How should we optimize cardiac resynchronization therapy?

Tony Stanton1*, Nathaniel M. Hawkins2, Kerry J. Hogg3, Nicholas E.R. Goodfield3, Mark C. Petrie4, and John J.V. McMurray5

1Department of Medicine, University of Queensland Princess Alexandra Hospital, Ipswich Road, Brisbane Q4102, Australia; 2University Hospital Aintree, Liverpool, UK; 3Stobhill Hospital, Glasgow, UK; 4Golden Jubilee National Hospital, Glasgow, UK; and 5Western Infirmary, Glasgow, UK

Received 26 November 2008; revised 26 June 2008; accepted 25 July 2008; online publish-ahead-of-print 28 August 2008

Optimization of cardiac resynchronization therapy is increasingly performed. Numerous methods have been proposed, many being echocardiographic. Both the technique and the timing of optimization are contentious. Whether acute haemodynamic benefits translate into long-term improvements in remodelling, symptoms, or prognosis is unknown. Recent guidelines from the American Society of Echocardiography advocate routine optimization. Here, we objectively review the principles, methods, timing, and evidence supporting optimization. Despite limited validation, optimization was included in landmark clinical trials and is inherent in evidence-based practice. Randomized controlled trials comparing methods are needed, with long-term clinical endpoints. For now, optimization should be performed using the iterative method, according to the CARE-HF protocol.

Keywords Optimization • Cardiac resynchronization therapy • Atrioventricular delay • Interventricular delay

Introduction

Cardiac resynchronization therapy (CRT) improves morbidity and mortality in patients with heart failure (HF).1–3 There are two important adjustable pacing parameters—the interventricular (VV) and atrioventricular (AV) delay. Although included in landmark clinical trials, the role of optimization remains uncertain. Recent guidelines from the American Society of Echocardiography advocate routine optimization of AV delay.7 Here, we objectively review the evidence supporting this statement. Why do we optimize CRT? How do we optimize CRT? When should we optimize CRT? And most importantly, does optimizing CRT benefit patients?

Search strategy

Databases including MEDLINE, EMBASE, PubMed, and the Cochrane Library were searched up to November 2007. The search strategy included both Medical Subject Heading (MeSH) terms (‘cardiac resynchronization’, ‘pacemaker’, ‘HF’, ‘optimization’, ‘delay’) and key words (‘atrioventricular’, ‘interventricular’, ‘dyssynchrony’), restricted to humans. Combinations of terms were used depending on the requirements of the database. No language restriction was initially employed. Clinical trial registers approved by the International Committee of Medical Journal Editors were examined for information regarding current or recently completed trials, including the US National Institutes of Health register (ClinicalTrials.gov). Bibliographies of all papers and review articles identified by the initial strategy were systematically hand-searched. Two reviewers independently scanned all the abstracts and identified potentially relevant articles. Disagreement was resolved by consensus and full text copies retrieved in the event of uncertainty. International conference proceedings were examined from 2000 to 2007 (American College of Cardiology, American Heart Association, European Society of Cardiology). Finally, websites of companies producing biventricular devices were examined for additional data. Of the 108 trials initially identified, 19 were excluded (five non-English language, eight pilot studies or case reports, and six by consensus opinion owing to inapplicable study population or design).

What is interventricular delay?

The VV delay signifies the delay between contraction of the right and left ventricles. In normal subjects right ventricular depolarization precedes left by a few milliseconds. Interventricular conduction times vary widely in patients with HF.9 By convention, a negative value indicates that LV activation precedes RV.
**Why do we optimize interventricular delay?**

CRT aims to restore synchronous ventricular contraction. This is impeded by suboptimal LV lead position, abnormal global activation, and regional conduction delays across infarcted myocardium. Tailored ventricular timing aims to compensate for these delays. None of the landmark CRT trials included VV optimization.

**How do we optimize interventricular delay?**

VV delay is optimized using device-based algorithms, echocardiographic cardiac output, tissue Doppler synchrony, invasive dP/dt\(_{\text{max}}\), blood pressure, surface electrocardiogram, and intracardiac electrogram (IEGM) methods. Two studies have optimized VV delay using tissue Doppler measures of synchrony. The first concurrently optimized AV delay in 51 patients, but failed to improve NYHA class, QOL score, or change in 6MWT. In the second report, optimization of interventricular synchrony using strain rate imaging was associated with increased cardiac output (4.6 ± 0.3 vs. 4.3 ± 0.3 L/min).

**Invasive left ventricular dP/dt\(_{\text{max}}\)**

A pressure sensor-tipped wire is inserted into the LV through a cardiac catheter. The maximal pressure change per unit of time (dP/dt\(_{\text{max}}\)) is considered a reliable method of assessing LV systolic function. Disadvantages include the invasive nature of the procedure, limited repeatability, time required, and cost of equipment. Four small, non-randomized studies demonstrated only a modest improvement in invasive dP/dt\(_{\text{max}}\) immediately after VV optimization (maximum 8%). No long-term follow-up or clinical outcomes were included (Table 1).

**Left ventricular outflow tract velocity time integral**

Interventricular delay is adjusted to maximize echocardiographic cardiac output. LVOT VTI is measured beneath the aortic valve cusps using pulsed-wave (PW) Doppler, then multiplied by the cross-sectional area of the LVOT to estimate stroke volume (SV). Cardiac output is calculated by multiplying SV with heart rate. This technique has been validated in patients with advanced HF against the Fick oxygen reference standard. Several limitations apply. Small changes in the angle between the incident ultrasound beam and outflow jet introduce significant error. Echocardiographic-derived cardiac output varies with cardiac medications, exercise, and posture. Short-term intra- and inter-observer variability in the measurement of cardiac output ranges from 4% to 10%. Obtaining a good quality signal in the LVOT may be difficult. Some authors have substituted maximal aortic valve VTI using continuous wave Doppler, and this approach is inadvisable as both cardiac output and aortic valve morphology contribute to the signal.

Three small, non-randomized studies optimized VV delay using LVOT VTI. Echocardiographic measures including cardiac output improved with optimized rather than simultaneous VV pacing. Improvement in clinical variables was however negligible.

Two large multicentre trials optimized VV delay using LVOT VTI. The non-randomized InSync III study examined 359 patients. Pre-discharge optimization increased stroke volume by 8.6%. Clinical outcomes at 6 months were compared against the historical treatment arm of the MIRACLE study. Results were mixed. Quality-of-life (QOL) score and NYHA class failed to improve when compared with the MIRACLE treatment group. However, median 6MWT increased by 15.1 m (53.0 (range 314.0 to 613.0) vs. 37.9 (range 437.0 to 248.8), P < 0.0001). The RHYTHM II ICD study randomized 121 patients in a 1:3 ratio to simultaneous vs. optimized biventricular (BiV) pacing. Optimization conferred no benefit in 6MWT, QOL, NYHA class or hospitalizations.

**Tissue Doppler synchrony**

Two studies have optimized VV delay using tissue Doppler measures of synchrony. The first concurrently optimized AV delay in 51 patients, but failed to improve NYHA class, QOL score, or change in 6MWT. In the second report, optimization of interventricular synchrony using strain rate imaging was associated with increased cardiac output (4.6 ± 0.3 vs. 4.3 ± 0.3 L/min).

**Expert Ease for Heart Failure™ algorithm**

Expert Ease for Heart Failure™ (EEHF) algorithm calculates the VV delay based on the intrinsic interventricular delay measured by the device during implantation. The algorithm was derived from unpublished acute haemodynamic data in the PATH-CHF II studies: optimal VV delay = −0.333 × (RV − LV electrical delay) − 20 ms.

The DECREASE-HF trial randomized 306 patients to simultaneous BiV, sequential BiV, or LV pacing. Sequential pacing was equivalent, but not superior, to simultaneous pacing for the composite primary endpoint of peak oxygen consumption and LV end-systolic dimension. The secondary echocardiographic endpoints are published. A trend towards greater improvement in LV dimensions and volumes was observed with simultaneous pacing, while measures of systolic function were similar between the two groups.

**What is atrioventricular delay?**

Atrial contraction contributes 20–30% to stroke volume at rest in patients with HF and left ventricular systolic dysfunction (LVSD). This contribution increases with higher heart rates. Impaired AV conduction reduces cardiac output and systolic blood pressure.

A long AV delay causes late ventricular contraction. Diastolic filling time (DFT) is reduced, causing fusion of the E- and A-waves of the mitral inflow Doppler (Figure 1). The atrial contribution to filling terminates significantly before depolarization of the ventricle, resulting in wasted diastole and suboptimal preload for ventricular contraction. Patients with HF often exhibit diastolic mitral regurgitation (MR). A left ventricular–atrial pressure gradient develops owing to high LV end-diastolic pressure and incomplete mitral valve closure. This further reduces preload and LV filling. AV programming of CRT can eliminate diastolic MR.
Table 1  Optimization of interventricular (VV) delay in cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Optimization method</th>
<th>Effect of optimization</th>
<th>Timing of optimization after implant</th>
<th>Mean VV delay (ms)</th>
<th>Optimal pre-excitation LV/Sim/RV (%)</th>
<th>AV delay optimized</th>
<th>Randomized</th>
<th>Blinded</th>
<th>Mean follow-up (months)</th>
<th>Further optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao et al.7</td>
<td>306</td>
<td>EEHF+ Echocardiographic LVOT VTI</td>
<td>None significant None significant</td>
<td>2 weeks Pre-discharge</td>
<td>48 ± 14 ms Not stated</td>
<td>Not stated EEHF+</td>
<td>Yes Double 6 months –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boriani et al.11</td>
<td>121</td>
<td>Echocardiographic LVOT VTI</td>
<td>None significant</td>
<td>None significant</td>
<td>Time of implant Discharge: +27.4 ms 3 months: +22.7 ms</td>
<td>61/15/24</td>
<td>Ritter method No No 3 months Not stated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leon et al.10</td>
<td>359</td>
<td>Echocardiographic LVOT VTI</td>
<td>+8.6% stroke volume +15.1 m 6MWT</td>
<td>Pre-discharge</td>
<td>Not stated</td>
<td>58/19/23</td>
<td>Ritter method No No 6 months 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bordachar et al.12</td>
<td>41</td>
<td>Echocardiographic LVOT VTI</td>
<td>+0.8 L/min CO by LVOT VTI +0.1 NYHA</td>
<td>Time of implant</td>
<td>Not stated</td>
<td>38/21/41</td>
<td>Ritter method No No 6 months 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortensen et al.13</td>
<td>34</td>
<td>Echocardiographic LVOT VTI</td>
<td>+7.3 m 6MWT</td>
<td>Pre-discharge</td>
<td>Discharge: +27.4 ms</td>
<td>60/25/15</td>
<td>Ritter method No No 6 months Not stated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanderheyden et al.14</td>
<td>20</td>
<td>Echocardiographic LVOT VTI</td>
<td>+26% LVOT VTI</td>
<td>2–5 days</td>
<td>Not stated</td>
<td>72/21/6</td>
<td>Iterative No No 6 months –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sogaard et al.15</td>
<td>20</td>
<td>Tissue Doppler imaging</td>
<td>+3.9% LVEF +7% DFT</td>
<td>24 h</td>
<td>Not stated</td>
<td>60/25/15</td>
<td>Ritter method No No 6 months Not stated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vidal et al.16</td>
<td>100</td>
<td>Tissue Doppler synchrony</td>
<td>+0.7 L/min CO AV VTI</td>
<td>24–72 h</td>
<td>Not stated</td>
<td>72/21/6</td>
<td>Iterative No No 6 months –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novak et al.17</td>
<td>16</td>
<td>Strain rate synchrony</td>
<td>+0.3 L/min CO by Fick</td>
<td>3 months</td>
<td>15.4 ± 10.7 ms</td>
<td>14/2/0</td>
<td>Meluzin method No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perego et al.18</td>
<td>12</td>
<td>Invasive dP/dt max</td>
<td>+6% invasive dP/dt</td>
<td>Time of implant</td>
<td>– 25 ms</td>
<td>75/25/0</td>
<td>Invasive dP/dt No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay et al.19</td>
<td>9</td>
<td>Invasive dP/dt max</td>
<td>Simultaneous optimal</td>
<td>Time of implant</td>
<td>Not stated</td>
<td>33/67/0</td>
<td>No No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Gelder et al.20</td>
<td>53</td>
<td>Invasive dP/dt max</td>
<td>+8% invasive dP/dt</td>
<td>&lt;24 h</td>
<td>Ischaemic: – 52 ms Idiopathic: – 28 ms</td>
<td>83/11/6</td>
<td>Invasive dP/dt No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurzidim et al.21</td>
<td>22</td>
<td>Invasive dP/dt max</td>
<td>+3% invasive dP/dt</td>
<td>Time of implant</td>
<td>– 37 ms</td>
<td>64/32/4</td>
<td>Invasive dP/dt No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burri et al.22</td>
<td>27</td>
<td>Radionuclide ventriculography</td>
<td>+0.4% LVEF</td>
<td>&lt;3 days</td>
<td>Not stated</td>
<td>44/33/22</td>
<td>Ritter method No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whinnett et al.22</td>
<td>15</td>
<td>Finger photo-plethysmography</td>
<td>+4 mmHg systolic BP</td>
<td>3–30 months</td>
<td>– 8 ms</td>
<td>Not stated</td>
<td>FPPG No No None –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6MWT, Six-minute walk test; CO, cardiac output; DFT, diastolic filling time; EEHF, Expert Ease for Heart Failure algorithm; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; VTI, velocity time integral; LV, left ventricle; RV, right ventricle; FPPG, finger photoplethysmography.
A short AV delay causes early ventricular contraction. DFT is increased, separating the E- and A-waves of the mitral inflow Doppler. However, end-diastolic filling is interrupted by the onset of ventricular contraction and early mitral valve closure, manifested as A-wave truncation (Figure 2).

The goal of optimizing AV delay is two-fold. First, to maximize DFT (i.e. separation of the E- and A-waves). Secondly, to allow complete end-diastolic filling (marked by the end of the A-wave) before the onset of LV contraction. AV delay is programmed during CRT implantation, and may be set empirically to 120 ms.36,48,49 The exact number of patients receiving optimization or empirical settings in clinical practice is unknown.

### Why do we optimize atrioventricular delay?

The evidence supporting optimization of AV delay originates from dual-chamber pacing studies (Table 2). All were small, short-term studies of echocardiographic or invasive haemodynamic measures. Only one trial involved more than 25 patients, included randomization or blinding, or recruited consecutive patients. None demonstrated an improvement in clinical outcome. Disparate optimization techniques and outcome measures were employed. Intra- and inter-observer variability were rarely documented.

In total, the studies included only 64 patients with HF. Extrapolating results from these historic studies to CRT candidates with severe HF is unwise without rigorous validation. Clearly, such patients have major structural and haemodynamic differences compared with conventional recipients of brady-pacemakers.

### How do we optimize atrioventricular delay?

Many echocardiographic and non-echocardiographic optimization methods have been proposed. These aim to optimize either DFT or markers of systolic function.

### Echocardiographic optimization methods

As with dual-chamber pacing, the evidence derives mainly from small, single centre, non-randomized studies (Table 3). Many different optimization methods were assessed with diverse definitions of response. Few studies included clinical outcomes.16,36,49–52 The timing of optimization after implant varied greatly, or was not documented. Many studies lacked or included only limited follow-up. Only three of these included a control group.16,36,49 Without controls, inferring long-term benefit from AV optimization is impossible. The results may simply reflect the effects of CRT alone.

Some studies compared the ‘optimal’ AV delay with selected short or long comparator AV delays.50,53–55 This exaggerates the purported benefit. Few compared optimization with standard ‘out of box’ settings.16,36,49 All but one study performed optimization at rest in the supine position.54 Extrapolation to standing or exercising patients is unfounded. Most techniques require validation in unselected HF patients beyond the research environment. Intra- and inter-observer variability were rarely documented.

### Optimization of diastolic filling time

#### Iterative method

This method uses mitral valve PW Doppler.1 DFT is measured from the start of the E-wave until the end of the A-wave. A long AV delay is programmed and reduced in 20 ms steps until the A-wave truncates. The interval is then increased in 10 ms increments. The shortest AV delay without A-wave truncation is selected to maximize DFT.

A retrospective study examined 215 patients who underwent AV optimization within 30 days of CRT implantation.57 The majority were optimized using Ritter’s method (see below), the remainder using the iterative method. Over a mean follow-up period of 23 months, NYHA class and LVEF improved significantly. With no control group, as alluded to earlier, it is impossible to quantify the effects of AV optimization alone. The only direct benefit attributable to optimization was in ‘diastolic function stage’, which improved only in 9% of patients. Remarkably, the authors concluded that assessment of DFT was useful in all patients undergoing CRT.

The iterative method was recently compared against no optimization in a non-randomized observational cohort study of 100 patients.58 AV delay was optimized in 38 patients in conjunction with optimization of VV delay using tissue Doppler imaging. No significant improvement occurred in any clinical endpoint, including NYHA class, QOL score, change in 6MWT, death, or cardiac transplantation. Although Doppler-derived cardiac output increased at 6-month follow-up, LV dimensions and EF were unchanged.

#### Ritter’s method

This method is derived from dual-chamber pacing studies,58–60 with only limited validation in patients with HF.61 Two extreme AV delays are programmed. A short interval (AVshort) with clear A-wave truncation and a long interval (AVlong) without A-wave attenuation (e.g. 30 ms and 200 ms).59,62 For each, the time between QRS onset and completion of the A-wave is measured. The optimal AV delay is calculated using the formula: $AV_{opt} = AV_{short} + [(AV_{long} + QA_{long}) - (AV_{short} + QA_{short})].35,62 This is simplified to $AV_{opt} = AV_{long} - (QA_{short} - QA_{long}).59,62 Essentially, this calculates the longest DFT without interruption of the A-wave. Calculation rather than testing multiple AV delays reduces the procedure time to around 5 min.61,62

Whether or not the derived AV delay is ‘optimal’ in patients with HF is unclear. Major haemodynamic and structural differences exist compared to patients with preserved EF and high-degree AV block. In particular, calculation based on shifts in the mitral valve closure point may be inaccurate in the presence of high LV end-diastolic pressure.35,59 Only one small study (n = 10) validated Ritter’s method in patients with LVSD requiring DDD pacing.61 The ‘optimal’ AV interval was unusually defined by maximal LVEF as measured by radionuclide ventriculography. A good correlation was observed with Ritter’s method (intra-class quotient 0.92).
Ritter’s method, aortic valve VTI, and a device-based algorithm were compared in a prospective study involving 28 patients. The algorithm most accurately predicted optimal AV delay defined by invasive dP/dt max in both atrial-sensed and atrial-paced modes. Ritter’s method was the least accurate technique.

Mitral inflow velocity time integral

The mitral inflow VTI theoretically represents the LV filling volume, assuming a constant mitral valve area. The AV delay is adjusted to maximize the mitral inflow VTI. Four methods of AV optimization were compared in 30 patients against invasive dP/dt max (mitral inflow VTI, DFT, aortic valve VTI, and Ritter’s method). The ‘optimal’ AV delay was predicted in 97% of patients by mitral inflow VTI, in 67% by DFT, and in 43% by aortic valve VTI. Ritter’s method was correct in none.

Simplified (Meluzin) mitral inflow method

Meluzin et al. proposed a method to align the end of ventricular filling and onset of ventricular contraction, using a single recording of transmitral flow lasting 5–10 s. The maximum AV delay allowing full ventricular capture, lowered by 5–10 ms, is designated the ‘long AV delay’. The time between the end of the A-wave and onset of systolic MR is measured (termed ‘t1’). The optimal AV delay is obtained by subtracting ‘t1’ from the ‘long AV delay’. This technique is again limited by the need for detectable MR.

Only one study optimized CRT using the Meluzin method. Eighteen patients were studied 3 months after CRT implantation. No follow-up or randomization was included. The ‘optimal’ AV delay was simply compared with optimal AV delay −50 ms and +28 ms at this single timepoint. Cardiac output calculated by right heart catheterization was significantly higher (4.5 ± 0.7 L/min) at the mean optimal AV delay of 149 ± 17 ms, compared with 4.3 ± 0.7 L/min and 4.4 ± 0.8 L/min at optimal AV delay −50 ms and +28 ms, respectively.

Diastolic mitral regurgitation (Ishikawa) method

Diastolic MR is observed in many patients with HF, as a consequence of elevated LV end-diastolic pressure. This method aims to minimize diastolic MR. A long AV delay is selected to induce diastolic MR. The optimal AV delay is calculated by subtracting the duration of diastolic MR from the initial long AV delay.

A single study examined the Ishikawa method in just five consecutive patients. The ‘optimal’ delay was compared with selected longer and shorter delays (±25 ms). The reason for choosing these comparators is unclear. Echocardiographic cardiac output and DFT were greatest at the optimal AV delay. With no control group, the improvement in NYHA class over a mean of 2.3 years (1.4 ± 0.5 vs. 3.6 ± 0.5, P < 0.001) may simply reflect the effect of CRT alone.

Ismer method

A bipolar oesophageal electrode is passed to provide a left atrial electrogram. A mitral valve PW Doppler trace and real-time pacemaker markers from the oesophageal electrode are obtained. A complex formula involving these measurements is used to estimate the optimal AV delay.

A single study compared the Ismer method against greatly longer and shorter AV delays (±50 ms) in 11 patients. There was no randomization, follow-up, or clinical outcomes. Despite conducting 26 tests for significance, only one was positive; LVEF at optimal AV delay (28 ± 12%) was significantly higher than that at optimal AV delay, −50 ms (20 ± 7%). However, LVEF failed to improve when compared with baseline (27.3 ± 11.9%).

Optimization of markers of systolic function

Left ventricular outflow tract velocity time integral

Atrial-ventricular delay is incrementally adjusted to maximize echocardiographic cardiac output. Three small studies have employed LVOT VTI to optimize CRT. The first included 36 patients. There was no randomization, follow-up, or clinical outcomes. The so-called ‘optimal’ AV delay was defined solely by the greatest
LVOT VTI. The limitations are highlighted by the marked variation in optimal delay during exercise, and even between supine and seated positions (99 ± 19 ms vs. 84 ± 22 ms, P = 0.052). At peak heart rate, the optimal AV delay increased by over 100 ms.

The second study included just 19 patients. Again the 'optimal' AV delay was defined by the greatest LVOT VTI. Again there was no randomization. Although NYHA class improved at 6 months, the benefit (if any) attributable to optimization is impossible to discern. The simultaneous optimization of AV and VV delay, coupled with the lack of control group, precludes conclusions regarding AV delay alone.

A third study included 33 patients but was again neither randomized nor blinded. EF, myocardial performance index (MPI), and E/Ea (a marker of diastolic function) all improved significantly immediately post-optimization. Results after 43 ± 5 days follow-up were mixed. While 6MWT and N-terminal pro B type natriuretic peptide significantly improved, EF and QOL were unchanged. Once again the absence of controls hinders interpretation.
Table 3  Echocardiographic optimization of atrioventricular (AV) delay in cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Echocardiographic optimization method</th>
<th>Effect of optimization</th>
<th>Timing of optimization after implant</th>
<th>Mean AV delay (ms)</th>
<th>VV delay optimized</th>
<th>Randomized</th>
<th>Blinded</th>
<th>Mean follow-up (months)</th>
<th>Further optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawhney et al.36</td>
<td>40</td>
<td>Aortic valve VTI</td>
<td>+10 points QOL, +0.6 NYHA, +4.4% LVEF</td>
<td>&lt;24 h</td>
<td>119 ± 34</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Meluzin et al.53</td>
<td>18</td>
<td>Mitral inflow</td>
<td>+0.2 L/min CO by Swan Ganz</td>
<td>3 months</td>
<td>148 ± 17</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Porciani et al.69</td>
<td>21</td>
<td>Myocardial performance index</td>
<td>−0.49 MPI</td>
<td>&lt;24 h</td>
<td>97 ± 27</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Scharf et al.16</td>
<td>36</td>
<td>LVOT VTI</td>
<td>+0.047 cm/s LVOT VTI per 10 b.p.m. increase per 20 ms increase AV delay</td>
<td>Not stated</td>
<td>99 ± 19</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Riedlbachova et al.51</td>
<td>19</td>
<td>LVOT CO</td>
<td>+0.6 L/min LVOT CO, +2.7% LVEF, −1 NYHA</td>
<td>Not stated</td>
<td>140</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>Not stated</td>
</tr>
<tr>
<td>Inoue et al.56</td>
<td>5</td>
<td>Ishikawa diastolic MR</td>
<td>+0.8 L/min LVOT CO, +38 ms DFT, −2.2 NYHA</td>
<td>Not stated</td>
<td>133 ± 66</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>Yes</td>
</tr>
<tr>
<td>O’Donnell 200534</td>
<td>40</td>
<td>Ritter method</td>
<td>93% of patients required re-optimization</td>
<td>&lt;24 h</td>
<td>126</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>Yes</td>
</tr>
<tr>
<td>Melzer et al.55</td>
<td>11</td>
<td>Isner method</td>
<td>+12% LVEF, echo dysynchrony non-significant</td>
<td>Not stated</td>
<td>106 ± 38</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Jansen et al.35</td>
<td>30</td>
<td>Mitral VTI, DFT, Aortic valve VTI, Ritter method</td>
<td>+233 dynes/s (+32%), (1) &gt; (2) &gt; (3) &gt; (4) correlation with invasive LV dP/dtmax</td>
<td>&lt;24 h</td>
<td>120 ± 26</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Kerlan et al.27</td>
<td>40</td>
<td>Aortic valve VTI, Ritter method</td>
<td>(1) +19% aortic valve VTI, (2)−12%</td>
<td>&lt;24 h</td>
<td>119 ± 34</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Kedia et al.57</td>
<td>215</td>
<td>Ritter method or iterative method</td>
<td>No mortality difference +9% of patients ≥ 1 diastolic stage</td>
<td>&lt;30 days</td>
<td>135 ± 40</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>13</td>
<td>Not stated</td>
</tr>
<tr>
<td>Stockburger et al.26</td>
<td>26</td>
<td>LVPEI, IVD, (4) FTc, (4) MPI</td>
<td>−27 ms LVPEI, −43 ms IVD, +0.09 FTc, −0.36 MPI</td>
<td>&lt;3 days</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>21</td>
<td>Not stated</td>
</tr>
<tr>
<td>Porciani et al.95</td>
<td>22</td>
<td>Myocardial performance index</td>
<td>−0.40 MPI, 82% of patients required re-optimization</td>
<td>&lt;1 week</td>
<td>115 ± 24</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Morales et al.49</td>
<td>41</td>
<td>Doppler dP/dt</td>
<td>+0.9 NYHA, +4.6% LVEF</td>
<td>2–4 months</td>
<td>103</td>
<td>No</td>
<td>No</td>
<td>Single</td>
<td>6</td>
<td>Not stated</td>
</tr>
<tr>
<td>Gold 200738</td>
<td>28</td>
<td>Ritter method</td>
<td>maximal invasive LV dP/dtmax using EEHF+</td>
<td>Not stated</td>
<td>134 ± 45</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Zhang et al.16</td>
<td>31</td>
<td>Ritter method</td>
<td>56% of patients required re-optimization</td>
<td>&lt;24 h</td>
<td>99 ± 30</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>16</td>
<td>Yes</td>
</tr>
<tr>
<td>Vidal et al.16</td>
<td>100</td>
<td>Iterative</td>
<td>+0.7 L/min CO by aortic valve VTI, +52 m 6MWT</td>
<td>24−72 h</td>
<td>137</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>Not stated</td>
</tr>
<tr>
<td>Hardt et al.24</td>
<td>33</td>
<td>LVOT VTI</td>
<td>+26 m 6MWT, −599 ng/L NT-proBNP</td>
<td>31 ± 8 weeks</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>43 days</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

AVD, atrioventricular delay; CO, cardiac output; dP/dtmax, maximal change in pressure/change in time; E, maximum E-wave from mitral inflow; Ea, maximum E-wave derived from tissue Doppler imaging of the mitral annulus; EEHF+, Expert Ease for Heart Failure algorithm; FTc, left ventricular filling fraction; IVD, interventricular delay; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVPEI, left ventricular pre-ejection interval; MPI, myocardial performance index; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; QOL, quality-of-life by Minnesota Living with Heart Failure Questionnaire; VTI, velocity time integral.
Aortic valve velocity time integral
A single blind study randomized 40 patients to aortic VTI-optimized AV delay (mean 119 ± 34 ms) or an empirical 120 ms. Those optimized had an improvement in the subjective variables of QOL and NYHA class at 3 months, but not the objective variables measured (6MWT, LVEF, or LV volumes). The lack of a primary endpoint must raise concerns regarding multiple hypothesis testing. Subsequently, the same group found significantly different optimal AV delays when comparing the aortic valve VTI and Ritter methods (119 ± 34 ms vs. 95 ± 24 ms, respectively). It is unclear whether results originate from the same cohort, given the discrepancies but also similarities in baseline characteristics (both n = 40, mean optimal AV delay 119 ± 34 ms, mean NYHA class 3.1). The aortic valve VTI method, acting as both outcome measure and comparator, exhibited the highest increase from baseline.

Doppler-derived dP/dtmax
The AV delay is adjusted to produce the greatest dP/dt. The MR CW Doppler velocity curve represents the instantaneous pressure difference between the LV and atriun in systole. The normally steep downward gradient is reduced in LVSD. Time (dt) is measured between two points on the MR jet (1 m/s and 3 m/s). These points correspond to LV–LA gradients of 4 mmHg and 36 mmHg, respectively, according to the modified Bernoulli equation (pressure gradient = 4v²). Thus, dP is a constant at 32 mmHg. This approach is limited by the need for detectable MR. The technique has been validated against cardiac catheterization in patients with HF.

A recent study allocated 41 consecutive patients on a 2:1 basis to optimization using Doppler-derived dP/dtmax or an empirical AV delay of 120 ms. Adequate images were obtained in 23 of 26 patients. Intra- and inter-observer repeatability were excellent (r = 0.99 and 0.98, respectively). At 6 months, the optimized group had a significantly lower NYHA class (2.1 ± 0.1 vs. 3.0 ± 0.2, P < 0.01) and higher echocardiographic LVEF (32.1 ± 1.0 vs. 27.5 ± 1.6, P < 0.05).

Myocardial performance index
MPI is calculated as the sum of isovolumic contraction and relaxation time divided by ejection time. It is considered a measure of global cardiac function. In 170 patients, MPI differentiated between those with normal LV function, moderate HF (NYHA class II, LVEF 30–50%), and severe HF (NYHA class III–IV, awaiting cardiac transplantation). MPI also correlated with invasive dP/dtmax in 34 subjects with varying degrees of LV dysfunction (r = 0.82, P < 0.0001). Ejection time is the interval between the start and end of aortic flow. Isovolumic contraction is measured from the mitral A-wave terminus to the onset of aortic flow. Isovolumic relaxation is measured from the aortic flow terminus to the onset of the mitral E-wave. Improvement in MPI is signaled by a lower numerical value.

Two small studies have ‘optimized CRT’ using MPI. Neither included any randomization or clinical outcomes. Optimization reduced MPI by 0.49 in 21 patients. No other outcome measure was assessed. In the second study of 26 patients, one of three pre-specified AV delays was selected based on agreement between three additional echocardiographic measures (LV pre-ejection interval, VV delay, and the filling fraction of the cardiac cycle). Thirteen patients were considered optimal at 90 ms, 10 at 120 ms, and three at 150 ms. Whether AV optimization contributed to subsequent remodelling is unknown, given the lack of control group.

Do different echocardiographic methods produce different atrioventricular delays?
The evidence calls into question the entire concept of the so-called ‘optimal’ AV delay (Table 3). The supposedly optimal mean delay ranged from 97 ms to 148 ms, despite recruitment of similar patients. In accordance with international guidelines, patients typically had symptomatic HF (NYHA III/IV) with prolonged QRS duration ≥120 ms and EF ≤35%. Direct comparison of methods raise similar doubts. In 40 patients, the optimal AV delay was 119 ± 34 ms using AV VTI, but only 95 ± 24 ms using Ritter’s method. Another study compared AV VTI and Ritter’s method in 28 patients. The optimal AV delays were comparable in atrial-sensed mode (121 ± 28 ms vs. 122 ± 28 ms), but not in atrial-paced mode (160 ± 35 ms vs. 118 ± 33 ms). ‘Optimal’ appears to be defined largely by the methods of optimization and measures of response.

Non-echocardiographic optimization methods
Studies of non-echocardiographic optimization of AV delay are summarized in Table 4.

Invasive left ventricular dP/dtmax
PATH-CHF and PATH-CHF II trials optimized AV delay at implantation using invasive LV dP/dtmax (Table 4). Short-term follow-up demonstrated improvements in exercise capacity and QOL. Three other studies totalling 100 patients optimized AV delay at implantation using invasive LV dP/dtmax (Table 4). No follow-up was undertaken. Invasive dP/dtmax increased acutely by up to 22%.

Impedance cardioigraphy
Impedance cardioigraphy (ICG) was initially used to ‘optimize’ AV delay in patients with dual-chamber pacemakers. Cardio output is evaluated non-invasively by measuring changes in impedance of an alternating current applied across the patient’s thorax. The correlation with invasive measurements is highly variable, particularly in patients with HF.

Four studies totalling 83 patients have optimized AV delay using ICG (Table 4). Again, all were acute studies with no follow-up. Correlations between AV delay determined by echocardiography and ICG were good (r = 0.84, r = 0.74). However, the actual benefit of AV optimization was either negligible (±2% cardiac output) or impossible to determine.
<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Optimization method</th>
<th>Effect of optimization</th>
<th>Timing of optimization after implant</th>
<th>Mean AV delay (ms)</th>
<th>VV delay optimized</th>
<th>Randomized</th>
<th>Blinded</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATH-CHF72</td>
<td>41</td>
<td>Invasive LV dP/dt_{max}</td>
<td>6MWT + 44 m, MLHFQ = 19.3, peak VO₂ = 1.8</td>
<td>Time of implant</td>
<td>112 ± 33</td>
<td>No</td>
<td>Yes</td>
<td>Single</td>
<td>1</td>
</tr>
<tr>
<td>PATH-CHF II73</td>
<td>86</td>
<td>Invasive LV dP/dt_{max}</td>
<td>6MWT +47 m, MLHFQ = 8.1, peak VO₂ = 2.5</td>
<td>Time of implant</td>
<td>119 ± 32</td>
<td>No</td>
<td>Yes</td>
<td>Single</td>
<td>3</td>
</tr>
<tr>
<td>Aurrichio et al.75</td>
<td>27</td>
<td>Invasive LV dP/dt_{max}</td>
<td>+22%</td>
<td>Time of implant</td>
<td>98 ± 52</td>
<td>Yes</td>
<td>Yes</td>
<td>Single</td>
<td>None</td>
</tr>
<tr>
<td>Aurrichio et al.76</td>
<td>39</td>
<td>Invasive LV dP/dt_{max}</td>
<td>+77 mmHg/s (+14%)</td>
<td>Time of implant</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Single</td>
<td>None</td>
</tr>
<tr>
<td>van Gelder et al.75</td>
<td>34</td>
<td>Invasive LV dP/dt_{max}</td>
<td>+89 mmHg/s (+10%)</td>
<td>Time of implant</td>
<td>147 ± 32</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Tse et al.82</td>
<td>6</td>
<td>Impedance cardiography</td>
<td>Unclear</td>
<td>Not stated</td>
<td>153 ± 24</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Santos et al.81</td>
<td>7</td>
<td>Impedance cardiography</td>
<td>+2% CO by impedance cardiography</td>
<td>Not stated</td>
<td>137 ± 26</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Braun et al.83</td>
<td>24</td>
<td>Impedance cardiography</td>
<td>Unclear</td>
<td>1 month</td>
<td>121 ± 18</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Heinroth et al.84</td>
<td>46</td>
<td>Impedance cardiography</td>
<td>0.46 L/min (+11%) CO by impedance cardiography</td>
<td>3–5 days</td>
<td>119</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Butter et al.85</td>
<td>57</td>
<td>FPPG</td>
<td>+16.1 mmHg invasive aortic pulse pressure</td>
<td>Time of implant</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Whinnett et al.82</td>
<td>15</td>
<td>FPPG</td>
<td>+21 mmHg systolic blood pressure</td>
<td>3–30 months</td>
<td>168</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Whinnett et al.86</td>
<td>12</td>
<td>FPPG</td>
<td>+17.4 mmHg systolic blood pressure</td>
<td>1–24 months</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Porciani et al.85</td>
<td>20</td>
<td>Intracardiac electrogram</td>
<td>+3% ejection fraction, −3.0 T_{mv} 12-SD</td>
<td>9 ± 8 months</td>
<td>168 ± 28</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

BiV, biventricular; LV, left ventricular; LV dP/dt_{max}, left ventricular maximal change in pressure/change in time; 6MWT, 6-min walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; FPPG, finger photoplethysmography; CO, cardiac output; VTI, velocity time integral; T_{mv}, 12-SD, standard deviation of time to minimal systolic volume for six basal and six mid-LV segments.
document baseline measurements prior to optimization. The third study adjusted AV and VV delay concurrently, increasing mean cardiac output by 11.2%. Alternatively, dedicated equipment may confound results. 

**Finger photoplethysmography**

Finger photoplethysmography (FPPG) non-invasively measures change in blood pressure. Measurement is possible using a conventional pulse oximetry probe with appropriate software and correction algorithms. Signal variations owing to pacing and random errors may confound results. Alternatively, dedicated equipment is commercially available. A rapidly responding inflatable finger cuff maintains the volume of the finger constant during the cardiac cycle. A photoelectric photoplethysmograph and a volume-clamp circuit determines beat-to-beat blood pressure changes.

Three studies have demonstrated acute improvement in blood pressure following AV optimization using FPPG. Optimal AV delay was defined by invasive aortic pulse pressure in 57 patients. FPPG successfully identified this optimal delay in 78% of cases. In two smaller studies using FPPG increased non-invasive systolic blood pressure by 17 mmHg and 21 mmHg. No clinical outcomes were assessed.

**Expert Ease for Heart Failure**

Expert Ease for Heart Failure (EEHF) algorithm calculates both sensed and paced AV delays by measuring the intrinsic-sensed and paced AV intervals (from the device) and QRS duration (from surface ECG). Calculation includes coefficients that vary depending on the pacing chamber (LV or Biv) and LV lead location.

When compared with Ritter’s method and AV VTI, the EEHF algorithm was superior in predicting optimal AV delay as determined by invasive LV dp/dtmax. Results correlated closely with the maximum achievable LV dp/dtmax (R² = 0.99, P < 0.0001).

**Intracardiac electrogram (IEGM)**

Optimization of both AV and VV delays using an IEGM method has recently been described. The optimal delays correlated closely with those derived using echocardiographic aortic VTI methods (all correlation coefficients > 95%, P < 0.05). The same IEGM optimization method has been shown to reduce LV dyssynchrony and improve systolic function as measured by three-dimensional echo. A prospective, multicentre trial investigating this method is currently recruiting patients.

**Peak endocardial acceleration**

Peak endocardial acceleration (PEA) detects mechanical acceleration of the heart through a microaccelerometer located at the distal end of the ventricular lead. The amplitude of the PEA signal varies with myocardial contractility. In 15 patients with dual-chamber pacemakers, optimal AV delays determined by PEA analysis correlated with those obtained using Ritter’s method (r = 0.79, P = 0.0012).

The ongoing CLEAR (Clinical Evaluation of Advanced Resynchronization) study is a multicentre randomized, single-blind, controlled trial in patients with NYHA Class III or IV HF. PEA-based optimization will be compared with optimization according to the investigating centre’s standard clinical practice.

**How was atrioventricular delay optimized in clinical trials of cardiac resynchronization therapy?**

Most of the landmark clinical trials included AV optimization (Table 5). The COMPANION trial employed the device-based Expert Ease for Heart FailureTM algorithm to optimize AV delay but not VV delay. The MUSTIC trial specified Ritter’s formula for optimizing AV delay. The methods described in the MIRACLE and CARE-HF design publications are unclear. Both involve Doppler echocardiography of transmural flow. Both advise that ‘the AV delay is set at a value which provides maximum separation of the E and A waves, representing passive ventricular filling and atrial contraction, respectively’. Subsequent publications by the MIRACLE study group refer to Ritter’s method. In contrast, Appendix 8 of the CARE-HF Investigational Plan describes the iterative method. On the basis of these trials, recent guidelines from the American Society of Echocardiography recommend AV optimization using either the iterative or the Ritter method.

**How often should we optimize atrioventricular delay?**

The timing of optimization poses many questions. When should initial optimization be performed? Does the optimal AV delay change over time? Who requires repeat optimization? When should re-optimization occur? Optimization was performed within days of implantation in almost all studies and clinical trials (Tables 2 and 4). The schedule of re-assessment was similar in the MIRACLE and CARE-HF trials. Optimization was performed pre-discharge, and after 3, 6, and 9 months in the MIRACLE trial. In CARE-HF, optimization occurred pre-discharge, and after 3, 9, and 18 months. The results of optimization in these clinical trials are not yet reported.

Several small studies have documented variation of AV delay over time. Although no significant change occurred in mean optimal AV delay, change in individual patients was common. Temporal variations were specifically examined in three studies involving between 22 and 40 patients. About 56–82% of patients required re-optimization during follow-up ranging from 3 months to a mean of 16 months. Such changes are to be expected, given the effects of CRT on remodeling and systolic function. Analysis of clinical trial data would improve our understanding of temporal variation in AV delay.

**Should we optimize only the so-called ‘non-responders’?**

Some have advocated optimizing only the so-called ‘non-responders’. No published evidence supports this standpoint.

---

**Table 5**

<table>
<thead>
<tr>
<th>Study</th>
<th>Optimization Method</th>
<th>Timing of Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE</td>
<td>Expert Ease for Heart Failure</td>
<td>Pre-discharge</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>Expert Ease for Heart Failure</td>
<td>3, 6, 9, 18 months</td>
</tr>
<tr>
<td>COMPANION</td>
<td>Device-based Expert Ease for Heart Failure</td>
<td>Pre-discharge</td>
</tr>
<tr>
<td>MUSTIC</td>
<td>Ritter’s formula</td>
<td>Pre-discharge</td>
</tr>
</tbody>
</table>

---

**Figure 1**

A schematic diagram illustrating the timing of optimization in clinical trials of cardiac resynchronization therapy.
<table>
<thead>
<tr>
<th>Study acronym</th>
<th>n</th>
<th>Echocardiographic optimization method</th>
<th>Alternative optimization method</th>
<th>Follow-up (months)</th>
<th>Timing of optimization after implant</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC-SR5</td>
<td>48</td>
<td>Ritter’s method</td>
<td>None</td>
<td>3</td>
<td>Time of implant</td>
<td>6MWT, (+73) m, (P &lt; 0.001)</td>
</tr>
<tr>
<td>MUSTIC-AF17</td>
<td>37</td>
<td>None</td>
<td>None</td>
<td>3</td>
<td>None</td>
<td>6MWT, (+32) m, (P = 0.05)</td>
</tr>
<tr>
<td>MIRACLE3</td>
<td>453</td>
<td>Ritter’s method</td>
<td>None</td>
<td>6</td>
<td>Pre-discharge, 3 and 6 months</td>
<td>6MWT, (+29) m, (P = 0.005)</td>
</tr>
<tr>
<td>MIRACLE -ICD5</td>
<td>369</td>
<td>Ritter’s method</td>
<td>None</td>
<td>6</td>
<td>Pre-discharge, 3 and 6 months</td>
<td>6MWT, (+2) m, (P = 0.36)</td>
</tr>
<tr>
<td>MIRACLE -ICD II6</td>
<td>186</td>
<td>Ritter’s method</td>
<td>None</td>
<td>6</td>
<td>Pre-discharge, 6 months</td>
<td>6MWT, (+5) m, (P = 0.59)</td>
</tr>
<tr>
<td>CONTAK-CD118</td>
<td>490</td>
<td>None</td>
<td>None</td>
<td>6</td>
<td>None</td>
<td>6MWT, (+20) m, (P = 0.043)</td>
</tr>
<tr>
<td>COMPANION2</td>
<td>1520</td>
<td>None</td>
<td>Device-based algorithm</td>
<td>16.2 (Median)</td>
<td>Time of implant</td>
<td>Death, Admission, HR 0.81, (P = 0.015)</td>
</tr>
<tr>
<td>CARE-HF3</td>
<td>813</td>
<td>Iterative method</td>
<td>None</td>
<td>29.4 (Mean)</td>
<td>Pre-discharge 3, 9 and 18 months</td>
<td>Death or MACE HR 0.63, (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

\(6\text{MWT} = 6\) min walk test, HF = heart failure, HR = hazard ratio, MACE = major adverse cardiovascular event, MLHFQ = Minnesota Living with Heart Failure Questionnaire, NYHA = New York Heart Association, VO\(_2\) = oxygen consumption (mL/min/kg).
The entire concept of ‘response’ is questionable. Although numerous clinical and volumetric measurements have been proposed, there is no agreed definition of response. To restrict optimization to ‘non-responders’ may deny ‘responders’ additional benefit. Recent analysis of the CARE-HF trial revealed the prognostic benefits of CRT to be independent of symptom severity.

**Conclusion**

Optimizing CRT has major financial implications in clinical practice. The cost of echocardiographic equipment, staff, training, and patient transport are all significant. Many questions remain unanswered. Sequential BV pacing fails to improve clinical outcomes. Routine optimization of VV delay cannot be recommended. The physiological basis and acute haemodynamic benefit of optimizing AV delay are undeniable. Whether this translates into long-term improvements in remodelling, symptoms, or prognosis is unknown. Randomized controlled trials comparing methods are needed, with long-term clinical endpoints.

Despite limited validation, optimization was included in landmark clinical trials and is inherent to evidence-based practice. Patients in the landmark clinical trials were optimized using transmural Doppler. It is impossible to separate the benefits of CRT with optimization from that of CRT alone. Nor should we try. Mitral Doppler. It is impossible to separate the benefits of CRT with optimization from that of CRT alone. Nor should we try.


Rao RK, Kumar UN, Schafer J, Wilmot E, De Lurgo D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. Circulation 2007;115:2136–2144.


Optimization of cardiac resynchronization therapy

77. van Gelder BM, Bracke FA, Meijer A, Pijls NH. The hemodynamic effect of intrinsic conduction during left ventricular pacing as compared to biventricular pacing. J Am Coll Cardiol 2005; 46:2305 – 2310.
The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.