**REVIEW**

**Right ventricular apex pacing: Is it obsolete?**

La stimulation apicale ventriculaire droite : est-elle obsolète?

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Received 9 May 2008; received in revised form 14 October 2008; accepted 14 October 2008 Available online 8 January 2009

**KEYWORDS**
Cardiac pacing; Ventricular dyssynchrony; Atrioventricular block

**Summary**
Clinical trials in patients with pacemakers for sinus node dysfunction or atrioventricular block have highlighted the fact that desynchronization of ventricular contraction induced by right ventricular apical pacing is associated with long-term morbidity and mortality. These clinical data confirm pathophysiological results indicating that right ventricular apical pacing causes abnormal ventricular contraction, reduces pump function and leads to myocardial hypertrophy and ultrastructural abnormalities. In this manuscript, we discuss the clinical evidence for the adverse and beneficial effects of various right ventricular pacing sites, left ventricular pacing sites and biventricular pacing. We also propose a decisional algorithm for pacing modalities, based on atrioventricular conduction, left ventricular function and expected lifespan.

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**MOTS CLÉS**
Stimulation cardiaque ; Asynchronisme ventriculaire ; Bloc auriculoventriculaire

**Résumé**
Les essais cliniques réalisés chez les patients stimulés pour une dysfonction sinusal ou un bloc auriculoventriculaire ont mis en évidence une relation de causalité entre l’asynchronisme de contraction ventriculaire induite par la stimulation ventriculaire droite apicale et la morbidité à long terme de ces patients. Ces données viennent confirmer les résultats physiopathologiques qui montrent que la stimulation ventriculaire droite engendre des anomalies de la cinétique ventriculaire, réduit la fonction contractile et induit une hypertrophie et des anomalies ultrastructurales myocardiques. Dans cet article, les auteurs détaillent les avantages et les inconvénients des sites de stimulation ventriculaire droite, gauche ou biventriculaire et proposent un arbre décisionnel pour une stimulation cardiaque physiologique, basé sur la conduction auriculoventriculaire, la fraction d’éjection ventriculaire gauche et l’espérance de vie.

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Cardiac pacing is still the only effective treatment for severe cardiac impulse formation or propagation disturbances. Despite nearly 50 years having elapsed since the first human implantations [1], the optimal pacing mode and ventricular pacing site have not been defined clearly.

**Pathophysiologica consequences of right ventricular apical pacing**

The right ventricular apex is the pacing site that is used most frequently, because it can be reached easily and allows a chronically stable position and stimulation threshold. However, even if apical pacing results in haemodynamically efficient contraction, it remains antiphysiological, because the wave front propagates slowly through the common myocardium with no capture of the His-Purkinje system. The adverse consequences of right ventricular apical pacing were shown more than 80 years ago in mammals [2], but only recently in humans [3]. The deleterious effect is due to the asynchrony of ventricular activation; myocardial regions located close to the pacing lead contract first and stretch not-yet-activated remote regions. By virtue of the local Frank-Starling mechanism, this stretching increases the force of the local contraction of these remote regions and, in turn, stretches — paradoxically — regions activated earlier [4].

Using two models of pacing-induced cardiomyopathies, Spragg et al. studied the effects of asynchronous ventricular activation on the expression of proteins involved in myocyte contraction and arrhythmia vulnerability [5]. In cardiomyopathies induced by high-rate right ventricular apical pacing, they observed significant differences in the expression of these proteins, whereas such a gradient was not noted in high-rate atrial-pacing-induced cardiomyopathies in which ventricular activation was synchronous. The lateral left ventricular free wall (late-activated) shows the most pronounced cellular derangements, such as down-regulation of protein kinases, proteins involved in calcium homeostasis and intercellular connections. The heterogeneous expression of these proteins creates an intramyocardial gradient, which can lead to ventricular dysfunction and may favour arrhythmia genesis. Other authors have demonstrated that prolonged right ventricular apical pacing induces dystrophic fibro-fatty myocardial tissue development, mitochondrial disorganization [6], perfusion abnormalities and localized hypertrophy of the late-contracting myocardial regions [7].

Haemodynamically, asynchronous myocardial contraction decreases significantly the stroke volume and shifts rightward the left ventricular end-systolic pressure—volume relationship. Mismatch between the relaxation of early- and late-contracting regions leads to a decrease in left ventricular filling time and Doppler E-wave velocities [8].

**Clinical consequences of right ventricular apical pacing**

Two decades ago, the development of dual-chamber pacing represented a significant technological improvement; it allowed ventricular pacing to be synchronized with the atria and was hence adopted quickly as the ‘physiological’ pacing mode. However, large randomized clinical trials showed that despite the maintenance of auriculovenous synchrony, DDD/R pacing did not reduce death compared with VVI/R pacing [9], and provided only modest benefits in progression of heart failure and atrial fibrillation [10,11], which became evident only after many years of follow-up [10].

The inability to show a clear superiority of ‘physiological’ dual-chamber pacing over ‘non physiological’ ventricular pacing might be explained by the right ventricular pacing that is performed in both modes. A retrospective analysis of the MOST [12] and MADIT [13] studies showed that the risks of atrial fibrillation and heart failure hospitalization are linked directly to the cumulative percentage of ventricular pacing, regardless of pacing mode. Furthermore, the DAVID trial [14] was terminated prematurely because of the high incidence of death and worsening of heart failure in the DDD/R (70 beats/min) pacing mode compared with the VVI/R (40 beats/min) mode. Conversely, single-chamber atrial pacing in patients with sinus node dysfunction preserves left ventricular function and reduces the incidence of atrial fibrillation significantly compared with dual-chamber pacing [15].

**Alternatives to right ventricular apical pacing**

Recognition of the adverse effects associated with right ventricular apical pacing fuelled research aimed at finding a means of abolishing or at least reducing these effects. Two strategies have been investigated: the first favours spontaneous atrioventricular conduction to minimize unnecessary ventricular pacing; the second involves pacing alternative ventricular sites to attenuate the deleterious effects of right ventricular apical pacing in patients in whom atrioventricular conduction is absent or unreliable.

**Minimizing unnecessary ventricular pacing**

In cases of sinus node dysfunction, AAI/R pacing prevents excessive bradycardia, provides chronotropic support if needed and hence corrects symptoms without any risk of adverse effects due to ventricular pacing. However, the risk of atrioventricular block in these patients, although low (annual incidence estimated at 1% [16]), leads in most cases to the implantation of a dual-chamber device without a significant increase in the cost-effectiveness of the procedure. Programming long atrioventricular delays with hysteresis (an additional increase in the atrioventricular delay) in the DDD/R pacing mode yields functional AAI/R behaviour, but a
percentage of ventricular pacing cannot be avoided, especially in cases where there is a long PR interval.

More recently, new atrial-based ‘dual-chamber minimal ventricular pacing’ modes have been developed to reduce undesirable ventricular pacing without risk of symptomatic atrioventricular block. Functioning in an AAIR pacing mode, these pacemakers (AAISafeR® [Sorin Group]) and MVP® (Medronic) can pace (or detect) atria and monitor the atrioventricular conduction. If a critical number of P waves are not followed by a QRS complex, the pacemaker switches automatically to the DDD/R pacing mode. The MVP mode allows respective reductions of 99.1 and 60.1% in ventricular pacing in patients with sinus node disease and atrioventricular block compared with the DDD/R mode, without sacrificing atrioventricular synchrony [17]. According to the recent pacing guidelines of the European Society of Cardiology [18], these atrial-based minimal ventricular pacing modes are now recommended (class IIa, level of evidence C) as an alternative to conventional dual-chamber pacing in patients who essentially need atrial support.

Alternative ventricular pacing sites

Right ventricular pacing sites

Ventricular pacing may be unavoidable in many patients because of unreliable or absent atrioventricular conduction or permanent atrial fibrillation; interest has therefore focused on alternative ventricular pacing sites that can provide haemodynamic support without the adverse effects of apical pacing. Because pacing leads are usually implanted along the transvenous route, right ventricular pacing sites have been studied more intensively than other sites. Direct His bundle pacing is an attractive alternative in cases of suprahisian atrioventricular block [19,20]. His capture induces normal propagation of the impulse along the Purkinje system, thereby preserving the physiological ventricular activation sequence [21]. Studies from Deshmukh et al. [19] defined selective Hisian pacing criteria: (1) His-Purkinje-mediated cardiac activation and repolarization, as evidenced by electrocardiogram concordance of QRS and T-wave complexes; (2) the pace-ventricular interval (Vp-V) almost identical to the His-ventricular interval (H-V); (3) output criteria (the His bundle is captured at low output, while both the His bundle and ventricular fibres are captured when the output is increased [widening of QRS complex at high output]). In 2004, the same authors [20] published a series of 54 patients with dilated cardiomyopathy, LVEF 23 ±11%, permanent atrial fibrillation and QRS duration less than 120 ms, in whom selective Hisian pacing was obtained in 66% of cases. After a follow-up of 42 months, 29 patients were still alive and improvements in the ejection fraction and in clinical and haemodynamic parameters of left ventricular functioning had been achieved.

Recently, Zannon et al. [22] published a study demonstrating the feasibility of direct Hisian pacing in 24 of 26 patients with a standard pacemaker indication and preserved His-bundle conduction. However, the time needed to reach the His bundle with the permanent catheter varied from 2 to 60 min, and approximately 3.8 ±2.5 attempts were required. The acute pacing threshold was 2.3 ±1 V (at 0.5 ms) and the detected potential was 2.9 ±2 mV.

These studies have shown that permanent pacing of the His bundle is a reliable and effective method for preventing the desynchronization and negative effects of right ventricular apical pacing. However, it is a complex method that requires longer implant times, cannot be carried out in all patients and presents high-pacing thresholds. There is also the theoretical risk of His bundle damage and blockade, induced by the trauma and injury caused by the screw-in lead.

Positioning of the stimulation lead on the upper interventricular septum, close to the His bundle but without pacing it directly, allows capture of the septum and, secondarily, the His-Purkinje system. This approach results, therefore, in a QRS complex that is slightly different from the intrinsic one, without impairing synchronous activation of the heart. The term para-Hisian pacing has been used by Deshmukh et al. [19] to define this form of stimulation, reflecting the electrophysiological manoeuvre used currently to differentiate retrograde conduction over the AV node from conduction over an accessory AV pathway [23]. This pacing site differs from selective Hisian pacing in that pacing thresholds are lower, paced QRS complexes are larger and increasing the output induces QRS shortening because the His bundle is captured [24].

Occhetta et al. [25] compared para-Hisian to right ventricular apical pacing in 16 patients who were implanted with a dual-chamber pacemaker connected to a screw-in lead positioned in close proximity to the His bundle and to a right ventricular apical lead. After two randomized 6-month periods of either para-Hisian or conventional pacing, the authors showed that para-Hisian pacing was associated with a significant improvement in NYHA functional class, exercise tolerance, quality of life score, mitral and tricuspid regurgitation severity, and interventricular mechanical delay. With a mean follow-up of 21 months per patient, the pacing threshold remained stable (implant 0.7 ±0.5 V; follow-up 0.9 ±0.7 V; p = 0.08). The ejection fraction maintained medium- to long-term stable values, confirming that para-Hisian pacing can prevent deterioration of left ventricular function [25].

Hisian and para-Hisian pacing sites are incontestably the most physiological and thus the least deleterious, but are relatively laborious to use. Septal pacing, however, seems to be achieved more easily. Victor et al. [26] compared the short-term (3-month) effects of septal pacing at the junction between the upper and middle septal segments with those of right ventricular apical pacing in 28 patients with atrial fibrillation who underwent ablation of the atrioventricular node. Septal pacing was associated with a shorter QRS duration (145 ±4 ms versus 170 ±4 ms; p < 0.01) and a normal QRS axis. Alteration of left ventricular pump function was observed only in patients whose preimplant LVEF was less than or equal to 45%. In a study randomizing septal and apical pacing, Tse et al. [27] observed alteration of left ventricular function only after 18 months of apical pacing. These results seem to indicate that long-term septal pacing prevents left ventricular function deterioration, especially if the preimplant LVEF is low. However, larger randomized studies are needed to obtain further confirmation.

The right ventricular outflow tract is the pacing site that has been studied most extensively. de Cock et al. [28] showed a haemodynamic benefit with this pacing site...
compared with the right apex. However, the ROVA trial—a randomized crossover study in patients with permanent atrial fibrillation—had a neutral outcome after a 3-month survey [29]. These studies were limited by small numbers of patients and the absence of precise positioning of the pacing lead within the right ventricular outflow tract. Despite the fact that it is the most favourable site, the septal wall was paced in only 61% of cases of right ventricular outflow tract pacing [30]. Mond et al. [31] described a technique that can facilitate deployment of the lead specifically into the septal wall of the right ventricular outflow tract. The technique consists of performing the stylet with a generous distal curve and a posterior angulation on the distal 2 cm, and enabled the septal wall to be reached in all cases. The authors consider it to be a simple and reproducible technique that can increase the comparability of right ventricular outflow tract pacing studies.

Left ventricular pacing sites

In patients with normal left ventricular function, left ventricular pacing has been shown to be less harmful than right ventricular apical pacing [32]. Furthermore, pacing at the inferoapical left ventricular septum and the epicardium of the left ventricular apex yields a left ventricular pumping function that closely approximates function during normal ventricular conduction [33]. These results may be explained by the rapid engagement of the specialized conduction systems in the left ventricular wall near its 'break-out' site [33]. Left ventricular apex pacing can be achieved by minithoracotomy, making this site attractive for paediatric patients, in whom leads are often positioned epicardially and the previsionnal pacing duration is often long.

Blanc et al. [34] assessed the outcome of 22 patients with left bundle branch block who were NYHA functional class III or IV and were paced transvenously exclusively in the left ventricle. After 12 months, the authors noted a significant improvement in functional capacities and blood norepinephrine levels, a reverse remodelling with a significant increase in the LVEF and a decrease in left ventricular diameters [34]. Other immediate positive results of left ventricular pacing have been reported by Nelson et al. [35]; pacing the left ventricle improves the strength of its contractions \( (dP/dt) \), with a consequent decrease in myocardial oxygen consumption. These favourable effects can be explained by the ventricular asynchrony observed in patients with left bundle branch block. As the left lateral wall contraction is delayed markedly, its premature stimulation resynchronizes its contraction with that of the septal wall [36,37], resulting in a decrease in mitral regurgitation and an improvement in contraction effectiveness [38]. It should be noted, however, that these results can only be applied to left bundle branch block patients and that there are actually no data supporting isolated left ventricular pacing in patients with atrioventricular block and normal ventricular activation sequence.

Biventricular pacing

Because right ventricular apical pacing results in an activation that is similar to that of left bundle branch block, it seemed reasonable to predict that the results of upgrading dual-chamber pacemakers to a biventricular device in patients with left ventricular dysfunction would be as favourable as those of biventricular pacing in patients with left bundle branch block [39]. However, when the haemodynamic conditions of patients with atrial fibrillation who underwent atrioventricular node ablation and were paced only in the right ventricular apex were compared with those of similar patients who were paced biventrically, the benefit of biventricular pacing did not appear to be so pronounced [40]. This may be due to the fact that the benefit obtained by the rate control itself minimizes considerably the adverse effects of right apical pacing.

Marai et al. [41] compared the modifications in functional class and echocardiographic indices induced by upgrading of patients paced previously for conventional indications with those in patients paced de novo with a resynchronization device. Despite the small and retrospective enrolment in this study, the results showed clearly that the improvements noted in each population were similar and allowed the authors to conclude that patients paced at the right ventricular apex, and with validated criteria for resynchronization, benefit from a biventricular device [41].

Furthermore, in a cross-over randomized study of patients paced previously at the right ventricle, who were NYHA functional class III or IV despite optimal drug treatment and had ventricular dysynchrony (interventricular delay >40 ms or left ventricular pre-ejection delay >140 ms), Leclercq et al. [42] showed that biventricular stimulation improved NYHA functional class, 6-min walked distance and quality of life score by 18, 29, and 19%, respectively, compared with single right ventricular pacing. Based on this growing evidence, the authors of cardiac pacing and resynchronization therapy guidelines recommend the use of a biventricular device in heart failure patients with NYHA functional class III—IV symptoms, LVEF less than or equal to 35%, left ventricular dilation and a conventional indication for permanent pacing. In these patients, preimplantation QRS duration greater than or equal to 120 ms is no longer a selection criterion [18].

Modalities of physiological pacing

Given the various data presented previously, it appears that the choice of pacing mode and site must draw on several variables that can be integrated into a decisional algorithm (Fig. 1).

The choice of pacing mode must be preceded by an assessment of atrioventricular and intraventricular conduction. If they are normal (sinus node dysfunction) or in cases of intermittent atrioventricular block, an atrial-based dual-chamber with minimal ventricular pacing is recommended. This strategy avoids deleterious unnecessary ventricular pacing and prevents bradycardia due to unpredictable atrioventricular block. However, if the atrioventricular block is permanent, ventricular pacing support becomes unavoidable. Many studies have shown that heart failure induced by ventricular dyssynchrony develops after many years of apical pacing [43], which is why right ventricular apical pacing can be advised in the elderly population with atrioventricular block and short life expectancy.
As far as resynchronization is concerned, indications are not clearly defined. In a subgroup analysis of the DAVID trial [44], patients with abnormal intraventricular conduction (QRS duration $\geq$110 ms) had worse outcomes after right ventricular apical pacing than those with narrow QRS complexes. In the MOST study, only 10% of patients had heart failure during follow-up; they were more likely to have a lower ejection fraction, myocardial infarction and a worse NYHA functional class compared with patients who did not experience heart failure [45]. The APAF study [46] aimed to assess whether the extent of left ventricular asynchrony during right ventricular apical pacing could be predicted by clinical, electrocardiographic or echographic findings obtained during sinus rhythm. The main conclusion was that an abnormal baseline electromechanical left ventricular delay and a QRS duration greater than 85 ms were independent predictors of an abnormal electromechanical left ventricular delay during right ventricular pacing.

Thus, biventricular pacing may be beneficial for patients with pre-existing left ventricular dysfunction (LVEF < 35%) and for patients with signs of ventricular dyssynchrony either on echo- or electrocardiography (abnormal intracardiac conduction), who are more likely to develop progressive heart failure after right ventricular apical pacing. Dual-chamber conventional pacing in patients without any clinical or echocardiographic sign of ventricular dyssynchrony seems acceptable as there is no evidence as yet favouring biventricular pacing. In all patients paced in the right ventricle, close echocardiographic monitoring must be carried out to detect any worsening of left ventricular function, which would then justify upgrading.

Ongoing studies [47,48] address this issue specifically. BIOPACE [48] compares the long-term effects (5-year follow-up) of conventional dual-chamber and biventricular pacing in patients without any indication for resynchronization. BLOCK HF [47] is a randomized trial designed to determine, in terms of time to first cardiac event, whether patients with atrioventricular block, left ventricular dysfunction (LVEF $\leq$50%) and mild-to-moderate heart failure (NYHA functional class I–III), who require pacing, benefit from biventricular pacing compared with right ventricular pacing alone. The results of these studies are expected to define clearly the yield of preventive biventricular pacing in these patients.

Figure 1. Proposed decisional algorithm for physiological cardiac pacing in patients without signs of congestive heart failure at the time of implant.
Conclusion
The concept of an ideal pacing modality is nothing but a dream. The realistic goal is to minimize impairment of left ventricular function. If ventricular pacing is needed, careful evaluation of spontaneous atrioventricular conduction and LVEF is mandatory. If atrioventricular conduction is maintained most of the time, every effort should be made to avoid unnecessary ventricular pacing. When the ventricle has to be paced frequently and ventricular function is not severely impaired, right ventricular pacing can be adopted, as alternative pacing sites have not shown any superiority thus far. In patients with severe left ventricular dysfunction and in whom permanent ventricular pacing is needed, biventricular pacing might be considered, but studies are still ongoing.

Conflict of interest
None.

References
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