Conventional right ventricular (RV) pacing can cause left ventricular (LV) dysfunction and even heart failure (HF) particularly if ventricular pacing is frequent. New onset HF has been observed in approximately one third of patients receiving RV pacing for acquired second- or third-degree atrioventricular block (AVB) after a median follow-up of nearly 8 years. An elegant study has shown recently that apparent pacing induced cardiomyopathy could occur even if the accumulative pacing percentage was <40%. Although there has been rapid progress in medication and device therapy for HF, it is still a burden on the public health systems and better prevention remains important. Avoiding the use of a potentially harmful device when a good alternative is available is a matter of serious consideration.

**Response by Arenas et al on p 729**

Single- or dual-chamber pacemakers with RV pacing are undoubtedly the main therapy for symptomatic AVB. With increasing evidence of potential adverse effects of permanent RV pacing mainly because of systolic dyssynchrony, other pacing modalities or pacing modes are being considered. Biventricular pacing is one of the options and has been shown to be potentially superior to RV pacing even for those who require pacing but do not have a conventional indication for biventricular pacing. Biventricular pacing is emerging as a realistic treatment option to prevent RV pacing induced LV dysfunction for symptomatic patients with advanced AVB.

**Prevalence and Indications for Pacing in AVB—The Size of the Problem**

Despite the lack of accurate epidemiology data for AVB, it is clear that it is not uncommon in both apparently healthy populations and those with overt heart disease. Approximately 1% to 2% of normal subjects have first-degree AVB which increases to 5% in men over the age of 60 with cardiac diseases. The prevalence of second-degree AVB for Mobitz II block is estimated to be 3% in patients with HF, and it is estimated that 5% to 10% of people will develop a third-degree heart block in those >70 years old and having a history of heart disease. In clinical practice, decisions for pacemaker implantation are determined by symptoms and pacing indications as in the guidelines which are based on expert opinion from experience because there is no other effective treatment for bradycardia and no major randomized trials. According to the updated ACC/AHA/HRS Guidelines for Device-Based Therapy and European Society of Cardiology guidelines on cardiac pacing and
cardiac resynchronization therapy (CRT),\textsuperscript{12} RV pacing is indicated for third-degree block and advanced second-degree AVB with symptoms, ventricular arrhythmias, operation-induced or advanced AVB caused by ablation of atrial fibrillation, medical conditions requiring drug therapy that may exacerbate the bradycardia, atrial fibrillation with long pauses.

The majority of patients with Mobitz type I second-degree AVB do not require a permanent pacemaker, but it should be considered for persistent and symptomatic Mobitz type I second-degree AVB, which also might be associated with an increased risk of HF.\textsuperscript{11,12} Although first-degree AVB is traditionally considered to be a benign condition, it was found recently to be associated with an increased risk of atrial fibrillation and all-cause mortality in community populations, and to be related to HF and mortality in patients with stable coronary artery disease.\textsuperscript{9} Hence, first-degree AVB is likely to be an electric marker of more severe underlying disease.\textsuperscript{11} In summary, the various forms of AVB are common and a substantial number of patients will receive a pacemaker, and therefore identification of the best pacing mode will have a widespread impact.

**Comparison of RV and Biventricular Pacing for AVB Patients**

Dual-chamber pacing with leads fixed in the RV and right atrium has been the main therapy for AVB and restoration of AV synchrony is relatively easy to implement. However, detrimental effects attributed to long-term RV pacing, including LV adverse remodeling, cardiac dysfunction, and the occurrence of HF, have been consistently reported\textsuperscript{14–21} (Figure 1). Those receiving the most pacing are likely at greatest risk.\textsuperscript{15,16,22} Attempts to reduce the negative effects are mainly focused on minimizing ventricular pacing in sinus node disease, optimizing pacemaker settings, and seeking better pacing sites. An alternative approach is to use a site other than the RV apex in an attempt to reduce pacing-induced ventricular dyssynchrony.\textsuperscript{5,23,24} Other pacing sites include the RV mid or low septum, the RV inflow tract, the RV outflow tract, and the His bundle region. However, true RV septal pacing and His bundle pacing are limited by the difficulty of achieving stable lead positions.\textsuperscript{25,26} The most commonly used alternative site is the RV outflow tract, but there is as yet no randomized trial evidence that supports the superiority of this pacing site compared with RV apical pacing.\textsuperscript{27}

Biventricular pacing is a well-established therapy for HF patients with LV ejection fraction (LVEF) <35\% and wide QRS complex duration. It has also been shown to produce improvement on LV function and reverse LV remodeling when upgrading RV pacing to biventricular pacing in those who develop LV systolic dysfunction.\textsuperscript{28} The recognition that intraventricular systolic incoordination (dyssynchrony) can be corrected with biventricular pacing is an important reason that promotes indications for biventricular pacing to evolve.\textsuperscript{12} Intriguingly, 8\% to 15\% of patients with advanced HF have symptomatic bradycardia which necessitates pacemaker therapy and, conversely, it is estimated that up to 40\% of patients with permanent pacemakers have HF or LV systolic dysfunction because of frequent RV pacing and their underlying cardiac disease.\textsuperscript{29} In addition, many patients with HF and preserved LVEF have an evidence of ventricular dyssynchrony at rest and on exercise which may be worsened by RV apical pacing.\textsuperscript{30} Biventricular pacing has been promising in recent randomized controlled clinical trials comparing biventricular and RV pacing irrespective of baseline LV systolic function (Table).\textsuperscript{6,7,31,32}

**Evidence for Biventricular Pacing for Heart Block With Depressed EF**

In a randomize trial conducted in patients with AV node ablation for atrial fibrillation, biventricular pacing was first proven to be superior to RV pacing, achieving better exercise capacity and LVEF, especially for those with pre-existing HF.\textsuperscript{33} These benefits were also confirmed in a later meta-analysis.\textsuperscript{34} Because the pathophysiology of complete AVB and AV node ablation are similar, this adds support to the notion that biventricular pacing should be used routinely in patients with LV dysfunction and conventional indications for pacing. A direct comparison between biventricular pacing and RV pacing in patients with AVB was performed in the Homburg Biventricular Pacing Evaluation (HOBIPACE) randomized study. Although the sample size was small (n=30), biventricular pacing was superior to conventional RV pacing in reduction of LV volumes, and improvement of LVEF, quality of life, maximal and submaximal exercise capacity.\textsuperscript{35} A similar effect was also found in the Conventional Versus Multisite Pac- ing for Brady Arrhythmia Therapy (COMBAT) study.\textsuperscript{36} More evidence came from the randomized Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (BLOCK HF) study, which had a much larger sample size (n=691; 134 with first degree, 227 with second degree, and 329 patients with third-degree AVB).\textsuperscript{6} Patients were randomized to CRT-Pacemaker, CRT-Defibrillator , or RV apical pacing. At a mean follow-up of 37 months and median ventricular pacing burden of >97\%, patients receiving biventricular pacing had a significant 26\% reduction in the combined end point (all-cause mortality, urgent care for HF or increase in LV end-systolic
### Table. Major Clinical Trials That Compared the Use of RV Pacing Versus Biventricular Pacing in Patients With Bradycardia Indications

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Inclusion Criteria</th>
<th>Treatment</th>
<th>Follow-Up Time</th>
<th>End Point End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOBIPACE&lt;sup&gt;33&lt;/sup&gt;</td>
<td>30</td>
<td>Patients with permanent ventricular pacing indication and LV end-diastolic diameter ≥60 mm and LVEF ≤40%</td>
<td>After run-in phase, patients randomized to 2 pacing mode: RV (3 mo)–biventricular (3 mo) and biventricular (3 mo)–RV (3 mo)</td>
<td>Follow-up performed for 2 to 3-mo study periods with crossover to the complementary pacing mode</td>
<td>LV end-systolic volume, LV ejection fraction, and peak oxygen consumption</td>
<td>More improvement of LV function, QoL, and maximal as well as submaximal exercise capacity with biventricular pacing than with RV pacing</td>
</tr>
<tr>
<td>COMBAT&lt;sup&gt;34&lt;/sup&gt;</td>
<td>68</td>
<td>AVB with pacemaker indications and NYHA Class II–IV, and LVEF ≤40%</td>
<td>Complete: 30 Type II: 19 Advance: 11</td>
<td>Group A: RV pacing–biventricular Pacing and crossed back to RV pacing Group B: biventricular Pacing–RV pacing–biventricular pacing</td>
<td>Each mode lasting at least 3 mo</td>
<td>QoL and NYHA Class</td>
</tr>
<tr>
<td>PACE and extended follow-up&lt;sup&gt;7,31&lt;/sup&gt;</td>
<td>177</td>
<td>Bradycardia and LVEF ≥45%</td>
<td>104 AV block patients</td>
<td>Biventricular pacing (n=89) and RV pacing (n=88) at 1 y biventricular pacing (n=82) and RV pacing (n=81)</td>
<td>1 y and extended to 2 y</td>
<td>LVESV and LVEF</td>
</tr>
<tr>
<td>PREVENT-HF&lt;sup&gt;32&lt;/sup&gt;</td>
<td>108</td>
<td>Patients with an expected ventricular pacing percentage ≥80%</td>
<td>108 with AV block</td>
<td>Biventricular pacing (n=50) RV pacing (n=58)</td>
<td>12 mo</td>
<td>Primary end point: LV end-diastolic volume Secondary end points: LVESV, LVEF, and a combination of HF events and cardiovascular hospitalizations, mitral regurgitation</td>
</tr>
<tr>
<td>BLOCK HF&lt;sup&gt;6&lt;/sup&gt;</td>
<td>691</td>
<td>AV block with NYHA I–III and LVEF ≤50%</td>
<td>First-degree: 134 Second-degree: 227 Third-degree: 329</td>
<td>Biventricular group (n=349) and RV group (n=342)</td>
<td>37 mo</td>
<td>Death from any cause, an urgent care visit for HF requiring intravenous therapy, or an increase in the LVESV index of 15%</td>
</tr>
<tr>
<td>BioPACE trial&lt;sup&gt;43&lt;/sup&gt;</td>
<td>1810</td>
<td>Indication for implantation of a ventricular pacemaker according to guideline or anticipated need for frequent ventricular pacing</td>
<td>N/A</td>
<td>Biventricular group (n=902) and RV group (n=908)</td>
<td>5.6 y</td>
<td>Combination of time-to-death or first hospitalization because of HF</td>
</tr>
</tbody>
</table>

AVB indicates atrioventricular block; BIOPACE, Atrioventricular Block to Prevent Cardiac Desynchronization; BLOCK HF, Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block; HF, heart failure; HOBIPACE, Homburg Biventricular Pacing Evaluation; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, new York heart association; PACE, Pacing to Avoid Cardiac Enlargement; QoL, quality of life; and RV, right ventricular.
volume index >15%) when compared with RV pacing. The benefits were similar in the CRT-Pacemaker and CRT-Defibrillator groups. The superiority of biventricular pacing to RV pacing for the secondary end points (death or hospitalization for HF) was also established with posterior probability of a combined hazard ratio >0.9775.

This landmark trial provided promising evidence that biventricular pacing is able to prevent LV remodeling, HF events, and mortality caused by conventional RV pacing in patients with mild or modest systolic dysfunction. With these results, the Food and Drug Administration (FDA) approved the use of biventricular pacing in those with AVB associated with high ventricular pacing percentage, mild to moderate HF symptoms, and LVEF≤50%.37

Evidence of Biventricular Pacing for Advanced AVB Patients With Normal LVEF

Patients with normal LVEF seem more resistant to the adverse effects of RV pacing, but LV dysfunction is still commonly observed especially in those with frequent and long-term ventricular pacing. However, the depression of LV systolic function can become manifest at an early stage and may persist after the cessation of pacing. Biventricular pacing may avoid this negative impact. This hypothesis was tested in the Pacing to Avoid Cardiac Enlargement (PACE) trial, which was the first randomized, controlled, multicenter study that compared biventricular pacing with RV pacing in bradycardia patients with a pacing indication and normal LVEF.7 At 1-year follow-up, RV pacing resulted in a significant reduction of LVEF and enlargement of LV end-systolic volume which were prevented by biventricular pacing (Figure 2). Benefit was shown in the subgroup of patients with AVB. Extended 2-year follow-up demonstrated further deterioration of LVEF and LV end-systolic volume in the RV pacing group, but no deterioration in the biventricular pacing group.33 Long-term follow-up of this trial confirmed the same pattern and also that HF hospitalizations were less frequent in the biventricular pacing arm.44 Further analysis showed that the development of pacing-induced systolic dyssynchrony was associated with LVEF reduction and LV adverse remodeling.4 This trial provided good evidence for a progression of LV remodeling and eventually HF caused by RV pacing which was prevented by biventricular pacing in patients with bradycardia and normal LVEF. Moreover, the potential mechanism of the benefit of biventricular pacing appeared to be related to the correction of systolic dyssynchrony.

Despite these encouraging studies, the evidence is not yet sufficiently strong to support widespread adoption of biventricular pacing in patients with normal LVEF because of conflicting results from other trials. The Progressive Ventricular Dysfunction Prevention in Pacemaker Patients (PREVENT-HF) trial found little difference in LV volumes, LVEF, mitral regurgitation, or the combination of HF events and cardiovascular hospitalization at 1-year follow-up between biventricular and RV pacing groups.36 The main criticism of this trial was small sample size (n=108 with ventricular pacing percentages ≥80%) and high crossover rate from biventricular to RV pacing.45 The preliminary results of the larger (n=1,810) Biventricular pacing for Atroventricular Block to Prevent Cardiac Desynchronization (BIPACE) study43 were released at the annual meeting of the European Society of Cardiology in 2014. The composite end point of death or first HF hospitalization was similar between biventricular and RV pacing.
groups although there was a nonsignificant trend for superiority of biventricular pacing (P=0.08). More details are necessary to decipher which subgroups really benefit from biventricular pacing. This neutral result might be related to the high rate of implantation failure for biventricular pacing (14.1%). Other details, such as biventricular pacing percentage and the battery longevity in the biventricular pacing arm, which could have an impact, were not reported.

Currently, any benefit of prophylactic biventricular pacing in patients with bradycardia and normal LVEF seems marginal. Given the fact that nearly 30% of all CRT implants were upgraded from RV pacing in a registry, and that the pacing population is commonly elderly and vulnerable to developing HF because of age-related increase in chamber stiffness, hypertension, LV hypertrophy, diabetes mellitus, and coronary artery disease, some feel that the de novo use of biventricular pacing should not be criticized in AVB patients when the aim is to prevent LV remodeling. The identification of patients at high risk to develop LV dysfunction or HF from RV pacing would be useful, but at the moment there is not even consensus on a definition of frequent ventricular pacing that increases this risk.

**Biventricular Pacing in First-Degree AVB**

Although first-degree AVB usually causes no symptoms and does not require any special treatment, it is an independent predictor of all-cause mortality in the general population and is independently associated with HF hospitalization, mortality, and the combined end point of HF hospitalization or cardiovascular mortality in coronary artery disease patients. Irrespective of baseline LV function, dual-chamber pacemakers can improve the symptoms in those with a P-R interval ≥0.30 s. Around half of patients with biventricular pacing for standard HF indications have first-degree AVB, but the value of biventricular pacing in these patients is not clear. In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, CRT was associated with a reduction in the all-cause, cardiac, and HF hospitalization rates. First-degree AVB was present in 52% of the subjects and reduction in relative risk (CRT versus optimal medical therapy) was 29% for those with normal P-R intervals but was 46% (P<0.01) for those with P-R prolongation. The authors concluded that P-R prolongation may affect mortality and HF hospitalizations in patients with systolic dysfunction, HF, and a wide QRS complex, and that the effect of P-R prolongation may be attenuated by CRT.

**Practical Issues of Biventricular Pacing for Heart Block Patients in Real-World Practice**

At present, however, there is no evidence for a reduction of mortality with biventricular pacing when compared with RV pacing, which might be ascribed to the relatively short duration of follow-up in patients studied. For those patients with normal LVEF, mortality and HF hospitalizations are much less frequent with RV pacing than in patients with reduced LVEF. The main challenge in these patients is to detect the vulnerable group before implantation to avoid closing the door after the horse has bolted. Despite the lack of a consensus on the risk factors for developing LV dysfunction, a wider QRS in combination with underlying heart diseases have been suggested as potential predictors. However, it must be acknowledged in the elderly in whom pacing is being undertaken primarily to prevent syncope and who have a relatively short-life expectancy, it is obviously reasonable to implant a standard RV pacemaker, particularly in view of the increased complexity and expense of biventricular pacing.

The implantation of biventricular pacemakers requires extra skill in placing the LV lead into the coronary sinus and its branches. Although this can be a technical challenge in the markedly enlarged LV in HF subjects, it seems to be technically much easier in the normal or near normal sized heart. Furthermore, technological advances have significantly improved the ability to access to the coronary sinus and increased the success rate of LV lead implantation with fewer complications. The expanding application of biventricular pacing in AVB patients will be challenged because of higher cost. Data to compare the cost-effectiveness between RV pacing and biventricular pacing are scanty, but the cost of implantation may be outweighed by the clinical improvement and savings from reduced hospital admissions in those with AVB and reduced LVEF.

In patients who are receiving RV pacing, many centers do not routinely perform echocardiography to evaluate ventricular function, and signs of HF might be missed until more serious symptoms or a HF hospitalization occur. Therefore, it is recommended to monitor cardiac function on a regular basis so that upgrading to biventricular pacing can be implemented without delay if evidence of LV adverse remodeling and reduced LVEF is present.

**Conclusions**

Biventricular pacing reverses LV remodeling and reduces HF hospitalization and mortality in patients with established HF, low LVEF, and wide QRS. It is also beneficial in patients with mild HF who require frequent ventricular pacing, in whom biventricular pacing could be remarkably more beneficial than routine RV pacing. Apart from these established roles, biventricular pacing is evolved to be an appropriate consideration for the broader pacing population. Although it holds promise, a preventive role of biventricular pacing avoiding HF in subjects with normal LVEF remains controversial. Although guidelines do not currently recommend routine biventricular pacing for all patients with heart block, with the increasingly recognized potential for harmful effects of RV pacing and accumulating evidence of the benefits of biventricular pacing, the "one move, double the gains" strategy deserves more attention and discussion.

**Disclosures**

None.
References


Response to Fang Fang, MB, PhD, John E. Sanderson, MD, Cheuk-man Yu, MD

Ivan A. Arenas, MD, PhD, Jason Jacobson, MD, Gervasio A. Lamas, MD

Fang et al in the counterpart review for this debate have for the most part agreed that the evidence for the “one move, double the gains” strategy to support the widespread use of biventricular pacing in all patients with heart block is not robust. Fang et al agreed with our view that current data do not support the use of biventricular pacing in patients with preserved left ventricular (LV) ejection fraction. Still, they failed to conclude that the supporting evidence for patients with mild LV dysfunction is at most, observational. In fact, they did not comment on important details of BLOCK HF; this trial did not show any effect on mortality. Moreover, the decreased event rate of the combined primary endpoint was driven mostly by changes in LV geometry and heart failure (HF) hospitalizations. Importantly, the trial randomized patients with mild to severe LV dysfunction, and approximately one third of participants were in NYHA class 3, but the effect of prepacing LV ejection fraction/functional class on outcomes was not reported. We agree the available evidence favors the use of biventricular pacing in patients with moderate to severe LV dysfunction with concurrent advanced atrioventricular block and expected high percentage of ventricular pacing. However, for patients with mild LV dysfunction with frequent right ventricular (RV) pacing, it remains unclear if biventricular pacing is better than a watchful approach (eg, RV pacing and biventricular pacing if needed). Based on the results of BLOCK HF, the Food and Drug Administration (FDA) approved the use of biventricular pacing for patients with atrioventricular block with NYHA class 1 to 3 and LV ejection fraction ≤50% who are expected to have frequent ventricular pacing. This may lead to unnecessary biventricular pacing placements without certainty about costs/benefits. Furthermore, it is about that this approval may decrease the interest of the scientific community to further investigate predictors of LV dysfunction after right ventricular pacing, and may shut the funding from industry to support a well-powered trial to answer the unresolved questions. At this juncture, patient history and a baseline echocardiogram are likely our best shot to better assist patients with heart block when considering pacemaker options. We are left with the message that not all patients who require permanent right ventricular pacing will develop clinical HF or worsening LV function. For those patients who may develop HF/LV dysfunction, there is a time frame that could be of months to years depending on prepacing LV function and history of HF (and other unknown factors). Recommending biventricular pacing for all heart block patients may be equivalent to recommend biventricular pacing to all patients with pre-existent LBBB. Upgrading to biventricular pacing once a patient develops a clinical indication (eg, unexplained drop in LV ejection fraction) is feasible and it is not associated with higher complication rates compared with an upfront biventricular pacing approach.

References
Should All Patients With Heart Block Receive Biventricular Pacing?: All Heart Block Patients With a Pacemaker Indication Should Receive Biventricular Pacing: One Move, Double the Gains?
Fang Fang, John E. Sanderson and Cheuk-man Yu

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