ABSTRACT. Background: It is well documented that approximately 30% of target patients do not benefit from cardiac resynchronization therapy (CRT). Attempts at imaging contractile dyssynchrony for selection have had modest results at best, and the 12-lead electrocardiogram (ECG) criterion remains sub-optimal. The high-resolution signal-averaged electrocardiogram (SAECG), with its ability to distinguish late potentials, may provide significant advantages over the 12-lead ECG. Our goal is to compare SAECG and 12-lead ECG with respect to QRS measurement in CRT. Methods: Twenty patients scheduled for CRT were analyzed with two SAECG recordings, one immediately prior to their procedure and one shortly after. QRS durations derived from these recordings were compared to respective surface QRS durations pre- and post procedure. Ten-minute three-lead orthogonal SAECG recordings were sampled at 1000 Hz and signal-averaged offline using 40–300 Hz bandpass filter. Late potential duration was defined as the duration that the filtered QRS complex remained $\geq 40 \mu V$. Results: Paired data were available in 20 patients, 17 male; mean age $72.50 \pm 9.67$ years. The SAECG QRS duration was significantly greater than the 12-lead QRS duration pre-procedure ($203.00 \pm 35.77$ ms versus $178.25 \pm 37.23$ ms, $p=0.05$); however, post-CRT values did not differ ($175.50 \pm 23.21$ ms versus $175.20 \pm 36.19$ ms, $p=0.932$). A significant reduction in QRS duration was only observed in the SAECG, and this was entirely due to reduction in late potential duration ($78.85 \pm 29.23$ ms to $46.25 \pm 16.01$ ms $p=0.001$). Conclusion: The SAECG is able to better quantify QRS length pre-CRT and determine changes in QRS duration post CRT by measuring late potential reduction.

KEYWORDS. 12-lead electrocardiogram, cardiac resynchronization therapy, late potentials, QRS duration, signal-averaged electrocardiogram, ventricular dyssynchrony.

Introduction

Despite recent progress in pharmaceutical therapies and treatments, congestive heart failure (CHF) remains a common cause of morbidity and mortality in Western countries, and an ever-increasing burden on the healthcare system. Cardiac resynchronization therapy (CRT) is a proven therapy for patients with heart failure and wide QRS, particularly in those with left bundle branch block (LBBB). This treatment has become an accepted option for CHF patients and current guidelines assign it the highest grade of recommendation. However, it has been well established that 25–30% of patients receiving CRT do not show clinical benefit. Current Canadian guidelines for the medical use of CRT call for a 12-lead electrocardiogram (ECG) QRS duration
patient response to CRT. Recent data suggest the benefit is greatest in patients with LBBB and QRS over 150 ms. Nonetheless there does appear to be observed benefit in patients with narrower QRS but these patients are difficult to target. Studies examining mechanical dyssynchrony have not correlated well with patient response to CRT.

The aim of our study is to compare the difference between the QRS duration measured by the 12-lead ECG and the signal-averaged electrocardiogram (SAECG) in patients both before and after CRT. In particular, we assessed the association between CRT and changes in late potential (LP) durations, as measured by the SAECG to determine what impact this treatment has on the terminal QRS region.

Methods and protocol

Inclusion and exclusion criteria

All patients over the age of 18 years scheduled for CRT in the Kingston General Hospital Arrhythmia Clinic were screened for the study. Patients listed as CRT generator replacements were excluded. Patients eligible for upgrades (from single or dual pacemakers/ICDs) were included. All patients scheduled for CRT met the Canadian guidelines criteria for implantation. The study design and protocol were approved by the Queen’s University Health Sciences Research Ethics Board Committee.

Patient recruitment

All enrolled patients provided two 10-min SAECG recordings, one immediately prior to their CRT procedure and one shortly after (either on the same day or the next day). All patients also had 12-lead ECG recordings pre- and post procedure. All 12-lead ECG recordings were performed by a trained ECG technician from the division of cardiology and lead placement followed standard guidelines. ECGs were gained at 10 mm/mV and filtered between 0.16 Hz and 150 Hz. QRS duration was measured with a digital caliper and (Iconico, New York, NY) from a standard 25 mm/s ECG, from the lead exhibiting the longest QRS duration.

SAECG recording and analysis

All SAECG recordings were performed with a high-resolution recording device (ELA Medical, Paris, France). Careful skin preparation and positioning of silver chloride electrodes in an orthogonal manner were performed preceding the high-resolution recording, as directed by the device manual. All three leads (XYZ) were bipolar and consisted of a positive (+) and negative (−) component. The X lead was generated by electrodes placed on the right (+) and left (−) mid-axillary line at the level of the fifth rib, the Y lead from electrodes at the top of the manubrium (−) and below the xiphoid process (+), and the Z lead from electrodes placed anterior (+) and posterior (−) on the fourth intercostal space to the left of sternum. After attachment of the electrodes, patients were asked to lay still and supine for the full 10-min recording to minimize noise from muscle movements. Derived analogue signals were amplified 10,000 times and bandpass filtered between 1 and 300 Hz. The analogue data were sampled at 1 kHz with a 12-bit resolution. Approximately 500 beats were stored per recording for offline analysis. QRS duration was calculated in the time domain, and the power of each complex/wave was assessed through a frequency domain by a novel automated algorithm. At least 200 beats were averaged per recording with a 10% error limit from the selected QRS template. Late potentials were measured as the duration of terminal signal below 40 mV. High-frequency domains were analyzed using a bandwidth of 20–150 Hz.

Statistical analysis

Comparisons between QRS duration measured by the two different methods before and after CRT was done with a paired two-tailed Student t-test assuming unequal variance. The difference between frequency pre and post CRT was carried out via the Wilcoxon signed rank test. A probability value of <0.05 was considered statistically significant. The Spearman rank correlation was used to determine if changes in LP duration were associated with changes in frequency.

Results

Of the 22 patients enrolled, paired data were available on 20: mean age 72.50 ± 9.67 years (Table 1). There was no statistically significant difference in QRS duration before and after CRT, measuring a value of 178.25 ± 37.23 ms pre CRT and 175.20 ± 36.19 ms post CRT (p = 0.305) using the standard 12-lead ECG (Figure 1). In contrast, the SAECG was able to show a statistically significant difference in QRS duration, measuring 203.00 ± 35.77 ms pre CRT and 175.50 ± 23.22 ms post CRT (p = 0.009) with an average reduction of 27.50 ± 33.33 ms (Figure 1). The difference between QRS durations as obtained by SAECG and 12-lead ECG was significant when measured before but not after CRT, with values of 24.75 ± 14.74 ms (p = 0.05) and 32.60 ± 26.42 ms (p = 0.932), respectively (Figure 1). The correlation in QRS reduction as measured by SAECG and 12-lead ECG was significant when measured before but not after CRT, with values of 24.75 ± 14.74 ms (p = 0.05) and 32.60 ± 26.42 ms (p = 0.932), respectively (Figure 1). The correlation in QRS reduction as measured by SAECG and 12-lead ECG is depicted in Figure 2. In addition, there was a statistically significant reduction in LP duration, measuring at 78.85 ± 29.23 ms pre CRT and 46.25 ± 16.01 ms post CRT (p < 0.001), with an average reduction of 32.60 ± 26.45 ms (Figure 3). When the LP duration is subtracted from the QRS duration measured by SAECG, the durations were 124.15 ± 27.87 ms pre CRT and 129.25 ± 17.55 ms post CRT (p = 0.523). When measured by SAECG, 14 patients experienced a reduction in QRS duration compared with 11 patients when measured by...
12-lead ECG. In addition, 17 patients experienced a reduction in LP duration. Analysis of early QRS high-frequency regions revealed median values of 561.60 KμV/s pre and 247.72 KμV/s post CRT (p=0.002). There was no correlation between LP reduction and frequency reduction (Pearson correlation coefficient of 0.021, p=0.930).

**Discussion**

The aim of our study was to assess the use of SAECG in the measurement of QRS duration compared with standard 12-lead ECG before and after CRT and to explore the effects of this therapy on LP duration. Our results indicate that there is a significant difference between the two methods. The SAECG provides a larger value of QRS duration before CRT than 12-lead ECG. This observation may be explained, in part, by the ability of this method to detect LPs at the terminal region of the QRS complex. However, there was no significant difference in QRS durations measured after the procedure. This may be due to the effect of biventricular pacing, which results in reduction of the late terminal activation of the QRS complex, an event that is more difficult to visualize using standard 12-lead ECG. This invites speculation that the SAECG may be a more useful tool for selecting patients eligible for CRT. Further support of this idea is provided by a recent study conducted by Andrikopoulos et al, which demonstrated that QRS duration as measured by SAECG not only better predicts association between electrical and mechanical dyssynchrony, but also reduces the number of patients that qualify for CRT compared with screening using 12-lead ECG. In their study, they report 60.4% of patients qualifying for CRT (QRS duration >120 ms) when assessed with SAECG versus 69.4% when assessed with 12-lead ECG and digital calipers (p=0.041). In addition, echocardiographic evidence of dyssynchrony had a greater correlation with QRS duration measured by SAECG than 12-lead ECG (r=0.45, p=0.001 versus r=0.35, p<0.01). The larger average QRS duration reported in our study is likely accounted for by our smaller sample size.

**Table 1.** Patient characteristics.

<table>
<thead>
<tr>
<th>Patient demographic</th>
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<tbody>
<tr>
<td>Age</td>
<td>73.72 ± 9.49</td>
</tr>
<tr>
<td>Sex</td>
<td>16 M, 2 F</td>
</tr>
<tr>
<td>Ischemic versus non-ischemic</td>
<td>14 versus 4</td>
</tr>
<tr>
<td>LVEF</td>
<td>24.17 ± 6.42%</td>
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<tr>
<td>Response to CRT</td>
<td>12 responders, 3 non-responders, 3 lost to follow up</td>
</tr>
</tbody>
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CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction.

**Figure 1:** Average QRS durations (ms) as measured by both 12-lead electrocardiogram (ECG) and signal-averaged ECG before (pre) and after (post) CRT.
Figure 2: Bland–Altman plot depicting correlation between QRS reduction as measured by SAECG (x-axis) and standard 12-lead electrocardiogram (y-axis).

Figure 3: Average late potential durations (ms) as measured by signal-averaged electrocardiogram both before (pre) and after (post) CRT.
The SAECG measured a significant difference in QRS duration before and after CRT ($p=0.009$) compared with the 12-lead ECG, which was not able to measure any significant difference or reduction ($p=0.305$). The SAECG also measured a significant reduction in LP duration ($p<0.001$) as a result of CRT. Interestingly, when we subtract the LP duration from both the pre and post CRT QRS durations, the resulting measurements are not statistically different ($p=0.523$). This presents the interesting notion that the reduction in QRS duration observed via SAECG may be largely due to the reduction in LP duration. It is also conceivable that the lack of reduction observed with the 12-lead ECG method is accounted for by its inability to detect these terminal signals prior to CRT. This, in turn, raises the possibility that LP reduction may play a role in the therapeutic benefits of CRT. Though there was a significant reduction in median QRS frequency from 56.160 to 247.72 KHz, it was not correlated with LP reduction. The physiologic mechanism or clinical significance of these high-frequency regions and their reduction in CRT may be a subject of future studies.

LPs are low-amplitude signals whose activation is delayed in CRT may be a subject of future studies. They represent either slowed conduction or prolonged depolarization pathways that arise due to areas of diseased myocardium.12,13 LPs have been described in different states of heart disease including various cardiomyopathies; however, the most common etiology is infarction.13,14 Indeed, early studies showed that 39–93% of patients in whom LPs were detected after an acute myocardial infarction (AMI) experienced sustained ventricular tachycardia (VT) or sudden cardiac death (SCD), and that the presence of LPs is an independent variable in predicting these events.14,15 Though this correlation was ultimately determined to have a low positive predictive value by itself, combining it with LVEF and previous history of arrhythmias may increase its accuracy.16,17 Conversely, the negative predictive value of LPs in determining the occurrence of sustained VT or SCD is high.13 Therefore, given the connection between LPs and poor cardiovascular outcome, the reduction in LP duration that results from CRT may account for some of the antiarrhythmic benefits of this intervention. These benefits were outlined in the study conducted by Cleland et al15 but were not fully explained. One possibility is that the left ventricular lead may be advancing the delayed segments of myocardium thereby reducing the potential for re-entry and minimizing the risk of SCD. If this is the case, then there may be a role for the utilization of SAECG not only in screening potential candidates for CRT, but for quantifying the benefits to the patient after the procedure as well. This notion is further supported by our data indicating 12 patients experienced reduction in QRS length as measured by SAECG versus 10 patients when measured via 12-lead ECG.

Conclusion

The results of this study demonstrate that the SAECG is able to better quantify QRS duration pre and post CRT. We also demonstrated the likely importance of LPs in the CRT patient population. Further large-scale epidemiological studies with adequate follow up should be conducted to assess the clinical utility of the SAECG in determining candidacy and response to CRT.

References


