Left ventricular end-systolic volume is a more sensitive marker of acute response to cardiac resynchronization therapy than contractility indices: Insights from an experimental study

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Abstract

Aims: There are conflicting data and no consensus on how to measure acute response to cardiac resynchronization therapy (CRT). This study investigates which contractility indices are best markers of acute CRT response.

Methods: In 8 anesthetized dogs with left bundle branch block we measured left ventricular (LV) pressure by micromanometer and end-diastolic (EDV) and end-systolic volumes (ESV) by sonomicrometry. Systolic function was measured as LV ejection fraction (EF), peak rate of LV pressure rise (LV \( \frac{dP}{dt_{\text{max}}} \)) and as a gold standard of contractility, LV end-systolic elastance (\( E_{\text{es}} \)) and volume axis intercept (\( V_0 \)) calculated from end-systolic pressure-volume relations (ESPVR). Responses to CRT were compared to inotropic stimulation by dobutamine.

Results: Both CRT and dobutamine caused reduction in ESV (\( P<0.01 \)) and increase in LV \( \frac{dP}{dt_{\text{max}}} \) (\( P<0.05 \)). Both interventions shifted the ESPVR upwards indicating increased contractility, but CRT which reduced \( V_0 \) (\( P<0.01 \)), caused no change in \( E_{\text{es}} \). Dobutamine markedly increased \( E_{\text{es}} \), which is the typical response to inotropic stimulation. Preload (EDV) was decreased (\( P<0.01 \)) by CRT, and there was no change in EF. When adjusting for the reduction in preload, CRT increased EF (\( P=0.02 \)) and caused a more marked increase in LV \( \frac{dP}{dt_{\text{max}}} \) (\( P<0.01 \)).

Conclusions: Increased contractility by CRT could not be identified by \( E_{\text{es}} \) which is a widely used reference method for contractility. Furthermore, reduction in preload by CRT attenuated improvement in contractility indices such as EF and LV \( \frac{dP}{dt_{\text{max}}} \). These results suggest that changes in LV volume may be more sensitive markers of acute CRT response than conventional contractility indices.
Keywords: Cardiac resynchronization therapy; left bundle branch block; contractility; pressure-volume relationship; end-systolic elastance
Introduction

Cardiac resynchronization therapy (CRT) is an effective therapy which is widely used in patients with congestive heart failure and electrical dyssynchrony.(1) A major limitation of CRT, however, is that about 1/3 of patients do not improve with CRT.(2) A number of different methods are proposed to optimize patient selection.(3) During the CRT implantation procedure, it is thought that therapy can be optimized by placing the pacing leads at sites which give the best possible acute response. With new image guiding systems for lead placement, options for multisite pacing and the introduction of permanent leadless cardiac pacemaker therapy, testing of acute response during lead placement has become increasingly important. A few years ago Prinzen and Auricchio, who reviewed the field, concluded that there was no consensus on which hemodynamic parameter should be used to identify acute response to CRT, and that the positive acute response has not shown to predict long-term response.(4, 5) It is still debated, and data are conflicting with regard to choice of hemodynamic parameters to identify acute response to CRT.(4-6) We hypothesised that this may reflect load dependency as a limitation of some of the conventional contractility indices. We used the left ventricular (LV) end-systolic pressure volume relationship (ESPVR) which is load-independent, as a reference method for LV contractility. Furthermore, the experimental design of the study allowed assessment of contractility at similar preload before and during CRT.

The aim of the present study was to determine mechanisms of acute response to CRT, and to identify parameters of LV systolic function reflecting successful resynchronization. The study was done in a dog model with left bundle branch block (LBBB) comparing responses to CRT and to increased myocardial contractility by dobutamine infusion. Changes in systolic function were measured by 1) LV ejection fraction (EF), 2) LV end-systolic volume (ESV), 3) LV stroke work (SW), 4) peak rate of LV pressure rise (LV dP/dt_{max}), and 5) by the ESPVR as a preload-independent measure of contractility, by
calculation of the end-systolic elastance ($E_{es}$) and volume axis intercept at zero LV pressure ($V_0$).
Methods

Twelve mongrel open-chest dogs (36±4kg) of either sex were ventilated and surgically prepared with introduction of pressure catheters, fluid-filled catheters, and vascular constrictors as previously described.(7) In each dog, six 2- to 3-mm sonomicrometric crystals (Sonometrics, London, Ontario, Canada) were implanted subendocardially. Four crystals with intramyocardial electromyograms (IM-EMGs) were placed anteriorly, posteriorly and laterally in the LV and in the interventricular septum at the equatorial level of the heart 4-5 cm from the apex. In addition, one crystal was implanted in the apex and one in the basal portion of the LV lateral wall. Data were digitized at 200 Hz. Pacemaker leads were attached epicardially on the middle third of the LV lateral wall, endocardially on the basal septum in the right ventricular outflow tract, and epicardially on the right atrium. The pericardium was loosely resutured following completion of instrumentation. Initial anesthesia consisted of a single dose of methadone (0.2 mg/kg) followed by propofol (3-4 mg/kg) to desired effect and a bolus of fentanyl (2-3 µg/kg). Propofol (0.2-1 mg/kg/min) and fentanyl (5-40 µg/kg/hr) were used for continuous anesthesia. LBBB was induced by radiofrequency ablation and successful induction of LBBB was confirmed by QRS-widening and LV contraction patterns typical for LBBB as described previously in our laboratory using the same animal model (Figure 1).(8)

Three dogs were excluded due to complications during initial surgery, and one because of total AV-block during ablation. At the end of the experiments, the animal was euthanized by an intracardiac injection of pentobarbital.

The National Animal Experimentation Board approved the study. The laboratory animals were supplied by the Center for Comparative Medicine, Oslo University Hospital, Rikshospitalet, Norway.
**Interventions**

**Pacemaker**

A Medtronic CRT-Pacemaker (InSync® III, Medtronic, Dublin, Ireland) was used in all animals. Biventricular pacing, referred to as CRT, was used with a fixed VV-delay of 4 ms. To compare data with similar heart rates, the right atrium was paced above the intrinsic rate with a fixed AV-delay of 80 ms. Measurements were obtained during continuous recordings and transient caval constrictions during LBBB, LBBB+CRT and LBBB+dobutamine. Data were collected before and 5-15 seconds, equivalent to ~10-30 heart beats, after changing the pacing mode.

**Dobutamine Infusion**

Dobutamine was infused at a continuous rate of 5 µg/kg/min to increase contractility. Data were collected after a clear positive inotropic response, assessed by LV dP/dt\text{max}, which occurred approximately 5 minutes after commencement of the infusion.

**Definitions and Data Analysis**

Electrical activation was defined as onset R in IM-EMGs and end-diastole as the time when 2 of 4 LV IM-EMGs in the equatorial plane were electrically activated.

**Calculations:**

LV volume was calculated from three pairs of crystals using a three-axis ellipsoid model (LV volume = \( \pi \cdot \text{longitudinal diameter} \cdot \text{antero-posterior diameter} \cdot \text{septal-to-lateral wall diameter}/6 \)).

SW was calculated as the area of the LV pressure–volume loop and used as an index of global cardiac performance.
Preload was reduced by transient caval constriction to construct the ESPVR (Figure 2). Data from each top left corner of the PV-loop when peak LV pressure >60 mmHg(9) during stable conditions was extracted and used to calculate E es and V0 using the least-square approach to a linear regression line. The shift in LV end-systolic pressures was quantified at the highest LV ESV where both curves (LBBB and CRT) overlapped (Figure 3).

**SW and Comparison during LBBB and CRT**

To further investigate changes in cardiac performance during CRT at similar preloads, we compared SW at the highest LV end-diastolic volume (EDV) in the operating volume range where the three curves (LBBB, LBBB+CRT and LBBB+dobutamine) overlapped.

**Statistical Analysis**

All values represent the mean of three consecutive heart cycles except data collected during transient caval constriction where we used consecutive beats. Values are expressed as mean±SD. For multiple comparisons, one-way repeated measure ANOVA followed by a post hoc test for relevant pairwise comparisons with Bonferroni adjusted p-values was used. For comparisons between LBBB and LBBB+CRT only, significance for mean difference was assessed using paired t-test. P<0.05 was considered significant. (SPSS 24, IBM Corp., Armonk, NY, USA).

The authors had full access to, and take full responsibility for, the integrity of the data. All authors have read and agreed to the manuscript as written.
Results

Induction of LBBB was successful in eight animals. When CRT was turned on, LV dP/dt\(_{\text{max}}\) increased moderately from 948±104 mmHg/s to 1052±110 mmHg/s (P<0.05) while EF, SV and SW were relatively unaltered (20±4% vs. 20±5%, 16.2±3.8 ml vs. 15.7±3.5 ml and 955±349 mmHg·ml vs. 916±245 mmHg·ml). There were moderate reductions in LV EDV (P<0.01) and LV ESV (P<0.01) (Table 1). When adjusting for the effect of preload reduction by comparing heart beats with similar LV EDVs, there was an increase in LV EF from 16±4% to 19±4% (P=0.02), SV from 11.5±2.7 ml to 13.8±2.9 ml (P<0.01), LV dP/dt\(_{\text{max}}\) from 764±70 mmHg/s to 1060±172 mmHg/s (P<0.01) and in SW from 672±152 mmHg·ml to 969±311 mmHg·ml (P=0.02) (Figure 4). When assessing LV function by ESPVR, which provides a preload-independent measure of contractility, there was an upward shift of the relationship as illustrated in Figures 2 and 3. The magnitude of the upward shift calculated as a change in the LV end-systolic pressure was 17±4 mmHg, from 60±21 mmHg to 77±19 mmHg (P<0.01). The upward shift of the ESPVR implies that the ventricle generated higher systolic pressure at any given LV EDV and indicates increased contractility. Therefore, as demonstrated by comparison at similar preloads, and by the ESPVR analysis, reduction in LV EDV attenuated the effects of CRT on contractility indices.

There was a striking difference between effects of CRT and dobutamine on the ESPVR. Whereas CRT caused a parallel upward shift with no significant change in E\(_{\text{es}}\), (3.8±1.3 mmHg/ml vs 3.7±1.3 mmHg/ml), dobutamine caused a marked increase in E\(_{\text{es}}\) from 3.8±1.3 mmHg/ml to 9.0±2.8 mmHg/ml (P<0.01). The upward shift of the ESPVR by CRT was associated with a reduction in V\(_{\text{o}}\) by 5±2 ml (45±20 to 40±21 ml (P<0.01)) (Figure 2 and 3).

Representative pressure-volume loops for LBBB and CRT are depicted in Figure 5. CRT shifted the pressure-volume loops leftwards, but loop area, which represents SW,
showed only minor changes. Hence, the ventricle became more efficient by producing essentially the same SW at lower LV volumes.

Figure 1 shows segment length traces with characteristic abnormal septal deformation and reduced septal shortening during LBBB with marked increase in septal shortening during CRT. Segment length traces during LBBB+dobutamine are displayed for comparison.

There were no significant shifts in the end-diastolic pressure-volume relation when comparing measurements with the CRT on and off.
Discussion

Evidence in favor of using acute hemodynamic response to predict long-term CRT response are conflicting and there is no consensus on which parameter to use when testing different lead positions during CRT device implantation. As shown in this study, assessment of acute response to CRT is challenging since some of the conventional contractility indices are preload-dependent. Our results suggest that LV volume changes may be better reflectors of acute response to CRT than changes in $E_{es}$ and conventional measurements of systolic function. Due to reductions in LV preload, measured as LV EDV, there was no immediate increase in LV EF, SV or SW with CRT. When comparing measurements at similar LV EDVs, however, there were significant improvement in all three indices. Furthermore, the ESPVR analysis, which is preload independent, confirmed that CRT caused an acute increase in contractility. The observation that CRT caused a parallel upward shift of the ESPVR implies that $E_{es}$ should not be used as an invasive gold standard when testing contractility responses to CRT. These novel findings are potentially important for interpretation of hemodynamic response to acute CRT, which is important clinically during device implantation when searching for optimal positions for pacing leads, and device reprogramming. Since the present study was experimental, the findings cannot be directly extrapolated to the clinical setting. Magnitude of changes in volumes and in contractility are probably different and may vary depending upon the underlying heart disease. However, the fundamental principle that changes in LV preload complicates interpretation of contractility indices and the limitation of $E_{es}$ as a reference method for contractility are likely to be valid in patients.

Response to CRT by different indices of LV systolic function

In the present study when adjusting for preload changes, responses to CRT and dobutamine with regard to LV EF, LV ESV and LV $dP/dt_{max}$ were in principle similar although changes were more marked with the dobutamine dose that was tested. This was in contrast
to the ESPVR, which showed entirely different responses to CRT and dobutamine. In general, when using the ESPVR to assess contractility, both an increase in $E_{es}$ and a reduction in $V_0$, may reflect increase in contractility. The parallel upward-shift of ESPVR with CRT implies that the ventricle generated higher pressures at any given volume, indicating more forceful LV contractions, and hence increased contractility. Due to need for invasive LV pressure and complexity of analysis, assessment of ESPVR and calculation of $E_{es}$ and $V_0$ are not used in clinical routine.

The apparent inconsistency between increment in $E_{es}$ when contractility was increased by dobutamine, and unchanged with CRT, probably reflects different mechanism for the two interventions. With dobutamine, the entire LV myocardium is stimulated to contract more vigorously due to stimulation of myocardial $\beta$-adrenoceptors, and explains increased systolic stiffness as reflected in higher $E_{es}$.

With CRT, there is presumably no acute increase in contractile force in individual segments, but better coordinated contractions of different segments result in improved function. The apparent inconsistency between the observed increase in LV $dP/dt_{\text{max}}$ with no change in $E_{es}$ by CRT may be explained by difference in timing of activation of different walls. Since LV $dP/dt_{\text{max}}$ occurs in early systole, it is mainly the force generated by early-activated myocardium which contributes to LV $dP/dt_{\text{max}}$ during LBBB. When CRT is turned on, and provided there are optimally synchronized contractions, force generated by the entire ventricle contributes to LV $dP/dt_{\text{max}}$. The unchanged $E_{es}$ might reflect that both early and late activated myocardium are fully activated in late systole, even during LBBB, and therefore CRT has little effect on LV systolic stiffness. This proposed mechanism could not be tested in the animal model used in the present study.
The leftward shift of the ESPVR by CRT is equivalent to the heart contracting to a lower volume. This can be explained through a schematic model (Figure 6) which illustrates the movement of the septum and LV lateral wall during LBBB and normal activation. Here, the box constitutes the heart, and the two piston pumps represent the septum and LV free wall. The pistons’ movement during LBBB symbolizes the segmental movement shown in Figure 1. During normal electrical activation, both pistons move simultaneously inward (systole) and outward (diastole). During LBBB, contractions of the different walls are out of phase, and the piston representing the septum reaches its maximal inward distance before aortic valve closure (AVC). Once the valve is closed, it has already moved slightly outward. At the same time, the LV lateral wall piston reaches its maximal inward distance at AVC, and the LV ESV is larger compared to normal electrical activation. Once these motions are synchronized, similar to when CRT is turned on, both pistons reach their maximal inward distance at AVC producing a smaller LV ESV.

**Comparison to previous studies**

Burkhoff et al.(13), who studied ESPVR in an isolated heart preparation, found that ventricular pacing, which is equivalent to electrical dyssynchrony, caused a slight but significant decrease in $E_{es}$ and increase in $V_0$. Park et al.(14) observed in an experimental study that ventricular pacing shifted the ESPVR downwards with little change in $E_{es}$ compared to atrial pacing while $V_0$ increased. Although the animals in these two studies did not have LBBB, they show that induction of dyssynchrony by ventricular pacing results in less developed force in the ventricle. Taken together, these studies and the present study, show that volume shift are more consistent than changes in $E_{es}$ when evaluating systolic function during electrical dyssynchrony by ESPVR.

In a non-invasive clinical study of long-term response to CRT, LV volume changes, including $V_0$, and not estimates of $E_{es}$ were associated with clinical endpoints.(15) The
measurements were done 6 and 12 months after device implantation. Clinical studies on acute response to CRT have mainly evaluated systolic parameters such as LV dP/dt\text{max} (5, 6, 16-19), LV EF (6, 16), SW (6, 19) and SV (6, 19) rather than acute changes in LV end-diastolic and end-systolic volumes. In a clinical study using conductance catheters to measure volumes, SV and SW improved during CRT treatment. (20) The study did not state end-diastolic or end-systolic volumes, however, both volumes were reduced in Figure 2 representing an LBBB-patient receiving CRT. This seems consistent with our results, and encourages a more quantitative clinical study to confirm these findings. Previous studies have not adequately assessed isolated changes in preload by CRT, which also are affected by changes in lead placement, AV- and VV-delays and heart rate. Hence, this complicates comparisons within and between studies. In stable HF, which applies to the majority of patients during CRT implantation, an intervention improving systolic function could led to a more efficient ventricle with the same output measured by systolic parameters. This is supported by our data showing a reduction in preload and relatively unaltered cardiac output, SV and SW with CRT. To our knowledge, there is no previous experimental or clinical study evaluating the acute effects of CRT on the ESPVR.

**Clinical implications**

The observation that CRT caused no change in $E_{es}$ implies that this may not be suitable as a reference method when validating novel methods to measure acute response to CRT. The modest increments in LV dP/dt\text{max} indicates that this parameter may be of value as a marker of acute response, however, the magnitude of change will be attenuated by reduction in preload. This could explain the disappointing results in clinical studies where there was no association between the acute change in LV dP/dt\text{max} by CRT and outcome. (5, 17) Changes in LV EF turned out to be highly preload dependent and limits the value of this parameter as a marker of acute CRT response. Future research regarding acute CRT response, programing and electrode placement should in addition to evaluating changes in
conventional measurements of systolic function, also include measurements of preload by volume, pressure or potentially diameter.

**Limitations and comments on methodology**

In the present study, we used a heavily instrumented animal model with LBBB and reduced systolic function. Care should be taken when extrapolating our data to patients who have a heterogeneous etiology to their underlying heart failure. We have previously shown that our preparation has features typical for LBBB in humans with early activation of septum and late activation of the LV lateral wall. As shown in recordings from the present study in Figure 1, septal flash in the early activated septum and corresponding preejection lengthening in the LV lateral wall were diminished with CRT. Therefore, cardiac mechanical features and responses to CRT resemble what is observed clinically. Although the magnitude of responses to CRT may not be representative for the clinical situation, the model should be valid for studying fundamental mechanisms of acute response to CRT.

A strength of the animal model was the use of sonomicrometry, which is considered to be the gold standard for measuring LV dimensions, and high fidelity catheters to measure LV pressure, which combined are used to evaluate LV pressure-volume loops obtained by caval constriction. Absolute volume may not always be correct with sonomicrometry due to subendocardial location of crystals.

CRT led to a 15 ms reduction in the AV-delay compared to LBBB (Table 1) which could account for some of the observed change in preload by early cessation of atrial mediated filling. This possible effect on preload was estimated by multiplying the maximal LV volume flow rate from onset P in the ECG to LV end-diastole with the reduction in AV-delay in each experiment. This constituted only 10% of the total reduction in preload, and does not affect the principle finding of changes in the ESPVRs during CRT.
We used fixed pacing settings and lead placements with no attempt of further optimization. Examining these two factors would have prolonged the protocol sustainably. Previous studies have not shown benefits of optimization strategies based on pacing algorithms or echocardiography(21, 22) but this is an ongoing research question in the field.

**Conclusion**

Acute response to CRT was evidenced by reductions in LV end-diastolic and end-systolic volumes. LV end-systolic elastance, which is a widely used reference method for contractility, was unchanged. This was different from response to pure inotropic stimulation which caused marked increase in LV end-systolic elastance. Because CRT reduced LV preload, indices such as EF and stroke volume which are preload-dependent, show little or no improvement although contractility and efficiency were increased. Although stroke volume, stroke work and LV dP/dt\(_{\text{max}}\) are parameters assessing response to CRT, our study demonstrates and explains shortcomings of these parameters, which could account for some of the apparent inconsistency between studies. This suggests that LV volume changes rather than conventional indices of systolic function and contractility should be used to evaluate acute CRT response. Clinical studies should be conducted to determine if acute LV volume changes occur in patients receiving CRT, and if these potential changes could serve as predictors of long-term response to CRT.

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Acknowledgments

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Conflict of interest

None declared.
Reference List


Figures

Figure 1

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○ Aortic valve opening  ■ Aortic valve closure

Figure 2

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- - - - LBBB  ——— LBBB+CRT  X End-systolic pressure volume points
Figure 3

LV pressure (mmHg) vs LV volume (ml)

- LBBB
- LBBB+CRT
- LBBB+dobutamine

+ End-systolic pressure-volume points
Figure 4

[Bar charts showing comparisons between LBBB and LBBB+CRT in Non-corrected and Preload-corrected conditions for Ejection fraction, Stroke work, Stroke volume, and LV dP/dt_max.]

*P<0.05
Figure 5

LV pressure (mmHg)

LV volume (ml)

- LBBB
- LBBB+CRT
X End-diastole
Figure 6

End-diastole

End-systole

Normal Electrical Activation

LBBB
**Figure 1:** Data from one representative experiment showing changes in septal and LV lateral wall contraction during baseline, LBBB, LBBB+CRT and LBBB with dobutamine infusion. In the second column, changes typical of LBBB are seen with early contraction of the septum and stretch of the LV lateral wall. CRT induced contraction patterns resembling baseline as seen in the third column.

**Figure 2:** Representative LV pressure-volume loops during LBBB and CRT with corresponding end-systolic pressure volume relations (ESPVRs). Recordings were done during transient caval constrictions. Crosses, forming the ESPVR on the top left corner of each pressure-volume loop, indicate the ESPV-point for each loop. There were minimal changes in the slopes ($E_{es}$) of the ESPVRs, but a distinct parallel shift signifying improved systolic function. The straight lines represent the ESPVR. $E_{es}$ was 4.6 mmHg/ml during LBBB and 4.3 mmHg/ml during LBBB+CRT in this example. See Table 1 for group data.

**Figure 3:** The end-systolic pressure volume relation (ESPVR) showing the end-systolic elastance ($E_{es}$) during LBBB, LBBB+CRT and LBBB with dobutamine infusion for a representative experiment. The vertical solid line shows the shift from LBBB to CRT were data were extracted for comparison. There were non-significant small changes in $E_{es}$ when CRT was turned on, while $E_{es}$ increased during dobutamine infusion. There was a parallel shift of the ESPVR with CRT, corresponding to a decrease in $V_0$.

**Figure 4:** Column bar graph showing non-corrected and pre-load corrected changes in LV EF, stroke volume, stroke work and LV dP/dt$_{max}$ induced by CRT during LBBB. In the left panel, there were alterations in preload and changes in systolic parameters were minimal. When comparing data at the same preload, however, there were significant increases in all parameters with the CRT on compared to LBBB (right panel). The height of the bars show the mean value while the whiskers represent the standard deviation in each situation. *$P<0.05$ when compared to LBBB, also marked in blue.
Figure 5: Pressure-volume loops during LBBB and CRT. CRT shifted the loop to the left with a reduction in end-diastolic and end-systolic volumes. Peak LV pressure and stroke work (SW) were unaltered during CRT (Table 1). Thus, the ventricle becomes more efficient during CRT by generating the same amount of SW (loop area) despite a reduction in preload.

Figure 6: Schematic model of the heart shown as a box with the septum and LV lateral wall represented by pistons pumps (top). During normal contraction, the pistons reach their maximal inward positions simultaneously (bottom left). During LBBB, however, the early-activated septal piston commences relaxation and outward motion, once the LV lateral wall piston reaches its maximal inward distance. Hence, the box never reaches the same end-systolic volume (ESV) (bottom right). Once these motions are synchronized, similar to when CRT is turned on, both pistons reach their maximal inward distance at valve closure, producing a smaller ESV.
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**Volume derived parameters**

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**Pressure derived parameters**

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<th>LBBB</th>
<th>LBBB+CRT</th>
<th>LBBB dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV dP/dt$_{\text{max}}$, mmHg/s</td>
<td>948±104</td>
<td>1052±110*</td>
<td>1757±332*</td>
</tr>
<tr>
<td>LV pressure max, mmHg</td>
<td>83±7</td>
<td>83±6</td>
<td>108±13*</td>
</tr>
<tr>
<td>LV ED pressure, mmHg</td>
<td>10.9±2.2</td>
<td>10.0±2.4*</td>
<td>10.2±2.6</td>
</tr>
<tr>
<td>LV dP/dt$_{\text{min}}$, mmHg/s</td>
<td>-1046±152</td>
<td>-1138±150*</td>
<td>-1634±227*</td>
</tr>
</tbody>
</table>

**ES pressure-volume relation**

<table>
<thead>
<tr>
<th></th>
<th>LBBB</th>
<th>LBBB+CRT</th>
<th>LBBB dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{es}}$, mmHg/ml</td>
<td>3.8±1.3</td>
<td>3.7±1.3</td>
<td>9.0±2.8*</td>
</tr>
<tr>
<td>$V_0$, ml</td>
<td>45±20</td>
<td>40±21*</td>
<td>49±16</td>
</tr>
</tbody>
</table>

Values are given as mean (±SD). *P<0.05 when compared to LBBB using ANOVA with post-hoc analysis. †P<0.05 when compared to LBBB using paired t-test. LBBB=left bundle branch block; CRT=cardiac resynchronization therapy; LV=left ventricular; BPM=beats per minute; AV=atrio-ventricular; ED=end-diastolic; ES=end-systolic; $E_{\text{es}}$=end-systolic elastance; $V_0$=the end-systolic pressure-volume relation volume axis intercept.