

Cardiac resynchronization therapy during rest and exercise: comparison of two optimization methods

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Aims Optimal exercise programming of cardiac resynchronization therapy (CRT) devices is unknown. We aimed to: (i) investigate variations in optimal atrioventricular (AV) and interventricular (VV) delays from rest to exercise, assessed by both echocardiography and an automated intracardiac electrogram (IEGM) method; (ii) evaluate the acute haemodynamic impact of CRT optimization performed during exercise. **Methods and results** Twenty-four heart failure patients, previously implanted with a CRT defibrillator, underwent AV and VV delay optimization, by echocardiography and IEGM methods, both at rest and during supine bicycle exercise. Rest-to-exercise variations in optimal VV delay were observed in 58% of patients. Conversely, optimal AV delay did not change during exercise compared with rest. Substantial agreement of AV and VV delays was observed between both the optimization methods. Exercise optimization of VV delay by either method improved intraventricular dyssynchrony and increased aortic velocity time integral compared with the resting setting ($P < 0.001$). **Conclusion** In patients implanted with a CRT device, optimal VV delay varied considerably from rest to exercise, while AV delay did not change. Re-assessment of the optimal pacing configuration during supine exercise, by echocardiography as well as IEGM methods, yielded an additional haemodynamic benefit to that provided by resting optimization.

Introduction

Cardiac resynchronization therapy (CRT) is a valuable treatment for patients with moderate to severe heart failure and ventricular conduction delay.^{1,2} CRT has been shown to improve resting and exercise left ventricular (LV) function by reducing inter- and intraventricular dyssynchrony.^{3,4} Resynchronization of left (LV) and right ventricular (RV) contraction is usually achieved by biventricular pacing, as the effects of LV pacing alone are still under investigation.⁵ During biventricular pacing, individual optimization of pacemaker settings may further improve CRT beneficial effects by tailoring the sequence of ventricular activation.^{6–11}

Contemporary CRT devices permit programming of both the atrioventricular (AV) and the interventricular (VV)

delay. Multiple studies have shown that echocardiographic optimization of AV and VV delays can improve cardiac output by increasing diastolic filling time and reducing LV dyssynchrony.^{6–11} Nevertheless, routine performance of echocardiographic optimization is limited by several factors, including time requirement and lack of a standard protocol. A novel intracardiac electrogram (IEGM) method has therefore been recently developed in order to simplify the optimization procedure. The IEGM method is based on the analysis of atrial intrinsic depolarization and interventricular conduction delay (IVCD) by an automated programmer algorithm. This new method has been under evaluation as an alternative to the standard echocardiographic optimization.^{12,13}

Currently, individual optimization of a CRT device is performed by echocardiography only during resting conditions. However, exercise may induce dynamic changes in LV activation pattern in heart failure patients.¹⁴ These changes

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may vary considerably from one patient to the other and cause exercise-induced variations in haemodynamic parameters.¹⁴ To date, limited information is available on optimal CRT programming during exercise,^{3,15} and it is still unknown whether CRT optimization performed during exercise may provide further haemodynamic benefits compared with resting optimization.

The aim of our study was: (i) to investigate the effects of exercise on optimal AV and VV delays, assessed by both echocardiography and the IEGM methods; (ii) to compare both the optimization methods with regard to the recommended AV and VV delays. In addition, we sought to evaluate the impact of CRT optimization on acute haemodynamic variables performed both at rest and during exercise.

Methods

Patient selection

All patients, who had been implanted according to the current guidelines¹⁶ with a St. Jude Medical CRT defibrillator between November 2003 and March 2007 at Karolinska University Hospital, were screened for enrolment. Patients were excluded from the study if they had: (i) complete AV block; (ii) atrial fibrillation; (iii) suboptimal echocardiographic images; (iv) inability to perform supine exercise echocardiography. Enrolment began in September 2006 and ended in April 2007. Patient characteristics were collected through clinical examination and medical record review at the time of inclusion in the study. The local Ethics Committee approved the study protocol and all patients provided written informed consent to participation.

Study protocol

All patients first underwent AV and VV delay optimization under rest conditions. The optimization was carried out according to both the IEGM- and the echocardiogram-based method in a random order. The patients then performed two consecutive supine bicycle exercise tests (exercise A and exercise B). For this purpose, we used a bicycle ergometer with a possibility of left lateral tilt to facilitate ultrasound measurements (Ergoline GmbH & Co KG, Bitz, Germany). The workload was kept constant at 30 W during the test. Each exercise was performed during spontaneous rhythm until a steady 20-beat increase in heart rate was achieved. Thereafter, AV and VV delay optimization was carried out according to the IEGM (exercise A) or the echocardiogram method (exercise B). Exercises A and B were performed in a random order, and a resting period of at least 15 min was allowed in between for complete recovery of the patient and a decrease in heart rate to the resting values. Heart rate was constantly monitored throughout the examination. Right arm blood pressure was measured at rest and at the end of the exercise.

Echocardiographic optimization

Transthoracic Doppler echocardiography was performed using a Vivid 7 system (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer (Doppler frequency 5.0–3.5 MHz). Echocardiographic images were recorded during spontaneous rhythm and sequential biventricular pacing with different pacing configurations. Acquisitions were digitally stored on a dedicated server and post-processed using a workstation (GE EchoPAC sw only, version 5.1.0, Horten, Norway). A standard evaluation of LV volumes was performed according to Simpson's rule and LV ejection fraction was calculated for each patient.

Pulsed-wave Doppler was used to record aortic flow velocities in the LV outflow tract (LVOT). At rest AV and VV delays were optimized

by on-line analysis of the LVOT velocity time integral (VTI).^{9,15,17,18} Care was taken to maintain the same transducer position and sample volume location throughout the recordings. LVOT VTI was averaged over at least three consecutive cardiac cycles, in order to reduce the variability due to respiration. AV delay optimization was performed during atrial triggered simultaneous biventricular pacing. AV delays were analysed between 80 and 180 ms, with steps of 20 ms. Paced AV delay was calculated as the sum of sensed AV delay and an off-set factor of 50 ms or lower, in order to ensure atrial-synchronized ventricular pacing. VV delay optimization was performed after AV delay programming. We analysed VV intervals ranging from –40 ms (LV pacing first) to +40 ms (RV pacing first), with steps of 20 ms. An equilibrium period of 1–2 min was maintained between echocardiographic recordings to allow haemodynamic stabilization. Optimal AV and VV delays were determined by the highest mean value of LVOT VTI.^{9,15–18}

Intraventricular dyssynchrony was assessed by colour-coded tissue velocity imaging (TVI) during spontaneous rhythm and sequential biventricular pacing with IEGM- and echo-optimized delays. TVI images were obtained in the apical four-chamber view at a frame rate >100 frames/s. Sample volumes were placed in the basal portions of the septum and LV lateral wall and the time from the QRS onset to the peak systolic myocardial velocity at each point was measured. The septal-to-lateral delay in peak systolic velocities was calculated as a measure of intraventricular dyssynchrony.¹⁹

Off-line analysis included LVOT VTI measurement during exercise and intraventricular dyssynchrony assessment at rest and during exercise. All images were recorded by an experienced sonographer and analysed by one skilled blinded operator. The mean value of at least three consecutive cardiac cycles was taken for each echocardiographic variable. Intraobserver and interobserver variability, calculated in 10 patients and expressed by the coefficient of variation (%) between two assessments were, respectively, 2.9 and 4.0% for AV delay, 5.7 and 6.6% for VV delay.

Intracardiac electrogram optimization

The IEGM optimization was performed according to an automated programmer algorithm which calculates the optimal AV and then VV delays from measurements performed during specific sensing and pacing tests (QuickOpt™, St Jude Medical, St Paul, MN, USA).^{12,13}

In synthesis, mitral valve closure is estimated by measuring the interatrial conduction time (P-wave duration).²⁰ The IEGM P-wave duration represents the sum of right and left atrial activation. The algorithm utilizes this measurement to calculate the optimal sensed and paced AV delays, with the goal of maximizing preload and allowing for proper timing of mitral valve closure. For VV delay optimization, paced and sensed tests are performed to characterize the conduction properties of the ventricles. Onset of isovolumic contraction is measured using the peak of the R wave. IVCDs are calculated by evaluating simultaneous RV and LV IEGMs and measuring the time between the peaks of the R waves. The goal is to time the RV and LV activation, so that the paced wave fronts can resynchronize ventricular contraction.

More in detail, for AV delay optimization the algorithm measures the width of the atrial intrinsic depolarization and adds an off-set factor of 30 ms if the intrinsic depolarization is greater than or equal to 100 ms, or 60 ms if the intrinsic depolarization is <100 ms. The off-set factor makes it possible to deliver ventricular pacing after the completion of atrial electrical activation and mechanical contraction. Paced AV delay is calculated as the sum of sensed AV delay and the pacing latency (50 ms). The VV delay algorithm includes two components: the conduction delay (Δ) and the correction term (ϵ). Δ is the difference between the time of peak intrinsic activation on the LV lead (R_{LV}) and the RV lead (R_{RV}) [$\Delta = R_{LV} - R_{RV}$]. The correction term (ϵ) is the difference in the IVCD between two ventricular paced propagation waveform time delays. IVCD'RL is the interventricular conduction delay when the

RV lead is paced and the delay is sensed at the LV lead. IVCD^{*}LR is the interventricular conduction delay when the LV lead is paced and the delay is sensed at the RV lead. During the test, each chamber is paced with a short AV delay to ensure the absence of fusion. The correction term equation is $\epsilon = \text{IVCD}^*\text{LR} - \text{IVCD}^*\text{RL}$. The IEGM optimal VV delay is calculated as $\text{VV} = 0.5 (\Delta + \epsilon)$. If $\text{VV} > 0$, the LV is activated first; if $\text{VV} < 0$, the RV is activated first.

After performing the automated programmer-based optimization, LVOT VTI and LV dyssynchrony were assessed by echocardiography at the IEGM recommended delays. Both at rest and during exercise, the values of LVOT VTI and LV dyssynchrony at the optimal echo and IEGM settings were compared, and related to those measured during spontaneous rhythm (without biventricular stimulation).

The reproducibility of the IEGM method, calculated in 10 patients and expressed by the coefficient of variation (%) between two separate measurements, was good for all the parameters (3.3% for AV delay; 6.5% for VV delay).

Statistical analysis

Continuous data are presented as mean and standard deviation or as median and inter-quartile range (P_{25} ; P_{75}). The data were analysed using a one-way repeated measures ANOVA with 'methods' (spontaneous, IEGM, and echo) as the within-subjects variable. In the event of inhomogeneous variances and covariances, the MIXED in SAS[®] procedure was used. The covariance structure unstructured (UN) was then performed. If the F ratio for the factor 'method' was significant, *post hoc* contrasts between mean values were performed and 95% CI were calculated for the mean differences. Since the distribution of some variables was positively skewed, log-transformation was performed before the analyses. For dependent samples t -test and sign test were used to analyse data variation from rest to exercise during spontaneous rhythm and biventricular pacing. $P < 0.05$ was considered statistically significant. Correlations between continuous variables were calculated with Pearson correlation coefficient. Spearman rank correlation coefficient was calculated for continuous variables that are not normally distributed. Weighted-Kappa with quadratic weights was used to assess the agreement between methods, and between rest and exercise measurements of non-continuous pacemaker parameters.

Results

A total of 63 patients were screened for the study. Thirty-nine patients were not enrolled because of atrial fibrillation ($n = 11$), complete AV block ($n = 5$), inability to perform an exercise test ($n = 10$), suboptimal echocardiographic images ($n = 5$), and refusal to participate in the study ($n = 8$). The remaining 24 patients were included in the study. Patient characteristics at the time of enrolment are presented in *Table 1*. The mean time of CRT treatment was 10 ± 2 months. Thirteen patients (54%) were in NYHA class II, 11 (46%) in class III. Accordingly, diuretics were taken only by 19 patients (79%). All patients completed the study protocol without chest pain or any complication. No significant differences in heart rate and blood pressure were observed between exercises A and B. Both exercises induced a similar percentage increase in the rate pressure product ($+58 \pm 27\%$ vs. $+47 \pm 19\%$, $P = 0.11$), and in heart rate ($+38 \pm 16\%$ vs. $+34 \pm 9\%$, $P = 0.22$).

Echocardiographic optimization of atrioventricular and interventricular delay at rest and during exercise

Echo-optimized AV and VV delays, at rest and during supine exercise are presented in *Table 2*. The optimal AV delay at

Table 1 Characteristics of the study population at the time of enrolment ($n = 24$)

Age (years)	63 \pm 9
Sex (M/F)	19/5
Aetiology (ischaemic/non-ischaemic, %)	58/42
NYHA class	2.5 \pm 0.5
QRS duration (ms)	183 \pm 46
Mean time of CRT treatment (months)	10 \pm 8
LV lead position (lateral/posterolateral, n)	12/12
RV lead position (septal/apical, n)	5/19
LVEDV (mL)	185 \pm 65
LVESV (mL)	120 \pm 58
LVEF (%)	36 \pm 9
Concomitant therapy (n , %)	
Loop diuretics	19 (79%)
ACE-inhibitors	19 (79%)
Beta-blockers	24 (100%)
Spironolactone	15 (63%)

NYHA, New York Heart Association; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

rest, as assessed by echocardiography, was 140 ms (120–155 ms). No significant difference in AV delay was observed between rest and exercise ($P = 0.26$).

Median VV delay at rest was 0 ms (0–0 ms). As reported in *Table 3*, the optimal pacing configuration at rest was achieved by simultaneous biventricular pacing in 17 patients (71%), LV pre-activation in five patients (21%), and RV pre-activation in two patients (8%). In the RV pre-activated patients, the underlying aetiology was ischaemic heart disease with intraventricular conduction delay, and the LV lead placement was mid-posterolateral and lateral. Exercise induced a change in VV delay programming in 14 patients (58%). Rest-exercise variations in optimal VV delay ranged from 20 to 60 ms, with a median value of 20 ms. We could not find any concordance between rest and exercise optimal VV delays (weighted Kappa = -0.05).

Intracardiac electrogram optimization of atrioventricular and interventricular delay at rest and during exercise

Optimized AV and VV delays, according to the IEGM method, are presented in *Tables 2* and *3*. No significant changes in AV delays were observed between rest and exercise ($P = 0.43$).

Median VV delay at rest was 0 ms (-20 to 10 ms). During exercise, VV delay programming changed in 13 patients (54%), with variations ranging from 5 to 70 ms (median 10 ms). In 10 of these patients, changes in optimal VV delay were detected by both the echocardiogram and the IEGM method. We could not find any predictor of rest-exercise variations in VV delay, determined by either method.

Comparison of atrioventricular and interventricular delay optimization by echo vs. intracardiac electrogram

For each delay, the agreement between the echocardiogram- and the IEGM-based method, at rest and during exercise, is reported as Kappa values in *Table 2*.

Table 2 Echocardiogram and intracardiac electrogram (IEGM)-optimized delay values

		Echo median (P_{25} , P_{75}) (ms), mean \pm SD (ms)	IEGM median (P_{25} , P_{75}) (ms), mean \pm SD (ms)	Echo vs. IEGM weighted Kappa (95% CI)
AV delay (ms)	Rest	140 (120–155), 135 \pm 28	130 (100–140), 124 \pm 21	0.55 (0.31, 0.79)
	Exercise	125 (100–140), 128 \pm 23	130 (100–140), 126 \pm 20	0.64 (0.36, 0.92)
VV delay (ms)	Rest	0 (0–0), -6 ± 18	0 (–20 to 10), -6 ± 17	0.38 (–0.22, 1.0)
	Exercise	0 (–10 to 0), -3 ± 15	0 (–18 to 10), -1 ± 15	0.71 (0.53, 0.89)

AV, atrioventricular interval; VV, interventricular interval; echo, echocardiogram; IEGM, intracardiac electrogram.

Table 3 Optimal VV delay distribution at rest and during exercise, according to echocardiogram and IEGM optimization

VV delay (ms)	Echo		IEGM	
	Rest (n, %)	Exercise (n, %)	Rest (n, %)	Exercise (n, %)
Simultaneous	17 (71)	14 (58)	15 (63)	15 (63)
LV pre-activation	5 (21)	6 (25)	9 (37)	7 (29)
RV pre-activation	2 (8)	4 (17)	–	2 (8)

VV, interventricular interval; Echo, echocardiogram; IEGM, intracardiac electrogram; LV, left ventricular; RV, right ventricular.

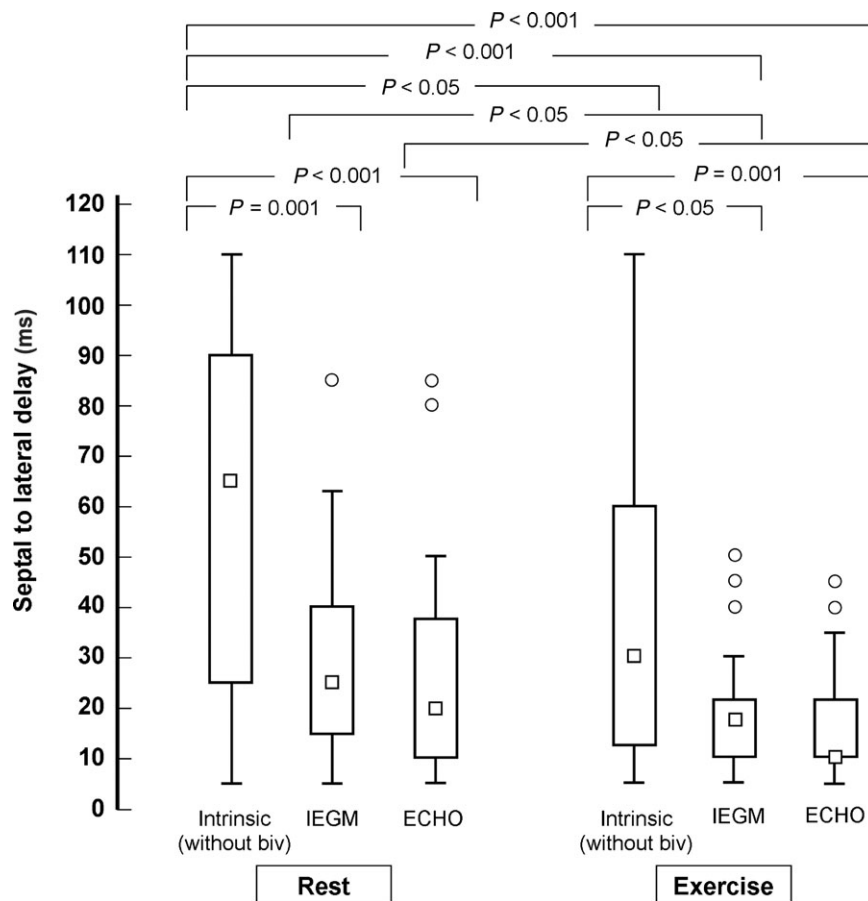


Figure 1 Boxplot (25th–75th percentile), median values (open squares) and outliers (open circles) showing distributions in septal-to-lateral delay during intrinsic rhythm (without biventricular stimulation) and during cardiac resynchronization therapy with intracardiac electrogram and echo-optimized atrioventricular and interventricular delays, both at rest and during exercise. IEGM, intracardiac electrogram; ECHO, echocardiogram; biv, biventricular pacing.

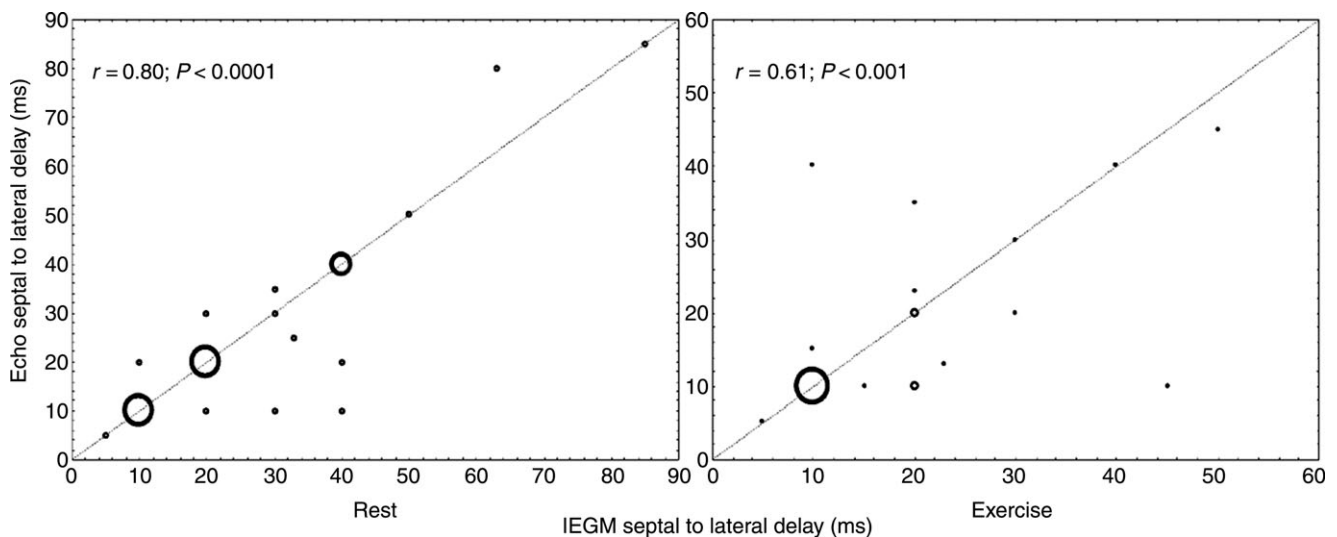


Figure 2 Plot of septal-to-lateral delay after echocardiographic vs. IEGM optimization of atrioventricular and interventricular delays. The left part refers to rest and the right to exercise. The relative frequencies of the number of data represented by a single plot position are indicated with circles of varying sizes. IEGM, intracardiac electrogram; ECHO, echocardiogram.

A substantial agreement in deriving optimized AV delays was observed between the echocardiogram and the IEGM method, both at rest and during exercise. The agreement in optimizing VV delay between the two methods was fair at rest, and became stronger during exercise.

Effects of optimized cardiac resynchronization therapy on left ventricular dyssynchrony at rest and during exercise

Figure 1 reports septal-to-lateral delay among all patients during spontaneous rhythm (without biventricular stimulation), and during CRT with IEGM and echo-optimized AV and VV delays. At rest, median (range) septal-to-lateral delay during spontaneous rhythm was 65 ms (25–90 ms). During CRT with the IEGM optimal setting, the delay decreased to 25 ms, ranging from 15 to 40 ms ($P = 0.001$). A similar reduction was observed after the echocardiographic optimization ($P = 0.0003$ vs. spontaneous rhythm; $P = 0.94$ vs. IEGM).

During exercise we observed a shortening in septal-to-lateral delay during spontaneous rhythm (from 65 ms, range 25–90 ms, to 30 ms, range 13–60 ms, $P = 0.006$). The delay further decreased to 18 ms (10–22 ms) during CRT with the IEGM optimal setting ($P = 0.036$), and was reduced to a similar extent by the echocardiographic optimization ($P = 0.001$ vs. spontaneous rhythm; $P = 0.56$ vs. IEGM).

As shown in *Figure 2*, a significant correlation was found between septal-to-lateral delay measured after the IEGM and the echocardiographic optimization, both at rest ($r = 0.80$; $P < 0.0001$) and during exercise ($r = 0.61$; $P = 0.001$).

Effects of optimized cardiac resynchronization therapy on aortic flow at rest and during exercise

Figure 3 shows values of LVOT VTI among all patients during spontaneous rhythm (without biventricular stimulation), and during CRT with IEGM and echo-optimized AV and VV delays. At rest, median (range) VTI during spontaneous rhythm

was 13.65 cm (11.53–17.92 cm) and increased during CRT with both the IEGM and the echocardiogram-based setting ($P < 0.0001$ vs. spontaneous rhythm for both). A small, albeit significant, difference in LVOT VTI between the two methods was observed at rest (15.18 cm, range 13.03–19.82 cm, with IEGM vs. 15.53 cm, range 13.32–20.78 cm, with echocardiography, $P = 0.003$), but not during exercise.

Exercise was associated with an increase in LVOT VTI during spontaneous rhythm (from 13.65 cm, range 11.53–17.92 cm, to 15.95 cm, range 13.20–19.95 cm, $P < 0.0001$). Biventricular pacing with the IEGM optimal setting improved LVOT VTI to 17.08 cm, range 13.72–21.75 cm ($P < 0.0001$). A similar increase was induced by the echocardiographic optimization ($P < 0.0001$ vs. spontaneous rhythm; $P = 0.06$ vs. IEGM). Re-assessment of the optimal AV/VV configuration during exercise by echocardiography was more effective on LVOT VTI than maintaining the same pacing configuration as at rest (17.14 cm, range 13.57–21.56 cm, vs. 16.52 cm, range 13.52–20.75 cm, $P < 0.001$). Similar results were found with the IEGM method ($P < 0.001$).

As shown in *Figure 4*, a strong linear relationship was found between LVOT VTI measured after the IEGM and the echocardiographic optimization, both at rest ($r = 0.98$; $P < 0.0001$) and during exercise ($r = 0.99$; $P = 0.001$).

Discussion

This study has shown that in a high proportion of heart failure patients implanted with a CRT defibrillator, optimal VV delay differed significantly from rest to exercise, while optimized AV delay did not change. Furthermore, a substantial agreement in optimizing AV delay was observed between the echocardiogram and the IEGM method. With regard to VV delay, the agreement between both the optimization methods was stronger during exercise than at rest. Optimization performed during exercise resulted in a shortening of septal-to-lateral delay and a further increase in haemodynamic parameters, compared with that provided by resting optimization.

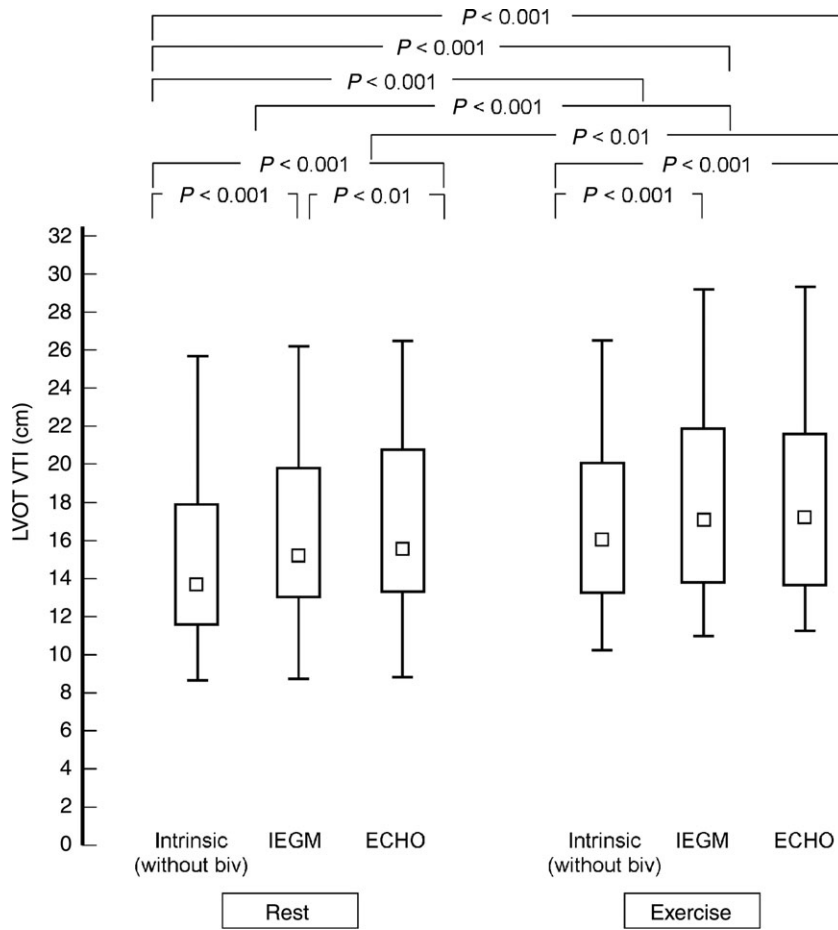


Figure 3 Boxplot (25th–75th percentile), median values (□) showing distributions in LVOT VTI during intrinsic rhythm (without biventricular stimulation) and during cardiac resynchronization therapy with IEGM and echo-optimized atrioventricular and interventricular delays, both at rest and during exercise. IEGM, intracardiac electrogram; ECHO, echocardiogram; LVOT, left ventricular outflow tract; VTI, velocity time integral; biv, biventricular pacing.

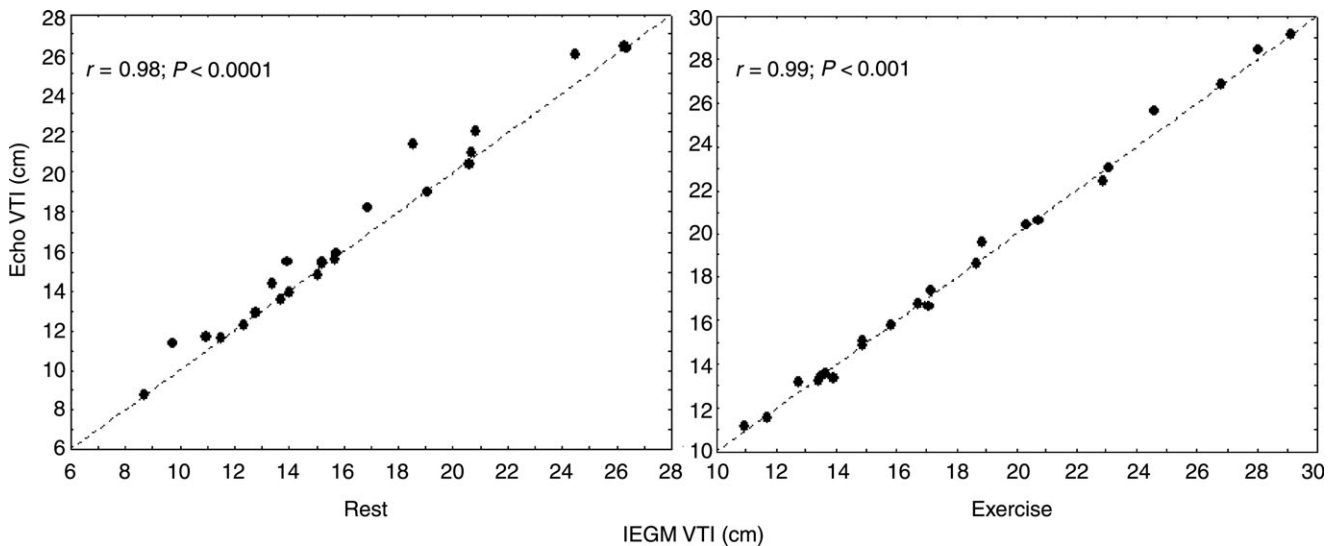


Figure 4 Plot of left ventricular outflow tract VTI after echocardiographic vs. IEGM optimization of atrioventricular and interventricular delay. The left part refers to rest and the right to exercise. IEGM, intracardiac electrogram; ECHO, echocardiogram; VTI, velocity time integral.

Rest-to-exercise variations in optimal cardiac resynchronization therapy programming

To date, most of the studies on CRT optimization have been performed in resting conditions, and questions about optimal CRT programming during exercise are still unresolved.²¹ In a recent study, Lafitte *et al.* observed exercise-induced changes in LV dyssynchrony in heart failure patients (without CRT) undergoing a bicycle exercise test, thus suggesting that a fixed activation sequence during biventricular pacing may not be physiological.¹⁴

As regards AV delay, it is still unclear whether it should be kept constant, shortened or prolonged during exercise, in order to maximize the haemodynamic benefit. In previous multicenter CRT trials, a relatively short AV delay was selected at rest to ensure ventricular capture, and it was programmed either fixed or with dynamic shortening.^{22,23} More recently, Scharf *et al.* suggested that in CRT patients, the AV delay should be prolonged at increased heart rates (20 ms per 10 bpm) to improve the haemodynamic response to exercise.¹⁵ Studies suggest that in heart failure patients the dilatation and myocardial stretch of the atria, related to LV dysfunction and loading conditions, may alter the intra-atrial conduction pattern.²⁴ This can be responsible for the need for fixed or even dynamic lengthening AV delays in CRT programming. Our results showed no significant changes in optimal AV delays from rest to exercise, whether assessed by echocardiography or IEGM methods. Similar results were reported by Melzer *et al.*²⁵ during sub-maximal exercise in VDD mode, whereas under DDD stimulation AV delay was found to shorten with increasing heart rates. Taken together, these findings seem to support the use of a fixed AV delay in CRT devices, different from conventional pacemaker systems, in which a rate shortening AV delay has been shown to improve exercise tolerance.²⁶

With regard to optimal VV delay, significant changes during exercise were observed in a high proportion of patients in our study. We could not find any concordance between VV delays optimized at rest and during exercise. Bordachar *et al.*³ reported similar variations in optimal VV delay in 57% of patients undergoing an echo-guided CRT optimization during a bicycle test. These findings can probably be explained by individual exercise-induced variations in the ventricular activation pattern. In line with previous observations,¹⁴ in our study exercise modified the extent of intraventricular dyssynchrony, as reflected by a shortening in septal-to-lateral delay during spontaneous rhythm. This spontaneous improvement in dyssynchrony probably explains the lack of concordance between resting and exercise optimal VV delays. It is well known that long-term CRT results in structural remodelling and the optimal pacing configuration tends to vary over time.^{27–29} Therefore, we do not know whether our findings would be the same after a further extended period of CRT therapy.

Effects of a cardiac resynchronization therapy optimization performed during exercise

Several studies have shown that AV and VV delay optimization improves LV systolic performance and stroke volume by decreasing intraventricular and interventricular dyssynchrony.^{6–11} Our study provides further insights into CRT optimization during exercise. Echocardiogram- and IEGM-optimized biventricular pacing provided a similar

haemodynamic improvement, compared with spontaneous rhythm. Importantly, a re-assessment of the optimal pacing configuration during exercise led to an additional increase in stroke volume when compared with the resting optimized setting. The increase in stroke volume was coupled with a significant reduction in intraventricular dyssynchrony, which was similar in both the IEGM and the standard echocardiographic optimization. As significant changes in optimal programming were observed for VV, and not for AV delay, it is conceivable that VV delay re-assessment during exercise provided the highest additional haemodynamic contribution.

Comparison of echocardiographic vs. intracardiac electrogram-based optimization

Echocardiography is the most widely adopted method for CRT optimization,²¹ but it is time-consuming, and expertise- and cost-demanding. Therefore, echocardiographic optimization of a CRT device is not routinely performed in practice and it is often limited only to selected groups of patients (i.e. patients who do not respond to CRT).²¹ In the light of these considerations, a novel automated programmer-based method was developed as an alternative to the echocardiographic optimization. The IEGM method recommends the optimal AV and VV programming based on the analysis of endocavitary electrograms. The test can be easily performed during routine device follow-up. Previous studies have documented a good concordance in defining optimal AV and VV delays at rest between the IEGM and the echo-based method, with similar acute haemodynamic effects.^{12,13} In the present study, we specifically aimed to compare the IEGM and echo-based method not only at rest, but also during exercise, a condition where an echo-independent modality of device programming may be particularly attractive. Of note, this is the first study evaluating the feasibility of IEGM optimization during physical stress. Our results show a good agreement between the two methods with regard to resting and exercise AV delay optimization. For VV delay optimization, the degree of concordance was higher during exercise. The differences in protocol set-up between the two optimization procedures may account for some discrepancies in deriving optimal VV delay. In fact, for practical reasons, the echo-guided VV delay optimization was performed according to a 20 ms stepwise protocol, in order to limit the number of recordings during exercise. Conversely, the programmer-based method can use a 10 ms stepwise protocol. At peak heart rates, the IEGM optimization provided haemodynamic benefits similar to the echocardiographic procedure, these findings further suggesting that the IEGM method can be considered an alternative to the standard echocardiographic optimization,^{12,13,30} with the advantage of being feasible in daily practice also during a walking or treadmill test.

Clinical implications

The dynamic changes in optimal device programming and the beneficial effects provided by AV and VV optimization indicate that re-evaluations of the device parameters at rest and during exercise may further improve the response to CRT. Of note, the haemodynamic effects of CRT optimization were evaluated in terms of Doppler echocardiographic parameters, and further studies are required to investigate

whether a repeated tailoring approach can impact clinical outcome measures. The implementation in CRT devices of algorithms allowing automatic VV delay optimization during exercise could be a useful feature, as well as separate rest-exercise programming options.

Study limitations

AV delay optimization using the IEGM method cannot be performed if there is no measurable atrial activity, for example, due to severe bradycardia. In the event of complete AV block, optimal VV timing cannot be determined by the IEGM algorithm, as intrinsic activation of the LV and RV chambers is required.

Several echocardiographic methods for AV delay optimization are currently used in clinical practice.²¹ We optimized AV delay by evaluating an index of LV systolic function (i.e. aortic VTI), in line with another study on IEGM optimization,¹² and according to previous observations, suggesting that AV delay optimization provides a greater haemodynamic improvement in CRT patients when guided by the aortic VTI method, compared with the diastolic filling time method.¹⁸ The optimization of AV delay by other echocardiographic parameters, evaluating LV diastolic function, may have led to different results. However, a lack of significant changes in sensed AV delay from rest to exercise was observed by Melzer *et al.*,²⁵ by using a combined ECG-echo method based on diastolic optimization.

Changes in stroke volume were assessed with Doppler echocardiography. No invasive control was performed.

In line with previous studies,³⁻¹⁰ a wide inter-individual variability in optimal VV delay was observed. Simultaneous biventricular pacing was the most represented optimal setting, whereas RV pre-activation was suggested by echo at rest in 8% of the cases, and LV pre-activation only in 21% of patients. Such variations in VV delay may be related to different patterns of mechanical activation and LV lead positioning.⁹ Since the analysis of LV contraction pattern, in terms of sites of latest activation, was not performed, the mechanisms underlying different resynchronization sequences could not be detailed.

The effects of echo- and IEGM-optimized CRT were evaluated in relation to spontaneous rhythm (without biventricular pacing). Likewise, haemodynamic benefits were mainly related to biventricular pacing, more than to optimization. However, our aim was not to confirm the beneficial effects of CRT vs. spontaneous rhythm, but rather to evaluate whether there are differences between the IEGM- and the echo-based CRT setting, in terms of dyssynchrony and aortic flow. Whether AV and VV delay optimization can provide not only an acute haemodynamic effect, but also a clinical improvement, is currently unknown.

Conclusion

Significant rest-exercise changes in optimal VV delay, but not in AV delay, were observed in heart failure patients undergoing CRT optimization according to both the echocardiographic and the IEGM method. Re-assessment of optimal device programming during exercise resulted in an improvement in LV dyssynchrony and haemodynamic parameters, giving an additional benefit to that provided by a resting optimization. The IEGM method may be a feasible

alternative to the standard echocardiographic approach both at rest and during exercise.

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