Atrioventricular and interventricular delay optimization in cardiac resynchronization therapy: physiological principles and overview of available methods

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Abstract In this review, the physiological rationale for atrioventricular and interventricular delay optimization of cardiac resynchronization therapy is discussed including the influence of exercise and long-term cardiac resynchronization therapy. The broad spectrum of both invasive and non-invasive optimization methods is reviewed with critical appraisal of the literature. Although the spectrum of both invasive and non-invasive optimization methods is broad, no single method can be recommend for standard practice as large-scale studies using hard endpoints are lacking. Current efforts mainly investigate optimization during resting conditions; however, there is a need to develop automated algorithms to implement dynamic optimization in order to adapt to physiological alterations during exercise and after anatomical remodeling.

Keywords Cardiac resynchronization therapy · Heart failure · Physiology · Atrioventricular delay · Interventricular delay

Introduction

In patients with symptomatic systolic heart failure and prolonged QRS duration, cardiac resynchronization therapy (CRT) has proven to be of additional value on top of recommended medical therapy [1, 2]. Nevertheless, there remain a considerable number of non-responders to CRT that can be as high as 30% [3]. The non-response can be partly caused by inappropriate settings of atrioventricular (AV) and interventricular (VV) intervals leading to persistent atrioventricular, interventricular and intraventricular dysynchrony. In this review, we will discuss the physiological and pathophysiological rationale for AV and VV optimization followed by an overview of available optimization methods.

Physiological electrical activation and mechanical contraction

A coordinate contraction sequence of the heart chambers is facilitated by rapid activation via the specialized conduction system. The cardiac action potential originates in the sinus node and reaches the atrioventricular node (AV node) within 100 milliseconds (ms). Slowing of conducting through the AV node delays the onset of ventricular activation with approximately 80 ms to allow optimal atrial contribution to ventricular preload. Rapid conduction of the electrical impulse through the His bundle, bundle branches and the Purkinje system activates the whole left ventricle (LV) within 60–80 ms. Ventricular activation proceeds from subendocardially located breakthroughs of the bundle branches to the epicardium in a centrifugally and tangentially direction [4].

Cardiac output is dependent on preload (Frank–Starling relation), afterload and myocardial contractility. The latter is not only influenced by neurohormones, but also dependent on heart rate (staircase phenomenon or Bowditch effect) and afterload (Anrep effect). Autonomic and neurohormonal regulatory mechanisms ensure adequate cardiac output under varying physiological conditions. Regulation and feedback is provided by pressure sensors in the venous and arterial vascular system [5].
Sympathetic stimulation at increasing heart rate shortens AV delay and ventricular systole, thus preventing atrial systole to occur against a closed mitral valve during exercise. Shortening of ventricular systole also enables longer ventricular filling time [6].

Pathophysiological electrical activation and mechanical contraction

Apart from decreased myocardial contractility, there are several other causes for decreased cardiac output in heart failure. First, in a subset of patients, there is a disturbance in coordination of atrial and ventricular activation with suboptimal timing of atrial contraction (AV dyssynchrony).

The atrial contraction enhances ventricular preload by optimizing sarcomere length of ventricular myocytes prior to contraction which in turn increases LV stroke volume. This booster function generates an increase in LV end-diastolic pressure at a relatively low mean venous pressure, thus protecting the pulmonary system from edema [7]. In case of a shortened or prolonged AV conduction, this preload enhancement is diminished or even lost. As the atrial booster effect also contributes to timely closure of the atrioventricular valves, a prolonged AV delay can also lead to premature inversion of the atrioventricular pressure gradient resulting in diastolic mitral regurgitation [6, 8].

Secondly, a large number of heart failure patients have ventricular conduction disturbances, predominantly left bundle branch block (LBBB). Although the term “block” suggests an abrupt interruption of conduction, there is a spectrum of conduction abnormalities varying from a proximal barrier to a more diffuse slowing of conduction. As a consequence, the LV is electrically activated throughout myocardial tissue [9]. Compared to the specialized conduction system, conduction velocity in myocardial tissue is slower and the activation front spreads preferentially in a circumferential than in a perpendicular direction [10]. This can lead to mechanical interventricular (and intraventricular) dyssynchrony.

Because of their serial alignment and intimate anatomical relationship, the mechanical properties of both ventricles are influenced by each other. This close interaction is further influenced by the interventricular septum and pericardium. Changes in preload or afterload of one ventricle alter the pressure in the other ventricle [11, 12]. Although this interaction is negligible in the healthy heart, both systolic and diastolic interactions are augmented in case of heart failure [13, 14]. Difference in activation timing with the right ventricle (RV) contracting earlier than the LV (as with LBBB) deteriorates LV function [15, 16].

Thirdly, asynchronous electrical activation of the LV in case of LBBB leads to an altered contraction pattern. Initially, the septum shortens during the isovolumic contraction time, causing an early systolic stretching of the opposing, still non-activated posterolateral wall. Eventually, this posterolateral wall is activated late and exhibits a late systolic or even post-systolic shortening after the aforementioned early systolic stretching. This intraventricular dyssynchrony reduces the efficiency of the LV pumping function as part of the metabolic energy is wasted in intraventricular volume shifts rather than in ventricular ejection [17].

Atrioventricular and interventricular synchrony in CRT

Physiological rationale for optimization

As outlined above, from a physiological point of view, it seems reasonable to assume that correction of atrio-, inter- and intraventricular dyssynchrony improves cardiac function and efficiency. In the contemporary era of CRT, this can be achieved by programming both AV and VV timings.

It should be stressed that intrinsic AV, programmed AV and programmed VV delay can all influence ventricular activation and filling. Thus, depending on the device settings, there can be up to three activation fronts that potentially determine the degree of intraventricular dysynchrony: intrinsic right bundle branch activation, right and left ventricular pacing, respectively (Fig. 1) [16].

The interaction between these three activation fronts is illustrated in Fig. 2 showing a 12-lead electrocardiogram (ECG) recording during three different programmed AV delays in two patients with a CRT device. In Fig. 2a, it can
be appreciated that there is a progressive change in QRS morphology between the AV delays. As the intrinsic PR interval of this patient is 156 ms, there is progressive change in QRS morphology between different AV delays. At an AV delay of 170 ms, there is maximal contribution of all 3 activation fronts resulting in the smallest QRS complex. Panel B in case of a very long intrinsic PR interval of 289 ms, there is no change in QRS complex at different AV delays as intrinsic conduction does not contribute to ventricular activation.

Most patients not only have variable intra-atrial, interventricular and intraventricular conduction delays, but also different positions of right atrial, RV and LV leads, making it difficult to predict the optimal AV and VV timings [18]. This supports the concept of an individualized and tailored optimization of AV and VV timings.

The importance of AV and VV optimization has already been shown in general pacing. RV single chamber pacing disturbs the temporal relation between atria and ventricles leading to decreased ventricular performance especially in case of compromised cardiac function [19, 20]. In the early nineties, the use of DDD pacing was proposed in patients with refractory terminal heart failure and a long atrioventricular delay [21]. It was anticipated that improvement in the atrioventricular dyssynchrony by sequential atrioventricular pacing would lead to improved outcome. However, this potentially beneficial effect was hampered by the aggravated inter- and intraventricular dyssynchrony caused by RV pacing [22]. These observations have set the base for the current therapy of biventricular pacing.

It has been demonstrated that diastolic mitral valve regurgitation (MR) can be reversed by AV sequential pacing with short AV intervals [23]. The mechanism for improvement in functional systolic MR is more complex. It is caused by an imbalance between closing and tethering forces on the mitral valve leaflets. Due to LV and mitral valve annular dilation, there is a restrictive leaflet motion requiring a higher (systolic) transmitral pressure gradient to close the valve [24]. Moreover, LV dyssynchrony can lead to dyssynchronous contraction of both papillary muscles contributing to a synchronization of tethering forces [25]. In contrast, closing forces are reduced as a consequence of decreased LV systolic function. CRT improves LV systolic function and can result in an immediate reduction of MR [24]. In patients with late activation of the posterior papillary muscle, an acute reduction can also be observed with CRT. Long-term resynchronization induces LV reverse remodeling with reduction in LV and mitral annular dimension resulting in further improvement in MR [26].

Evidence for atrioventricular optimization

The beneficial effect of optimizing AV timing has been mainly investigated in patients with an indication for permanent dual-chamber (right atrial and RV) pacing. The majority of these small-scale, non-randomized studies focus on acute hemodynamic effects of atrioventricular optimization without evaluation of long-term morbidity and mortality. However, these results cannot be directly extrapolated to the CRT population [27].

In a CRT population, the PAcing TTherapies in Congestive Heart Failure (PATH-CHF) trial demonstrated a significant acute hemodynamic effect of varying the AV delay in RV, LV and biventricular pacing [28, 29]. Interestingly, the optimal AV delay for left ventricular dP/dt_max (LV dP/dt_max) was significantly shorter for RV and
biventricular pacing compared to LV pacing in the group of responders. This variable acute hemodynamic response to different AV delays was also observed in the PATH-CHF-II trial [30]. This could be explained by the fact that during left ventricular pacing, a left-sided atrioventricular delay is set which should be longer to allow fusion with intrinsic conduction coming from the normal-conducting right bundle branch (Fig. 1).

An example of the effect of varying AV delay during left ventricular pacing is shown in Fig. 3. At an AV delay that is programmed 40 ms shorter than the intrinsic PR interval (indicated as “AV1” in Fig. 3), there is fusion with intrinsic right bundle branch conduction which can be appreciated from the surface ECG and RV electrogram. Fusion is lost with shorter AV delays (AV2, AV3 and AV4) [31].

Atrial sensing or atrial pacing will result in different optimal AV delays and has to be accounted for during optimization. Compared to atrial sensing, the optimal AV delay needs to be prolonged during atrial pacing in order to obtain similar synchronization. In practice, one could first optimize AV and VV delays during atrial pacing to match QRS morphology of the optimal AV delay obtained during atrial pacing (Fig. 4) [32].

Only a small number of prospective and/or randomized clinical studies compare the optimization of AV delay to an empirical AV delay. Although these studies are small scale and use different optimization techniques, optimization of the AV delay shows a significant beneficial effect on acute hemodynamic response, New York Heart Association (NYHA) class, LV ejection fraction and brain natriuretic peptide level [33–35].

So far, there has been no large-scale, prospective and randomized trial evaluating the effect of AV optimization on morbidity and mortality. Nevertheless, most large CRT trials applied some form of AV delay optimization [1–3, 18]. It is unknown whether the beneficial effects of CRT in these trials would also be present without AV delay optimization. Based on the trials’ methodology and results, current guidelines of the European Society of Cardiology are recommended to optimize the AV delay [36].

Evidence for interventricular optimization

The relative position of right and left ventricular leads also influences timing of activation. As a consequence, VV optimization may compensate for suboptimal lead placement [37]. However, even in case of optimal lead placement, VV delay optimization can be of importance: some patients exhibit a significant delay between LV pacemaker stimulation and LV depolarization which can be counteracted by pre-exciting the LV pacing lead relative to the RV pacing lead (Fig. 5).

None of the larger CRT trials included VV optimization in their protocol, partly because this feature was not available at time of inclusion [38]. In smaller studies, an
improvement in acute hemodynamic response measured by LV $dP/dt_{\text{max}}$ [39, 40], exercise capacity [41] and echocardiographic left ventricular ejection fraction has been demonstrated [42, 43]. However, the larger, randomized DECREASE-HF trial showed a trend toward greater reduction in left ventricular systolic diameter for the group with simultaneous biventricular pacing compared to sequential biventricular pacing [44], and the single-

![Fig. 4](image_url)

**Fig. 4** Example of the difference in optimal paced AV (PAV) interval and optimal sensed AV (SAV) interval. In this patient, CRT was optimized during sequential AV pacing using LV $dP/dt_{\text{max}}$. The optimal PAV interval was 150 ms resulting in a LV $dP/dt_{\text{max}}$ of 862 mmHg/s. To determine the optimal SAV interval, the stimulation rate was reduced below the intrinsic sinus rate, and a 12-lead electrocardiogram was recorded during incremental shortening of the SAV interval. At a SAV interval of 110 ms, the QRS complex matches the QRS complex at the optimal PAV interval. Determination of optimal SAV interval is also confirmed by the LV $dP/dt_{\text{max}}$ measurement.

![Fig. 5](image_url)

**Fig. 5** Twelve-lead electrocardiogram recording during RV pacing (left panel), LV pacing (middle panel) and biventricular (BV) pacing with VV delay of 80 ms (right panel). The total activation time, defined as time from onset of pacing until the end of the QRS complex, indicated between the two vertical dotted lines in each panel. During RV pacing, the total activation time is 218 ms; however, it is increased during LV pacing until 274 ms. During BV pacing, this delayed activation can be compensated by pre-activating LV 80 ms before RV pacing.
blinded, randomized RHYTHM-II trial did not find a benefit on functional endpoints of VV optimization compared to simultaneous biventricular pacing [45]. The recent randomized, multicenter RESPONSE-HF trial evaluated the effect of VV optimization on top of AV optimization. Patients who were non-responders after 3 months of CRT (with simultaneous biventricular pacing) were randomized to either sequential biventricular pacing with VV optimization or simultaneous biventricular pacing. Non-response was defined on the basis of NYHA class and 6-min hall walk distance. After 9 months of follow-up, the response rate in the sequential group \((n = 29)\) was 18.9% higher than the simultaneous group \((n = 36)\) [46].

In all but one of these studies [39], VV delay optimization was performed on top of prior AV optimization. In the overall CRT population, the benefit of VV optimization compared to simultaneous biventricular pacing is relatively small: van Gelder et al. noted a mean increase in LV \(\frac{dP}{dt}\text{max}\) of 66 mmHg/s (7%) on top of simultaneous biventricular pacing with optimized AV delay [40]. VV optimization may probably be more beneficial in a subset of patients who show no or little response to CRT. It can be concluded on the basis of current data that the role of VV optimization is still under debate. This could partly be explained by the use of inaccurate optimization methods with high inter- and intraobserver variability.

There is no consensus in what order to optimize the AV and VV delays. However, in a small study, the hemodynamic effect (measured by fingerphotoplethysmography) of simultaneously adjusting AV and VV delays was evaluated. There was a curvilinear effect with a clear optimal combination of AV and VV delays. VV optimization provided an additional, but smaller hemodynamic effect compared to AV optimization alone [47].

Intra-individual variation in optimal AV and VV delays

The optimal AV and VV delays should not be regarded as static values, but may vary in time and in different circumstances. In general, optimization of AV and VV delays is performed during resting conditions in a supine or sitting position, thus neglecting the effect of exercise. In the healthy heart, AV conduction time shortens during exercise as a result of increased sympathetic tone and inter- and intraventricular activation delays are virtually absent and not different from the resting condition [48]. This is also the rationale for rate-adaptive atrial pacing with progressive shortening of the programmed AV delay during exercise. However, in the CRT population, it is questionable whether rate-adaptive pacing is favorable, as the effect of exercise on atrial and ventricular conduction is more heterogeneous and complex [49]. Several small studies investigating the effect of exercise on the optimal AV delay reported mixed results: some reported individual variation in optimal AV delay during exercise [50], others advise prolongation of the AV delay during exercise [51] while others notice no change in optimal AV delay [52].

VV optimization during exercise has been only sporadically investigated, using different optimization methods and including a limited number of patients. Lafitte et al. reported a change in interventricular dyssynchrony (defined as the interventricular mechanical delay) during bicycle exercise testing in 60% of 65 heart failure patients [48]. In contrast, Valzania et al. showed no significant change in interventricular mechanical delay during dobutamine stress testing [53]. Two other small studies showed that the optimal VV delay changes during bicycle exercise testing in about 55% of patients [52, 54]. In one study in patients with atrial fibrillation and absent intrinsic AV conduction, a decrease in optimal VV delay with increasing pacing rate was noted [55].

Besides the effect of exercise, optimal AV and VV delays may also change in time as a result of reverse remodeling. Also here, data regarding the effect of long-term CRT on optimal AV and VV delays are limited and contradicting. In one study, there was a decrease in optimal AV delay and increase in LV pre-excitation in VV setting after 6 months of CRT [56]; however, another study showed an opposite effect after 9 months of CRT [57]. Although patient population was comparable, both trials used different optimization methods.

The large prospective, randomized and multicenter “Frequent Optimization Study Using the QuickOpt method (FREEDOM)” trial compared frequent AV and VV optimization every 3 months using an algorithm based on the intracardiac electrogram to standard care with empiric programming or one-time optimization at the discretion of the investigator. A heart failure clinical composite score was used as primary endpoint after 12 months of follow-up. In 1,525 patients analyzed, there was no significant difference in primary endpoint regardless of optimization [58].

Methods for optimization of AV and VV delays

There are numerous invasive and non-invasive methods available to optimize both AV and VV delays. It seems reasonable to assume that optimal delays result in highest forward stroke volume. The ideal optimization method should therefore be able to measure left ventricular (forward) stroke volume or an equivalent in a preferably reproducible, easy-to-perform and non-invasive way.
Invasive optimization methods

First derivate of left ventricular pressure pulse

The ultimate way to determine contractile properties is measuring the force that is generated by a muscle; however, it is not possible to measure this in clinical practice. As an alternative, the rate of left ventricular pressure change (LV $dP/dt$) has been proposed [59, 60]. Pressure is defined as force per unit area and is thus related to wall force. The rate of pressure development is influenced by the contractile properties of the LV. Changes in contractility alter the slope of the pressure curve resulting in an increased or decreased peak rise in intraventricular pressure ($dP/dt_{max}$) during isovolumetric contraction [61]. However, LV $dP/dt$ is a complex function that is not only dependent on contractility, but also dependent on preload, afterload and heart rate [62, 63]. However, within physiological limits, LV $dP/dt_{max}$ shows mainly dependence on contractility and preload [64]. This properties make LV $dP/dt_{max}$ a useful instrument to evaluate the effect of both AV and VV delays on myocardial performance.

LV $dP/dt$ is optimally derived from a left ventricular pressure curve obtained by a micromanometer that is introduced endovascular into the LV [65]. We have previously described an alternative method using a 0.014 high-fidelity pressure wire (Radiwire, St. Jude Medical Inc., St. Paul, MN, USA) introduced either retrogradely or transseptally into the LV [40]. In order to adequately determine the effect of different pacing settings on LV $dP/dt_{max}$, different protocols have been described [65, 66].

In order to overcome the influence of heart rate on LV $dP/dt$, the atrium is paced at 5–10 beats above the intrinsic rate. In patients with atrial fibrillation, ventricular stimulation is performed above the intrinsic rate to ensure continuous capture. First, a baseline LV $dP/dt_{max}$ is measured and averaged out over several heart beats or seconds, excluding premature and post-extrasystolic beats from analysis. After baseline measurement, AV optimization is performed first during simultaneous biventricular pacing. The optimal AV delay with the highest LV $dP/dt_{max}$ is selected to perform the subsequent VV optimization. The optimization procedure should proceed under stable conditions to minimize any influence on LV $dP/dt$ measurement.

This method has the advantage that it is easily implemented, even during the implantation procedure. Interpretation is not dependent on operator skills or technical limitations as with echocardiography. Also, it allows the evaluation of multiple pacing sites in a short time frame. Due to these characteristics, it is a suitable method to evaluate the acute hemodynamic effect of different pacing sites, either epicardially or even endocardially as has been demonstrated in a recent case report [67]. As an example, we implanted a left endocardial lead in a patient who showed no clinical or echocardiographic response to standard CRT. The definite LV pacing site was determined with optimal LV $dP/dt_{max}$ during a temporary pacing study of different endocardial sites. At long-term follow-up, there were both clinical and echocardiographic improvements.

A disadvantage of the LV $dP/dt_{max}$ optimization method is its invasive nature. However, as only a 4-French guiding wire can be introduced via the radial artery or even via transeptal puncture.

The use of continuous wave Doppler imaging of the mitral regurgitation signal is advocated as a non-invasive alternative to determine LV $dP/dt_{max}$ [68]. Importantly, this method does not measure the true maximal LV $dP/dt$, but an averaged slope of the left ventricular pressure curve between 4 mmHg and 36 mmHg. This measure has not been validated in an experimental physiological set-up, as has been in case of invasively measured LV $dP/dt_{max}$ [61, 63, 64]. Further, it requires the presence of a detectable mitral regurgitation signal which is not always present [69], has a lower temporal resolution than the invasive method and is more laborious to average over multiple heart beats.

Both PATH-CHF and PATH-CHF II trials used invasive LV $dP/dt_{max}$ to optimize the AV delay [30, 65]. So far, there are no randomized controlled trials evaluating the long-term outcome of CRT optimization by LV $dP/dt_{max}$.

Pressure–volume loops

LV pressure–volume loops can be used to calculate stroke work defined as the integrated area within the pressure–volume loop (in mmHg mL). This index is mainly dependent on contractility and preload with little effect of changes in afterload [64].

To acquire pressure–volume curves, a 6-French or 7-French pressure-conductance catheter is inserted in the LV via the femoral artery. The signals are digitized and transformed to pressure–volume loops by dedicated software [64, 70].

Except for its invasiveness, there are other disadvantages to the use of pressure–volume loops. The relatively inaccurate measurement of LV volume in dilated hearts combined with a low signal-to-noise ratio make it difficult to acquire a reliable signal in heart failure patients [71]. Also, the pressure-conductance catheter needs calibrating, has a larger size and is more expensive compared to the micromanometer used for left ventricular pressure measurements [72].
In contrary to LV $dP/dt_{\text{max}}$, measurement, the pressure–volume loop covers both the systolic and the diastolic phases of the cardiac cycle and incorporates both pressure and volume changes. This makes stroke work more sensitive to measure CRT-induced volume changes caused by alteration in mitral regurgitation. Further, the internal flow fraction derived from the conductance signals can be used to quantify LV mechanical dys synchrony [73]. In selected cases, this dys synchrony index could be used to support the indication for resynchronization therapy [74].

Compared to LV $dP/dt_{\text{max}}$, pressure–volume loops have been used only limited in early cardiac resynchronization studies [71]. Interestingly, when evaluating the acute hemodynamic response to CRT by both LV $dP/dt_{\text{max}}$ and stroke work, both measures do not match in up to 50% of the cases when using a cutoff value of 10% change to define response to CRT [72]. A sustained long-term hemodynamic response at 6 months has been demonstrated in a small-scale trial [70].

Automated algorithms

Several manufacturers of CRT devices have implemented automated algorithms to adjust AV and/or VV delays. As the optimal delays may change in time as a consequence of reverse remodeling after CRT as well as during exercise, these algorithms may be of additional value. However, adaptation during exercise can only be achieved if optimization performed continuously in a closed loop configuration. Optimization for reverse remodeling could be performed intermittently with automated algorithms.

Algorithms based on the intracardiac electrogram

QuickOpt. The QuickOpt algorithm (St. Jude Medical, St. Paul, MN, USA) has been designed to optimize both AV and VV delays using intracardiac electrograms. It has been demonstrated that the optimal AV delay can be calculated by measuring the time difference between onset of right atrial activation and end of left atrial activation using the intracardiac electrogram [75]. The QuickOpt algorithm uses the right intra-atrial electrogram to calculate the interatrial conduction delay. Depending on this delay, an offset is added to determine the optimal AV delay. For VV delay optimization, it is assumed that ventricular activation is optimal when the two depolarization wave fronts from right and left ventricular leads meet near the interventricular septum. The optimal VV delay is based on the conduction delay of both intrinsic rhythm and ventricular pacing. To measure this delay, intracardiac electrograms of both right and left ventricular leads are used. The interval between intrinsic activation of RV and LV leads is defined $\delta$, and the difference between RV pacing to LV sensing and LV pacing to RV sensing is defined $\epsilon$. The optimal VV interval is then calculated using the formula $0.5 (\delta + \epsilon)$. Although the algorithm shows a strong linear correlation with echocardiographic measurement of aortic velocity time integral [76], there is no correlation with the optimal VV delay determined by LV $dP/dt_{\text{max}}$ [77]. The correlation with the optimal AV and VV delays measured by echocardiography (using the iterative method for AV optimization and left ventricular outflow tract velocity time integral for VV optimization) is also poor [78].

The recent FREEDOM trial demonstrated that frequent optimization using QuickOpt did not significantly influence outcome as defined by the heart failure clinical composite score [58]. However, these results may be due to inaccuracy of the QuickOpt algorithm.

SMART-AV. The SMART-AV electrogram optimization algorithm (Boston Scientific Corporation, St. Paul, MN, USA) is part of the Expert Ease for Heart Failure feature and has been developed from results of large clinical trials [3, 30, 79]. Both sensed and paced AV delays are derived from the intracardiac electrogram and added to the QRS duration on the surface electrocardiogram in either mode. A correction factor is used depending on left ventricular lead position. This algorithm has been compared to two echocardiographic optimization methods (Ritter’s and aortic velocity time integral method). In 28 patients examined, the electrogram optimization method correlated significantly better with LV $dP/dt_{\text{max}}$ than the Ritter method [80]. The ongoing randomized, multicenter SMART-AV trial has been designed to compare the effect of different atrioventricular optimization methods on left ventricular remodeling. The electrogram optimization method will be compared to echocardiographic AV optimization (iterative method) and a fixed AV delay [81].

Peak endocardial acceleration

During the isovolumetric contraction period, the myocardium generates vibrations that are transmitted throughout the heart. The audible frequencies of these vibrations can be appreciated as the first (and second) heart sound. With a microaccelerometer (SonR, Sorin Biomedica, Saluggia, Italy) located on a lead inside the heart, it is possible to record the full-frequency spectrum and derive the peak endocardial acceleration (PEA). Early experimental research has shown that changes in PEA correlates well with changes in contractility induced by inotropic stimulation [82]. The optimal AV delay determined by PEA correlates well with those obtained by echocardiography (Ritter’s method) [83–85]. In CRT, PEA increases significantly during LV or biventricular pacing compared to RV pacing only [86].
The randomized, multicenter CLinical Evaluation of Advanced Resynchronization (CLEAR) study compared AV and VV optimization by PEA to standard care for the composite endpoint of NYHA class, heart failure hospitalization and quality of life at 12 months in 186 patients. Patients optimized with PEA (n = 66) showed a significantly higher response rate [87].

**Finger photoplethysmography**

The conventional pulse oximetry probe measures the arterial pulsations of the fingertip vascular bed using a photo detector. It is possible to measure systolic blood pressure, pulse pressure and mean arterial pressure. As aortic pulse pressure is influenced by stroke volume and thus left ventricular performance, finger photoplethysmography may be used to optimize atrioventricular and interventricular delay. It seems a promising tool in cardiac resynchronization optimization because of its non-invasive nature and high reproducibility. However, measurements are highly influenced by waveform reflections in the arterial system and autonomic effects on peripheral resistance.

To overcome these issues, measurements are only taken a few beats after an atrioventricular delay change and an algorithm is used to correct for vasodilation and/or vasoconstriction. In patients who show a positive change in aortic pulse pressure during CRT (invasively measured), finger photoplethysmography (using the correction algorithm described) was able to predict the AV delay with the highest aortic pulse pressure change in up to 80% of the patients [88].

Another technique uses a volume-clamp circuit around the finger that dynamically follows arterial pressure (Finapres Medical System, Amsterdam, the Netherlands) [89]. The use of systolic blood pressure change measured by this technique responds to changing AV intervals and is claimed to be highly reproducible [89, 90]. Alternatively, Nexfin (BMEYE B.V., Amsterdam, the Netherlands) combines the volume-clamp technique with a dedicated algorithm to calculate stroke volume [91]. This method shows a good agreement with aortic valve velocity integral (LVOT-VTI) to optimize both AV and VV delays. In a few small-scale, uncontrolled studies, the optimal AV delay was defined as the delay with the highest stroke distance measured by LVOT-VTI, but there is no correlation with outcome [35, 51]. In a post hoc analysis, the InSync III study compared AV optimization using LVOT stroke volume to simultaneous biventricular pacing. There was only a significant improvement in 6-min walking test (6MWT) compared to the control group; quality of life and NYHA class were not significantly different [95]. Also, the previously described RHYTHM II ICD trial used LVOT-VTI measurements for VV optimization, but reported no benefit on functional endpoints [45]. One small, non-randomized study used LVOT-VTI to optimize both AV and VV delays after 3 months of non-optimized CRT and concluded that the method was feasible, reproducible and able to improve response to CRT [96].

**Pulsed wave left ventricular outflow tract velocity time integral (LVOT-VTI).** Sawhney et al. showed in a randomized, prospective trial in 40 patients that compared to an empirical AV delay of 120 ms, AV optimization using AV-VTI yields a significant improvement in NYHA class, quality of life and 6MWT [33]. Another prospective study in 40 patients compared AV optimization by AV-VTI to the Ritter’s method and concluded that the AV-VTI method resulted in greater systolic improvement [97]. However, the methodology of both studies has been questioned [27].

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**Tissue Doppler imaging (TDI).** Although TDI has the potential to assess left ventricular dyssynchrony, it is subject to high inter- and intra-observer variability [96, 98]. TDI was used to optimize VV delay and was compared to empirical AV and VV delays by Vidal et al. in 100 patients [99]. The optimal VV delay was defined as the setting with the greatest superposition of TDI curves of opposing LV walls in 2-chamber and 4-chamber view. There was only a significant improvement in 6MWT in the optimized group. However, 25% of patients in the optimized group did not receive AV optimization because of atrial fibrillation and a power calculation justifying the included number of patients was not performed.

Echocardiography

Echocardiographic techniques for optimization of both AV and VV delays have been comprehensively described in recent review papers [27, 93, 94]. In general, echocardiography is a widely available and non-invasive technique without significant burden for the patient. However, these optimization techniques are subject of higher intra- and interobserver variability than invasive measurements. Still, echocardiography remains a cornerstone in CRT because of its ability to evaluate response to CRT in terms of reverse remodeling and to identify other factors that might influence a non-response to CRT (e.g. RV failure, pulmonary hypertension, valvular disease).

Evaluation of LV systolic function

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**Continuous wave aortic valve velocity time integral (AV-VTI).** Sawhney et al. showed in a randomized, prospective trial in 40 patients that compared to an empirical AV delay of 120 ms, AV optimization using AV-VTI yields a significant improvement in NYHA class, quality of life and 6MWT [33]. Another prospective study in 40 patients compared AV optimization by AV-VTI to the Ritter’s method and concluded that the AV-VTI method resulted in greater systolic improvement [97]. However, the methodology of both studies has been questioned [27].

**LV dP/dt.** Even though proposed as a surrogate for invasive LV dP/dt\(_{\text{max}}\) measurement [68], this measurement is not recommended as optimization method as reproducibility has been reported as suboptimal [96].

**Tissue Doppler imaging (TDI).** Although TDI has the potential to assess left ventricular dyssynchrony, it is subject to high inter- and intra-observer variability [96, 98]. TDI was used to optimize VV delay and was compared to empirical AV and VV delays by Vidal et al. in 100 patients [99]. The optimal VV delay was defined as the setting with the greatest superposition of TDI curves of opposing LV walls in 2-chamber and 4-chamber view. There was only a significant improvement in 6MWT in the optimized group. However, 25% of patients in the optimized group did not receive AV optimization because of atrial fibrillation and a power calculation justifying the included number of patients was not performed.
patients is lacking. Another study used TDI based on measurement of regional electromechanical delay of 18 LV segments in the 3 apical views. The AV and VV delays were defined as optimal when the basal septal segment and the segments containing the right and left ventricular leads (as identified by computer tomography) were synchronized. Comparing a limited number of VV intervals, derived optimal VV delay coincided with the greatest cardiac output as measured by thermodilution. Although complex and time-consuming, this method is one of the few based on the underlying physiological concept of synchronizing the three activation fronts [100].

Evaluation of LV diastolic function

Iterative method. The AV delay is shortened by increments of 20 ms until truncation of the A-wave on the pulsed Doppler transmitral flow pattern. Next, the AV delay is increased again by increments of 10 ms until A-wave truncation disappears. The latter is defined as the optimal AV delay. The iterative method was used for AV optimization in the CARE-HF trial and the aforementioned study of Vidal et al. [99, 101].

Ritter’s formula. This method was originally proposed for patients with complete heart block [102]. Even though it has only been presented as an abstract and no further validation has been published, its use has been extrapolated to the CRT population without extensive validation. The formula defines the optimal AV delay as the AV interval that bridges the end of the A-wave with closure of the mitral valve or the onset of ventricular contraction. To do so, the time from onset of QRS complex to time of termination of the A-wave (QA interval) is measured at both a long (AV\textsubscript{long}) and a short AV delays (AV\textsubscript{short}). The optimal AV delay is calculated from following formula: AV\textsubscript{opt} = AV\textsubscript{long} – (QA\textsubscript{short} – QA\textsubscript{long}). Ritter’s formula has also been compared to the QuickOpt algorithm and AV-VTI for AV optimization using LV dP/dt\textsubscript{max} as gold standard. This study showed that Ritter’s formula was least accurate [80].

Mitral inflow velocity time integral. On the pulsed Doppler transmitral flow pattern, the VTI is calculated representing the stroke distance of mitral inflow as a surrogate of LV filling volume. The AV delay with the largest VTI is considered the optimal setting. The method showed a good correlation with optimization by LV dP/dt\textsubscript{max} (r = 0.96) in a small study of 30 patients [103].

Meluzin’s method. A simplified method to merge the end of atrial contraction with mitral valve closure was proposed by Meluzin [104]. A long AV delay is programmed and the pulsed Doppler transmitral inflow pattern is recorded. The time between end of the A-wave and onset of systolic mitral regurgitation is calculated. This time is subtracted from the programmed AV delay to determine the optimal AV interval. The method was only validated in a study of 18 patients which showed a significantly higher cardiac output measured by thermodilution when comparing the optimal AV delay to longer and shorter AV delays [104]. Obviously, application of this method is dependent on a clear mitral regurgitation signal.

Evaluation of LV systolic and diastolic function

Myocardial performance index (MPI). The MPI (or Tei index) is based on cardiac timing intervals and has been introduced as a measurement incorporating both LV systolic and diastolic functions. The mitral-closure-to-opening (MCO) interval is measured on the pulsed Doppler transmitral flow signal, and the ejection time (ET) is derived from the pulsed Doppler LVOT flow signal. As the total of the isovolumetric contraction and relaxation time (ICT and IRT) is obtained by subtracting ET from MCO, the index incorporates both systolic and diastolic indices [105]. Two small studies used MPI to optimize AV delay [106, 107] and/or VV delay [106]. Both studies lacked a control group and well-defined endpoints.

Conclusion

Experimental physiological and pathophysiological research supports the rationale to optimize AV and VV delays in CRT. Although there is a spectrum of possible optimization methods, no evident golden standard has emerged, partly due to the lack of large-scale studies evaluating these methods to outcome. Thus, at present, no single method can be recommended for standard practice. Present studies support the physiological rationale for AV optimization, but data concerning VV optimization are still conflicting. As the incremental benefit of VV optimization is relatively small, the effect is probably more of importance in a subset of CRT patients (with special attention for non-responders). Although current efforts mainly investigate optimization during resting conditions, there is a need to develop automated algorithms to implement dynamic optimization in order to adapt to physiological alterations during exercise and after anatomical remodeling.

Conflict of interest Berry M. van Gelder is a consultant for Medtronic Trading NL B.V. All other authors state that they have no conflicting interests to declare.

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