



# Relationship between left ventricular stimulation characteristics at implantation and echocardiographic response after 6 months of cardiac resynchronization therapy

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## Aims

Although the electrical stimulation of an ischaemic tissue adversely affects the left ventricular (LV) systolic function, the optimal stimulation site in patients with non-ischaemic cardiomyopathy has not been systematically studied. We hypothesized that the local stimulation characteristics at the time of device implantation predict the response to cardiac resynchronization therapy (CRT).

## Methods and results

We measured the impedance, sensing, and capture threshold of a bipolar LV lead in 138 patients with non-ischaemic cardiomyopathy undergoing first implantation of CRT device for drug refractory heart failure. All patients underwent echocardiography at baseline and at 6 months post-implantation. An absence of favourable response to CRT was defined as <15% decrease in echocardiographic LV end-systolic volume (LVESV) at 6 months. Echocardiographic response to CRT was observed in 70% of patients. The LV lead measurements predicted neither the optimal stimulation site nor the response to CRT. Left ventricular capture threshold ( $1.50 \pm 1.1$  vs.  $1.32 \pm 0.8$  V) and impedance ( $725 \pm 287$  vs.  $720 \pm 261 \Omega$ ) were similar between the responders and the non-responders. Independent of baseline LV ejection fraction or ESV, the LV R-wave amplitude at implantation was significantly higher ( $P = 0.0038$ ) in responders ( $12.7 \pm 5.2$  mV) than in non-responders ( $9.7 \pm 6.3$  mV), with an area under the receiver operating characteristic curve of 0.7.

## Conclusion

Response to CRT, as determined by decrease in LVESV at 6 months, was associated with significantly higher LV R-wave amplitude at the time of device implantation.

## Keywords

Cardiac resynchronization therapy • Left ventricular stimulation • Ventricular pacing • Heart failure

## Introduction

For the past several years, cardiac resynchronization therapy (CRT) has been playing an important role in the management of patients suffering from congestive heart failure.<sup>1–3</sup> However, ~30% of the recipients do not respond to CRT, which may be partially related to the site of implantation of the left ventricular (LV) lead.<sup>4,5</sup> Based on some pilot studies and a few large trials, the LV lead is preferentially implanted in the lateral or posterolateral position.<sup>6,7</sup> In patients presenting with ischaemic heart disease, the

myocardial properties at the site of the LV lead implantation seem to determine its sensing and stimulation characteristics, as well as the response to CRT. Direct stimulation of an ischaemic zone appears to have adverse haemodynamic consequences.<sup>8,9</sup> However, the relationships among the site of stimulation, the electrical lead characteristics, and the response to CRT in patients presenting with non-ischaemic dilated cardiomyopathy are poorly defined.

The patients suffering from non-ischaemic cardiomyopathy were prospectively studied to examine the relationships between (i) the

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LV lead location and the lead impedance, stimulation threshold, and sensing characteristics, (ii) the LV lead location and the echocardiographic response to CRT, and (iii) the lead impedance, stimulation threshold, and sensing characteristics and the response to CRT.

## Patient population and methods

This study included 138 patients suffering from non-ischaemic dilated cardiomyopathy, who were suitable candidates for CRT. Patients were eligible for inclusion in the study if they had (i) no history of myocardial infarction, no symptoms of angina, and no significant coronary artery stenosis (>50%), (ii) symptomatic heart failure New York Heart Association class III or IV despite optimal medical management, (iii) LV ejection fraction (LVEF) <35%, and (iv) QRS duration >120 ms.

## Triple-chamber cardioverter defibrillator implantation

All patients underwent implantation of a triple-chamber cardioverter defibrillator (Medtronic, Boston Scientific, Saint Jude Medical, Sorin Biomedica, and Biotronik). The right atrial and the right ventricular leads were implanted using standard techniques. An Attain® Bipolar, model OTW 4194 (Medtronic Inc. Minneapolis, MN, USA) was used universally to avoid lead-related inconsistencies in its electrical characteristics. Using percutaneous techniques, the lead was advanced via the coronary sinus to an anterior, lateral, or posterior tributary. In clinical practice, a lateral or a posterior vein is usually targeted. In this study, priority was given to lead stability, appropriate threshold, and absence of diaphragmatic pacing. Intra-operative haemodynamic evaluation was not performed. On the lateral fluoroscopic view, a lead that appeared lying in the great cardiac vein with its distal segment in a small tributary oriented towards the lateral wall was considered as lying in an anterior position. At the time of implantation, the amplitude of local electrogram, pacing impedance, and capture threshold were measured in bipolar mode, which was the chronic pacing mode. Within 48 h after system implantation, the optimal atrio-ventricular delay was chosen so as to allow maximal transmural filling without truncation of the A wave on echocardiography. The ventriculo-ventricular delay was set at 0 ms in all patients.

## Echocardiography

Echocardiogram (Vivid 7, GE Healthcare, Horton, Norway) was blindly obtained before and after 6 months of successful biventricular stimulation in each patient. End-systolic (ESV) and end-diastolic volumes and LVEF were measured, using Simpson's biplane method in four-chamber and two-chamber views, as recommended by the American Society of Echocardiography.<sup>10</sup>

## Fluoroscopic lead position

The LV lead position was verified on biplane frontal and left lateral orthogonal fluoroscopic projections at the time of lead implantation and within 2 days, thereafter.

Patients were classified as responders to therapy after 6 months of successful biventricular pacing, if they were alive and LVESV had decreased by  $\geq 15\%$  when compared with the baseline measurement.

## Statistical analyses

The results are expressed as mean  $\pm$  SD or percentages. Mean values were compared using analysis of variance or, in case of inhomogeneous variance, by the Mann–Whitney/Wilcoxon two-sample test (Kruskal–Wallis test for two groups). The likelihood of response to CRT was examined by the  $\chi^2$  test. Correlations were examined by logistic regression analysis. EPI INFO software was used for analyses. The intra-observer correlation values for standard echocardiographic quantification were determined in 15 patients in a previous study.<sup>11</sup> The intra-observer correlation for the calculation of the LVESV was 0.95. A *P*-value <0.05 was considered significant.

## Results

The clinical and echocardiographic characteristics of the patients included in this study are shown in Table 1. The LV lead was implanted on the lateral wall in 80 patients (58%), anterior wall in 31 (23%), and the posterior wall in 26 patients (19%). At the time of implantation, the mean LV capture threshold was  $1.45 \pm 1.0$  V, the R-wave amplitude was  $11.8 \pm 5.7$  mV, and the LV lead impedance was  $723 \pm 279$   $\Omega$ .

## Effect of left ventricular lead position on the electrical measurements

At the time of implantation, the mean capture threshold, the R-wave amplitude, and the lead impedance were similar at all the LV lead implantation sites (Table 2).

## Effect of left ventricular lead position on the echocardiographic response

After 6 months of CRT, 97 patients (70%) were classified as responders and 41 patients (30%) as non-responders. No baseline clinical, electrocardiographic, or echocardiographic variable was predictive of response to CRT (Table 3). Echocardiographic

**Table 1** Clinical and echocardiographical characteristic of 138 patients at baseline

Age (years)	65.4 $\pm$ 13.1
Men/women	99/39
QRS duration (ms)	150 $\pm$ 32.7
New York Heart Association class	3.1 $\pm$ 0.6
Drug therapy	
Angiotensin-converting enzyme inhibitor	118 (86)
Angiotensin II receptor blocker	16 (12)
Beta-adrenergic blocker	124 (90)
Diuretic	114 (83)
Aldosterone antagonist	85 (62)
Left ventricular	
Ejection fraction (%)	27.2 $\pm$ 7.2
End-systolic volume (mL)	117.4 $\pm$ 58.1
End-diastolic volume (mL)	161.3 $\pm$ 68.4

Values are means  $\pm$  SD or numbers (per cent) of observations.

**Table 2** Relation between left ventricular stimulation site and electrical lead characteristics

	Anterior (n = 31)	Lateral (n = 80)	Posterior (n = 26)	P
R-wave (mV)	12.1 ± 6.7	10.9 ± 5.5	12.3 ± 5.9	0.31
Threshold (V)	1.6 ± 1.3	1.4 ± 0.9	1.3 ± 0.7	0.93
Impedance (Ω)	741 ± 239	712 ± 307	763 ± 251	0.33

Values are means ± SD.

**Table 3** Baseline clinical and echocardiographic characteristics of responders vs. non-responders to cardiac resynchronization therapy

	Responders (n = 97)	Non-responders (n = 41)
Age (years)	63.4 ± 14.6	68.9 ± 9.5
Men/women	70/27	29/12
QRS duration (ms)	150 ± 31.8	151 ± 34.9
New York Heart Association class	3.0 ± 0.6	3.1 ± 0.6
Drug therapy		
Angiotensin-converting enzyme inhibitor	82 (85)	36 (88)
Angiotensin II receptor blocker	12 (12)	4 (10)
Beta-adrenergic blocker	86 (89)	38 (93)
Diuretic	81 (84)	33 (80)
Aldosterone antagonist	59 (61)	26 (63)
Left ventricular		
Ejection fraction (%)	26.8 ± 6.8	28 ± 8
End-systolic volume (mL)	120 ± 56.6	111.4 ± 60.4
End-diastolic volume (mL)	160 ± 66.2	153 ± 73.8

Values are means ± SD or numbers (per cent) of observations. All between-group differences are statistically non-significant.

improvement was similar between the patients with the lead placed in the anterior (70.8%), lateral (69.2%), and posterior (70.9%) positions ( $P = 0.97$ ).

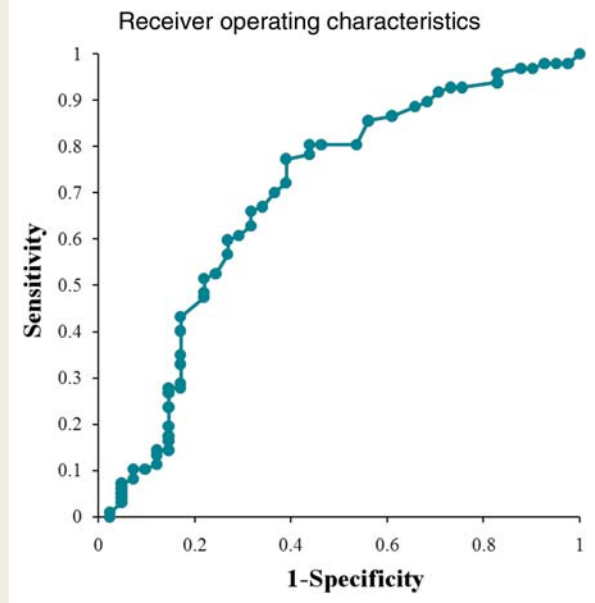
### Effect of the pacemaker parameters on the echocardiographic response

Comparing the responders with the non-responders, the mean LV capture threshold ( $1.5 \pm 1.1$  vs.  $1.32 \pm 0.8$  V) and the mean impedance ( $725 \pm 287$  vs.  $720 \pm 261$  Ω) were similar at the time of implantation. However, the mean LV electrogram amplitude ( $12.7 \pm 5.2$  vs.  $9.7 \pm 6.3$  mV) was significantly higher ( $P = 0.0038$ ) in responders than in the non-responders (Table 4). Using R-wave amplitude as predictive of the response to CRT, the area under the receiver operator characteristics curve was 0.7. The point on the curve that was associated with the highest sensitivity (77%) and specificity (61%) corresponded to an amplitude of 9.3 mV (Figure 1).

**Table 4** Left ventricular lead characteristics at implantation

	Responders (n = 97)	Non-responders (n = 41)	P
Left ventricular			
Threshold	1.5 ± 1.1	1.32 ± 0.8	Ns
Impedance	725 ± 287	720 ± 261	Ns
R-wave amplitude	12.7 ± 5.2	9.7 ± 6.3	0.004

Values are means ± SD.



**Figure 1** Receiver operating characteristics curve: sensitivity and specificity of continuous measurements of R-wave amplitude as a predictor of response to cardiac resynchronization therapy.

### Regression analysis

We found no correlation between the R-wave amplitude at the time of device implantation and LVESV or LVEF ( $r = 0.07$  and  $r = 0.14$ , respectively;  $P = \text{ns}$ ).

### Discussion

This study investigated the influence of the electrical characteristics at the site of LV stimulation in CRT recipients suffering from non-ischaemic dilated cardiomyopathy. We observed that the site of LV stimulation did not influence the response to CRT. Furthermore, the site of LV stimulation had no effect on pacing impedance, R-wave amplitude, or capture threshold. In contrast, LV R-wave amplitude at the time of CRT device implantation was significantly higher in responders than non-responders. LV R-wave amplitude emerged as the only predictor of favourable response to CRT.

The choice of optimal site of LV stimulation in CRT remains controversial. This study selected a homogeneous population by excluding the patients with ischaemic heart disease. A recent short-term study involving similar population with idiopathic dilated cardiomyopathy and wide QRS reported similar results.<sup>12</sup> Although the site of stimulation at the time of system implantation seemed to play a key role in improving haemodynamic function, no site was identified, in that study, as a priori optimal. Furthermore, stimulation of the lateral wall did not seem to provide any added benefit when compared with that of the other walls. These observations were confirmed in our study. In a considerable proportion of patients, reverse LV remodelling was not more prominent among the patients who had the lead implanted on the lateral wall when compared with those who had the lead implanted on the anterior or the posterior wall. Different results might, however, be obtained from the patients suffering from ischaemic heart disease, or in a mixed population of patients with and without ischaemic heart disease.

The optimal site of LV stimulation varies between individuals. Our study was designed to determine whether the electrical characteristics of the LV lead measured at the time of implantation were related to the long-term response to therapy, and whether they could be used to optimize the site of stimulation. Although the capture threshold and the impedance were not predictive, R-wave amplitude was significantly higher in responders. The amplitude of the R-wave sampled by a ventricular lead depends on several factors, including (i) the orientation of the sensing bipole with respect to the ventricular depolarization vector wherein an axis perpendicular to the bipole would be associated with a low signal amplitude, (ii) the amount of viable myocardium in the vicinity of the electrode since the fibrotic, necrotic, or ischaemic tissue would be expected to generate a signal of lower amplitude than healthy myocardium, and (iii) the signal's slew rate, which is decreased when a zone of diseased tissue is sampled. We, therefore hypothesized that, in any given patient, myocardial area associated with a high R-wave amplitude would be a sign of greater tissue viability and greater contractile reserve than a zone of decreased signal amplitude due to fibrotic, necrotic, or ischaemic tissue. In bipolar configuration, the R-wave amplitude depends on the depolarization of tissue in the immediate vicinity of the electrodes. This is in contrast to a wide region sampled by the electrodes in unipolar configuration.

Although LV R-wave amplitude predicted response to CRT, this study did not determine whether the measurement of the bipolar R-wave amplitude at the time of LV lead implantation enabled the identification of viable myocardial tissue with high contractile reserve. This correlation could only be confirmed by (i) studying a larger patient population, (ii) comparing the effects of LV stimulation at the site of high LV electrogram vs. that at the site of low R-wave amplitude, and (iii) objectively (using imaging techniques) demonstrating the concordance between the zones of low R-wave amplitude and those with anatomically or functionally abnormal myocardium.

### Limitations of our study

The present study included 138 patients suffering from non-ischaemic dilated cardiomyopathy without the history of

myocardial infarction, angina, and coronary artery stenosis >50%. The binary threshold of 50% may not be accurate since acute myocardial infarction is known to result from the <50% stenosis. We did not perform magnetic resonance imaging, positron emission tomography scan, or stress echocardiography to look for non-viable scar tissue. Moreover, the present data cannot be extrapolated to patients with ischaemic cardiomyopathy and myocardial scar. The measurements were made with the pacing systems analyser at the time of CRT device implantation to collect a homogeneous set of measurements of lead characteristics. Microdislodgement of the lead imperceptible on radiographic examination could have been the cause of marked variations in the electrogram amplitude and pacing parameters following implantation. It would have been relevant to follow-up the evolution of the LV R-wave amplitude and to correlate it with the clinical outcome. However, this analysis could not be undertaken since many of the currently used devices do not have the LV sensing function and also because the signal processing varies between different manufacturers. An echocardiographic assessment of cardiac intraventricular and interventricular dyssynchrony would have probably reinforced the power of the study. The response to resynchronization was assessed after 6 months of biventricular pacing. Results obtained on longer follow-up are definitely warranted.

## Conclusion

In CRT recipients presenting with non-ischaemic cardiomyopathy, the likelihood of response to treatment, when determined by interval decrease in the LVESV, was similar among those with the leads implanted in the anterior, lateral, and posterior LV sites. Furthermore, the pacing and the sensing characteristics of the LV lead were similar at all the three sites. The CRT responders had significantly higher amplitude of the LV lead electrogram at the time of implantation.

**Conflict of interest:** none declared.

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