CLINICAL DECISION-MAKING

Optimization of ICD Programming: How Crucial is the AV Interval?

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Introduction

Implantable cardioverter-defibrillators (ICDs) save lives by delivering therapy to terminate life-threatening ventricular arrhythmias for patients at risk. Modern devices have pacing and advanced arrhythmia detection capabilities that may add value over and above that provided by the single chamber VVI programmed ICD "shock box," considered by some to be the "gold standard." A dual chamber device can provide rate-responsive atrial pacing for patients who develop chronotropic incompetence, provide atrioventricular (AV) synchrony if first-, second-, or third-degree heart block develops, and aid in discerning between supraventricular and ventricular tachycardias.

Most US clinicians choose to implant dual chamber (DDD) ICDs unless cardiac resynchronization therapy (CRT) is indicated. Controlled clinical trials have demonstrated that dual chamber programmed ICDs or atrial-based programmed ICDs are non-inferior to VVI programmed devices. Little emphasis has been placed on issues related to heart rate or AV interval, even though these parameters may be important. Compelling data suggest that a high percentage of right ventricular (RV) pacing can have adverse consequences. Some RV pacing, on the other hand, may provide benefit by an unknown mechanism, perhaps in part by maintaining normal AV relationships. AV synchrony, defined as a normal relationship between both atrial and ventricular contraction, may have important physiologic, hemodynamic, and electrophysiologic consequences, but this has not been addressed carefully. Here, we consider the AV relationship as an under-recognized but potentially important parameter that should be considered when making management decisions for patients who undergo ICD therapy.

One day in the clinic: an ICD candidate with a long PR interval (summary in Table 1)

A 69-year-old man on optimal medical therapy for long-standing ischemic cardiomyopathy, NYHA Class III congestive heart failure, and a left ventricular ejection fraction of 25% has a resting pulse of 40 and a QRS complex width of 90 ms. The PR interval is 290 ms. Although an ICD is indicated, would it be best to implant a single chamber device programmed VVI, a dual chamber device programmed DDDR with minimization of RV pacing, one programmed DDDR with optimization of the AV interval, or one that provides CRT?
Table 1: What ICD options would you recommend for this patient?

<table>
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<th>Summary of clinical characteristics</th>
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<tr>
<td>Longstanding ischemic cardiomyopathy, NYHA Class III heart failure</td>
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<tr>
<td>Left ventricular ejection fraction = 25%</td>
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<td>Resting heart rate = 40</td>
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<tr>
<td>QRS width = 90 ms</td>
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<td>PR interval = 290 ms</td>
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Implantable cardioverter-defibrillator options
- VVI – 40
- DDI pacing
- DDDR with AV Search Hysteresis
- Managed ventricular pacing with rate responsive AAA
  - DDD pacing
- Cardiac resynchronization therapy pacing

PR interval prolongation is common among patients undergoing device implantation

PR interval prolongation appears to be common in the ICD population. In the COMPANION Trial, a study of patients in whom resynchronization was considered necessary, about 50% of patients had PR intervals exceeding 200 ms. The Marquis MVP ICD Download Study demonstrated a dynamic relationship between the cumulative percent of atrial pacing and the PR interval. Approximately 15% of patients in this study were considered to have “severe AV decoupling” with ≥40% of the AV intervals ≥300 ms (Figure 1a,b).5

Is a prolonged AV interval a marker of risk?

Epidemiologic data from the Framingham Study showed that first-degree AV block (PR intervals >200 ms, the electrocardiographic equivalent of AV prolongation) is associated with increased risk of total mortality in the general population.6 For this group, the unadjusted risk of all cause mortality was 2.72 (2.11–3.51, p≤0.001) and multivariable adjusted risk was 1.44 (CI 1.09–1.91, p=0.01). The unadjusted risk of atrial fibrillation in patients with first-degree AV block was 4.26 (CI 2.85–6.38) and a multivariable adjusted risk was 2.06 (CI 1.36–3.12), with both p values <0.001. Although not an ICD population, these data suggest prolonged PR intervals are an independent risk factor for adverse outcomes. These data do not indicate, however, that shortening the PR interval would improve outcomes or that prolonged PR intervals cause serious adverse hemodynamic consequences per se.

The INTRINSIC RV study1 was a large randomized controlled clinical trial that included patients who were ICD candidates. They received a dual chamber ICD, programmed either VVI or DDDR (with AV Search Hysteresis in all randomized and many non-randomized trials) in long-term follow-up. This non-inferiority trial showed that dual chamber programming to reduce unnecessary RV pacing was associated with similar outcomes in heart failure hospitalization and total mortality compared with VVI programming. Patients who had more than 20% RV pacing after device implant were not randomized and were programmed according to physician preference; most devices remained programmed DDDR with AV Search Hysteresis.

INTRINSIC RV showed that about 20% of patients had RV pacing at levels >20%, even with AV Search Hysteresis programmed on. These patients were at greater risk of heart failure hospitalizations and total mortality than patients with less RV pacing.1,4 These and other data confirm that >40% RV pacing incurs very high risk.4

Although a high percentage of RV pacing was associated with adverse outcomes, RV pacing in the range of 10% to 20% was associated with similar, if not better, outcomes to patients who received up to 10% RV pacing. These data suggest that some degree of RV pacing is not harmful and may be beneficial (perhaps by maintaining AV synchrony). However, for patients with prolonged PR intervals who have ICDs programmed DDDR, RV pacing may be excessive despite attempts to minimize RV pacing with AV Search Hysteresis programmed as long as 300 ms. The outcomes of patients with prolonged PR intervals who have frequent RV pacing may be influenced by factors other than RV pacing alone.

Managed ventricular pacing (MVP) can substantially reduce the incidence of RV pacing even for patients with very long PR intervals, but this may come at the price of transient AV block and the adverse effects of long PR intervals. Retrospective data from the MVP trial in which MVP programming (AAIR <-> DDDR mode switch) was compared with VVI programming7 in ICD patients suggested that prolonged PR intervals (≥230 ms) were associated with increased risk of total mortality or heart failure hospitalizations compared with VVI 40 programming.8 Patients with PR intervals <230 ms had similar outcomes regardless of device programming (VVI versus MVP).

Atrial-based pacing does not appear to be a risk if the pulse is within the physiologic range, in contrast to faster intrinsic heart rates with AAI pacing or DDDR with AV Search Hysteresis.2,9 With MVP, however, atrial-based rate responsive pacing could cause marked PR prolongation well beyond the 300 ms limit set with AV Search Hysteresis, causing a risk for hemodynamic deterioration and proarrhythmia.10 Further, there could be adverse hemodynamic consequences of very long PR intervals (i.e. AV decoupling). These data from MVP point to the fact that patients with PR interval prolongation may be at greater risk than those with normal PR intervals.

Although these data suggest that PR interval prolongation may be problematic, especially when present at baseline, and perhaps even more with rate responsive atrial-based pacing, the DAVID II Trial did not show any harm with atrial-based pacing at a rate of 70 compared with VVI pacing at a rate of 40 in a population of ICD candidates.11 DAVID II, however, differed from MVP since there was no atrial-based rate responsive pacing that could further prolong the PR interval at faster rates. Also, patients with prolonged PR intervals were excluded from DAVID II, so the actual risk of marked PR prolongation was not evaluated.
The risk is further highlighted in a post hoc analysis of the COMPANION trial, a study of patients indicated for CRT with wide QRS complexes, systolic ventricular impairment, and severe symptomatic heart failure despite optimal medical therapy. These data, reported in part at the 2010 Heart Rhythm Society meeting, and undergoing detailed analysis, suggest PR interval prolongation may be a modifiable risk factor. To date, no prospective study has indicated that specific PR interval programming, even in those undergoing CRT implantation, influences outcomes.

A recent analysis of heart failure patients randomized to CRT pacing or optimal medical therapy in the CARE-HF trial suggested that although baseline QRS width had a low predictive value, PR interval prolongation was a strong predictor of unfavorable outcomes. Gervais and colleagues found after 3 months of therapy that PR interval shortening due to CRT may also be a sign of successful CRT response and improved outcomes. The PR interval was one of the most predictive variables in this population ($\chi^2 = 12.3, p<0.001$), but variability of the PR interval was quite low. Most patients had normal PR intervals; patients with markedly prolonged PR intervals were not included.

There are several important reasons that make it difficult to determine what might be the optimal PR interval in patients receiving ICDs. First, a high degree of variability may exist in terms of the AV interval that is ideal for each patient. Along these same lines, the best PR interval may be different depending upon whether a given patient is in normal sinus rhythm or is receiving atrial pacing. Patients with prolonged PR intervals often have other comorbidities. Next, there is no good way to modify the PR interval to determine outcomes without altering QRS activation. Finally, measurement techniques to determine the optimal PR interval may be subject to question.

What are some consequences of a prolonged PR interval?

The exact mechanism by which PR interval prolongation may adversely influence outcomes, especially in patients with heart failure, remains somewhat uncertain. PR prolongation can cause late diastolic mitral regurgitation, loss, and/or reduction of presystolic ventricular filling, and a pseudo-pacemaker syndrome (Table 2).
Diastolic mitral regurgitation has been shown echocardiographically when the PR interval is quite long (in the range of 300 ms) and has been shown acutely with measurement of the pulmonary capillary wedge pressure. Ventricular pacing with a shorter PR interval for patients with marked first-degree AV block decreased diastolic mitral regurgitation and eliminated large V waves.17

Nishimura et al.18 have shown that patients with left ventricular dysfunction studied acutely with AV pacing intervals between 60 and 240 ms will have cardiac output differences that are highly significant (p=0.0007) when the optimal AV delay is determined. Changes in atrial filling, as measured by the E and A waves (and their ratio), and cardiac output, measured by the aortic velocity time integral, exist. Ultimately, differences in contractility related to the degree of diastolic ventricular filling occur.

What is the best method to assess AV synchrony?

Several methods have been used to assess the parameters associated with changes in the PR interval (Table 3). +dP/dT and cardiac output determinations have been performed acutely, but these are invasive, represent one heart rate, and are performed in the supine position only. The aortic velocity-time integral (VTI) and mitral inflow E/A ratio have been assessed by echocardiography, but again, these measures are acute and their validity is uncertain. Furthermore, the meaning of a change in these parameters and the reproducibility at different heart rates and in different positions remain uncertain. A 6-min walk has been considered as a method to assess the influence of the AV interval, but it has not yet been validated by outcome measures. Treadmill testing monitoring myocardial oxygen consumption (MVO2) can be performed, but its pertinence, and reproducibility, similar to the 6-min walk test, are open to debate. Mortality can be assessed in patients with long PR intervals, but the relationship and causality of the PR interval to this outcome remain uncertain.

Table 3: Options to assess the AV interval

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<th>Parameter</th>
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<tr>
<td>+dP/dT</td>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Aortic velocity time integral</td>
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<tr>
<td>Mitral inflow: E/A ratio</td>
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<tr>
<td>6-minute walk</td>
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<tr>
<td>Treadmill with myocardial oxygen consumption (MVO2)</td>
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<tr>
<td>Functional class</td>
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<td>Mortality</td>
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To highlight this in a CRT evaluation utilizing echocardiographic optimization via aortic VTI, Sawhney et al.19 determined that 75% who were optimized versus 40% who had empiric therapy improved by at least one NYHA Functional Class (p<0.03). There was improvement in the quality-of-life score between the two groups (p<0.03) but there was no change in the 6-min walk test, and there were only 20 patients in each group. No patient had a very long PR interval. The optimal AV delay was highly variable from patient to patient (60–200 ms), and the study was not blinded.

Although there has been much controversy regarding optimization of the PR interval in patients undergoing CRT, no consensus yet has determined whether it is a valuable parameter to optimize and by which method this is best achieved. The FREEDOM (A Frequent Optimization Study using the QuickOpt Method) Trial, a prospective double-blind randomized study of 1,647 CRT patients, evaluated an automated versus manual approach at AV and VV optimization and showed no difference in a heart failure clinical composite score between groups.

Is the PR interval even important?

Several acute studies have questioned the importance of the PR interval. In one randomized pacing study by Gold et al.,20 acute measurements of pressure and cardiac output, as well as ejection fraction, did not seem to be statistically different in the group as a whole, but this study was an acute study performed in a small number of patients and there was wide variability in differences in ejection fraction when comparing VVI pacing to VDD pacing. Auricchio et al.21 evaluated acutely varying AV delays in patients while monitoring changes in pulse pressure and changes in +dP/dT. As suggested from these acute data, there was wide variability in the hemodynamics and contractility based on the programmed AV interval between patients. There was a large amount of individual variability such that it can be difficult to determine what the optimal value would be for the group as a whole, but individualized optimization could take place. It would be important to show how differences in outcome measures related to hemodynamic and echocardiographic optimization.

This problem is further compounded by the fact that atrial pacing can further delay atrial activation and activate the atria in a more non-uniform fashion such that the optimal AV delay may vary with pacing compared with the optimal AV delay without pacing. Gold et al.22 showed that the optimal AV delay with CRT determined by the percent left ventricular dP/dT max was 283 ms with atrial pacing but was 140 ms with atrial sensing. There was a wide amount of variability.

The dilemma for our patient

A patient who is an ICD candidate but has normal QRS complex, sinus bradycardia, and prolonged PR interval
poses a dilemma. The best ICD to implant remains in question. Although data have addressed the issue of AV optimization, studies have not considered the importance of the AV interval in CRT patients with a narrow QRS complex.

Although a VVI device may be the best option, our patient may have adverse hemodynamic consequences from PR prolongation and may be at risk for other adverse outcomes including progressive heart block. Further, a VVI device will offer no atrial rate responsive support pacing that may be necessary in a patient with sinus bradycardia.

It would be unwise, however, to implant a dual chamber rate responsive (i.e. DDDR) ICD to shorten the AV interval intentionally as this would likely cause 100% RV pacing and place the patient at risk for serious consequences.

A dual chamber rate responsive device that provides a dynamic balance between a modest percentage of RV pacing that can maintain a reasonable AV interval may offset adverse consequences and improve long-term outcomes. DDDR with AV Search Hysteresis may provide this balance in patients with some PR interval prolongation, but this may not be effective if the PR interval is quite long and becomes longer due to atrial-based rate responsive pacing.

A device that minimizes RV pacing by providing AAIR support pacing and mode switching to DDDR only when there is evidence of AV block (MVP programming) does not appear to be the solution, based upon available data. Extreme AV delays may be worse than no ventricular pacing at all as ventricular pacing can help maintain the AV interval in a physiologic range. There may be a balance between the AV interval and the percent RV pacing. A decision regarding programming must be made, taking into account the trade-off between excess RV pacing and extremes in the AV interval so that a happy medium can be achieved.

It seems conceivable that our patient may benefit from CRT pacing to restore and maintain a physiologic AV interval rather than backup VVI, AAI, DDI, or DDD pacing. However, biventricular activation may have adverse hemodynamic effects compared with intrinsic conduction in the setting of a narrow QRS. It is therefore premature to recommend a CRT ICD for our patient who has a narrow QRS complex, sinus bradycardia, and prolonged PR interval. The best pacing modality for our patient still remains uncertain.

**Conclusion**

The PR interval is generally disregarded when it comes to ICD device selection, yet PR interval prolongation is common, can predict outcomes, and may be a modifiable risk factor. Properly timed AV synchrony can improve hemodynamics, but the excess RV pacing that may ensue is a problem. When it comes to ICD programming and determination of the device to implant for a given patient, it is important to recognize the underlying heart rate and AV interval. Patients who are ICD candidates and have prolonged PR intervals may potentially benefit from shortening of that interval to improve AV synchrony. The role of CRT pacing in this regard remains unresolved, but it would be reasonable to perform a study to evaluate the importance of AV synchrony.

**References**


