

Ventricular pacing: to pace or not to pace

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This editorial refers to ‘Difference in percentage of ventricular pacing between two algorithms for minimizing ventricular pacing: results of the IDEAL RVP (Identify the Best Algorithm for Reducing Unnecessary Right Ventricular Pacing) study’ by Y. Murakami et al., on page 96.

Pacing from the right ventricular apex has been the clinical standard for decades but has recently come into question with a growing trend towards reducing ventricular pacing as much as possible. The earliest devices provided asynchronous ventricular pacing in patients whose indication for pacing was asystolic complete heart block. RV apical pacing was literally the difference between life and death. Over the decades, as technology has advanced allowing the medical community to more closely model normal cardiac physiology, we have seen the progressive introduction of demand function, single-chamber atrial pacing, dual-chamber pacing, dual-chamber rate-modulated pacing, and in the past decade, cardiac resynchronization pacing. During this evolution, it has been noted that pacing from the right ventricular apex, even in the presence of high-grade AV block, may contribute to ventricular dysfunction associated with the disordered ventricular activation sequence associated with the paced left bundle branch block pattern.

‘Pacemaker syndrome’ or the adverse haemodynamics associated with a technically normal pacing system was rarely recognized in the late 1960s when complete heart block was the indication for implantation. Its recognition blossomed in the 1980s with the introduction of dual-chamber pacing systems and an increase in the relative indications for permanent pacing including individuals who only needed pacing on an intermittent basis or whose primary indication for pacing was sinus node dysfunction. Pacemaker syndrome was usually associated with a loss of appropriate atrial transport (atrioventricular synchrony) and was able to be corrected by upgrading a patient with a single-chamber VVI pacing system to a DDD pacing system.^{1–3} The standard location

for the ventricular lead during the first four decades of cardiac pacing was the RV apex. The first generation of DDD pacemakers had limited AV delay programmability such that there was either full ventricular pacing or consistent ventricular fusion. On the basis of multiple studies, DDD pacing was clinically superior to VVI pacing, particularly when pacing was required for a large percentage of the time. The progressive symptoms of heart failure occurring over the ensuing decades were attributed to the progression of the patient’s underlying disease.

It was not until the onset of cardiac resynchronization therapy that the clinical community began to appreciate the potentially adverse consequences of a disordered ventricular activation sequence, be it spontaneous as with an endogenous left bundle branch block or iatrogenic with RV apical ventricular pacing.

On the basis of pacing studies demonstrating DDD pacing was superior to VVI pacing, the device manufacturers introduced dual-chamber ICDs (VVED). The medical profession rapidly embraced dual-chamber ICDs, reasoning that both haemodynamics and supraventricular tachycardia discrimination with the addition of the atrial lead would be improved. No studies had been done. In the late 1990s, the DAVID trial was initiated in an effort to determine whether there was a benefit of DDD pacing over VVI pacing in a population of patients requiring ICD therapy.⁴ One of the entry criteria to participate in the DAVID trial was the requirement that the patient did not require pacing. The patients were then assigned to one of two groups, one with the pacing component of the ICD programmed to VVI at 40 bpm providing back-up heart rate support should delivery of high-voltage therapy be followed by a period of asystole. The second group was programmed to the DDD mode at a base rate of 70 bpm. Programming the AV delay was left to the discretion of the investigator at each participating medical centre. A majority of physicians left the paced and sensed AV delays at the shipped values of 170/150 ms, respectively. The primary endpoint for the DAVID study was a composite endpoint of death or worsening or new heart failure resulting in hospitalization. The data were monitored on a periodic basis by the

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Data Safety and Monitoring Board, with the investigators at each centre blinded to the results. The study was stopped prematurely in 2002 owing to an increase in the primary endpoint in the DDD group compared with the VVI group. The initial assumption was that the adverse outcome in the DDD group was directly due to the abnormal ventricular activation sequence although the study was not designed to evaluate that specific question. In the light of the DAVID results, investigators involved in other studies such as the Mode Selection Trial (MOST), MADIT II, and Midas^{5–8} retrospectively examined their data and arrived at a similar conclusion. Those patients with a significant percentage of ventricular pacing had a higher incidence of heart failure, hospitalizations, and atrial fibrillation, leading to an effort to develop algorithms that would minimize ventricular pacing. Except for MIDAS, all the other studies involved patients who either did not require pacing at all or required primarily atrial pacing.

There were two other hypotheses for the adverse impact associated with an increase in ventricular pacing in the above studies. One was that the adverse effects seen in the DDD group was due to too high a paced rate essentially increasing metabolic demand with worsening ischaemia and ventricular dysfunction. The DAVID II trial was initiated to compare VVI pacing at 40 with AAI pacing at 70 in a second group of patients who required ICD but not pacemaker therapy. This study was not terminated prematurely, and when the data were examined, there was virtually no difference between the two groups, effectively excluding the higher base rate pacing as a culprit.

The second hypothesis involved the AV delay. In a patient with intact AV nodal conduction, the only way to achieve ventricular pacing is to programme too short an AV delay. Sharma *et al.*⁹ examined the bradycardia diagnostics integral to the St Jude Medical ICDs that were implanted in the DAVID study. They found a group of patients in whom the physician had programmed a long AV delay to facilitate intrinsic AV nodal conduction. This resulted in three distinct groups of patients. If the percent ventricular pacing exceeded 40%, there was a high incidence of adverse haemodynamic effects including worsening heart failure. The lowest percentage of ventricular pacing was associated with VVI pacing (<4%); however, unlike the data that were originally presented in the DAVID study, this very low incidence of ventricular pacing was not associated with the best results. Rather, the lowest incidence of adverse events was associated with the long AV delay group. Patients who require an ICD commonly have significant ventricular dysfunction. They are likely to have intermittent first and even higher grades of AV block, although documenting this is difficult because there were no special diagnostics that would allow these episodes to be captured and counted. Although VVI pacing protects the patients from asystole, it does not maintain AV synchrony, nor support the patient at a higher rate for intermittent potentially adverse events that could contribute to some of the endpoints. The long AV delay group had an incidence of ventricular pacing of ~11%, and it was this subgroup that had the lowest incidence of heart failure and other complications. The results of this analysis were presented at the annual scientific sessions of the Heart Rhythm Society in 2005 and published the same year, but it was not generally appreciated by the clinical community.

During the same time period, Boston Scientific sponsored the INTRINSIC RV trial.¹⁰ It was virtually identical to DAVID except in one very important area. Programming the AV delay was specifically defined in the study protocol. Entry criteria included a requirement for high-voltage therapy and intact AV nodal conduction such that the patient did not require pacing support. There was a VVI group and a DDD group. The DDD group was further divided into a fixed AV delay of 200 ms (which was longer than the usual AV delay programmed in the DAVID trial) or an AV delay of 200 ms plus Boston Scientific's AV Search Hysteresis[®] (AVSH) algorithm, which could increase the AV delay to a maximum of 300 ms and would maintain the longer AV delay as long as AV nodal conduction was intact and shorter than 300 ms. The study results were presented in 2007 by Olshansky *et al.*¹⁰ Similar to DAVID, this study demonstrated that the group with >40% ventricular pacing had the highest adverse event rate. Also, similar to the DAVID trial, the group programmed to the VVI mode had the lowest incidence of ventricular pacing, but this group did not have the lowest incidence of endpoint events. The lowest incidence of endpoint events occurred in the DDD group in which the AVSH algorithm had been enabled with an 11–19% incidence of ventricular pacing.

Even preceding the results of the DAVID study, manufacturers had been looking at various algorithms designed to minimize ventricular pacing in the patients who required atrial pacing with only back-up ventricular support should high-grade AV block develop. Although some groups were strong advocates of dedicated single-chamber atrial pacing, many physicians were concerned that either the progression of AV conduction system disease or the addition of drugs that could further compromise AV nodal conduction might lead to problems in the usual pacemaker patient who is elderly. Further, even though AV nodal conduction at rest was intact, if the AV conduction system was stressed by higher rates, the patient could develop AAIR pacemaker syndrome,^{11,12} where the atrial paced, ventricular sensed interval, rather than shortening as occurs with normal physiology,^{13,14} would progressively lengthen, causing the atrium to be depolarized and contract against a closed mitral and tricuspid valve associated with the systolic contraction caused by the previous atrial paced complex conducted with a first-degree AV block. It was increasingly recognized that marked first-degree AV block could be very symptomatic at low activity levels and that a permanent dual-chamber pacing system was indicated with impressive clinical improvement despite the occurrence of virtually 100% ventricular pacing.^{15,16}

Acknowledging that unnecessary ventricular pacing could have adverse haemodynamic consequences with worsening cardiac function, precipitation of clinically symptomatic heart failure, and predisposing to atrial fibrillation, manufacturers pursued two different routes in attempting to minimize unnecessary ventricular pacing. The first included the introduction of a variety of paced and sensed AV delay hysteresis algorithms. With these algorithms, the clinician sets the AV delays that would be most appropriate for the patient if AV block were to develop. As long as atrioventricular nodal conduction was intact, the programmed AV delay would be extended by a second interval (a delta), and as long as a sensed R-wave occurred within this extended paced or sensed AV delay, the system would function as if it were a single-chamber

atrial pacemaker. With the occurrence of ventricular pacing at the end of the extended AV delay anywhere from 1 to a programmable number of cycles depending on the specific algorithm, the AV delay extension would be suspended and the AV delay would be shortened to the original programmed value.^{17,18} After a period of time or a predetermined number of cycles, the pulse generator would perform a search by extending the AV delay. If the AV block had resolved and a sensed R-wave was detected within the extended AV delay, the AV delay would remain at that longer interval until such time as ventricular pacing again occurred, causing the AV delay to shorten to its programmed value. Currently, all manufacturers have algorithms that function along these lines and all have unique terms to describe their specific algorithm. As a group, I will simply call these AV Hysteresis algorithms.

The second approach was exemplified by Medtronic with their Managed Ventricular Pacing[®] (MVP) algorithm.^{19,20} This algorithm basically says 'no' to any and all ventricular pacing unless high-grade AV block is present. Profound first-degree AV block will persist as long as the sensed R-wave occurs before the next paced or sensed atrial event is detected. If intermittent low-grade second-degree AV block less than a stable 2:1 block occurs but is not sustained, the algorithm will allow for potentially long pauses (up to two paced or sensed atrial cycles) on a repeated but not consecutive basis. Even complete heart block might not disengage the MVP algorithm if there is a sufficiently rapid ventricular escape rhythm. If and when the algorithm is disengaged, similar to the AV Hysteresis algorithms, there is a search function occurring periodically where the system withholds a ventricular output and looks to see whether intact AV nodal conduction has returned, at which time it will resume the MVP algorithm. In the electrically unstable patient, the pauses in the ventricular rate may predispose to pause-dependent tachyarrhythmias such as Torsade-de-Pointes. A related but not identical algorithm was introduced by Sorin-ELA called AAsafeR[®].²¹ It differs from Medtronic's MVP algorithm in that it incorporates a programmable maximum AV delay up to 450 ms to prevent the potential marked pauses that have been reported with the MVP algorithm. It also incorporates a variety of event counter diagnostics including a tabulation of the number of times the device exited the AAsafeR algorithm, the reasons for exiting, and examples captured on electrogram snapshots.

Murakami *et al.*²² reported the results of the Medtronic-sponsored IDEAL RVP study. This study compared Medtronic's AV Hysteresis algorithm (Search AV+) with their MVP algorithm. As both algorithms were available in the Medtronic Adapta[®] dual-chamber pacemaker, this was a within-patient, randomized, crossover-designed study where each mode was engaged for 1 month. The specific end result was the percentage of ventricular pacing. The net results were predictable. There were single-digit percentages of ventricular pacing in the MVP mode, whereas there was a significantly higher percentage of ventricular pacing in the Search AV+ mode. Although this is statistically significant, the question that should be asked and was not able to be assessed was whether this was clinically significant, and more importantly, was the lesser degree of ventricular pacing in association with the MVP algorithm always safe given only 1 month of follow-up for each arm of the study. In addition, there are no internal diagnostics included in the Medtronic Adapta pacemaker to count

the number of times the system exited MVP to restore DDD pacing or the specific arrhythmias that induced the exit from MVP. Although ventricular pacing is currently considered to be less than optimal, this is ventricular pacing with an abnormal ventricular activation sequence. One cannot determine from the event counter diagnostics whether the ventricular paced beat was a fusion with a near-normal ventricular activation sequence or a fully paced wide QRS complex. One hundred and forty patients were enrolled in the study but 13 dropped out, leaving 127 patients for analysis. The maximal paced and sensed AV delay with the Search AV+ algorithm enabled was 500 and 450 ms, respectively, although the maximal allowed AV delay was not a requirement of the study. The per cent atrial pacing was similar in both pacing modes. The study did not exclude patients with AV block, and in *Table 4*, patients with various degrees of AV block had a significantly lower percentage of ventricular pacing than the Search AV+ group. To look just at the per cent ventricular pacing, 57.5% of the patients had <10% ventricular pacing when MVP was enabled, whereas this was 38.6% in patients programmed with Search AV+ ($P < 0.0001$). Although this is highly significant on a statistical basis, the question if this is either safe or appropriate must be asked. With respect to patients with normal AV conduction, if based on the literature, 40% ventricular pacing is the cut-off for adverse consequences of ventricular pacing, 100% of the patients when programmed to the MVP had <10% ventricular, whereas this was 79.6% when the Search AV+ algorithm had been enabled. One hundred per cent of the MVP mode had <40% ventricular pacing, whereas this was 98.1% when programmed to the Search AV+ algorithm.

The analysis of the Intrinsic RV study and the re-analysis of the bradycardia diagnostics from the DAVID study suggest that maintaining both rate and AV synchrony are important to patients with impaired ventricular function. Most ICD patients, whether this be for primary prevention or secondary prevention, have impaired ventricular function. With respect to patients who require pacing support for standard indications, Chlidakis *et al.*²³ demonstrated that the long-term outcome is based on underlying ventricular function independent of ventricular pacing or intact AV nodal conduction.

The follow-up period of only 1 month in each pacing mode in the IDEAL RVP trial precludes an assessment of the long-term consequences of each of the pacing modalities. In addition, although the data are relatively strong with respect to maintaining AV synchrony and a normal ventricular activation when both the PR interval and the QRS duration are normal, there are no data available with respect to the patient who has an abnormal ventricular activation sequence.²⁴ There are data with respect to patients with significant first-degree AV block with a normal ventricular activation sequence will often do better with dual-chamber pacing programmed to an appropriate AV delay despite the forced abnormal ventricular activation sequence. There is limited but enticing evidence that pacing from the RV outflow tract may be able to provide the needed ventricular pacing with a near-normal ventricular activation sequence. This would allow the clinician to programme an optimal AV delay for a given patient while still maintaining near-normal ventricular function in the setting of ventricular pacing. A study involving patients with AV block who

will require ventricular pacing comparing RV apical pacing RV outflow tract pacing with biventricular pacing needs to be done with a follow-up of 5 years or longer.

As Murakami *et al.* point out, the IDEAL RVP study was not designed to assess the clinical value of one mode over the other. The follow-up interval was too short and the lack of diagnostics internal to the pacemaker limited their ability to determine how the system functioned between office visits and whether or not this was always optimal for each subject. Disease is rarely static, and the requirements at the time of implantation will change with the progression of disease as well as the addition of pharmacological therapy and various co-morbidities. It is strongly recommended that as we go forward, for those patients who require ventricular pacing, even in the presence of 'just' first-degree AV block, one should select a physiologically appropriate AV delay rather than the blanket desire to eliminate all ventricular pacing. Combining this with an alternate site of ventricular pacing might further improve the long-term outcomes but this has yet to be proved.

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