Effect of Long-Term Right Ventricular Pacing in Young Adults With Structurally Normal Heart

Sandeep Sagar, MD, PhD; Win-Kuang Shen, MD; Samuel J. Asirvatham, MD; Yong-Mei Cha, MD; Raul E. Espinosa, MD; Paul A. Friedman, MD; David O. Hodge, MS; Thomas M. Munger, MD; Co-burn J. Porter, MD; Robert F. Rea, MD; David L. Hayes, MD; Arshad Jahangir, MD

Background—Right ventricular pacing increases the risk of heart failure in adults with structural heart disease. The impact of prolonged right ventricular pacing in adults without structural heart disease is not fully characterized and may depend on interactions of pacing with abnormal substrate predisposing to ventricular dysfunction.

Methods and Results—We assessed the effect of right ventricular pacing in patients who underwent pacemaker implantation for isolated congenital atrioventricular block between 1964 and 2005. To assess for immunologic contribution to cardiac dysfunction, outcomes were compared between patients with (Ab+) and without (Ab−) antinuclear antibody during adulthood and an age- and sex-matched Olmsted County, Minnesota, population. Of 103 patients (mean±SD age, 32±19 years), 18 were Ab+. Long-term survival free of new heart failure after pacemaker implantation in isolated congenital atrioventricular block patients was worse than in the matched population (P<0.001). This difference was attributable to the development of heart failure in 12 Ab+ patients (67%; P<0.001), without differences between Ab− patients (2%) and the matched population (2%; P=0.7). Compared with baseline, at last follow-up, left ventricular ejection fraction did not decline in Ab− (53±9% to 57±12%) but decreased in Ab+ (52±10% to 38±12%; P=0.03) patients. Survival was similar in Ab− patients and the Minnesota population (98%; P=0.7) but worse in Ab+ patients (79%; P<0.01).

Conclusions—The natural history of patients with isolated congenital atrioventricular block who require pacing depends upon their antibody status. Antinuclear antibody status was a predictor for the development of heart failure and death. Long-term right ventricular pacing alone does not appear to be associated with development of heart failure, deterioration in ventricular function, or reduced survival in Ab− isolated congenital atrioventricular block patients. (Circulation. 2010;121:1698-1705.)

Key Words: antibodies ■ atrioventricular block ■ follow-up studies ■ death ■ heart defects, congenital ■ heart failure ■ cardiac pacing, artificial

Right ventricular (RV) pacing is associated with increased risk of heart failure (HF) in adults with structural heart disease (SHD).1,2 It is unclear whether this propensity for deterioration in cardiac function results exclusively from pacing-induced ventricular dyssynchrony or from the interaction of pacing with an abnormal substrate.3–11 Comorbid illnesses are frequently present in patients with indications for pacemaker implantation. Therefore, the establishment of a cause-and-effect relationship between pacing method and location and pacing-induced cardiac dysfunction continues to be challenging.

Clinical Perspective on p 1705

Patients with isolated congenital complete atrioventricular block (ICAVB) represent a unique patient group in which to investigate the effects of long-term RV pacing. They usually are younger, are without SHD, and are available for long-term follow-up. Although recent studies have reported pacing-induced ventricular remodeling and poor outcomes in patients with ICAVB, risk factors associated with the detrimental effect of pacing continue to be poorly defined.8,9

Immune-mediated cardiomyopathy has been recognized in patients with a positive rheumatoid factor test result12–16 and in infants born to mothers with antinuclear antibodies (ANAs).12–17,20 Thus, we hypothesized that the presence of ANA in adult congenital ICAVB patients may be associated with worse outcomes after pacemaker implantation.

In this observational study, we assessed the effect of prolonged RV pacing on the development of HF, ventricular function, and actuarial survival in ICAVB patients with (Ab+) and without (Ab−) ANA and compared these findings with those from an age- and sex-matched Minnesota popula-
Table 1. Baseline Characteristics of ICAVB Ab\(^{-}\) and Ab\(^{+}\) Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Ab(^{-})</th>
<th>Ab(^{+})</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>103</td>
<td>85</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>66 (64)</td>
<td>59 (69)</td>
<td>7 (39)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age at diagnosis, mean±SD, y</td>
<td>12±13</td>
<td>13±14</td>
<td>11±10</td>
<td>0.90</td>
</tr>
<tr>
<td>Age at pacemaker implantation, y</td>
<td>32±19</td>
<td>30±19</td>
<td>39±17</td>
<td>0.06</td>
</tr>
<tr>
<td>Range</td>
<td>1 wk-77 y</td>
<td>1 wk-77 y</td>
<td>1 wk-64 y</td>
<td></td>
</tr>
<tr>
<td>Age distribution, n (%)</td>
<td>≥20 y</td>
<td>30 (29)</td>
<td>26 (31)</td>
<td>2 (11)</td>
</tr>
<tr>
<td></td>
<td>21–44 y</td>
<td>37 (36)</td>
<td>43 (51)</td>
<td>9 (50)</td>
</tr>
<tr>
<td></td>
<td>45–60 y</td>
<td>30 (29)</td>
<td>10 (12)</td>
<td>7 (39)</td>
</tr>
<tr>
<td></td>
<td>&gt;60 y</td>
<td>7 (7)</td>
<td>6 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Pacemaker mode at implantation, n (%)</td>
<td>Single chamber paced</td>
<td>71 (69)</td>
<td>57 (67)</td>
<td>14 (78)</td>
</tr>
<tr>
<td></td>
<td>Dual chamber paced</td>
<td>32 (31)</td>
<td>28 (33)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Symptoms at pacemaker implantation, n (%)</td>
<td>Lightheadedness</td>
<td>32 (31)</td>
<td>26 (31)</td>
<td>6 (33)</td>
</tr>
<tr>
<td></td>
<td>Syncope/near syncope</td>
<td>19 (18)</td>
<td>10 (12)</td>
<td>9 (50)</td>
</tr>
<tr>
<td></td>
<td>PVT (TdP/VF)</td>
<td>4 (4)</td>
<td>0</td>
<td>4 (22)</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>8 (8)</td>
<td>6 (7)</td>
<td>2 (11)</td>
</tr>
<tr>
<td></td>
<td>Exercise limitation</td>
<td>10 (10)</td>
<td>5 (6)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Comorbid conditions at pacemaker implantation, n (%)</td>
<td>Dyspnea at rest</td>
<td>36 (35)</td>
<td>28 (33)</td>
<td>8 (44)</td>
</tr>
<tr>
<td></td>
<td>Easy fatigability</td>
<td>15 (15)</td>
<td>9 (11)</td>
<td>6 (33)</td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

(Continued)
HF was used as a time-dependent covariate to show an association between HF, death, and cardiac death. The following values are reported as mean±SD: age at diagnosis and pacemaker implantation, left ventricular (LV) ejection fraction (LVEF), LV end-diastolic dimension (LVEDD), duration of follow-up, age at death, and cardiac death. Values of P<0.05 were considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Demographic Characteristics

Four hundred nineteen patients who had pacemakers implanted for congenital heart block between 1964 and 2005 were identified. Of these, 315 patients were excluded because of the presence of congenital SHD (septal defects, valvular defects, Ebstein anomaly, transposition of great vessels), and 1 patient did not consent to the use of data for research purposes, leaving 103 patients with ICAVB. Eighty-five patients (83%) were Ab−, and 18 (17%) were Ab+. Of the 85 Ab− patients, ANA status was confirmed by ELISA at Mayo Clinic in 25 patients. In 3 of the 11 Ab+ patients who were alive in 2007, the antibody titers were elevated at 35.9, 10.3, and 10.9 U (reference value ≤1.0 U). The baseline characteristics of ICAVB patients at the time of pacemaker implantation are summarized in Table 1. The mean age at diagnosis of ICAVB was 12±13 years. Other than 13 neonates who had pacemakers implanted at diagnosis, all patients had a resting heart rate of >55 bpm with an appropriate increase in rate with activity and were asymptomatic at diagnosis. Pacemakers were implanted once the patients became symptomatic (mean age, 32±19 years; Table 1).

Endocardial pacing accounted for all the systems other than the 16 neonates, who had epicardial pacemakers before their first birthdays. Their systems were upgraded to dual-chamber endocardial RV pacemakers. On the basis of procedural reports and chest x-rays, 91 patients had the RV lead in the RV apex position. The lead was implanted higher on the midseptum, but not in the outflow tract, in the other 13 (13%). Lead location was based on operator preference. Seventy-seven (89%) of the Ab− compared with 14 (78%) of the Ab+ patients were paced from the RV apex. Twelve patients (13%) had pacemaker implantation before 1975, and 31 (30%) has pacemaker implantation before 1980 when echocardiography was not yet readily available. Baseline echocardiography before pacemaker implantation was performed in 61 Ab− patients (72%) and 12 Ab+ patients (67%). Presenting symptoms, comorbid conditions, and chest radiographic findings in Ab− and Ab+ patients are summarized in Table 1. At pacemaker implantation, no significant difference in mean LVEF existed between Ab− patients (53±9%) and Ab+ patients (52±10%; P=0.97), but the mean LVEDD was higher in Ab+ patients (57±4 versus 53±7 mm; P=0.05).

Symptom Resolution After Pacemaker Implantation

The mean follow-up after pacemaker implantation was 17±9 and 21±7 years (longest, 39 and 29 years) in Ab− and Ab+ patients, respectively (Table 2). Only 1 patient was lost to follow-up. Complete symptom relief for which the pacemaker was implanted was achieved in 82 Ab− patients (96%) but in only 2 Ab+ patients (11%; P<0.001; Table 2).

Device-Related Complications

Lead revision and end-of-battery-life pack changes were the most common device-associated problems. The lead loop was increased in the 28 children who underwent pacemaker implantation before 10 years of age. One patient developed a
pocket infection that required intravenous antibiotics and device revision. The atrial lead was revised in 1 patient and the RV lead in 2 patients after lead fracture.

**Survival Free of HF**

The observed long-term survival free of new HF after pacemaker implantation in the overall ICAVB group was significantly worse than that of the age- and sex-specific Olmsted County population rates (\(P<0.001\); Figure 1A). This difference was attributable solely to the development of HF in 12 Ab\(^+\) patients (67%; \(P<0.001\); Figure 1B), with no difference between the Ab\(^-\) patients (2%) and the Olmsted County population (2%; \(P=0.7\); Figure 1B). At 10 and 20 years, the survival free of HF in the Minnesota population was 99% and 98%, respectively, compared with 98% and 98% in Ab\(^-\) patients and 100% and 79% in Ab\(^+\) patients (\(P<0.001\)).

Only 2 Ab\(^-\) patients (2%) but 12 Ab\(^+\) patients (67%; \(P<0.001\); Figure 1B) developed new HF (Table 2). Both Ab\(^-\) patients had coronary artery disease (CAD), and their HF developed after acute MI. Nine of the 12 Ab\(^+\) patients had no identifiable cause of their HF; the remaining 3 had CAD and an MI preceding HF. HF occurred in 8 of the 12 patients (67%) from the ANA-positive group paced from the RV apex compared with 4 of the remaining 6 (67%) who were paced from the midseptum. There was no statistical difference in the development of HF based on lead location in the RV (\(P=0.4\)). After pacemaker implantation, the mean interval that HF symptoms developed was 19.6±5 years, with mild HF symptoms in 9 patients (New York Heart Association functional class II) and severe class III to IV symptoms in 3 patients.

**Ventricular Function and Dimension After Pacemaker Implantation**

A follow-up echocardiogram was available in 73 Ab\(^-\) patients (86%) and 15 Ab\(^+\) patients (83%). When the ICAVB patients were considered as a whole, there was no difference at last follow-up in LVEF (53±13% versus 51±10% at baseline; \(P=0.4\)) and LVEDD (52±8 versus 53±7 mm; \(P=0.7\)). However, significant differences were present between Ab\(^-\) patients and Ab\(^+\) patients (Figure 1C and 1D). In Ab\(^-\) patients, no significant change in LVEF at baseline (53±9%) to last follow-up (57±12%; \(P=0.7\)) or in LVEDD (53±7 versus 50±7 mm; \(P=0.95\)) was noted. In contrast, in Ab\(^+\) patients, LVEF deteriorated from 52±10% to 38±12% (\(P=0.03\)), and LVEDD increased from 57±4 to 62±6 mm (\(P=0.01\); Figure 1C and 1D). The percentage of patients with LVEF <50% at baseline was not different (16% [14 of 85] of Ab\(^-\) patients versus 17% [3 of 18] of Ab\(^+\) patients; \(P=0.5\); Table 1), but the proportions decreased to 12% (10 of 85; \(P=0.01\)) of Ab\(^-\) patients compared with an increase to 50%
56 The observed survival after pacemaker implantation in ICAVB patients was not different from expected survival in the Olmsted County population ($P=0.09$; Figure 2A). However, the long-term overall survival (Figure 2B) and survival from cardiac death (Figure 2C) were worse in Ab$^+$ patients. Noncardiac deaths accounted for all but 1 death in the Ab$^-$ patients (Table 2). The 10- and 20-year survival rates free of cardiac death in Ab$^-$ patients were 98% and 98% compared with 100% and 79% in Ab$^+$ patients, respectively ($P<0.001$; Figure 2C).

Over the mean follow-up of $20\pm7$ years, a significantly higher percentage of Ab$^+$ patients died compared with the percentage of Ab$^-$ patients ($P>0.001$; Table 2). The mean age at cardiac death was similar ($63\pm11$ years in Ab$^+$ patients versus $73\pm12$ years in Ab$^-$ patients). Six of 7 Ab$^+$ patients died of cardiac causes compared with 1 of 8 Ab$^-$ patients. Four Ab$^+$ patients died of progressive HF; 1 died after acute MI; 1 experienced sudden death; and 1 suffered fatal stroke. Death occurred within $3.8\pm5.4$ years after the diagnosis of HF and within 2 years of diagnosis of New York Heart Association class III to IV HF. None of the Ab$^-$ patients died of HF; 1 died after an acute MI at 80 years of age; 4 died of noncardiac causes ($P<0.05$ compared with Ab$^+$); 2 died after a stroke; and the cause of 1 death was unclear (Table 2).

**Mortality Predictors**

Univariate predictors of mortality with HR, confidence interval, and $P$ values are summarized in Table 3. Presence of ANA, age at pacemaker implantation, radiological evidence of pulmonary congestion, near syncope, hyperlipidemia, and hypertension were predictors of increased mortality. In Ab$^-$ patients, age at pacemaker implantation and presence of hyperlipidemia, hypertension, CAD, HF, palpitations, and near syncope were associated with mortality. When used as a time-dependent covariate, HF demonstrated a strong association with death (HR, 82.2; $P<0.001$) and cardiac death (HR, 95.5; $P=0.001$).

**Discussion**

The main finding of our study is that ANA status, rather than RV pacing alone, determines the long-term clinical outcome after pacemaker implantation in ICAVB patients. HF and mortality incidence were significantly higher in the Ab$^+$ patients than in the Ab$^-$ patients and in the Minnesota population, and the presence of a positive ANA was a strong independent predictor for the development of HF. These results suggest a complex interaction between the presence of an abnormal substrate and RV pacing underlying poor long-term outcomes in these patients.

RV pacing may adversely affect cardiac function and contribute to worsening HF in patients with SHD and LV dysfunction. Ventricular dyssynchrony is thought to accentuate the progression of cardiac failure in those with compromised cardiac reserves. In younger patients without SHD, the potential of RV pacing to compromise cardiac function and clinical outcome is not fully defined. In the present study, ICAVB patients without SHD did not exhibit worsening of ventricular function, HF, or mortality with prolonged RV pacing as long as other causes for ventricular dysfunction, including abnormal antibody status, were excluded. This finding contrasts with the findings...
of Thambo et al, who reported increased ventricular dyssynchrony, LV dilation, and reduction in cardiac output and exercise capacity in their cohort of 23 patients with congenital complete heart block after 10 years of RV pacing. None of the patients were reported to develop HF, and there was no discussion of mortality. The antibody status of these patients was not reported, and it is possible that mechanisms other than ventricular dyssynchrony such as immune-mediated alterations in ventricular function may have contributed to LV dysfunction. As shown by Chen et al, most patients requiring ablation of the atrioventricular junction for atrial fibrillation do not develop deterioration in ventricular function with RV pacing, suggesting that ventricular dyssynchrony alone may not be responsible for worsening HF.

ICAVB commonly occurs in children born to mothers with systemic lupus erythematosus. It has been demonstrated that neonates of Ab mothers have a much higher rate of both atrioventricular block and organic heart disease than those born to Ab mothers, suggesting that an immune-mediated process may lead to worse outcomes. In another study, infants born to Ab mothers had deterioration in cardiac and clinical status 3.7 to 9.3 years after diagnosis of ICAVB. Four died of HF, and 7 required cardiac transplantation. Myocardial biopsy demonstrated inflammatory myocarditis. The authors concluded that infants born to Ab mothers had a 5% to 11% risk of developing late cardiomyopathy. This finding is consistent with that of Kim et al, who demonstrated that 3 of their 4 patients with congenital atrioventricular block who developed HF tested positive for ANA. Our study extends these observations into adulthood by showing that the natural history of ICAVB depends on patients’ antibody status because survival free of HF and death was worse in those who were Ab.

Several reports demonstrate a greater incidence of HF and ventricular dysfunction in patients with rheumatoid arthritis, independent of CAD, compared with the general population. Patients who are positive for rheumatoid factor appear to be at higher risk of developing HF than patients who are negative for rheumatoid factor. These findings are concordant with our demonstration that ANA ICAVB patients who were paced were at greater risk for new HF and had a higher rate of cardiac mortality compared with Ab patients. In Ab patients, predictors of HF and mortality were similar to those seen in the general population, including the presence of hyperlipidemia, CAD, advanced age, and HF.

The potential limitations of our study include its retrospective nature and lack of ANA titer in all patients. Echocardiography was not performed in all patients at the time of pacemaker implantation, but echocardiographic follow-up was available in >80%. A multivariate analysis for mortality was not feasible with the limited number of patients in this study. Despite the small sample size, to the best of our knowledge, this is the largest study of ICAVB patients who...
underwent pacemaker implantation and were followed up late into adulthood and the first to differentiate clinical outcomes on the basis of antibody status in adults.

Conclusions
This study demonstrates that in ICAVB patients without SHD at the time of pacemaker implantation, pacing from the RV position does not appear to have a detrimental effect on heart size or performance. The risk of HF after pacemaker implantation is not solely the result of abnormal ventricular activation but instead is an interaction between pacing and abnormal myocardial substrate. In ICAVB patients, positive antibody status may predispose to cardiomyopathy and worse clinical outcomes. ANA testing should supplement the assessment of ventricular size and function by echocardiography to identify high-risk patients who might progress to HF. The mechanism of ventricular dilation and decline in systolic function in antibody-positive patients requires additional study to identify protective strategies against adverse remodeling over time.30,31

Acknowledgments
Dr Sagar is a Clinician-Investigator Fellow in the Division of Cardiovascular Diseases. D.O. Hodge performed the statistical analysis.

Sources of Funding
Dr Jahangir is supported by grants from the National Institute on Aging (AG21201), National Heart, Lung and Blood Institute (HL089542) and the Marriott Mitochondrial Medicine Awards, Mayo Clinic.

Disclosures
Dr Hayes received honorarium and consulting and advisory fees from Medtronic, St. Jude, and Boston Scientific. The remaining authors report no conflicts.

References
This study elucidates the long term effect of right ventricular (RV) pacing on clinical outcomes in patients who underwent pacemaker implantation for symptomatic isolated congenital complete atrioventricular block (ICAVB). Over a mean follow-up of 20 years (longest 39 years) the observed survival free of new heart failure (HF) after pacemaker implant in the overall ICAVB group was significantly worse than that of the age- and sex-specific Olmsted County, Minnesota population rates. This difference was, however, attributable to the development of HF and ventricular dysfunction in those who had tested positive for antinuclear antibody (ANA) during adulthood with no difference between the antibody negative ICAVB patients and the Olmsted County population. The presence of a positive ANA was a strong predictor for the development of HF and death. These results suggest that in young patients without structural heart disease, pacing from the RV position does not appear to have a detrimental effect on heart size or performance. The risk of HF after pacemaker implant is not solely the result of abnormal ventricular activation, but instead an interaction between pacing and abnormal myocardial substrate. In ICAVB patients, positive antibody status may predispose to cardiomyopathy and worse clinical outcomes. ANA testing should supplement the assessment of ventricular size and function by echocardiography to identify high-risk patients who might progress to HF.
Effect of Long-Term Right Ventricular Pacing in Young Adults With Structurally Normal Heart


_Circulation_. 2010;121:1698-1705; originally published online April 5, 2010; doi: 10.1161/CIRCULATIONAHA.109.866343

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/15/1698

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/