Potential pro-arrhythmic effect of cardiac resynchronization therapy

Osama Tayeh a,⇑, Waleed Farouk a, Abdo ElAzab a, Hassan Khald a, Antonio Curnis b

a Critical Care Department, Faculty of Medicine, Cairo University b Cardiothoracic Department, Spedali Civili, Brescia University

a Egypt, b Italy

A decline in mortality due to pump failure has been clearly documented after cardiac resynchronization therapy (CRT), however the impact on sudden cardiac death and the development of malignant ventricular arrhythmias remains questionable. Our study aims to investigate this alleged pro-arrhythmic effect of CRT using surface electrocardiogram (ECG) markers of pro-arrhythmia.

Methods: Seventy five patients, who received CRT were included in this study. Manual measurement of corrected QT interval (QTc), T peak-end (T_{pe}) interval, QT dispersion (QTd) and T peak-end dispersion during baseline 12 lead surface ECG and after applying atrial-biventricular pacing were done. Arrhythmias post CRT was recorded from ECG, 24 h holter monitoring or pacemaker programmer event recorder.

Results: QTc interval showed significant prolongation after CRT (498.9 ± 50.8 vs. 476.2 ± 41.6 msec, P = 0.0001). Comparing patients with major arrhythmogenic events (MAE) and increased frequency of premature ventricular contractions (PVCs) post CRT pacing to those patients without arrhythmias, there was a significant prolongation of the QTc interval (527 ± 63.29 vs. 496.95 ± 45.2 msec, P = 0.043) and T_{pe} interval (94.16 ± 9 vs. 87.41 ± 16.37 msec, P = 0.049). While in the arrhythmogenic group, there was an insignificant decrease in QTd and T peak-end dispersion. Conclusion: QTc and T_{pe} intervals are a potential predictor of occurrence of MAE and PVCs. On the other hand, T_{pe} dispersion and QTd did not show a predictive potential for arrhythmia.

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Introduction

Cardiac resynchronization therapy (CRT) has become an established adjunctive treatment to optimal pharmacologic therapy in patients with advanced chronic heart failure. Several controlled studies have demonstrated the efficacy of CRT in improving hemodynamics and symptoms in the acute setting as well as during chronic follow-up. The hemodynamic improvements begin almost immediately after pacing is initiated as evidenced by increases in aortic pulse pressure, left ventricular dP/dt max (rate of rise of left ventricular pressure), and stroke volume [1,2]. Long-term results demonstrated evidence of reverse remodeling, increased exercise capacity and functional class, improved quality of life and decreased hospitalization rates [3–7]. In addition, favorable
neurohormonal effects of resynchronization therapy are demonstrated by reduced sympathetic nervous activity, [8] and increased heart rate variability [9,10].

On the other hand, the capability of CRT technology to reduce all-cause cardiac mortality is less well established. A decline in mortality due to pump failure has been clearly documented; [3] however, the impact on sudden cardiac death and the development of malignant ventricular arrhythmias remain questionable [11,12]. Meta-analysis of nine randomized trials of CRT showed a significant reduction in all-cause mortality by 21% [13]. However, there was a non-significant excess in the number of sudden cardiac deaths. This meta-analysis did not include mortality data from two of the larger CRT studies (COMPANION [11] and CARE-HF trials), that had the statistical power to demonstrate mortality benefit. In the COMPANION study there was a significant 36% mortality reduction in CRT group ($P = 0.003$), as compared to optimal medical treatment alone group. However, sudden cardiac death accounted for a substantially greater fraction of all deaths in CRT versus optimal medical treatment group (36.6% vs. 23.4%). Similarly, in CARE-HF there was a significant decrease in all cause mortality in the CRT group versus pharmacologic therapy ($P < 0.002$). However, the percentage of sudden deaths was higher in the CRT group versus non-sudden cardiac deaths (35.4% vs. 31.7%).

Some studies suggest that bi-ventricular pacing could decrease the incidence of ventricular arrhythmia [13–16] by improving dispersion of repolarization and neurohormonal signaling [10,17–19]. Whereas other studies showed that CRT does not decrease the frequency of ventricular arrhythmias [20] and might exceed to potentiating a pro-arrhythmic effect [21–26] due to reversal of myocardial depolarization through epicardial stimulation as occurs in LV pacing via the coronary sinus [21,27,28] and even promoting sudden – presumed arrhythmic – cardiac deaths [29]. This was supported by some case reports showing de novo development and/or increase incidence of ventricular arrhythmias after CRT [30–33].

In this context, our study aimed to investigate this alleged pro-arrhythmogenic effect of cardiac resynchronization therapy via epicardial left ventricular pacing.

Patients and methods

Seventy five patients were studied from June 2008 to June 2011 after informed consent from the patients and approval of the study by the ethical committee at the Critical Care Department, governmental Kasr Al Ainy Medical School, Cairo University, according to the declaration of Helsinki. All the patients had atrio-biventricular pacemakers implanted as adjunct management strategy for advanced congestive heart failure. The following inclusion criteria were adopted: (1) heart failure from any cause, (2) moderate-to-severe HF (New York Heart Association functional class III or IV) despite optimal medical treatment (3) left BBB with QRS duration ≥120 msec, and (4) left ventricular ejection fraction (LVEF) ≤35% [34].

The ECG was recorded with a standard digital recorder 12 simultaneous leads at a paper speed of 25 mm/s (Nihon Kohden CardioFax GEM-ECG-9020 K Interpretive Electrocardiograph Machine). Because of no standardized proven experience with automatic algorithms for ECG interval measurement, manual measurement was performed for surface electrocardiographic (ECG) markers, which are used to assess liability of potentially life threatening arrhythmias to occur either de novo, or for increased its frequency (i.e., pro-arrhythmia). These electrocardiographic markers included corrected QT interval (QTc), $T_{\text{peak}}-T_{\text{end}}$ ($T_{\text{p-e}}$) interval in addition to QT dispersion (QTd) and $T_{\text{peak-end}}$ dispersion (Fig. 1) [35–39] Measurements were performed by two independent and experienced personnel.

The QT interval was measured from the beginning of the QRS to the end of T wave, defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line. Since the duration of the QT interval is heart rate dependent, heart rate correction formula was applied in our study (Bazett’s formula: $\text{QTc} = \frac{\text{QT}}{\sqrt{RR}}$). The QT dispersion was defined as the difference be-

![Figure 1. Diagram demonstrating different intervals measured from surface ECG in our study.](image)
between the maximum and minimum QT interval of the 12 leads (QT_{max}–QT_{min}) [35].

The T_{p-e} was measured in each precordial lead and obtained from the difference between QT interval and QT_{peak} interval; measured from the beginning of the QRS until the peak of the T wave. In the case of negative or biphasic T waves, QT_{peak} was measured to the nadir of the T wave. The presence of pathological U waves complicates the determination of the precise QT interval duration, when U wave overlaps with the T wave, the end of the T wave was defined as the nadir between the T and U waves. T peak-end dispersion defined as (T_{p-e} maximum–T_{p-e} minimum), also it was calculated from the precordial leads [36].

Sudden cardiac death (SCD) was defined as a natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptom. For the purposes of this study, major arrhythmogenic events (MAE) were defined as a combination of SCD and/or resuscitation from a potentially fatal ventricular tachyarrhythmia [37].

Patients were followed up to 12 months. Data were collected from the clinical follow up of the patients and medical records including electrocardiograms at baseline before and after applying CRT pacemaker. Also data from 24 h holter monitoring and CRT device event recorder during interrogation by programmer were collected (Fig. 2).

Statistical analysis

The comparison of continuous variables (QTc interval, T_{peak-end} interval) assessed at baseline and during CRT therapy was performed using paired t-test analysis. For QT dispersion analysis (QT_{max}–QT_{min}) and T_{peak-end} dispersion analysis (T_{peak-end} maximum–T_{peak-end} minimum) the nonparametric Mann–Whitney’s or Wilcoxon matched pairs test were used. GraphPad software® version 3.06 was used. Statistical significance was established as P value ≤0.05.

Results

This study included 75 patients, with mean age (57 ± 11.6) years, 63 (84%) were males and 12 (16%) were female. Forty patients (53.4%) had dilated cardiomyopathy, whereas 35 patients (46.6%) suffered from ischemic cardiomyopathy. Among the study group, 33 patients (44%) suffered from hypertension, 29 patients (38.6%) had diabetes, whereas 13 patients (17.4%) suffered from both. Before device implantation, 29 patients (38.8%) were in NYHA class III, 26 patients (34.6%) in class III-IV, and 20 patients (26.6%) were in class IV. As regards medical treatment for heart failure, 73 patients (97.3%) were given loop diuretics, 72 patients (96%) received spironolactone, 67 patients (89.3%) used angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARBs), 19 patients (25.3%) were on digoxin, while 46 patients (61%) were maintained on maximum tolerated dose of B-blockers and 32 patients (42%) received amiodarone.

Sixty nine patients (92%) had CRT-P devices while six patients (8%) had CRT-D devices implanted. Pacemaker trademark were 42 St. Jude Medical and 33 Biotronik. In 46 patients the coronary sinus leads were positioned in lateral branch, 16 in posterior branch, 9 in anterolateral branch and 4 in anterior branch. AV and VV delays were programmed empirically to 100-120 ms and 0 ms respectively and if the patient did not respond well, it was optimized by echocardiography. The complications encountered were two left ventricular leads dislodgement, 5 patients with phrenic nerve stimulation, 1 patient with pneumothorax but all of these complications were safely solved.

During follow up after device implantation, 62 patients (82.7%) were clinical responders (defined as...
as ≥1 NYHA class improvement from baseline [40]). Thirty eight patients (50.7%) improved to NYHA class I and 24 patients (32%) to class II. On the other hand, 13 patients (17.3%) showed no improvement in NYHA class after device implantation (i.e., non responders).

Echocardiographic variables: there was a significant increase in the ejection fraction after CRT implantation from 30.08 ± 3.97 to 38.24 ± 4.3 (P < 0.0001). Similarly, LVESV showed a significant decrease one year post CRT from 69.4 ± 8.9 to 58.8 ± 9.5 ml (P < 0.0001).

Effect of CRT pacing on ECG variables: it was found that bi-ventricular pacing caused a significant decrease in QRS duration from 146.9 ± 19 msec to 128 ± 16.8 msec (P = 0.0001). On the other hand, the corrected QT interval showed significant prolongation after CRT from 476.2 ± 41.6 to 498.9 ± 50.8 msec (P = 0.0001). As regards QT dispersion and Tp-e dispersion, both showed insignificant rise after bi-ventricular pacing, while Tp-e interval showed insignificant decrease post CRT (Table 1).

### ECG variables in patients with MAE versus patients without MAE

Major arrhythmogenic events occurred within three months of implantation in four patients (5.3%) in our study group. All of them were males, three with ischemic cardiomyopathy, and one with dilated cardiomyopathy. Three of them suffered sudden cardiac death whereas the fourth suffered from sustained ventricular tachycardia that was managed with intravenous amiodarone infusion (Fig. 3). These patients showed insignificant decrease in QTc, QT dispersion and Tp-e dispersion, whereas there was an insignificant increase in Tp-e interval when compared to patients without MAE (Table 2).

### ECG variables in patients showing increased and decreased incidence of premature ventricular contractions (PVCS) post CRT pacing

Eight patients (10.6%) developed increase in the frequency of PVCs post CRT that started within 24 h post bi-ventricular pacing, three of whom had occasional premature beats showing R on T phenomenon (Fig. 4). These patients showed an insignificant increase in QTc (Fig. 5), Tp-e intervals and QT dispersion, whereas there was an insignif-

| ECG variables before and after CRT pacing in the total study population. |
|-----------------------------|-----------------------------|---------------------|
|                            | Before CRT                  | After CRT           | P value     |
| QRS duration (msec.)        | 146.9 ± 19                  | 128 ± 16.8          | 0.0001      |
| QTc (msec.)                 | 476.2 ± 41.6                | 498.9 ± 50.8        | 0.0001      |
| QT dispersion (msec.)       | 31.3 ± 14.7                 | 31.6 ± 16.6         | 0.889       |
| Tp-e interval (msec.)       | 89.6 ± 17.4                 | 88.2 ± 15.7         | 0.377       |
| Tp-e dispersion (msec.)     | 17.5 ± 10.3                 | 19.4 ± 7.6          | 0.165       |

Figure 3. Upper panel (A) showing increased frequency of PVCs post CRT pacing. Lower panel (B) showing development of ventricular tachycardia in the same patient.
icant decrease in $T_{p-e}$ dispersion when compared to patients without PVCs post biventricular pacing (Table 3).

While patients who showed a decreased incidence in the frequency of PVCs post CRT showed a significant decrease in QTc interval ($426 \pm 21.07$ vs. $496.9 \pm 45.2$ msec, $P = 0.043$), but a non significant increase as regards QT dispersion and $T_{p-e}$ interval and a non significant decline in $T_{p-e}$ interval as compared to patients without decreased incidence PVCs post biventricular pacing (Table 4).

Table 2. ECG variables in patients with MAE vs. patients without MAE. MAE = Major arrhythmogenic events, N = number.

<table>
<thead>
<tr>
<th>Post CRT pacing</th>
<th>no MAE (N = 71)</th>
<th>MAE (N = 4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (msec.)</td>
<td>496.95 ± 45.22</td>
<td>487 ± 37.44</td>
<td>0.307</td>
</tr>
<tr>
<td>QT dispersion (msec.)</td>
<td>31.66 ± 17.09</td>
<td>25 ± 12.91</td>
<td>0.496</td>
</tr>
<tr>
<td>$T_{p-e}$ interval (msec.)</td>
<td>87.41 ± 16.37</td>
<td>90 ± 8.16</td>
<td>0.062</td>
</tr>
<tr>
<td>$T_{p-e}$ dispersion (msec.)</td>
<td>19.41 ± 6.95</td>
<td>18.75 ± 14.36</td>
<td>0.856</td>
</tr>
</tbody>
</table>

Figure 4. Post CRT pacing; 24-hour holter tracing showing PVC with R on T phenomenon.

Figure 5. Upper panel (A) showing intrinsic rhythm with QTc = 424 msec. Lower panel (B) showing prolongation of QTc to 527 msec after applying CRT pacing (manual measurement).

ECG variables in patients showing increased PVCs and MAE after CRT pacing

When grouping patients with MAE who developed increased frequency of PVCs post CRT into one group and comparing them to the patients without arrhythmias post CRT, there was a significant prolongation of the QTc interval ($527 \pm 63.29$ vs. $496.95 \pm 45.2$ msec, $P = 0.043$) and the $T_{p-e}$ interval ($94.16 \pm 9$ vs. $87.41 \pm 16.37$ msec, $P = 0.049$) in patients with MAE and increased frequency of PVCs. On the other hand, there was insignificant...
decrease in QT dispersion and Tp-e dispersion in patients with MAE and increased frequency of PVCS (Table 5).

Effect of clinical responders to CRT on paced ECG variables

Patients showing clinical response by improving by one or more NYHA class during follow up after bi-ventricular pacing expressed insignificant decrease in QTc, and Tp-e dispersion than non responders, while there was an insignificant rise in QT dispersion, and Tp-e interval (Table 6).

Discussion

Markers of pro-arrhythmia from surface ECG has been studied in various clinical settings [35–39]. We therefore used it to study the effect of CRT pacing on surface ECG as a markers of pro-arrhythmia.

QTc interval prolongation from baseline in the setting of heart failure, ischemic heart disease, and usage of the antiarrhythmic medications was found to be a strong predictor of major arrhythmogenic events [36,38]. In our study, QTc showed significant prolongation in all our study population after biventricular pacing.

QT dispersion predicts mortality in patients with myocardial infarction and heart failure [39,41]. Increased QTd has also been shown to be a marker for SCD, [42] occurrence of torsade de pointes [27] and MAE [36]. Applying CRT pacing in our study induced an increase in QT dispersion that was insignificant. This is in contrast to Berger et al [19] who demonstrated that biventricular pacing was associated with a significant reduction of QT dispersion.
An increase in $T_{peak-end}$ dispersion has been shown to provide the substrate for the development of torsade de pointes especially under long QT conditions [28,43–45]. This is more pronounced in case of epicardial activation of the LV wall [21,27,46,47]. Our data showed a non-significant increased $T_{p-e}$ dispersion among biventricular paced patients.

$T_{p-e}$ interval has been suggested as a surrogate index of transmural dispersion of repolarization [48,49]. In addition, prolonged $T_{p-e}$ interval is associated with inducibility as well as spontaneous development of ventricular tachycardia in patients with organic heart disease, [50–52] and is a strong predictor of torsade de pointes.[38] Biventricular pacing caused an insignificant decrease in $T_{p-e}$ interval in our study group. This finding was similar to Chalil et al [36] and Medina-Ravell et al [27], where left ventricular epicardial pacing resulted in non-significant increase in $T_{p-e}$ interval.

In our total study population, biventricular pacing induced a significant increase in QTc interval. Patients with increased frequency of PVCs post CRT expressed no significant change in surface ECG parameters of pro-arrhythmia in comparison to patients without PVCs post biventricular pacing. On the other hand, three patients (4%) showed a decreased frequency of PVCs post CRT, they expressed a significant decrease in QTc interval ($426 \pm 21.07$ vs. $496.9 \pm 45.2$ msec, $P = 0.043$), and an insignificant decline in $T_{p-e}$ interval. There were, however, insignificant increases in QTd and $T_{p-e}$ dispersion, as compared to patients without PVCs post biventricular pacing.

In patients showing MAE there was insignificant increase in $T_{p-e}$ interval ($P = 0.062$), while QTc, QTd, and $T_{p-e}$ dispersion shows insignificant decline as compared to patients without MAE. Patients with MAE and those who developed increased frequency of PVCs post CRT were placed in one group and compared to the group of patients without arrhythmias. In the latter group, there was a significant prolongation both of the QTc interval ($527 \pm 63.29$ vs. $496.95 \pm 45.2$ msec, $P = 0.043$) and $T_{p-e}$ interval ($94.16 \pm 9$ vs. $87.41 \pm 16.37$ msec, $P = 0.049$), while there was an insignificant decrease in QTd and $T_{p-e}$ dispersion in the former group.

One finding of our study is that pro-arrhythmic ECG markers started developing almost immediately after applying biventricular pacing and that MAE occurred in the early post implantation period (within three months in our study) which agrees with the findings of Turitto et al. [32] Luo Nian-sang et al. [52] and Kurita et al. [53].

Conclusion

CRT delays death from progressive HF, but not from all causes, namely presumed sudden arrhythmic deaths. In that context, we conducted our study aiming to develop strategies to predict the alleged pro-arrhythmic effect induced by CRT using LV epicardial biventricular pacing. We concluded that QTc and $T_{p-e}$ intervals seem to be a potential predictor of occurrence of MAE and less serious arrhythmogenic events (PVCs). On the other hand, $T_{p-e}$ dispersion and QTD did not show a similar potential for arrhythmia prediction.

Study limitations

Study was conducted on a relatively small number of cases. A relatively larger number is needed to confirm these results. Manual measurement of ECG variables can be inaccurate, but no single automated measurement method has been validated yet. However, in our study there has been a fairly acceptable inter and intra-observer reproducibility of manual measurements of the various ECG intervals used.

References


