Baseline delayed left ventricular activation predicts long-term clinical outcome in cardiac resynchronization therapy recipients

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Aims
We undertook this analysis to assess the relationship between delayed left ventricular activation time (LVAT), assessed prior to cardiac resynchronization therapy (CRT), with the long-term clinical outcomes in CRT recipients. We also sought to determine if baseline LVAT had similar predictive value in patients who were versus were not chronically paced prior to CRT.

Methods and results
Baseline pre-implant electrocardiograms (ECGs) of 219 consecutive patients undergoing CRT were analysed. Of these, 68 (31%) were chronically right ventricular (RV)-paced pre-CRT. Maximum LVAT was measured as QRS-duration minus time from QRS onset to the first notch in the QRS. Cox models were used to assess the association between LVAT and clinical outcome (death or cardiac transplant). Over a median follow-up of 56 months, 92 patients (42%) died and 10 (5%) underwent cardiac transplant. In the non-RV-paced group an independent linear relationship between LVAT and outcome [hazard ratio (HR) 0.67 per 50 ms increase in LVAT; 95% confidence interval (CI) 0.46–0.99] was observed. An LVAT ≥ 125 ms was associated with a markedly lower risk of outcome (adjusted HR 0.51; 95% CI 0.30–0.86) in these patients. Despite a similar incidence of death or cardiac transplantation in the RV-paced group vs. the non-paced one, no significant association between LVAT and outcome was observed in the RV-paced group.

Conclusion
Baseline LVAT, a simple ECG measure, independently predicts long-term outcome with CRT in non-RV paced patients. However, prolonged LVAT is not associated with an altered prognosis in patients chronically RV paced prior to CRT.

Keywords
Cardiac resynchronization therapy • Response • Electrocardiography • Left ventricular activation time • Outcome • Ventricular pacing

Introduction
Left bundle branch block (LBBB) leads to dyssynchronous mechanical activation of the left ventricle (LV) and is associated with progressive dilation and electrical remodelling in patients with heart failure. Cardiac resynchronization therapy (CRT) aims at synchronizing contraction within the LV, between the right and left ventricles, as well as between the atria and the ventricles. Cardiac resynchronization therapy has been shown to improve cardiac function, quality of life, and survival.1–3 The concept of resynchronization seems also to extend to patients with heart failure who are chronically right ventricular (RV) paced and exhibit iatrogenic-induced dyssynchronous mechanical activation. While CRT has been shown to improve electrical and LV mechanical synchrony4–6 and reverse LV remodelling in patients who were chronically RV paced prior to CRT, the efficacy of CRT in these patients is less certain.8

To date, the main approach identifying CRT candidates is based on QRS prolongation as measured on surface electrocardiogram (ECG) indicating electrical dyssynchrony.7,9–12 However, despite fulfilling standard selection criteria for CRT, ~30% of patients
LVAT and long-term outcome in CRT

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do not derive significant benefit.\textsuperscript{13,14} There is substantial interest in methods to predict which patients will respond to CRT. Analysis of left ventricular activation sequence in patients with LBBB has been shown to predict reverse remodelling.\textsuperscript{15} As delayed LVAT of left ventricular activation sequence in patients with LBBB in methods to predict which patients will respond to CRT. Analyse ejection fraction (EF) values \(\leq\)

The study population consisted of consecutive patients with LV lead position and QRS duration. The purpose of this study was to evaluate the predictive value of baseline LVAT on long-term clinical outcome in a mixed population of patients treated with CRT.

**Methods**

**Study population**

The study population consisted of consecutive patients with LV ejection fraction (EF) values \(\leq 0.35\), QRS durations \(\geq 120\) ms, and New York Heart Association (NYHA) III or IV symptoms despite optimal medical therapy who underwent successful CRT implantation between April 1999 and October 2006. A total of 219 patients with either ischaemic or non-ischaemic cardiomyopathy had pre- and post-implantation ECGs available for review and were included in the analysis. The protocol was reviewed and approved by the Conjoint Ethics Committee at the University of Calgary.

**Electrocardiogram analysis**

Standard supine 12-lead surface ECGs (25 mm/s, 10 mm/mV) prior to and following CRT implantation were analysed blinded to outcome results with the use of digital calipers at 200% magnification calibrated for paper speed 25 mm/s. The widest QRS complex (QRS\textsubscript{max}) in any lead was used for measuring the intrinsic or paced QRS duration. Biventricular stimulation could result in QRS shortening (QRS\textsubscript{pre} – QRS\textsubscript{post} \(> 0\) ms) or not. QRS axis was defined as follows: normal frontal plane axis (\(-30\) to \(90\)°), left-axis deviation (\(-30\) to \(-89\)°), and right-axis deviation (\(-90\) to \(89\)°). Left bundle branch block was defined as QRS\textsubscript{max} \(\geq 120\) ms with an rS or QS pattern in lead V1 with coexistent R wave but absent Q wave in either lead I or V6. The criteria for right bundle branch block (RBBB) included a QRS\textsubscript{max} \(\geq 120\) ms with a wide R (R prime) in lead V1 and a wide terminal S wave in leads I and V6.

Analyses of RV and LV activation times from baseline ECGs were performed as described previously.\textsuperscript{15} In brief, the time (ms) between QRS onset and first notch in any of the \(\geq 2\) adjacent leads was measured as RV activation time (RVAT), excluding notches in the first 40 ms of the S wave in V1 and V2. In RV-paced patients measurements were taken starting from the RV pacemaker stimulus. The LVAT was calculated as difference of QRS duration minus RVAT for each lead and the longest LVAT (LVAT\textsubscript{max}) was determined (Figure 1). In five patients a notch could not be clearly delineated and therefore LVAT\textsubscript{max} was estimated with the use of linear regression.\textsuperscript{15}

**Cardiac resynchronization therapy implantation**

Contrast venography and intraoperative fluoroscopy (left anterior oblique of \(30\)–\(60\)° and right anterior oblique of \(30\)–\(45\)°) were used to target a basal or mid-lateral or postero-lateral coronary sinus pacing site. However, other stimulation sites were reached in some of the patients due to the coronary sinus anatomy, the aim of achieving satisfactory pacing thresholds without phrenic nerve capture and targeting viable myocardium in patients with ischaemic cardiomyopathy.

**Left ventricular lead position**

Data on LV lead position were assessed and categorized from post-implantation chest radiographs. Analyses were performed blinded to outcome results as described previously.\textsuperscript{16} Due to the known deleterious effect of an anterior lead position\textsuperscript{16,17} we simplified the categorization and divided the LV lead position in an anterior or non-anterior location.

**Clinical data**

The primary study outcome was all-cause mortality or cardiac transplant. The vital status of all patients as of December 2010 was verified, with no patient lost to follow-up. Baseline data on NYHA class and LVEF before implantation were retrospectively assessed from the medical records.

**Statistical analysis**

Continuous variables are presented as mean \(\pm\) standard deviation or median and interquartile range. Differences in continuous data were evaluated using a Mann–Whitney U test. Categorical data were compared using a Fisher’s exact test. The log-rank test statistic was used to compare unadjusted event rates. Cox models were used to assess the univariate and multivariable association between predictive variable and outcome. The following variables were included in the multivariable models: age, gender, baseline LVEF, NYHA class, QRS duration, baseline atrial fibrillation (AF), aetiology of LV dysfunction, anterior

Figure 1 Example of left ventricular activation time measurement in a non-right ventricular paced patient (A) and in a right ventricular-paced patient (B). The left ventricular activation time was calculated as difference of QRS duration minus right ventricular activation time.

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lead position, and medications. LVATmax were assessed both as a continuous variable to assess for biologic plausibility and as a dichotomized variable for clinical prediction. A pre-defined cut-point for LVATmax ≥ 125 ms was chosen based on previously published data.15

While the sample size was limited, patients were considered in terms of important sub-groups (LBBB vs. RBBB, intrinsic conduction vs. prior continuous RV pacing) due to the potential for effect modification by these variables. Evidence for multiplicative statistical interaction was investigated by using a term that included the product of chronic RV pacing and LVATmax (i.e. LVATmax × the presence vs. absence of chronic RV pacing pre-CRT).

Clinical outcomes are presented using the Kaplan–Meier method. All tests were performed at a significance level α = 0.05. Analyses were performed using Stata, version 11.

Results

Baseline patient characteristics

A total of 179 men and 40 women (18%) with a mean age of 67 ± 10 years were included. Ischaemic cardiomyopathy was present in 69% of the patients and mean LVEF measured 23.2 ± 7.8%. Sixty-eight patients (31%) were chronically RV paced. Baseline-unpaced QRS revealed LBBB morphology in 119 (79%), RBBB morphology in 14 (9%), and unspecific intraventricular conduction delay in 18 (12%) patients.

Patients who were RV paced were paced 100% of the time (median 100%, lower quartile 100%, upper quartile 100%). They were significantly older than patients who were unpaced (P = 0.022) and had a higher rate of AF (P < 0.001) before implantation (Table 1). Considering ECG features RV-paced patients more often presented with left anterior axis deviation (P < 0.001), as well as a significantly longer QRS duration (P < 0.001) and baseline LVATmax (P = 0.002) (Table 2). With respect to other baseline characteristics (gender, aetiology of cardiomyopathy, NYHA class, LVEF, medication, and duration of follow-up) both groups were well matched.

Cardiac resynchronization therapy implant type, lead position, atrial fibrillation, and percentage biventricular pacing

A CRT pacemaker was implanted in 12% and a CRT defibrillator was implanted in 88%. Left ventricular lead position was categorized as posterior, lateral, or anterior in 40, 51, and 9% of patients, respectively. An anterior lead position was present in 9% of unpaced and 10% of RV-paced patients (Table 2). At baseline 28% of patients had been diagnosed with ‘permanent AF’ prior to CRT implantation. During follow-up, 22 of the 61 patients (36%) with ‘permanent AF’ at baseline exhibited SR at follow-up presentation (12 patients (43%) in the non-paced group and 10

| Table 1 | Comparison of baseline characteristics in unpaced and right ventricular-paced patients |
|---|---|---|---|
| | Total (n = 219) | Unpaced group (n = 151) | RV-paced group (n = 68) | P value |
| Baseline | | | | |
| Age (years)* | 67 ± 10 | 66 ± 10 | 70 ± 10 | 0.022 |
| Male, n (%) | 179 (82) | 121 (80) | 58 (85) | 0.360 |
| Ischaemic aetiology, n (%) | 150 (69) | 102 (68) | 48 (71) | 0.654 |
| NYHA functional class* | 3.3 ± 0.5 | 3.3 ± 0.5 | 3.3 ± 0.5 | 0.576 |
| ECG features | | | | |
| Atrial fibrillation, n (%) | 61 (28) | 28 (19) | 33 (49) | <0.001 |
| QRS duration (ms)* | 180 ± 40 | 166 ± 32 | 213 ± 37 | <0.001 |
| Frontal plane axis (°) a,b | −39 (−70; 24) | −15 (−49; 33) | −70 (−81; −51) | <0.001 |
| Leftward deviation, n (%) | 105 (48) | 56 (37) | 49 (72) | <0.001 |
| Rightward deviation, n (%) | 31 (14) | 15 (10) | 16 (24) | 0.008 |
| LVATmax (ms)b | 101 (81; 125) | 100 (74; 120) | 114 (88; 126) | 0.002 |
| LVATmax ≥ 125 ms | 95 (43) | 58 (38) | 37 (54) | 0.027 |
| LVEF (%) | 23 ± 8 | 23 ± 8 | 24 ± 8 | 0.689 |
| Medication, n (%) | | | | |
| Beta-blockers | 177 (81) | 119 (79) | 58 (86) | 0.153 |
| ACE or ARB | 208 (95) | 142 (94) | 66 (97) | 0.360 |
| Diuretics | 193 (88) | 134 (89) | 59 (86) | 0.644 |
| Potassium-sparing diuretic | 126 (58) | 90 (60) | 36 (53) | 0.378 |
| Digoxin | 125 (57) | 87 (57) | 38 (56) | 0.703 |
| Follow-up (months)b | 56 (27; 76) | 56 (26; 72) | 56 (30; 80) | 0.665 |

NYHA, New York Heart Association; LVATmax, longest left ventricular activation time; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction.

*aData given as mean and standard deviation.

*bData given as median and quartiles.
patients (30%) in the RV-paced group). Only two patients with AF underwent atrioventricular junction ablation.

Overall, patients had >90% biventricular pacing (median 99%, lower quartile 96%, and upper quartile 100%), as assessed using device diagnostics and 24 h ambulatory ECG monitoring. The patients with AF had similar, high rates of biventricular pacing (median 97%, lower quartile 94%, and upper quartile 100%).

Changes in electrocardiographic features post-implantation

Mean QRS duration significantly decreased from $180 \pm 40$ ms pre-implantation to $165 \pm 26$ ms post-implantation ($P < 0.001$) and 64% of patients experienced QRS shortening (Table 2). Right ventricular--paced patients more often revealed a shortening of QRS duration with a median of $-45$ ms ($-64$; $-18$) vs. $-9$ ms ($-27$; $9$) in unpaced patients ($P < 0.001$).

Clinical outcome

Over a median follow-up of 56 months, 92 patients (42%) died and 10 (5%) underwent cardiac transplantation. The clinical outcome in unpaced and RV-paced patients was similar, with 67 (44%) vs. 25 (37%) deaths ($P = 0.3$) and 6 (4%) vs. 4 (6%) transplants (log-rank $P = 0.5$) in the two groups, respectively. Moreover, RV pacing was not associated with a worse outcome after adjustment for age, gender, baseline LVEF, NYHA class, QRS duration, baseline AF, aetiology of LV dysfunction, anterior lead position, and medications. In the non-RV paced group an independent linear relationship between LVATmax and outcome (HR 0.67 per 50 ms increase in LVATmax, 95% CI 0.46–1.0; $P = 0.04$) was observed. Delayed LVATmax was associated with a lower risk of death or transplant in non-paced patients (adjusted HR 0.51; 95% CI 0.30–0.86; $P = 0.02$).

Despite a similar risk of death or transplant, no significant relationship between LVAT max and outcome was found in the total study population an LVAT max $\geq 125$ ms was associated with a markedly lower risk of death or transplant (HR 0.62; 95% CI 0.40–0.98; $P = 0.04$) despite adjustment for age, gender, baseline LVEF, NYHA class, QRS duration, baseline AF, aetiology of LV dysfunction, anterior lead position, and medications. In the non-RV paced group an independent linear relationship between LVATmax and outcome (HR 0.67 for 50 ms increase in LVATmax, 95% CI 0.46–1.0; $P = 0.04$) was observed. Delayed LVATmax was associated with a lower risk of death or transplant in non-paced patients (adjusted HR 0.51; 95% CI 0.30–0.86; $P = 0.02$).

Excluding patients with RBBB morphology from clinical outcome analysis confirmed no significant differences in death (41 vs. 37%; $P = 0.6$) or cardiac transplant (4 vs. 6%; $P = 0.3$) between unpaced and RV-paced patients.

Predictors of all-cause mortality and heart transplantation

In the total study population an LVAT max $\geq 125$ ms was associated with a markedly lower risk of death or transplant (HR 0.62; 95% CI 0.40–0.98; $P = 0.04$) despite adjustment for age, gender, baseline LVEF, NYHA class, QRS duration, baseline AF, aetiology of LV dysfunction, anterior lead position, and medications. In the non-RV paced group an independent linear relationship between LVATmax and outcome (HR 0.67 per 50 ms increase in LVATmax, 95% CI 0.46–1.0; $P = 0.04$) was observed. Delayed LVATmax was associated with a lower risk of death or transplant in non-paced patients (adjusted HR 0.51; 95% CI 0.30–0.86; $P = 0.02$).
Discussion

Main findings of the study

To our knowledge this is the first study to assess the value of LVAT\textsubscript{max} for predicting long-term outcome in a mixed population of unpaced and RV-paced patients. Our results confirm the predictive value of baseline LVAT\textsubscript{max} and extend this finding to the prediction of long-term clinical outcome. However, prolonged LVAT\textsubscript{max} was only predictive in non-paced patients.

Patients

Large randomized trials\textsuperscript{1,19} have shown that CRT reduces mortality among patients with sinus rhythm (SR), NYHA Class II–IV symptoms, a QRS duration $\geq$ 120 ms, and an LVEF $\leq$ 0.35.\textsuperscript{9 – 12} The efficacy of CRT among patients with chronic RV pacing (31%) and AF (28%) is less clear.\textsuperscript{20,21} There were some baseline differences between RV paced and unpaced patients in this study that may have influenced our results and appropriate multivariable modelling was used. Patients who were RV paced and underwent CRT upgrade were older and more often presented with AF than patients with primary CRT implantation, which is in line with previous data.\textsuperscript{7,22} Right ventricular pacing resulted in a longer baseline QRS duration and additional placement of an LV lead in a greater reduction of QRS duration compared with unpaced patients.

Clinical outcome

Death or cardiac transplant was chosen as the primary outcome. Five-year mortality rates were 44% in unpaced patients and 37% in RV-paced patients, and are in line with registry data.\textsuperscript{23} The high mortality rate in patients with RBBB (79%) was surprising, but adds to the evidence of worse prognosis in patients with RBBB morphology undergoing CRT implantation reported previously.\textsuperscript{23,24} Unfortunately, data on echocardiographic LV dyssynchrony and comorbidities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group</th>
<th>Non-paced group</th>
<th>RV-paced group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (1.0; 1.0)</td>
<td>–</td>
<td>1.0 (1.0; 1.0)</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.4 (1.2; 4.9)$^*$</td>
<td>2.6 (1.3; 5.2)$^{**}$</td>
<td>2.5 (1.1; 5.7)$^*$</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>1.0 (1.0; 1.0)</td>
<td>–</td>
<td>1.0 (1.0; 1.0)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.7 (1.1; 2.5)$^*$</td>
<td>1.7 (1.2; 6.2)$^{**}$</td>
<td>1.6 (1.0; 2.7)$^*$</td>
</tr>
<tr>
<td>Baseline AF</td>
<td>1.2 (0.7; 1.8)</td>
<td>–</td>
<td>1.0 (0.5; 1.8)</td>
</tr>
<tr>
<td>QRS duration</td>
<td>1.0 (1.0; 1.0)</td>
<td>–</td>
<td>1.0 (1.0; 1.0)</td>
</tr>
<tr>
<td>Aetiology of LV dysfunction</td>
<td>1.7 (1.0; 2.8)$^*$</td>
<td>1.7 (1.0; 2.8)$^*$</td>
<td>1.5 (0.8; 2.7)</td>
</tr>
<tr>
<td>Anterior lead position</td>
<td>1.8 (0.9; 3.4)</td>
<td>–</td>
<td>1.3 (0.6; 2.9)</td>
</tr>
<tr>
<td>Medications</td>
<td>1.5 (0.9; 2.4)</td>
<td>–</td>
<td>1.4 (0.9; 2.4)</td>
</tr>
<tr>
<td>LVAT\textsubscript{max} $\geq$ 125 ms</td>
<td>0.6 (0.4; 0.9)$^*$</td>
<td>0.6 (0.4; 0.9)$^*$</td>
<td>0.5 (0.3; 0.8)$^*$</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; LV, left ventricular.

$^*$P < 0.05, $^{**}$P < 0.01.

Figure 2 Kaplan–Meier curves of patients with delayed left ventricular activation time ($>\text{125 ms}$) and less delayed left ventricular activation time ($<\text{125 ms}$) in patients who are not right ventricular paced (A) and in patients who are chronically right ventricular paced (B).

Table 3 Summary of hazard ratios (95% confidence interval) by delayed LVAT\textsubscript{max}
LVATmax, an easily measured ECG parameter, and evaluated its value in the selection of adequate CRT candidates. The lack of electrical dyssynchrony and therefore might be of additional value for LV lead position and QRS duration. To fully judge on the influence of LV lead position the number of patients with a prolonged QRS duration (>0.30–0.86; \( P = 0.015 \)) was observed in the RV-paced cohort and in patients with RBBB morphology. The greater the LVATmax, the higher the amount of risk reduction with CRT implantation. This association remained significant despite adjustment for LV lead position and QRS duration. To fully judge on the influence of LV lead position the number of patients with a detrimental anterior position was probably too low.

To further assess the independent value of LVATmax, the predictive value of a prolonged QRS duration (>160 ms) was evaluated separately. Sweeney et al. reported a weak association of QRS duration with reverse remodelling probability in univariate analysis, which was replaced by LVATmax in the multivariable model. Consistently our analysis revealed no significant influence of QRS duration in adjusted models. Even a cut-off of 160 ms failed to reliably detect patients at low risk of death or transplant. One might speculate that delayed LVATmax more specifically displays the different pathogenesis of delayed LV activation. Patients chronically RV paced present with a functional LBBB, however, this does not reflect an underlying conduction abnormality and distinguishes these patients from those with endogenous LBBB. Furthermore, notches in the QRS might be influenced by the location of the RV lead.

### Study limitations
This was a retrospective study and has its limitations associated with this type of analysis. To minimize follow-up bias and bias in outcome ascertainment, we focused on all-cause mortality and heart transplant as primary outcome. Further, adjustment for factors associated with primary outcome was undertaken in all patients. However, this did not significantly alter the observed results.

### Conclusion
A simple ECG measure, prolonged LVATmax, independently predicts improved long-term outcome with CRT in non-RV-paced patients. However, prolonged LVATmax was not associated with an altered prognosis in patients chronically RV paced prior to CRT.

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