Haemodynamic vector personalization of a quadripolar left ventricular lead used for cardiac resynchronization therapy: use of surface electrocardiogram and interventricular time delays

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Aims
The choice of left ventricular pacing configurations (LVPCs) of quadripolar leads used for cardiac resynchronization therapy (CRT) affects haemodynamic response and thus may be a tool for device optimization. The value of surface electrocardiograms and interventricular time delays (IVDs) for optimization is unknown.

Methods and results
Sixteen patients implanted with a CRT device with a quadripolar LV lead underwent invasive testing of LV $\frac{dP}{dt}$. QRS durations at baseline (bl) and during biventricular pacing (biv) were measured using different LVPCs (total of 141 LVPCs; 8.8 per patient). Variations in QRS duration during biv were calculated for each patient ($\Delta$QRS) and, when compared with intrinsic QRS duration, for all LVPCs ($\Delta$QRS$_{LVPC}$). Interventricular time delays between the poles of the LV lead were obtained from intracardiac electrograms. $\Delta$IVD was calculated as $\Delta$IVD$_{max} - \Delta$IVD$_{min}$. Parameters were correlated with LV $\frac{dP}{dt}$. $\Delta$QRS and $\Delta$QRS$_{LVPC}$ both significantly correlated with LV $\frac{dP}{dt}$ ($P < 0.01$). Correlation was found for patients with ischaemic ($P < 0.001$) and non-ischaemic cardiomyopathy ($P < 0.05$), and for patients with bl QRS duration $>168$ ms ($P < 0.001$), but not $<168$ ms ($P = ns$). The LVPC with shortest QRS duration also yielded maximal LV $\frac{dP}{dt}$ in 6 of 16 patients (37.5%), and was equal or better in LV $\frac{dP}{dt}$ in 12 of 16 patients (75%). $\Delta$IVD neither correlated with $\Delta$QRS nor $\Delta$LV $\frac{dP}{dt}$.

Conclusion
$\Delta$QRS predicts the maximal value of vector personalization in the individual. Reductions in QRS width, but not IVDs, correlate with acute haemodynamic response. Intraindividually, in 75% of patients, the LVPC with the shortest QRS duration gives equal or superior haemodynamic results when compared with the LVPC with longest QRS duration.

Keywords
Cardiac resynchronization therapy • Quadripolar lead • Haemodynamics • QRS duration • Interventricular time delays

Introduction
Cardiac resynchronization therapy (CRT) has been shown to improve symptoms, quality of life, exercise capacity, cardiac function, and to reduce all-cause and heart failure morbidity and mortality in selected heart failure patients\(^1\)–\(^6\) and is therefore indicated for patients with depressed left ventricular (LV) function, New York Heart Association Class II–IV heart failure, and a wide QRS complex.\(^7\)

However, the rate of non-responsiveness remains high. While the reasons for non-response are complex and manifold, optimal pacing site and -settings may increase treatment success. A recently introduced quadripolar LV lead (Quartet\textsuperscript{TM}, St Jude Medical) offers 10 LV pacing configurations (LVPCs) and was mainly developed to
What’s new?

- The selection of a pacing configuration of a quadripolar left ventricular lead affects haemodynamics and QRS width.
- Variations in QRS width and acute haemodynamic response (according to the selection of the pacing vector) correlate. QRS variation therefore can be used to screen for the individual benefit of vector personalization.
- Programming the quadripolar lead to the vector that provokes the shortest QRS duration gives equal or superior haemodynamic response compared with other vectors in 75% of patients.
- Sensed interventricular time delays do not correlate with acute haemodynamics.

Methods

We have previously published the results of a clinical trial (German Clinical Trials Registry DRKS00000573) on acute haemodynamics during biventricular pacing (biv) using a quadripolar LV lead (QuartetTM, St Jude Medical), which offers a maximum of 10 LVPCs. While in these measurements has been described in our initial publication. Briefly, LV QRS duration was measured from the first deflection until return to baseline (bl). QRS duration was measured by an electrophysiologist, who was unaware of the results of the haemodynamic measurements. QRS duration was measured from the first deflection until return to bl in any lead of the 12-lead surface ECG (Figure 1). Left ventricular dP/dt measurement has been described in our initial publication. Briefly, LV dP/dt was measured at bl and during biv in all possible LVPCs, and the percentage change in LV dP/dt was calculated, beat-by-beat, as compared with preceding bl without pacing. These changes were averaged over a 2 min pacing period for each LVPC ($\Delta$LV dP/dt$_{LVPC}$).

QRS duration was measured during bl and during simultaneous (VV delay = 0 ms) biv at an individually optimized atroventricular (AV) delay in all possible LVPCs. QRS complexes with maximal QRS duration during biv (i.e. the least decrease of QRS duration during biv) and minimal QRS duration during biv (i.e. the maximal decrease in QRS duration during biv) were subtracted ($\Delta$QRS). $\Delta$QRS thus expresses, in the individual, the maximal variation in QRS duration during biv in all possible LVPCs. $\Delta$QRS$_{LVPC}$ was calculated for every LVPC as the difference of QRS duration during biv and bl, and thus expresses the decline in QRS duration for the corresponding LVPC.

$\Delta$LV dP/dt was calculated in every patient as maximal minus minimal changes in LV dP/dt during biv, thus expresses the maximal intra-individual variation in LV dP/dt during biv with respect to the programmed LVPC.

Statistical analyses were performed using SAS Version 9.2, ©SAS Institute Inc., for linear regression and GraphPad Prism Version 5.0c, ©GraphPad Software, Inc., otherwise. Paired observations were compared using Student’s t-test and repeated-measure analysis of variance with Bonferroni’s correction, where appropriate. For correlation, we calculated Pearson’s correlation coefficient $r$ and the 95% confidence interval (CI). A $P$-value < 0.05 (two-sided) was considered statistically significant.

Results

As previously described, a CRT device (Promote QuadraTM, St Jude Medical) with a quadripolar LV electrode (QuartetTM, St Jude Medical) was implanted in 20 patients; in 16 of these, a total of 145 LVPCs were invasively tested by the measurement of LV dP/dt. In three patients, ECGs of four additional LVPCs could not be adequately measured due to missing data ($n = 2$) or low quality ($n = 2$). Therefore, ECGs of 141 paced QRS complexes and 16 bl QRS complexes were measured. Mean QRS duration at bl was $171.1 \pm 20.6$ ms. Biventricular pacing reduced the QRS duration significantly in all LVPCs ($P < 0.0001$). Averaged minimal (123.1 ± 16.9 ms) and maximal (140.0 ± 17.7 ms) QRS duration were significantly different ($P < 0.0001$).

Longer bl QRS duration by trend predicted lower bl LV dP/dt ($P = 0.06$).

$\Delta$QRS, as the maximal variation in QRS duration during biv in all possible pacing configurations, correlates significantly with $\Delta$LV dP/dt (Figure 2; slope = 0.69 ± 0.23, $P < 0.001$). Thus, with larger variations in QRS duration during biv at all LVPCs ($\Delta$QRS), larger variations in acute haemodynamic response ($\Delta$LV dP/dt) with respect to the choice of the LVPC can be expected.
Figure 1 Example of the changes in QRS duration with respect to the selected LVPC in the patient with the minimal (A) and the maximal (B) $\Delta$QRS.
Over all patients, ΔQRS$_{LVPC}$ significantly correlates with ΔLV dP/dt$_{LVPC}$ (Figure 3; slope = $-0.22 \pm 0.05$, $P < 0.0001$). This correlation was found both for patients with ischaemic (Figure 4A; slope = $-0.41 \pm 0.11$, $P < 0.001$) and non-ischaemic cardiomyopathy (Figure 4A; slope = $-0.12 \pm 0.05$, $P < 0.05$). A correlation was found for patients with wide ($> 168$ ms) QRS complex (Figure 4B; slope = $-0.29 \pm 0.08$, $P < 0.001$), but not for those with a bl QRS duration $< 168$ ms (Figure 4B; slope = $-0.12 \pm 0.06$, $P = \text{ns}$).

Intraindividually, in 6 of 16 patients (37.5%), the LVPC with greatest reduction in QRS width (ΔQRS$_{LVPC}$) also offered maximal increase in ΔLV dP/dt$_{LVPC}$. In 12 of 16 patients (75%), the LVPC with maximal reduction in QRS duration (i.e. the shortest QRS duration; ΔQRS$_{LVPC}$) resulted in better (11 of 16) or equal (1 of 16) increase in ΔLV dP/dt$_{LVPC}$ than the LVPC that resulted in the least increase (the longest QRS duration during biv) in ΔLV dP/dt$_{LVPC}$.

The mean time delay of the local signal in RV and LV (averaged over the four poles) was 84.0 ± 36.2 ms. Latest activation occurred in the distal pole in four, in M2 in six, in M3 in four, and in the proximal pole P4 in five patients (simultaneous activation of two poles in three patients). The time delay was maximal (latest activation) in a pole that also offered maximal haemodynamic benefit in only 3 of 16 patients.

The averaged ΔIVD in all patients was 20.4 ± 12.3 ms (time delay along the quadripolar LV electrode). ΔIVD neither correlated with ΔQRS ($r = -0.27$, 95% CI: $-0.67$ to 0.26, $P = 0.32$) nor with ΔLV dP/dt ($r = -0.38$, 95% CI: $-0.74$ to 0.15, $P = 0.15$).

**Discussion**

A large amount of evidence shows that CRT has beneficial effects in patients with heart failure and electrocardiographic signs of asynchrony. However, in the aforementioned large clinical trials, a persistently consistent number of patients remain non-responders. While no universal definition of non-response exists, some clinical features, such as the amount of myocardial scar, the extent of mitral regurgitation, and the bl QRS duration and morphology may be predictive. One means of treating non-responders is optimization of device settings, which usually includes optimization of the AV- and VV-intervals, guided by electrocardiography, echocardiography, and/or device-based algorithms. As cumulative evidence...
suggests that the choice of the LVPC of a quadripolar LV lead affects haemodynamics and electromechanical parameters,11–13 adequate selection of the LVPC arises as an additional option to individually optimize device settings. While a growing number of programming opportunities may allow an improved individual optimization, it must be acknowledged that, in daily practice, such methods must be easily accessible, reliable, and promptly accomplishable. In our initial study,13 we have chosen invasive assessment of LV dp/dt with a LV pressure wire. This certainly is not feasible for all patients in a routine clinical setting. Others have chosen echocardiography, which is time-consuming, operator-dependent, and dependent on imaging quality. Electrocardiography is easily accessible, standard for every CRT follow-up visit, and thus might be a tool to optimize the patient’s device according to the optimal LVPC. Our results show that ΔQRS, as the maximal difference in the QRS duration between the LVPCs, is useful to screen whether the choice of LVPCs in the individual gives rise to large changes in haemodynamics. With larger changes in the QRS duration, larger effects on acute haemodynamics can be expected. The correlation of ΔQRSLVPC and ΔLV dp/dtLVPC gives evidence that greater reduction in QRS duration is linked to a more pronounced acute haemodynamic effect. These results are in line with previous studies that have examined the role of bl and paced QRS duration on response rates in patients undergoing CRT with a standard LV lead.20 Effects were more pronounced in patients with ischaemic heart disease, which may be related to the more heterogeneous activation pattern in these patients,21 and more pronounced in patients with longer bl QRS duration (here defined as >168 ms). The latter finding most likely reflects the more heterogeneous activation pattern in patients with shorter bl QRS duration, and is in line with subgroup analyses from large multicentre trials, which have shown a more pronounced CRT effect in patients with longer bl QRS duration.4–6 Intraindividually, selection of the optimal LVPC guided by ΔQRSLVPC gave optimal results in 37.5% of patients and equal or better results than the worst LVPC in 75% of patients.

Measurement of IVDs seems to be a comprehensive approach: pacing from the latest activated site should yield the optimal effect. Indeed, the time interval from the Q-wave in the surface ECG to the local LV signal (QLV interval) has been shown to be predictive for response to CRT in a large cohort of patients.22 It has however not been shown that this is true for the individual. Nevertheless, this concept is implemented in current programmer software (St Jude Medical, Merlin PCS 16.2.1), which offers an algorithm which proposes the optimal LVPC based on automatic measurement of RV-sensed or RV-paced time delays. We could however not find a correlation of IVDs with QRS duration or LV dp/dt in our measurements of RV-sensed local electrograms. Our results therefore do not support the use of the algorithm that uses RV-sensed electrograms to optimize CRT devices with respect to the selected LVPC. A reason for this discrepancy might be the electromechanical delay, which has been shown to be pronounced especially in late activated myocardium.23

Limitations

Due to the invasive nature and the lengthy protocol, the number of included patients is small. Our evaluation of measurements of IVDs to predict haemodynamic response is negative; however, measurements of RV-paced electrograms might be more reasonable, since CRT usually is delivered during biv. It is unclear whether acute haemodynamic response translates into chronic beneficial effects. Therefore, it remains to be examined whether it is beneficial with respect to clinical endpoints to individually optimize CRT patients according to the LVPC.

Conclusion

ΔQRS predicts the maximal value of vector personalization in the individual and might serve as a screening tool: Larger variations in QRS duration predict larger variations in acute haemodynamics. Overall, reduction in QRS duration correlates with acute haemodynamic response. Intraindividually, in 75% of patients, the LVPC with the shortest QRS duration gives equal or superior haemodynamic results when compared with the LVPC with longest QRS duration.

Conflict of interest: J.B., M.H., F.S., T.F., and S.A. are investigators in clinical trials sponsored by St Jude Medical. T.F. and S.A. have received a research grant and lecture fees from St Jude Medical not pertaining to this project.

References

A 65-year-old man with hypertension, diabetes, and hypercholesterolaemia presented to our emergency room in 2005 with chest pain. He had severe left anterior descending (LAD) and left circumflex artery (LCx) stenosis and staged hybrid revascularization was performed. Five years later, he developed flank pain followed by chest pain; the latter was associated with anterior ST elevations and repeated episodes of polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation (VF). Angiography showed a proximal LAD occlusion, thrombus within the proximal LCx, and total occlusion of the distal LCx. Balloon angioplasty restored flow to LCx then LAD arteries. Despite intubation, β-blockade, lidocaine, repeated boluses of amiodarone and then procainamide, overdrive ventricular pacing, and an intra-aortic balloon pump, the patient had an additional 38 episodes of PMVT and VF; each was successfully defibrillated. Thoracic spinal anaesthesia was considered; however, it was considered high risk given the recent administration of bivalirudin. Thus, a decision was made to institute therapeutic hypothermia. A target temperature of 33°C was maintained over the next 24 h. Within 1 h of initiation of hypothermia, all ventricular arrhythmias ceased (Figure). We suggest that therapeutic moderate hypothermia be considered in patients with electrical storm refractory to conventional measures.