Ventricular pacing can be lifesaving for patients with complete atrioventricular block (AVB). Since the introduction of permanent transvenous cardiac pacing >40 years ago, the right ventricular (RV) apex has been the preferred site for ventricular stimulation. This location provides good fixation and low capture thresholds. However, RV apical pacing may induce cardiac dyssynchrony. Hence, it has been suggested that all patients with symptomatic AVB (regardless of current indication for biventricular pacing), with anticipated high RV pacing burden, should receive preventive biventricular pacing. In this article, we review the physiological effects of RV pacing, data from observational studies (Table I in the Data Supplement),1–6 and available randomized trials comparing biventricular versus RV pacing (Table).7–16

Response by Fang et al on p 738

Since the initial report of the use of endocardial pacing to treat complete AVB by Furman and Schwedel in 195917, pacemakers have evolved dramatically into complex devices with the ability to sequentially pace the atrium and both ventricles. Between 1993 and 2009, 2.9 million patients received a permanent pacemaker in the United States.18 During this time, overall pacemaker use increased by 55.6%. However, although the use of dual chamber (DDD) pacemakers increased by at least 40%, the use of single-chamber ventricular (VVI) pacemakers decreased =50%,18 despite the evidence from large pacing trials19–21 indicating no major differences in outcomes between single and dual chamber pacing modes. In fact, by 2009, DDD pacemakers accounted for 82% of all implants (VVI for only 14%).18 These statistics speak loudly about the impact of technology on daily clinical practice. A similar quandary now exists with regards to biventricular pacing. We suggest that the global utilization of biventricular pacing for all bradycardia patients is not supported by existing data, and that evidence-based application of technology is the best choice for our patients.

Activation Pathways and Cardiac Performance During RV Pacing

The sequence of electric activation of the heart is the physiological determinant of mechanical atrioventricular synchrony and intra left ventricular (LV) synchrony; both of which are independent and additive in contributing to normal cardiac performance and to pacing hemodynamics.22–23 Studies in isolated human hearts24 showed that normal ventricular excitation starts synchronously at 3 widely different endocardial locations in the LV, with RV activation to follow closely (5–10 ms after LV activation). In contrast, RV-paced wavefronts propagate slowly from apex (or pacing site) to base.25 This slowing is presumably because of predominant cell-to-cell propagation with limited or no engagement of the Purkinje conduction system. The effect of ventricular activation on cardiac performance during pacing has been extensively investigated. Boerth and Covell26 reported that during RV outflow-tract

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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stimulation the mechanical efficiency of the LV was decreased without primary effects on cardiac contractility. Rosenqvist et al27 reported that LV ejection fraction (LVEF) and cardiac output were higher during single-chamber atrial than during either DDD or VVI modes. The septum shows a paradoxical pattern of movement during systole in most patients with VVI or DDD pacing, which was associated with a 20% to 25% impairment of the septal regional EF. Other studies have shown that asynchronous ventricular activation can increase, or even cause, mitral regurgitation,28

## Table. Randomized Controlled Studies Comparing Right Ventricular and Biventricular Pacing

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>Year</th>
<th>n</th>
<th>Follow-Up (Mean)</th>
<th>Mean LVEF±SD (%)</th>
<th>Main Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Patients after atrioventricular node ablation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Brignole et al,7 OPSITE study</td>
<td>2005</td>
<td>56</td>
<td>Crossover study; 3-mo treatment period</td>
<td>38±14</td>
<td>Quality-of-life and functional class were better in the biventricular group (P&lt;0.05). LVEF improved by 5% and 10% in the RV and biventricular groups (P&lt;0.05)</td>
</tr>
<tr>
<td>Doshi et al,8 The Pave study</td>
<td>2005</td>
<td>184</td>
<td>6 mo</td>
<td>45±15</td>
<td>Biventricular group had greater improvement in 6-minute walk distance. No differences in quality-of-life. LVEF was higher (46±13) in the biventricular group compared with RV pacing group (41±13) (P&lt;0.05)</td>
</tr>
<tr>
<td>Orlov et al,9 AVAIL CLS/CRT</td>
<td>2010</td>
<td>108</td>
<td>6 mo</td>
<td>57±7</td>
<td>No differences in 6-minute walk, quality-of-life, or mortality. LVEF did not change in the RV pacing group but slightly improved in the biventricular group (from 56.1±9.4% to 59.3±7.7%); (P&lt;0.05)</td>
</tr>
<tr>
<td>Brignole et al10</td>
<td>2011</td>
<td>186</td>
<td>20 mo</td>
<td>37±14</td>
<td>Primary composite end point of death from HF, HFH, or worsening HF occurred less in the biventricular vs RV pacing (11% vs 26% respectively; P&lt;0.01). No differences in total mortality (P=0.37)</td>
</tr>
<tr>
<td>Patients with atrioventricular block</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Kindermann et al,11 HOBIPACE study</td>
<td>2006</td>
<td>30</td>
<td>Crossover design; 3-mo treatment period</td>
<td>26±7</td>
<td>Biventricular pacing reduced LV volume (P&lt;0.01), NT-proBNP levels (P&lt;0.01), and improved quality-of-life (P=0.01). There was a 22% relative improvement in LVEF (P&lt;0.01) and functional parameters compared with RV pacing</td>
</tr>
<tr>
<td>Yu et al,12 PACE study</td>
<td>2009</td>
<td>177</td>
<td>12 mo</td>
<td>61±6</td>
<td>LVEF was lower in RV pacing vs biventricular group (54.8±9.1% vs 62.2±7.0%; P&lt;0.05), and LV volume higher (RV group: 35.7±16.3 mL; biventricular group: 27.6±10.4 mL; P&lt;0.05). There were no differences in HF or mortality</td>
</tr>
<tr>
<td>Chan et al,13 PACE study</td>
<td>2011</td>
<td>177</td>
<td>2 y</td>
<td>61±6</td>
<td>Compared with biventricular pacing, RV pacing was associated with increased in LV end-systolic volume (+13.0 mL; P&lt;0.01) and decreased in LVEF (−9.9%; P&lt;0.01). There were no differences in quality-of-life, 6-minute halt-walk distance, and no differences in HFH or mortality</td>
</tr>
<tr>
<td>Albertsen et al14</td>
<td>2008</td>
<td>55</td>
<td>12 mo</td>
<td>Median quartiles 59 (57–61)</td>
<td>LVEF was not different between groups after 12 mo. NT-proBNP was unchanged in the DDD(R) group during follow-up but decreased significantly in the biventricular group (P=0.02)</td>
</tr>
<tr>
<td>Stockburger,15 PREVENT-HF</td>
<td>2011</td>
<td>108</td>
<td>12 mo</td>
<td>54±12</td>
<td>Intention-to-treat and on-treatment analyses revealed no significant differences in outcomes. LVEF and HF events did not differ between groups.</td>
</tr>
<tr>
<td>Curtis et al,16 BLOCK HF</td>
<td>2013</td>
<td>691</td>
<td>37 mo</td>
<td>40±8</td>
<td>Primary composite end point of death from any cause, an urgent care visit for HF that required intravenous therapy, or a 15% or more increase in left ventricular end-systolic volume index occurred least frequently in patients assigned to biventricular pacing (hazard ratio, 0.74; 95% CI, 0.6 to 0.9).</td>
</tr>
</tbody>
</table>

AVAIL CLS/CRT indicates the AV Node Ablation With CLS and CRT Pacing Therapies for Treatment of AF trial; BLOCK HF, the Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block trial; CI, confidence interval; HF, heart failure; HFH, heart failure hospitalizations; HOBIPACE, Homburg Biventricular Pacing Evaluation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; OPSITE, Optimal Pacing SITE; PACE, Pacing to Avoid Cardiac Enlargement; PREVENT-HF, Preventing Ventricular Dysfunction in Pacemaker Patients Without Advanced Heart Failure; and RV, right ventricular.
increase LV remodeling,\textsuperscript{29} change myocardial perfusion,\textsuperscript{30} and ventricular geometry.\textsuperscript{31} These unphysiological effects have been attributed to an abnormal late activation of the lateral wall of the LV, which results in a redistribution of myocardial strain and work, with less effective contraction.\textsuperscript{32} Although RV apical pacing has some resemblance in the surface ECG with a native left bundle branch block (LBBB), the activation pathways, electromechanical delay, and LV synchrony largely differ between both conditions. Moreover, with RV pacing, the LV is activated more rapidly than with LBBB, even when a LBBB is present before pacing.\textsuperscript{33} Therefore, it is not intellectually rigorous to fully extrapolate the detrimental effects of LBBB and the benefits of cardiac resynchronization therapy (CRT) to all patients who need RV pacing.

But can the physiological findings attributed to RV pacing–induced cardiac dyssynchrony translate into meaningful clinical outcomes such as heart failure hospitalizations (HFH) and mortality? Can these outcomes be improved by preventive biventricular pacing?

**Lessons From Large Trials of Atrial Based Versus Ventricular Pacing Modes**

In 1994, the first randomized trial comparing single-chamber atrial with VVI pacing in patients with normal AV conduction was reported.\textsuperscript{34} This relatively small trial included 225 patients (mean age of 76 years) with sinus node dysfunction and normal QRS and reported no significant differences in survival during the initial follow-up of 3.3 years. However, longer follow-up to a mean of 5.5 years showed that cardiovascular death had occurred in more patients in the ventricular pacing group compared with the atrial pacing group ($P<0.01$).\textsuperscript{35} Moreover, New York Heart Association (NYHA) class was significantly lower in the atrial pacing group (NYHA class I, 84%) compared with the ventricular pacing group (NYHA class I, 65%). This study was relevant because it was the first to suggest that the ventricular dyssynchrony caused by RV pacing might have detectable clinical consequences. Yet, tempting as it may be, we cannot extrapolate the benefit of avoidance of RV pacing a patient with a narrow QRS to the conclusion that CRT is beneficial in all patients with AVB.

Subsequently, larger pacing trials included in aggregate >7000 bradycardia patients; the Pacemaker Selection in the Elderly (PASE) trial,\textsuperscript{16} the Canadian Trial of Physiologic Pacing (CTOPP),\textsuperscript{37} the United Kingdom Pacing and Cardiovascular Events (UKPACE),\textsuperscript{21} and the Mode Selection Trial in Sinus Node Dysfunction (MOST).\textsuperscript{19} investigated the outcomes of physiological DDD pacemakers versus ventricular pacing. Overall, these large pacing trials\textsuperscript{37} showed some benefit in reducing atrial fibrillation (AF) rates (in MOST and CTOPP), but only MOST showed slightly fewer HFH in the DDD pacing group (10.3%) than in the ventricular pacing group (12.3%; $P=0.02$). However, no reduction in mortality was seen in any individual trial. An individual patient data meta-analysis\textsuperscript{37} of these major pacing trials, including the trial by Andersen, MOST, UKPACE, PASE, and CTOPP, investigated the aggregate effect of DDD versus ventricular pacing mode on mortality, stroke, heart failure (HF), or AF. There was no significant reduction in mortality (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.77–1.03; $P=0.15$) or HF (HR, 0.89; 95% CI, 0.87–1.03; $P=0.01$) with DDD pacing, only a reduction in AF (HR, 0.80; 95% CI, 0.72–0.89; $P<0.01$) and borderline reduction in stroke (HR, 0.81; 95% CI, 0.67–0.99; $P=0.03$).\textsuperscript{37} Hence, in aggregate, there were no major clinical benefits derived from physiological pacing compared with ventricular pacing. These findings contrasted sharply with the growing body of physiological data in favor of AV synchrony, puzzled the scientific community, and were ignored by the practice community.

The modern impetus for understanding the consequences of desynchronization by RV pacing was spearheaded by Sweeney et al.\textsuperscript{38} In a retrospective analysis of MOST, a 6-year trial comparing rate-modulated ventricular with DDD pacing (VVIR versus DDDR) in 2010, patients with sinus node dysfunction, the authors found that the risk of HFH increased with the cumulative percentage of RV pacing.\textsuperscript{38} Thus, in retrospect, it was thought that the benefits of AV synchrony in these large trials could have been offset by LV dyssynchrony. However, the association of RV pacing with HFH and AF seen in MOST did not permit a conclusion, but rather posited a hypothesis, which was subsequently tested in the Search AV Extension and Managed Ventricular Pacing for Promoting Atroventricular Conduction trial (SAVE-PaCE).

The SAVE-PaCE study\textsuperscript{39} investigated the outcomes of conventional DDD pacing compared with a pacing strategy to reduce RV pacing. Thus, 1065 patients with sinus node disease, intact atrioventricular conduction, and a normal QRS interval were randomized to either pacing strategy (535 versus 530 patients). The median burden of ventricular pacing was significantly less in the group assigned to DDD minimal RV pacing than in the group assigned to conventional DDD pacing (9.1% versus 99.0%, $P<0.01$), whereas the burden of atrial pacing was similar between the groups. There was a 40% reduction in the relative risk of persistent AF in patients with DDD minimal ventricular pacing when compared with those with conventional DDD pacing, however, the mortality rate was not significantly different between the 2 groups (4.9% for DDD minimal ventricular pacing versus 5.4% in the group receiving conventional DDD pacing), and there were no differences in HFH.\textsuperscript{39} Thus, for patients with sinus node dysfunction, it is best to avoid RV pacing. Such avoidance reduces AF and may reduce HFH, but there is no evidence that it reduces mortality. Although this strategy does not apply to patients with fixed complete heart block, patients with first and second degree AVB and intermittent third degree AVB might benefit from minimization of RV pacing.

Admittedly, the benefit of reducing ventricular pacing for the most serious end points was modest. For instance, in MOST, overall rates of HFH for patients with a ventricular pacing burden >90%, after a median follow-up of 33.1 months, were 12% and 16% in the DDDR and VVIR groups,
respectively. Moreover, for the subset of patients with normal LVEF, narrow baseline QRS, and no history of HF, who were paced >80% or >40% of the time in the VVIR or DDRR modes, the predicted 2-year probability of developing HF was <2%. In UKPACE, which randomized patients with high degree AVB, the median percentage of ventricular pacing was 94% in the single chamber and 99% in the DDRR group. The mean annual mortality rates were 7.2% in the single-chamber group and 7.4% in the DDRR group, and the annual HFH rates were 3.2% and 3.3% respectively. Similar mortality and HFH rates were seen in CTOPP. It is important to note that the patients studied were bradycardia patients. As a rule, they had a low background prevalence of HF, and when LVEF was measured, the median was in the normal range. Thus, the detrimental effects of ventricular desynchronization were relatively minimal.

In contrast, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial enrolled implantable cardioverter defibrillator (ICD) patients with significant LV dysfunction (mean LVEF of 27%), a population vulnerable to any downward perturbation in LVEF and different from the bradycardia patients discussed above. They found that when compared with backup ventricular demand pacing at 40 beats per minute (VVI-40), permanent DDRR pacing at 70 beats per minute (DDDR-70) was associated with higher risk of a combined outcome of death from any cause or HFH (relative hazard, 1.61; 95% CI, 1.06–2.44; P=0.03). Although the component end points did not reach statistical significance, they did trend in favor of VVI-40 for reduction in events. Rates of HFH at 1 year were 13.3% and 22.6% for VVI-40 and DDRR-70 groups (9.3% excess of HFH in the DDRR group; P=0.07), whereas death rates were 6.5% and 10.1%, respectively (P=0.15). Patients included in the DAVID trial had normal AV conduction and no pacing needs, so that the primary difference from a ventricular pacing perspective is that because of traditional AV timing, the DDRR-70 group paced ventricle nearly 60% of all ventricular beats. The VVI-40 group, not needing bradycardia pacing, had 1% ventricular pacing. Additional analyses of percentage of ventricular pacing showed a breakpoint at 40% pacing, above which adverse outcomes became more prevalent. Although these observations cannot be extrapolated to patients with AVB that require bradycardia pacing, they indicate that patients with LV dysfunction sufficient to require ICD placement are highly susceptible to ill effects from frequent ventricular pacing. Moreover, the data from MOST allow us to infer that patients with severe baseline LV dysfunction are far more vulnerable than are patients with preserved LV function. This has been further explored in subanalyses of the Second Multicenter Automated Defibrillator Implantation Trial (MADIT II) and the Inhibition of Unnecessary RV Pacing With AV Search Hysteresis in ICDs (INTRINSIC RV) that included ICD patients programmed in the DDRD mode. In these trials, cumulative RV pacing was also associated with higher rates of HF/mortality or VT-VF therapy.

Clinical Outcomes of RV Pacing in Observational Studies

Observational studies reporting effects from long-term RV pacing are mostly retrospective in nature involve a small to moderate sample size (n=55–304) and encompass a wide range of follow-up (1–7.8 years; Table I in the Data Supplement). Most of these studies were conducted in patients with AF and subsequent RV pacing after atroventricular node (AVN) ablation. Overall, they showed that for patients with normal LV function preimplantation, there were no changes in LVEF after 12 to 20 months of RV pacing. Moreover, 8% to 15% of patients experienced a decline in LVEF or developed HF after 4 to 8 years of pacing. It is apparent from these observations that most patients do not develop adverse clinical outcomes after prolonged RV pacing. Hence, it does not seem appropriate to place preventive biventricular pacers in all individuals that may require permanent ventricular pacing, particularly when this minority of patients can often undergo LV lead implantation should their clinical situation require it. In fact, data from the European CRT survey comparing outcomes of nearly 2400 CRT implant procedures (=30% CRT upgrades), suggests no differences in clinical outcomes or complication rates between upgrades and de novo CRT procedures. This survey showed that individuals undergoing CRT upgrade are older have more ischemic pathogenesis of HF, more prevalence of AF, wider QRS at the time of upgrade, but similar functional class and slightly better LVEF compared with patients having de novo CRT procedures.

Randomized Clinical Trials Comparing RV and Biventricular Pacing

Information from 9 trials comparing RV and biventricular pacing including a total of 1595 patients is shown in Table. Four studies enrolled patients with AF after AVN ablation, and 5 studies (n=1061) were conducted in patients with AVB.

RV Versus Biventricular Pacing in Patients With AF After AVN Ablation

The sample size of these studies ranged from 56 to 186 patients with a maximal follow-up duration of 20 months. The studies by Brignole et al, Doshi et al, and Orlov et al conducted in patients with relatively preserved LVEF (38% to 55%) found that patients who received biventricular pacers had a modest improvement in LVEF (2% to 5% absolute EF increase), and some improvement in quality of life scores or walking distance compared with patients receiving RV pacing. The Ablate and Pace in Atrial Fibrillation (APAF) published in 2011 was the only trial showing benefits in terms of HFH. However, this study enrolled 186 patients who were in drug-refractory HF with depressed LV function and wide QRS complexes and in whom a clinical decision had been made to undertake AV nodal ablation and biventricular pacing. Indeed, nearly 50% of patients had LVEF<35% and >40% required ICD placement at the time of enrollment, resembling more the population of
the DAVID trial. In these patients, the primary composite end point of death from HF, HFH, or worsening HF occurred less often in the biventricular group (11%) compared with the RV group (26%). However, there were no differences in mortality. As expected, the greatest benefit was seen in patients who already met CRT requirements, but there was only a borderline significant reduction in the risk of HF; HR (0.41; 95% CI, 0.17–0.99; P=0.05), when the analysis was confined to individuals with LVEF>35% (n=140). The authors did not report the baseline characteristics of this subgroup. A meta-analysis including the APAF trial as well as of the trials by Brignole et al, Doshi et al, and Orlov et al with a total of 534 patients found that compared with RV pacing, biventricular pacing was associated with an absolute increase in LVEF (2.6%; 95% CI, 1.69–3.44), improvement in quality of life, but no significant improvement in 6-minute walk distance and no significant improvement in mortality. Therefore, in patients with refractory AF that undergo AVN ablation, biventricular pacing may provide clinical benefit only in patients who have LV dysfunction, whereas for those with normal or near normal LV function, there is no apparent clinical benefit. Thus, the modest differences in LVEF between RV and biventricular pacing are likely to be clinically relevant only in patients with symptomatic HF and reduced ventricular function.

**RV Versus Biventricular Pacing in Patients With AVB**

Two trials enrolled patients with reduced LVEF and 3 trials randomized patients with normal or nearly normal LVEF (Table).

The Homburg Biventricular Pacing Evaluation (HOBIPACE) trial reported in 2006 was a prospective, randomized crossover study that compared 3 months of RV pacing with 3 months of biventricular pacing in 30 patients with LVEF <40% (with most participants having LVEF<30%). The average participant of this study was in HF (NYHA functional class 3.0±0.6) had low LVEF ≥26% and a long QRS (≥174 ms) with a LBBB (63% of participants had complete LBBB); hence most participants were already eligible for ICD and CRT. Both RV and biventricular pacing were associated with improvement in LVEF and reduced LV end-diastolic and end-systolic volumes. However, biventricular pacing resulted in a 6.3% absolute increase in LVEF compared with RV pacing (34.8±8.9 versus 28.5±11.2; P<0.01; relative increase of 22%, P<0.01), reduced LV end-systolic volume by 17% (P<0.01), and peak oxygen consumption by 12% (P<0.01). In RV-paced patients, benefits were mostly seen in those who received septal RV leads. Of note, similar to other trials, the physiological response to biventricular pacing showed a wide range from absent to large. In contrast, the studies by Albertsen et al and Stockburger et al included patients with normal LVEF and borderline QRS duration (117 and 123 ms). The average follow-up was 12 months in both studies. In these trials, there were no differences in outcomes, which included LVEF changes and HFH rates.

Similarly, The Pacing to Avoid Cardiac Enlargement (PACE) trial found that in individuals with normal LVEF randomized to RV or biventricular pacing, there were no differences in functional class, HFH, or mortality after 12 months of follow-up. However, after 1 year of follow-up, patients in the RV group had a reduction in LVEF (from 61.5±6.6% to 54.8±9.2%; P<0.01), whereas the LVEF in the biventricular pacing group remained unchanged (from 61.8±6.7% to 62.2±7%). LV end-systolic volume increased in the RV pacing group (from 28.4±10.7 to 35.7±16.2 mL; P<0.01) but did not significantly change in the biventricular group (from 28.2±9.4 to 27.6±10.2 mL). Chan et al reported a 2-year follow-up of the PACE trial. There was a small additional mean absolute reduction in LVEF of 1.8% compared with LVEF at 1 year (P<0.05) and an absolute mean increase in LV end-systolic volume of 2.6 mL in the RV group (P<0.05), whereas for the average biventricular patient, LVEF and LV size remained stable. However, after 2 years of follow-up, there were no differences in quality-of-life assessment, 6-minute hall–walk distance, or clinical outcomes (HFH or mortality). Overall, these trials found biventricular pacing to have a modest impact on LVEF and LV volume compared with RV pacing but no differences in HFH or mortality.

The Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (BLOCK HF) trial is the most recent and largest trial comparing RV and biventricular pacing modes in patients with indication for pacing and evidence that they would require frequent ventricular pacing (2nd and 3rd degree AVB or first degree AVB with a PR interval of at least 300 ms when paced at 100 beats per minute) and a LVEF of ≤50%. BLOCK HF enrolled 691 patients with LV dysfunction (average LVEF 40%), 30% had LVEF<35% and near a third of participants (n=207) had an ICD placed at the time of pacemaker insertion. Participants were in NYHA class I, II, or III and not meeting current indications for CRT to receive DDDR or BIV-DDDR pacing. The median percentage of ventricular pacing during follow-up was >97% for both pacing groups, and the mean follow-up was 37 months. The combined primary end point was unusual in that it combined morphological and clinical variables (increase in left ventricular end-systolic volume index >15% or urgent care visit for HF or death). Such end points are even harder to interpret than the usual combined clinical end points. Regardless, the primary end point occurred more often in the RV pacing group with a 26% relative reduction in the biventricular group, largely driven by change in LV end-systolic volume which occurred in 160 patients in the biventricular group compared with 190 patients in the RV group. Urgent care visits for HF occurred in 56 and 61 patients and death occurred in 17 and 14 patients in the biventricular and RV groups, respectively, a small clinical difference. In this trial, a Bayesian analysis was utilized and its comparability to traditional analyses is unclear. HFH occurred in 21% and 26% of the biventricular and RV groups, respectively, which represents a 5% absolute risk reduction (n=14 events). Although this study would seem to suggest that biventricular pacing might be the mode of choice for patients with AVB, patient selection again weakens the assertion. The
study was heavily seeded with low EF, HF patients: 30% of the participants of this study had LVEF<35% and a third of individuals were NYHA class III patients who already might benefit from a biventricular ICD. Furthermore, nearly 50% of participants in this study were not in complete heart block and could benefit from atrial-based minimal ventricular pacing. Thus, BLOCK HF suggests that there is at least a group of patients with LV dysfunction requiring bradycardia pacing, in whom biventricular pacing will possibly yield at least modest clinical benefit, so long as baseline LV function is known. It is not clear, however, whether the benefit is isolated to patients who should be receiving an ICD anyways. Moreover, the 5% absolute risk reduction by biventricular pacing in this population could be offset by the higher rate of complications related to this procedure (10.3% in BLOCK HF).

Available trial data suggest that for individuals with normal LVEF, the use of preventive biventricular pacing has no clinical benefits in terms of HFH or mortality. In those with moderate to severe LV dysfunction (LVEF<55%), biventricular pacing improves functional capacity and reduces HFH. However, for patients with LVEF between 35% and 50%, the benefit of preventive biventricular pacing is unclear, and predicting deterioration of LV function after prolonged RV pacing in this population is clinically relevant. Hence, long-term follow-up studies investigating the role of biventricular pacing in AVB patients with mildly reduced LV function are needed. BLOCK HF provided the longest follow-up of the available trials comparing RV and biventricular pacing (mean follow-up, 3.7 years; Table). However, BLOCK HF also included high-risk patients with low LVEF.

Prior HFH, coronary artery disease, male sex, and wider paced QRS duration after implantation may predict worse outcomes after prolonged RV pacing.58 In MOST, NYHA class at the time of pacemaker implantation, history of myocardial infarction, low baseline LVEF, and prolonged QRS duration (spontaneously or with RV pacing) predicted HFH.40 Still, there is a lack of validated predictors to guide on the table decisions to find the RV location that best suits a particular patient or to decide if a particular patient will benefit most for biventricular pacing. Indeed, the best strategy seems to be to know the patients’ LVEF and their functional class before pacemaker implantation, data obtainable with a bedside echo and a short conversation rather than the shotgun overuse of technology in every case. Of note, other RV pacing locations have been associated with less cardiac dyssynchrony when compared with RV apical pacing. These include para-Hisian pacing, RV septum, right ventricular outflow tract in the septal region, and the pulmonary infundibulum. Pacing from the RV septum results in a shorter QRS compared with pacing from other RV sites.40 Pacing failure in this setting occurs more often in patients with AF, RV dilatation, or high-grade tricuspid insufficiency.47 However, a meta-analysis by Shimony et al,48 including a total of 754 patients from 14 studies, found no significant differences in terms of quality of life, functional tests (walking test, maximum oxygen consumption), and morbidity/mortality. A favorable effect on LVEF was demonstrated for follow-up periods of >12 months and for patients with LVEF ≤45%. Current large randomized studies are comparing right ventricular outflow tract and RV septum with RV apical pacing.49

So ultimately, we are left with the question of what patient who does not concurrently require a biventricular ICD requires biventricular bradycardia pacing alone? Biventricular bradycardia pacemakers account for <10% of implants in the United States.18 Biventricular pacers are more expensive and associated with more complications. These may lead to hospitalizations and reoperations in 10% to 15% of patients.8,11,12 In the BLOCK HF trial,16 10.3% of patients had events related to the procedure or device. LV lead–related complications occurred in 6.4% of patients (dislodgement 3%). Moreover, 4.9% had serious adverse events related to CRT within 6 months (eg, lead damage, pacing failure, and diaphragmatic pacing). The rate of complications may be at least as high in clinical practice. Furthermore, biventricular implantation is more technically complex with a success rate ≤90% (when compared with a success rate of ≥98% using single ventricular leads). It requires longer fluoroscopic times and usually requires the use of contrast agents to define the coronary venous anatomy.

Although the reported incidence of severe immediate reactions to contrast material is low (0.1–0.4%), contrast-induced nephropathy can occur in 8% of all patients and ≤12% of patients requiring >95 cm3 of contrast for LV lead placement.50 Patients with chronic kidney disease and HF are particularly susceptible. AV conduction defects may account for ≥50% to 55% of pacemaker implants, and one-third of patients who need a pacemaker have LV systolic impairment.51,52 In addition, only 50% to 70% of patients with a clear indication will benefit from CRT therapy.53 Thus, the widespread use of biventricular pacemakers in patients with AVB would invariably result in a higher number of complications in the community, without clearly defined benefit for a small number of patients.

Although biventricular pacing coupled with ICD therapy reduces HF and mortality in patients with low LVEF, LBBB, and HF symptoms, the data supporting the widespread application of biventricular bradycardia pacing to all patients with heart block is insufficient. Although changes in LVEF and LV volumes are often cited as evidence of benefit, pacemaker therapies must be calibrated to reduce hard clinical end points, such as HF and mortality. Patient selection for biventricular ICDs can be as simple as an echo and a short conversation about symptoms and length of time since the last myocardial infarction or revascularization. Still, the answer may be more nuanced, as alternative RV pacing sites may minimize the ill effects of apical RV pacing. For patients with AVB that have some intrinsic conduction, atrial-based minimal ventricular pacing mode in DDD devices may help to reduce unnecessary RV pacing.44 Overall, however, the one size fits all approach to ventricular pacing in this population is not supported by available trial data, which does not support universal biventricular pacing.
Disclosures
None.

References


Key Words: biventricular pacing | cardiac resynchronization therapy | heart block | pacemaker, artificial

**Arenas et al  Biventricular Pacing in Patients With Heart Block 737**
Arenas et al have nicely summarized much of the information we have on dual chamber (DDD) and biventricular pacing. They have concluded that the available trial data do not support universal biventricular pacing for heart block. But in our view, the data do support wider use than currently. We would like to make the following comments:

The authors make a comparison with the now historical debate on whether DDD pacing is superior to ventricular pacing only to illustrate how at that time there was a disconnect between clinical trials (no difference in mortality) and clinical practice (large increase in DDD pacemaker implantations) and to suggest this should be avoided now with biventricular pacing. However, clinicians favoring DDD pacing based on their opinion that the atria are present for a purpose were subsequently proven right. Meta-analyses found significant beneficial effects with DDD pacing for prevention of atrial fibrillation and pacemaker syndrome and providing better exercise capacity. Prevention of atrial fibrillation and pacemaker syndrome may even be more important to an elderly patient than a few months of extra life. Furthermore, nearly all the trials, Arenas et al quote relate to patients with sick sinus syndrome. Patients with chronic atrioventricular block are a different population; for example, sick sinus syndrome is more common in women, atrioventricular block is more prevalent in men, and the associated risk factors are different. Therefore, the relevance of the data from this earlier debate about pacing is questionable.

There is considerable information demonstrating that RV apical pacing has acute adverse consequences on left ventricular (LV) function (albeit differing from left bundle branch block). It is hard not to conclude that asynchronous contraction will have deleterious long-term consequences on LV function and that biventricular pacing should be preferable. As noted, there is conclusive evidence that biventricular pacing definitely improves LV function, reduces mortality, and improves quality of life in those with damaged LVs. The question is whether this benefit can be realized in those with apparently more normal LV function and prevents further deterioration. We accept that although at present the data from the clinical trials in terms of mortality are conflicting, it is not clear if other benefits, such as quality of life, which is equally important, may be improved.

Although Arenas et al state “....changes in LV ejection fraction and LV volumes are often cited as evidence of benefit, pacemaker therapies must be calibrated to reduce hard clinical endpoints, such as HF and mortality,” this is not the whole story. Quality of life may be more important is this elderly group of patients. Arenas et al conclude that “Overall, however, the ‘one size fits all’ approach to ventricular pacing in this population is not supported by available trial data, which does not support universal biventricular pacing.” But they are also guilty of another “one size fits all” mentality when they, and frequently trialists, assert dogmatically that the results of large clinical trials are definitive and apply to all subjects; and that if mortality is not reduced the therapy is not worth considering further. This outlook inhibits the development of more tailored and individually directed therapy which is increasingly common in other branches of medicine, such as oncology. We need to develop better criteria to identify those patients who may benefit substantially in terms of quality, as well as quantity of life, from new therapies. This group of patients may be obscured or lost in large clinical trials using only a mortality end point. Our article is designed to stimulate debate and further research to focus on these issues and to promote the best pacing therapy for each individual patient. In this regard much remains to be done.

References
Routine Use of Biventricular Pacing Is Not Warranted for Patients With Heart Block
Ivan A. Arenas, Jason Jacobson and Gervasio A. Lamas

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<table>
<thead>
<tr>
<th>Study/reference</th>
<th>Year</th>
<th>Type of study/population</th>
<th>n</th>
<th>Follow up (mean)</th>
<th>Mean LVEF±SD (%)</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kay GN et al (1). The Ablate and Pace trial.</td>
<td>1998</td>
<td>Prospective study, AF patients with AVN ablation.</td>
<td>156</td>
<td>12 months</td>
<td>50±20</td>
<td>LVEF improved (from 31% to 41%; p&lt;0.01) in patients with reduced LVEF pre-pacing. There were no significant changes in functional capacity evaluated by duration in a treadmill or VO2max.</td>
</tr>
<tr>
<td>Tops LF et al (2)</td>
<td>2006</td>
<td>Retrospective study, AF patients with AVN ablation.</td>
<td>55</td>
<td>3.8 years</td>
<td>48±7</td>
<td>LVEF decreased (from 48 ± 7% to 43 ± 7%; p &lt; 0.05), LV end-diastolic volume increased (from 116 ± 39 ml to 130 ± 52 ml; p &lt; 0.05) and HF worsen but only in patients with LV dyssynchrony.</td>
</tr>
<tr>
<td>Chen L et al (3)</td>
<td>2008</td>
<td>Retrospective study, AF patients with AVN ablation.</td>
<td>286</td>
<td>20 months</td>
<td>48±18</td>
<td>No change in LVEF overall. 13% LVEF improved &gt;10%, 15% of patients LVEF decreased &gt;15% and 72% had no change in LVEF.</td>
</tr>
<tr>
<td>Poçi D et al (4)</td>
<td>2009</td>
<td>Retrospective study, AF patients with AVN ablation.</td>
<td>213</td>
<td>6 years</td>
<td>55±12</td>
<td>13% developed HF or LVEF &lt; 45%; New HF happened after an average time of 44 months following AVN ablation. For those with history of HF, 26% developed aggravation of HF during follow-up.</td>
</tr>
<tr>
<td>Tan ES et al (5)</td>
<td>2008</td>
<td>Retrospective study, AF patients with AVN ablation.</td>
<td>121</td>
<td>4.3 years</td>
<td>Mean fractional shortening 28±10</td>
<td>HFH occurred in 20% patients, predominantly in patients with history of HF. LV end systolic diameter decreased and fractional shortening improved.</td>
</tr>
<tr>
<td>Zhang XH et al (6)</td>
<td>2008</td>
<td>Retrospective study, patients with acquired AVB that received RV pacing (81.9% DDD; 18.1% VVI)</td>
<td>304</td>
<td>7.8 years</td>
<td>65±10</td>
<td>26% developed new-onset HF; those with paced QRS&gt;165 ms had higher incidence of HF (sensitivity/specificity: 58/64%; p&lt;0.01). The mean duration of pacing from pacemaker implantation to onset of HF was 6.5 ± 5.7 years (range 0.2–27.7 years).</td>
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AF: Atrial fibrillation; AVN: atrioventricular node ablation; AVB: Atrioventricular block; LVEF: left ventricular ejection fraction; HFH: Heart failure Hospitalization.