

# Midterm ‘super-response’ to cardiac resynchronization therapy by biventricular pacing with fusion: insights from electro-anatomical mapping

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## Aims

Some authors recommend avoiding fusion with left ventricular (LV) intrinsic depolarization during cardiac resynchronization therapy (CRT). If fusion is still present during optimized biventricular (Biv) pacing and its long-term effects on the response to CRT are currently unknown. The aim of the study was to analyse the endocardial LV activation pattern induced by echocardiographically optimized Biv pacing and its influence on LV reverse remodelling.

## Methods and results

Contact electro-anatomical mapping was performed in 15 heart failure (HF) patients with left bundle branch block and echocardiographically optimized CRT (seven ischaemic aetiology,  $64 \pm 8$  years, three women, New York Heart Association class  $3 \pm 0.4$ , LV ejection fraction  $25 \pm 5\%$ ). Left ventricular activation maps were performed in sinus rhythm (SR), during DDD right ventricular apical (RVA) and optimized Biv pacing. Fusion with intrinsic rhythm during pacing was considered when LV septal activation was produced at least partially by intrinsic depolarization, when compared with LV activation map during SR. Patients were considered responders to CRT if they had  $\geq 10\%$  reduction in LV end-systolic volume (LVESV) after 6 months of CRT. During SR, the LV breakthrough was mid-septal ( $n = 12$ ), basal septum ( $n = 2$ ), and apical ( $n = 1$ ). During RVA pacing, LV breakthrough shifted apical in all patients. Right ventricular apical/Biv pacing proved fusion with intrinsic depolarization in 8 of 15 patients. The PR interval was shorter in patients with fusion RVA/Biv pacing ( $164 \pm 24$  vs.  $234 \pm 55$  ms,  $P = 0.006$ ). There was a trend for shorter LV activation time ( $LV_{at}$ ) in patients with fusion during RVA pacing ( $87 \pm 33$  vs.  $113 \pm 21$  ms,  $P = 0.08$ ) as well as during optimized Biv pacing ( $83 \pm 18$  vs.  $104 \pm 24$  ms,  $P = 0.07$ ), although  $LV_{at}$  was similar in SR ( $100 \pm 22$  vs.  $106 \pm 20$ ,  $P = NS$ ). In patients with fusion, 6 months responder rate was significantly higher (100 vs. 28.5%,  $P < 0.007$ ) as was the degree of LVESV reduction ( $39 \pm 17$  vs.  $1.0 \pm 14\%$ ,  $P < 0.001$ ).

## Conclusion

Biventricular pacing with fusion may substantially increase the structural responder rate probably by shortening  $LV_{at}$ .

## Keywords

Cardiac resynchronization therapy • RVA pacing • Fusion • Activation time

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## Introduction

In patients with wide QRS and New York Heart Association (NYHA) class 3 or 4 heart failure (HF) on optimal medical therapy, cardiac resynchronization therapy (CRT) improves functional status and quality of life and reduces HF-related hospitalizations and total mortality.<sup>1</sup> Unfortunately, only 60<sup>1</sup> to 70%<sup>2</sup> of patients have a clinical response. Moreover, long-term survival is improved with CRT only if associated with LV reverse remodelling, defined as  $\geq 10\%$  reduction in LV end-systolic volume (LVESV),<sup>3</sup> a structural response that is present in only 56% of patients.<sup>2</sup> Although identification of mechanical intraventricular dyssynchrony seemed appealing, with some data showing a superior effect of CRT in patients with a concordance between maximum delay area and LV lead position,<sup>4</sup> a recent prospective trial did not show a good correlation of any of the echocardiographic parameters used to assess baseline intraventricular dyssynchrony with clinical or structural response to CRT.<sup>2</sup> Besides poor reproducibility of these parameters<sup>5</sup> and complex torsion movement of the asynchronous, failing LV,<sup>6</sup> another possible explanation could reside in the pacing configuration used. Acute data suggest that in patients with normal AV conduction allowing partial intrinsic depolarization of the LV (fusion) during CRT produce a superior haemodynamic response.<sup>7</sup> However, due to presumed variability in AV conduction and lack of data on chronic effects of fusion, the majority of authors try to avoid it<sup>8</sup> and prefer biventricular (Biv) pacing with the shortest possible AV delay, as determined by echocardiography. This introduces right ventricular (RV) pacing, which might change the timing and the pattern of LV depolarization.

The present investigation aimed to analyse endocardial LV activation pattern to test if fusion is still present after echocardiographically optimized Biv pacing and to determine its influence on LV reverse remodelling.

## Methods

### Patients

Between October 2006 and February 2007, 15 consecutive patients admitted to CRT were included in the study. Eligibility criteria for CRT were chronic moderate to severe HF (NYHA class III or IV), moderate to severe LV systolic dysfunction [LV ejection fraction (LVEF)  $\leq 35\%$ ], and a QRS complex  $\geq 120$  ms. Ischaemic heart disease was considered the aetiology of LV systolic dysfunction in the presence of significant coronary artery stenosis ( $\geq 50\%$  in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction and/or previous coronary revascularization. The study protocol was approved by the Institution's Ethics Committee and written informed consent was obtained in all cases.

### Cardiac resynchronization therapy device implantation

The right atrial and ventricular leads were positioned conventionally [right atrial appendage and RV apical (RVA)]. After coronary sinus (CS) was cannulated with an 8F guiding catheter, an occlusive retrograde CS angiogram was obtained. The LV pacing lead (Easytrak 4512-80, Guidant Corporation, St Paul, MN, USA) was inserted in a lateral or postero-lateral vein. All leads were connected to a

dual-chamber Biv implantable pacemaker or cardioverter-defibrillator (Contak Renewal IV or H195, Guidant Corporation).

### Echocardiographic evaluation

All patients underwent standard transthoracic 2D and colour-Doppler echocardiography before implantation, 1 day after implantation (for optimization), and after 6 months of CRT. Images were obtained in the parasternal and apical views with a commercially available system (Vivid 7, General Electric, Milwaukee, WI, USA), using a 3.5 MHz transducer. Left ventricular volumes (LVEDV and LVESV) and LVEF were calculated using the biplane Simpson's technique. Echocardiographic optimization was performed step-wise: first AV interval (by the Ritter method, choosing the shortest AV interval that yielded the longest diastolic filling time without truncation of the A wave) followed by the VV interval (the optimum VV was considered as the one that yielded the best intraventricular synchrony as demonstrated by TDI, with a greater superposition of the displacement curves of two opposite LV walls as described previously).<sup>9</sup> Patients were classified as responders to CRT if they had LV reverse remodelling ( $\geq 10\%$  reduction in LVESV at 6 months follow-up).

### Mapping procedure

Contact electro-anatomical activation mapping (CARTO, Biosense Webster) of the LV endocardium was performed from 1 to 3 days after the implantation of a CRT or CRT-D device. Activation maps were obtained during intrinsic rhythm, during RVA and during Biv pacing (both in DDD mode with AV interval programmed equal to echocardiographically optimized AV interval). Fusion with intrinsic rhythm during pacing was considered when LV septal activation was produced at least partially by intrinsic depolarization, when compared with LV activation map during sinus rhythm (SR), i.e. single-fused wave-front or double wave-front resulting from intrinsic depolarization and apical depolarization due to RVA pacing. Using multiple radioscopic projections, the LV lead electrode position was localized within the anatomical map. Rectilinear distance between the LV lead electrode and the area of maximum delay was determined in each map. Activation maps (intrinsic vs. RVA pacing) were superposed, and rectilinear distance between the areas of maximum delay was determined. The time interval from the beginning of QRS (from 12-lead electrocardiogram) to the earliest (breakthrough) point on the LV activation map during intrinsic rhythm as well as total LV activation time (LV<sub>act</sub>) were measured. The time interval from the beginning of QRS to RV-detected electrogram (RV<sub>EGM</sub>) was determined with the CRT device programmed in the ODO mode. We arbitrarily defined a significant shift in the location of the most delayed area as an increase of  $> 3$  cm in the distance from most delayed area to LV lead electrodes with RVA pacing ( $\Delta d$ ).

### Statistical analysis

The measured values are expressed as mean  $\pm$  SD. Data showing Gaussian distribution were compared in the subgroups using paired and Student's *t*-tests. Dichotomous variables and non-parametric data were compared using  $\chi^2$  and Wilcoxon testing, respectively. The level of significance was set at 0.05.

## Results

### Patients

Baseline characteristics of the 15 patients included in this study are summarized in Table 1. Mean age was  $67 \pm 8$  years (three women);

**Table 1** Baseline patient characteristics (n = 15)

Sex (female/male)	3/12
Age (years)	67 ± 8
Aetiology (ischaemic/idiopathic)	7/8
NYHA functional class	3 ± 0.4
LV end-diastolic dimension (mm)	73 ± 10
LV end-systolic dimension (mm)	59 ± 12
LV ejection fraction (%)	25 ± 5
Sinus rhythm	15 (100%)
PR interval (ms)	197 ± 54
QRS width (ms)	181 ± 13
Interval [bQRS–earliest point on the LV activation map] during intrinsic rhythm (ms)	7 ± 7
Interval [bQRS–RV <sub>EGM</sub> ] during intrinsic rhythm (ms)	50 ± 14
Interval [bQRS–earliest point on the LV activation map] during RVA pacing (ms)	30 ± 10
Total LV endocardial activation time, intrinsic rhythm (ms)	99 ± 30
Total LV endocardial activation time, RVA pacing (ms)	102 ± 21
Total LV endocardial activation time, optimized (ms)	93 ± 23

NYHA, New York Heart Association; LV, left ventricular; PR, QRS, and nQRS, narrow QRS complex; LBBB, left bundle branch block; bQRS, beginning of QRS; RVA, right ventricular apical; RV<sub>EGM</sub>, RV lead detected intracardiac electrogram.

the aetiology of LV systolic dysfunction was ischaemic in seven patients. Mean baseline LVEF was 25 ± 5%. All patients were in SR and QRS morphology was left bundle branch block (LBBB) type in all 15 patients.

## The breakthrough

The breakthrough of LV endocardial activation during SR was mid-septal (n = 12, 80%), basal septum (n = 2, 13%), and apical (n = 1, 7%). Mean time interval from the beginning of QRS complex on 12-lead electrocardiogram to the earliest point on the LV activation map during intrinsic rhythm was 7 ± 7 ms; mean time interval from the beginning of QRS complex to RV<sub>EGM</sub> was 50 ± 14 ms. With RVA pacing, the LV endocardial breakthrough was always apical (Figure 1), 30 ± 10 ms from the RV pacing artefact on 12-lead electrocardiogram.

## Maximum delay area

The most delayed area during SR was postero-lateral or lateral in 13 patients (87%) and antero-lateral in 2 patients (13%). During RVA pacing, the most delayed area was unchanged only in three patients (20%), in 80% of them (n = 12) shifting to more anterior positions (Figure 1). The mean shift was 33 ± 9 mm. However, the mean distance from most delayed area to LV lead electrode was not significantly changed in this population (39.5 ± 20.5 mm during intrinsic rhythm vs. 41.8 ± 10.8 mm with RVA pacing, P = NS). When we compared patients with significant shift during RVA pacing (n = 5) vs. patients with a non-significant shift (n = 10), there was no difference in the rate of structural responders: only 60% in the first group vs. 70% in the second group. Overall,

there was also a slight increase in total LV<sub>at</sub> with RVA pacing (102 ± 21 vs. 99 ± 30 ms during intrinsic rhythm, P = NS).

## Effects of fusion with left ventricular intrinsic depolarization

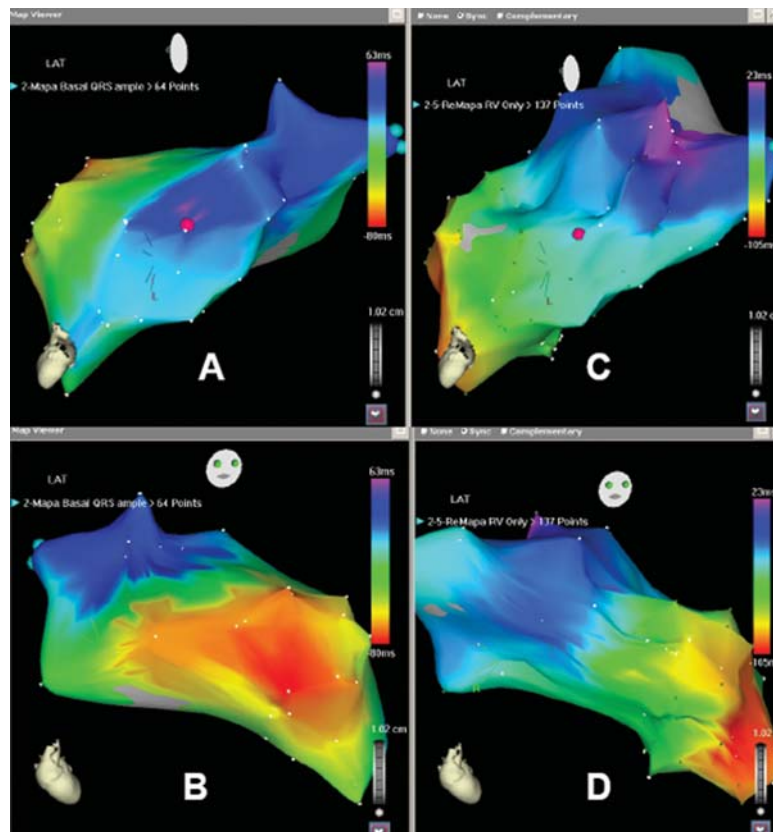
According to LV activation maps, with the optimized echocardiographic AV interval used for DDD RVA/Biv pacing, there was fusion with intrinsic rhythm in 8 of 15 patients (Figure 2). The mean shift in the most delayed area of activation during RVA pacing as well as the mean distance from most delayed area to LV lead electrodes in SR and during RVA pacing were similar with fusion and with pure RVA pacing (32 ± 11 vs. 30 ± 10 mm, 37 ± 23 vs. 43 ± 18 mm, respectively 40 ± 14 vs. 44 ± 7, P = NS for all comparisons). There was a trend towards shorter LV<sub>at</sub> in the fusion group during RVA pacing (87 ± 32 vs. 113 ± 21 ms, P = 0.08) as well as during optimum Biv pacing (83 ± 18 vs. 104 ± 24, P = 0.07). All the patients with fusion (100%) were structural responders at 6 months vs. only two of seven (28.5%) in the group with pure Biv pacing (P < 0.007), despite a similar baseline clinical profile (Table 2), except for a significantly shorter PR interval (164 ± 24 vs. 234 ± 55 ms, P = 0.006). In the group with fusion, the degree of reverse remodelling (evaluated by LVESV reduction) was also significantly higher than that in patients with pure RVA pacing: 39 ± 17 vs. 1.0 ± 14% (P < 0.001).

## Discussion

Although it was previously assumed that RVA pacing is similar to LBBB in the presence of LV systolic dysfunction, this study confirms that in patients with chronic HF (CHF) subjected to CRT, RVA pacing changes the LV activation pattern, even in the presence of LBBB, producing overall an increase (although not statistically significant) in LV<sub>at</sub> and in the distance from maximum delay area to the LV lead. More importantly, the rate of structural responders to CRT was impressively higher (P < 0.007) in patients in whom RVA/Biv pacing allows partial intrinsic activation of the LV than in patients with pure capture during RVA/Biv pacing. A possible explanation is that CRT with fusion creates three activation wave fronts (instead of two during pure Biv pacing), therefore shortening LV<sub>at</sub> (Figure 3).

## Breakthrough area

In this series of CHF patients with LBBB, the breakthrough of LV activation was most frequently mid-septal and only rarely apical (1 of 15 patients). This finding differs from a previous study of contact and non-contact mapping in 23 patients with CHF and LBBB,<sup>10</sup> in which the breakthrough was most often apical (by trans-septal depolarization through RBBB). However, the majority of publications are consistent with our data: classical electrophysiological mapping,<sup>11</sup> contact mapping,<sup>12</sup> and non-contact mapping<sup>13</sup> have shown that the location of breakthrough is mid- or basal septum<sup>14</sup> in the majority of patients. Consistently, in our series of patients, the time interval from the beginning of QRS to the earliest point on the LV activation map is by far shorter than the time interval from the beginning of QRS to the detected RV<sub>EGM</sub> (7 ± 7



**Figure 1** Left-ventricular activation maps from the same patient during intrinsic rhythm (A and B) and RVA pacing (C and D) in left lateral (A and C) and RAO (B and D) projections. Baseline there was a perfect concordance between the area of maximum delay and LV lead position (pink floating spot). During RVA pacing, the area of maximum delay shifted 5 cm in a more basal position.

vs.  $50 \pm 14$  ms,  $P < 0.05$ ) despite the fact that RV lead was placed apical (i.e. in the proximity of RBB) (Table 1).

### Area of left ventricular maximum delay

Right ventricular apical pacing has deleterious effects in patients with LV systolic dysfunction<sup>15</sup> as well as in patients with normal baseline LV systolic function,<sup>16</sup> mainly by induction of intraventricular dyssynchrony. In our study, RVA pacing increases the  $LV_{at}$  and changes the location of the latest LV endocardial activation area (in 80% of cases to more anterior positions). The  $LV_{at}$  increase with RVA pacing is smaller than that in other studies because they assessed it epicardially,<sup>17</sup> but the presence of fusion in 8 of 15 patients probably contributed as well. Studies of classic LV endocardial mapping<sup>18</sup> and contact electro-anatomical endocardial mapping<sup>19</sup> also showed changes in the LV endocardial activation pattern during RVA pacing, with shifts in the location of maximum delay area in more postero-inferior<sup>18</sup> or antero-lateral<sup>19</sup> positions.

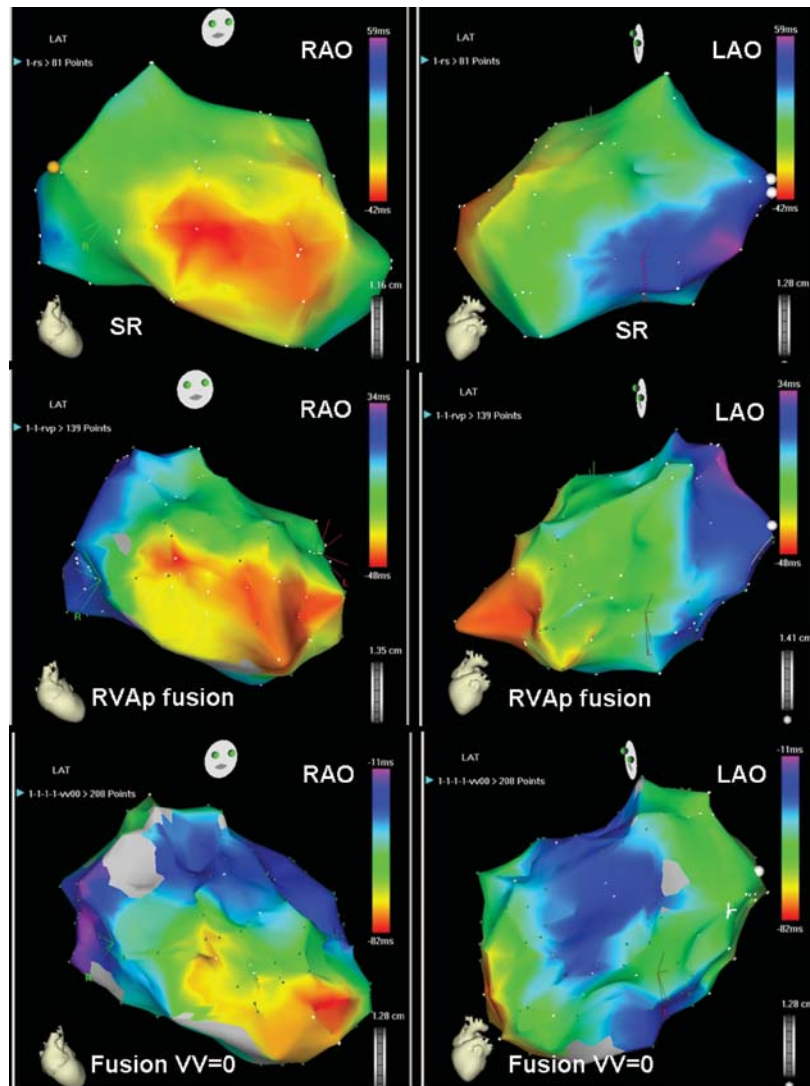
Currently, there is no direct evidence for a significant shift of activation on LV epicardium (where the LV lead is usually placed). However, indirect data on epicardial activation using body surface potential mapping consistently suggest that LV epicardial activation patterns change during RVA pacing, even in patients

with LV systolic dysfunction and LBBB.<sup>20,21</sup> Moreover, in studies of surgically delivered LV lead for CRT, placing the LV leads at sites of maximum electrical delay during RVA pacing significantly increased the percentage of responders.<sup>22</sup>

More important, recent mechanical data on 2D radial strain seems to confirm that RVA pacing changes the location of the area with the most delayed systolic peak.<sup>23</sup>

### Effects of fusion during cardiac resynchronization therapy

It seems tempting to try to avoid LV activation shift induced by RVA pacing, at least in CRT patients with normal AV conduction and concordant LV lead position. One alternative would be to program the CRT device to allow partial or complete intrinsic depolarization of the interventricular septum (fusion pacing), creating three activation fronts instead of two during pure Biv pacing. Acute invasive haemodynamic data proved that in patients with normal AV conduction, CRT with fusion is superior to any optimized Biv configuration in improving  $LV_{at}$ <sup>7,24</sup> as well as RV systolic performance.<sup>25</sup> Our study suggests that the mechanism of this improved performance is a shorter  $LV_{at}$  which probably produces superior resynchronization. Despite the theoretical drawbacks of fusion (potential for losing optimal fusion because of disease



**Figure 2** Example in which echocardiographic AV optimization permitted CRT with fusion. On the top, activation maps during SR showing a mid-septal breakthrough, a postero-lateral most delayed activation area and  $LV_{at}$  of 101 ms. On the middle, activation maps during RVA pacing with fusion with the intrinsic depolarization, showing the two septal breakthroughs, a change in the most delayed activation area (antero-lateral) and a shortening in  $LV_{at}$  to 82 ms. On the bottom, activation maps with the addition of a third wave front from the CS lead, showing the maintenance of the same septal breakthroughs, a change of the most delayed area of activation towards intermediate positions and a further shortening of  $LV_{at}$  to 71 ms.

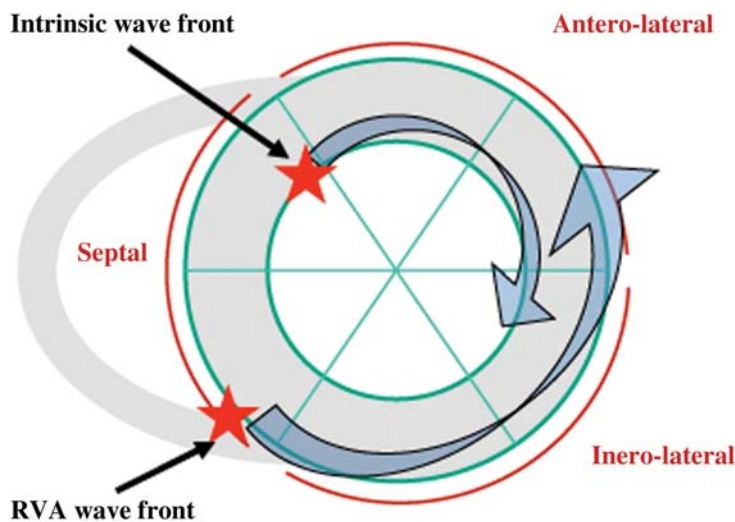
progression or spontaneous variation in AV conduction, lack of data on long-term effects of fusion CRT), in this study CRT with fusion produced an impressive rate of 100% structural responders at 6 months. Programming the AV delay to obtain CRT with optimal fusion can be challenging considering the variability of PR interval. However, a recent long-term prospective study in 40 patients used a non-invasive algorithm to obtain CRT with optimal fusion, observing the same high rate of structural response, with a similar level of reverse remodelling at 6 months.<sup>26</sup> On the top of that, the same group recently demonstrated by serial ECG and ECG exercise test that CRT with optimal fusion can be maintained and that a Wenckebach point during atrial stimulation of less 500 ms can reliably predict fusion maintenance.<sup>27</sup>

The significantly shorter PR interval, a non-significant smaller LVESV at baseline in patients with fusion during CRT, may suggest also that they had a less advanced heart disease and a less dilated LV. However, the  $LV_{at}$  during intrinsic rhythm that was not different in patients with fusion vs. patients with pure Biv pacing, which is an argument against this hypothesis. Concordantly, MIRACLE trial found similar baseline LV dimensions in non-responders when compared with responders, despite a significantly larger proportion of patients with long PR interval in the former group.<sup>28</sup> It seems tempting to speculate that the optimization method which starts with AV interval (diastolic optimization) might also contribute, since the 'optimum' AVI was practically identical in these two patient populations despite very different

**Table 2** Comparison between characteristics of patients with pure RVA pacing (n = 7) and with RVA/Biv pacing with fusion (n = 8)

	RVA (n = 7)	Fusion (n = 8)	P-value
Sex (female/male)	1/6	2/6	NS
Age (years)	73 ± 7	63 ± 6	NS
Aetiology (ischaemic/idiopathic)	4/3	3/5	NS
NYHA functional class	3.2 ± 0.4	2.9 ± 0.4	NS
PR interval (ms)	234 ± 55	164 ± 24	0.006
AV interval (ms)	136 ± 12	140 ± 0	NS
VV interval (ms)	-9 ± 15	-15 ± 16	NS
QRS width (ms)	164 ± 34	179 ± 14	NS
LV lead			
Maximum delay area intrinsic (mm)	39.3 ± 17.8	36.5 ± 23	NS
Maximum delay area RVA pacing (mm)	42.6 ± 13.4	40.2 ± 13.6	NS
Mean shift in activation pattern (mm)	32.3 ± 9.3	32.0 ± 11	NS
Significant shift (n/n)	2/7	3/8	NS
Total LV activation time intrinsic rhythm (ms)	106 ± 20	100 ± 22	NS
Total LV activation time RVA pacing (ms)	113 ± 21	87 ± 33	0.08
Total LV activation time optimized pacing (ms)	104 ± 24	83 ± 18	0.07
Baseline LV ejection fraction (%)	23 ± 5	25 ± 5	NS
Baseline LVESV (mL)	221 ± 56	176 ± 49	NS
6 months follow-up LVESV (mL)	218 ± 50	107 ± 48	<0.001
Reduction of LVESV (%)	1 ± 14	39 ± 17	<0.001
Structural responders (%; n/n)	28.5 (2/7)	100 (8/8)	0.001

NYHA, New York Heart Association; AV, atrioventricular; LV, left ventricular; PR, QRS, and nQRS, narrow QRS complex; RVA, right ventricular apical.



**Figure 3** Schematic of the mechanism by which the fusion between RVA pacing and partial intrinsic LV endocardial depolarization shortens LV<sub>at</sub>. The most delayed area during SR (intrinsic LV endocardial depolarization) was postero-lateral or lateral in >80% of patients. During RVA pacing, the most delayed area shifted to anterior or antero-lateral in ~90% of patients. Thus, fusion between these two wave fronts takes less time to depolarize the LV. Adding a third wave front from the epicardial LV further diminishes the total duration of the LV<sub>at</sub>.

baseline PR interval. In patients with long PR interval, this constantly introduces RVA pacing, possibly worsening LV function. This is suggested also by the trend to increase LV<sub>at</sub> in long PR

interval patients during DDD RVA pacing as well as during Biv pacing at the optimized AVI. Invasive haemodynamical data showed that in one-third of patients with similar long PR, there

is a worsening of LV systolic and diastolic function when paced with short AVI.<sup>29</sup>

An alternative to fusion would be to correct the effects of RVA pacing by triple site pacing, although this might be technically challenging. Recent data show that dual site RV pacing associated with LV pacing produced superior LV resynchronization and systolic performance when compared with conventional Biv pacing<sup>30</sup> and that reverse remodelling with dual site LV pacing associated with RV pacing is superior to conventional Biv pacing.<sup>31</sup> These data strengthen the idea of the superiority of three activation fronts during CRT (a situation reproduced during CRT with fusion).

## Limitations

The results might be limited by the contact mapping technology. Rectilinear measurements underestimate distances on a curved surface. However, the precision in anatomical details is superior to non-contact mapping, although the latter can map the activation sequence using one beat. The protocol used for RVA pacing (DDD with echocardiographically optimized AVI), which permits fusion with intrinsic rhythm in a significant proportion of patients, may also obscure the changes in LV activation. Finally, this study is limited by our small sample size, which could explain the lack of statistical significance in the differences in LV<sub>at</sub>. However, the important difference observed with pure RVA pacing and with fusion warrants attention and further research.

## Conclusions

In the majority of CHF patients eligible for CRT, LV activation breakthrough during intrinsic rhythm is located in mid- or basal septum. Pure RVA pacing changes LV endocardial activation sequence and prolongs LV<sub>at</sub> in the vast majority of cases. Partial intrinsic depolarization of the LV during CRT may substantially increase the rate of structural responders. This suggests that pure RVA/Biv pacing should be avoided whenever possible.

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