events (Figure 1) $p \leq 0.01$. Post CRT upgrade females, compared to males, had significant reduction in ΔVA -5.0 ± 15.2 *vs.* -0.56 ± 25.1, respectively, p=0.043. Similarly, older patients >65 had greater reduction in events that those under 65 -4.24 ± 0.54 *vs.* -3.0 ± 0.71, respectively, p=0.029. Neither the LV lead position,the pacing polarity, baseline LV size, heart failure class, nor voltage sensed by the LV lead had a significant impact on the ΔVA in the short term after CRT implantation (p=ns, all) (Table 2).

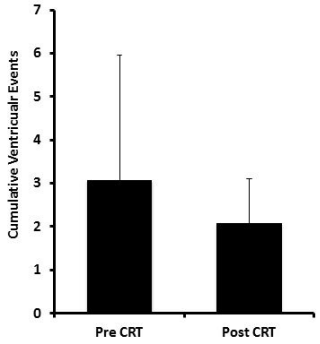

Figure 1: Cumulative burden of ventricular events pre *vs.* post CRT upgrade (3.1 ± 14.4 and 2.1 ± 5.2; p=0.53 Wilcoxon signed rank test).

Discussion

In this study, we have demonstrated that patients with high burden of VA, those that are older than 65 and females experience reduction in VA as a result of resynchronization therapy.

CRT has emerged as a vital method for improving overall outcomes in the management of patients with mild to severe heart failure and ventricular dyssynchrony, as CRT has been shown to improve morbidity and mortality in these patients [1,2,12]. A decrease [9,10] or no change [13] in the burden of ventricular arrhythmias has been reported with cardiac resynchronization, but these studies looked at long term changes and are affected by the reverse remodeling of the myocardium. An improvement in the burden of the VA appears to be most pronounced in CRT responders, which suggests that reverse remodeling may have a pivotal role in this process [8,10]. Therefore, the pure electrophysiologic effect of CRT therapy can only be reliably assessed before significant reverse remodeling occurs [13]. Our study suggests that the reported decrease in VA burden occurs early after the initiation of CRT and is maintained in the long term [10]. To our knowledge, this is the first study that shows that CRT benefits the elderly and those with a preexisting VA burden.

At the very fundamental level, the presence of myocardial scar and viable tissue creates milieu for ventricular arrhythmia by allowing non-homogenous spread of depolarization wavefront and the creation of reentry [6,14-17]. At the same time, one could construe that under correct circumstances colliding wavefronts of depolarization resulting from CRT may also extinguish the reentry. Diminishing of intraventricular conduction delay, and prevention of pause-dependent tachyarrhythmias, as seen with CRT, may contribute to this phenomenon as well [18]. All these effects could be dependent on LV location [19] and proximity to the scar [5]. Neither the LV lead position, the pacing polarity nor LV lead sensed voltage (a surrogate of scar proximity) affected the change in VA in our population.

It is well established that female patients derive more benefit from CRT with respect to mortality and heart failure hospitalization [20]. Meta-analysis of CRT trials also showed a decrease in VA burden in females in long-term observations [21]. Our study shows that this effect may be independent of reverse remodeling and is present early after the initiation of CRT. Many factors have been proposed to explain gender differences in response to CRT, including smaller LV mass and a higher prevalence of non-ischemic etiology of cardiomyopathy in females but these factors would hardly explain the findings in our study, as these are seen only after LV remodeling [22-25]. On the other hand, greater electrical dyssynchrony and conduction disturbance seen in women may enhance response to CRT, even in the early stages of therapy by virtue of restoring electrical synchrony.

Both ICD and CRT therapy have a well-documented effectiveness in older patients with respect to both mortality and symptom improvement [26-29]. Our data suggest that these patients experience the benefit of reduction of VA as well.

Our population is comprised of predominantly African American patients, but we do not believe that the racial differences are responsible for our observation as Black patients derive at least similar benefit from cardiac resynchronization as the Caucasians [30]. On the other hand, subgroup analysis of African Americans enrolled in some but not all ICD trials suggest no mortality benefits of defibrillation therapy [31-33].

We acknowledge that our study is observational in nature and is hindered by small sample size. Also, our patients are predominantly male and of African American ancestry, which can potentially affect the applicability of our study results to the general population.

Conclusions

In conclusion, in this study we provide initial evidence that in patients with similar electrophysiological substrate, CRT reduces VA burden, particularly in patients with preexisting VA, women and those older than 65.

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