

# Role of the AV Interval in DDD Pacing: Insights into Programming with Respect to Ventricular Function when AV Nodal Conduction is Intact

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## Introduction :

The original indication for permanent pacing was complete heart block. The original pacing mode was asynchronous ventricular (VOO) pacing and the results were spectacular but the number of patients who would benefit from these early pacemakers was very limited. Since this early experience, the indications have grown as have the available pacing modes, the complexity and versatility of these devices and a recognition that when programmed inappropriately, these device may contribute to congestive heart failure and other adverse consequences. In the late 1970's to early 1980's, the medical profession first began to appreciate the adverse consequences associated with the loss of AV synchrony (pacemaker syndrome). In the early 1990's, the first reports started to appear that patients with intact AV nodal conduction and a normal ventricular activation pattern might do better with AAI pacing as compared to DDD pacing although the results were mixed. Coincident with this growing recognition that AAI might be better than DDD were early studies suggesting that patients with refractory congestive heart failure, if associated with a left bundle branch block, might benefit from dual chamber pacing even in the absence of second or third degree AV block or sinus node dysfunction. Two underlying electrophysiologic states correctable by cardiac pacing and thus able to positively impact the management of congestive heart failure were identified in CHF patients. One was first degree AV block even though implantation of a DDD pacemaker to control the AV delay would force an abnormal ventricular activation sequence. This suggested that AV delay in some patients may be as if not more important than a normal ventricular activation sequence. The second was the disordered ventricular activation sequence resulting in mechanical dyssynchrony. This second mechanism could be addressed by stimulating a site other than the RV apex or simultaneously stimulating both the septal and postero-lateral walls of the left ventricle to improve mechanical dyssynchrony associated with the abnormal ventricular activation pattern. Dual site stimulation was first called biventricular pacing and is now known as cardiac resynchronization therapy. The role of CRT is being discussed in other articles in this symposium. The purpose of this paper is to address the

current status of dual chamber pacing with respect to its impact on ventricular function and programming the AV delay in patients who need a pacemaker for standard indications.

The DAVID study<sup>1</sup> was a prospective randomized trial comparing single and dual chamber pacing in a group of patients being implanted with an ICD. Over the previous decade since the introduction of dual chamber ICDs, these had become the favored selection based on two presumptions. The first is that the atrial channel would provide improved arrhythmia discrimination. The second was based on the pacemaker literature with respect to pacemaker syndrome and the demonstration that dual chamber pacing was superior to single chamber ventricular pacing. There was data suggesting that one had to be very careful in programming the SVT discriminators to gain a benefit from the atrial channel with respect to improved specificity for recognition of ventricular tachyarrhythmias. If care was not taken, the results could be worse, not better than a single chamber ICD. The DAVID investigators wanted to evaluate the second presumption – that DDD pacing in an ICD was superior to VVI pacing. The entry criteria required that the patients needed an ICD but did not require pacing support. One group was randomized to VVI pacing at a base rate of 40 bpm to provide back-up protection but otherwise allow the intrinsic rhythm to dominate. The second group was programmed to the DDD mode at a base rate of 60 bpm with AV delay programming left to the decision of each investigator. A majority left the paced and sensed AV delays at the shipped setting (170/150 ms) which resulted in ventricular pacing usurping control of the normal conduction system. The primary endpoint was hospitalization for new onset or worsening congestive heart failure and/or mortality. While the investigators were blinded as to the results, the Data Safety Monitoring Board reviewed the data on a regular basis and terminated the study prematurely because of a statistically significant increase in the primary endpoint in the DDD group rather than the VVI group. On review, the investigators concluded that the forced ventricular pacing in the DDD group causing a left bundle branch block contributed to the increased incidence of congestive heart failure. The incidence of ventricular pacing in the DDD group was 70% while it was only 4% in the VVI group. Based on the DAVID trial, the investigators in a number of other prospective studies (MOST<sup>2</sup>, MADIT II<sup>3</sup>, Midas 6<sup>4</sup>) focusing on other issues

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<sup>1</sup> The DAVID Trial Investigators, Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. *JAMA* 2002; 288:3115-23.

<sup>2</sup> Shukla HH, Hellkamp AS, James EA, Flaker GC, Lee KL, Sweeney MO, Lamas GA, Heart failure hospitalization is more common in pacemaker patients with sinus node dysfunction and a prolonged paced QRS duration, *Heart Rhythm* 2005; 2: 245-251

<sup>3</sup> O'Keefe JH, Jones PG, Thompson RC, Bateman TM, McGhie AI, Ramza BM, Steinhaus DM, Effect of chronic right ventricular apical pacing on left ventricular function, *American J Cardiology* 2005; 95: 771-773

<sup>4</sup> Freudenberger RS, Wilson AC, Lawrence-Nelson J, Hare JM, Kostis JB, Permanent pacing is a risk factor for the development of heart failure, *American J Cardiology* 2005; 95: 671-674

but comparing VVI to DDD re-examined their data and corroborated the findings of DAVID. An increased incidence of ventricular pacing when AV nodal conduction was otherwise intact was associated with an increased incidence of congestive heart failure and atrial fibrillation. This seems contradictory to the experience with CRT where a short AV delay is intentionally programmed but the setting is different – patients with CRT start with a bundle branch block and severe CHF whereas the above studies focused on patients with normal ventricular function and a narrow QRS complex.

Over the past couple of years, based on these results, physicians have been programming very long AV delays or implementing algorithms to achieve functional AAI pacing even at the expense of a marked first degree AV block. Where AV nodal conduction and the ventricular activation sequence is normal, this is prudent and appropriate with a growing literature to support this approach. However, blindly programming a long AV delay may, for selected patients, be as counterproductive as programming a short AV delay in the presence of intact AV nodal conduction.

### **Clinical vs Device Measurement of AV Delay:**

Many physicians do not appreciate that there is a difference between the pacemaker's definition of a PR interval and the clinician's definition. The standard clinical measurement of the PR interval starts with the onset of the P wave to the onset of the QRS complex as recorded on a standard surface electrocardiogram. The pacemaker starts its measurements with the intrinsic deflection of the atrial depolarization and ends its measurement with the intrinsic deflection of the ventricular depolarization (Figure 1a, 1b). It is the exception that the pacemaker detects with the atrial or ventricular depolarization at the leading edge of the respective P wave or QRS complex. In addition, when atrial pacing is involved, there may be a delay (latency) between the atrial stimulus and the onset of the atrial depolarization. There may also be an intra- and interatrial conduction delay (Figure 1B). Thus, the AR interval is likely to be significantly longer than the PR interval and these differences must be taken into account during the evaluation of the patient and programming of the pacemaker.

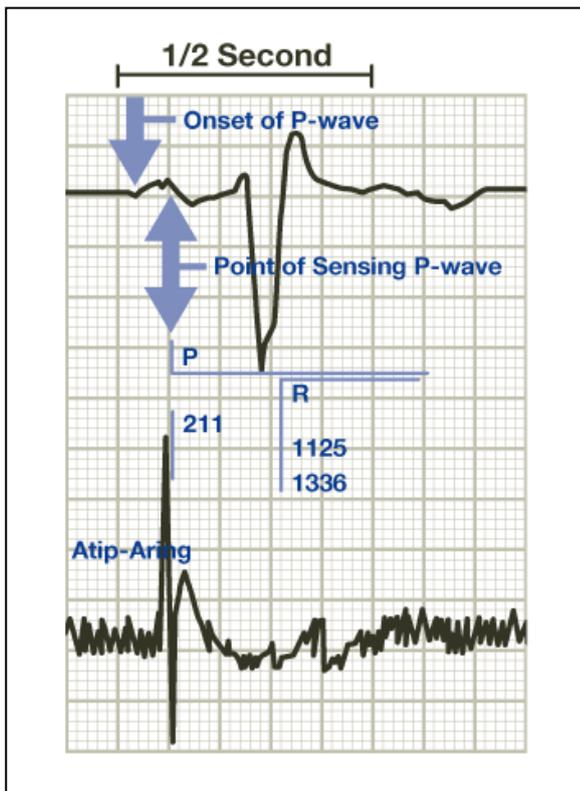


Figure 1A

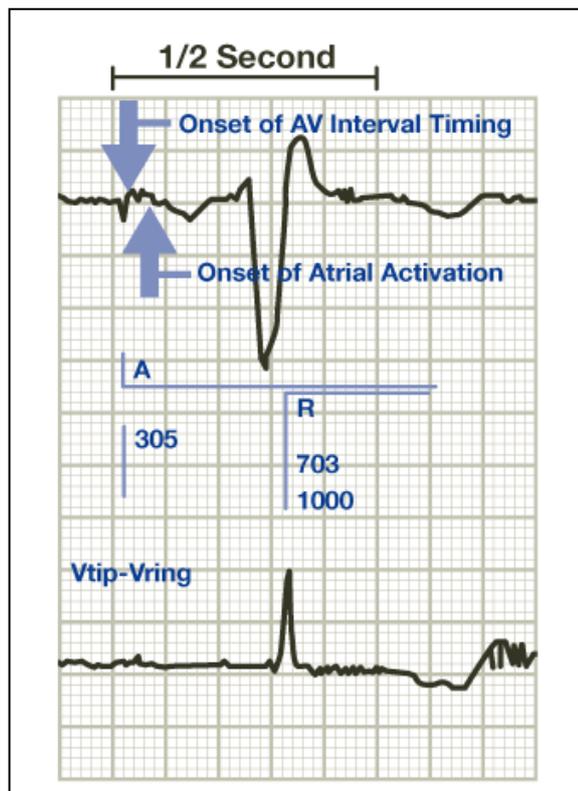


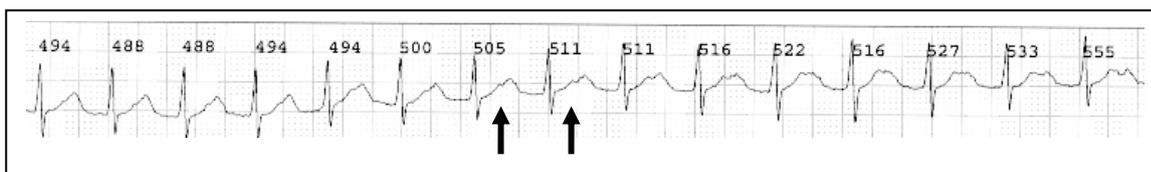
Figure 1B

**Figure 1A:** Surface ECG and simultaneous atrial bipolar electrogram during atrial sensed ventricular sensing. The intrinsic deflection of the P wave occurs well-after the onset of the P wave. The PR interval according to the pacemaker is 211 ms.

**Figure 1B:** Surface ECG and simultaneous ventricular bipolar electrogram during atrial pacing ventricular sensing. The “R” according the pacemaker occurs towards the end of the conducted QRS complex. The AR interval as measured from the atrial stimulus to the intrinsic deflection of the QRS complex was 305 ms. The PR interval associated with this complex was 180 ms. This is what should be taken into account when deciding whether the AV delay should be extended sufficiently to allow for intact conduction or adjusted to totally control the AV interval even if there was ventricular pacing.

**First degree AV block:**

In the excitement following DAVID and the retrospective analyses of MOST, MADIT II and other studies, a presumption has developed that if the ventricular activation sequence is basically normal as indicated by a narrow QRS, single chamber atrial pacing should take precedence over AV pacing short of second or third degree AV block. However, first degree AV block may be associated with exercise intolerance and shortness of breath as the native P wave coincides with the ST-T wave of the preceding conducted QRS complex even with a normal ventricular activation sequence (Figure 2).



**Figure 2: Rhythm strip from a Holter monitor. The patient had first degree AV block and with mild activities, a significant increase in his sinus rate and dyspnea on exertion that was out of proportion to the level of activity. Ventricular function was normal as assessed with Doppler echocardiography. These symptoms resolved with an increase in exercise tolerance following implantation of a dual chamber pacemaker despite ventricular pacing with its associated abnormal ventricular activation sequence. The upward directed arrows identify two of the sinus P waves in the ST-T wave segment driving the next QRS complex.**

In the original Guidelines for pacemaker implantation, first degree AV block was considered a Class III indication meaning that there was a general consensus that pacing was not required. There are a number of studies over the past decade that have demonstrated the adverse hemodynamic effects of first degree AV block, even when the resultant ventricular activation pattern was normal<sup>5,6,7,8</sup>. In the studies by Vardas<sup>7</sup> and Schwaab<sup>8</sup>, there was improvement in acute cardiac function with DDD pacing and its associated abnormal ventricular activation sequence compared to AAI pacing with the first degree AV block. In a study by Iliev<sup>9</sup>, an AR interval  $\geq 270$  ms

<sup>5</sup> Barold SS, Indications for permanent cardiac pacing in first degree AV block: Class I, II or III? PACE 1996; 19: 747-751.

<sup>6</sup> Kim YH, O’Nunain S, Trouto T, et al, Pseudo-pacemaker syndrome following inadvertent fast pathway ablation for atrioventricular nodal reentrant tachycardia, J Cardiovasc Electrophysiol 1993; 4: 178-182+

<sup>7</sup> Vardas PE, et al, AAIR vs DDDR pacing in patients with impaired sinus node chronotropy. An echocardiographic and cardiopulmonary study, PACE 1997; 20: 1762-1768.

<sup>8</sup> Schwaab B, et al., AAIR vs DDDR pacing in the bradycardia tachycardia syndrome. A prospective randomized double-blind crossover trial, PACE 2001; 24: 1485-1595

<sup>9</sup> Iliev H, et al, Preserving normal ventricular activation versus atrioventricular delay optimization during pacing. The role of intrinsic atrioventricular conduction and pacing rate, PACE 2000; 23: 74-83.

was associated with better cardiac performance associated with AV interval optimization as compared to normal ventricular activation. The ACC/AHA/HRS 2002<sup>10</sup> guidelines to indications for pacemaker implantation have elevated first degree AV block to a Class II indication when there are significant symptoms associated with this rhythm. The symptom complex associated with first degree AV block has been called pseudo-pacemaker syndrome. At increased sinus rates, the sinus P wave coincides with the ST-T wave of the previously conducted QRS complex causing the atrium to contract against a closed mitral and tricuspid valve limiting the atrial contribution to ventricular filling and by causing the atrium to contract against a closed mitral and tricuspid valve, contributing to pulmonary and systemic vascular congestion, effectively congestive heart failure with a mechanically normal heart.

The normal physiology of native AV conduction is to progressively shorten the PR interval as the rate increases in response to a physiologic stress. This is the positive dromotropic effect of catecholamines<sup>11,12</sup>. There is an entity termed the AAIR Pacemaker Syndrome, which is similar to symptomatic first degree AV block. With exercise and an increase in the atrial paced rate due to rate modulation, the AR interval fails to appropriately shorten causing the paced P wave to coincide with the ST-T wave associated with the previously conducted QRS complex<sup>13</sup>. Indeed, in patients with sick sinus syndrome, the failure to appropriately shorten the AR interval with progressive increases in rate is not uncommon<sup>14</sup>. This was one reason for the introduction of progressive shortening of the paced or sensed AV delay as the atrial rate increased.<sup>15</sup> Others have also shown that simply programming a long AV delay may be counterproductive, even in patients with intact AV nodal conduction<sup>16,17</sup>. Allowing the AAI pacing mode to persist as the atrial rate

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<sup>10</sup> Gregoratos G, Abrams J, Epstein AE, et al, ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices, A report of the ACC/AHA Task Force on Practice Guidelines, *Circulation* 2002; 106: 2145-2161

<sup>11</sup> Luceri RM, Brownstein SL, Vardeman L, Goldstein S, PR interval behavior during exercise, implications for physiologic pacemakers, *PACE* 1990; 13: 1719-1723.

<sup>12</sup> Barbieri D, Percoco GF, Toselli T, et al, AV delay and exercise stress tests: Behavior in normal subjects, *PACE* 1990; 13: 1724-1727.

<sup>13</sup> Den Dulk K, Lindemans FW, Brugada P, Smeets JLRM, Wellens HJJ, Pacemaker Syndrome with AAI Rate variable pacing: Importance of atrioventricular conduction properties, medications and pacemaker programmability, *PACE* 1988; 11: 1226-1233

<sup>14</sup> Mabo P, Pouillot C, Kermarrec A, et al, Lack of physiologic adaptation of the atrioventricular interval to heart rate in patients chronically paced in the AAIR mode, *PACE* 1991; 14: 2133-2142.

<sup>15</sup> Ritter P, Vai F, Bonnet JL, et al, Rate adaptive atrioventricular delay improves cardiopulmonary performance in patients with a dual chamber pacemaker for complete heart block, *Eur J Cardiac Pacing and Electrophysiol* 1991; 11: 31-38.

<sup>16</sup> Pieterse MGC, Den Dulk K, van Gelder BM, van Mechelen R, Wellens HJJ, Programming a long paced atrioventricular interval may be risky in DDDR pacing, *PACE* 1994; 17: 252-257.

<sup>17</sup> Kindermann M, Frohlig G, Doerr T, Schieffer H, Optimizing the AV delay in DDD pacemaker patients with preserved AV conduction, *Heartweb*, 1996; 2: Article 96110023 (<http://www.webaxis.com/heartweb/1196/pacing/0006.htm>)

increases may be associated with symptoms as originally described by Den Dulk and others due to the failure to appropriately shorten the AR interval during either physiologic or device-based increases in the atrial rate. This becomes even more common in the elderly patients who may be on beta-adrenergic blocking or calcium channel blocking drugs for the treatment of hypertension, ischemic heart disease and other conditions.

A recent study used Doppler echocardiography to assess the myocardial performance index (MPI) in patients with sinus node dysfunction and intact AV nodal conduction<sup>18</sup>. MPI had been previously used to optimize paced and sensed AV delays in the setting of AV block. The investigators used a phonocardiogram to identify the first heart sound defining the end of diastole and ventricular filling. The MPI is a ratio of the sum of the isovolumic contraction and isovolumic relaxation periods divided by the left ventricular ejection time. A low number identifies a better left ventricular function. They measured the MPI in the AAI mode was compared to the MPI in the DDD mode after the AV delay was adjusted to provide an optimal AV delay in the resting supine state. The ratio of the MPI in the AAI mode to that measured at the optimal AV delay in the DDD mode was defined as “relative MPI” or rMPI. The investigators also measured a relative atrioventricular interval (rAVI), which was defined as the ratio of the AR interval measured during AAI pacing to the optimal AV delay measured during DDD pacing.

The native PR interval in this group of patients was 161 ms  $\pm$  31 ms and the intrinsic QRS duration was 92  $\pm$  12 ms. The mean optimal AV delay in the DDD mode was 139  $\pm$  22 ms which, interestingly, is very close to the mean AV delay being used in CRT systems. The atrial stimulus to R wave interval (AR) correlated with the rMPI. With atrial pacing, the AR interval commonly increased quite markedly. This is due to the site of stimulation and subsequent inter- and intra-atrial conduction.

When the rAVI was  $> 1.73$  meaning that the AR interval was significantly longer than the PR interval, DDD pacing was superior to AAI pacing. This is consistent with prior studies in patients with first degree AV block who have been shown to benefit from an optimal AV delay despite ventricular pacing with the abnormal ventricular activation sequence. When the rAVI was  $< 1.5$ , AAI pacing tended to be superior. The investigators noted that there was no way to assess this simply from the surface ECG and indeed, in virtually all the patients in this study, the PR interval associated with the native rhythm was normal.

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<sup>18</sup> Kato M, Dote K, Sasaki S, Goto K, Takemoto H, Habara S, Hasegawa D, Matsuda O, Determination of the optimal atrioventricular interval in sick sinus syndrome during DDD pacing, PACE 2005; 28: 892-897

The major limitation of the study by Kato and the other studies cited is that they were acute without long term follow-up. In addition they assessed cardiac function in a single physiologic state supine at rest except for the Vardas paper which was at rest and exercise.

## **Discussion:**

While David and the retrospective analysis of MADIT II, MOST and other studies have significantly impacted the practice of medicine with respect to programming AV delay, they have also caused the pendulum to swing too far towards blindly programming a long AV delay when AV nodal conduction is intact but compromised. Vardas, Schwaab and Iliev have shown that in the presence of first degree AV block as measured from the surface ECG, there may be an acute improvement in cardiac function by carefully programming the AV delay despite forcing an abnormal ventricular activation sequence. Kato and associates have demonstrated that even with a normal PR interval, there may be a significant difference between even the normal PR interval and the AR interval. In that setting, a careful assessment of the AV delay may also demonstrate improved cardiac function with AV pacing despite the disordered ventricular activation sequence.

The goal of therapy is to improve cardiac function, not worsen it. These studies demonstrate that cardiac physiology is complex and while we now appreciate that forcing ventricular pacing when it is not needed may contribute to congestive heart failure, blindly eliminating all ventricular pacing in patients who have a primary indication for pacing, particularly sinus node dysfunction, may provide a false sense of reassurance that we are providing optimal therapy for these patients. It is important to carefully evaluate each patient. Those patients with normal baseline ventricular function may be able to initially compensate for any inadequacies associated with the pacing prescription making it difficult to prove a long term adverse consequence.