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Therapeutic Minimization of Ventricular Pacing to Prevent Atrial Fibrillation, Heart Failure, and Death

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Abnormalities of cardiac impulse formation and propagation have been recognized as symptomatic and potentially lethal causes of cardiovascular illness for more than two centuries.[1,2] Sinus node dysfunction (SND) is the dominant indication for cardiac pacing and refers to a broad array of abnormalities in sinus node and atrial impulse formation and propagation. These include persistent sinus bradycardia and chronotropic incompetence without identifiable causes, paroxysmal or persistent sinus arrest with replacement by subsidiary escape rhythms in the atrioventricular (AV) junction or ventricular myocardium, and paroxysmal or persistent atrial fibrillation (AF). The frequent association of paroxysmal AF and sinus bradycardia or sinus inertia, which may oscillate suddenly from one to the other and is usually accompanied by symptoms, is termed the "tachy-brady" syndrome. The only effective treatment for the symptomatic bradycardia component is permanent cardiac pacing. This issue of *Cardiology Rounds* reviews cardiac pacing and discusses therapeutic interventions using newer pacing modalities designed to optimize the AV conduction and intrinsic ventricular activation sequences in individual patients.

Background and significance

Despite nearly 20 years of clinical research involving thousands of patients in North America and Europe, the optimal pacing mode, pacing system, and ventricular stimulation site for bradycardia support during SND are unknown. In SND, atrial pacing (AAI/R) preserves ventricular propagation and reduces the risk of atrial fibrillation (AF) and congestive heart failure compared to ventricular pacing (VVI/R).[3-5] Ventricular pacing has been considered as "nonphysiologic" because it cannot provide AV synchrony. Dual-chamber (DDD/R) pacing was developed 2 decades ago to restore AV synchronization in patients with atrioventricular block (AVB) and represented a significant technological advance. This led to an emphasis on AV synchronization in cardiac pacing and DDD/R was quickly adopted as the "physiologic" pacing mode for all bradycardia-pacing conditions. Although the maintenance of AV synchrony afforded by conventional DDD/R is intuitively superior to VVI/R, this has been surprisingly difficult to prove. Large randomized clinical trials (RCTs) involving thousands of patients with either SND or AVB reached a consensus that despite maintenance of AV synchrony, DDD/R pacing does not reduce death compared to VVI/R pacing and has negligible benefits on the progression of heart failure and AF that emerge only after many years of follow-up.[6-8] In contradistinction, much smaller RCTs have consistently demonstrated that AAI/R reduces the risk of AF, heart failure, and cardiovascular death compared to DDD/R pacing in SND.[3-5] Importantly, the majority of patients in RCTs of pacing modes had normal ventricular function and no prior history of heart failure (Figure 1).

The puzzling inability to demonstrate an advantage to "physiologic" DDD/R pacing versus VVI/R pacing has recently been reconciled on the basis of ventricular desynchronization imposed by right ventricular apical (RVA) pacing. Similarly, the benefits of AAI/R pacing versus VVI/R pacing in SND can be explained by maintenance of both AV and ventricular (VV) synchrony.

The first convincing evidence for the concept of ventricular desynchronization imposed by unnecessary and physiologically deleterious RVA pacing came from an analysis of the MOde Selection Trial (MOST); Figures 2-4.[9] Statistical modeling revealed that the risks of heart failure hospitalization and AF could be directly linked to the RVA pacing burden (cumulative percent ventricular pacing [Cum%VP]), regardless of pacing mode. The lowest risks of heart failure and AF were observed in patients randomized

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Figure 1: Summary of clinical trial data: atrial based/ physiologic pacing benefits (vs. VVI/R)

Study	Mortality	Hospitalization for CHF	Atrial fibrillation	Stroke
Danish I AAI/R vs VVI/R; All SND pts	—	↓ But not until after 3 years FU	↓ Both acute and chronic	NS
CTOPP Physiologic vs ventricular pacing; ~40% of pts had SND	—	—	↓ But not until 2 years FU	—
MOST Dual-chamber vs single chamber; All SND pts	—	↓ But still 10% at 36 months	↓ But still 24%-25% at 36 months	—
DAVID No indication for pacing		↑ (Composite endpoint) Decreased LVEF	NS	NS
MADIT II ? Indication for pacing		↑	NS	NS
Danish I AAI/R vs DDD/R or DDD/R = L		↑ Decrease LVFS	↑ Increased LA diameter	

NS = Not a studies endpoint — **No difference observed**

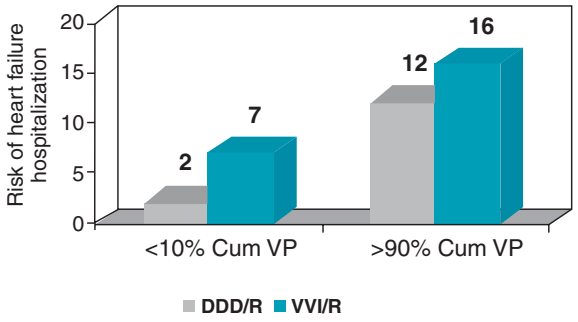
Despite maintenance of AV synchrony, dual-chamber pacing does not improve survival or prevent stroke when compared with ventricular pacing. DDD/R pacing is associated with modest or negligible reductions in AF and heart failure compared to VVI/R pacing. FU = Follow-up; LA = Left atrial; LVEF = Left ventricular ejection fraction; LVFS = Left ventricular fractional shortening; SND = sinus node dysfunction

to DDD/R, but with a very low Cum%VP ("functional" AAI/R pacing). The highest risks of heart failure and AF were observed in the VVI/R mode and this risk was constant even at very low levels of Cum%VP.[9]

The negative consequences of ventricular desynchronization due to RVA pacing were further indicated by adverse outcomes in RCTs of ICD therapy. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial tested the hypothesis that DDD/R pacing at a lower rate of 70 beats/minute (BPM) enables optimal heart failure management and reduces heart failure hospitalization compared to ventricular-only back-up pacing (VVI 40 BPM).[10] The study was terminated prematurely due to excess heart failure and death in the DDD/R arm. Similarly, although implanted converter defibrillators (ICDs) have been shown to be effective for the primary prevention of sudden cardiac death in appropriately selected patient populations, this comes at the cost of an increased risk of heart failure hospitalization.[11,12]

An analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II demonstrated a similar relationship between Cum%VP and heart failure, ventricular arrhythmias, and death that was insensitive to ICD system and pacing mode (single or dual).[13] The fact that 54% of the patients in MADIT II had "simple" single-chamber ICD systems indicates that the common interpretation from the DAVID trial – that "complex" ICDs cause worsening of systolic heart failure – is incorrect. The accurate interpretation of the clinical evidence is that any unnecessary RVA pacing may worsen heart failure, particularly in the failing ventricle. Single-chamber RVA pacing confers the highest risk of heart failure hospitalization for any percentage of ventricular pacing relative to other pacing modes.[9] The importance of proper synchronization in ventricular activation and contraction, apparent from the above-mentioned clinical trials, can be regarded as the practical implication of extensive physiologic research performed during the past 75 years, knowledge that has been surprisingly neglected for decades.

Figure 2: Relationship between pacing mode, cumulative percent ventricular pacing (Cum%VP), and heart failure hospitalization in the MOde Selection Trial (MOST)[9]



Risk of heart failure is much higher in either mode when Cum%VP is very high (>90%). As expected, it is higher in VVI/R vs DDD/R, presumably due to the combined detrimental effects of the loss of AV and VV synchrony. However, the risk of heart failure is much lower when Cum%VP is lower in either mode. Furthermore, the risk is essentially "0" in the DDD/R group when Cum%VP was very low, resembling "functional" atrial pacing.

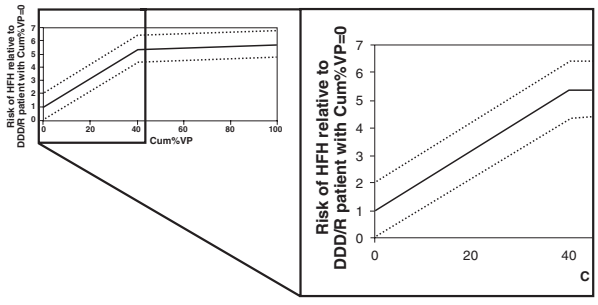
Pathophysiologic basis of RVA pacing

Asynchronous ventricular activation

Optimal left ventricular (LV) pumping function and energetically efficient contraction require a normal electrical activation sequence that is derived from participation of distal components in the specialized conduction system (the main bundle branches and their distal ramifications). Pacing at virtually any ventricular site disturbs the natural patterns of activation and contraction. Ironically, of all the ventricular sites, the RV apex appears to be the least favorable, hemodynamically.[14] Endocardial mapping studies have demonstrated that RVA pacing mimics the activation patterns of left bundle branch block (LBBB),[15] resulting in earlier RV than LV activation (interventricular dyssynchrony) and, within the LV, earlier septal than free-wall activation (intraventricular dyssynchrony). This altered activation sequence can be explained by the conduction of an electrical wavefront through the ventricular myocardium rather than through the His-Purkinje system.

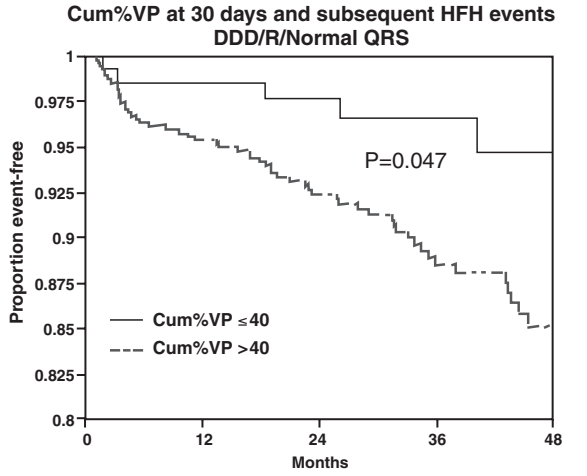
It is critically important to recognize that the RV apex has become the most commonly applied site for ventricular pacing simply because it is convenient and easy for the implanter to reach with available leads and typically yields chronically stable mechanical positions and stimulation thresholds.

Figure 3: Increasing risk of heart failure hospitalization with Cum%VP in the DDD/R mode in MOST[9]



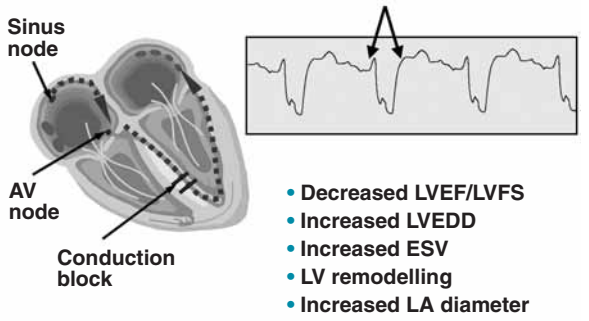
When compared with Cum%VP >40%, relative risk constant at a 2.6-fold increase over patients with Cum%VP ≤40%. The relative risk increased by 54% for each 10% increase in Cum%VP between 0 and 40%.

Figure 4: Time to first heart failure hospitalization by Cum%VP > or ≤40% in the DDD/R mode in MOST[9]



The plot shows an early, sustained, and increasing incidence of heart failure hospitalization among DDD/R patients with a Cum%VP >40% compared to ≤40%

Figure 5: Schematic representation of ventricular desynchronization due to right ventricular apical pacing



When a portion of the heart is prematurely stimulated, the activation sequence changes markedly, generating regions of both early and delayed contraction. Early shortening of the stimulation site is wasted work because pressure is low and no ejection is occurring. Late activation of regions remote to the stimulator occurs at higher stress because the early site has already developed tension, yet it is also characterized by wasted work because the early activated territory may now undergo paradoxical stretch. The net result is a decline in systolic function of about 20% with reduced cardiac output, increased end-systolic volume (ESV) and wall stress, delayed relaxation, and decreased efficiency.

Impaired LV systolic function

More than 75 years ago, it was already demonstrated that ventricular pacing results in adverse hemodynamic consequences in mammals.[16] The cause of the reduction in pump function is asynchronous electrical activation (Figure 5).[14] It results in paradoxical septal-wall motion and delayed lateral-wall contraction leading to inter- and intraventricular dyssynchrony. Synchrony of contraction is important because it results in a more effective and energetically efficient ejection.[17] The mechanical effect of asynchronous electrical activation is quite dramatic because the various regions not only differ in terms of the onset time of contraction, but also in the pattern of contraction. Early contraction of regions close to the pacing site causes stretching of remote regions that are not yet activated. This stretching further delays shortening of these late activation regions and increases the force of local contractions by virtue of a (local) Frank-Starling mechanism. Due to their vigorous contractions, the late activated regions impose loading on the earlier activated territories, which then undergo systolic paradoxical stretch. This reciprocated stretching of regions within the LV wall leads to a less effective and energetically efficient contraction.[17] Local differences in contraction patterns in the paced ventricle imply a redistribution of mechanical work, perfusion, and oxygen demand within the LV wall;[18-21] this is reflected by perfusion defects in many patients with angiographically-normal coronary arteries exposed to chronic RVA pacing.[22] These defects are primarily over the inferior and apical segments where the pacing electrode was located and their presence is associated with lower ejection fractions and a higher percentage of wall-motion abnormalities.[22] These regional perfusion and oxygen uptake abnormalities resemble those described in LBBB and are reversible after RVA pacing is stopped, even after 2 years of pacing.[23]

The hemodynamic consequence of discoordinated LV contraction are reductions in contractility and relaxation. Poorer contractility is reflected by decreases in stroke work and increases in LV pressure, as well as a rightward shift of the LV end-systolic pressure-volume relationship.[14] The latter indicates that the LV operates at a consistently larger volume.[24,25] The combination of these effects leads to a decrease in LV ejection time and ejection fraction (EF), and has been demonstrated in numerous studies on short-[26,27] and long-term RVA stimulation.[22,23,28]

Ventricular remodeling and cellular changes

Recently, Nahmali et al demonstrated that EF decreases gradually over 1 week of RVA pacing.[29] Furthermore, after cessation of pacing, recovery of baseline EF is delayed for up to 32 hours. This "mechanical memory" appears to be the mechanical equivalent of the well-known "T-wave" or "cardiac memory" (referring to abnormal repolarization after cessation of ventricular pacing).[30] It seems likely that alterations in the ion channels (eg, the transient outward potassium channel and the L-type calcium channel[31,32]) also play a role in the early contractile maladaptation to ventricular pacing.

Longer lasting (weeks to years) asynchronous ventricular activation results in regional structural changes that may further deteriorate LV function. Within several months of VDD pacing in canine hearts, ventricular dilatation occurs.[25] In addition, the LV wall becomes asymmetrically hypertrophied,[25,33] likely induced by a combination of overall myocardial stretch, regional differences in mechanical load,[25] and increased neurohormonal stimulation.[34] This asymmetric LV remodeling effect of RVA pacing has recently been reported in patients with congenital complete AVB who are exposed to chronic RVA pacing.[35]

The late activated and most hypertrophied regions show the most pronounced cellular derangements.[36] These derangements include down-regulation of proteins involved in calcium homeostasis and in connexin 43, the major gap-junction protein. Furthermore, in RVA-paced dogs, perfusion abnormalities of the septum and free wall coincided with elevated tissue norepinephrine levels, indicating a mismatch of perfusion and innervation.[34] Dystrophic calcifications, disorganized mitochondria, and myofibrillar cellular disarray have been described with RVA pacing.[37,38] Myofibrillar disarray may be due to abnormal stress vectors resulting from an altered sequence of contraction.[37]

In order to put the potential harm of RVA pacing into perspective, it is worth noting some of the similarities between the long-term consequences of ventricular pacing and a moderate-

sized myocardial infarction. These similarities include a reduction of 10%-20% in global LV pumping function; increased mechanical work in the remote regions; increased neurohormonal stimulation; and a 20%-30% ventricular hypertrophy. Ventricular dilatation, however, is more pronounced after a coronary occlusion than after ventricular pacing.[25,39]

A new paradigm for physiologically optimal ventricular pacing

Recognition of the adverse effects of RVA pacing has stimulated interest in strategies to either abolish or attenuate these effects. Two approaches have been investigated:

- manipulation of conventional pacing modes and timing cycle operation among patients with reliable AV conduction in order to minimize unnecessary ventricular pacing and preserve normal ventricular conduction
- pacing at alternate site(s) in the ventricles to attenuate the adverse effects imposed by ventricular desynchronization when ventricular pacing cannot be avoided and/or abnormal ventricular conduction is already present.

Dual-chamber minimal ventricular pacing

In order to prevent the adverse effects of ventricular desynchronization by RVA pacing, the 4 goals of optimized ventricular pacing in patients with intact AV conduction and normal ventricular conduction are:

- prevention of symptomatic bradycardia
- provision of physiologic chronotropic support, if needed
- maintainance of AV synchrony, when necessary
- maintainance of normal ventricular activation sequence whenever possible.

Minimizing ventricular pacing with conventional single or dual-chamber pacemakers and ICDs

Two conventional solutions to reduce the chronic adverse effects of RVA pacing have been proposed. Single chamber AAI/R pacing and dual-chamber modes (DDD/R or DDI/R) with fixed or dynamic long AV intervals have been suggested for ICD and pacemaker systems in order to provide atrial support, while reducing ventricular pacing. By definition, AAI/R pacing eliminates ventricular pacing and may provide effective pacing support for patients with intact AV conduction. Although the annualized risk of AVB is low during AAI/R pacing in carefully selected patients, for >50% of cases, the first manifestation is syncope.[5,40,41] Since the fundamental purpose of cardiac pacing is to prevent symptomatic bradycardia, not every cardiologist is ready to sacrifice definite bradycardia prevention with ventricular pacing for a lower risk of developing heart failure and AF. Furthermore, in ICDs, standard AAI/R pacing does not consider ventricular activity; therefore, during a ventricular arrhythmia, asynchronous atrial pacing can blank (conceal) ventricular events, possibly resulting in a delay in arrhythmia detection with potentially lethal consequences.[42,43] Since the inclusion of a ventricular pacing lead in ICDs is mandatory to detect ventricular arrhythmias, to deliver antitachycardia pacing and ventricular defibrillation therapy, and to prevent potentially lethal post-defibrillation bradycardia, an algorithm is warranted to effectively utilize the information from the ventricular lead within the context of an AAI/R mode.

Unlike AAI/R pacing, DDD/R or DDI/R pacing precludes the possibility of syncope due to AVB. Optimal DDD/R pacing operation imposes restrictions on maximum allowable AV delays, particularly during atrial sensing, in order to maintain sinus tracking at elevated rates and provide adequate detection windows for recognizing atrial tachyarrhythmia as required by mode-switching. DDD/R operation in dual-chamber ICDs is even more complex and imposes further restrictions ("interlocks") on maximum allowable AV delays to prevent competitive pacing during ventricular tachycardia, which might result in detection failure due to inviolable cross-chamber blanking periods. Consequently, the maximum allowable AV delay during conventional DDD/R pacing operation has been in the range of 120-200 milliseconds (ms). AV delays in this range have also been shown to optimize cardiac performance during continuous RV apical stimulation while dual-chamber pacing.[44] These data, however, were derived from patients with persistent heart block in whom "preservation" of a normal ventricular activation sequence was not possible. The AV interval is thus confined and the common consequence is a high Cum%VP in the majority of patients with SND, including those with intact AV conduction.[9,10] In the majority of patients, this high Cum%VP is due to the overlap of baseline PR intervals with recommended programmed AV delays. Thus, conventional DDD/R pacing condemns the majority of patients with SND to a lifetime of "forced" ventricular desynchronization.[9]

Manipulation of AV intervals in the DDD/R mode among patients with intact AV conduction may permit "functional" AAI/R operation and reduce unnecessary ventricular pacing, thereby preserving a normal ventricular activation sequence. Long AV delays interfere with optimal DDD/R operation by creating timing cycle conflicts that may compromise upper rate behavior and AF recognition, and predispose to endless loop tachycardias.[45] Static long AV delays (250-350 ms) are not highly effective in preventing unnecessary ventricular pacing in many pacemaker and ICD patients because of unanticipated dynamic variations in AV nodal conduction.[5,45,46] Athough static long AV delays (≥250 ms) may attenuate the effect of ventricular pacing on LV function seen during shorter AV delays, significantly increased left atrial diameters persist compared to AAI/R pacing.[5] Automatic AV interval extension algorithms may also reduce undesirable ventricular pacing; however, the modest reduction in Cum%VP[47,48] is probably insufficient to fully realize the potential clinical benefits.[9]

Ironically, the majority of patients treated with pacemakers for SND, including those with dilated cardiomyopathy, reduced ejection fraction, and heart failure, who are candidates for primary prevention ICD therapy, have a normal ventricular activation sequence that manifests as a QRS duration of <120 ms on the baseline electrocardiogram.[7,49] Furthermore, most patients have reliable AV conduction[7,49] that remains stable over time.[40] For example, in the MOST trial, the baseline PR interval was normal (<200 ms) or mildly prolonged in the majority of patients. Such patients could theoretically be served with AAI/R pacing that would preserve normal ventricular activation. Nonetheless, most patients with SND indicated for cardiac pacing receive DDD/R systems because of the small, but potentially serious risk of syncope due to progressive conduction system disease resulting in AV block.[5,40,41,50,51] A

ventricular lead is required for ICDs, but many ICD patients receive dual-chamber systems because of the need for physiologic pacing support and the desire to exploit atrial activity for discriminating supraventricular and ventricular tachycardias.[52-55]

A novel strategy for minimizing ventricular pacing: MVP

Managed ventricular pacing (MVP) was developed to address the inherent limitations of AAI/R, VVI/R, and DDD/R modes for reducing undesirable ventricular pacing.[56,57] The failure of these modes to minimize unnecessary ventricular pacing is inherent to the fundamental principle of the dual-chamber timing cycle operation, where each ventricular paced event is synchronized to every atrial event. In order to fully realize the benefits of minimizing ventricular pacing, MVP abandons this fundamental principle by uncoupling atrial activity from ventricular pacing.[58,59]

During normal operation, only the atrium is paced (resembling AAI/R mode), while the ventricle is monitored on a beat-to-beat basis to verify intact AV conduction. For a transient loss of AV conduction (an A-A interval missing a ventricular-sensed event), a synchronized ventricular back-up pace is provided and AAI/R pacing continues. For persistent loss of AV conduction, MVP switches to the DDD/R mode for 1 minute. Tests for return to normal AV conduction are performed by inhibiting ventricular pacing for 1 cycle. AV conduction tests are administered at geometrically progressive time intervals (1, 2, 4, 8, …minutes) and, if AV conduction is detected, the mode of operation returns to AAI/R with ventricular monitoring. During AF, MVP operates in the DDI/R mode. As a result, MVP responds appropriately to all pacing conditions (intrinsic conduction [AAI/R], AV block [DDD/R], AF [DDI/R]).

MVP allows for intermittent, single, missed ventricular beats, mimicking normal AV node physiology and only provides ventricular pacing when AV conduction is deemed inadequate. This determination is made over a sequence of beats and not by imposing a fixed or dynamic AV interval, which means that MVP imposes no constraint on the AV interval (beyond the A-A interval) and provides true functional AAI/R pacing. Two consecutive RCTs have demonstrated that MVP is safe and effective. It reduces the mean Cum%VP to <5% in 91% of patients and <1% in 78% of patients.[56,57] This reduction in Cum%VP is achieved without sacrificing atrial pacing support, AV synchrony, and ventricular synchrony (unlike the VVI mode), and without forced ventricular desynchronization due to RVA pacing (unlike the DDD/R or DDI/R modes).

Primum non nocere

Given our current knowledge of the potentially serious adverse side effects of RVA pacing, the part of Hippocrates' law stating: "First, do no harm," should be kept in mind. Thus, the one-dimensional thinking that has dominated the practice of cardiac pacing for >25 years must now be abandoned. The technique of cardiac pacing must be tailored to the patient's AV conduction and ventricular conduction status.

In situations when AV conduction and ventricular conduction are normal, the optimal pacing strategy should provide predominantly atrial support and rely on AV conduction to maximally preserve normal ventricular conduction. This position is supported by a recent American Heart Association Science Advisory[60] stating: "On the basis of the evidence indicating that ventricular pacing is associated with a higher incidence of AF in patients with SND, a patient who has a history of AF and needs a pacemaker for bradycardia should receive a physiological pacemaker (dual-chamber or atrial) rather than a single-chamber ventricular pacemaker. For patients who need a dual-chamber pacemaker, efforts should be made to program the device to minimize the amount of ventricular pacing when AV conduction is intact by extending the AV delay, programming the device to a non atrial tracking mode such as DDI/R, or implanting a device with an algorithm that minimizes ventricular pacing." This strategy should serve the vast majority of patients treated with pacemakers for SND,[7,49] and many patients indicated for ICD therapy. A dual-chamber, minimal ventricular pacing strategy (such as MVP[48,49]) is recommended to prevent syncope due to unpredictable AV block or relative ventricular bradycardia during paroxysmal AF.[50,57,58]

No RCT has demonstrated superior outcomes with DDD/R or DDI/R pacing and extended AV intervals relative to AAI/R pacing or any other pacing mode. Similarly, the clinical benefit of MVP has not yet been demonstrated in RCTs, although these are ongoing. It is reasonable to hypothesize that preservation of normal ventricular conduction by avoiding unnecessary RVA stimulation will reduce the risk of AF, heart failure, and death reported among patients with pacemakers and ICDs.[9,10,13] Future investigations will help establish which patients are likely to benefit and whether some methods for achieving minimization are superior to others.

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