Congenital Heart Disease

Detrimental Ventricular Remodeling in Patients With Congenital Complete Heart Block and Chronic Right Ventricular Apical Pacing

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Background—Although dual-chamber pacing improves cardiac function in patients with complete congenital atrioventricular block (CCAVB) by restoring physiological heart rate and atrioventricular synchronization, the long-term detrimental effect of asynchronous electromechanical activation induced by apical right ventricular pacing (RVP) has not been well clarified.

Methods and Results—Twenty-three CCAVB adults (24±3 years) with a DDD transvenous pacemaker underwent conventional echocardiography before implantation and, after at least 5 years of RVP, an exercise test and echocardiography coupled with tissue Doppler imaging and tissue tracking. They were compared with 30 matched healthy control subjects. After 10±3 years of RVP, CCAVB adults had significantly higher values versus controls in terms of intra–left ventricular (LV) asynchrony (respectively, 59±18 versus 19±9 ms, P<0.001), extent of LV myocardium displaying delayed longitudinal contraction (39±15% versus 10±7%, P<0.01), and septal-to-posterior wall-motion delay (84±26 versus 18±9 ms, P<0.01). The ratio of late-activated posterior to early-activated septal wall thickness was higher after long-term RVP than before (1.3±0.2 vs 1±0.1, P=0.05) and was higher than in controls (1±0.1, P<0.05). The percentage of patients with increased LV end-diastolic diameter was higher after long-term RVP than before implantation and was higher than in controls (57% versus 13%, P<0.05, and 57% versus 0%, P<0.01, respectively). CCAVB patients with long-term RVP had a lower cardiac output than controls (3.8±0.6 versus 4.9±0.8 L/min, P<0.05) and lower exercise performance (123±24 versus 185±39 W, P<0.001).

Conclusions—Prolonged ventricular dyssynchrony induced by long-term endovenous RVP is associated with deleterious LV remodeling, LV dilatation, LV asymmetrical hypertrophy, and low exercise capacity. These new data highlight the importance of the ventricular activation sequence in all patients with chronic ventricular pacing. (Circulation. 2004;110:3766-3772.)

Key Words: heart block ■ pacing ■ ventricles ■ imaging ■ heart defects, congenital

Congenital complete atrioventricular block (CCAVB) is a rare condition with an estimated incidence between 1/15 000 and 1/22 000 in live-born infants.1–5 Specific indications for cardiac pacing in CCAVB are summarized in the American College of Cardiology/American Heart Association Task Force Report.6 The prognosis for patients with this condition after pacemaker implantation has been considered benign, with a normal life expectancy and exercise capacity.7–9

Traditionally, the right ventricular (RV) apex has been the endocardial pacing site of choice in these patients. It is expected that restoration of physiological heart rate and atrioventricular synchrony by dual-chamber pacing would improve cardiac function and exercise capacity in patients with CCAVB; however, the long-term effect of an asynchronous ventricular electromechanical activation has not been evaluated. In particular, the relationships between long-term RV pacing-induced regional workload differences and morphological modifications of the left ventricle (LV) are not known. Echocardiography with tissue Doppler imaging (TDI) has recently emerged as a useful noninvasive modality that is capable of direct quantification of mechanical dyssynchrony.10–13 The present study was designed to assess the consequences of long-term permanent RV pacing on LV morphology, structure, dyssynchrony, function, and exercise performance in a homo-
TABLE 1. Comparison Between Demographic Data in Controls and Patients After Long-Term Follow-Up

<table>
<thead>
<tr>
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<th>Controls (n=30)</th>
<th>Patients (n=23)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
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<td>24±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Men, %</td>
<td>63</td>
<td>61</td>
<td>NS</td>
</tr>
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<td>BSA, m²</td>
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<td>1.7±0.4</td>
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<td>Rest heart rate, bpm</td>
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<td>NS</td>
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<td>NYHA class</td>
<td>1=0</td>
<td>1.7±0.3</td>
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</table>

BSA indicates body surface area; NYHA, New York Heart Association.

generative population of adults undergoing chronic pacing for CCAVB.

Methods

Study Population

The study population comprised 23 adult patients (age >18 years) with CCAVB who had undergone permanent cardiac pacing for accepted indications. CCAVB was defined as the permanent absence of electrical or mechanical relation between atrial and ventricular contraction. Patients were selected on the basis of having had a dual-chamber device with ventricular pacing from the RV apex for a minimum of 5 years. Patients with a history of surgery, infections, myopathies, metabolic disorders, or significant cardiac malformations were excluded from the study. In addition, a control group consisting of 30 healthy volunteers who were matched for age, gender, weight, and height were studied. Baseline characteristics of these patients are presented in Table 1. All patients provided written informed consent for the study. The institutional Clinical Research and Ethics Committee approved this study.

Study Protocol

All patients underwent echocardiography before implantation and after long-term endovenous dual-chamber pacing and exercise testing after long-term endovenous dual-chamber pacing. Control subjects underwent echocardiography and an exercise test.

Echocardiography

Before Pacemaker Implantation

A transthoracic echocardiography examination was performed to define cardiac anatomy, ventricular function, and valvular competence. LV posterior and septal wall thickness and LV end-diastolic and end-systolic diameters were obtained by averaging the measurements over 3 consecutive cardiac cycles with M-mode echocardiography. LV end-diastolic dimensions were measured, and percentile values (percentile of heart size corrected for weight) were estimated. Pathological end-diastolic diameter was defined as LV end-diastolic diameter greater than the 97th percentile.14,15 The following parameters of ventricular dyssynchrony were evaluated: (1) interventricular dyssynchrony, defined as the difference between the aortic and pulmonary pre ejection delays and determined by measuring the time from onset of the QRS to the beginning of each respective systolic ejection by pulse-wave Doppler; and (2) septal to posterior wall-motion delay, defined as the shortest interval between maximal displacement of the LV septum and that of the posterior LV wall as determined by M-mode echocardiography in short-axis view at the papillary muscle level.

After Chronic Dual-Chamber Endocardial Pacing

A transthoracic echocardiogram coupled with TDI and tissue tracking was performed with a 2.5- to 5-MHz imaging probe connected to a Vingmed-General Electric ultrasound system (System 5). To minimize variability between examinations, all echocardiographic examinations were performed by one echocardiographer. All images were recorded digitally and analyzed offline. Analysis was performed to determine hemodynamic variables and those of ventricular dyssynchrony by averaging the respective measurements of 3 consecutive cardiac cycles. During all echocardiographic examinations, the atrioventricular delay was individually optimized at rest with a rate-adaptive AV-delay algorithm activated.

Hemodynamic Variables

The following hemodynamic variables were evaluated: (1) LV filling time, determined by pulse-wave Doppler transmitral flow and defined as the time between onset of the E wave and the end of the A wave; (2) cardiac output and stroke volume, determined by the LV outflow method16,17; (3) ejection fraction, measured with echocardiography using the 4-cavity Simpson method; and (4) severity of mitral regurgitation, assessed by the percentage of jet area relative to the left atrial size in the apical 4-chamber and 2-chamber views, as described previously.10

Parameters of Ventricular Dyssynchrony

The following parameters of ventricular dyssynchrony were evaluated:

1. Interventricular dyssynchrony.18

2. Intra-LV dyssynchrony, determined with TDI to assess segmental wall motion as described previously. In brief, TDI was applied by placing the sample volume in the middle of the basal and mid-segmental portions of the septal, lateral, inferior, anterior, posterior, and anteroseptal walls. Gain and filter settings were adjusted as needed to eliminate background noise, which enabled the evaluation of a clear tissue signal. TDI velocities were recorded and measured at a sweep speed of 100 mm/s with online calipers. Variation in the peak of segmental LV contraction was evaluated by determining the electromechanical delay for each segment, defined as the interval between the onset of the QRS and the peak of each segmental contraction. Intra-LV dyssynchrony was defined as the delay between the shortest and longest electromechanical delays of the 12-segment electromechanical delay cited above.19-21

3. Delayed longitudinal contraction (DLC), calculated using TDI coupled with tissue tracking and strain rate. A segment was considered to have DLC if the strain rate analysis demonstrated motion that reflected true shortening and if the end of the segmental contraction occurred after the aortic valve closure. DLC is presented as the number of segments demonstrating DLC, expressed as a percentage of the total number of segments evaluated.11,22,23

4. Septal to posterior wall-motion delay.24

The same parameters were measured after programming of the pacemaker in the VVI mode at 40 bpm to analyze the spontaneous ventricular depolarization (escape rhythm).

Exercise Capacity

All patients underwent a symptom-limited bicycle ergometer test. During exercise, the pacemaker was programmed to VDD or DDDR (2 patients had developed associated sinus node dysfunction), with an upper limit pacing rate fixed at maximum for each patient’s age.

Statistical Analysis

All data are presented as mean±SD or percentages. Quantitative variables were analyzed with the Kruskal-Wallis test, whereas proportions were compared with the Fisher exact test. Statistical significance was established at P<0.05. The intraobserver correlation for the parameters of dyssynchrony was assessed in 15 patients and reached 0.94 for interventricular dyssynchrony, 0.93 for the septal to posterior wall motion delay, 0.92 for the intra-LV delay with TDI, and 0.92 for the DLC, which shows high reproducibility.

Results

All patients completed the study protocol.
Before the First Implantation
The echocardiographic ejection fraction was 69±6%, and no patient presented with significant mitral regurgitation. Mean LV end-diastolic diameter p was the 93rd percentile (SD±4), and mean LV end-systolic diameter p was the 94th percentile (SD±5). The escape rhythm was junctional (QRS width <120 ms) in 19 patients and ventricular (QRS width >120 ms) in 4. Pacing was initiated at an average age of 8±5.4 years. Ten patients had received an initial dual-chamber epicardial pacing device before secondary implantation of a dual-chamber endocardial pacemaker. For the remaining 13 patients, the first pacemaker was a transvenous system.

After Long-Term Endocardial RV Pacing
There were no significant differences in the baseline characteristics of the 2 groups studied (patients and controls). The mean body surface area (BSA) was 1.7±0.4 m² in patients with CCAVB compared with 1.6±0.4 m² in controls (P=NS). The duration of transvenous dual-chamber apical RV pacing ranged from 6 to 18 years (mean 9±3 years). All patients were programmed in VDD or DDD/DDDR (2 patients developed associated sinus node dysfunction) with 100% ventricular pacing at a mean resting heart rate of 69±9 bpm (65±7 bpm in controls, P=NS; 49±11 bpm before implantation, P<0.05). All patients underwent echocardiographic optimization of the AV delay (longest filling time without truncation of the A wave). The mean AV delay was 148±18 ms, and the upper-rate cutoff was 177±08 bpm. Mean QRS duration was 158±23 ms (87±6 ms in controls, P<0.001; 119±27 ms before implantation, P<0.05). After long-term endocardial pacing, 3 patients (13%) presented with New York Heart Association functional class II–III with LV ejection fractions of 39%, 41%, and 46% respectively. The remaining 20 patients were asymptomatic and presented with an LV ejection fraction >55%.

Echocardiographic Evaluation Before and After Long-Term RV Pacing
Echocardiography examinations performed before the first implantation in spontaneous rhythm (baseline) and after chronic RV pacing showed LV remodeling with LV dilatation and asymmetrical hypertrophy. The ratio of posterior to septal wall thickness was 1±0.1 before implantation versus 1.3±0.2 (P<0.05) after long-term RV pacing. Before implantation, 13% of patients showed an abnormal body surface area–adjusted LV end-diastolic diameter versus 57% of patients after long-term atrial synchronized RV pacing (P<0.05). Both interventricular dyssynchrony (55±18 versus 25±8 ms, P<0.01) and the septal to posterior wall-motion delay (84±26 versus 41±16 ms, P<0.05) were higher after long-term RV pacing than before implantation (Figures 1 and 2).

Echocardiographic Comparison of Chronic RV Pacing With Controls
After long-term dual-chamber RV pacing, CCAVB patients presented with LV dilatation and asymmetrical hypertrophy compared with healthy controls. The ratio of posterior to septal wall thickness (1.3±0.2 versus 1±0.1, P<0.05), mean LV end-diastolic diameter (55±7 versus 46±6 mm, P<0.05), and the percentage of patients with abnormal LV end-diastolic diameter (57% versus 0%, P<0.001) were higher in CCAVB patients after long-term RV pacing than in controls.
Mean cardiac output was decreased in patients after chronic RV pacing compared with controls (3.8±0.6 versus 4.9±0.8 L/min, P<0.05). Stroke volume was 55.07±11 mL/beat for patients after long-term pacing and 75.38±8 mL/beat for controls (P<0.05). The ratio of the area of mitral regurgitation to the area of the left atria was higher than in controls (16±8 versus 5±2, P<0.05). LV filling time was shorter than for controls (415±39 versus 477±51 ms, P<0.05). Interventricular dyssynchrony (55±18 versus 18±11 ms, P<0.01), intra-LV dyssynchrony (59±18 versus 19±9 ms, P<0.01), extent of LV myocardium displaying delayed longitudinal contraction (39±15 versus 10±7%, P<0.05), and septal-to-posterior wall-motion delay (84±26 versus 18±9 ms, P<0.05) were significantly higher after chronic RV pacing than in controls.

**Exercise Capacity**

During exercise testing, the performance of patients with chronic RV pacing was significantly lower than that of matched controls (123±24 versus 185±39 W, P<0.01). Maximal heart rate achieved during exercise was not significantly different between these groups (169±16 versus 175±19 bpm, P=NS).

**Echocardiographic Comparison With the Pacemaker Programmed in the VVI Mode at 40 bpm**

An echocardiography examination was performed in 20 of the 23 patients with the pacemaker programmed in the VVI mode at 40 bpm to analyze spontaneous ventricular depolarization. Six patients did not present with any escape rhythm, 11 patients presented with a junctional escape rhythm (QRS width <120 ms), and 3 patients had a ventricular escape rhythm (QRS width >120 ms).

Interventricular dyssynchrony (31±10 ms, P<0.05), intra-LV dyssynchrony (36±11 ms, P<0.05), extent of LV myocardium displaying delayed longitudinal contraction (26±10, P<0.05), and septal-to-posterior wall-motion delay (51±16 ms, P<0.05) were significantly less with the escape spontaneous rhythm than with the chronic RV pacing rhythm. In contrast, there were no significant differences in terms of LV end-diastolic diameter (52±08 mm, P=NS) and ratio of posterior/septal wall thickness (1.25±0.2, P=NS).

**Discussion**

This study presents new information regarding the detrimental effect of long-term apical RV pacing in patients with congenital heart block. First, it confirms that long-term apical RV pacing induces significant dyssynchrony, with important...
differences in the electromechanical activation of the different LV segments and marked postsystolic contraction. Second, it demonstrates that this significant LV dyssynchrony leads to the development of regional differences in LV morphology. Accordingly, we observed LV remodeling with a thinning of the early-activated segments and hypertrophy of the later-activated segments. Third, it demonstrates that despite physiological heart rate and atrioventricular synchrony, patients with congenital heart block paced at the apex of the RV have lower exercise capacity than matched controls. These new data highlight the importance of the ventricular activation sequence not only in patients with CCAVB but in all patients with chronic atrial-synchronized pacing.

### TABLE 2. Comparison Between Controls and Patients After Long-Term Follow-Up

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<tr>
<th></th>
<th>Long-Term RV Pacing</th>
<th>Controls</th>
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<td>Cardiac output, L/min</td>
<td>3.8±0.6*</td>
<td>4.9±0.8</td>
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<tr>
<td>Mean LV EDD, mm</td>
<td>55±7†</td>
<td>46±6</td>
</tr>
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<td>Pathological LV EDD, %</td>
<td>52†</td>
<td>0</td>
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<tr>
<td>Ratio posterior/septal wall</td>
<td>1.3±0.2†</td>
<td>1±0.1</td>
</tr>
<tr>
<td>Ratio mitral regurgitation/left atrium</td>
<td>16±8*</td>
<td>5±2</td>
</tr>
<tr>
<td>LV filling time, ms</td>
<td>415±39†</td>
<td>477±51</td>
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<tr>
<td>Interventricular dyssynchrony, ms</td>
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<tr>
<td>Intra-LV delay, ms</td>
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<td>Septal/posterior wall delay, ms</td>
<td>84±26†</td>
<td>18±9</td>
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<td>DLC, %</td>
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<td>Exercise, W</td>
<td>123±24†</td>
<td>185±39</td>
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EDD indicates end-diastolic diameter.

*P<0.05; †P<0.01.

### TABLE 3. Patient-by-Patient Data Before First Implantation of a Pacemaker and After Long-Term Endocardial RV Pacing

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<th>Patient No.</th>
<th>Age, y</th>
<th>Age at Implantation, y</th>
<th>Initial Lead System</th>
<th>Duration of Endocardial Pacing, y</th>
<th>Ratio Septal/Posterio Walls</th>
<th>Interventricular Dyssynchrony, ms</th>
<th>SPWMD, ms</th>
<th>Ratio Septal/Posterio Walls</th>
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</table>

SPWMD indicates septal-to-posterior wall-motion delay.
creased mechanical dispersion of motion between the different LV segments, represented by the intra-LV dysynchrony and the large extent of myocardium displaying postsystolic contraction, results in increased mitral regurgitation and decreased cardiac output. The early-activated LV segments shorten at low stress, whereas the late-activated segments contract during high-load conditions with higher metabolic demand. A part of regional systolic contribution is therefore wasted because the latest-activated components cause post-systolic contraction and because contraction of the earliest-activated segments occurs when the pressure remains too low to open the valves. This results in reduced mechanoenergetic LV efficiency and modifications in LV structure.

Prolonged Ventricular Dyssynchrony and Differences in Regional LV Structure
Long-term asynchronous electrical activation leads to increased LV cavity volume and to asymmetrical changes in LV wall thickness.25 For patients with spontaneous rhythm, LV remodeling and dilatation resulting in stretching of LV myocardial fibers have been postulated to compensate for slow heart rate by increasing stroke volume.26 Limited information exists regarding the LV adaptation in implanted patients with congenital heart block. Recent evidence suggests that some patients with congenital heart block may eventually develop a dilated cardiomyopathy.26,27 The present study demonstrates that long-term apical RV pacing does not counteract LV dilatation, but rather that it may actually aggravate it. Prolonged dyssynchrony, postsystolic contractions, and RV pacing–induced mitral regurgitation represent the major pathophysiological components of this LV maladaptation.

The ventricular wall is known to adapt to changes in workload by changing global or regional LV geometry. By inducing delay between the electromechanical activation of the LV segments, apical RV pacing results in important differences in regional workload, a major regulator of local cardiac growth. In the present study, the early-activated septal wall became thinner, whereas the late-activated posterior wall became hypertrophied.

Exercise Limitation in Patients With Congenital Heart Block and Atrial-Synchronized Apical RV Pacing
In the absence of pacing, patients with congenital heart block do not typically give histories of exercise intolerance despite persistent low resting and exercise heart rates; however, previous studies have clearly demonstrated that once patients have had pacemakers implanted, their exercise performance improves significantly.7 In the present cohort of adults with chronic apical pacing, the same observation was noted with low exercise-induced symptoms; however, the exercise performance of the cohort was significantly lower than that of healthy matched control subjects. Despite an adapted heart rate and physiologic atrioventricular synchrony, prolonged dual-chamber endocardial pacing at the RV apex clearly limits exercise capacity. There were no differences between the 2 groups in terms of body surface area; however, a parameter such as fitness may interfere with this comparison.

Alternative Pacing Site
The importance of a normalized sequence of ventricular activation is further supported by the present data. In patients with congenital block, a physiological sequence of electrical activation should be preserved. This would consist of pacing the RV at alternative sites. High septal or outflow tract RV pacing are proposed in this specific group of patients. However, acute and midterm results are controversial, and long-term studies are needed to prove the superiority of these sites compared with the RV apex.28,29 In patients with heart failure and ventricular conduction delay or RV pacing, biventricular pacing provides wall-motion resynchronization and enhancement of systolic function while lowering myocardial oxygen consumption, reducing chamber volumes, and assisting in long-term reverse remodeling.30–33 This specific pacing mode might be recommended in a subset of symptomatic patients with CCAVB, LV dilatation, and marked ventricular dysynchrony.

Study Limitations
Using the M-mode echocardiographic technique, we could only calculate the LV thickness for the septal and posterior walls. Data on the anterior and lateral walls could not be obtained. The method of measurement of mitral regurgitation was limited, and the absence of exercise data before pacing is a limitation of the study.

We cannot determine whether the LV dilatation observed in chronically paced CCAVB patients resulted from the detrimental effects of the asynchronous activation sequence of the LV walls or whether these features represent a disease-specific natural progression of congenital heart block itself. Nevertheless, in the latter case, the present study would suggest that apical RV pacing is likely to worsen deleterious LV remodeling.

Conclusions
Chronic apical RV pacing in patients with congenital heart block is associated with deleterious LV remodeling. Although apical RV pacing restores physiologic heart rate and atrioventricular synchrony, these patients present with lower exercise capacity than matched controls owing to significant LV electromechanical dysynchrony that leads to marked postsystolic contraction.

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Detrimental Ventricular Remodeling in Patients With Congenital Complete Heart Block and Chronic Right Ventricular Apical Pacing

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