Left ventricular dyssynchrony from right ventricular pacing depends on intraventricular conduction pattern in intrinsic rhythm

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Aims Right ventricular pacing (RVP) prolongs ventricular activation and may induce mechanical dysynchrony. We hypothesized that the severity of RVP-associated ventricular mechanical dysynchrony may depend on the intrinsic intraventricular conduction pattern.

Methods and results Sixty-five patients with a single- or dual-chamber RV pacemaker were included. Forty-seven patients with ejection fraction (EF) ≤35%, 17 with no bundle branch block (BBB), 16 with right bundle branch block (RBBB), and 14 with left bundle branch block (LBBB). Eighteen patients with EF ≤35% and no BBB served as a control group. Echocardiographic dyssynchrony parameters [aortic pre-ejection delay (AoPEP), interventricular mechanical delay, delayed posterior left ventricular wall motion, and septal-to-posterior wall motion delay (SPWMD)] were evaluated in all patients with and without RVP. No dyssynchrony was found in patients with no BBB, RBBB, and in the control group, whereas LBBB patients showed significant dyssynchrony in AoPEP and SPWMD. RVP had a significant negative impact on all dyssynchrony parameters in patients with no BBB or LBBB. RVP induced significantly less severe dyssynchrony in RBBB patients. With RVP 100, 94, 56 and 16% of patients with LBBB, without BBB, RBBB, and from the control group, respectively, fulfilled the CARE-HF criteria for ventricular dyssynchrony.

Conclusion RVP worsens mechanical ventricular dyssynchrony in patients with reduced EF. These effects are most pronounced in patients with either normal QRS width or LBBB during intrinsic rhythm. In contrast, patients with an RBBB during intrinsic rhythm without RVP evidenced a better preserved haemodynamic function and mechanical synchrony with RVP, despite a comparable extent of pacing-induced QRS prolongation.

KEYWORDS Left bundle branch block; Right bundle branch block; Mechanical ventricular dyssynchrony

Introduction

QRS prolongation in left bundle branch block (LBBB) is associated with dysynchronous ventricular contraction and a depressed left ventricular ejection fraction (LVEF).1 Cardiac resynchronization therapy (CRT) reduces mortality and improves severe heart failure (HF) in selected patients with LBBB and low EF ≤35%.2-6 The presence of a right bundle branch block (RBBB) pattern has also been shown to be an independent predictor of mortality in HF patients, similar to an LBBB pattern.7 Although patients with RBBB have also been included in most CRT trials, the absolute proportion of enrolled patients is comparatively low (e.g. 10% of patients included in the COMPANION trial).5 Retrospective analyses of the major trials showed no significant CRT-associated benefit in patients with RBBB.5,6,9 However, some smaller studies reported discrepant findings and suggested that patients with RBBB and evidence of significant echocardiographic intraventricular mechanical dyssynchrony are likely to respond well to CRT.10 Thus, it remains unclear whether HF patients with RBBB may benefit from CRT.

In patients with a conventional bradycardia indication for a single- or dual-chamber pacemaker, the most commonly applied site of ventricular pacing is the right ventricular (RV) apex, mainly due to the ease of access and the long-term lead stability. However, right ventricular apical
pacing (RVP) is the haemodynamically least favourable of all ventricular pacing sites.\(^1\)\(^1\) RVP creates an artificially induced intraventricular conduction delay, which is associated with negative effects on systolic function and which might lead to adverse myocardial remodelling with progressive ventricular dilatation and HF.\(^1\)\(^2\)\(^3\)\(^1\) There is increasing evidence that biventricular morbidity and hospitalizations for decompensated congestive HF who need permanent ventricular pacing support.\(^1\)\(^3\)\(^6\)\(^7\)\(^8\)\(^9\) Since atrioventricular (AV) conduction defects account for \(\sim 50\%\) of pacemaker implants and \(\sim 30\%\) of patients with a conventional indication for a pacemaker present with reduced LV function, the additional dysfunction induced by RVP is of important clinical relevance.\(^1\)\(^1\) For this reason, it seems mandatory to identify more precisely patients who might benefit from long-term biventricular pacing instead of conventional RVP. It has not been investigated conclusively whether the intrinsic electrical conduction properties (without pacing) may influence the severity of RVP-induced mechanical ventricular dyssynchrony and whether the presence of an intrinsic RBBB might have a protective effect against RVP-induced dyssynchrony.

Thus, the aim of this study was to evaluate the influence of different types of intrinsic intraventricular conduction abnormalities on RVP-induced ventricular mechanical dyssynchrony in patients with severely reduced LV function.

**Methods**

**Patients**

We screened 152 consecutive patients from our pacemaker clinic who presented with a conventional single- or dual-chamber RV pacemaker (right ventricular apical pacing) and sinus rhythm (SR) without being permanently pacemaker-dependent. Fifty-one patients presented with an EF \(\leq 35\%\). All but four of these patients presented with adequate echocardiographic image quality for dysynchrony assessment. The remaining 47 patients comprised the study group and were divided into three subgroups. Group 1 without BBB (QRS < 120 ms; \(n = 17\)), group 2 with BBB (\(n = 16\)), and group 3 with LBBB (\(n = 14\)) in intrinsic rhythm without RVP. There were no significant differences between the three groups concerning underlying coronary artery disease and the average EF. Incidence of coronary artery disease was \(65\%\) in group 1, \(63\%\) in group 2, and \(64\%\) in group 3, respectively (\(P = \text{n.s.}\)). EF was \(31 \pm 4\%\) in group 1, \(31 \pm 3\%\) in group 2, and \(29 \pm 4\%\) in group 3, respectively (\(P = \text{n.s.}\)). Medication concerning ACE-inhibitors/angiotensin receptor blockers, \(\beta\)-blockers, loop-diuretics, or spironolactone was comparable in the three subgroups (\(P = \text{n.s.}\)).

Eighteen patients with an EF > 35\% with normal intraventricular conduction (QRS < 120 ms) in intrinsic rhythm without RVP served as a control group (\(n = 18\)).

Baseline characteristics of the study cohort are outlined in Table 1.

**Echocardiography**

Echocardiography recordings were made using a 2.5–3.5 MHz transducer interfaced with a diagnostic ultrasound system (Apio SSA-700A, Toshiba). All patients were examined in the left semi-supine position using standard parasternal, short- and long-axis, and apical views. LVEF was obtained from the apical four-chamber view according to modified Simpson’s rule (method of discs).

The presence of mechanical dyssynchrony was assessed by previously described conventional parameters (Figures 1–4):

1. **Aortic pre-ejection delay (AoPEP)** by PW-Doppler: time from QRS onset to aortic flow onset determined from PW-Doppler velocity signals proximal to the aortic valve in the LV outflow tract. Intraventricular dyssynchrony is defined by an AoPEP of > 140 ms (Figure 1).
2. **Interventricular mechanical delay (IVMD)** by PW-Doppler: time difference between AoPEP (Figure 1) and pulmonary pre-ejection delay (QRS onset to pulmonary flow onset determined from PW-Doppler velocity signals proximal to the pulmonary valve in the RV outflow tract). Interventricular dyssynchrony is defined by an IVMD of > 40 ms (Figure 2).
3. **Septal-posterior wall motion delay (SPWMD)** by M-mode: interval between maximal posterior and septal displacement of left posterior and septal wall using a mono-dimensional short-axis view at the papillary muscle level. Intraventricular dyssynchrony is defined by an SPWMD of > 130 ms (Figure 3). All SPWMD measurements were verified by a second observer and a common agreement was made in cases with discordant measurements of > 10 ms.
4. **Delayed posterior wall motion (PD)** by M-mode: time difference between QRS onset to onset of the E-wave at pulsed Doppler transmitral flow and time from QRS onset to peak systolic movement of the posterior wall using a mono-dimensional long-axis view. Intraventricular dyssynchrony is defined by a PD < 0 ms (Figure 4A and B).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of included patients (n = 65)</th>
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<tr>
<td>EF &gt; 35% (n = 18)</td>
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<td>Age (years) (range) 67 ± 11 (53–83)</td>
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<td>Male gender</td>
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<td>Ejection fraction (%) (range) 55 ± 6 (45–70)</td>
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<tr>
<td>Structural heart disease</td>
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<td>Coronary artery disease</td>
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<td>Dilative cardiomyopathy</td>
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<td>Valvular heart disease</td>
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<td>Lyme disease</td>
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<td>None</td>
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<td>Duration of pacing (months) (range) 24 ± 18 (6–66)</td>
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<td>Pacemaker indication</td>
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<tr>
<td>High grade AV block</td>
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<tr>
<td>Sinus node dysfunction</td>
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<td>Brady-tachy syndrome</td>
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<td>Medication</td>
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<td>ACE-inhibitors or ARB</td>
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<td>(\beta)-blockers</td>
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<td>Spironolactone</td>
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<td>Digoxin</td>
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ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

**Electrocardiogram**

Electrocardiogram (ECG) was performed at a speed of 50 mm/s and 1 mV/cm standardization. A 12-lead surface resting ECG was obtained during intrinsic SR and during RVP. QRS duration was measured from the first to the last sharp vector crossing the isoelectric line in all leads and the maximum value was used.
In addition to the markers for ventricular dyssynchrony, a marker for the assessment of global LV systolic function was analysed. The maximal LV rate of pressure rise ($LV \cdot dP/dt_{\text{max}}$) was measured from the mitral regurgitant CW-Doppler signal. $LV \cdot dP/dt$ was assessed by using the acceleration of the mitral regurgitation jet from 1 to 3 m/s in the CW-Doppler signal to determine the rate of pressure rise. Significantly depressed global LV systolic function is defined by an $LV \cdot dP/dt < 800 \text{ mmHg/s}$ (Figure 5).18–21

ECG and echocardiographic recordings were performed simultaneously during intrinsic rhythm and during active RVP with a short AV-delay to ensure complete ventricular capture (typically 100 ms sensed AV-delay). All measurements were acquired during stable resting conditions and averaged from three consecutive beats. In all patients, heart rate during echocardiographic examination was between 50 and 100 bpm in both intrinsic rhythm and RVP. All patients were normotensive without hyper- or hypotensive episodes at the time of examination.
Figure 3  Septal-to-posterior wall motion delay. It is the interval between maximal posterior and septal displacement of left posterior and septal wall using a mono-dimensional short-axis view at the papillary muscle level. Intraventricular dyssynchrony is defined by a septal-to-posterior wall motion delay of $\geq 130$ ms.

Figure 4  (A and B) Delayed activation of the posterior left ventricular wall. It is the time difference between QRS onset to onset of the $E$-wave at pulsed Doppler transmitral flow and time from QRS onset to peak systolic movement of the posterior wall using a mono-dimensional long-axis view. Intraventricular dyssynchrony is defined by a delayed posterior wall motion $<0$ ms.
Figure 5  Early systolic contractility of the left ventricle (LV + dP/dt). LV + dP/dt can be assessed by using the acceleration of the mitral regurgitation jet from 1 to 3 m/s in the continuous waved Doppler signal to determine the rate of pressure rise. Abnormal values are defined by an LV + dP/dt < 800 mmHg/s.

Statistical analysis
Statistical analysis was performed with SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). Data distributions were first assessed for normality and for aberrancies. Continuous variables are expressed as mean ± SD. Wilcoxon’s test was used for comparisons between no pacing and RVP. A Mann–Whitney U test was used to compare non-parametric data between two independent groups. A P-value of <0.05 was used to assess statistical significance.

Results
QRS duration
QRS duration during intrinsic rhythm without pacing showed no significant difference between patients with EF ≤ 35% (group 1) and the control group (96 ± 9 vs. 93 ± 10 ms; P = 0.30). Intrinsic QRS duration was 132 ± 17 ms in patients with RBBB and 137 ± 20 ms in patients with LBBB (P = 0.20). Paced QRS duration during RVP was significantly prolonged compared with the intrinsic rhythm in all groups (without BBB: 181 ± 18 ms with RVP vs. 96 ± 9 ms without RVP; P < 0.001, with RBBB: 177 ± 16 ms with RVP vs. 132 ± 17 ms without RVP; P < 0.001, with LBBB: 180 ± 20 ms with RVP vs. 137 ± 20 ms without RVP; P < 0.001, and control group: 152 ± 18 ms with RVP vs. 93 ± 10 ms without RVP; P < 0.001). In patients without BBB, paced QRS duration during RVP was significantly longer in patients with an EF ≤ 35% than in patients with an EF >35% (181 ± 18 ms, Δ 85 ms vs. 152 ± 18 ms, Δ 58 ms; P < 0.001). Patients with intrinsic BBB (LBBB or RBBB) showed a comparable increase in QRS duration with RVP (180 ± 20 ms, Δ 43 ms vs. 177 ± 17 ms, Δ 45 ms; P = 0.47).

Mechanical dyssynchrony
During intrinsic rhythm without RVP, there was on average no evidence of clinically relevant mechanical dyssynchrony in patients without BBB (AoPEP, 119 ± 16 ms, IVMD, 23 ± 13 ms; SPWMD, 102 ± 25 ms; and PD, 20 ± 11 ms), with RBBB (AoPEP, 112 ± 14 ms; IVMD, 15 ± 9 ms; SPWMD, 95 ± 21 ms; and PD, 9 ± 24 ms), and in the control group (AoPEP, 111 ± 20 ms; IVMD, 17 ± 13 ms; SPWMD, 91 ± 28 ms; and PD, 1 ± 28 ms). In contrast, LBBB patients showed a higher degree of mechanical dyssynchrony with a prolongation of AoPEP (142 ± 18 ms) and SPWMD (143 ± 19 ms), whereas IVMD (34 ± 10 ms) was slightly below the cut-off value for dyssynchrony and PD (4 ± 23 ms) was normal.

Patients with reduced EF ≤ 35% and either normal QRS width or RBBB without RVP showed no significant dyssynchrony. In contrast, patients with reduced EF ≤ 35% and LBBB without RVP showed significant alterations in several dyssynchrony markers. During intrinsic rhythm AoPEP, IVMD, and SPWMD were significantly longer in patients with LBBB compared with patients without BBB (P = 0.001, P = 0.02, and P = 0.04, respectively) and with RBBB (P = 0.01, P = 0.02, and P = 0.01, respectively).

RVP had a significant negative impact on all dyssynchrony parameters in patients with either no BBB or LBBB during intrinsic rhythm (Table 2).

In contrast, RVP had less negative impact on the dyssynchrony parameters in patients with intrinsic RBBB, where AoPEP and SPWMD were unaffected by RVP and only IVMD and PD deteriorated significantly but to a lesser degree when compared with the other subgroups.

In the control group, only AoPEP was significantly prolonged with RVP (Table 2).

During intrinsic rhythm, two of three CARE-HF echo criteria for mechanical dyssynchrony were met in 0% of the patients from the control group, 6% of the patients without BBB, 0% of the patients with RBBB, and in 72% of the patients with LBBB without RVP. The proportion of patients with two of three positive CARE-HF criteria increased during RVP to 16% (control group), 94% (no BBB), 56% (RBBB), and 100% (LBBB) (Tables 3 and 4).
aggravated by global LV dysfunction, but also modulated by the intrinsic electrical conduction properties without pacing.

The negative impact of RVP on the ventricular contraction pattern was most prominent in patients with severely reduced EF and LBBB and slightly less severe in patients with reduced EF and normal electrical conduction (no BBB). In comparison, RVP had a somewhat less pronounced negative impact on the ventricular dysynchrony in patients with an RBBB pattern during intrinsic rhythm. Dysynchrony caused by RVP translated directly into reduced global LV systolic function again most distinct in LBBB patients and to a lesser degree in RBBB patients.

During LBBB, the LV lateral wall is one of the latest activated regions as demonstrated by electrophysiological, haemodynamic, and echocardiographic data leading to LV intraventricular dyssynchrony. In RBBB, the RV free wall contracts later than the interventricular septum and the LV lateral wall, thus questioning the requirement for LV pre-excitation to improve haemodynamics and ventricular synchrony. A recent analysis of biventricular or single-chamber pacing on LV function and dysynchrony showed that less mechanical dysynchrony was induced in failing hearts with RBBB than with LBBB, despite similar prolongation of QRS duration. The MIRACLE trial found only little or no improvement with CRT in patients with intrinsic RBBB. Our results would support these findings. Paced QRS duration during RVP was significantly prolonged to a similar extend in all groups of patients with reduced EF independent of the intraventricular conduction properties without pacing. At the same time, intraventricular dysynchrony was significantly less distinct in patients with intrinsic RBBB compared with those with LBBB or no BBB.

As 20–30% of HF patients do not respond to CRT, despite wide QRS width in multicentre randomized CRT-trials, our results add further evidence that a prolonged QRS duration per se might not be the ideal predictor for upgrading patients from RVP to biventricular pacing. Thus, in patients with reduced EF, the implantation of an additional LV lead seems not to be mandatory in a relevant number of patients with intrinsic RBBB. Recent data have also shown that the degree of LV dysynchrony induced by RVP is variable and the evidence of the benefit of upgrading from RVP to biventricular pacing is still scarce.

However, HF patients with normal QRS width (no BBB) during intrinsic rhythm, reduced EF ≤ 35%, and a
conventional bradycardia pacemaker indication are likely to develop ventricular dysynchrony during frequent RVP and should therefore be considered as CRT candidates. A corresponding recommendation was given in the current ESC/ACC/AHA/HRS guidelines as a class IIa indication.33,34

Limitations
In terms of echocardiographic analysis, more sophisticated techniques might be needed to determine left intraventricular mechanical dyssynchrony more precisely.35,36 It is currently under investigation that which echocardiographic parameters allow optimal prospective identification of CRT responders. In the PROSPECT study, the investigated echo measures of mechanical dyssynchrony only slightly improved the identification of CRT responders.37 With improvements in practicability, three-dimensional echocardiographic analysis of ventricular dysynchrony or myocardial strain analyses by speckle tracking techniques might be promising alternatives.

The present analysis focuses on the acute, short-term impact of RVP on ventricular dyssynchrony and does not provide information about the long-term consequences. However, previous studies have demonstrated a close link between ventricular dyssynchrony and long-term clinical outcome.38

Conclusion
In conclusion, we have demonstrated that RVP has an immediate negative impact on global systolic performance and worsens mechanical ventricular dyssynchrony in patients with reduced EF. These effects are most pronounced in patients with either normal QRS width or LBBB during intrinsic rhythm. In contrast, patients with an RBBB during intrinsic rhythm without RVP evidenced a better preserved haemodynamic function and mechanical synchrony with RVP, despite a comparable extent of pacing-induced QRS prolongation.

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