

Proarrhythmic versus antiarrhythmic mechanisms of cardiac resynchronization therapy

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Introduction

Cardiac resynchronization therapy (CRT) has recently become an established therapy for patients with NYHA class III/IV systolic heart failure and prolonged QRS duration [1]. In addition to improvement in exercise capacity, NYHA symptoms class, and quality of life, evidence of the arrest or reversal of ventricular remodeling has been demonstrated [2]. A recent meta-analysis found that CRT reduces mortality from progressive heart failure and suggested a trend toward longer survival in patients treated with CRT [3]. Total mortality was also reduced in two recent trials, one of which included CRT in combination with defibrillation therapy, while the other did not [4, 5].

Although a delayed or halted progression of cardiac dysfunction may be sufficient to prevent malignant ventricular tachyarrhythmias, there is still lingering uncertainty regarding the presence and magnitude of antiarrhythmic effects of CRT *per se*. Furthermore, there is experimental as well as anecdotal clinical evidence that left ventricular pacing may have proarrhythmic potential. The present review examines the available experimental and clinical evidence of potential proarrhythmic effects of CRT and the proposed electrophysiological mechanisms. Similarly, the evidence for antiarrhythmic effects of CRT will be reviewed. A potential proarrhythmic effect of CRT in a subgroup of patients is an issue of considerable importance in view of the current controversy regarding the need of ICD backup in a majority of, if not in all

patients receiving CRT. The arguments for [6] and against [7] this position seem to reflect, in part, differing points of views on each side of the Atlantic ocean.

Evidence for a proarrhythmic effect of left ventricular pacing

Experimental evidence

Medina-Ravell et al were the first to point out that the common design for CRT, i.e. simultaneous pacing of the right ventricular endocardium and left ventricular epicardium, is associated with a non-physiological ventricular activation sequence [8]. This may augment transmural heterogeneity of repolarization intrinsic to ventricular myocardium and, as a consequence, prolong the QT and JT intervals on the ECG. The cellular mechanisms underlying the pacing site-dependent alterations in ventricular repolarization were studied in an experimental model consisting of an arterially perfused rabbit left ventricular (LV) wedge preparation in which transmembrane action potentials from endocardium and epicardium could be simultaneously recorded together with a transmural ECG. In the experimental preparation, transmural dispersion of repolarization (TDR) was defined as the difference between the longest and shortest repolarization times across the LV wall. The authors showed that switching from endocardial to epicardial pacing resulted in a change of activation sequence between epicardium and endocardium, which was associated with an increase in QT interval and TDR without a parallel increase in endocardial and epicardial transmembrane action potential duration (APD).

A more recent study examined the cellular basis for QT prolongation after reversal of the direction of activation of the LV wall [9]. Based on previous investigations documenting the contribution of M cells to TDR, this study postulated that

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Received: 29.08.2006

Accepted: 31.08.2006

delayed activation and repolarization of M cells, coupled with earlier activation and repolarization of epicardial cells, may result in QT prolongation, development of transmural heterogeneity, and torsade de pointes after a shift from endocardial to epicardial activation of the LV wall in the absence and presence of rapidly activating delayed rectifier potassium current (I_{Kr}) blockade. This hypothesis was tested in a 1-dimensional mathematical model of transmural conduction as well as in the coronary-perfused canine LV wedge preparation. The results of the mathematical simulation and the experimental data confirmed that intrinsic heterogeneity exists within the ventricular myocardium and that this electrical heterogeneity is amplified when the normal direction of activation of the ventricular wall is reversed. Epicardial activation augments TDR because the epicardial action potential activates and repolarizes earlier and the M cells with the longest APD located in the deep subendocardium activate and repolarize later compared with endocardial activation of the ventricular wall. The additional conduction delay encountered between epicardial and M regions during epicardial stimulation contributes to the amplification of TDR. The delayed activation and repolarization of the M cells, when coupled with earlier activation and repolarization of epicardial cells, creates the substrate for the development of reentry.

In another experimental study, the role of voltage output, interventricular delay, and pacing sites in the development of ventricular arrhythmias were investigated during biventricular pacing or LV pacing [10]. Voltage-sensitive dye was used in ischemic Langerdorff-perfused guinea pig hearts to measure ventricular activation times and examine conduction patterns during multisite pacing from three right ventricular (RV) and four LV sites. Isochronal maps of RV and LV activation were plotted. Ischemia was produced by gradually halving the perfusion output. Pacing the RV apex and the base of the LV anterior wall was associated with the most homogeneous and rapid activation pattern and no inducible arrhythmia. On the other hand, simultaneous RV and LV pacing at high voltage output induced ventricular fibrillation with complex three-dimensional propagation patterns, independent of the pacing sites.

Clinical evidence

In an early report by Medina-Ravell et al. [8], the QT interval, JT interval, and TDR were measured in 29 patients with heart failure during RV endocardial pacing, biventricular pacing, and LV epicardial pacing. LV epicardial pacing and biven-

tricular pacing led to significant QT and JT prolongation. LV epicardial pacing also enhanced TDR, defined as the interval between the peak and the end of the T wave ($T_{\text{peak-end}}$). Frequent R-on-T extrasystoles generated by biventricular and LV pacing but completely inhibited by RV pacing occurred in 4 patients, of whom one patient developed multiple episodes of nonsustained polymorphic ventricular tachyarrhythmia (VT) and another suffered incessant Torsade de Pointes (TdP) VT. These data suggested that, in a subpopulation of patients with prolonged QT interval, secondary to heart failure, electrolyte abnormalities, or exposure to agents with class III antiarrhythmic actions, a biventricular or LV epicardial pacing induced increase in QT interval and TDR may be a potential risk for the development of TdP. Several case reports subsequently followed that showed the *de novo* development and/or increase of VT after CRT [11, 12]. A recent case report from our laboratory is typical of these reports [13]. The development of polymorphic VT following CRT seems to occur in the early post-operative period. There is no data to suggest that this early proarrhythmic effect persists or can be mitigated during long term follow up. Experimental studies suggest that change in transmural activation can result in remodeling of cardiac repolarization [14, 15]. Whether prolonged CRT results in electrical remodeling that improves the underlying ventricular dispersion of repolarization in a particular patient requires further investigation.

Evidence for an antiarrhythmic effect of cardiac resynchronization therapy

Experimental evidence

There are very few experimental studies that examined direct antiarrhythmic effects of CRT. Restivo et al. [16] published one of the early experimental studies that demonstrated a direct antiarrhythmic effect of carefully applied dual site ventricular stimulation in the canine post-infarction model. In this model, a one stage ligation of the left anterior descending artery results in an anteroseptal infarction with a surviving electrophysiologically abnormal epicardial layer. A figure of eight reentrant ventricular tachycardia could be induced by programmed premature stimulation. Refractoriness in the surviving epicardial layer is distributed as eccentrically layered contours that increase monotonically toward the core of the infarction. A premature stimulus would result in an arc of functional conduction block at sites of dispersion of repolarization, usually at the border of the ischemic zone.

Subsequent reentrant activation is dependent on both the extent of the arc of functional block and the degree of conduction delay of the circulating wave front before refractoriness expires at sites proximal to arc allowing re-excitation to take place. The spatial distribution of refractoriness on the heart could be modified by a dual site ventricular stimulation during the basic rhythm. In the study, one pacing site was the RV outflow tract while the second site was the ischemic LV zone. Properly sequenced stimulation at the two sites could modify the spatial distribution of refractoriness in a way that prevented the induction of reentry. Prevention of reentry was the result of several factors, but primarily due to reduction and/or modification of the extent of the arc of functional conduction block. Biventricular pacing with asynchronous premature stimulation at the ischemic site with prolonged refractoriness in comparison to the RV site could “peel back” refractoriness in the ischemic zone and abolish entirely the arc of block.

Clinical evidence

In the last few years several clinical reports have strongly suggested that cardiac structural and contractile reverse remodeling following CRT could also result in a favorable antiarrhythmic effect. These clinical reports could be grouped in two main categories: A) favorable changes in the overall incidence of spontaneous VT, and B) amelioration of the arrhythmogenic substrates associated with reduced systolic function and heart failure.

A. Favorable changes in the overall incidence of VT. A comprehensive analysis of the combined InSync-ICD and Contact-CD population found that CRT was associated with no measurable increase in the incidence of polymorphic VT or reduction in monomorphic VT [17]. However, other reports showed evidence that the incidence of malignant VT is reduced following CRT. These reports relied on the decrease in appropriate ICD therapy in patients with CRT as evidence of an antiarrhythmic effect [18, 19]. There is also anecdotal evidence that electrical storm may be suppressed by ICD [20, 21]. On the other hand, a surrogate marker of the antiarrhythmic effect of CRT could be invoked from studies that analyzed the changes in the inducibility of VT following CRT [22–24]. In one study, the induction of VT was reduced in patients with significant LV reverse remodeling after 6 months of implanting a CRT device [24]. There was a striking difference between patients with loss of inducibility and patient who remained inducible. Patient with loss of inducibility had a significant reduction

in LV end-diastolic and end-systolic volumes compared to patients who remained inducible. The antiarrhythmic effect was attributed to reduced LV wall stress and its consequent effect on LV structure.

B. Amelioration of the arrhythmogenic substrates. The arrhythmogenic substrates in patients with depressed LV systolic function and heart failure include dispersion of repolarization, altered neurohumoral signaling, alteration in calcium homeostasis, altered conduction, myocardial ischemia, and genetic predisposition [25]. There is clinical evidence that, at least, the first two substrates are ameliorated following successful CRT with evidence of reversible remodeling.

1) Improvement of dispersion of repolarization: Using high-resolution surface electrocardiogram (ECG), Berger et al showed that biventricular pacing was associated with a significant reduction of ECG markers of ventricular dispersion of repolarization including interlead QT dispersion, RMS $T_{\text{peak-end}}$ interval, T_{peak} -amplitude, and the area (integral) of the $T_{\text{peak-end}}$ curve [26]. In another ECG simulation study, repolarization indices associated with CRT were found to be related to pacing-induced activation sequence rather than TDR [27]. TDR during biventricular and LV epicardial pacing was not larger than TDR during conventional RV endocardial pacing.

A positive microvolt T-wave alternans (TWA) is considered an indirect marker of increased dispersion of repolarization as well as a strong independent predictor of malignant VT and sudden cardiac death [28]. In a preliminary study by Turitto et al. [29], the prevalence of TWA during different pacing modalities was investigated in a group of patients who received CRT. TWA was recorded, during atrial pacing (AAI) at a rate of 110/min, as well as during DDD-RV pacing and DDD-biventricular pacing at the same rate and with short atrioventricular delay, in order to obtain ventricular capture. Criteria for positive TWA were: alternans > 1 min with Valt (square root of alternans power) $> 1.9 \mu\text{v}$ and alternans ratio (ratio of alternans to standard deviation of background noise) > 3 in ≥ 1 orthogonal lead or ≥ 2 precordial leads. In this study, AAI and RV pacing resulted into a high prevalence of tachycardia-induced TWA, while BiV pacing was associated with amelioration of all TWA indices.

2) Amelioration of abnormal neurohumoral signaling: There is plethora of clinical reports showing that CRT induces favorable neurohumoral changes. This has been shown utilizing direct recordings of sympathetic nerve activity [30], or

indirect indices of sympathetic activity like ^{132}I -MBIG uptake, which is used as an index of neural norepinephrine reuptake and retention [31]. There is also data showing decrease in brain natriuretic peptide (BNP) levels which is used as an index of LV end-diastolic pressure [31]. Favorable changes in heart rate profile and heart rate variability (HRV) have also been shown following CRT and are used as surrogate markers of the sympathetic-parasympathetic interaction to the heart [32–34]. In one study, patients with sub-optimal LV lead position associated with no significant functional and structural improvement had no change, or even worsening, of HRV [34]. Lack of HRV improvement four weeks after CRT identified patients at high risk for major cardiovascular events [34]. Another surrogate marker of the autonomic nervous system is baroreceptor sensitivity. A recent case report showed that CRT could significantly improve this particular index [35].

Conclusions

Available evidence supports the hypothesis that CRT results into favorable structural as well as electrical remodeling. The latter seems to be related, to a large extent, to the amelioration of the arrhythmogenic substrates associated with depressed LV systolic function and heart failure. However, a direct electrophysiological effect due to favorable remodeling of repolarization with reduction of the dispersion of repolarization can not be ruled out. On the other hand, in a small subgroup of patient, CRT could increase the dispersion of repolarization and induce malignant VT. There is a current debate of whether an ICD backup is indicated in a majority of, if not all, patient with CRT. Because some patients may receive a CRT-pacemaker rather than a CRT-defibrillator, it is imperative that criteria for the selection of this group of patients with presumably low risk for sudden arrhythmic death as well as the proarrhythmic effect of CRT be clearly defined.

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