**APPENDIX**

**The influence of right ventricular stimulation on acute response to cardiac resynchronisation therapy**

This appendix presents data on the effects of RVapex, LVand BiV stimulation, using LVdP/dtmax as the outcome measure instead of LV stroke work. Data were derived from exactly the same patient population and experiments. For further details see the Methods section of the main paper. In addition, LVdP/dtmax response is defined as 10% improvement compared with baseline [1].

**Hemodynamic measurements**

Acute haemodynamic responses of RVapex, LVand BiV stimulation are presented in Fig. 1. These results are similar to LV stroke work. However, no significant difference in LVdP/dtmax increase was observed between LV and BiV stimulation. There is a significant increase in LVdP/dtmax during BiVsept compared with baseline (Δ+9±10, p=0.001). In contrast to LV stroke work, there is a significant difference between LV and Bivsept in favour of LV stimulation (∆+13±10% vs ∆+9±10%, p=0.024, respectively).

**The effect of right ventricular stimulation on CRT**

There was a substantial variation in individual LVdP/dtmax response during BiV and LV stimulation, as shown in Fig. 2. Compared with BiV stimulation, in 28 patients LVdP/dtmax improved during LVstimulation, whereas LVdP/dtmax decreased in 12 patients. No difference (<10% variation) in LVdP/dtmax response between BiV stimulation and LVstimulation was found in only 1 patient.

LVdP/dtmax response is defined as 10% improvement compared with baseline [1]. Applying that cut-off, 1 of 22 responders (5%) during BiV stimulation became non-responders by switching to LV stimulation. Conversely, 5 of 19 non-responders (26%) changed to responders by the same manoeuvre.

To evaluate the effect of intrinsic RBB conduction in CRT, PQ-time was related to LVdP/dtmax response during various stimulation modalities (Fig. 3). No significant effects of PQ-time on LVdP/dtmax response were found. To further evaluate determinants of response to RVapex, LV and BiV stimulation, regression analysis was performed using clinical, haemodynamic and CMR parameters as presented in Table 1. Multivariate regression analysis showed that a stringent LBBB is significantly correlated with LVdP/dtmax response during RVapex stimulation, this was not found during other stimulation modalities.

**Conclusion**

In summary, the numbers of patients improving by RV, LV and BiV stimulation are comparable, although the magnitude of the response (in percentages) is smaller. The same applies for changes when switching from BiV to LV stimulation. However, when comparing the effects of stimulation on changes in LVdP/dtmax and LV stroke work in the individual patient, no significant correlation was found. In a previous study comparing these two outcome measures, we showed that acute LV stroke work improvement is superior in predicting long-term outcome compared with LVdP/dtmax [2] explaining our present choice. Based on this we feel that the results using LVdP/dtmax as the outcome measure should be interpreted with extreme caution.

**Figure 1: Acute effect of different stimulation modalities on LVdP/dtmax compared with baseline.**



The stimulation modalities (right ventricular apex (RVapex), posterolateral (LV), posterolateral and right ventricular apex stimulation (BiV)) versus left ventricular stroke work response (% change compared with baseline).

\* = p<0.001, compared with baseline

**Figure 2: Individual LVdP/dtmax effect of switching off RV stimulation.**



Dot-line plot showing left ventricular stroke work response during biventricular (BiV) stimulation and posterolateral (LV) stimulation for individual patients. The dotted line represents the cut-off for non-response, defined as a left ventricular dP/dtmax  improvement of ≤ 10% [1].

**Figure 3: Correlation between baseline PQ-time and left ventricular LVdP/dtmax.**



A) Right ventricular apex (RVapex) stimulation, B) Posterolateral (LV) stimulation and C) Posterolateral and right ventricular apex (BiV) stimulation. No significant relations were found.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***∆LVdP/dtmax RVapex******Univariate*** ***β p*** | ***∆LVdP/dtmax RVapex******Multivariate***  ***β p*** | ***∆LVdP/dtmax LV******Univariate*** ***β p*** | ***∆LVdP/dtmax LV******Multivariate*** ***β p*** | ***∆LVdP/dtmax BiV*** ***Univariate*** ***β p*** | ***∆LVdP/dtmax BiV*** ***Multivariate*** ***β p*** | ***∆LVdP/dtmax BiV - LV******Univariate*** ***β p*** |
| Ischaemic (n/y) | -1.43 | 0.55 |  |  | -6.1 | 0.11 |  |  | -8.50 | 0.17 |  |  | -2.41 | 0.62 |
| Stringent LBBB (n/y) | 7.48 | <0.01 | 6.87 | <0.01 | 12.21 | <0.01 | 7.46 | 0.24 | 14.92 | 0.02 | 8.77 | 0.30 | 2.72 | 0.60 |
| PQ-time (ms) | <-0.01 | 0.95 |  |  | -0.02 | 0.71 |  |  | -0.10 | 0.36 |  |  | -0.07 | 0.37 |
| Scar (%) | -0.24 | 0.14 |  |  | -0.65 | 0.05 | -0.55 | 0.09 | -0.83 | 0.05 | -0.83 | 0.05 | -0.19 | 0.39 |
| Septal scar (n/y) | -2.81 | 0.34 |  |  | -5.81 | 0.33 |  |  | -9.21 | 0.21 |  |  | -3.40 | 0.36 |
| PL scar (n/y) | -1.18 | 0.65 |  |  | -2.18 | 0.60 |  |  | -8.28 | 0.22 |  |  | -6.11 | 0.23 |
| RVEDV (ml) | -0.02 | 0.53 |  |  | 0.03 | 0.37 |  |  | 0.04 | 0.50 |  |  | <0.01 | 0.88 |
| RVESV (ml) | -0.04 | 0.16 |  |  | 0.05 | 0.21 |  |  | 0.03 | 0.64 |  |  | -0.02 | 0.70 |
| RVEF (%) | 0.15 | 0.04 | 0.09 | 0.24 | -0.12 | 0.34 |  |  | <-0.01 | 0.99 |  |  | 0.12 | 0.45 |
| LVEDV (ml) | 0.01 | 0.44 |  |  | 0.06 | <0.01 |  |  | 0.07 | 0.07 |  |  | <0.01 | 0.77 |
| LVESV (ml) | <0.01 | 0.76 |  |  | 0.07 | <0.01 |  |  | 0.09 | 0.04 |  |  | 0.02 | 0.59 |
| LVEF (%) | 0.23 | 0.14 |  |  | -0.45 | 0.08 | <0.01 | 0.99 | -0.85 | 0.05 | -0.58 | 0.24 | -0.40 | 0.22 |
| LVSW (L·mmHg) | 1.00 | 0.04 | 0.80 | 0.08 | 0.61 | 0.45 |  |  | 0.48 | 0.72 |  |  | -0.13 | 0.90 |
| LVdP/dtmax (mmHg/s) | <-0.01 | 0.83 |  |  | -0.02 | 0.05 | -0.02 | 0.09 | <-0.01 | 0.59 |  |  | 0.01 | 0.39 |

**Table 1:** Univariate and multivariate analysis of baseline parameters as predictor for left ventricular dP/dtmax response during RVapex stimulation, LV, Biv stimulation and the difference between Biv and LV stimulation.

Left bundle branch block (LBBB), stringent LBBB according to Strauss criteria (see Methods), *PL* posterolateral, *RVEDV* right ventricular end-diastolic volume, *RVESV* right ventricular end-systolic volume, *RVEF* right ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *LVSW* left ventricular stroke work, *LVdP/dtmax* left ventricular dP/dtmax, *RVapex*, right ventricular apex, *BiV* biventricular, *LV* left ventricular only

Model multivariate analysis ∆ LVdP/dtmax RVapex: RVEF, LVSW and stringent LBBB.

Model multivariate analysis ∆ LVdP/dtmax LV: Scar, LVEF, LVdP/dtmax and stringent LBBB

Model multivariate analysis ∆ LVdP/dtmax Biv: Scar, LVEF and stringent LBBB.

Multivariate regression analysis shows that baseline LVSW is significantly correlated with LVdP/dtmax response during RVapex stimulation, however, this result was not found during the other pacing modalities. Further, the amount of scar seem to be significantly correlated with LVdP/dtmax response to Biv stimulation. Since the presence of scar is very little, this result should be interpreted with caution.

Reference List

 1 Ginks MR, Duckett SG, Kapetanakis S, et al. Multi-site left ventricular pacing as a potential treatment for patients with posterolateral scar: insights from cardiac magnetic resonance imaging and invasive haemodynamic assessment. Europace 2012 Mar;14(3):373-9.

 2 de Roest GJ, Allaart CP, Kleijn SA, et al. Prediction of long-term outcome of cardiac resynchronization therapy by acute pressure-volume loop measurements. Eur J Heart Fail 2012 Nov 25.