# Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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# Chapter 15

## Cardiac resynchronization therapy in patients with ischemic vs. non-ischemic heart failure: Differential effect of optimizing interventricular pacing interval

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## ABSTRACT

**Background:** Whether sequential biventricular pacing provides substantial benefits over conventional simultaneous stimulation remains unclear, particularly regarding the differences between ischemic and non-ischemic patients. The purpose of this study was to evaluate the acute effect of inter-ventricular pacing interval (V-V) optimization on left ventricular (LV) systolic performance and dyssynchrony in ischemic vs. non-ischemic patients.

**Methods:** 69 consecutive patients underwent cardiac resynchronization therapy. Within 3 days after implantation, V-V was optimized by measuring (every 20 ms interval) LV systolic performance (LV outflow-tract velocity-time-integral, LVOT-VTI) and LV dyssynchrony (using tissue Doppler imaging). Optimal pacing configuration was the one achieving maximal increase in LVOT-VTI.

**Results:** Optimized sequential pacing provided a significant improvement in LVOT-VTI compared to simultaneous stimulation (from 138±42 mm to 163±38 mm, $p<0.001$) and was associated with a significant reduction in LV dyssynchrony (from 33±31 ms to 19±24 ms, $p<0.001$). The increase in LVOT-VTI and LV ejection fraction after implantation was greater in non-ischemic as compared to ischemic patients ($p<0.001$). However, V-V optimization yielded a larger improvement in LV systolic performance in ischemic patients ($p = 0.03$). Consequently, the 2 groups showed comparable response after V-V optimization. A significant correlation was observed between LV scar tissue and optimal V-V interval ($r = 0.58$, $p<0.001$), with a larger extent of scar related to a larger level of LV pre-activation, probably reflecting slow intra-LV conduction.

**Conclusions:** Optimized sequential biventricular pacing further increased LV systolic performance as compared to simultaneous stimulation, particularly in ischemic patients where the presence of a large scar was correlated with a larger LV pre-activation.

## INTRODUCTION

Cardiac resynchronization therapy (CRT) is currently considered an important breakthrough in the treatment of selected patients with drug-refractory heart failure and has rapidly evolved from the experimental stage into an established treatment modality.[1]

In the first generations of CRT devices both left ventricular (LV) and right ventricular (RV) pacing leads were activated simultaneously in order to resynchronize LV contraction. A novel feature on the more recent generations of CRT devices allows separate (sequential) timing of activation of the LV and RV pacing leads through a programmable inter-ventricular (V-V) pacing interval. Since this option is available, several studies have focused on the possibility of further enhancing the beneficial effects of CRT through optimization of the V-V pacing interval. Preliminary data have demonstrated that optimized sequential CRT, rather than simultaneous CRT, is able to further improve LV systolic performance, as measured by LV stroke volume or dP/dt.[2-9] In contrast, other studies demonstrated no or only limited additional clinical or echocardiographic benefits of V-V optimization compared with "standard" simultaneous CRT.[10,11] Moreover, the effect of V-V optimization on LV dyssynchrony has not been extensively studied and no data are available on the potential advantage of sequential CRT in patients with ischemic heart failure (who may demonstrate a less favorable response to CRT in absence of V-V optimization)[12] as compared to patients with non-ischemic heart failure. Accordingly, the purpose of this study was to evaluate the acute effects of varying degrees of RV or LV pre-activation on both LV hemodynamic profile and LV dyssynchrony. In addition, the beneficial effects of V-V optimization were compared between patients with ischemic and non-ischemic heart failure.

## METHODS

### Patient population

Sixty-nine consecutive heart failure patients, scheduled for implantation of a biventricular pacemaker, were included in this study. Patients were selected for CRT based on the following characteristics: LV ejection fraction (LVEF) ≤35%, QRS duration >120 ms and NYHA functional class III or IV, despite optimal medical treatment. Etiology was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or history of myocardial infarction or previous revascularization. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded.

## Device implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead (Easytrak 4512-80, Guidant Corp., or Attain-SD 4189, Medtronic Inc) was inserted through the coronary sinus, using an 8Fr-guiding catheter, and positioned in the lateral or postero-lateral vein. The right atrial and ventricular leads were positioned conventionally. The 3 leads were connected to a biventricular pacing device and, when an indication for an internal defibrillator existed, a combined device was implanted (Contak CD or Renewal, Guidant Corp., or Insync III-CD or Marquis, Medtronic Inc). These devices have two separate channels for RV and LV pacing with a programmable V-V interval. In all patients the implantation of the CRT device was successful without major complications.

## Study protocol

Before CRT, echocardiography was performed to evaluate LV dimensions and systolic function, whereas the extent of LV mechanical dyssynchrony was derived from tissue Doppler imaging (TDI). Within 3 days after implantation pacemaker settings were optimized. The atrio-ventricular interval was adjusted to maximize mitral inflow duration, as assessed with pulsed-wave Doppler echocardiography using the "iterative" method.[13] Next, V-V interval was modified by advancing LV or RV pacing by 20 ms intervals. For each patient seven different V-V intervals were examined: simultaneous biventricular pacing (= 0 ms), LV pre-activation (LV60 = 60 ms, LV40 = 40 ms and LV20 = 20 ms) and RV pre-activation (RV60 = 60 ms, RV40 = 40 ms and RV20 = 20 ms). For each combination, LV systolic function and the extent of LV dyssynchrony were assessed. Each recording period was preceded by a stabilization period of 3-5 minutes.

## Echocardiography

### *Image acquisition*

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric Healthcare, Horten, Norway). Images were obtained using a 3.5-Mhz transducer, at a depth of 16 cm in the apical views. For the TDI images, the sector width was adjusted to obtain a frame rate of at least 100 frames/second; pulse repetition frequencies were between 500 Hz and 1 kHz, resulting in aliasing velocities

between 16 and 32 cm/s. To minimize variability between examinations, all echocardiographic recordings were performed by the same operator. During the pulsed-wave Doppler acquisitions, an effort was made to maintain the same position of the sample throughout the investigation. All images were recorded digitally in cine-loop format and analyzed offline with commercial software EchoPac 6.1 (General Electric-Vingmed). Off-line analysis was performed by a different observer and was blinded to the pacing mode. Each parameter was measured and averaged over three consecutive beats during sinus rhythm.

### *Analysis of LV systolic function and LV dyssynchrony*

LV end-systolic and end-diastolic volumes were determined from the conventional apical 2- and 4-chamber views and LV ejection fraction (EF) was calculated using the biplane Simpson's technique. During V-V optimization, LV systolic function and the extent of LV dyssynchrony were assessed for each interval. As previously described,[6,9] the acute changes in LV systolic performance were quantified by measuring the LV outflow-tract velocity-time integral (LVOT VTI), using pulsed-wave Doppler during end-expiratory apnea. After the optimization of the pacemaker, patients were maintained in the individually optimized sequential biventricular pacing configuration that was defined as the setting with the highest LVOT VTI and LV volumes and EF were recalculated. An absolute increase in LVEF ≥5% was considered as a significant positive response to CRT.[14]

To quantify the extent of LV dyssynchrony, the maximum delay in peak velocity between the earliest and the latest activated segments within the basal segments of septum, inferior, anterior and lateral wall was calculated.[15] From previous observations, a delay ≥65 ms was considered to represent significant LV dyssynchrony.[15] Inter-observer agreement and intra-observer agreement for assessment of LV dyssynchrony were 90% and 96% respectively.[16]

## Statistical analysis

Continuous data are presented as mean±SD; dichotomous data are presented as numbers and percentage. Student *t* test and $\chi^2$ test were used for appropriate comparisons. Sequential data measurements, in the total population and in the groups of patients with and without ischemic cardiomyopathy, were analyzed by repeated measures analysis of variance (ANOVA) followed by post hoc Scheffe's correction for multiple tests. A two-way ANOVA analysis was performed for comparison of time trends between patients with and without ischemic cardiomyopathy. Simultaneous biventricular pacing was considered as the reference pacing configuration to compare all sequential configurations and to assess the correlation between the change in LVOT VTI and LV dyssynchrony. Pearson's correlation coefficient was used to

quantify correlations between quantitative variables. Agreement for the optimal V-V interval between LVOT VTI and LV dyssynchrony was assessed using weighted κ statistics. A p-value <0.05 was considered to be statistically significant. A statistical software program SPSS 12.0 (SPSS Inc, Chicago, Il, USA) was used for statistical analysis.

## RESULTS

### Pre-implantation data

Sixty-nine patients were included (58 men; mean age 66±10 years). Baseline patient characteristics are summarized in Table 1. Most patients were in NYHA class III (88%), and 41 (59%) patients had ischemic heart failure. Echocardiography revealed severe LV dilatation and dysfunction (mean LV end-diastolic volume 251±74 ml, mean LVEF 22.9±7.8%). The mean extent of LV dyssynchrony was 75±24 ms.

**Table 1.** Baseline patient characteristics (n = 69)

| | |
|---|---|
| Age (years) | 66 ± 10 |
| Gender, M / F | 58 / 11 |
| NYHA class | |
| III | 61 (88%) |
| IV | 8 (12%) |
| QRS duration (ms) | 163 ± 32 |
| Rhythm | |
| Sinus rhythm | 57 (83%) |
| Atrial fibrillation | 12 (17%) |
| Etiology | |
| Ischemic | 41 (59%) |
| Idiopathic | 28 (41%) |
| LVEF (%) | 22.9 ± 7.8 |
| LVEDV (ml) | 251 ± 74 |
| LVESV (ml) | 196 ± 73 |
| LVOT VTI (mm) | 118 ± 36 |
| LV dyssynchrony (ms) | 75 ± 24 |

LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVOT VTI = left ventricular out-flow tract velocity-time integral.

## Simultaneous and sequential CRT

After CRT implantation, simultaneous CRT (V-V interval = 0 ms) resulted in a significant improvement of the cardiac output: LVOT VTI increased from 118±36 mm at baseline to 138±42 mm ($p<0.001$) after CRT; LVEF improved from 22.9±7.8% to 28.7±5.6% ($p<0.001$). A total of 34 (49%) patients showed a significant increase (≥5%) in LVEF. In addition, compared with baseline, simultaneous CRT significantly reduced LV dyssynchrony from 75±24 ms to 33±31 ms ($p<0.001$).

The LV systolic performance was further improved by optimizing the V-V interval, with the LVOT VTI increasing from 138±42 mm during simultaneous CRT to 163±38 mm ($p<0.001$) during sequential CRT and LVEF improving from 28.7±5.6% to 34.3±6.9% ($p<0.001$). In addition, LV dyssynchrony decreased from 33±31 ms to 19±24 ms ($p<0.001$). The percentage of significant response to CRT increased from 49% to 74% (51 patients).

In 18 patients (26%) the highest LVOT VTI was achieved during simultaneous CRT. In the remaining 51 patients (74%), LV pre-activation was the optimal setting in 38 patients (55%), with LV60 in 11 patients (16%), LV40 in 11 patients (16%) and LV20 in 16 patients (23%). For 13 patients (19%) RV pre-activation was the optimal setting, with RV60 in 1 patient (2%) and RV20 in 12 patients (17%); no patient had an optimal cardiac output at RV40 (Figure 1).

The concordance between V-V intervals yielding the highest LVOT VTI and the lowest LV dyssynchrony was excellent (weighted kappa = 0.88, $p<0.001$) (Figure 2 and Table 2). In addition, the absolute changes in LV dyssynchrony, showed a significant correlation ($r = 0.58$; $p<0.001$) with the absolute changes in LVOT VTI. Figure 3 shows an example of a patient with an optimal V-V interval of LV60 and how changes in LV dyssynchrony and LVOT VTI were clearly correlated.

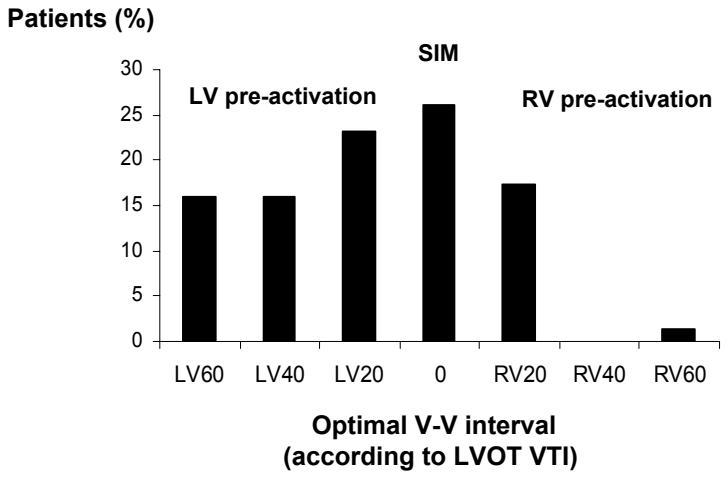


**Figure 1.** Distribution of optimal V-V interval configuration resulting in highest left ventricular cardiac output (LVOT VTI).
LV = left ventricle; RV = right ventricle; SIM = simultaneous.

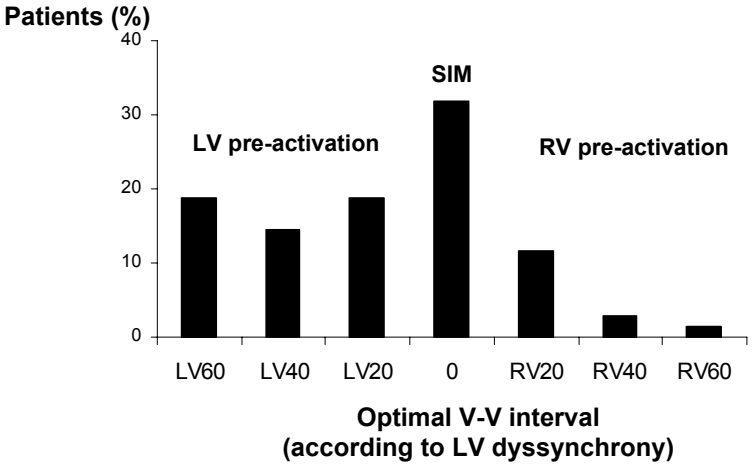


**Figure 2.** Distribution of optimal V-V interval configuration resulting in least left ventricular dyssynchrony.
LV = left ventricle; RV = right ventricle; SIM = simultaneous.

**Table 2.** Kappa statistic for LVOT VTI-optimized V-V interval vs. LV dyssynchrony-optimized V-V interval

| LVOT VTI / LV dyssynchrony | LV60 | LV40 | LV20 | 0 | RV20 | RV40 | RV60 | Total |
|---|---|---|---|---|---|---|---|---|
| **LV60** | **9** | 0 | 1 | 1 | 2 | 0 | 0 | 13 |
| **LV40** | 0 | **11** | 0 | 0 | 0 | 0 | 0 | 11 |
| **LV20** | 1 | 0 | **11** | 1 | 0 | 0 | 0 | 13 |
| **0** | 1 | 0 | 2 | **15** | 2 | 0 | 0 | 20 |
| **RV20** | 0 | 0 | 2 | 0 | **7** | 0 | 0 | 9 |
| **RV40** | 0 | 0 | 0 | 1 | 1 | **0** | 0 | 2 |
| **RV60** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 1 |
| **Total** | 11 | 11 | 16 | 18 | 12 | 0 | 1 | **69** |

Weighted Kappa = 0.88, $p<0.001$; LVOT VTI = left ventricular out-flow tract velocity-time integral

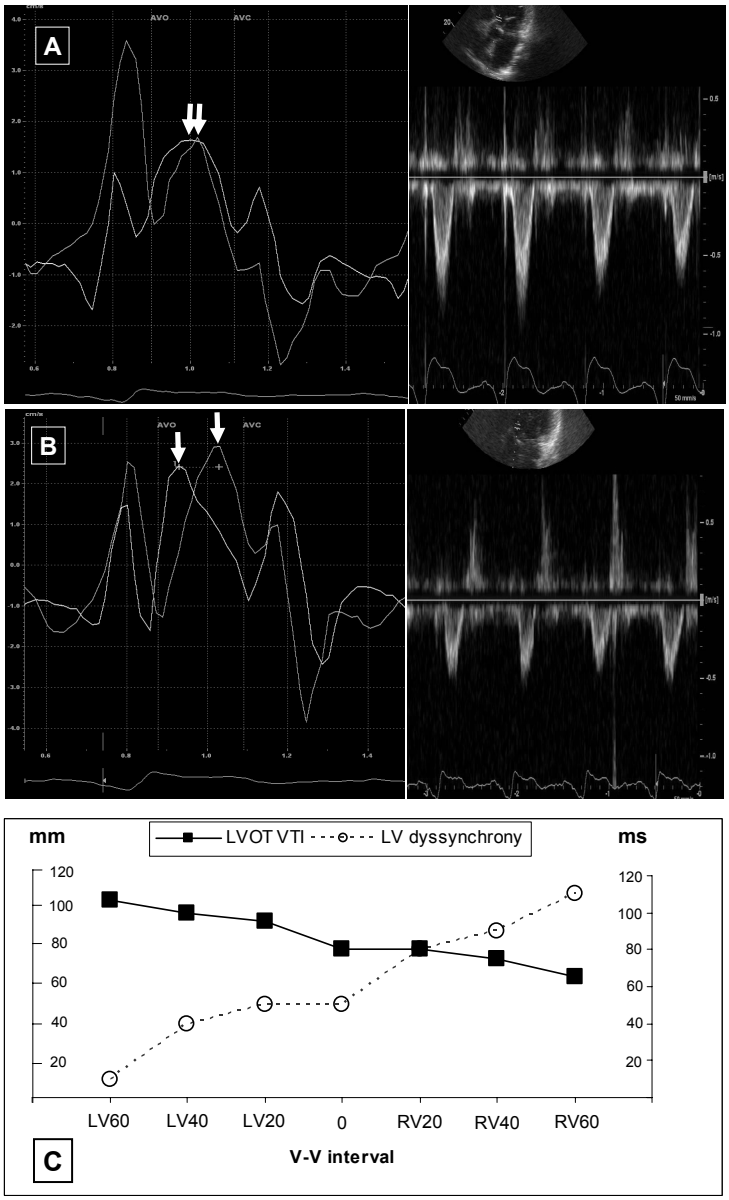


**Figure 3.** An example of patient with optimal V-V interval of LV60.

A: LV dyssynchrony and LV out-flow-tract velocity-time integral (LVOT VTI) at V-V interval of LV60.

B: LV dyssynchrony and LVOT VTI during simultaneous CRT.

C: Changes of LV dyssynchrony and LVOT VTI during V-V interval optimization.

## V-V interval optimization in ischemic vs. non-ischemic cardiomyopathy

After implantation, simultaneous CRT (V-V interval = 0 ms) resulted in a significant improvement of LVOT VTI and LVEF ($p<0.01$) both in ischemic and non-ischemic patients (Table 3). However, this improvement (change from baseline to simultaneous CRT) was larger in non-ischemic patients (with a relative increase in LVOT VTI of 29±30 mm and in LVEF of 8.1±6.2%) as compared to ischemic patients (with a relative increase in LVOT VTI of 14±14 mm and in LVEF of 3.4±5.5%, $p<0.001$ vs. non-ischemic patients). Consequently, among non-ischemic patients, 19 (68%) patients showed an increase ≥5% in LVEF, while among ischemic patients, only 14 (34%) patients had a significant response to CRT.

In turn, V-V optimization yielded a larger improvement of LVOT VTI and LVEF (change from simultaneous CRT to optimized sequential stimulation) in ischemic patients (Table 3); a relative increase in LVOT VTI of 34±25 mm in ischemic patients vs. a relative increase of 16±15 mm in non-ischemic patients ($p = 0.03$ ischemic vs. non-ischemic patients); a relative increase in LVEF of 7.6±6.1% vs. 4.4±5.9% in ischemic patients ($p = 0.02$ ischemic vs. non-ischemic patients). Consequently, the percentage of ischemic patients that showed a significant improvement in LVEF (≥5%) increased from 34% to 71% (29 patients), while in non-ischemic patients this percentage increased from 68% to 78% (22 patients). Importantly, after V-V optimization the percentage of CRT responders was similar between ischemic and non-ischemic patients.

**Table 3.** Left ventricular out-flow tract velocity-time integral (LVOT VTI) and left ventricular ejection fraction (LVEF) at baseline, during simultaneous and optimized sequential CRT, in ischemic and non-ischemic patients

| | **Ischemic patients n = 41** | **Non-ischemic patients n = 28** | p-value (ischemic vs. non-ischemic) |
|---|---|---|---|
| **LVOT VTI (mm)** | | | |
| Baseline | 116 ± 34 | 120 ± 39 | NS |
| Simultaneous CRT | 129 ± 41* | 149 ± 41* | **<0.001** |
| Optimized sequential CRT | 163 ± 37* | 165 ± 41* | NS |
| **LVEF (%)** | | | |
| Baseline | 23.2 ± 8.2 | 22.4 ± 6.8 | NS |
| Simultaneous CRT | 26.7 ± 5.3* | 30.3 ± 5.1* | **<0.001** |
| Optimized sequential CRT | 34.1 ± 6.6* | 34.5 ± 6.9* | NS |

*: $p<0.01$ (two-way ANOVA)

### V-V pacing interval vs. the extent of scar tissue

In 24 patients (58%) with ischemic heart failure, a nuclear perfusion study was obtained during the clinical course, using single-photon emission computed tomography (SPECT, triple head camera system, GCA 9300/HG, Toshiba Corp.) and technetium-99m tetrofosmin. To quantify the extension of the scar tissue, tracer uptake was analyzed quantitatively using a standard 17-segment model and categorized on a 4-point scale: 0, tracer activity > 75% (normal, viable); 1, tracer activity = 50%-75% (minimal scar); 2, tracer activity = 25%-50% (moderate scar); 3, tracer activity < 25% (extensive scar).[17] Summation of the segmental scores yielded the total scar score, with the higher scores indicating more scar tissue (reflecting the extent of damage per patient).

Extensive regions of scar tissue were present, as indicated by a total scar score of 16.3±6.0 per patient. A significant correlation ($r = 0.89$; $p<0.001$) was observed between the SPECT total scar score and the optimal V-V interval. Figure 4 indicated that a higher scar score (representing more scar tissue), is associated with a higher level of pre-activation of the LV (patients with an optimal V-V interval of LV60 had a mean scar score of 22±3, whereas patients with an optimal V-V interval of LV20 had a mean scar score of 13±3).

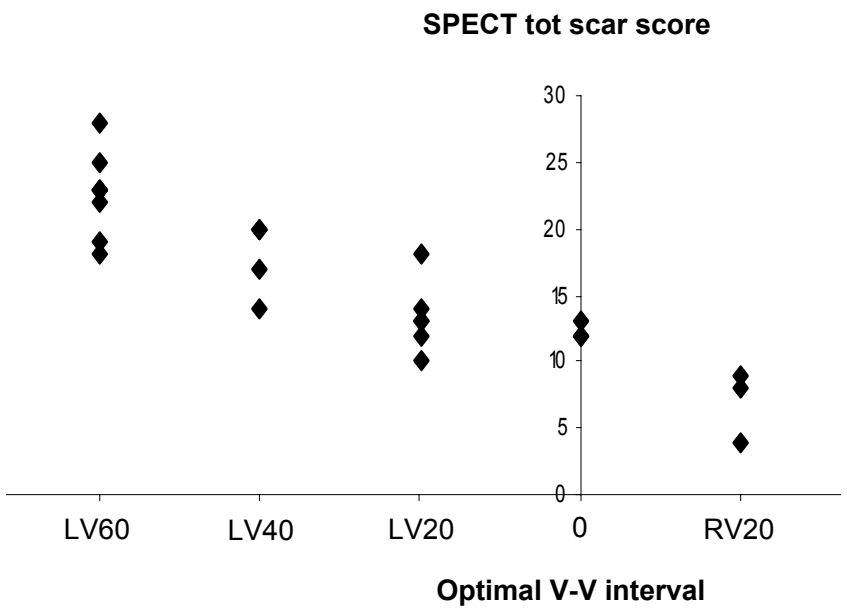


**Figure 4.** Correlation between the SPECT total scar score and the optimal V-V interval. $r = 0.89$, $p<0.001$, $y = -0.19x + 10.68$.

## DISCUSSION

The findings of the current study can be summarized as follows: 1) Optimized sequential CRT provides a significant improvement in LV hemodynamic performance compared to conventional simultaneous stimulation. This hemodynamic improvement was associated with a significant reduction of LV dyssynchrony; 2) the increase in LVOT VTI and LVEF after implantation (simultaneous CRT) was significantly greater in non-ischemic as compared to ischemic heart failure patients. However, V-V interval optimization yielded to a larger improvement of LVOT VTI and LVEF in patients with ischemic heart failure and resulted in a comparable percentage of CRT responders in ischemic and non-ischemic heart failure patients; 3) a direct relation was observed between the extent of scar tissue and the optimal V-V interval, with a larger extent of scar tissue related to a higher level of LV pre-activation.

### Simultaneous vs. sequential CRT

CRT is now considered an important therapeutic option in the treatment of patients with end-stage heart failure,[1] but still up to 30% of patients do not have a favorable response to CRT.[18] Since new pacemakers allow a separate activation of the ventricular leads, several studies have investigated whether the tailored programming of V-V interval could decrease the percentage of non-responders or convert non-responders to partial or complete responders. In fact, a recent multi-center study showed that almost 50% of patients who did not exhibit a positive response to CRT had inadequate device settings (temporary VVI back-up setting)[19] and that improved LV filling and systolic function could be achieved by optimizing the pacemaker settings. In addition, V-V optimization may also further increase the hemodynamic benefit of CRT in patients with a positive response to CRT.

Preliminary data from small single-center studies, demonstrated that optimized sequential CRT, rather than simultaneous CRT, can further improve different short-term outcomes of LV systolic performance, such as stroke volume, dP/dt, LV filling time, myocardial performance index etc.[2-8] Only few data are available on the effect of V-V optimization on LV dyssynchrony. Three trials further investigated whether there is a significant difference between optimized sequential CRT and simultaneous CRT in long-term outcome.[9-11] The InSync III study[9] showed in 397 patients that stroke volume at short-term follow-up and exercise capacity at long-term follow-up could be improved by echocardiographic optimization of the V-V interval. The DECREASE-HF trial[10] evaluated 306 patients and did not reveal a significant difference between sequential and simultaneous CRT in the improvement of LV size and function after 6 months of CRT. However, the V-V interval was programmed on the basis of intrinsic interventricular conduction measured from intra-cardiac electrocardiograms at the time of the implantation and was not individually optimized according to the hemodynamic response.

The RHYTHM II ICD study[11] evaluated in 121 patients the improvement in clinical end-points, such as NYHA class and 6-minute walking distance, after echocardiographic optimization of the V-V interval with standard simultaneous CRT. No additional benefit was demonstrated, but the potential favorable effect on LV remodeling and function was not evaluated. These inhomogeneous results may be explained by different factors: 1) different parameters have been used to optimize the V-V interval, which included intrinsic conduction from the intracardiac electrocardiogram, invasive and non-invasive dP/dt, stroke volume, LV filling time, LV dyssynchrony and other echocardiographic parameters. No large studies have pointed out the superiority of one method of V-V optimization over another; 2) different end-points (clinical improvement vs. echocardiographic improvement) have been used to evaluate the effects of V-V optimization, 3) it is possible that V-V interval optimization has a clear advantage over simultaneous CRT only in specific sub-groups of patients such as those with a slow inter- and intra-ventricular conduction (e.g. after myocardial infarction with extensive scar formation).

## V-V interval optimization in ischemic and non-ischemic cardiomyopathy

Recent data have suggested a slower and more attenuated response to CRT in patients with ischemic cardiomyopathy as compared to non-ischemic cardiomyopathy, probably related to repetitive episodes of ischemia or to the presence of scar tissue.[12] Initial single-center studies suggested that the amount and distribution of myocardial scar may be important determinants of response to CRT, limiting LV reverse remodeling and improvement of systolic function.[20,21] However, in these patients the best mechanical efficiency may be achieved using different pacemaker settings (and in particular the inter-ventricular activation) that might compensate for the conduction abnormalities due to the presence of ischemic and/or scar tissue.

In the current study, immediately after implantation (simultaneous pacing) a significantly better response to CRT was observed in non-ischemic patients (68% of patients with an increase ≥5% in LVEF as compared to 34% of ischemic patients). However, additional V-V optimization in patients with ischemic heart failure increased the percentage of patients with significant response to CRT from 34% to 71%. These results may be explained by the fact that the extent of myocardial scar tissue has an influence on the optimal V-V interval setting. In the current study, the presence of large areas of scar tissue was indeed related to a larger level of LV pre-activation, probably as a compensation for slow intra-ventricular conduction caused by scar tissue within the left ventricle. These findings are in line with data reported by van Gelder et al[7] showing that the mean V-V interval was significantly longer and more often with LV pre-excitation in patients with ischemic cardiomyopathy.

## Study limitations

The patient cohort in the current study is relatively small, and larger populations are needed to confirm these results, particularly regarding the differences between ischemic and non-ischemic patients. In addition, the benefit of V-V interval optimization was observed acutely after CRT implantation, but the long-term effect of V-V optimization on clinical and echocardiographic outcome was not evaluated. In particular, the acute benefit of V-V optimization on LV systolic performance was assessed using LVOT VTI and LVEF; these measures were not supported by an invasive measurement but, although with a certain beat-to-beat variability, they have been previously demonstrated to be reliable and reproducible. Furthermore, in the study protocol atrio-ventricular delay optimization was not repeated after V-V delay optimization since there is no consensus so far on its potential usefulness.

## Conclusions

Optimized sequential CRT provides a significant improvement of LV hemodynamic performance as compared to conventional simultaneous CRT, which is associated with a further reduction in LV dyssynchrony. Particularly in patients with ischemic heart failure, V-V interval optimization increased the response rate from 39% to 73% acutely after CRT and a larger extent of scar tissue was related to a larger level of LV pre-activation.

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