Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization

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An optimized atrioventricular (AV) interval can maximize the benefits of cardiac resynchronization therapy (CRT). If programmed poorly, it may curtail beneficial effects of CRT. AV optimization will not convert non-responder to responder, but may convert under-responder to improved status. There are many echocardiographic techniques for AV optimization but there is no universally accepted gold standard. The optimal AV delay varies with time, necessitating periodic re-evaluation. As the optimal AV delay may lengthen on exercise, a rate-adaptive AV delay should not be routinely programmed. Intra- and interatrial conduction delays may require AV junctional ablation when AV optimization is impossible in patients with a poor clinical response. Fusion with the spontaneous QRS complex may be acceptable on a trial basis to seek a better clinical response or with a short PR interval. Routine VV optimization is presently controversial but programming may prove beneficial in some patients with a suboptimal CRT response where no cause is found. It may partially compensate for less than optimal left ventricular (LV) lead position and may correct for heterogeneous ventricular activation including a prolonged LV latency interval and slow conduction (scarring) near the LV pacing site. Routine VV optimization is generally programmed using the aortic velocity-time integral, and long-term variations of the optimal value necessitate periodic re-evaluation.

KEYWORDS
Cardiac resynchronization; Biventricular pacing; Echocardiography; Atrioventricular interval; Interventricular interval

Programming the atrioventricular interval

Although optimization of the left-sided atrioventricular (AV) interval is important, the benefits of acute and long-term cardiac resynchronization therapy (CRT) to heart failure (HF) patients depends mostly on reliable resynchronization (with the proper choice of left ventricular (LV) pacing site) and less on AV optimization itself.1,2 Programming of the left-sided AV interval should not be ignored because appropriate AV interval timing can maximize the benefit of CRT, but if programmed poorly, it has the potential to curtail the beneficial effects. AV optimization will not convert a non-responder to responder, but it may convert an under-responder to improved status. The optimal AV delay in CRT patients exhibits great variability from patient to patient.1,3 Consequently, empirical programming of the AV interval is suboptimal in many patients and is generally not recommended.

The optimal atrioventricular relationship

Optimized AV synchrony is achieved by an AV delay that provides the best left atrial contribution to LV filling, the maximum stroke volume, shortening of the isovolumic contraction phase, and the longest diastolic filling time (Figure 1). The shortest AV delay should not compromise the transmitral Doppler A wave and the end of atrial contraction should coincide with onset of rise in LV pressure. In addition, it should eliminate diastolic mitral regurgitation in patients with a long PR interval.4,5 The optimal AV delay setting results in maximal stroke volume and cardiac output by virtue of complete late-diastolic filling by atrial contraction and the maximum LV diastolic filling time.

Prolonged atrioventricular conduction and too long atrioventricular delay

Prolonged AV conduction is not uncommon in HF patients. In this situation, atrial contraction occurs too early in diastole and results in ineffective or decreased atrial contribution to cardiac output (Figure 1). Atrial depolarization begins too early, causing superimposition of atrial contraction on the early diastolic LV-filling phase. On the transmitral Doppler signal, a relatively early A wave fuses with a relatively late E wave resulting in shortening of the LV diastolic filling time. A prolonged PR/AV interval induces diastolic mitral regurgitation. Following atrial contraction, the mitral valve remains open because LV contraction is delayed and LV

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AV optimization after CRT. It is presently unclear if the patient is expected to alternate between atrial sensed and paced events.

Mitrail inflow (Ritter) method
AV delay optimization of conventional and CRT devices is commonly performed by the Ritter method \(^{11,12}\) that evaluates transmitral flow using pulsed wave Doppler. This well-known method assumes that LV diastolic filling is optimized when mitral valve closure because of LV systole coincides with the end of the Doppler A wave. This approach provides the longest diastolic filling time and allows completion of LV end-diastolic filling prior to LV contraction. The method does not assess forward output. Ritter’s method has been evaluated in patients with normal LV ejection fractions and dual-chamber pacemakers for an AV block.\(^{11,12}\) In a study evaluating 40 CRT patients with severe HF, the optimized AV delay by the aortic velocity–time integral (VTI) method was significantly longer than that calculated from the Ritter method.\(^{6}\) In CRT patients with normal or short PR interval (\(<150\) ms), this method cannot ensure biventricular pacing with the long AV delay used for the second part of the protocol. Furthermore, it is difficult to determine whether the A wave is abbreviated or not as increased LVEDP in HF promotes mitral valve closure immediately after the A wave. The Ritter method is also difficult to carry out at high heart rates. Finally, there is evidence that it may not represent the maximum achievable haemodynamic benefit.\(^{6}\)

Iterative method
This method involves programming a long AV delay and then shortening it by 20 ms increments, when monitoring pulse wave Doppler transmitral inflow until truncation of the A wave is noted.\(^{13}\) Optimal AV delay is then identified by lengthening the AV delay in 10-ms increments until A wave truncation is no longer present.\(^{10}\)

Velocity–time integral methods
AV delay optimization with Doppler echocardiography is often done by assessing the VTI of flow across the LV outflow tract, aortic, or mitral valves.\(^{4,6,14–19}\) Such VTI measures are directly proportional to LV stroke volume. The optimal AV delay is associated with the largest VTI. LV stroke volume can be estimated by measuring the diameter of the LV outflow tract (in the parasternal long axis view) to calculate its area (assumed circular) and by using pulsed wave Doppler to interrogate the LV outflow tract (in the apical 5-chamber view) to obtain its VTI. The product of LV outflow tract area and its VTI gives stroke volume. Small changes in the angle of incidence between the outflow jet and ultrasound beam or a small measurement error of LV outflow tract diameter can introduce significant inaccuracy into the calculated stroke volume. Thoroughly trained sonographers are needed to maintain consistency in methodology.

Aortic VTI obtained by continuous wave Doppler is more reproducible than LV outflow tract VTI measured by pulsed wave Doppler. Changes in aortic VTI can serve as a surrogate for changes in stroke volume as it is directly proportional to the LV outflow tract VTI. The mitral VTI is usually obtained from the apical 4-chamber view using pulsed wave Doppler to sample at the tip of the mitral valve leaflets. Diastolic flow including both the E and A waves are

**Diastolic pressure exceeds left atrial pressure during atrial relaxation, a situation producing diastolic mitral regurgitation, a decrease in preload LV filling.** Diastolic flow including both the E and A waves are

**Short atrioventricular delay**
A short AV delay results in premature LV contraction, causing premature mitral valve closure which compromises the left atrial contribution to LV filling. LV filling during atrial contraction is interrupted by LV contraction (early mitral valve closure) resulting in truncation of the relatively late A wave on the trans-mitral Doppler signal and a relatively early E-wave so that the LV filling time lengthens with widely separated E and A waves (Figure 1). The low LVEDP and loss in preload are reflected in a decreased LV \((dP/dt)_\text{max}\) and LV stroke volume.

**Echocardiographic methodology**
There are many ways of optimizing the AV delay. Currently, there is no universally accepted gold standard.\(^{4,6–9,10}\) The results may vary according to the recording technique and therefore vary substantially in performance.\(^{6}\) The method used often depends on local expertise and resources. The American Society of Echocardiography recently proposed a simplified pulsed Doppler mitral inflow technique because no consensus currently exists for the routine performance of AV optimization after CRT.\(^{10}\) It is presently unclear which patients do not require AV optimization based on the duration of their PR interval. Timing of mechanical left atrial to LV events during CRT may differ markedly, depending on whether the right atrium is sensed or paced. Thus, AV interval programming becomes even more complex if the patient is expected to alternate between atrial sensed and paced events.
included in the VTI. Stroke volume cannot be derived from the mitral VTI.

A randomized, prospective, single-blind trial compared AV optimization guided by aortic VTI at AV intervals between 60 and 200 ms (n = 20) to an empirically programmed AV interval of 120 ms (n = 20). Both groups were programmed to the biventricular VDD mode. When comparing echo Doppler-guided optimization to an empirical AV delay, aortic VTI improved by 4.0 ± 1.7 cm vs. 1.8 ± 3.6 cm (P < 0.02), LV EF increased by 7.8 ± 6.2% vs. 3.4 ± 4.4% (P < 0.02), and after 3 months, New York Heart Association (NYHA) functional class improved by 1.0 ± 0.5 vs. 0.4 ± 0.6 class points (P < 0.01) and quality-of-life score improved by 23 ± 13 vs. 13 ± 11 points (P < 0.03).

Atrioventricular delay optimization guided by LV dP/dt determination

The peak rate of rise of LV pressure during isovolumetric contraction [dP/dt]max is a sensitive index of LV contractility. It is measured during cardiac catheterization but can also be estimated non-invasively from the continuous-wave Doppler mitral regurgitation velocity envelope (Figure 2).21

Velocity–time integral of transmitial flow

Jansen et al.8 evaluated various echocardiographic methods of AV delay optimization to determine which resulted in the highest LV (dP/dt)max measured with a sensor-tipped pressure guide wire in 30 HF patients <24 h after CRT device implantation. Echocardiographic methods included VTI of transmitial flow, diastolic filling time, VTI of the LV outflow tract or aorta, and Ritter’s formula. The maximal VTI of mitral inflow was found to be the most accurate method based on LV (dP/dt)max (Figure 3).

Fusion with the spontaneously conducted QRS complex

van Gelder et al. investigated the haemodynamic effect of intrinsic conduction during LV pacing when compared with biventricular pacing in 34 patients with NYHA functional class III or IV, sinus rhythm with normal AV conduction, left bundle branch block, QRS > 130 ms, and optimal medical therapy. LV (dP/dt)max index was measured invasively during LV and simultaneous biventricular pacing. The AV interval was varied in four steps starting with an AV interval 40 ms shorter than the intrinsic PQ time and increased with 25% for each step causing progressive fusion between paced complexes and intrinsic AV conduction. LV (dP/dt)max was higher with LV than biventricular pacing provided that LV pacing was associated with ventricular fusion caused by intrinsic activation via the right bundle branch.

The role of possible fusion on a long-term basis was investigated by Pires et al.23 who evaluated the predictors of a CRT response. One of the factors was the absence of first-degree AV block which was associated with a statistically significant better response to CRT. It is unclear why CRT patients with first-degree AV block did not fare as well as those with normal AV conduction. The long PR interval may be a marker of more advanced disease. On the other hand, an enhanced haemodynamic response in patients with normal AV conduction might have been related to ‘concealed resynchronization’ or fusion as suggested by Kurzidim et al.24

The clinical implications of fusion are unclear. At present, it is best to programme the AV delay to avoid all forms of ventricular fusion until more data are available, and a reliable way is found to synchronize right bundle branch activity with LV stimulation. Some degree of fusion may be inevitable in patients with a short PR interval where it may be acceptable short of AV junctional ablation that would guarantee the elimination of fusion. Although the harmful or beneficial haemodynamic impact of fusion cannot be predicted in individual patients, we believe that programming the AV delay to promote fusion may be worthwhile on a trial basis in a patient with a suboptimal response to CRT (no cause found) where depolarization occurs entirely by pacing at the exclusion of fusion.

Rate adaptation and exercise

Exercise testing in CRT patients is technically difficult and inconvenient. There is preliminary evidence in acute studies suggesting that the short AV delay at rest should be prolonged in many patients during exercise to achieve optimal LV systolic performance.25 Whinnet et al.26 optimized the AV delay on exercise with a non-echocardiographic method. They were able to predict the optimal AV delay on exercise with a series of pacing measurements at rest. Interestingly, in their 20 patients, the optimal AV delay on exercise was shorter than that at rest in 11 patients, longer in eight and unchanged in one. This is in contrast to the proven benefit of programming rate-adaptive shortening of the AV delay in patients with conventional DDDR pacemakers. The dynamic changes of LV dyssynchrony during the exercise may partially explain what appears to be paradoxical behaviour of the AV delay on exercise.27 In the meantime, it might be wise to programme the CRT devices initially without dynamic shortening of the AV delay in patients with normal sinus node function and reconsider this approach according to the subsequent

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**Figure 2** Doppler-derived dP/dt determined by measuring the time difference (ΔT) between two points on the continuous-wave mitral regurgitation spectral signal corresponding to 1 and 3 m/s. These points correspond to pressure gradients between the left ventricle and left atrium of 4 and 36 mmHg according to the modified Bernoulli equation (ΔP = 4v²). dP/dt is determined by this change in pressure (32 mmHg) divided by the time difference. P is the pressure, T the time, and v the velocity. Reproduced with permission from Barold et al.48
There are no data about the long-term stability of the optimal AV interval during activity states. In some CRT patients with severe chronotropic incompetence, DDDR pacing with a rate-adaptive AV delay may provide incremental benefit on exercise capacity. Therefore, if atrial pacing is likely to occur during the exercise, a treadmill test can be performed to demonstrate the optimal adjustment of the rate-adaptive AV delay.

Long-term evaluation of the atrioventricular delay

The optimal follow-up and long-term programming of the AV delay is uncertain. There is preliminary evidence suggesting that the optimal AV and VV interval changes with time in patients undergoing CRT. Biventricular stimulation will result in LV reverse remodelling with changes in LV end-diastolic and end-systolic volumes and pressures over time. This dynamic process also includes autonomic changes and may take several months before a new steady state of maximum improvement in LV function is reached. The status of AV interval optimization should therefore be assessed periodically. Further studies are needed to determine how often the AV interval needs to be optimized.

Intra- and interatrial conduction delay

Intra- and interatrial conduction delays are now being recognized as important abnormalities in HF patients. These abnormalities of conduction should be suspected in patients with extensive atrial myocardial disease and those with prior surgical procedures such as mitral valve replacement and maze procedure.

Interatrial conduction delay

Interatrial conduction delay is characterized by a wide and notched P wave (>120 ms) traditionally in lead II with a wide terminal negative deflection in lead V1. Interatrial conduction time is also measured as the activation time from the high right atrium or onset of the P wave to the distal coronary sinus (60–85 ms). With interatrial conduction delay, left atrial contraction occurs late and even during LV systole. Consequently, the need to programme a long AV delay to compensate for delayed left atrial contraction can preclude resynchronization because of competing spontaneous AV conduction. When the ECG suggests interatrial conduction delay, one should look for delayed left atrial activation at the time of CRT implantation so that the atrial lead can be placed in the interatrial septum where pacing produces a more simultaneous activation of both atria and abbreviates total atrial activation time. In the presence of established CRT with an atrial lead in the right atrial appendage, restoration of mechanical left-sided AV synchrony requires simultaneous biatral pacing performed by the implantation of a second atrial lead.
either in the proximal coronary sinus of low atrium near the coronary sinus to preempt left atrial systole.\textsuperscript{40,41} Difficult cases can be managed by AV nodal ablation to permit extension of the AV delay to promote mechanical left-sided AV synchrony although biventricular implantable cardioverter defibrillators may limit the maximum programmable AV delay.\textsuperscript{42}

**Intra-atrial conduction delay (late atrial sensing)**

In some patients with right intra-atrial conduction delay, conduction from the sinus node to the right atrial appendage (site of atrial sensing) is delayed in the absence of significant conduction delay from sinus node to the AV junction or sometimes to the left atrium. In this situation, left atrial activation may take place or may even be completed by the time the

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**Figure 4** Diagrammatic representation of simultaneous biventricular pacing (Panel 1) showing the impact of prolonged left ventricular (LV) latency interval and slow conduction (due to scar tissue or myocardial fibrosis) from the LV pacing site. (A) During uncomplicated simultaneous biventricular pacing, impulse propagation from both pacing sites produces balanced activation (fusion from the two pacing sites) of right ventricular (RV) and left ventricular wavefronts. (B) In the presence of a prolonged left ventricular latency interval (dashed black arrow), left ventricular activation occurs relatively late and the right ventricular wavefront depolarizes more myocardium causing a longer biventricular activation time. (C) Slow conduction in the proximity of the left ventricular pacing site produces a similar effect as in (B). (D) Coexistence of abnormal left ventricular latency interval and slow conduction at the left ventricular pacing site. Major portions of the left ventricle are now depolarized by the right ventricular wavefront with minimal fusion from left ventricular pacing. This produces further prolongation of the biventricular activation time. Panel 2. Compensatory programming of the interventricular interval for an increased left ventricular latency interval (dashed black arrow). (A) Simultaneous activation of both ventricles (shown on the left) results in relatively late left ventricular activation and more myocardium depolarized by the right ventricular wavefront. (B) Interventricular programming permits left ventricular pre-excitation to compensate for the abnormal left ventricular latency interval. Both ventricles are activated synchronously resulting in a shorter biventricular activation time. (C) Monochamber left ventricular pacing may induce some degree of fusion with native conduction on the right side of the heart depending on the programmed atrioventricular delay. This approach can potentially provide improved haemodynamics in patients with a markedly prolonged left ventricular latency interval which cannot be overcome by programming maximum interventricular intervals for left ventricular pre-excitation. A high left ventricular output may somewhat reduce the latency interval. BIV, biventricular; LV, left ventricle; RV, right ventricle; CRT, cardiac resynchronization therapy; spont, spontaneous. Modified with permission from Herweg \textit{et al.}\textsuperscript{47}
device senses the right atrial electrogram. The AS–VS interval (where AS is the atrial sensed event and VS the ventricular sensed event) becomes quite short because AS is delayed but VS is not. Thus, it may be impossible to programme an optimal AV delay without interference from the emergence of a comparatively early VS event because of competing spontaneous conduction. In such a case, VS produces potentially harmful ventricular fusion or incomplete cardiac resynchronization. In a difficult situation, ablation of the fast pathway of the AV node or complete AV junctional ablation can be performed with satisfactory results.42

Impact of interventricular interval programming on the effective atrioventricular delay

In most of the devices (all American manufacturers except Boston Scientific/Guidant), the ventricular channel advanced by VV interval programming will be paced at the PV/AV delay seen on the programmer. In Guidant devices, PV/AV timing applies to the RV channel and if LV activation is advanced by VV interval programming, the LV AV delay can be calculated by subtracting the VV interval from the PV/AV delay shown in the programmer.43

Programming the interventricular interval

The usefulness of programming the VV interval is controversial in view of two recent trials showing no benefit.44,45 The recent DECREASE-HF multicentre randomized trial (which evaluated 306 CRT patients at the end of 6 months) revealed no benefit of VV programming.45 However, the VV interval was programmed on the basis of intrinsic conduction only and the spontaneous QRS complex had to be ≥150 ms for enrolment.45 In contrast, the recent INSYNC III study demonstrated that LV stroke volume was increased with sequential CRT by individualizing the optimal VV interval echocardiographically in each patient.46 Other assessments of the role of VV programmability reported in the literature tend to be difficult to evaluate because of the varied cut-off of the spontaneous QRS duration for inclusion in the various studies, the different testing procedures, and methodology of concomitant AV delay optimization.47,48 Nevertheless, they suggest that VV programming may be beneficial in some patients. Despite conflicting results and a rather limited or moderate improvement in LV function or stroke volume, LV optimization may prove beneficial in some patients with an suboptimal response to CRT in whom no cause is found. It may partially compensate for less than optimal LV lead position by tailoring ventricular timing and may also correct for individual heterogeneous ventricular activation patterns including a prolonged LV latency interval and an area of slow conduction related to scarring near the site of LV pacing49 (Figure 4).

Although VV programmability may produce only a limited response, it may be important clinically. Its benefit appears additive to AV interval optimization. The optimal VV delay

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**Figure 5** Interventricular interval delay using left ventricular outflow tract (LVOT) measurements of blood flow velocities for estimation of stroke volume (SV). Stroke volume is exponentially related to the left ventricular outflow tract diameter and directly to the velocity–time integral (VTI) of the left ventricular outflow tract. Variation of the interventricular interval (VV) interval affects the stroke volume as evidenced by varying volume–time integral measurements that can serve as surrogate markers for resynchronization. The optimal interventricular interval in this example is derived from pacing the right ventricle (RV) 40 ms before the left ventricle (LV). The optimal atrioventricular delay becomes equal to (optimal AS-LVP) minus the 40 ms interventricular interval. LVP, monochamber LV pacing. Reproduced with permission from Gassis S, Leon AR. Cardiac resynchronization therapy: strategies for device programming, troubleshooting and follow-up. J Interv Card Electrophysiol 2005;13:209–22.
may change with the passage of time, and individual changes cannot be accurately predicted. Detailed regular re-evaluations and periodic reprogramming seem appropriate.

Programming the VV interval is guided by the same techniques as AV delay optimization using mostly the aortic VTI method (Figure 5). Determination of the extent of residual LV dyssynchrony after VV programming requires more sophisticated echocardiographic techniques such as tissue Doppler imaging. Contemporary biventricular devices permit VV programming usually in steps from +80 ms (LV first) to −80 ms (RV first). These values are based on the concept that CRT with sequential rather than simultaneous pacing may yield better mechanical efficiency. Programming VV timing requires determination of the optimal AV delay first (usually from the time of atrial sensing to the LV stimulus) during monochamber LV pacing. This AV delay is then used during VV optimization if the RV is not pre-excited simply because the LV is either activated simultaneously with the RV (VV = 0) or is pre-excited.

The optimal VV delay has shown a heterogeneous response with great variability from patient to patient. The optimal VV delay cannot be identified clinically in the majority of patients. Consequently adjustment of the VV delay must be individualized. Although VV programmability produces a rather limited improvement in LV function or stroke volume, in individual patients with a less than desirable CRT response it can sometimes lead to significant improvement. VV interval optimization aims at decreasing LV dyssynchrony, providing more simultaneous LV activation and reducing mitral regurgitation in some patients. The range of optimal VV delays is relatively narrow and must be individualized. Although VV programmability produces a rather limited improvement in LV function or stroke volume, in individual patients with a less than desirable CRT response it can sometimes lead to significant improvement.

Prior to VV interval optimization, consideration should be given to pacing lead configuration and the presence of anodal capture (which reduces the VV interval to zero). Further, careful analysis of the 12-lead ECG during RV, LV, and biventricular pacing is crucial.

**Interventricular interval optimization on exercise**

A recent study assessed the impact of sequential biventricular pacing during exercise. Simultaneous biventricular pacing was optimal during exercise in only ~25% of patients. Most of the improvement was observed with short VV delays, ranging from 12 to 20 ms. Optimized sequential biventricular pacing offered substantial additional benefit when considering the aortic VTI and mitral regurgitation. Differences between resting and exercise optimization were observed in more than half of the patients.

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