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CHAPTER 7

Why, how and when do we need to optimize the setting of cardiac resynchronization therapy?

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1. INTRODUCTION

At present, up to 40% of patients do not show improvement in left ventricular (LV) performance or clinical symptoms after cardiac resynchronization therapy (CRT). This suboptimal response may be secondary to several pre-implantation and implantation issues such as lack of LV mechanical dyssynchrony, the presence of substantial scar tissue or non-optimal LV lead position. Furthermore, the presence of suboptimal LV filling time (atrioventricular [AV] dyssynchrony) or remaining LV dyssynchrony after CRT may reduce benefit of this therapy. Current CRT devices allow manipulation of the AV and interventricular (VV) timings in order to maximize LV filling and stroke volume. However, multiple single center and few multicenter trials have provided controversial data on the beneficial effects of AV and VV intervals optimization on cardiac performance and clinical status. In addition, multiple methodologies have been proposed to optimize AV and VV intervals but no consensus has been reached on which methodology should preferably be used. Finally, whether AV and VV intervals may be evaluated and adjusted periodically remains also controversial. The present article reviews the clinical evidence on AV and VV interval optimization by addressing why, how and when we need to optimize AV and VV intervals.

2. WHY DO WE NEED TO OPTIMIZE CRT SETTING?

Management of heart failure patients after CRT implantation should include the evaluation of the effects of CRT on LV hemodynamics and mechanics. A suboptimal programming of the AV and/or VV interval may partially contribute to the presence of AV or LV dyssynchrony and, consequently, may curtail the beneficial effects of CRT. The hemodynamic importance of AV interval optimization was first demonstrated in studies with dual chamber pacemakers; next, these benefits were confirmed also in CRT recipients. Auricchio et al. demonstrated in 39 heart failure patients treated with CRT that the maximum rate of increase of LV pressure (dP/dt max) and pulse pressure were measured at different AV and VV intervals. The maximum hemodynamic benefit occurred at the AV interval that provided the optimal LV diastolic filling and did not decrease the LV end-diastolic pressure. In addition, several prospective studies have demonstrated the benefits of tailored optimized sequential biventricular pacing strategies. In 41 heart failure patients receiving CRT, Bordachar et al. evaluated the effect of several sequential VV intervals on LV dyssynchrony, as assessed with pulsed-wave tissue Doppler imaging (TDI) and hemodynamics (cardiac output and mitral regurgitation). Changes in LV dyssynchrony were strongly correlated with changes in
cardiac output and mitral regurgitation. An optimized VV interval provided the most LV synchronous contraction, the largest cardiac output, and significantly reduced the severity of mitral regurgitation.\textsuperscript{10}

### 3. HOW TO OPTIMIZE THE AV AND VV INTERVALS?

#### 3.1 AV interval optimization

About 20-30\% of the resting stroke volume in heart failure patients is due to atrial contraction. A too short AV interval results in early LV contraction and mitral valve closure, thereby reducing left atrial contribution to LV filling (resulting in truncation of the A wave on pulsed-wave Doppler transmitral inflow). In contrast a too long AV interval is characterized by early left atrial contraction, with fusion of E and A wave, with reduction of LV filling time and possible induction of diastolic mitral regurgitation. Both these conditions result in impaired LV filling with a reduction in LV perfor-

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**Figure 1.** Effect of AV interval programming on echocardiographic pulsed-wave Doppler transmitral inflow. An optimal AV interval (upper panel) permits completion of the left atrial contraction and the mitral valve closes at the end of the A wave. When the AV interval is too long (middle panel), left atrial contraction occurs prematurely, and the A wave is superimposed to the E wave (fusion of E and A wave). The LV diastolic filling time is shortened and diastolic mitral regurgitation can occur. In contrast, when the AV interval is too short (lower panel), LV contraction occurs earlier and the mitral valve closes before completion of left atrial contraction. On pulsed-wave Doppler recordings of the transmitral inflow truncation of the A wave is observed.
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The optimal AV interval is the shortest AV delay that does not compromise left atrial contribution to the LV diastolic filling (Figure 1). Several echocardiographic and non-echocardiographic methods have been proposed to optimize the AV interval (Table 1). Using echocardiography, the AV interval can be optimized by maximizing LV diastolic filling or LV hemodynamics. The iterative method evaluates the effects of the AV interval on LV diastolic filling. A long AV interval is first programmed and the LV diastolic filling pattern is evaluated on the pulsed-wave Doppler transmitral inflow. Thereafter the AV interval is shortened by increments of 20 ms until truncation of the A wave occurs. The optimal AV interval is then identified by increasing the AV delay in 10 ms increments until the A wave is not longer truncated (Figure 2). The multicenter, randomized CARE-HF trial optimized the AV interval with this method. However, the effects of performing routinely AV interval optimization on clinical outcome or LV systolic function and remodeling have not been reported. The Ritter’s method is also based on pulsed-wave Doppler recordings of the transmitral inflow. With this method, two extreme AV intervals are programmed: a long AV interval with A wave attenuation (AV_long) and a short AV interval with A wave truncation (AV_short). For each

Table 1. AV interval optimization methods

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Abbreviations = LV = left ventricular; VTI = velocity time integral.

Figure 2. AV interval optimization with the iterative method. From a long AV interval (left panel), the AV interval is shortened by 20 ms steps until the A wave is truncated (middle panel, yellow arrow). Thereafter, the AV interval is increased to obtain the optimal AV interval (the shortest AV interval without truncation of the A wave) (right panel).
AV interval, the time between the QRS complex onset to the completion of the A-wave is measured. The optimal AV interval is calculated with the formula: $$AV_{\text{short}} + [(AV_{\text{long}} + QA_{\text{long}}) - (AV_{\text{short}} + QA_{\text{short}})]$$ (Figure 3). This method has been used in several multicenter trials (MUSTIC, MIRACLE, InSyncIII). However, the clinical use of this method may be limited in patients with high heart rate or with an intrinsic AV interval <150 ms. In addition, measurement of LV filling volume may be a useful method to optimize the AV interval. On pulsed-wave Doppler recordings of the transmitral inflow, the measurement of the velocity time integral (VTI) is a surrogate for LV filling volume (Figure 4). The optimal AV interval is defined by the largest VTI. Another method to optimize AV interval is the method described by Meluzin. The AV interval is optimized by aligning the end of LV filling and the onset of ventricular contraction. On pulsed-wave Doppler recordings of the transmitral inflow, a long AV interval is defined as the maximum AV delay that allows full ventricular capture (lowered by 5-10 s). Thereafter, the time between the end of the A wave and the onset of the mitral regurgitation spectral signal is measured ($t_1$). The difference between the long AV interval and the $t_1$ yields the optimal AV interval. The use of this method in clinical practice may be limited by the need for detectable mitral regurgitation signal. Echocardiographic methods that optimize AV interval based on LV hemodynamics include measurement of stroke volume on pulsed- or continuous-wave Doppler recordings of the LV outflow tract (LVOT) or the non-invasive measurement of LV $dP/dt_{\text{max}}$ on continuous-wave Doppler spectral.
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The product of the LVOT cross-sectional area and VTI measured on the pulsed- or continuous-wave Doppler recordings of the LVOT or aortic valve yields the stroke volume. The optimal AV interval is defined by the largest stroke volume. The measurement of the LV dP/dt_{max} provides information on LV contractility. Non-invasive measurement of this parameter is performed on the continuous-wave Doppler spectral signal of the mitral regurgitation. First, the time

**Figure 4.** Mitral inflow velocity time integral to optimize the AV interval. The mitral inflow velocity time integral (VTI) is a surrogate for LV filling volume, assuming a constant mitral valve area. The optimal AV interval yields the largest mitral VTI.

**Figure 5.** Echocardiographic methods to optimize the AV interval based on LV systolic function. Measurement of LV dP/dt_{max} as indicator of LV performance that permit AV interval optimization.
The difference between two points of the spectral signal is measured (usually between 1 m/s and 3 m/s time points). Then, the pressure gradient between these two points is calculated according to Bernoulli equation. The optimal AV interval corresponds to the highest value of LV $dP/dt_{\text{max}}$. Finally, the measurement of the myocardial performance index may be a useful method to optimize the AV interval. The myocardial performance index is a comprehensive measurement of LV function. This index is calculated as the sum of isovolumic contraction and relaxation times divided by the ejection time (Figure 6). The optimal AV interval is defined by the lowest myocardial performance index.

Several non-echocardiographic methods have been proposed to optimize AV interval. The aforementioned measurement of the LV $dP/dt_{\text{max}}$ can be performed invasively. During CRT device implantation, this parameter can be measured and the AV interval can be set. However, this invasive approach limits its usability in routine clinical follow-up. Acoustic cardiography was proposed as fast and reproducible method to optimize CRT setting. Moreover, impedance cardiography optimizes the AV interval by measuring changes in the impedance of an alternating current applied across the thorax of the patient. These changes indicate the cardiac output. With the use of intracardiac electrograms the optimal AV interval can be defined by measuring electrical conduction delays (i.e., AV interval and QRS duration) that maximize LV hemodynamics.
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### 3.2 VV interval optimization

VV interval is the time delay between the contraction of the right and LV. In normal subjects, the right and left ventricle are not simultaneously activated. In heart failure patients (particularly in the presence of left bundle branch block) the electrical activation delay between both ventricles is more pronounced with a prolongation of LV pre-ejection time and a shortening of LV ejection time. CRT partially reduces this electrical activation delay, by pacing both the right and left ventricle. However, the first generation of CRT devices could not differentiate the pacing channels and both ventricles were always paced simultaneously. The recent generation of CRT devices allows tailoring the activation delays between right and left ventricle (VV interval), aiming a more physiological activation. The most common methods used to optimize VV interval are based on the assessment of surrogates of stroke volume or cardiac output (LVOT VTI) or on the assessment of mechanical dyssynchrony (Table 2).

The echocardiographic method based on the assessment of LV systolic performance (LVOT VTI) has been discussed in the AV interval optimization section. Similarly, the largest LVOT VTI defines the optimal VV interval (Figure 7).

In contrast to AV interval optimization, measurement of mechanical dyssynchrony at different levels (interventricular and intra-LV dyssynchrony) may constitute a further helpful tool to select the optimal VV interval setting. Interventricular dyssynchrony is assessed by the difference between the left and right pre-ejection time measured with pulsed-wave Doppler echocardiography at LVOT and right ventricular outflow tract, respectively. Intra-LV dyssynchrony mainly measured with TDI is also

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Abbreviations = LV = left ventricular; TDI = tissue Doppler imaging; VTI = velocity time integral.
used as effective means of guiding VV interval optimization.\textsuperscript{13, 25} The time difference between peak systolic velocity of 2 or 4 opposing walls or the standard deviation of time to peak systolic velocity of 12 LV segments are the most common methods to measure intra-LV dyssynchrony (Figure 8A). In addition, speckle tracking echocardiography and real time 3-dimensional echocardiography are valuable novel techniques for intra-LV dyssynchrony assessment but so far no studies investigated the role of these techniques for VV interval optimization (Figure 8 B, C).\textsuperscript{26}

Several non-echocardiographic methods have been also proposed to optimize VV interval (Table 2). However, the majority of these methods are not routinely used in clinical practice because they require invasive measurements (i.e. invasive LV dP/dt\textsubscript{max}) or are time-consuming or not widely available (i.e radionuclide ventriculography, acoustic cardiography or finger photo-pletismography).\textsuperscript{24, 21, 27, 28}

Among the non-echocardiographic methods, surface ECG derived methods are the simplest and widely available. Different parameters have been proposed, with measurement of QRS duration at surface ECG in different VV intervals as the easiest method.\textsuperscript{29, 30} A substantial agreement was shown between the selection of the optimal VV interval based on the narrowest QRS duration and on LVOT VTI measured with echocardiography among 5 tested VV intervals (LV pre-excitation of 80 and 40 ms, simultaneous pacing, and right ventricle pre-excitation of 40 and 80 ms; Figure 9).\textsuperscript{29} This study proposed a combined approach for VV interval optimization

Figure 7. Example of VV interval optimization by measuring stroke volume and cardiac output. Velocity-time integral (VTI) at left ventricular outflow tract (LVOT) is measured with pulsed-wave Doppler echocardiography. Stroke volume can be derived by multiplying the cross sectional area (CSA) with VTI. Cardiac output can be derived by multiplying stroke volume with heart rate (HR). CSA = π/4 X LVOT diameter; Stroke volume = CSA X VTI; Cardiac output = stroke volume X HR.
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**Figure 8.** Examples of VV interval optimizations by measuring LV mechanical dyssynchrony. Panel A. Tissue Doppler imaging (left) permits the assessment of the time difference between peak systolic velocities of two opposing walls (septal and lateral wall). Panel B. Speckle-tracking echocardiography (middle) permits the assessment of radial dyssynchrony from the parasternal short-axis view at papillary muscle level. Radial dyssynchrony is defined as the time difference between the peak systolic radial strain of the antero-septal and posterior wall. Panel C. Real time 3D echocardiography (right) permits the assessment of systolic dyssynchrony index (SDI). The LV 3D model is automatically subdivided into 17 standard wedge-shaped (apart from the apex) subvolumes. For each volumetric segment, the time interval to reach the minimum systolic volume is automatically calculated. The standard deviation of these timings for 16 segments (excluding the true apex) is expressed as a percentage of the cardiac cycle, obtaining the SDI.

**Figure 9.** Example of VV interval optimization by measuring QRS duration at surface ECG. The Figure shows QRS complex in D1 and V1 leads for 5 VV intervals. Among these 5 QRS duration measurements, the value corresponding to the narrowest QRS duration was considered as the ECG-optimized VV interval. In this example the ECG-optimized VV interval was simultaneous (LV and RV VV interval = 0 ms). LV: left ventricle; RV: right ventricle.
with ECG and echocardiography in 2 steps: first VV interval may be selected by the ECG recording at the 5 VV intervals (LV pre-excitation of 80 and 40 ms, simultaneous pacing, and right ventricle pre-excitation of 40 and 80 ms); next the interval with the greatest QRS duration shortening could be scanned in depth with pulsed-wave Doppler echocardiography (20 ms steps) to determine the optimal VV interval. Such an approach may save time reducing the number of VV intervals that should be tested with echocardiography.99

Finally, several methods based on automated algorithms typical of different manufacturers have been proposed for VV interval optimization, the majority of them are based on the intracardiac electrograms.22, 31-33

3.3 Which method?

At present there are no gold standard methods for AV and VV optimization. Recently, Thomas et al. compared different echocardiographic measurements used for VV interval optimization.34 The authors showed that among different measurements used for VV interval optimization, LVOT VTI and interventricular dyssynchrony were the most feasible (100% and 93% of feasibility, respectively). Furthermore, LVOT VTI resulted the most reproducible with a coefficient of variation of only 3.0%.34 Conversely, Zuber et al. found a poor performance of LVOT VTI as method to optimize CRT settings as compared to acoustic cardiography.21 These controversial results and the absence of a well recognized gold standard method to optimize the setting of the CRT devices claim warrant further larger studies to address this issue.

3.4 Under which conditions?

Preliminary data suggested that AV and VV optimization may improve LV filling and hemodynamic performance. However different physiologic conditions like rest and exercise may markedly change the heart rate and loading conditions of the heart, and therefore some authors hypothesized that in CRT recipients an optimal setting determined at rest may be different during exercise.35, 36 Particularly, the optimal AV interval was shown to be different between rest and during semisupine bicycle exercise in a considerable proportion of patients and the same group also demonstrated a similar behaviour of optimal VV interval that differed in 57% of the patients between rest and during exercise.35, 36 These preliminary observations may have important clinical implications since one of the major benefits of CRT is the improvement of exercise capacity. However, no studies investigated the potential long-term clinical benefit of
this strategy. Furthermore, an important field of research may be the development of CRT devices that, similarly to particular dual chamber pacemakers, are able to find the optimal setting automatically (for both AV and also VV interval), and reset it regularly at rest and during exercise.

3.5 Which interval first?

A recurrent question that was never completely addressed in the various studies, is whether AV optimization should be followed by VV optimization or vice versa (or even simultaneously). Indeed, performing this procedure in different order not necessarily produces the same results. The common clinical practice is to optimize the AV interval first, followed by VV optimization; in all studies, AV and VV intervals were optimized separately. It could be possible however that a method that permits simultaneous optimization of the AV and VV intervals may provide additional hemodynamic benefit.

4. WHEN DO WE NEED TO OPTIMIZE THE CRT SETTINGS?

Preliminary evidence showed that the optimal settings obtained immediately after CRT implantation may change during follow-up. Valzania et al. demonstrated in 14 patients who underwent CRT and were followed for 12 months, that optimal AV and VV intervals changed over time. In particular a difference ≥ 40 ms in the optimal VV interval was observed in 57% of the patients at 12 months follow-up. More recently, Zhang et al. underscored the importance of periodic reassessment of the optimal AV delay in CRT recipients; indeed the optimal AV delay had changed (as compared to acutely after CRT implantation) in 56% of the patients at long-term follow-up.

Therefore, the optimal setting of the CRT devices changes during follow up, as loading LV conditions change over time due to LV (reverse) remodeling. Periodic tailoring of CRT devices seems important in order to maintain or improve a positive hemodynamic effect over the long term, and to enhance benefit from CRT. In the daily practice however, systematic optimization and periodic reassessment of AV and VV intervals may not be feasible, but could be restricted to non-responder patients, to potentially improve the effect of CRT. A practical algorithm to decide when this procedure should be performed is proposed in Figure 10.
Several data from single-center studies showed that the optimal AV settings further improved hemodynamic benefits of CRT. At present, only one single-blind randomized trial investigated the impact of AV delay optimization based on aortic VTI on clinical status 3 months after CRT.\textsuperscript{38} The authors showed that 75% of the patients in the arm with optimized AV delay had an improvement by at least 1 New York Heart Association functional class whereas only 40% of the patients in the arm with empiric AV delay had an improvement by at least 1 New York Heart Association functional class (p < 0.03).\textsuperscript{38}

**Figure 10:** Algorithm to decide when to optimize AV and VV interval during follow-up
LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association

### 5. CLINICAL EVIDENCE AND TRIALS ON AV AND VV INTERVAL OPTIMIZATION
Similar to AV interval optimization, several data from small single center studies demonstrated that sequential CRT after VV interval optimization, rather than simultaneous CRT, may acutely further improve LV systolic performance (stroke volume, \(dP/dt_{\text{max}}\)) and LV dyssynchrony.\(^4\) Sogaard et al.\(^{13}\) showed for the first time the additional benefits on the LV systolic function of the sequential biventricular pacing after VV optimization performed using tissue tracking echocardiography. However, Vidal et al.\(^{25}\) in single center, nonrandomized clinical study did not show differences in the numbers of CRT non-responders between patients with and without AV and VV intervals optimized.

Finally, 3 multicenter trials investigated the benefits of VV interval optimization on long-term outcomes (InSyncIII, RHYTHM II ICD and DECREASE-HF).\(^{17, 39, 40}\) The InSyncIII clinical study\(^{17}\) evaluated the clinical effect of optimized sequential CRT as compared to the control group (optimal pharmacological medical therapy alone) and to the treatment group (simultaneous biventricular pacing) of the MIRACLE trial. They demonstrated that: 1. optimized sequential CRT significantly improved functional status as compared to the control group; 2. the optimal VV interval showed a relative narrow range between right ventricular pre-excitation of 40 ms and LV pre-excitation of 40 ms, with a higher prevalence of LV pre-excitation; 3. controversial results about the clinical benefits of optimized sequential CRT as compared to simultaneous biventricular pacing (optimized sequential CRT significantly improved only the 6 minute walking distance but not NYHA functional class or quality of life).

In the RHYTHM II ICD study\(^{39}\) CRT recipients were included randomly assigned in a 1:3 ratio to receive simultaneous biventricular pacing or optimized sequential CRT. After AV interval optimization based on LV filling pattern, optimal VV interval was set at the maximum stroke volume derived by LVOT VTI. The authors evaluated the improvement in clinical end-points, such as NYHA class and 6 minute walking test, after 3 and 6 months follow-up. Similar to InSync III, no additional clinical benefit was demonstrated by the optimized sequential CRT over the simultaneous biventricular pacing.

The DECREASE-HF trial\(^{40}\) evaluated 306 patients with advanced heart failure and QRS duration \(\geq 150\) ms comparing simultaneous biventricular pacing, optimized sequential CRT, and LV pacing alone. Although all 3 pacing modalities led to reduced LV size and improved LV systolic function, there was a trend toward a greater benefit in patients with sequential and simultaneous pacing as compared to LV pacing alone. Furthermore, despite the trial was not designed to specifically compare simultaneous biventricular pacing vs. optimized sequential CRT, no significant differences between these 2 pacing modalities were observed in terms of improvement of LV size and function after 6 months of CRT. Of interest in this trial, the VV interval was
programmed based on intracardiac electrocardiograms at the time of the implantation and was not individually optimized according to the hemodynamic response. In light of this evidence, AV and VV interval optimization may be beneficial in some groups of heart failure patients treated with CRT, improving the clinical status and LV performance. Non-responder patients and ischemic heart failure patients with extensive myocardial scar tissue may benefit most likely from VV interval optimization. Particularly, in ischemic heart failure patients, the inter- and intraventricular conduction of the electrical pulse is very slow and may require larger LV pre-excitation.

Finally, whether AV and VV interval optimization may result in better long-term outcome awaits further studies.

6. FUTURE PERSPECTIVES AND CONCLUSIONS

Single center studies pointed out the additional hemodynamic benefits provided by the optimized CRT setting. Several echocardiographic and non-echocardiographic techniques have been used to perform this operation but so far there is no accepted gold standard method. In addition, what are the best physiologic conditions (rest or during exercise) to perform the AV and VV optimization and which interval should be optimized first, are issues that still need further study. Furthermore, it has been demonstrated that optimal CRT settings may change during follow-up, but when repeat optimization should be performed is unclear. Thus far, the available multicenter trials did show modest clinical benefits of AV and VV interval optimization at mid- or long-term follow-up. It remains to investigate whether AV and VV interval optimization may improve the long-term survival.
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