Clinical research

Contractile response and mitral regurgitation after temporary interruption of long-term cardiac resynchronization therapy


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Aims Cardiac resynchronization therapy (CRT) utilizing biventricular pacing (BVP) is a promising treatment modality for symptomatic patients with chronic left ventricular (LV) systolic dysfunction and intraventricular conduction delay. Clinical studies have shown short-term improvement in contractile function and mid-term improvement in clinical status with CRT. The objective of this study was to evaluate the haemodynamic consequences of temporary interruption of CRT after long-term stimulation.

Methods and results Twenty patients (16 men, 4 women) with LV dysfunction and New York Heart Association class III or IV heart failure, despite optimal medical therapy and a QRS interval of at least 120 ms, received a transvenous BVP system at the age of 66 (interquartile range, 61–69). Patients were studied after a median duration of 427 days (interquartile range, 281–563) of continuous CRT and again 72 h after cessation of BVP. Withdrawal of CRT resulted in a significant decline in maximal rate of LV systolic pressure rise from 711 mmHg/s (interquartile range, 640–816) to 442 mmHg/s (interquartile range, 389–582) (P = 0.0001) and increases in mitral effective regurgitant orifice area from 4.8 mm² (interquartile range, 0.0–7.8) to 9.1 mm² (interquartile range, 5.7–13.3) (P = 0.0001), mitral regurgitant volume from 7.8 mL (interquartile range, 0.0–11.5) to 16.0 mL (interquartile range, 10.7–20.8) (P = 0.0001) and fraction from 13.8% (interquartile range, 0.0–19.2) to 27.7% (interquartile range, 14.6–34.0) (P = 0.0002) determined by Doppler echocardiography.

Conclusion Cessation of long-term BVP leads to a decline in LV systolic performance and an increase in functional mitral regurgitation. These results indicate a sustained benefit of long-term CRT and support the notion to maintain CRT indefinitely.

KEYWORDS Cardiac resynchronization therapy; Contractility; Heart failure; Mitral regurgitation

Introduction Cardiac resynchronization therapy (CRT) utilizing biventricular pacing (BVP) is a promising non-pharmacological treatment option for patients with symptomatic systolic heart failure and mechanical dyssynchrony due to an intraventricular conduction abnormality. Several studies have documented an acute haemodynamic benefit1,2 and mid-term improvement in clinical status3,4 with the potential for improved long-term survival.5 Mitral regurgitation (MR) is a common finding in patients with left ventricular (LV) systolic dysfunction and an independent predictor of mortality.6 Several studies have shown that CRT reduces functional MR, both acutely and in trials lasting up to 6 months.3,7–10 Altogether, there is a robust body of evidence that initiation of BVP leads to immediate beneficial haemodynamic changes. Maintenance of these improvements might be expected to result in LV reverse remodelling, which has been observed previously.3,8–11 Nevertheless, CRT is interrupted in approximately one-third of patients in the long-run for different reasons.12 While acute haemodynamic benefits immediately revert as soon as pacing is halted,1 there is little information about the consequences resulting from withdrawal of long-term CRT. We hypothesized that CRT interruption after long-term BVP would lead to early haemodynamic deterioration. Therefore, the aim of this prospective clinical study was to evaluate LV systolic performance and functional MR after temporary BVP interruption in patients clinically stable on long-term CRT.

Methods Patients At baseline, all patients had moderate or severe (New York Heart Association functional class III or IV) chronic heart failure due to either ischaemic or idiopathic cardiomyopathy without aortic valve disease despite optimal medical treatment, an ejection fraction of 35% or less, and a QRS interval of 120 ms or more. A total of 225 patients underwent invasive haemodynamic testing to assess eligibility for chronic CRT. Of those, 136 patients were classified...
as responders based on an increase in the maximal rate of LV pressure rise \( (dP/dt_{\text{max}}) \) of at least 20% and received a transvenous BVP device for clinical reasons with the LV pacing electrode implanted through the coronary sinus and positioned in a lateral cardiac vein. The atrioventricular delay was optimized under Doppler echocardiographic guidance to maximize LV filling time. A total of 21 patients were randomly selected for the study after long-term BVP; all of them gave informed consent before enrolment. The recruiting physician had no knowledge of the clinical history and echocardiographic data at the time of patient inclusion.

### Study design

All patients were studied by echocardiography after long-term CRT. Thereafter, the BVP mode was deactivated temporarily and patients were restudied after an equilibration period of 72 h keeping all medications constant. Brachial artery blood pressure was measured in each case after completion of the echocardiographic examination with the patient still in supine position. One patient experienced intolerable congestive heart failure symptoms shortly after suspension of CRT, the BVP mode was reactivated for clinical reasons and the patient was excluded from the study. The remaining 20 patients completed the study and their data were included in the statistical analysis. Patient characteristics stratified according to the heart failure aetiology are summarized in Table 1.

### Echocardiography

A comprehensive two-dimensional and Doppler transthoracic echocardiographic study was performed with a phased-array system (Sonos 4500 or 5500, Philips Medical Ultrasound [Agilent], Andover, MA, USA) using second harmonic imaging (1.8–3.6 MHz) to enhance endocardial border delineation. Image acquisition was performed with the patient in the left lateral decubitus position. End-diastolic and end-systolic frames were selected from the same cardiac cycle. End-diastole was identified by the onset of the R-wave on the simultaneously recorded electrocardiogram. End-systole was identified as the smallest LV cavity size just before mitral valve opening. LV dimensions were measured by two-dimension guided M-mode method. The shape of the LV was described by the sphericity index calculated by dividing the maximum short-axis by the maximum long-axis dimension. LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated by the modified Simpson’s rule utilizing the built-in quantitative programs; total stroke volume and ejection fraction were calculated as EDV – ESV and (EDV – ESV)/EDV, respectively. LV diastolic filling time was determined from the pulsed-wave Doppler tracing with the sample volume placed at the tip of the mitral leaflets. The degree of systolic MR was assessed by colour Doppler flow imaging and the proximal isovelocity surface area (PISA) method. The border of the largest regurgitant jet area in the apical four-chamber view was traced and measured by computerized planimetry. The effective regurgitant orifice area and regurgitant volume were calculated using the PISA method. The same aliasing velocity was used in individual patients for both studies. Mitral regurgitant fraction was calculated as per cent of the total LV stroke volume. The maximal rate of LV pressure rise \( (dP/dt_{\text{max}}) \) was estimated by measuring the time interval between 1 and 3 m/s on the MR continuous-wave Doppler spectrum. In case of an incomplete continuous-wave Doppler signal due to trivial MR, \( dP/dt_{\text{max}} \) was determined from the rising slope of the Doppler spectrum in early systole. Thereby, measurement of \( dP/dt_{\text{max}} \) was feasible in all patients. All measurements and calculations were performed online during the examination by the same cardiologist in triplicate from consecutive cardiac cycles and averaged for statistical analysis.

### Statistical analysis

The sample size for this prospective study was estimated on the basis of two preceding studies that evaluated the acute haemodynamic effect of CRT initiation. Assuming that temporary cessation of CRT would exert a converse effect of the same magnitude and standard deviation, 20 patients would yield 80% power to detect a significant difference with the use of a two-sided alpha level of 0.05. Data are presented as median values and interquartile range for continuous variables and absolute frequencies for categorical variables unless specified otherwise. For continuous variables, the paired Wilcoxon test was used to compare data during and after withdrawal of CRT. The relation between the change in echocardiographic parameters was analysed by linear regression analysis. A two-sided probability value of \( P < 0.05 \) was considered statistically significant. The intraobserver variability of echocardiographic measurements was assessed by the primary reader performing a second analysis of 10 randomly selected studies on stored video images. Interobserver variability was tested by a second blinded observer for the same randomly selected studies. Intra- and interobserver variabilities were calculated as percentage difference. The percentage difference was calculated for each pair of measurements as \( \frac{\text{measurement 1} - \text{measurement 2}}{\text{measurement 1}} \times 100 \). 

### Results

#### Study population

Twenty patients were studied after a median duration of 427 days (interquartile range, 281–563) of continuous CRT and...
again 72 h after cessation of BVP. Seventeen patients reported worsening of their functional status 72 h after CRT withdrawal, while the remaining three patients noted no change.

**Echocardiographic measurements**

LVESV and LVEDV increased significantly after CRT withdrawal and there was also a trend towards a decrease in total stroke volume (Table 2). Significant decreases were observed in LV ejection fraction and diastolic filling time. In contrast, neither LV end-diastolic diameter nor sphericity index showed significant change. Likewise, left atrial size remained unchanged. Importantly, systolic and diastolic blood pressure decreased significantly. Nevertheless, MR measured by two different methods worsened significantly after CRT interruption (Table 3). Furthermore, LV contractility as assessed by Doppler-derived dP/dt max decreased significantly from 711 mmHg/s (interquartile range, 640–816) to 442 mmHg/s (interquartile range, 389–582) (P = 0.0001) after withdrawal of CRT. The decrease in contractility was uniform in all but one patient, in whom no change in dP/dt max was noted (Figure 1). Worsening of MR did not correlate with any change in echocardiographic geometric parameters. However, a correlation was observed between the decrease in dP/dt max and the increase in mitral effective regurgitant orifice area (P = 0.045). Individual examples are depicted in Figures 2 and 3.

**Repeatability of measurements**

Intraobserver variability was as follows: 4.5 ± 4.2% for dP/dt max, 10.7 ± 8.7% for MR jet area, and 10.2 ± 12.3% for mitral regurgitant volume. For interobserver variability, the corresponding values were 6.5 ± 4.9%, 12.2 ± 11.3%, and 12.2 ± 8.4%, respectively.

**Discussion**

CRT using BVP has an established role in the management of drug-refractory systolic heart failure in patients with LV dysynchrony. However, most clinical studies have a relatively short follow-up period of 3–6 months, and there is little information about the consequences resulting from withdrawal of long-term CRT. The main result of the current study is that CRT termination after prolonged treatment has detrimental effects on patient haemodynamics. This study is the first to comprehensively investigate the haemodynamic consequences of CRT withdrawal after long-term stimulation and supports the notion to maintain CRT indefinitely.

**Mitral regurgitation**

Functional MR occurs, despite a structurally normal valve, as a consequence of spatial or functional alterations. MR was evaluated in our study by two different methods and increased significantly after temporary suspension of CRT. Systolic blood pressure is a major determinant of mitral regurgitant volume. MR is expected to worsen in the setting of elevated blood pressure and improve with lower blood pressure. However, MR severity increased in our study in spite of a lower systemic arterial pressure. Our results nicely mirror the findings of Breithardt et al., who have elegantly demonstrated that the effective mitral regurgitant orifice area decreased immediately after first-time initiation of CRT. Apparently, some of the mechanisms responsible for amelioration of functional MR with CRT also

| Table 2 | Echocardiographic and haemodynamic variables of 20 patients during long-term CRT and 72 h after CRT discontinuation (Off) |
|-----------------|-----------------|-----------------|
| CRT | Off | P-value |
| LVEDD (mm) | 65 (58–69) | 65 (58–71) | 0.12 |
| Sphericity index | 0.71 (0.66–0.77) | 0.70 (0.66–0.76) | 0.49 |
| LVEDV (mL) | 167 (142–221) | 183 (143–222) | 0.034 |
| LVESV (mL) | 128 (77–170) | 140 (91–187) | 0.006 |
| Total stroke volume (mL) | 51 (41–59) | 43 (37–53) | 0.096 |
| Ejection fraction (%) | 27 (22–37) | 24 (19–32) | 0.0006 |
| Left atrial end-systolic area (cm²) | 22 (18–30) | 24 (18–30) | 0.43 |
| Diastolic filling time (ms) | 432 (374–464) | 385 (355–435) | 0.003 |
| Systolic blood pressure (mmHg) | 119 (115–128) | 101 (95–123) | 0.0004 |
| Diastolic blood pressure (mmHg) | 62 (60–77) | 52 (46–51) | 0.0004 |
| Heart rate (min⁻¹) | 70 (69–72) | 69 (65–70) | 0.039 |

LVEDD, left ventricular end-diastolic diameter.

| Table 3 | MR in 20 patients during long-term CRT and 72 h after CRT discontinuation (Off) |
|-----------------|-----------------|-----------------|
| CRT | Off | P-value |
| MR jet area (mm²) | 4.1 (0.8–6.3) | 5.9 (2.2–7.5) | 0.002 |
| Relative MR jet area (%) | 13.8 (4.1–23.1) | 20.3 (13.1–26.1) | 0.004 |
| Effective regurgitant orifice area (mm²) | 4.8 (0.0–7.8) | 9.1 (5.7–13.3) | 0.0001 |
| Regurgitant volume (mL) | 7.8 (0.0–11.5) | 16.0 (10.7–20.8) | 0.0001 |
| Regurgitant fraction (%) | 13.8 (0.0–19.2) | 27.7 (14.6–34.0) | 0.0002 |
Intraventricular conduction delay, particularly with left bundle-branch block pattern, adversely influences ventricular function by dyssynchronous LV wall motion. It is conceivable, that delayed electrical activation of the LV lateral wall also adversely affects the timing of force development in the anterolateral papillary muscle and worsens MR. Indeed, functional MR is strongly associated with prolongation of the QRS complex in general, and with left bundle-branch block in particular. Conversely, CRT could significantly improve the efficacy of mitral valve closure by concomitant stimulation of the LV lateral wall with the adjacent anterolateral papillary muscle and explain the immediate decrease in MR with initiation of CRT. Functional MR can also be a consequence of a modified LV geometry affecting the mitral valve apparatus. We did not find any relation between changes in echocardiographic geometric parameters and worsening of MR. This may indicate that the predominant mechanism for worsening of MR after CRT withdrawal is not the result of simple distortion of the mitral valve, but rather related to dyssynchronous papillary muscle contraction. Indeed, a shortened interpapillary muscle time delay with initiation of CRT was significantly correlated with reductions in MR. This increase in MR severity in our study cannot be accounted for by other factors because all other parameters, in particular cardiac medication, remained unchanged during the 72 h time interval between measurements.

Yu et al. have evaluated 25 patients after 3 months of CRT and could demonstrate an immediate increase MR severity when the pacemaker was turned off. However, MR was assessed only by the change in jet area relative to left atrial area. Colour Doppler flow imaging represents a rather crude measure of MR severity that is dependent on jet direction and machine settings. Our study confirms and extends the observation of Yu et al. First, the more sophisticated PISA method used in our study allows reliable measurement of the instantaneous regurgitant flow and regurgitant orifice area and is preferable for accurate quantitative assessment of MR severity. Second, most studies have a relatively short follow-up period of 3–6 months, while our patients were studied after prolonged CRT. Worsening MR after discontinuation of CRT may also contribute to the increase in BNP levels observed by Sinha et al.
The degree of MR observed in our patients after CRT withdrawal was in the mild to moderate range. However, even mild MR in patients with LV dysfunction is associated with reduced survival and MR tends to progress over time. Some but not all investigators have reported a significant reduction in MR in response to chronic CRT, regardless of whether the cause was idiopathic or ischaemic. The improvement in MR severity was paralleled by LV reverse remodelling. The degree to which the reduction in MR plays a role in LV reverse remodelling is currently unclear.

LV contractility

LV contractility indexed by Doppler-derived $dP/dt_{\max}$ decreased significantly after termination of CRT. This observation provides strong evidence that $dP/dt_{\max}$ is particularly sensitive to re-occurrence of LV dyssynchrony generating regions of both early and delayed contraction. Contraction of the early activated myocardium occurs before LV ejection and largely serves to increase pre-load on the late activated regions, which in turn stretches the already relaxing early activated territory resulting in a decline in LV systolic performance. The remarkable decline in $dP/dt_{\max}$ provides direct evidence of the magnitude by which CRT assists LV function even after prolonged treatment. The present study is consistent with a previous observation that LV systolic function even after the absence of CRT.

Importantly, $dP/dt_{\max}$ is a strong predictor of survival in patients with LV dysfunction. Whether improvement in LV contractility with CRT also translates into improved survival remains to be established. Our data do not permit firm conclusions about the observed relation between the decrease in $dP/dt_{\max}$ and worsening of MR. However, an in vitro experimental study has suggested that an increased transmitral pressure acting to close the mitral leaflets also decreases the regurgitant orifice area. Conversely, a decrease in LV systolic performance would be expected to increase functional MR.

Study limitations

The current study examined the haemodynamic consequences of CRT termination after long-term treatment. We did not systematically perform baseline measurements at the time of pacemaker implantation. Our results consistently demonstrated a highly significant change in haemodynamic parameters with CRT interruption, while all medications of the study patients were kept constant between measurements. Although no control group was studied, it would be most unlikely, that the observed results were due to any other effect rather than CRT interruption alone. On the basis of the known benefit, CRT could not be withheld from patients longer than 72 h for ethical reasons in order to document serial changes over a longer period without CRT. We did not perform echocardiographic measurements after re-institution of CRT, which could have reinforced our hypothesis by showing a return to the beneficial haemodynamic effect. However, it is reasonable to predict this very effect based on previously published studies. The sample size ($n=20$) was rather small, but provided sufficient data for a reliable statistical analysis.

Clinical relevance

The clinical relevance of our findings comes from the fact that CRT is interrupted in a substantial number of patients after successful implantation. A decline in LV systolic function and worsening of MR after interruption of CRT would be expected to exacerbate LV dilatation and further depress LV function. Moreover, even mild MR in patients with LV dysfunction is associated with reduced survival. Our study indicates that patients derive continuous haemodynamic benefit from CRT after long-term stimulation. Therefore, every effort should be made to maintain CRT indefinitely. Indeed, preliminary results indicate that CRT is well tolerated after 2 years of ongoing treatment.

Supplementary material: Supplementary material is available at European Heart Journal online.

Conflict of interest: none declared.

References


