Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35% A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay

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Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35%

A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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Abstract

Background: It is unclear whether physiologic pacing by either cardiac biventricular pacing (BiVP) or His-bundle pacing (HisBP) may prevent adverse structural and functional consequences known to occur among some patients who receive right ventricular pacing (RVP).

Aim: Our analysis sought to review existing literature to determine if BiVP and/or HisBP might prevent adverse remodeling and be associated with structural, functional, and clinical advantages compared with RVP among patients without severe left ventricular dysfunction (>35%) who required permanent pacing because of heart block.

Methods: A literature search was conducted using MEDLINE (through PubMed) and Embase to identify randomized trials and observational studies comparing the effects of BiVP or HisBP versus RVP on measurements of left ventricular dimensions, left ventricular ejection fraction (LVEF), heart failure functional classification, quality of life, 6-minute walk, hospitalizations, and mortality. Data from studies that met the appropriate population, intervention, comparator, and outcomes of interest were abstracted for meta-analysis. Studies that reported pooled outcomes among patients with LVEF both above and below 35% could not be included in the meta-analysis because of strict relationships with industry procedures that preclude retrieval of industry-retained unpublished data on the subset of patients with preserved left ventricular function.

Results: Evidence from 8 studies, including a total of 679 patients meeting the prespecified criteria for inclusion, was identified. Results were compared for BiVP versus RVP, HisBP versus RVP, and BiVP+HisBP versus RVP. Among patients who received physiologic pacing with either BiVP or HisBP, the LV end-diastolic and end-systolic volumes were significantly lower (mean duration of follow-up: 1.64 years; –2.77 mL [95% CI –4.37 to –1.1 mL]; p=0.001; and –7.09 mL [95% CI –11.27 to –2.91; p=0.0009]) and LVEF remained preserved or increased (mean duration of follow-up: 1.57 years; 5.328% [95% CI: 2.86%–7.8%; p<0.0001]). Data on clinical impact such as functional status and quality of life were not definitive. Data on hospitalizations were unavailable. There was no effect on mortality. Several studies stratified results by LVEF and found that patients with LVEF >35% but ≤52% were more likely to receive benefit from physiologic pacing. Patients with chronic atrial fibrillation who underwent atrioventricular node ablation and pacemaker implant demonstrated clear improvement in LVEF with BiVP or HisBP versus RVP.

Conclusion: Among patients with LVEF >35%, the LVEF remained preserved or increased with either BiVP or HisBP compared with RVP. However, patient-centered clinical outcome improvement appears to be limited primarily to patients who have chronic atrial fibrillation with rapid ventricular response rates and have undergone atrioventricular node ablation.
Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care. In response to reports from the Institute of Medicine (1, 2) and a mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) modified its methodology (3-5).

Evidence Review

The Task Force recognizes the need for objective, independent evidence review committees (ERCs) that include methodologists, epidemiologists, clinicians, and biostatisticians who systematically survey, abstract, and assess the evidence to address systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting) (2, 4-6). Practical considerations, including time and resource constraints, limit the ERCs to evidence that is relevant to key clinical questions and lends itself to systematic review and analysis that could affect the strength of corresponding recommendations. Recommendations developed by the writing committee on the basis of the systematic review are marked “SR.”

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The Task Force avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant RWI (Appendix 1). For transparency, ERC members’ comprehensive disclosure information is available online https://doi.org/10.1016/j.hrthm.2018.10.035), as is comprehensive disclosure information for the Task Force (http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces).

Glenn N. Levine, MD, FACC, FAHA, Chair
Chair, ACC/AHA Task Force on Clinical Practice Guidelines
Introduction

In the United States, the annual number of first pacemaker implants is 990 for every million inhabitants (7). This corresponds to an extrapolated 288,000 first implants each year. Evidence has shown that certain patient populations may experience adverse effects with conventional right ventricular pacing (RVP) even after implementing various algorithms to reduce unnecessary ventricular pacing (8-14). RVP raises concern because it causes undesired effects such as left ventricular desynchronization, proarrhythmia, promotion of heart failure, and increased mortality for patients with reduced left ventricular function (15, 16). Biventricular pacing (BiVP), known as cardiac resynchronization therapy, has been shown to attenuate ventricular dyssynchrony and to improve symptoms and prognosis in patients with a left ventricular ejection fraction (LVEF) of <35% and left bundle branch block (17-21). His bundle pacing (HisBP) has been postulated to mitigate many of the adverse effects of standard RVP and reduce dyssynchrony similar to BiVP (22-25). It is unclear whether either BiVP or HisBP (i.e., physiologic ventricular pacing) is superior to RVP in patients with an LVEF of >35%. Therefore, an independent ERC was commissioned to perform a systematic review of this clinical question, the results of which were considered by the writing committee for incorporation into the current guideline. The ERC posted the clinical question for open public comment on the AHA website. Comments that were received were incorporated into the final question before the literature review was initiated. This systematic review is published in conjunction with the guideline.

Methodology

Study Selection

A trained medical librarian screened the titles and abstracts of studies against predefined selection criteria (Data Supplement 1) using a software environment with features such as color coding and ranking of relevant key words. The literature search was conducted using MEDLINE (through PubMed) and Embase to identify randomized trials and observational studies performed between January 1, 1974, and May 25, 2017, comparing the effects of BiVP or HisBP versus RVP (Data Supplement 2). Randomized controlled trials and crossover trials were included. A second medical librarian performed quality control using the above tools. The chief medical officer of Doctor Evidence, LLC (Santa Monica, CA) and the project methodologist reviewed all included abstracts and a random sample of excluded abstracts, managed discrepancies between librarians, and decided on studies of uncertain eligibility. ERC members were divided into pairs and performed dual independent review of full-text articles in the DOC Library software platform (Doctor Evidence. 2016. DOC Library. Santa Monica, CA: Doctor Evidence, LLC). During this review, ERC members identified an additional 4 articles in the bibliography of the originally identified articles that met the inclusion criteria. Disagreements were resolved by consensus between the 2 reviewers and the ERC chair and vice chair.

Data from several studies could not be included in the analysis because the original publication included a population with mixed baseline LVEF. Most notably, this prevented inclusion of BLOCK HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) (26). Consideration was given to requesting the original data to permit subgroup analysis of patients with baseline LVEF of >35%. However, Task Force methodology does not permit data to be obtained for further analysis when it is in the possession of a commercial enterprise (in this case, Medtronic).
Data Extraction and Quality Assessment

Data extraction was performed using the DOC Data 2.0 (Doctor Evidence. 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) software platform using a standard template for predefined data points. Included studies were extracted by an evidence analyst with software validation/data entry error prevention and with each data point verified against the source article by a quality control. Discrepancies were resolved by the project methodologist and/or chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by an evidence audit specialist. An ontology specialist managed the naming of outcomes based on author-reported names and definitions.

For each included study, the following information was abstracted: study design, participant characteristics (age, race/ethnicity, sex, comorbid conditions), and duration of follow up. Risk of bias was assessed for each study included using the Cochrane Risk of Bias tool and Newcastle Ottawa Scale (Data Supplements 3 and 4). Studies were considered to have low risk of bias if there was low risk of bias for all domains or plausible bias was unlikely to alter results. Studies were considered to have high risk of bias if there was high risk of bias for ≥1 key domains and the plausible bias seriously weakened confidence in results.

Analysis

Meta-analysis was performed using the DOC Data 2.0 advanced web-based platform (Doctor Evidence. DOC Data, Version 2.0, Santa Monica, CA). For the primary analysis, a fixed-effect model was prespecified in the analysis plan because the search revealed only a small number of studies. In this scenario, the estimate of the between-studies variance would have poor precision and, therefore, a random-effects model could not be applied (27). For continuous outcomes, reported means and associated variance were pooled using the mean difference (MD). For binary outcomes, reported events and sample size were pooled using the relative risk (RR). Because meta-analysis is not a valid technique when only 2 studies provide data on an outcome, when this arose, the results from each study were considered qualitatively and findings addressed in the discussion.

In each of the meta-analyses conducted, statistics related to heterogeneity were calculated when possible. The most common measure of heterogeneity is the $I^2$ statistic, which describes the percentage of variability that is attributable to heterogeneity rather than sampling error. The $I^2$ cut-off values of 25%, 50%, and 75% were used to assign low, moderate, and high degrees of heterogeneity, respectively. Funnel plots are common method to identify heterogeneity. These plot the treatment effect relative to some measure of precision (typically the sample size or the standard error). Points that fall outside of a predefined funnel indicate excess variability, and nonfunnel-shaped scatter indicate potential bias in the estimates. The use of either of these methods to assess heterogeneity is questionable in the context of this project, because there are too few studies in most meta-analyses. When there was insufficient evidence to estimate between-study heterogeneity, fixed-effects models were used. The cases in which it was not feasible to pool the results for meta-analysis, narrative summary from each study was reported qualitatively.

Results

The literature search identified 953 titles and abstracts through MEDLINE/Embase database, using various combinations of identifiers for physiologic pacing such as cardiac resynchronization therapy, BiVP, His-bundle, and para His-bundle pacing as a comparator to RVP (either apical or septal). Nine hundred and thirty articles were excluded leaving 23 for full-text analysis. Sixteen were excluded for the
following reasons: population not of interest (n=5), comparison not of interest (n=3), duplicate publication (n=1), and outcome stratification not of interest (n=7) (Figure 1). Bibliography review of the included articles identified an additional 4 articles of the population of interest and 1 additional article with extended follow-up of an already included study. To avoid potential double counting of subjects, we excluded 4 studies which reported results for the same trial populations. Eight studies comprised the final analysis, 4 comparing BiVP versus RVP (N=438) (28-31) and 4 evaluated HisBP versus RVP (N=241) (25, 32-34) (Figure 2). The characteristics of the studies are summarized in Data Supplements 5 and 6.

BiVP versus RVP

Patients who received BiVP compared with RVP, after a mean duration of 1.91 years, were observed to have a smaller end-systolic volume (MD: –7.2039 mL; 95% CI: –11.95 to –2.46 mL; p=0.003; I²=12.31%), a smaller end-diastolic volume (MD: –2.7027 mL; 95% CI: –4.35 to –1.06 mL; p=0.0013; I²=0%) (Figure 3 and 4), and a higher LVEF (MD: 6.340%, 95% CI: 2.84–9.84%; p=0.0004; I²=0%) (Figure 5). Three studies reported the impact of BiVP on 6-minute walk distances and detected no significant difference with BiVP (MD: 6.736 m; 95% CI: –2.82 to 16.29 m; p=0.167; I²=0%) (28-30). Two of the studies observed no significant improvement in 6-minute walk distances (28, 30). The third study, which evaluated patients with chronic atrial fibrillation (AF) who underwent atrioventricular node ablation, found that at 6 months there was a significant improvement with both RV or BiVP but that BiVP resulted in a greater improvement in 6-minute walk distance (61.2±90 m versus 82.9±94.7 m; p=0.04) (29). Further subgroup analysis revealed that patients with either a LVEF of ≤45% or New York Heart Association class II/III heart failure received the greatest improvement (55.9±96.1 m versus 96.9±97.7 m; p=0.04; and 51.6±86.3 versus 78.9±92.2; p=0.01).

One study reported quality of life assessed by the 36-Item Short-Form Health Survey (SF-36) (30). Investigators detected no significant difference in SF-36 domains between the BiVP and RV pacing groups. The effects on mortality were not statistically significant (RR: 1.0758; 95% CI: 0.51–2.27; p=0.848).

HisBP Versus RVP

Although 4 studies that compared HisBP versus RVP met our inclusion criteria, meta-analysis could only be performed for LVEF and New York Heart Association class because these were the only parameters reported by ≥2 studies. Overall, HisBP was associated with a significantly greater LVEF compared with RVP (MD: 4.33%; 95% CI: 0.85–7.81%; p<0.01; I²=0%; mean duration of follow-up: 8.36 months) (Figure 6), and an improvement in functional class (MD: –0.21; 95% CI: –0.4 to –0.02; p=0.027; I²=28.40%; mean duration of follow-up: 8.71 months) (Figure 7) (25, 32, 34). Two of the HisBP trials measured 6-minute walk distance and reached discordant findings (32, 34). The earlier study of patients with chronic AF who underwent atrioventricular node ablation (34) reported a significant superiority of HisBP in the distance walked (378±60 m at baseline to 431±73 m at 6 month follow-up; p<0.05), which was not confirmed by the larger and more recent double-blind randomized crossover study of patients in sinus rhythm with high-grade atrioventricular block (6-minute walk distance after 1 year of HisBP 560±97 m versus after 1 year of RVP which was 558±109 m; p=0.84) (32).

Quality of life was reported by 2 studies that compared HisBP to RVP: one using the SF-36 survey (32) and the other using the Minnesota Living with Heart Failure Questionnaire (34). The studies reported discordant findings. Participants in the study that employed the SF-36 survey reported improvement in general health and vitality, regardless of treatment arm. Physiologic pacing did not confer additional benefit. Patients in the remaining study (34) reported a significant improvement in quality of life as assessed by their responses to the Minnesota Living with Heart Failure questionnaire. The baseline score for both groups was 32.5±15. A lower score indicates better quality of life. At 6
months’ follow-up, among patients who received BiVP, quality of life improved with a mean score of 16.2±8.7 (p<0.05); among patients who received RVP, the improvement in quality of life was less, with a mean score of 20.6±8.5 (p=not significant).

There was no statistical evidence of any effect on mortality as reported by 2 of the studies (32, 33).

BiVP + HisBP Versus RVP

When both BiVP and HisBP patients were pooled and compared with RVP patients, the effect of physiologic versus RVP became more evident. After a mean follow-up duration of 1.64 years, both left ventricular end-systolic volume and end-diastolic volume were reduced with physiologic pacing (–7.09 mL; 95% CI: –11.27 to –2.91 mL; p=0.0099; \(I^2=12.98\%\); and –2.74 mL; 95% CI: –4.37 to –1.1; p=0.001; \(I^2=0\%\), respectively) (Figure 8 and 9) (28, 30-32, 34), and LVEF, which declined with RVP remained preserved and in some studies increased (5.328%; 95% CI: 2.86–7.8; p<0.0001; \(I^2=39.11\%\)) (Figure 10).

Quality of life, as measured in 1 study using the Minnesota Living with Heart Failure questionnaire, also improved compared with baseline (34). Among the 5 studies that measured 6-minute walk distances, meta-analysis demonstrated no improvement (7.81 m; 95% CI: –1.52 to 17.15; p=0.10; \(I^2=0\%\); mean duration of follow-up: 1.51 years) (28-30, 32, 34). There was no effect on mortality (RR: 0.926; 95% CI: 0.55–1.57; p=0.773; \(I^2=0\%\)) (30-33).

Discussion

Our analysis of published trials indicates advantages of physiologic pacing for patients with intermediate and preserved LVEF and in particular for patients with chronic AF and rapid ventricular response rates who undergo atrioventricular node ablation (Table 1).

Patient-Centered Clinical Outcomes

Patients with chronic AF who underwent atrioventricular node ablation and pacemaker implant demonstrated improvement in 6-minute walk distances with either BiVP or HisBP, with only 1 study of 18 patients also observing improved quality of life and improved New York Heart Association functional class (29, 34). These findings are supported by results of a large, multicenter randomized trial that was not included in this meta-analysis. The study randomized 186 patients with AF and atrioventricular node ablation and a range of LVEF both above and below 35% to either RV or BiVP. (35). Patients in the cardiac resynchronization therapy arm were significantly less likely to reach the composite endpoint of death from heart failure, hospitalization for heart failure, or worsening heart failure symptoms regardless of whether their baseline LVEF was ≤35% or >35%.

Among patients in sinus rhythm, evidence indicates that physiologic pacing reduces the adverse remodeling observed with RVP (reduced end-systolic volume and end-diastolic volume and improved LVEF). The 1 study that measured quality of life also detected improvement as measured by the Minnesota Living with Heart Failure questionnaire (34).

Intermediate Ejection Fractions

Several studies reported outcomes stratified by LVEF (31, 32, 34). Two studies found the benefit of physiologic pacing to be greatest among patients with a LVEF of >35%, but ≤52% (32, 34). These patients were noted to have less of an increase in left ventricular end-systolic volume and no reduction in LVEF when they received physiologic pacing versus RVP. Patients who had normal left ventricular function at baseline and received physiologic pacing received no benefit compared with those who received right
ventricular pacing. The remaining study found no benefit for physiologic pacing regardless of baseline LVEF (31). Although we could not perform a meta-analysis of the data on this subgroup, the data suggest that patients with intermediate LVEFs are more likely to receive benefit.

**Percentage of Ventricular Pacing**

Individual study outcomes might have been affected by how much ventricular pacing patients received. To examine this, we reviewed each study to document the original indication for pacing as well as, when available, the percentage of ventricular pacing (Table 1). With the exception of 2 studies (29, 34), patients received pacemakers for standard indications of heart block or sinus node dysfunction with the expectation of requiring frequent ventricular pacing (34). Only 1 study stratified outcomes based on the percentage of ventricular pacing (33). This study observed fewer heart failure hospitalizations among patients who received HisBP only if they received ventricular pacing ≥40% of the time.

**Follow-up Duration**

The duration of follow-up did not appear to correlate with an improvement in clinically significant outcomes with physiologic pacing (Table 1). Patients who underwent atrioventricular node ablation and physiologic pacing showed significant improvement in clinical outcomes with only 6 to 12 months’ of follow-up (29, 34).

**Complications From Physiologic Pacing Versus RVP**

We sought to include studies with short as well as longer follow-up periods because these studies might be more likely to assess and report procedural complications associated with physiologic pacing to provide the writing committee with as much data as possible from which to draw their clinical recommendations. Table 2 lists reported complications requiring surgical revision or findings likely to impact battery longevity. These findings were not included in the meta-analysis but, overall, indicate physiologic pacing with either BiVP or HisBP to be associated with a slightly higher risk of lead revision because of either elevated pacing threshold or lead dislodgement. Battery longevity was not reported by any of the studies because of the follow-up period, but battery longevity is known to be reduced among patients who received BiVP given the need to pace the additional left ventricular lead. The effect of HisBP on battery longevity is unknown.

**Existing Studies Excluded From Meta-Analysis**

The ACC/AHA RWI procedures precluded retrieval of industry-retained unpublished data on the subset of patients with preserved left ventricular function for the patients with reduced left ventricular function (LVEF <50%), from the BLOCK HF study (26).

The BioPace (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) trial is the largest study to evaluate the potential benefit of BiVP versus RVP for patients who present with heart block and require permanent pacing (36). Study enrollment criteria permitted patients to enroll regardless of LVEF (36). The primary endpoint is death or first heart failure hospitalization, but it did not include any left ventricular remodeling outcome. Enrollment is complete, and the results were presented at European Society of Cardiology Scientific and Educational Sessions in 2014 (37). However, the study remains unpublished. Therefore, we could not include the findings or data in our analysis. Similar studies are needed to definitively answer the same question for HisBP.
Limitations

Our meta-analysis is limited by small numbers and a preponderance of single center studies. Also, the relatively short follow-up periods (1–3 years) limit the ability to assess potential benefits evident only over a longer period of time (e.g., hospitalizations and mortality) as well as potential costs of physiologic pacing (e.g., shorter battery longevity, device and/or lead malfunction, complications from more frequent generator replacements). Because of the limited number of studies, we included patients with chronic AF who underwent atrioventricular node ablation followed by pacemaker implantation, in addition to patients with atrial systolic function who required permanent pacing because of heart block. It is possible that the benefit of physiologic pacing may be different between these groups and that they should be considered separately.

Another potential limitation is that 2 of the studies used a crossover trial design. This methodology leaves the potential for bias based on the sequence in which patients receive the interventional therapy. It is possible that patients who were randomized to receive physiologic pacing first received a benefit that is maintained through the second half of the study when they are in the comparator arm (RVP). This potential for bias was considered but thought to be unlikely as evidence from 1 of the studies included found no statistical interaction between the order of study periods and the effect of physiologic pacing on LVEF (32).

Summary

To summarize our findings, both methods of physiologic pacing appear to mitigate the deleterious structural and functional effects of RVP. Patients with chronic AF and a rapid ventricular rate who undergo atrioventricular node ablation receive benefit from physiologic pacing with improvement in structural findings and 6-minute walk distance. Patients in sinus rhythm also receive benefits from physiologic pacing as manifest by the absence of adverse structural remodeling and reduced LVEF, which were observed with RVP, although functional capacity and quality of life did not appear to be affected. Patients with LVEF between 36% and 52% may be more likely to receive clinical benefit from physiologic pacing.
Figures and Tables

Figure 1. PRISMA Diagram

Identification
- 953 records identified through database searching (MEDLINE/Embase)

Screening
- 953 titles/abstracts screened
- 930 records excluded

Eligibility
- 23 full-text articles assessed for eligibility
- 16 full-text articles excluded
  - Reasons for exclusions:
    - 5 populations not of interest
    - 3 comparisons not of interest
    - 1 duplicate publication
    - 7 outcome stratifications not of interest

Included
- 7 studies included in database
- 4 articles identified in bibliography of included articles
- 1 article identified as extended follow-up of included studies
- 4 articles excluded from analysis due to overlapping populations

8 articles included in analysis
### Table 1. Pacing Modality and Clinical Outcomes

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Indication for PM</th>
<th>Follow-up</th>
<th>% Ventricular Paced</th>
<th>6-Min Walk</th>
<th>QOL</th>
<th>Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockburger et al., 2011 (31)</td>
<td>BiVP</td>
<td>108</td>
<td>Investigators asked to identify patients who were expected to require ventricular pacing ≥80%</td>
<td>1 y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Yu et al., 2014 (30)</td>
<td>BiVP</td>
<td>177</td>
<td>AV block or SSS &gt;2 y Mean duration 4.8±1.5 y</td>
<td></td>
<td>• RV 94±19.5 %</td>
<td>No change</td>
<td>No change</td>
<td>NR</td>
</tr>
<tr>
<td>Albertsen et al., 2011 (28)</td>
<td>BiVP</td>
<td>50</td>
<td>Complete heart block, permanent or paroxysmal</td>
<td>3 y</td>
<td>No change</td>
<td>No change</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Kronborg et al., 2014 (32)*</td>
<td>HisBP</td>
<td>38</td>
<td>High-grade AV block</td>
<td>1 y</td>
<td>&gt;99% both groups</td>
<td>No change</td>
<td>Improved in both groups equally</td>
<td>No change</td>
</tr>
<tr>
<td>Occhetta et al., 2006 (34)*</td>
<td>HisBP</td>
<td>18</td>
<td>AV node ablation</td>
<td>6 mo</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>
| Sharma et al., 2015 (33) | HisBP | 173 | • 38% SSS  
• 62% AV conduction disease  
• 25% Complete heart block | 2 y | Reported outcomes for 2 groups based on % ventricular pacing:  
• The entire study population  
• The subgroup with >40% ventricular pacing (47 patients with HisBP (63%) and 62 patients with RVP (62%). Among patients paced, >40% of the time they observed fewer heart failure hospitalizations (1 patient vs 9 patients, p=0.02) | NR | NR |
| Doshi et al., 2005 (29) | BiVP | 103 | AV node ablation | 6 mo | >99% | ↑ | No change | No change |
| Zanon et al., 2008 | HisBP | 12 | • AF with slow ventricular | Crossover design: 3 | AF group >97% Sinus rhythm | NR | NR | NR |
Slotwiner DJ, et al.
2018 Bradycardia Clinical Practice Guideline: Systematic Review

<table>
<thead>
<tr>
<th>(25)</th>
<th>response rate (n=4)</th>
<th>mo HisBP then 3 months RVP</th>
<th>group &gt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Second-degree AV block (n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Third-degree AV block (n=2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Crossover study design.
AF indicates atrial fibrillation; AV, atrioventricular; BiVP, biventricular pacing; HisBP, His-bundle pacing; NR, not reported; RV, right ventricular; RVP, right ventricular pacing; and SSS, sick sinus syndrome
### Table 2. Complications Associated With Pacemaker Implantation

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Pacing Modality</th>
<th>Complications of Physiologic Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockburger et al., 2011 (31)</td>
<td>BiVP</td>
<td>• Survival free of first adverse event was similar in both groups (p=0.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exact numbers not given, but authors report dual chamber pacemaker recipients had more atrial lead “issues,” and BiVP had left ventricular lead problems (phrenic nerve pacing).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Problems were evenly balanced between the 2 groups</td>
</tr>
<tr>
<td>Yu et al., 2014 (30)</td>
<td>BiVP</td>
<td>• Adverse events similar in RVP and BiVP groups (log-rank chi squared=0.899; p=0.343)</td>
</tr>
<tr>
<td>Albertsen et al., 2011 (28)</td>
<td>BiVP</td>
<td>NR</td>
</tr>
<tr>
<td>Doshi et al., 2005 (29)</td>
<td>BiVP</td>
<td>• BiVP had 21 complications (phrenic nerve, high threshold, left ventricular lead dislodgement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RVP had 6 complications (RV lead dislodgement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Note: Complications from RV lead were equal in both groups. So BiVP group had an excess 15 complications.</td>
</tr>
<tr>
<td>Kronborg et al., 2014 (32)</td>
<td>HisBP</td>
<td>• Pacing threshold rose among patients who received HisBP by the end of the study (1 y). Median threshold rose to 1.5 V (95% CI: 0.75-2.9); p=0.008.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 patient with HisBP developed exit block at 15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2 patients had intermittent loss of capture for seconds on the HisBP lead documented on 24-h electrocardiographic monitoring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No lead dislodgements</td>
</tr>
<tr>
<td>Occhetta et al., 2006 (34)</td>
<td>HisBP</td>
<td>• “Slight” dislodgement of 1 HisBP lead observed 1 mo after implant. Did not require surgical revision.</td>
</tr>
<tr>
<td>Sharma et al., 2015 (33)</td>
<td>HisBP</td>
<td>• 3 patients in HisBP group required ventricular lead revision (2 for loss of capture; 1 for high threshold)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2 patients in RVP group required surgical revision of the RV lead because of dislodgement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o 1 pneumothorax in RVP group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o 1 device infection in RVP group</td>
</tr>
<tr>
<td>Zanon et al., 2008 (25)</td>
<td>HisBP</td>
<td>NR</td>
</tr>
</tbody>
</table>

BiVP indicates biventricular pacing; HisBP, His-bundle pacing; NR, not reported; RV, right ventricular; and RVP, right ventricular pacing.
Figure 2. Studies Included in the Meta-Analyses With Selected Results

All analyses have been done in Fixed Effects.

Green-shaded boxes indicate that the results are statistically significant (p<0.05). Orange-shaded boxes indicate that only 2 studies reported results.

BIV indicates biventricular; CI, confidence interval; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, mean difference; NYHA, New York Heart Association; RR, relative risk; RV, right ventricular; RVP, right ventricular pacing; and SF-36, 36-Item Short-Form Health Survey.
Figure 3A. Forest Plots for BiVP Versus RVP, LV End-Systolic Volume

Heterogeneity is defined as: $Q(\text{df}=2)=2.28; \ p=0.32; \ i^2=12.31\%$.

BiVP indicates biventricular pacing; FE, fixed effects; LV, left ventricular; and RVP, right ventricular pacing.
Figure 3B. Funnel Plot for BiVP Versus RVP, LV End-Systolic Volume

BiVP indicates biventricular pacing; LV, left ventricular; and RVP, right ventricular pacing.
Figure 4A. Forest Plots for Biventricular Pacing (BiVP) Versus Right Ventricular Pacing (RVP), Left Ventricular (LV) End-Diastolic Volume

Heterogeneity is defined as: $Q (df=2)=1.78; p=0.41; I^2=0\%$.

BiVP indicates biventricular pacing; FE, fixed effects; LV, left ventricular; and RVP, right ventricular pacing.
Figure 4B. Funnel Plot for BiVP Versus RVP, LV End-Diastolic Volume

BiVP indicates biventricular pacing; LV, left ventricular; and RVP, right ventricular pacing.
Figure 5A. Forest Plot for BiVP Versus RVP, LVEF

Heterogeneity is defined as: $Q_{(df=2)}=1.88; p=0.39; I^2=0\%$.
BiVP indicates biventricular pacing; FE, fixed effects; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
Figure 5B. Funnel Plot for BiVP Versus RVP, LVEF

BiVP indicates biventricular pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
Figure 6A. Forest Plot for HisBP Versus RVP, LVEF

Heterogeneity is defined as: $Q(\text{df}=2)=0.77$; $p=0.68$; $I^2=0\%$.
FE indicates fixed effects; HisBP, His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
Figure 6B. Funnel Plot for HisBVP Versus RVP, LVEF

HisBP indicates His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
Figure 7A. Forest Plot for HisBP Versus RVP, NYHA Class

Heterogeneity is defined as: $Q (df=2) = 2.79; p=0.25; I^2=28.40\%$.
FE indicates fixed effects; HisBP, His bundle pacing; NYHA, New York Heart Association; and RVP, right ventricular pacing.
Figure 7B. Funnel Plot for HisBVP Versus RVP, NYHA Class

HisBP indicates His bundle pacing; NYHA, New York Heart Association; and RVP, right ventricular pacing.
Figure 8A. Forest Plot for BiVP and HisBP Versus RVP, LV End-Systolic Volume

Heterogeneity is defined as: Q (df=4)=2.30; p=0.68; \( I^2 = 12.98\% \).

BiVP indicates biventricular pacing; FE, fixed effects; HisBP, His bundle pacing; LV, left ventricular; and RVP, right ventricular pacing.
Figure 8B. Funnel Plot for BiVP and HisBP Versus RVP, LV End-Systolic Volume

BiVP indicates biventricular pacing; HisBP, His bundle pacing; LV, left ventricular; and RVP, right ventricular pacing.
Heterogeneity is defined as: $Q$ (df=4)=1.91; $p=0.75; I^2=0\%$.

BiVP indicates biventricular pacing; FE, fixed effects; HisBP, His bundle pacing; LV, left ventricular; and RVP, right ventricular pacing.
Figure 9B. Funnel Plot for BiVP and HisBP Versus RVP, LV End-Diastolic Volume

BiVP indicates biventricular pacing; HisBP, His bundle pacing; LV, left ventricular; and RVP, right ventricular pacing.
Figure 10A. Forest Plot for BiVP and HisBP Versus RVP, LVEF

Heterogeneity is defined as: $Q (df=5)=3.28; \ p=0.66; \ I^2=39.11\%$.

BiVP indicates biventricular pacing; FE, fixed effects; HisBP, His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
Figure 10B. Funnel Plot for BiVP and HisBP Versus RVP, LVEF

BiVP indicates biventricular pacing; HisBP, His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
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**Key Words**: ACC/AHA Evidence Review Committee • ACC/AHA Clinical Practice Guideline • atrioventricular block • biventricular pacing • cardiac resynchronization therapy • dual chamber pacing • heart block • His-bundle pacing • left ventricular ejection fraction • right ventricular pacing
Appendix 1. Author Relationships With Industry and Other Entities (Relevant)*—Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35%: A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay (June 2017)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
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<td>None</td>
</tr>
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<td>None</td>
<td>None</td>
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<td>None</td>
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</tbody>
</table>

This table represents the relationships of evidence review committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

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or device addressed in the document or makes a competing drug or device addressed in the document; or c) the person or a member of the person’s household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

*For transparency, the ERC members’ comprehensive disclosure information is available as an online supplement at https://doi.org/10.1016/j.hrthm.2018.10.035.

CMS reported research payments to Dr. Del-Carpio Munoz in November 2016. Dr. Del-Carpio Munoz personally receives no money from Boehringer Ingelheim as the PI for the GLORIA registry; his hospital receives some reimbursement. Boehringer Ingelheim was deemed not relevant to the ERC report.

ACC indicates American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; and VA, Veterans Affairs.
Appendix 2. Abbreviations

AF = atrial fibrillation
BiVP = biventricular pacing
CI = confidence interval
ERC = evidence review committee
HisBP = His-bundle pacing
LV = left ventricular
LVEF = left ventricular ejection fraction
MD = mean difference
NYHA = New York Heart Association
PICOTS = population, intervention, comparator, outcome, timing, setting
RV = right ventricular
RVP = right ventricular pacing
RWI = relationships with industry or other entities
SF-36 = 36-Item Short-Form Health Survey
References


