Optimal Pacing for Right Ventricular and Biventricular Devices

Minimizing, Maximizing, and Right Ventricular/Left Ventricular Site Considerations

Anne M. Gillis, MD

More than 1 million pacemakers and ≈400,000 implantable cardioverter defibrillators (ICDs) are implanted worldwide each year.1,2 These estimates include replacement devices that range 20% to 30% per annum depending on the type of device. Although there remains a preference for single-chamber ventricular pacing in developing countries, 70% of pacemakers presently implanted worldwide are dual-chamber systems. The number of pacing systems with cardiac resynchronization therapy (CRT) capability continues to grow—≈40,000 per year. Of ICDs implanted annually, 27% are single chamber, 32% dual chamber, and 41% CRT systems.1

During the past 2 decades, much has been learned from clinical studies to inform optimal device mode selection and device programming for the individual patient to maximize the benefits of cardiac implantable electronic device therapy, as well as to minimize any potential adverse outcomes. This review will highlight some of those advances and recommendations related to achieving optimal pacing therapy.

Right Ventricular Pacing

Adverse Effects of Frequent Right Ventricular Apical Pacing

Several clinical studies have reported that chronic right ventricular (RV) apical pacing causes detrimental cardiovascular outcomes, including adverse cardiac remodeling, atrial fibrillation (AF), congestive heart failure (HF), and mortality.3,9 The outcomes of some of these studies are summarized in Table I in the Data Supplement. It is important to emphasize that the adverse outcomes reported have been dependent on a high cumulative % of RV pacing, generally >40%.3,9,10 Furthermore, the increased risk of HF reported has been predominantly observed in those with preexisting left ventricular (LV) systolic dysfunction in many who were receiving unnecessary RV pacing.3,10,11

The potential mechanism(s) by which RV apical pacing increases the risk for AF and HF include both electric and mechanical dyssynchrony imposed by RV apical pacing that alters myocardial activation patterns and contraction sequence thus modifying myocardial strain and work resulting in less efficient contraction (Figure 1).3,12 These abnormal patterns cause LV remodeling, including chamber enlargement, cardiac hypertrophy, and functional mitral regurgitation. The functional mitral regurgitation contributes to atrial structural and electric remodeling providing a substrate for AF. Other maladaptive changes occur at the cellular level, including apoptosis, fibrosis, abnormal cell metabolism, and altered myocardial perfusion.

Minimizing RV Apical Pacing via Programming or Mode Selection

An important lesson learned from these clinical and experimental studies is that every effort should be made to minimize RV pacing and preserve the normal ventricular activation sequence in patients who do not require ventricular pacing 100% of the time (eg, those with sinus node dysfunction and preserved AV conduction, those with intermittent AV conduction block, and the patient with ICD without a bradycardia indication for pacing or a requirement for CRT).13–15 The strategies for minimizing unnecessary RV apical pacing are summarized in the Table and include the AAI mode where indicated,13,15 backup low rate VVI pacing in the presence of infrequent ventricular pacing (eg, most ICD recipients without symptomatic HF)13 or the use of specific programming algorithms in DDD systems to minimize RV pacing.15–17

The indication for the AAI mode in sinus node dysfunction is limited to select patients as the Danish Multicenter Randomized Trial on Single Atrial Lead Pacing versus Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) trial showed no major benefit of this mode when compared with DDDR systems.14,18 The reasons for preferring DDD to AAI pacing in patients with sinus node dysfunction include the presence of AV conduction abnormalities at time of pacemaker implantation (≤20%), the risk of developing AV conduction abnormalities over time, and the risk of significant complications at the time of system revision from AAI to DDD if required.14,18 Nevertheless, AAI might be considered in the younger patient with normal AV conduction, recognizing that...
it is difficult to predict the probability of developing AV conduction abnormalities over time.14

In the ICD population without a bradycardia pacing indication or need for CRT to treat HF, the indication for a DDD pacing system is weak.13 The DAVID II trial compared with AAI pacing (70 beats per minute) backup VVI pacing (40 beats per minute) in 600 patients requiring ICD therapy but without a clinical indication for bradycardia pacing.19 There was no difference in cardiovascular outcomes, including death or HF hospitalization, AF, syncope, or ICD shocks between the 2 groups. Atrial pacing with ventricular backup pacing was compared with backup VVI pacing in 1030 patients with an indication for ICD therapy in the absence of a clinical indication for bradycardia pacing.20 This trial was stopped after 2.4 years for futility. A significant difference in cardiovascular outcomes, including death, HF hospitalization, or significant HF events, was not observed between the 2 groups. Dual-chamber ICDs are more expensive, implantation is associated with a higher risk of significant complications and with current device technology and programming recommendations the evidence suggesting that dual-chamber ICDs improve detection of atrial tachyarrhythmias and reduce inappropriate shock therapy or provide other substantial clinical benefits is not compelling.13,16-23 Thus, it is hard to justify implanting dual-chamber ICDs in patients without a bradycardia indication for pacing. A recent Heart Rhythm Society consensus statement recommends a dual-chamber ICD for patients with a need for pacing because of sinus node disease, high-grade AV block, and drug-induced bradycardia and indicates that dual-chamber ICDs could be considered in patients with bradycardia-induced or pause-dependent ventricular tachyarrhythmias or in patients with documented atrial tachyarrhythmias.24

The programming algorithms available for minimizing RV pacing include programming long AV delays, programming a feature that permits adaptive/dynamic extension of the AV interval,15-17,25,26 or the use of specific algorithms that permit mode switching from AAI to DDD pacing when AV block occurs (Table).15,17 Comparisons of the adaptive/dynamic AV interval extension algorithms with the AAI/DDD mode switching algorithms have reported that the reduction in % ventricular pacing is greatest in the mode switching algorithms even in individuals with intermittent AV conduction abnormalities (Supplemental Figure I16,25,26; Materials in the Data Supplement).

### Table 1. Strategies to Minimize Right Ventricular Pacing

| AAI: Where clinically indicated—young patient with normal AV conduction |
| VVI backup 40–50 beats per minute |
| Patients with ICD without bradycardia |
| Patients with syncope 2° to transient AV block (eg, setting of bifascicular block where infrequent pacing expected) |
| DDD with long AV delay (220–300 ms) |
| Adaptive/dynamic AV delay algorithms |
| AV hysteresis (Biotronik) |
| AS search hysteresis (Boston Scientific) |
| Search AV+ (Medtronic) |
| Ventricular Intrinsic Preference (St Jude Medical) |
| Pacing Mode Switch from AAI to DDD |
| AAISafeR, AAISafeR2 (Sorin Group) |
| Managed Ventricular Pacing (Medtronic) |
| Reverse Mode Switch/RhythmIQ (Boston Scientific) |

Table 1 indicates implantable cardioverter defibrillator.
approach of programming longer AV delays such as used in the DANPACE trial and thus the magnitude of benefit may well be overestimated. Nevertheless, the data support the use of a strategy of minimizing unnecessary RV pacing to prevent AF.

Interestingly, algorithms for minimizing RV pacing have not shown to have a beneficial effect on cardiovascular outcomes in the pacemaker population previously exposed to a high cumulative % of RV pacing after a pulse generator replacement and algorithms subsequently programmed to minimize RV pacing. The Prefer for Elective Replacement (PreFER) Managed Ventricular Pacing investigators randomized 605 patients referred for pacemaker or ICD replacement to pacing in the DDD mode or the Managed Ventricular Pacing mode which mode switches from AAI to DDD. Reprinted from Sweeney et al with permission of the publisher. Copyright © 2007, Massachusetts Medical Society.

The greatest benefit of septal pacing was observed in patients with baseline LV systolic dysfunction (LVEF ≤40%-45%) or those followed up for >1 year (Figure 3). However, a benefit of high septal pacing on preservation of ventricular function or prevention of AF or HF events was not observed in the Protect-Pace study, which randomized 240 patients with high-grade AV block to high septal or RV apical pacing.38 It is now well established that pacing at the RV outflow tract or septal location can be achieved with acceptable pacing thresholds and minimal risk of complications, including lead dislodgement, and this approach seems to be increasingly adapted into clinical practice. Although promising, pacing from sites in the His bundle region remains problematic with lower success rates, higher pacing thresholds, and longer procedure times.35,37 Alternative RV pacing sites have not yet been shown to reduce significant cardiovascular events, such as AF or HF. One additional randomized clinical trial comparing septal locations with RV apical pacing is completing follow-up and when reported may provide valuable additional insights as to the clinical value of these alternate pacing sites.39

Alternative RV Pacing Sites

The RV apex has been the preferred site for RV lead placement because of the ease of implantation and low risk of lead dislodgement.30 With the development of active fixation leads, alternative RV pacing sites have been explored, including the RV outflow tract, the RV septum, and the His bundle region. Pacing from these sites is thought to be more physiological, engaging the Purkinje network earlier than apical pacing thus reducing or preventing the electric and mechanical dyssynchrony associated with RV apical pacing. Some data from acute or short-term randomized studies support this hypothesis.34–37 Most studies have used LVEF as a surrogate of clinical outcomes. The majority of studies have reported a preservation of LVEF with alternate site RV pacing when compared with reduced LVEF in those randomized to RV apical pacing. One recent randomized study in 142 pacemaker-dependent patients reported a greater improvement in functional capacity as assessed by 6-minute walk test in those paced at the RV septum when compared with RV apical pacing.36 A meta-analysis of 14 randomized clinical trials involving 754 patients reported that pacing from a non-RV apical pacing site was associated with a higher LVEF when compared with RV apical pacing.35

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Biventricular Versus RV Apical Pacing

Current guidelines indicate that CRT can be useful for patients with symptomatic HF and LVEF ≤35% who are expected
to require frequent ventricular pacing (>40%) after device implantation.\textsuperscript{40} Some investigators have investigated the use of biventricular pacing when compared with RV pacing in patients after AV junction ablation for rate control of AF or in the setting of high-grade AV block.\textsuperscript{8,41,42} Brignole et al\textsuperscript{42} randomized 186 patients after successful AV junction ablation and CRT device implantation to RV apical pacing or biventricular pacing with echo-guided optimization. They reported a significant reduction in the primary end point (a composite of HF death, HF hospitalization, or worsening HF) in the group treated with CRT (11%) when compared with the RV pacing group (26%; $P=0.005$). These findings are not surprising given that a significant proportion of this study population had symptomatic HF on enrolment and 46% had a baseline LVEF $\leq 45\%$. A meta-analysis including 534 patients enrolled in 4 randomized controlled trials comparing biventricular with RV pacing mode after AV junction ablation did not find a survival benefit associated with biventricular pacing.\textsuperscript{41} However, biventricular pacing was associated with modest but statistically significant increases in LVEF and measures of Quality of Life but not in functional capacity.\textsuperscript{41} It is important to emphasize that in the absence of significant underlying heart disease, survival after ablation of the AV node for management of AF is similar to the expected survival in the general population.\textsuperscript{13} Therefore, the decision to consider biventricular pacing instead of RV pacing in this setting should be based on the recommendations in current guidelines, which suggest that biventricular pacing may be considered in patients with moderately depressed LV systolic function (LVEF $\leq 45\%$) and mild HF symptoms.\textsuperscript{41}

The effects of RV pacing compared with biventricular pacing on LV adverse remodeling was assessed in 177 patients with bradycardia and normal LV function. (Table I; Figure II in the Data Supplement)\textsuperscript{6} At 1 and 2 years of follow-up, the LVEF was significantly lower in patients randomized to RV pacing (54.8±9.2% and 53.0±10.1%) compared with biventricular pacing (62.2±7.0% and 62.9±8.8%; $P<0.001$), and LV end-systolic volumes were significantly higher in the RV pacing group (35.7±16.2 and 38.3±20.3 mL) compared with the biventricular pacing group (27.6±10.2 and 25.3±10.2 mL; $P<0.001$).\textsuperscript{6,7} However, no differences in functional capacity, quality of life, or HF events were noted between the 2 groups. It is important to point out that many of this study population had intact AV conduction and would have benefited from device programming to minimize ventricular pacing. Thus, although this study provides evidence that LV remodeling is prevented with biventricular pacing, this approach has not yet been shown to have a significant clinical benefit in individuals with normal baseline LV function.

The approach of biventricular pacing compared with RV pacing in patients with AV block and some degree of LV dysfunction (LVEF $\leq 50\%$) was evaluated in the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) study.\textsuperscript{8} The investigators reported a significant reduction in the primary outcome, which was a composite of mortality, treatment for a HF event with intravenous drug therapy, or an increase in LV end-systolic volume index by $\geq 15\%$ in the group treated with biventricular pacing (Figure 4). An important limitation to this trial was the inclusion of patients with LVEF $\leq 35\%$ and an indication for an ICD comprising 30% of the study population. Differences in the primary outcome between the 2 pacemaker subgroups with LVEF $\leq 35\%$ was driven predominantly by an increase in LV end-systolic volume index. Nevertheless, a secondary outcome of HF hospitalizations was higher in the conventional pacemaker group when compared with that in the biventricular pacing group, supporting the study hypothesis in this pacing...
subgroup with mild LV dysfunction. Whether those with milder LV dysfunction derive the same benefit of biventricular pacing compared with those with lower ejection fractions has not yet been reported. Biventricular pacing is more expensive and associated with an increased risk of complications when compared with RV pacing. On the basis of existing data, one must exercise clinical judgment in recommending a biventricular pacing system instead of RV pacing in patients with mild LV dysfunction.

**Optimizing Biventricular/LV Pacing**

Although CRT has become an important adjunct in the management of patients with symptomatic HF, as many as one third of CRT recipients do not experience a clinical benefit. Factors that may improve response include identifying and achieving the optimal LV lead position, ensuring maximal percentage LV pacing and programming devices to maximize the hemodynamic benefits.

**LV Lead Position**

The ideal LV lead position varies between patients determined, in part, by the underlying heart disease and site of maximal electric/mechanical activation delay. Anatomically defined regions do not reliably predict response to CRT although there is general consensus from post hoc analyses of large randomized trials that apical pacing sites should be avoided. Many investigators have attempted to identify the best LV site targeting the region of latest mechanical activation using echocardiographic imaging. Two randomized studies using speckle-tracking echocardiography to identify the latest activated LV wall segment for lead placement have reported significant LV reverse remodeling or improvement in event-free survival from HF hospitalization. However, the use of such imaging modalities are time intensive.

Other investigators have suggested targeting the region of latest electric activation, the QLV interval, defined as the interval measured from onset of the QRS on the surface ECG to the first positive or negative peak of the LV electrogram (Figure 5). Using this approach, which can be assessed at the time of lead implantation, stimulation at sites with QLV ≥ 95 ms has been shown to be associated with significant improvement in LV reverse remodeling and Quality of Life (Figure 5). Two recent investigations have reported that pacing from the site of longest LV electric delay was associated with acute hemodynamic improvement as measured by improvements in LV dP/dtmax. Zanon et al assessed LV electric delay for optimization of the LV pacing site in 32 consecutive patients. Numerous pacing sites were evaluated in multiple veins. The highest LV dP/dtmax was measured at the longest QLV in 31 of 32 patients. A QLV interval >95 ms was associated with an increase in LV dP/dtmax of ≥ 10%. The observed hemodynamic benefits were independent of the anatomic lead position. Together, these data support the concept that targeting the site of maximal LV delay should guide LV lead positioning.

**Multipolar Leads**

Multipolar LV leads are undergoing clinical investigation and have been approved for clinical use in some geographies. Some studies suggest an acute hemodynamic benefit associated with multisite pacing compared with standard biventricular pacing. Other clinical benefits include reduction in phrenic nerve stimulation and reduction in stimulation thresholds. Additional studies will be required to determine whether this lead technology facilitates identifying the site of maximal LV activation delay and improves clinical outcomes over the long term.

**Optimizing Device Programming**

Optimization of AV and interventricular (VV) timing intervals has been suggested for improvement in clinical response rates in patients with CRT. Several different approaches using echocardiography, electrocardiographic, or intracardiac electrogram measurements have been investigated. Although small studies have reported acute hemodynamic benefits, these findings have not been replicated in large randomized clinical trials. A meta-analysis including 4356 patients from 12 studies comparing AV and VV optimization to empirical device programming failed to show a significant clinical benefit of these optimization strategies (Figure 6). This field of investigation has several limitations. There is uncertainty as to which hemodynamic parameter should be optimized. The measurements made in these studies were performed at rest, whereas it is recognized that the activity may influence the optimal AV and VV intervals. In addition, atrial pacing can influence the optimal AV interval because of longer intracardiac conduction times when pacing the right atrial appendage. Furthermore, the role of AV and VV optimization for the nonresponder population has not been adequately addressed. Nevertheless, independent of these limitations at this point in time routine use of these strategies cannot be recommended.

The effect of programmed AV delay on clinical outcomes was retrospectively evaluated in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-CRT) trial. Patients

![Figure 4](http://circep.ahajournals.org/)

**Figure 4.** The primary outcome in Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF; time to death, an urgent care visit for heart failure requiring intravenous therapy or an increase in left ventricular end-systolic volume index, ≥ 15%) was significantly reduced for the biventricular pacing group (n=186; 53.3%) compared with the right ventricular pacing group (n=220; 64.3%; P<0.001). Reprinted from Curtis et al with permission of the publisher. Copyright © 2013, Massachusetts Medical Society.
programmed to a short AV delay (<120 ms) experienced a significant reduction in the risk of HF or death when compared with those programmed to longer AV delays. Short AV delays were also associated with a greater reduction in LV end-systolic volume and echo measures of dyssynchrony. This clinical benefit can likely be attributed, in part, to increasing the % of biventricular pacing. Some clinical data suggest that optimizing the programmed AV delay during exercise and programming on rate adaptive delay features that allow shortening of the AV delay during activity may also improve functional capacity.

Maximizing % LV Pacing
The greatest magnitude of benefit of CRT therapy has been correlated with maintaining a high percentage of
biventricular pacing. In a retrospective analysis of >1800 patients, the greatest magnitude of benefit in reduction in HF hospitalization and mortality was achieved with biventricular pacing in >92%. The relationship of % biventricular pacing to cardiovascular symptoms and survival was evaluated in 36,935 patients followed up by remote monitoring in the ALTITUDE study. Worsening HF symptoms were associated with a lower % biventricular pacing. In this population, survival was significantly improved with % biventricular pacing >98.5% (the median value observed at the first remote follow-up assessment) including the patients with AF (Figure 7). On the basis of these data, every effort should be undertaken to achieve the highest possible percentage of biventricular pacing. This goal can be impeded because of programming longer AV delays, atrial tachyarrhythmias, or frequent ventricular premature beats. Effective biventricular pacing may be underestimated by device reported % pacing counts because of fusion or pseudofusion so the clinician needs to be attentive to this possibility during follow-up.

**LV or Biventricular Pacing?**

CRT is usually achieved via biventricular pacing. However, some clinical data suggest that LV-only pacing may achieve effective cardiac resynchronization and in some patients be more effective than biventricular pacing. Recently, an algorithm that provides RV-synchronized LV pacing when AV conduction is normal has been evaluated in patients with CRT. Patients randomized to the adaptive CRT algorithm experienced similar cardiac improvement when compared with the group randomized to echo-guided CRT optimization. Further retrospective analysis based on % LV-only pacing suggested some significant clinical benefits. The time to first HF hospitalization or death was significantly lower in the subgroup with cardiac resynchronization therapy was followed up in the ALTITUDE registry based on cumulative % biventricular (BIV) pacing dichotomized at 98.5% and atrial fibrillation (AFib) burden dichotomized at 5%. Reprinted from Hayes et al with permission of the publisher.

![Figure 6](http://circ.ahajournals.org/lookup/doi/10.1161/CIR.0b013e3182643fcb)

**Figure 6.** Meta-analysis of clinical studies evaluating AV and VV interval optimization on cardiovascular outcomes. Data from studies based on intention to treat. Reprinted from Auger et al with permission of the publisher. CI indicates confidence interval; CLEAR, Clinical Evaluation of Advanced Resynchronization; DECREASE HF, Device Evaluation of Contak Renewal 2 and Easytrak 2; FREEDOM, Frequent Optimization Study Using the QuickOpt Method; M-H, Mantel-Haenszel; OPT, optimization; RHYTHM-II, Resynchronization for the Hemodynamic Treatment of Heart Failure Management; and SMART-AV, SmartDelay Determined AV Optimization: Comparison of Other AV Delay Methods Used in Cardiac Resynchronization Therapy.

![Figure 7](http://circ.ahajournals.org/lookup/doi/10.1161/CIR.0b013e3182643fcb)

**Figure 7.** Survival in patients with cardiac resynchronization therapy was followed up in the ALTITUDE registry based on cumulative % biventricular (BIV) pacing dichotomized at 98.5% and atrial fibrillation (AFib) burden dichotomized at 5%. Reprinted from Hayes et al with permission of the publisher.
experiencing ≥50% synchronized LV pacing (Figure 8). In addition, this subgroup experienced a greater improvement in HF status (Figure 8). Prospective studies will be required to confirm these observations.

Summary
The results from numerous clinical studies provide guidance for optimizing outcomes related to RV or biventricular pacing in the pacemaker and ICD populations. (1) Programming algorithms to minimize RV pacing is imperative in patients with dual-chamber pacemakers who have intrinsic AV conduction or intermittent AV conduction block. (2) Dual-chamber ICDs should be avoided in candidates without an indication for bradycardia pacing. (3) Alternate RV septal pacing sites may be considered at the time of pacemaker implantation. (4) Biventricular pacing may be beneficial in some patients with mild LV dysfunction. (5) LV lead placement at the site of latest LV activation is desirable. (6) Programming CRT systems to achieve biventricular LV pacing >98.5% is important. (7) Protocols for AV and VV optimization in patients with CRT are not recommended after device implantation but may be considered for CRT nonresponders. (8) Novel algorithms to maximize the benefit of CRT are in evolution further.

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References
1. Data courtesy of Medtronic Inc. 2014.


Abraham WT, Linde C, Daubert JC; REVERSE Study Group. Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. Eur Heart J. 2012;33:2662–2671.


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Supplemental Material

Algorithms to Minimize RV Pacing

Two programming approaches have been developed to minimize RV pacing (Table 1). These include adaptive/dynamic algorithms permitting extension of the AV delay when intrinsic conduction is detected. The maximum AV delay permitted varies between the different device technologies and is determined by the programmed baseline AV delays and the programmed maximum allowed extension of the AV delays. The nuances of these adaptive algorithms have been recently described in detail. The second approach are mode switching algorithms that pace in the AAI mode when intrinsic AV conduction is detected but switches to dual chamber pacing when AV block occurs.

Several studies have compared the Managed Ventricular Pacing (MVP) mode switch algorithm to an AV search hysteresis algorithm. All three studies have reported a greater reduction in RV pacing with the MVP algorithm compared to the search AV hysteresis algorithm including in patients with intermittent AV block (Supplemental Figure 1). However, these differences have not been shown to impact clinical outcomes. The largest study conducted randomized 385 patients receiving dual chamber pacemakers to the MVP mode or search AV hysteresis programming. A significant reduction in % RV pacing was demonstrated in the group randomized to the MVP mode which persisted over one year of follow-up. Although the majority of patients enrolled had SND as the indication for pacing the overall burden of AF observed during follow-up was low and did not correlate with % RV pacing.
Anomalies of Mode Switching Functions

Overall the algorithms mode switching from AAI to DDD when AV block occurs have been demonstrated to be safe. Some unusual behaviors of the mode switching functions have been described in case reports.\textsuperscript{5,6} For example, the MVP algorithm is based on ventricular timing intervals which at times may allow longer pauses.\textsuperscript{5,6} Pause-dependent ventricular tachyarrhythmias have been reported as by design pauses in excess of just over twice the programmed lower rate may occur at onset of AV block prior to switching from AAI to DDD mode.\textsuperscript{6} Frequent VPBs have been reported to cause inappropriate mode switching from AAI to DDD mode.\textsuperscript{7} These examples are reminders that programming of devices must be individualized.
Supplemental References


Supplemental Table 1: Studies Reporting Potential Deleterious Effects of Frequent Right Ventricular Apical Pacing

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>DAVID(^8)</td>
<td>506 Patients with ICD</td>
<td>Prospective randomized DDDR lower rate 70 bpm vs Backup VVI Pacing lower rate 40 bpm.</td>
<td>1.61 increased relative risk of death or HF hospitalization.</td>
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<tr>
<td>MOST Substudy(^9)</td>
<td>1339 Patients</td>
<td>Retrospective analysis comparing DDDR vs VVIR pacing.</td>
<td>Cumulative % VP &gt; 40% in DDDR mode associated with 2.6 fold risk of HF hospitalization; Cumulative % VP &gt; 80% in VVIR mode associated with 2.5 fold risk of HF hospitalization; Risk of developing AF increased by 0.7% or 1.0 % for each 1% increment in cumulative % VP up to 80% in VVIR and DDDR groups respectively.</td>
</tr>
<tr>
<td>SAVE PACe(^10)</td>
<td>1065 Patients</td>
<td>Prospective Randomized DDDR (AV delays 120-180 ms) vs DDDR with algorithms to minimize ventricular pacing.</td>
<td>Median %VP 9.1 vs 99.0% in DDDR with minimal VP algorithms vs conventional DDDR; 40% reduction in relative risk of AF in DDDR group with algorithms to reduce VP compared to conventional DDDR.</td>
</tr>
<tr>
<td>PACE(^11,12)</td>
<td>177 Patients</td>
<td>Prospective Randomized BiV vs DDDR pacing.</td>
<td>LVEF lower in DDDR vs BiV-pacing group (54.8+/-9.1% vs. 62.2+/-7.0%, P&lt;0.001); LVESV higher in DDDR vs BiV pacing group (35.7+/-16.3 ml vs. 27.6+/-10.4 ml, P&lt;0.001). No difference in HF events.</td>
</tr>
<tr>
<td>BLOCK HF(^13)</td>
<td>691 Patients</td>
<td>Prospective Randomized BiV vs RV apical pacing (pacemaker or ICD based on clinical indications).</td>
<td>Significant reduction in primary outcome (composite endpoint of death, urgent HF visit requiring intravenous drug therapy or ≥ 15% increase in LVESV index) in BiV group compared to RV pacing group.</td>
</tr>
<tr>
<td>MADIT\textsuperscript{14}</td>
<td>567 ICD Patients</td>
<td>Retrospective analyses</td>
<td>During late phase of extended follow-up mortality increased in patients with % RV pacing &gt; 50% without baseline LBBB.</td>
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<tr>
<td>Extended Follow-up</td>
<td>65% RV paced \leq 50%</td>
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SND – sinus node disease  
BiV – biventricular  
LBBB – left bundle branch block  
VP – ventricular pacing
Supplemental Figure 1. Differences in median % RV pacing when pacemakers are programmed to either the MVP or search AV Hysteresis (SAV) algorithms based on underlying indication for pacing – sinus node disease (SND) or AV block and type of AV block. There were only 8 patients with intermittent complete AV block (i3°AVB) in the SAV group.
Data from Chen S et al Europace. 2014 Apr 4. [Epub ahead of print]
Supplemental Figure 2. Mean LVEF at baseline, 1 and 2 years follow-up in patients randomized to DDD or BiV pacing. LVEF decreased significantly over time in the RV apical pacing group. Data from Chan JY et al, Eur Heart J 2011;32:2533-2540.