A New Paradigm for Physiologic Ventricular Pacing

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Clinical trials in patients with pacemakers for sinus node dysfunction or atrioventricular block (AVB) and implantable cardioverter-defibrillators provide increasing evidence showing that desynchronization of ventricular electrical activation and contraction, induced by conventional right ventricular apex (RVA) pacing, is a serious threat for long-term cardiac morbidity and mortality. The risk of heart failure is increased even in hearts with initially normal pump function and in case of part-time ventricular pacing. These epidemiologic data fit with knowledge from decades of pathophysiological research, indicating that right ventricular (RV) pacing creates abnormal contraction, reduced pump function, hypertrophy, and ultrastructural abnormalities. This paper presents a new paradigm that aims to tailor ventricular pacing to the individual patient to achieve a way of pacing that is as physiologic as possible. In patients without AVB and no intraventricular conduction abnormalities, ventricular pacing should be avoided as much as possible, using atrial-based pacing. In patients with AVB, alternate single-site RV or left ventricular pacing or biventricular pacing may be superior to RVA pacing. Efforts to optimize the pacing mode or site should be greater in patients with a longer expected duration of pacing, poorer cardiac function, and larger mechanical asynchrony. Awareness of the problem of desynchronization should also lead to more regular monitoring of cardiac pump function and mechanical synchrony in any patient with ventricular pacing (J Am Coll Cardiol 2006;47:282–8) © 2006 by the American College of Cardiology Foundation

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). The only effective treatment for symptomatic bradycardia caused by sinus node dysfunction (SND) or atrioventricular block (AVB) is cardiac pacing. Despite nearly 20 years of clinical investigation, the optimal pacing mode, pacing system, and ventricular stimulation site for bradycardia support are unknown.

Dual-chamber (DDD/R) pacing was developed two decades ago to restore atrioventricular (AV) synchronization in patients with AVB and represented a significant technological advance. This led to an emphasis of AV synchronization in cardiac pacing, and DDDR was quickly adopted as the "physiologic" pacing mode. However, large randomized clinical trials (RCTs) in SND or AVB have reached a consensus that despite maintenance of AV synchrony, DDD/R pacing does not reduce death compared with single-site RVA pacing (VVI/R) and has surprisingly modest or even negligible benefits for progression of heart failure (HF) and atrial fibrillation (AF) that emerge only after many years of follow-up (2–4). However, much smaller RCTs have consistently shown that atrial pacing (AAI/R) reduces the risk of AF, HF, and death compared with VVI/R and DDD/R pacing in SND (5,6).

The puzzling inability to show an advantage of physiologic DDD/R versus nonphysiologic ventricular pacing may be explained by a factor common to all modes of ventricular pacing and also influencing short- and long-term cardiac pump function: ventricular synchrony. The first evidence for this concept came from a retrospective analysis of the Mode Selection Trial (MOST), in which the risks of HF hospitalization and AF could be directly linked to right ventricular apex (RVA) pacing burden (cumulative percent ventricular pacing [Cum%VP]) regardless of pacing mode (7). The lowest risks of HF and AF were observed in patients randomized to DDD/R (AV synchrony) but with a very low Cum%VP (ventricular synchrony), yielding functional atrial pacing in the context of a dual-chamber pacemaker.

The negative consequences of ventricular desynchronization attributable to RVA pacing were further indicated by adverse outcomes in RCTs of implantable cardioverter-defibrillator (ICD) therapy. The DAVID trial tested the hypothesis that DDD/R pacing at a lower rate of 70 beats/min would enable optimal HF management and reduce HF hospitalization and death compared with ventricular-only backup pacing (VVI, 40 beats/min) (8). The study was terminated prematurely and unexpectedly because of an excess of HF and deaths in the DDD/R arm. An analysis of the MADIT II trial showed a similar relationship between Cum%VP and HF, ventricular arrhythmias, and death that was insensitive to ICD system and pacing mode (9). A subsequent analysis of the DAVID trial reached the same conclusion as the MOST study—the lowest risks of HF worsening and death were observed in patients randomized to DDD/R but with low Cum%VP (10).
Interestingly, despite these provocative observations, clinical experience indicates that the majority of pacemaker patients tolerate chronic RVA pacing reasonably well. In the MOST study, only ~10% of patients had HF during follow-up and were more likely to have a lower ejection fraction (EF), myocardial infarction, and a worse New York Heart Association functional class compared with patients who did not experience HF (11). Although such clinical characteristics constitute a small portion of patients in RCTs of conventional pacemaker therapy, they define the typical ICD patient population and imply that the potentially harmful effects of RVA pacing are accelerated in the setting of systolic HF.

The importance of ventricular asynchrony is further supported by similarly poor outcomes in left bundle branch block (LBBB). Left bundle branch block results in an electrical activation sequence similar to that of RVA pacing (12) without changing AV synchrony. Left bundle branch block has been shown to be an independent predictor of cardiac morbidity and mortality, particularly in patients with systolic HF (13,14).

The concept of ventricular asynchrony represents the practical implication of extensive physiologic research, knowledge that has been surprisingly neglected in the practice of conventional cardiac pacing for decades.

**PATHOPHYSIOLOGICAL BASIS OF RVA PACING**

**Asynchronous ventricular activation.** Optimal left ventricular (LV) pumping function and energetically efficient contraction require a normal electrical activation sequence, derived from the participation of the distal components of the specialized conduction system. Pacing at virtually any ventricular site disturbs the natural pattern of activation and contraction because conduction of the electrical wave front takes place slowly through ventricular myocardium rather than through the His-Purkinje system.

Ironically, of all ventricular sites, the RVA appears seems to be hemodynamically least favorable (15). It is important to recognize that the RVA has become the most commonly applied site because it is convenient and easy for the implanter to reach with available leads and yields chronically stable mechanical positions and stimulation thresholds.

**Impaired LV systolic function.** More than 80 years ago, it was shown that ventricular pacing results in adverse hemodynamic consequences in mammals (16). This finding has been replicated numerous times in animal experiments and more recently in patients (17,18). The cause of this reduction in pump function is asynchronous electrical activation. (15). Animal studies have shown that the mechanical effect of asynchronous electrical activation is dramatic because the various regions differ not only in the time of onset of contraction, but also in the pattern of contraction. Early contracting regions close to the pacing site stretch not-yet-activated remote regions. This stretching further delays shortening of these late-activation regions and increases their force of local contraction by virtue of the (local) Frank-Starling mechanism. Because of their vigorous contraction, the late-activated regions impose loading on the earlier activated territories, which now undergo systolic paradoxical stretch (Fig. 1). This reciprocated stretching of regions within the LV wall causes a less effective and energetically less efficient contraction (19). The local differences in contraction pattern in the paced ventricle imply a redistribution of mechanical work, perfusion, and oxygen demand within the LV wall (20,21). In animals, ventricular pacing results in reductions in regional myocardial perfusion (20,22) and oxygen consumption near the pacing site (19,20,23). Perfusion defects and wall motion abnormalities have been shown in up to 65% among patients with angiographically normal coronary arteries exposed to chronic RVA pacing (24,25). These are mainly over the
inferior and apical segments where the pacing electrode was located and are reversible upon cessation of pacing (25).

The hemodynamic consequences of the discoordinate LV contraction are reduction in contractility and relaxation. The poorer contractility is reflected by decreases in stroke work and rate of increase of LV pressure, and a rightward shift of the LV end-systolic pressure-volume relationship (15). The latter indicates that the LV operates at a consistently larger volume. The combination of these effects leads to a lower LV ejection time (Fig. 1) and EF (17,24,25). The abnormal relaxation is caused by premature relaxation in early-activated regions and delayed contraction in others (Fig. 1) (15), expressed as a decrease in $\frac{dP}{dt}$ maximal rate of fall of LV pressure, increase in the relaxation time constant tau, and decrease of Doppler E-wave velocities. Right ventricular apex pacing may also lead to a reduction in diastolic filling time and preload-load because of delayed activation and contraction of the LV (26).

**Ventricular remodeling and cellular changes.** Early signs of cellular and molecular adaptation to disturbed activation are abnormal repolarization after stopping of ventricular pacing and a reduction in EF within hours of RVA pacing (17). Alterations in potassium and calcium channels likely play a role in these phenomena.

Longer-lasting (more than weeks) ventricular pacing results in ventricular dilatation and asymmetric LV hypertrophy (27,28). The more pronounced hypertrophy in the latest activated, pre-stretched regions (28) indicates that local mechanical load is an important stimulus in this remodeling process (Fig. 2). Increased sympathetic stimulation, resulting in elevated myocardial catecholamine levels (22), also contributes.

The late-activated, most-hypertrophied regions show the most pronounced cellular derangements (29) (Fig. 2), such as down-regulation of proteins involved in calcium homeostasis and impulse conduction. Dystrophic calcifications and disorganized mitochondria and myofibrillar cellular disarray (30) have been described with RVA pacing.

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

**Atrial-based dual-chamber minimal VVI/R.** The four goals of optimized ventricular pacing when AV and ventricular conduction are normal are: 1) to prevent symptomatic bradycardia, 2) to provide chronotropic support if needed, 3) to maintain AV synchrony when necessary, and 4) to maintain normal ventricular activation sequence whenever possible.

Two conventional solutions have been proposed in ICDs and pacemakers for providing atrial support while reducing ventricular pacing: single-chamber atrial pacing and dual-chamber modes (DDD/R or DDI/R) with fixed or dynamic long AV delays. By definition, AAI/R eliminates ventricular pacing and prevents bradycardia in patients with intact AV conduction. Although the risk of AVB is low during atrial pacing in carefully selected patients, the first manifestation is syncope in more than 50% of cases (6,31). Because the fundamental purpose of cardiac pacing is to prevent symptomatic bradycardia, not every cardiologist is ready to sacrifice bradycardia prevention for a lower risk of development of HF and AF. Furthermore, AAI/R in ICDs does not consider ventricular activity; therefore, during a ventricular arrhythmia AAI/R can blank (conceal) ventricular events, resulting in detection failure (32).

An alternate approach to minimize ventricular pacing while precluding the possibility of syncope caused by AVB is to use DDD/R or DDI/R with long AV delays. This approach may yield functional AAI/R behavior in the context of a dual-chamber pacemaker (6,33). However, dual-chamber pacemakers and ICDs impose limitations on maximum allowable AV delays to optimize upper-rate behavior and AF recognition and to prevent ventricular detection failures caused by cross-chamber blanking. The common consequence is high Cum%VP attributable to overlap with intrinsic AV conduction times, particularly during rate-responsive atrial pacing. The failure of these modes to minimize unnecessary ventricular pacing is inherent to the fundamental principle of DDD/R timing cycle operation, wherein a ventricular paced event is synchronized to every atrial event.

Newer atrial-based dual-chamber minimal ventricular pacing modes have been developed to specifically overcome the inherent limitations of AAI/R, VVI/R, and DDD/R.
modes for reducing undesirable ventricular pacing (34,35). By selectively uncoupling atrial from ventricular pacing activity, these modes safely and effectively reduce mean Cum%VP to <5% in pacemaker and ICD patients. This reduction in Cum%VP is achieved without sacrificing atrial support, AV synchrony, and ventricular synchrony (unlike VVI/R), and without ventricular desynchronization because of RVA pacing (unlike DDD/R or DDI/R).

**Optimal sites for myocardial stimulation when ventricular pacing cannot be avoided.** Ventricular pacing is unavoidable in many patients because of unreliable or absent AV conduction, or permanent AF. In recognition of this need, interest has focused on alternative site(s) ventricular pacing to maximize pumping function. These sites include the RV septum, His bundle, various LV sites, and combination of LV and RV (biventricular [BiV]).

**Alternate-site RV pacing.** Because pacing leads are usually implanted along the transvenous route, alternate sites within the RV have been studied intensively. The (high) RV septum seems to be the most promising site within the RV. Acute hemodynamic studies generally, although not consistently, show an advantage of high septal over RVA pacing (reviewed in De Cock et al. [36]). However, small enrollment and inconsistent experimental methods hinder the interpretation of these studies. Location of alternative pacing sites were not clearly specified, were largely topographic, and lacked consistent anatomic designation. There is conflicting evidence regarding whether QRS duration can be used to find the pacing position resulting in the best LV pump function (37,38).

With respect to long-term outcomes, the ROVA trial, a three-month randomized crossover study in patients with permanent AF, had a neutral outcome (39). However, other longer-term studies have shown that high septal pacing reduces perfusion defects, remodeling, and neurohormonal activation (40,41).

**Direct His bundle pacing.** Pacing the His bundle preserves native ventricular activation and yields QRS duration, electrical axis, and activation sequence identical to that of non-paced rhythm. Studies in the electrophysiology laboratory have shown favorable effects of His bundle pacing on cardiac performance compared with RVA pacing (42). Permanent His bundle pacing has been achieved in humans but requires considerable technical prowess to achieve even limited success (43).

**BiV pacing.** Biventricular pacing has been primarily introduced to correct pre-existing interventricular and intraventricular conduction delays, thereby improving ventricular pumping function. Because the activation pattern during RVA pacing is similar to that during LBBB, it is not surprising that preliminary results with upgrading RVA to BiV pacing systems have been encouraging among patients with systolic HF (44). However, the situation is less clear when RVA and BiV pacing are compared in AF patients immediately after AV nodal ablation (45). These results are similar to comparison of RVA and RV septal pacing in the ROVA study and suggest that the benefits of rate control in AF conceal the effect of asynchronous activation.

**LV pacing.** In hearts with normal ventricular conduction, LV pumping function is less adversely affected by pacing from most LV sites than by RVA pacing (15,46). Within the LV, some sites are better than others. Importantly, the better sites for normally conducting ventricles are different from those in ventricles with LBBB-like conduction abnormalities. Studies in animals (37) and children (47) have shown that pacing at the inferoapical LV septum and the epicardium of the LV apex yields LV pumping function that closely approximates function during normal ventricular conduction. These results may be explained by rapid engagement of the specialized conduction systems in the LV wall near its “break out” site (47). Left ventricular apex pacing can be achieved by mini-thoracotomy, making this site attractive for pediatric pacing, in which leads are often positioned epicardially.

**A DECISION ARCHITECTURE FOR SELECTING PHYSIOLOGICALLY OPTIMAL VENTRICULAR PACING**

**Primum non nocere.** With the current knowledge on the potentially serious adverse side effects of RVA pacing, it is time to apply the part of Hippocrates’ law that states “first, do no harm.” Thus, we propose an intellectual reinvention of cardiac pacing that rationalizes insights from physiological and clinical research. An overarching structure for this reinvention of cardiac pacing is conceptualized in Figure 3.

The foundation of this architecture is the assessment of AV conduction and ventricular conduction.

**AV conduction and ventricular conduction are normal: protect ventricular synchrony.** In this situation, the best site for stimulating the ventricle is from the atrium. The optimal pacing strategy should provide predominantly atrial support and rely on AV conduction to maximally preserve normal ventricular conduction. This strategy should serve the vast majority of patients treated with pacemakers for
SND and many patients indicated for ICD therapy. An atrial-based dual-chamber minimal ventricular pacing strategy is recommended to prevent bradycardia because of unpredictable AV or paroxysmal AF. It is crucial to remember that BiV or LV pacing induces dyssynchrony in hearts with normal ventricular conduction (48) and reduces LV pumping function in patients with no baseline dyssynchrony (49). Therefore, BiV or LV pacing is not the best solution for these patients.

**AV conduction is unreliable or absent and ventricular conduction is normal: prevent ventricular desynchronization.** In this situation, pacing from alternative ventricular sites can limit the imposition of abnormal physiology as compared with RVA pacing. Because alternate sites are, with current implant tools, usually not easy to access, the risks associated with abnormal ventricular activation because of RVA pacing should be weighed against the risks of more complex and expensive alternative ventricular pacing strategies. As pointed out below, use of alternative pacing sites seems especially advisable in the case of poor pump function and/or long-lasting pacing and presence of pronounced mechanical dyssynchrony during RVA pacing.

**Abnormal ventricular conduction regardless of AV conduction status: restore ventricular synchrony.** Left ventricular or BiV pacing should be used to correct pre-existing mechanical dyssynchrony associated with dilated cardiomyopathy and symptomatic HF, regardless of AV conduction status and independent of the need for bradycardia support. Presently, there are no RCT data showing superiority of LV or BiV pacing over RVA pacing for bradycardia support in patients with ventricular dyssynchrony in the absence of systolic HF. However, RVA-paced QRS duration has been positively correlated with the risk of HF hospitalization independent of baseline QRS duration (50). The implication of this observation is that pre-existing ventricular dyssynchrony can be made worse by RVA pacing, with clinical consequences. Accordingly, atrial-based dual-chamber minimal ventricular pacing can be recommended for this patient category until further data comparing alternative pacing strategies are available.

In addition to the presence of normal or abnormal AV and ventricular conduction, the approach to selecting the physiologically optimal pacing strategy may be influenced by four other variables.

**STATUS OF ATRIAL ELECTRICAL ACTIVITY.** Permanent AF precludes the possibility of atrial pacing for bradycardia support even when AV conduction and ventricular conduction are normal (group I). In this situation, the approach to bradycardia must focus on optimal ventricular pacing similar to that for group II.

**LV PUMPING FUNCTION.** The majority of patients with normal ventricular function seem to tolerate RVA pacing. In RCTs of pacemaker therapy (2,3,5) in which most patients had (near-)normal systolic function, it took three to five years before HF hospitalization attributed to RVA pacing became manifest. However, in the DAVID and MADIT II trials, this period was <1 year. Therefore, ventricular desynchronization is less tolerated in patients with pre-existing systolic HF (Fig. 4). Ventricular desynchronization may induce further reductions in pumping function and new-onset mitral regurgitation (51) that can be favorably modified by LV pacing (52).

Accordingly, in patients with poor pump function, RVA pacing should be avoided or even discontinued.

**EXPECTED DURATION OF PACING.** Although a five-year period for development of HF seems long in the elderly population, it is short in younger patients with congenital complete AVB (53). Left ventricular contractile dysfunction, including dilated cardiomyopathy, has been reported in such patients exposed to long-term RVA pacing (18,53). Therefore, a more careful selection of pacing sites seems advisable in young patients requiring ventricular pacing, particularly when the heart is still growing. Because in children the epicardial approach is often used, this could be exploited for access to better pacing sites than the RVA, such as the LV apex (37,47).

**MECHANICAL DYS SYNCHRONY.** In studies on cardiac resynchronization therapy, the presence of mechanical dyssynchrony has been shown to be highly predictive of clinical response (49,54). It seems reasonable to extrapolate this information to the bradycardia pacing population with the goal of minimizing mechanical dyssynchrony (55). Diagnostic tools such as sophisticated echocardiography may be helpful for identifying pacemaker patients at risk for adverse contraction patterns.

**Final comments.** These various novel approaches to pacing have not yet been fully investigated in RCTs. Ongoing
RCTs (SAVEPACe, DAVID II, INTRINSIC, MVP Trial) test the hypothesis that preservation of normal ventricular conduction by avoiding unnecessary RVA pacing reduces the risk of AF, HF, and death during pacemaker and ICD therapy. With respect to alternate site pacing, new tools are required to facilitate access to such sites (high RV septal, LV apex, LV septum). Ultimately, optimal positioning of the ventricular pacing lead may require acute assessment of mechanical asynchrony.

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