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Improved acute haemodynamic response to cardiac resynchronization therapy using multipoint pacing cannot solely be explained by better resynchronization☆

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ABSTRACT

Background: The recently developed quadripolar left ventricular (LV) leads have been developed to increase the benefit of cardiac resynchronization therapy (CRT). These leads offer the option to stimulate the LV on multiple sites (multipoint pacing, MPP). Invasive haemodynamic measurements have shown that MPP increases haemodynamic response.

Purpose: To investigate whether the beneficial effect of MPP can be explained by better electrical resynchronization.

Methods: Different LV lead locations were tested during biventricular (BiV) pacing and MPP in 29 CRT candidates. The 12-lead electrocardiogram (ECG) and the invasive LV pressure curves were measured simultaneously. The Kors matrix was used to convert the ECG into a vectorcardiogram (VCG). The acute haemodynamic benefit of MPP was compared with the reduction in QRS duration and VCG-derived QRS area.

Results: Out of the 29 patients, three patients were excluded due to missing LV pressures or ECG measurements. In the remaining 26 patients MPP resulted in a significant haemodynamic improvement compared to BiV pacing without a significant change in QRS duration and QRS area. In only 5 out of the 26 patients the QRS area decreased during MPP compared to BiV pacing. In 17 patients MPP did not change QRS duration and significantly increased QRS area but moved the direction of the maximal QRS vector (azimuth) more opposite from baseline compared to BiV pacing. In 4 patients the QRS area was small during baseline, indicating limited electrical dyssynchrony.

Conclusion: The acute haemodynamic benefit of MPP over BiV pacing is achieved by either electrical resynchronization (reduction in QRS area) or by a rotation of the maximal QRS vector, indicating a more LV dominated activation sequence. The latter property was found in two-thirds of the cohort studied.

Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with dyssynchrony induced heart failure (HF), for instance due to left bundle branch block (LBBB). CRT is known to reduce HF symptoms and mortality and to improve quality of life [1]. The technique of CRT is still being improved, either by methods to patient specifically optimize the CRT device settings or by optimizing the implantation of the CRT device. An example of the latter is the recently developed quadripolar left ventricular (LV) lead (a lead with 4 pacing electrodes).

The introduction of the quadripolar LV lead has led to a reduction of need to reimplant the lead due to phrenic nerve stimulation, high pacing thresholds or LV lead dislocation [2,3]. The quadripolar LV lead can also be used to stimulate the LV on multiple sites (multipoint pacing, MPP) [4]. Several small studies showed that MPP improves acute response to CRT [4–6] and echocardiographic response 1 year post-implantation [7]. However, the underlying mechanism of MPP and

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why it leads to an improved CRT response rate is still unclear. It has been suggested that the improved response to CRT is due to better electrical resynchronization, especially in case of infarcted regions [5,6].

The objective of the current study was to investigate whether the beneficial effect of MPP can indeed be explained by better resynchronization. In order to quantify electrical resynchronization, we use QRS duration as well as QRS area extracted from a 3D vectorcardiogram (VCG) [8]. QRS area reflects the amount of unopposed electrical forces, and thus is large in patients with a severe electrical ventricular dyssynchrony. Previously, QRS duration and/or QRS area was shown to be useful in optimizing CRT-device settings [8].

Methods

For the current study, the study population earlier described by Zanon et al. [5] was used. Twenty-nine consecutive candidates for CRT were enrolled. The local ethics board at the Santa Maria Della Misericordia Hospital approved the study and all patients provided written informed consent.

Procedure

The right ventricular (RV) lead was implanted in the midseptum and the atrial lead was placed in the right atrial appendage. All coronary veins were visualized using angiography and a quadripolar LV lead (Quartet, St. Jude Medical, St. Paul, MN, USA) was temporarily placed in all accessible LV veins to perform electrocardiographic and haemodynamic measurements. Standard biventricular (BiV) pacing was performed in the bipolar configuration with the 2 distal electrodes (D1-M2) or the 2 proximal electrodes (M3-P4) of the LV quadripolar lead. MPP stimulation was performed by means of simultaneous pacing of the two dipoles (LV1: D1-M2; LV-2: M3-P4). In patients with sinus rhythm BiV pacing and MPP were performed in the VDD mode (with a fixed atrioventricular (AV) delay of 130 ms). The VV-interval was always set to 0 ms. In patients with atrial fibrillation VVI pacing was performed at a rate 5 to 10 beats above the intrinsic ventricular rate.

Pressure measurements

The invasive pressure measurements to determine acute haemodynamic CRT response were taken with a Pressure-eWire Certus and PhysioMon software (St. Jude Medical Systems AB, Uppsala, Sweden). The tip of the pressure wire was placed in the LV cavity. The maximal increase in the rate of the LV pressure (LV dP/dt_{max}) was calculated from the LV pressure curves. Ventricular pacing measurements were alternated by baseline measurements. After each change in pace setting or lead position, ≥30 s elapsed before starting the pressure measurement to allow for haemodynamic stabilization. The average LV dP/dt_{max} was then calculated over a period of 15 s without any premature ventricular contractions and each measurement was repeated 3 times to minimize the impact of respiration and physiological variation. The baseline measurements just before and after each pace-setting were used to calculate relative changes in LV dP/dt_{max} measurements.

Electrophysiological measurements

Standard digital 12-lead ECG recordings were made throughout the procedure using the Bard LabSystem PRO EP V2.4a (C.R. Bard Inc., Lowell, MA, USA) at a sampling frequency of 1000 Hz. VCGs were constructed from these digital 12-lead ECGs using the Kors matrix [9]. These VCGs were analysed using customized software programmed in MATLAB R2016b (MathWorks, Natick, MA, USA) [10]. After defining the beginning and ending of the QRS complex, QRS duration and QRS area were calculated. Of note, QRS duration determined in this way is generally longer than the QRS duration measured by the 12-lead ECG, because it is measured as the difference between the earliest and latest deflection in any of the X, Y, and Z-leads. The QRS area is the combined area under the QRS complex curve of the three orthonormal axes X, Y, and Z calculated by: $(QRS^2_{area,x} + QRS^2_{area,y} + QRS^2_{area,z})^{1/2}$. The magnitude and direction of the maximum QRS vector in space, the point on the QRS loop with the maximal distance from the origin, was expressed by its amplitude and direction in the transversal plane (azimuth) and frontal plane (elevation).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics software version 24 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation or median [interquartile range] where appropriate and discrete variables as number (percentage). Linear correlations were evaluated by Pearson's correlation, and possible differences between groups were tested using the χ^2-test for discrete variables or the Kruskal-Wallis test followed by the Wilcoxon rank-sum test with Bonferroni correction for continuous variables. The differences between pace-settings for continuous variables were tested using the Friedman test followed by the Wilcoxon signed rank test with Bonferroni correction. A two-sided P-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 29 included patients, 26 patients completed all measurements. In two patients one ECG lead was not connected making it unsuitable for conversion to VCG, and in one patient the acute haemodynamic measurements of the MPP settings were not performed. The characteristics of the 26 remaining patients are presented in Table 1. The patient population represented a typical CRT population with patients having an average age of 73 years, being mostly male and half of them having ischemic cardiomyopathy. They all had a reduced LV ejection fraction (LVEF) and a prolonged QRS duration. Almost half of the patients had LBBB morphology, one quarter of the patients were pacemaker dependent and the other patients either had right bundle branch block (RBBB) or intraventricular conduction delay (IVCD).

Haemodynamic and electrocardiographic changes comparing baseline, BiV pacing, and MPP

When combining the data of all tested veins, BiV pacing significantly improved haemodynamics as compared to baseline (Fig. 1A). The ~18% increase in LV dP/dt_{max} coincided with a significant reduction in QRS area and QRS duration (Fig. 1B). MPP resulted in a further significant

Table 1
Baseline patient characteristics.

	n = 26
Age (y)	73 ± 8
Male (n, %)	22 (85)
NYHA functional class	
II (n, %)	6 (23)
III (n, %)	20 (77)
Ischemic cardiomyopathy (n, %)	15 (58)
Sinus rhythm (n, %)	18 (69)
Baseline LVEF (%)	32 ± 6
QRS duration (ms)	175 ± 19
LBBB (n, %)	12 (46)
IVCD (n, %)	3 (12)
RBBB (n, %)	4 (15)
Pacing dependent (n, %)	7 (27)

NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; LBBB = Left Bundle Branch Block; IVCD = Intraventricular Conduction Delay; RBBB = Right Bundle Branch Block.

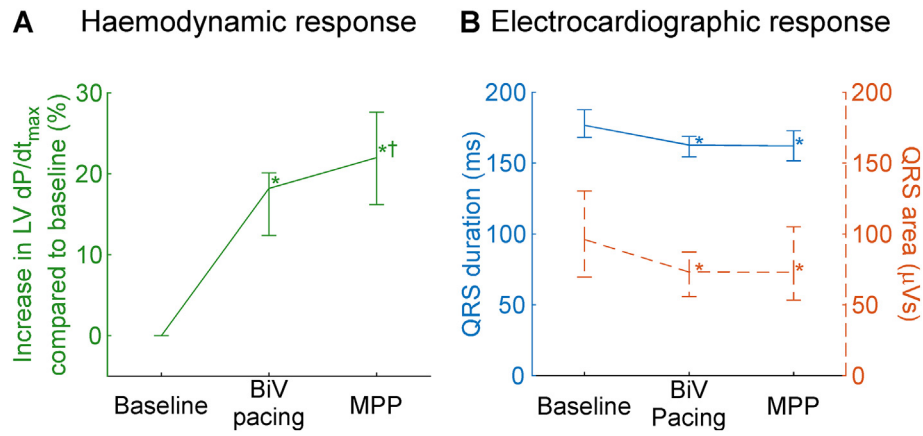

Fig. 1. LV dP/dt_{max} compared to baseline (**A**), QRS duration and QRS area (**B**) during Baseline, BiV pacing, or multipoint pacing (MPP). *P < 0.05 compared to Baseline using the Wilcoxon signed rank test with Bonferroni correction. †P < 0.05 compared to BiV pacing using the Wilcoxon signed rank test with Bonferroni correction.

~4% increase in LV dP/dt_{max} (Fig. 1A). However, this was not accompanied by a further reduction in either QRS area or QRS duration (Fig. 1B).

Differences between patients comparing MPP to BiV pacing

Since multiple coronary veins were tested per patient, the effect of MPP compared to BiV pacing in each vein could be investigated and the average overall effect in each patient could be determined. Within the entire cohort, three subgroups of patients were identified based on their relation between QRS area and LV dP/dt_{max}: 1) a subgroup with baseline QRS area ≥ 69 μVs in whom MPP resulted in an increase in LV dP/dt_{max} and a decrease in QRS area compared to the corresponding BiV pacing settings ($n = 5$); 2) a subgroup with baseline QRS area ≥ 69 μVs in whom MPP resulted in an increase in LV dP/dt_{max} but QRS area remained equal or even increased as compared to BiV pacing ($n = 17$); 3) a subgroup with baseline QRS area < 69

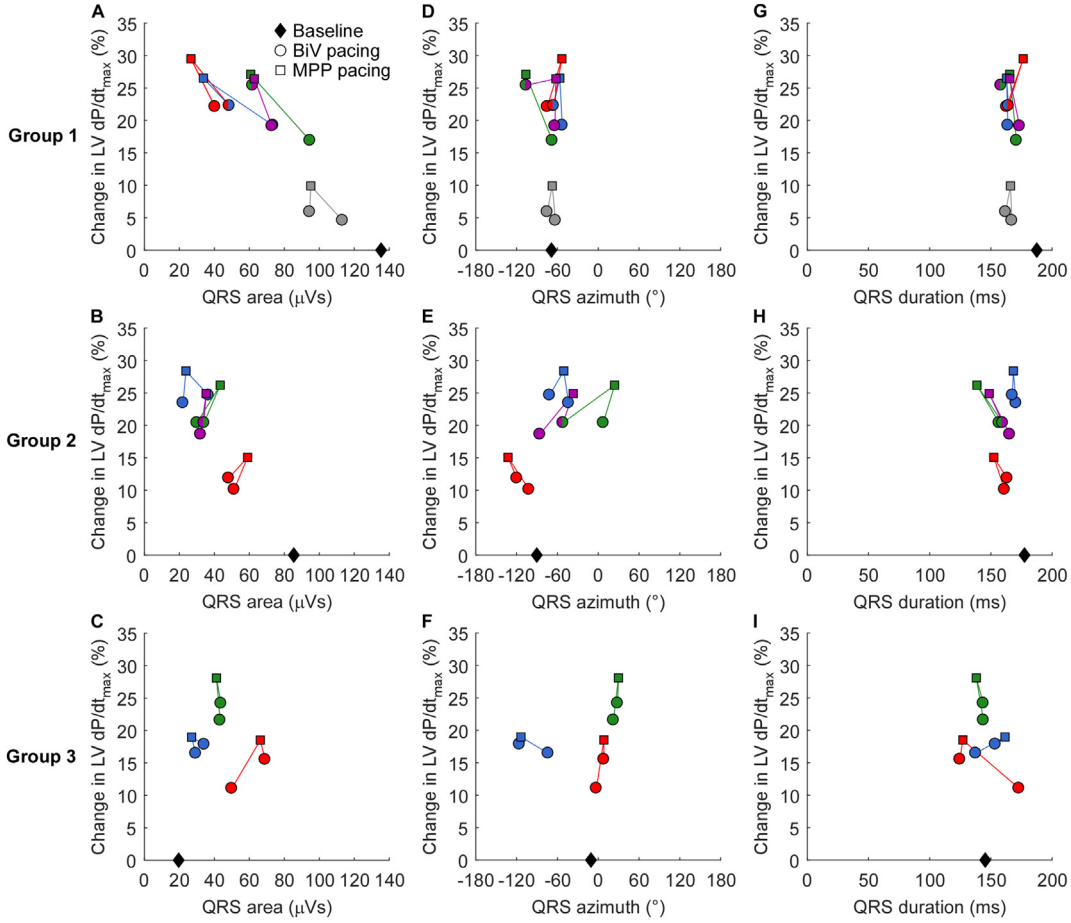

Fig. 2. Relation between VCG variables and LV dP/dt_{max} in three different patients. One colour indicates pacing sites in the same vein. Each of these sites were paced separately during BiV pacing (indicated with circles) and jointly during MPP (indicated with squares). BiV pacing setting and the corresponding MPP setting are connected by a solid line. In the example of group 1 (top row) the MPP pace settings decrease the QRS area and increase the LV dP/dt_{max} compared to the accompanying BiV pace settings. In the example of group 2 (middle row) the MPP pace settings increased the LV dP/dt_{max} but did not decrease the QRS area. In the example of group 3 (bottom row) the baseline QRS area was very small. QRS azimuth does not change much for group 1 (**D**) while there are more observable changes for group 2 (**E**). QRS durations do not differ much between different pace settings (**G**, **H**, **I**).

Table 2
Baseline patient characteristics for the different patient groups. Group 1: baseline QRS area ≥ 69 μVs and MPP corresponds to increase of LV dP/dt_{max} and decrease in QRS area compared to BiV pacing; Group 2: baseline QRS area ≥ 69 μVs and MPP corresponds to increase of LV dP/dt_{max} but no decrease in QRS area compared to BiV pacing; Group 3: baseline QRS area < 69 μVs.

	Group 1 ($n = 5$)	Group 2 ($n = 17$)	Group 3 ($n = 4$)
Age (y)	79 [68–83]	74 [66–79]	73 [61–80]
Male (n, %)	2 (40)	16 (94)	4 (100)
NYHA functional class			
II (n, %)	2 (40)	3 (18)	1 (25)
III (n, %)	3 (60)	14 (82)	3 (75)
Ischemic cardiomyopathy (n, %)	4 (80)	9 (53)	2 (50)
LBBB (n, %)	3 (60)	8 (47)	1 (25)
IVCD (n, %)	1 (20)	0 (0)	2 (50)
RBBB (n, %)	0 (0)	3 (18)	1 (25)
Pacemaker dependent (n, %)	1 (20)	6 (35)	0 (0)
Sinus rhythm (n, %)	5 (100)	12 (71)	1 (25)
Baseline LVEF (%)	30 [28–37]	30 [26–36]	36 [26–40]
Maximum increase in LV dP/dt_{max} (%)	27 [23–34]	33 [23–41]	22 [14–27]
Baseline QRS duration (ms)	173 [158–182]	177 [168–194]	161 [142–180]
Baseline QRS area (μVs)	124 [95–143]	92 [74–136]	26 [20–57]*,†
Q-LV_{max} (ms)	144 [98–159]	152 [129–167]	111 [101−120]
Baseline QRS azimuth (°)	−69 [−73 to −53]	−84 [−91 to −56]	−88 [−120 to −4]

NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; LBBB = Left Bundle Branch Block; IVCD = Intraventricular Conduction Delay; RBBB = Right Bundle Branch Block.
* $P < 0.05$ compared to group 1 using the Wilcoxon rank sum test.
† $P < 0.05$ compared to group 2 using the Wilcoxon rank sum test.

μVs ($n = 4$) (examples shown in Fig. 2). In Table 2 the patient characteristics of the different groups are shown. There were no significant baseline differences between group 1 and 2 while the patients in group 3 were more often in AF than patients in group 1 and had a significantly lower baseline QRS area than patients in group 1 and 2. The small baseline QRS area in group 3 suggests a lack of ventricular dyssynchrony at baseline [11].

Fig. 3 shows the changes in haemodynamic and electrocardiographic behaviour in the three different patient groups from baseline to BiV pacing and MPP. The increase in LV dP/dt_{max} due to BiV and MPP was not-significantly different between the three groups. In addition, the change in QRS duration was not significantly different between groups: for all 3 subgroups the QRS duration shortened between baseline and either BiV pacing or MPP, albeit it only a trend for the small group 3 ($p = 0.07$). While baseline QRS area was significantly lower in group 3 than in the other groups, during BiV pacing no significant differences between the groups were observed. During MPP, QRS area in group 2 was significantly larger than in group 3 ($p = 0.02$). Due to the way the subgroups were defined, QRS area in group 1 decreased significantly from BiV pacing to MPP while in group 2 there is a significant increase in QRS area. The only significant difference between group 2 and group 1 was the change in QRS azimuth between BiV pacing and MPP. While the angle of the maximal QRS vector did not change in group 1, there was a small but significant increase in QRS azimuth for patients in group 2 ($p = 0.04$; Group 1: $4 \pm 2°$; Group 2: $20 \pm 21°$; Fig. 3).

Discussion

The current study shows that in most patients the acute haemodynamic benefit of MPP over BiV pacing is achieved by either electrical resynchronization (reduction in QRS duration or QRS area) or by a rotation of the maximal QRS vector, which may be explained by a more LV dominated activation sequence. The latter property was found in two-thirds of the cohort studied.

Electrocardiographic changes between MPP and BiV pacing

The benefit of MPP compared to conventional CRT is often explained as an improvement in LV function by capturing a larger LV tissue area, resulting in a more uniform wavefront propagation throughout the ventricles, leading to a reduction in dyssynchrony. However, the authors are not aware of a formal proof of this theory. Previous research has shown that MPP was associated with a reduction in QRS duration when compared to BiV pacing [5,6]. However, this was not replicated in the current study. This discrepancy may be explained by the fact that in the current study QRS duration was measured on a digital signal from the vectorcardiogram, using the difference between the earliest deflection in any VCG lead and the latest VCG lead. In a recent study, De Pooter et al. [12] demonstrated that different methods to determine QRS duration (using a single lead vs. multiple leads combined) results in variations of at least 10%, the "global" QRS duration consistently providing the longest QRS duration. Moreover, the method to determine QRS duration influenced the prediction of CRT response. The strongest association with CRT response was seen using the post-CRT global QRS duration and the change in global QRS duration due to CRT [12]. In addition, the global QRS duration measurement, as also employed in the present study, has lower inter- and intraobserver variability compared to single lead QRS duration measurements when measuring QRS duration in LBBB and paced QRS complexes [13]. The changes in QRS duration in the present study are comparable to those in the study by De Pooter et al. Importantly, QRS area showed larger relative changes between BiV pacing or MPP and baseline. Moreover, QRS area has been shown to be highly reliable in terms of reproducibility [8,13] and it reflects both QRS duration and morphology. Probably as a result of this combination, previous studies have shown that QRS area predicts CRT response better than QRS duration [13].

Strong unopposed electrical forces generated within the heart, are the likely underlying mechanism of a large QRS area [14]. Therefore, we hypothesized that a lower QRS area upon initiation of CRT indicates more opposed electrical forces and thus better resynchronization. However, the added haemodynamic effect of MPP over BiV pacing coincided with a further reduction in QRS area in only 5 of the 26 patients. Interestingly, these patients predominantly had ischemic cardiomyopathy and a LBBB QRS morphology. However, group 2 contains a larger number of LBBB patients and ischemic patients. Therefore, this study does not support the idea that MPP mainly acts by resynchronization in ischemic patients, an idea that is supported by findings by De Pooter et al. [13]. While the additional benefit of MPP in these patients may be explained by better resynchronization, this does not seem to be the case in the majority of patients in this cohort.

Interestingly, in 17 of the remaining patients (comprising 65% of the cohort) an additional shift in the azimuth was seen during MPP, which indicates that the maximal QRS vector moved away from the direction during baseline. The baseline azimuth of ~80° indicates a RV to LV activation sequence. Therefore, the ~20° increase in azimuth indicates a more LV dominated activation sequence. In 6 patients in group 2 also LV single site pacing was performed and in 4 of these patients the QRS vector showed a similar change in direction during MPP and LV pacing. Of note, almost half of the patients in this group either have a RBBB morphology or are pacemaker dependent at baseline. However, when these patients were removed from this group, the rotation in QRS azimuth did not change significantly. Several studies indicate that an LV dominated activation sequence, created by LV-pre-excitation during BiV pacing (using VV-interval optimization) can increase the haemodynamic CRT response [15]. Moreover, a recent study showed that increasing the size of the early activated LV region produces a better haemodynamic improvement [16].

Altogether, this evidence suggests that in the majority of CRT patients the added haemodynamic effect of MPP could be explained by a more LV dominated activation sequence.

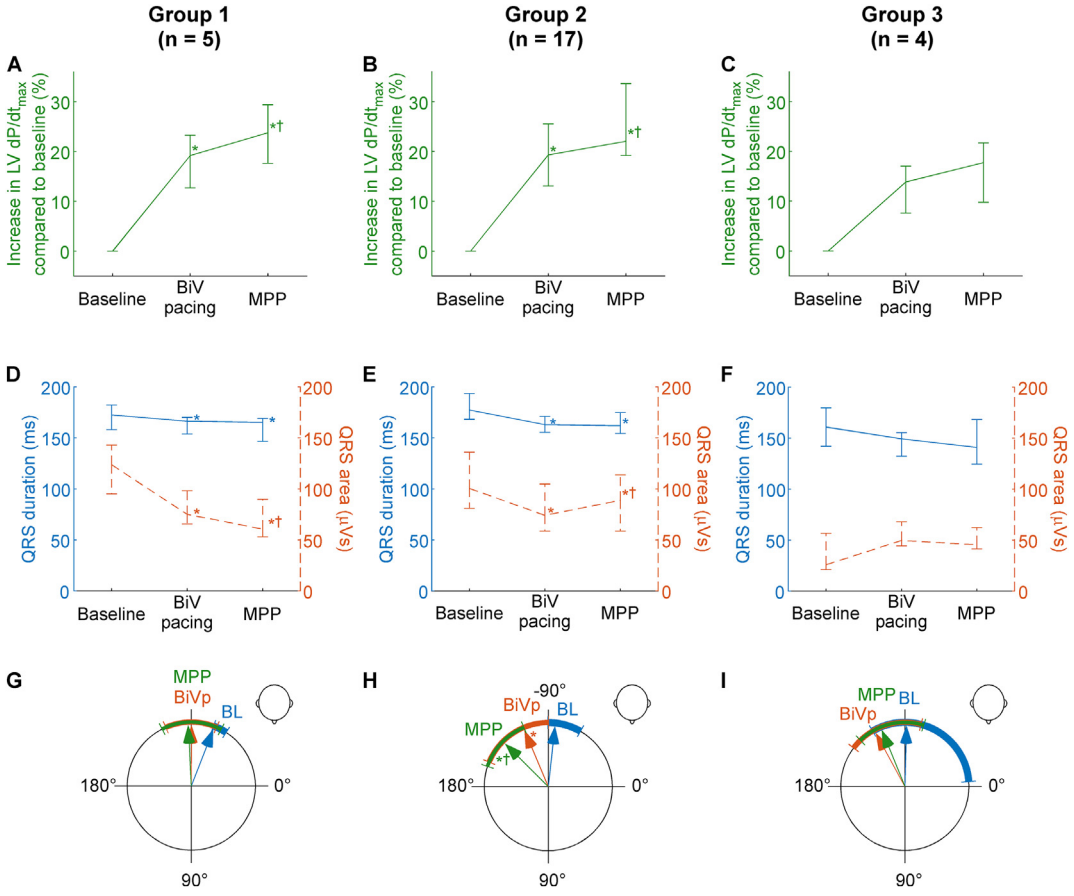

Fig. 3. Comparing haemodynamic and electrocardiographic changes in the three patient groups: Group 1: baseline QRS area ≥ 69 μVs and MPP corresponds to increase in LV dP/dt_{max} and decrease in QRS area compared to BiV pacing; Group 2: baseline QRS area ≥ 69 μVs and MPP corresponds to increase in LV dP/dt_{max} but no decrease in QRS area compared to BiV pacing; Group 3: baseline QRS area < 69 μVs. Shown are median and interquartile ranges for ΔLV dP/dt_{max} (top row), QRS duration and QRS area (middle row), and QRS azimuth (bottom row). *P < 0.05 compared to Baseline using the Wilcoxon signed rank test with Bonferroni correction. †P < 0.05 compared to BiV pacing using the Wilcoxon signed rank test with Bonferroni correction.

In the 4 patients of group 3, the baseline QRS area was very small at baseline resulting in no decrease in QRS area during BiV pacing. These patients all had a QRS area < 69 μVs, indicating that there is no delayed activation in the LV wall [11]. Interestingly these patients did show a trend towards an increase in LV dP/dt_{max}, which may be due to the programming of a physiological AV delay of 130 ms in patients with a relatively long intrinsic PR-interval (~200 ms) [17].

Haemodynamic improvement MPP vs BiV pacing

Several single center studies have shown that MPP often results in an acute haemodynamic improvement compared to conventional BiV pacing as was also shown in the current study [4–6]. Furthermore, a single center cross-sectional study suggests that this acute haemodynamic effect translates to a better echocardiographic response after approximately 1 year follow-up [7]. It should be noted that the additional increase in LV dP/dt_{max} is relatively low with on average being only 4%, but in some patients the increase was >10%. This could result in the conversion from non-responders to responders or even responders to super-responders. These data are contradicted by a recent study which used LV pressure-volume loops as the haemodynamic response measure [18]. Also, the multicentre prospective iSPOT study was not able to show a significant increase in LV dP/dt_{max} by multisite pacing as compared to single site LV pacing [19]. Of note, both last mentioned studies compared BiV and MPP at their optimal AV-delay. Moreover, preliminary results of the randomized controlled MORE-CRT MPP study have been presented in a late-breaking clinical trial session at the EHRA 2018 congress. These data showed that there was no significant clinical improvement by MPP in patients that did not respond to BiV pacing. Of note, in the current study the RV lead was placed at a mid-septum position while the more conventional location would be in the RV apex. However, in conventional CRT it has been shown that there is no difference in echocardiographic and clinical outcome between the two different RV lead locations. Therefore, the location of the RV lead probably did not play a role in the observed additional haemodynamic effect of MPP over BiV pacing.

Limitations

The current study was a relatively small, single-centre, non-randomized study. Furthermore, only acute haemodynamic measurements were used to define the optimal CRT device setting resulting in the best CRT-response. The results observed in this study should be tested in a larger cohort including besides acute haemodynamic measurements also longer term echocardiographic and clinical outcomes.

The acute haemodynamic measurements were not performed at a fixed heart rate. However, LV dP/dt_{max} is dependent on heart rate resulting in possible over or under estimations of the actual haemodynamic improvement [20].

Conclusion

The current study shows that the acute haemodynamic benefit of MPP over BiV pacing may be generated in two ways: electrical resynchronization, as expressed by reduction in QRS area, or a more

LV dominated activation sequence, in approximately two-thirds of CRT patients, as expressed by an increased azimuth.

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Declaration of interest

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