

REVIEW

Why and How We Should Avoid Right Ventricular Apical Pacing?

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ABSTRACT

A large body of evidence has emerged recently about the harmful effects of chronic right ventricular (RV) apical pacing on left ventricular (LV) function leading to an increase in morbidity and mortality. Right ventricular apical pacing is unphysiologic because it produces aberrant LV depolarization, and in turn mechanical LV dyssynchrony with resultant long-term unfavorable hemodynamic and structural changes. Although the data about RV pacing-induced LV dysfunction outlined in this discussion are persuasive, its clinical applicability in pacemaker practice remains challenging. The ongoing transition to new pacing sites will succeed only with major technologic improvements in lead implantation. Meanwhile, pacing algorithms minimizing right ventricular pacing might be preferable at least in patients with sick sinus syndrome or non-permanent atrioventricular block.

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INTRODUCTION

A large body of evidence has emerged recently about the harmful effects of chronic right ventricular (RV) pacing (mostly apical) on left ventricular (LV) function.¹⁻⁸ The findings in several important trials correlate with the abnormalities in LV function previously documented in experimental animals subjected to RV pacing.⁹⁻¹³ RV pacing is unphysiologic because it produces aberrant LV depolarization, and in turn mechanical LV dyssynchrony with resultant long-term unfavorable hemodynamic (abnormal systolic and diastolic function) and structural changes. Faced with proof that RV apical pacing causes an increase in morbidity and mortality, the question arises as to whether we should continue pacing the apical RV as the preferred site or consider alternative sites to minimize LV dysfunction. Although the data about RV pacing-induced LV dysfunction outlined in this discussion are persuasive its clinical applicability in pacemaker practice remains challenging.

ABBREVIATIONS

AF = atrial fibrillation
AV = atrioventricular
CHF = congestive heart failure
ICD = implantable cardioverter defibrillator
LA = left atrium
LV = left ventric-le(-ular)
LVEF = left ventricular ejection fraction
RV = right ventric-le(-ular)

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DAVID TRIAL

The DAVID trial compared the clinical effectiveness of dual chamber implantable cardioverter defibrillators (ICDs) programmed to the DDDR pacing mode at 70 ppm vs the VVI mode at 40 ppm.² The atrioventricular (AV) delay was programmed according to the clinical judgment of the investigators and was commonly set at 180 ms

thereby favoring ventricular pacing in the majority of patients. The study revealed a strong trend toward higher mortality and hospitalization for new or worsened congestive heart failure (CHF) in the DDDR group (with nearly 60% of ventricular beats being paced). The DAVID study suggested that unnecessary RV apical pacing delivered as part of the DDDR arm produced ventricular desynchronization with impaired LV hemodynamic performance that was ultimately harmful. The VVI group fared better because the programmed rate of 40 ppm minimized RV apical pacing (with 1% of ventricular beats being paced). The depression of LV function by RV apical pacing may be more important in ICD patients with poor LV function and/or a prior history of heart failure.

MADIT II TRIAL

In the MADIT II study (in which programming of the ICDs was not standardized), the development of new or worsened CHF was more common in the ICD arm (19.9%) compared with the conventional-treatment patients (14.9%).⁴ The higher incidence of CHF in the ICD group was in all likelihood due to ventricular desynchronization rather than myocardial injury from ICD shocks. Steinberg et al⁵ presented a subanalysis of the MADIT II trial at the 2003 Annual NASPE meeting and subsequently published in 2005,^{5a} indicating that the harmful effects of RV pacing were correlated with the percentage of ventricular pacing confirming the findings of the MOST Trial discussed below.

MOST TRIAL

The MOST study demonstrated an association between the percentage of RV pacing in the DDDR mode (with maintenance of AV synchrony) and CHF in patients with sick sinus syndrome and QRS <120 ms.³ The harmful consequences of RV pacing in the MOST trial appeared related to nonphysiologic LV contraction. A cumulative % of ventricular pacing index <10% was associated with the lower rates of CHF hospitalizations and an index >90% was associated with higher rates of hospitalization for CHF. For DDDR pacing, the risk of CHF increased linearly until the aforementioned % index reached 60% and then it formed a plateau. The MOST study also found a correlation between the cumulative % of ventricular pacing index and the development of atrial fibrillation (AF) presumably induced by LV dysfunction.

THE DANISH AAIR VS. DDDR TRIAL

Andersen et al¹ have reported the results of the first randomized trial comparing the AAIR and DDDR modes of pacing in 117 consecutive patients who received a first pacemaker for sick sinus syndrome. Patients were followed for 2.9±1.1 years and had normal AV conduction (according to previously used arbitrary criteria by these workers), and no bundle branch block. The primary endpoints were changes from baseline to last follow-up in left atrial (LA) size

and left ventricular (LV) function determined by M-mode echocardiography. The patients were randomized to three arms: AAIR, DDDR-s (short rate-adaptive AV delay- 110-150 ms) and DDDR-l (fixed long AV delay ≥250 ms) modes. The AV delay was not optimized because the study was designed to evaluate the effect of cumulative right ventricular pacing. The AAIR group exhibited no significant change in the LA and LV diameters and LV fractional shortening. However, the LA diameter increased significantly in both DDDR groups (more marked in the DDDR-s group), while left ventricular fractional shortening decreased significantly in the DDDR-s group but not in the DDDR-l group.

The AAIR vs. DDDR trial clearly documents the detrimental effects of ventricular desynchronization or LV dyssynchrony produced by long-term unphysiologic RV apical pacing.¹ The DDDR-s group with 90% proportion of RV pacing developed LA dilatation and decreased fractional shortening but the DDDR-l group with 17% proportion of RV pacing developed LA dilatation but no change in fractional shortening. Atrial fibrillation (which was diagnosed on the basis of a 12-lead ECG at planned follow-up visits) was more common in the DDDR group indicating that ventricular desynchronization promotes AF probably by causing LA dilatation.

COMPARISON OF THE DANISH AAIR VS. DDDR TRIAL WITH VVI(R) VS. DDD(R) TRIALS

The lack of LV desynchronization in the AAI mode may explain the remarkable benefit of AAI compared with VVI pacing obtained by the Danish Group in patients with the sick sinus syndrome in a protocol where the investigation focused only on the role of AV synchrony.¹⁴ In contrast, studies comparing the DDD(R) with the VVI(R) modes of pacing have yielded less impressive and somewhat inconsistent results probably because the benefit of AV synchrony was attenuated by the depressant effect of LV desynchronization in patients using the DDD(R) mode.¹⁵⁻¹⁸

The results of AAIR vs. DDDR study are in accordance with the data from the DAVID and MOST trials where the endpoint was hospitalization for CHF though sequential LV function was not evaluated in these two trials.^{2,3}

RIGHT VENTRICULAR PACING IN YOUNG PATIENTS

The harmful long-term effects of RV apical pacing have also been documented in children and young patients with congenital heart block.^{7,8} A study involving long-term follow-up (up to 19 years) of children with congenital AV block and no structural congenital cardiac defects and RV apical pacing demonstrated evidence of global LV dysfunction when compared with size-matched control patients.⁷ Another study from Bordeaux, France confirmed these findings by comparing echocardiographic data obtained before and after pacemaker implantation.⁸ Twenty-one patients with complete AV

block with RV apical pacing were followed for 8 ± 3 years and matched with healthy controls. The pacemaker patients displayed statistically significant asymmetric LV hypertrophy, LV dilatation, impairment of LV function compared to findings before pacemaker implantation and those of the controls.

MITRAL REGURGITATION INDUCED BY VENTRICULAR DESYNCHRONIZATION

LV desynchronization as with left bundle branch block or RV pacing may cause varying degrees of mitral regurgitation that aggravate the hemodynamic status in patients with dilated cardiomyopathy (idiopathic or ischemic). Left ventricular contraction initiated by apical RV pacing alters papillary muscle function with resultant derangement of the time sequence of activation of the mitral valve apparatus. The marked improvement of mitral regurgitation after cardiac resynchronization for standard indications (poor systolic LV function and LV dyssynchrony) is well-known.¹⁹⁻²² Patients with previously implanted RV pacemakers who undergo ventricular resynchronization also exhibit acute and long-term improvement in mitral regurgitation.^{20,23,24} However, some patients with a normal LV ejection (but with dyssynchrony) and RV pacemaker-induced severe mitral regurgitation and CHF may derive marked symptomatic improvement and can be spared mitral valve replacement by the institution of biventricular pacing.²⁵⁻²⁷

ARE THE ABNORMALITIES INDUCED BY LONG-TERM VENTRICULAR DESYNCHRONIZATION REVERSIBLE?

Chronic unphysiologic or RV pacing in dogs induces adverse cellular changes with myofibrillar disarray, asymmetric myocardial hypertrophy, LV dilatation and biochemical changes.⁹⁻¹³ The reversibility of these changes has not been studied.

In man, RV pacing produces reversible alterations in local myocardial blood flow that are more pronounced during pacing the RV apex than the outflow tract.^{28,29} In this regard, Nielsen et al²⁹ found reversible alterations in regional myocardial blood flow upon switching temporarily from chronic RV apical pacing to the AAI mode suggesting that perfusion defects are related to the altered pattern of ventricular depolarization. Thus, alterations in blood flow seem to reflect the changes in ventricular depolarization and may not have an important long-term detrimental impact on LV function.

In their myocardial blood flow study, Nielsen et al²⁹ programmed their DDD patients (the same as those in the DDDR-s group) to the AAI mode at the time of myocardial blood flow measurement. The LV ejection fraction measured during temporary AAI pacing was significantly higher than during DDD-s pacing and not different from the LV ejection fraction measured at the time of implantation about 22 months previously. In patients with systolic CHF and an implanted RV

pacemaker programmed with an optimal AV delay, cardiac resynchronization produces an immediate improvement in LV function and functional mitral regurgitation on the basis of a more coordinated LV contraction. On a long-term basis, there is evidence that such patients exhibit further improvement of LV function because of reverse remodeling suggesting some reversibility of LV dysfunction. These observations are in keeping with the observation that the mechanical left atrial (LA) remodeling caused by long-term VVI pacing is reversible upon the establishment of DDD pacing.³⁰

Much more work is needed to determine the reversibility of the LA and LV abnormalities engendered by ventricular desynchronization in patients with a variety of heart disease and LV function.

IF RV PACING IS POTENTIALLY HARMFUL, HOW SHOULD WE CHANGE OUR PRACTICE?

1. Do not pace if it is not necessary

This applies especially to ICD patients without sick sinus syndrome or AV block based on the results of the David trial.³¹ The VVI or DDI pacing mode (with a long AV delay) at a rate of 40 ppm may be appropriate for many patients to prevent unnecessary RV pacing.

2. Alternative single-site RV pacing

Pooled data from many studies suggest that RV outflow (or septal) pacing provides somewhat better acute hemodynamic performance than RV apical pacing.³² An acute improvement does not necessarily translate into long-term improvement in LV function. At present, long-term studies have shown mixed results in terms of LV function using RV pacing sites other than the RV apex.³³⁻⁴¹ The study of Tse et al²⁸ that compared RV outflow tract pacing vs. RV apical pacing in a small number of patients (with dual chamber pacemaker, optimal AV delay and >95% ventricular pacing) revealed a significant drop in LV ejection fraction only in the patients with RV apical pacing after 18 months (the longest follow-up of all the chronic studies). These findings should be confirmed in a larger number of patients with longer follow-up. The long-term studies of alternative site RV pacing are difficult to interpret because of the small number of patients, wide range of LV function, spectrum of underlying heart disease, lack of standardization of the RV pacing site, % ventricular pacing, different endpoints, and varying durations of follow-up mostly too short.⁴² At present it seems premature to abandon the RV apical site in the hope of preserving LV function and further standardized extensive multicenter studies involving large cohorts are needed to explore the role of alternative RV pacing sites.^{43,44}

3. Bifocal RV pacing

There is no evidence that dual-site RV pacing is superior to single-site pacing in the acute setting or in follow-up stud-

ies of a few months.⁴⁵⁻⁴⁹ However some workers now advocate dual-site RV pacing as an alternative to biventricular pacing in patients in whom LV pacing is not feasible but there is as yet no convincing evidence that this approach is worthwhile. However, preliminary results suggest that the addition of a second RV lead may be beneficial in patients with severe CHF refractory to traditional biventricular pacing (triple ventricular pacing).⁵⁰

4. AAI and AAIR pacing

The AAI and AAIR modes represent the only sure way of preventing RV-induced deterioration of LV function by promoting normal ventricular depolarization. The development of spontaneous complete heart block during AAI pacing in carefully selected patients is unusual but it is associated with syncope in about half the cases.⁵¹⁻⁵⁵ In the USA, single lead atrial pacing is rarely used for fear of litigation because its occurrence no matter how infrequent, is difficult to accept considering that the fundamental purpose of antibradycardia pacing is to prevent it. In Europe AAI and AAIR modes are considered viable and acceptable in carefully screened patients with sick sinus syndrome without bundle branch block and long PR interval.^{56,57}

5. His Bundle Pacing

The most ambitious attempt to maintain LV synchrony and LV function is through His bundle pacing.⁵⁸ This technique is in its infancy, technically demanding and can only be considered in patients without intraventricular conduction delay. The current role of this modality is presently unclear.

6. Ablate and Pace patients with atrial fibrillation. The PAVE Trial

The PAVE trial is the first prospective, randomized study to evaluate biventricular pacing (BVP) in patients with AF who underwent AV junctional ablation and received a permanent pacemaker.⁵⁹⁻⁶¹ Enrollment criteria included the presence of chronic AF for at least 1 month, New York Heart Association class I, II, or III, and inability to walk more than 450 meters during the 6-minute hall walk test. All patients were on a stable cardiovascular drug regimen. PAVE patients were enrolled regardless of their LV function.

A total of 252 patients were randomized in a 2:1 fashion to either ablation plus RV pacing (n=106) or ablation plus biventricular pacing (n=146). The primary endpoint was exercise capacity as measured by the 6-minute hall walk test, with secondary endpoints of functional capacity as measured by peak VO_2 , exercise duration, and quality-of-life score. Biventricular device implantation was unsuccessful in 21 patients, vs 0 unsuccessful RV pacing implants. The final population of patients eligible for analysis included 102 RV pacing patients and 82 biventricular pacing patients. There was no significant difference in baseline clinical characteristics between the 2

groups. After 3 months, patients in the RV pacing group began to experience a marked decline in exercise capacity, whereas patients in the biventricular pacing group maintained their functional status. The difference between the groups at 6 months (82 m vs. 56 m, a difference of 26 m) was statistically significant ($P = 0.03$).^{59,60}

Measurements of LV ejection fraction (LVEF) revealed a significant decline in RV pacing patients.⁶¹ LVEF in the RV pacing group dropped from 44.9% at the pre-implant time point to 40.7% at 6 months, while LVEF in the biventricular pacing group was stable over the follow-up period. The LVEF difference between the groups at 6 months (46.0% vs. 40.7%) was statistically significant ($P = 0.03$). A full analysis of the various subgroups is not yet available except for the study of Daoud et al who stratified the patients into LVEF $\leq 35\%$ (21 RV, 21 biventricular pacing), and LVEF $> 35\%$ (36 RV, 51 biventricular pacing). After 6 months, the improvement in the 6 minute walk was the same in both the RV and biventricular pacing groups starting with LVEF 35%. In contrast in the group with LVEF $\leq 35\%$, RV patients improved less while biventricular pacing patients improved more ($p = 0.07$). In addition more patients with biventricular pacing improved in distance walked while more RV patients worsened ($p < 0.04$).

The PAVE trial thus revealed that biventricular pacing provides a significant, meaningful improvement in functional capacity over RV pacing in patients with chronic AF after AV nodal ablation with a sustained benefit in the group with LV ejection $\leq 35\%$. On this basis it seems reasonable at this juncture to recommend biventricular pacing in "ablate and pace" patients with LVEF $\leq 35\%$ and wait for further data before considering biventricular pacing in the group with better LV function.

6. The best of both worlds

a. Old algorithms

Theoretically in patients with normal AV conduction, functional AAIR pacing should occur with virtual elimination of ventricular pacing by using the DDDR mode with a long AV delay (250-300 ms). The AAIR vs. DDDR Danish trial showed this was not possible at least with an AV delay of 250 ms (17% RV pacing), confirming data from a small number of studies that used AV delays as long as 300 ms or AV search hysteresis.^{1,62-67} The causes of the 17% incidence of ventricular pacing in the DDDR-I group in the Danish trial was not studied and may have involved many mechanisms such as ventricular fusion, pseudofusion beats etc.¹

b. Minimal RV pacing

In 1997 Andersen⁶⁸ an obvious proponent of AAI pacing wrote that "in the future, another technical solution may be available with modern units, i.e., automatic mode switching

from AAI to DDD..." for patients with sick sinus syndrome. Such devices are now available and their performance in minimizing RV pacing has been demonstrated but their long-term impact on LV function remains to be proven.^{69,70} With such new devices we will be able to give patients without AV block or bundle branch block, the best of both worlds: almost continuous physiologic ventricular depolarization through the His-Purkinje-system without the risk of AV block.

CONCLUSION

The results of the AAIR vs. DDDR, DAVID, MADIT II, MOST and PAVE trials should be considered a wake-up call to avoid RV pacing if possible and to investigate the use ventricular resynchronization (biventricular pacing or monochamber LV pacing) not only for treatment of existing LV dyssynchrony in patients with congestive heart failure and left bundle branch block, but for "primary prevention" in the first place in selected patients (especially those with LVEF $\leq 35\%$) who require ventricular pacing most of the time.⁶ The pacemaker landscape and "the way we do business" may change dramatically in the next few years. It is possible that univentricular RV pacing may be relegated to a far lesser role and replaced by biventricular or monochamber LV pacing⁷¹ as more data emerges about its potentially deleterious effect on LV function. We are likely to see a growth of triple ventricular pacing (2RV and 1 LV or 1RV and 2 LV) or even more complicated pacing arrangements.^{50,72} The move towards improved pacing modalities is particularly important in children with or without congenital cardiac defects in view of the long duration of pacing throughout life.⁷³ The ongoing transition to new pacing sites will succeed only with major technologic improvements in lead implantation.⁷⁴⁻⁸³ Meanwhile, pacing algorithms minimizing ventricular pacing in patients with sinus node dysfunction or intermittent AV block might be preferable.^{75,81}

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