Mechanical Effects on Right Ventricular Function from Left Bundle Branch Block and Cardiac Resynchronization Therapy

Brief Title: Left Ventricular Dyssynchrony and the Right Ventricle

Petter Storsten, MD, (1,2,3), John M. Aalen, MD, (1,2,3), Espen Boe, MD, PhD (1,3), Espen W. Remme, MSc, Dr.ing, (1,3), Ola Gjesdal, MD, PhD (2), Camilla Kjellstad Larsen, MD, (1,2,3), Øyvind Senstad Andersen, MD, (1,2,3), Morten Eriksen, MD, PhD, (1,3), Erik Kongsgaard, MD, PhD, (2,3), Jürgen Duchenne, MSc, PhD (4,5), Jens-Uwe Voigt, MD, PhD, (4,5), Otto A. Smiseth, MD, PhD, FACC, (1,2,3,6), Helge Skulstad, MD, PhD, (1,2,3,6).

[1]Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [2]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [3]Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [4]Department of Cardiovascular Sciences, KU Leuven - University of Leuven, Leuven, Belgium; [5]Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium; and [6]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Address for correspondence:
Helge Skulstad, MD, PhD, Department of Cardiology, Rikshospitalet, Oslo University Hospital, P.O. Box 4950 Nydalen, N-0424 Oslo, Norway. Phone: + 47 23 07 00 00, Fax: + 47 23 07 39 17E-mail: helsku@ous-hf.no

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Abstract:

Background: Right ventricular (RV) function influences prognosis in patients with left bundle branch block (LBBB) and cardiac resynchronization therapy (CRT). There is, however, limited insight into how LBBB and CRT affect RV function.
Objective: To study how LBBB and CRT modify RV free wall function by direct ventricular interaction.
Methods: In 24 LBBB patients with non-ischemic cardiomyopathy, RV and left ventricular (LV) strain by speckle-tracking echocardiography was measured before and after CRT. Underlying mechanisms were studied in 16 anesthetized dogs with ultrasonic dimension crystals and micromanometers.
Results: LBBB patients demonstrated distinct early systolic shortening in the RV free wall, which coincided with the typical abnormal early systolic septal shortening. In animals, it was demonstrated that this RV free wall contraction pattern resulted in reduced myocardial work as a large portion of the shortening occurred against low pressure during early systole, coinciding with abnormal leftward septal motion. RV systolic function was maintained by vigorous contraction in the late-activated LV lateral wall which pushed the septum towards the RV. CRT reduced abnormal septal motion and increased RV free wall work as there was less inefficient shortening against low pressure.
Conclusions: LBBB reduces workload on the RV free wall due to abnormal septal motion and delayed activation of the LV lateral wall. Restoring septal and LV function by CRT increases workload in RV free wall and may explain why patients with RV failure respond poorly to CRT.

Key Words: Cardiac Resynchronization Therapy, Heart Failure, Left Bundle Branch Block, Myocardial Work, Septal Flash, Right Ventricle.

Clinical Trial Registration: ClinicalTrials.gov number NCT02525185

Abbreviations: CRT: Cardiac resynchronization therapy, ECG: Electrocardiogram, EF: Ejection fraction, LBBB: Left bundle branch block, LV: Left ventricle, RV: Right ventricle.

Introduction

Left bundle branch block (LBBB) is a common finding in heart failure patients with left ventricular (LV) dysfunction and is associated with increased morbidity and mortality (1). The bundle branch block has a direct negative effect on LV contractile function, which contributes to heart failure (2). The influence of LBBB on right ventricular (RV) function, however, is not well known and there is conflicting data whether cardiac resynchronization therapy (CRT) improves RV function (3-7). RV function is shown to be an independent predictor of non-response to CRT, suggesting there may be important interaction between CRT and RV function (8).

LV function can modify RV function by either indirectly via the pulmonary circulation or through direct ventricular interaction (9,10). In patients with LBBB, there is typically abnormal contraction of the interventricular septum with marked early systolic shortening and leftward motion (11-13). This is followed by lengthening and rightward septal motion when the late-activated LV lateral wall starts contracting (14,15). Since the septum is an important contributor to RV function (16), this inefficient septal motion may also affect the RV. Theoretically, rightward septal systolic motion assists RV ejection, which may be of particular importance in a failing RV. Mathematical simulations have shown how work performed by the LV may support RV function during LBBB (17,18).

We have investigated how LBBB and CRT modify RV free wall function by direct ventricular interaction. In a clinical study, LBBB patients were examined before and after CRT. To extend the findings in the patients and to further explore mechanisms of the interaction we used an experimental animal model. In this model, we used sonomicrometry and invasive pressures as gold standard for evaluation of ventricular function.

Methods

Clinical Study

Study population

Fifty consecutive LBBB patients with non-ischemic cardiomyopathy referred for CRT were evaluated for inclusion. Patients with RV failure were excluded (n=5), defined as tricuspid annular plane systolic excursion (TAPSE) <17 mm (19), or if strain analysis of RV was not possible due to poor or inadequate echocardiographic image quality (n=21). Data from twenty-four patients were finally included (67±11 years, 11 females), with one in class I, fifteen in class II and eight in class III according to New York Heart Association functional classes. They were on optimal medical treatment, in sinus rhythm and TAPSE was 21±3 mm. LBBB was defined according to Strauss et al (20) and QRS duration was 162±12ms. Patients were included at the cardiology departments of Oslo University Hospital and University Hospitals Leuven from the study: Contractile Reserve in Dyssynchrony: A Novel Principle to Identify Candidates for Cardiac Resynchronization Therapy (CRID–CRT), ClinicalTrials.gov number NCT02525185.

Echocardiography and strain analysis

Two dimensional (2D) echocardiographic apical 4- and 2-chamber views were recorded (Vivid E9 or E95, GE Vingmed Ultrasound, Horten, Norway) at 79±20 frames/s. LV ejection fraction (EF) was calculated by the biplane Simpson's method. Contraction pattern in the RV was studied by strain analysis by speckle tracking echocardiography (Echopac 202, GE Vingmed Ultrasound, Horten, Norway) from an apical 4-chamber view focused on the RV. Both RV free wall global longitudinal strain (RV GLS) and septal longitudinal strain was measured as peak systolic strain and given as the mean value of three wall segments. Early systolic strain in the RV free wall was measured at the plateau in the descending strain curve typically seen in Figure 2. If no plateau could be identified the value

was set to zero. Recordings were performed prior to and within 3±3 days after CRT implantation.

Animal study

Animal preparation

Sixteen mongrel dogs of both sexes (37±3 kg) were anesthetized by either barbiturates and opioids (n=8) (thiopentone 25 mg/kg and morphine 100 mg IV, followed by infusion of morphine 50 to 100 mg/h and pentobarbital 50 mg IV every hour) or propofol and opioids (n=8) (single dose methadone 0.2 mg/kg, followed by propofol 3-4 mg/kg and a bolus of fentanyl 2-3 μg/kg, thereafter continuous infusion of propofol 0.2-1 mg/kg/min and fentanyl 5-40 μg/kg/hour). All animals were ventilated, surgically prepared and in ten animals LBBB was induced by radiofrequency ablation, as previously described (21,22). The National Animal Experimentation Board approved the study. The animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Oslo, Norway).

Micromanometer catheters (MPC 500, Millar Instruments Inc., Houston, TX, USA) were introduced trough the RV lateral wall into the RV cavity and via the carotid artery into the LV cavity. The micromanometers were adjusted by fluid-filled catheters in the right and left atria serving as pressure reference. Sonomicrometric crystals (Sonometrics, London, Ontario, Canada) were implanted in the myocardium in the RV free wall, septum and LV lateral wall (Figure 1). Data were sampled at 200 Hz.

Measurements and calculations

Peak systolic and end-diastolic pressures were measured from the two ventricles. End-diastole was defined at onset QRS. The maximum time derivative of RV and LV pressure (dP/dtmax) were calculated. Regional deformation was measured as longitudinal shortening

from the intramyocardial crystals in the RV free wall, septum and LV lateral wall. These traces were combined with ventricular pressures to construct ventricular pressure-segment length loops and these loop areas were used as regional work estimations (22).

RV global stroke work could not be calculated from pressure-volume loops by sonomicrometry due to complex anatomy. By combining LV or RV pressure with the corresponding short axis diameter trace, the diameter work was calculated as an one-dimensional approximation of stroke work. Some of this work, created by the septum and the respective ventricular free/lateral walls, was transferred by septum to work performed on the other ventricle as a direct ventricular interaction.

Early systolic shortening in the RV free wall was defined as shortening at the point of fifty percent of RV pressure rise from end-diastolic pressure to peak systolic pressure. The duration to fifty percent of total pressure rise was also acquired.

Experimental protocol

In ten animals recordings were performed during baseline, LBBB and CRT. Atrioventricular and interventricular delay was set at default, 80 and 4 ms respectively. In two of these dogs, additional recordings were also performed during CRT with increasing interventricular delay where the LV lateral wall was gradually activated later than the septum (4-16-32 ms and finally no resynchronization). Furthermore, from six previously performed experiments in our lab (22), we included additional analyses from isolated pacing of the LV lateral wall (atrioventricular delay 50 ms) in dogs without LBBB. The ventilator was temporarily switched off during all recordings.

Statistical Analysis

Values are presented as mean ± standard deviation (SD) unless stated otherwise. In the animal study, one-way repeated measures analysis of variance (ANOVA) was used to compare baseline, LBBB and CRT. Mauchly's test of sphericity was done, and if the

sphericity assumption was violated, Greenhouse-Geisser correction was performed. Post-hoc tests with Bonferroni adjustment were done when ANOVA showed significance. Pearson r was used for correlation. Paired t-tests were used to compare LV lateral wall pacing vs. baseline in dogs and also in the clinical study. $P<0.05$ was considered significant. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used.

Results:

Both the clinical and experimental study demonstrated that during LBBB there was an abnormal RV free wall contraction pattern in early systole, which was reduced by CRT (Central Illustration, Figure 2). These results are presented in detail below.

Clinical study

Longitudinal strain analysis demonstrated an abnormal contraction pattern with a distinctive early systolic shortening (Figure 2) in the RV free wall, followed by a "plateau" before it continued to shorten. This abnormal RV contraction pattern coincided with septal early systolic shortening as observed in 22 of 24 LBBB patients. CRT removed (n=13) or reduced (n=8) this early systolic shortening. RV GLS was not significantly increased by CRT (-24±4 vs. -23±4% in LBBB, NS). Septal early systolic shortening was -6±2% and RV early systolic shortening was -7±4% during LBBB, which correlated significantly ($r^2=0.57$, $P<0.01$).

CRT increased LVEF from 32±7 to 39±9% ($P<0.01$). Heart rate (70±12 vs 67±10 beats/minute, NS) and blood pressure (135±25/70±14 vs 133±18/73±13mmHg, NS) were unchanged during LBBB and CRT, respectively.

Animal study

Effects of LBBB

The animal study demonstrated identical abnormal RV contraction pattern, as seen in patients (Central Illustration and Figure 2). This appeared immediately when LBBB was

induced. LBBB slowed RV pressure rise (Table). The increase in early systolic shortening in the RV free wall occurred during low RV pressure (Central Illustration) with a corresponding decrease in regional work (Figure 3 and Table). Similarly, reductions in regional septal- (Figure 3) and LV short axis work were seen, coinciding with increased early systolic septal shortening and leftward septal motion, respectively. This was opposite to the LV lateral wall where regional work was increased (Table and Figure 3). The ventricular diameter traces also demonstrated that the typical septal flash seen in the LV diameter trace had its counterpart in the RV diameter trace (opposite flash) (Central Illustration), and an increase in RV short axis work (Table).

Effects of CRT

CRT reduced the duration of RV pressure rise and caused a rightward-and upward shift of the early systolic RV free wall pressure-dimension relationship (Figure 4 and Table). Furthermore, early systolic shortening during low pressure was reduced, and regional RV free wall work was increased (Figure 3 and Figure 4), despite no change in total shortening (Table). CRT restored septal and LV lateral wall function to baseline levels, demonstrated as increased septal work and decreased LV lateral wall work (Table and Figure 3). Finally, CRT reduced septal flash with a corresponding decrease in RV short axis work and increase in LV short axis work (Figure 4 and Table).

Hemodynamic changes during LBBB and CRT

LBBB and CRT did not alter LV and RV end-diastolic pressures, RV peak systolic pressures and heart rate compared to baseline (Table). LV peak systolic pressure was reduced by LBBB, however there was no change when CRT was applied.

Alteration in interventricular delay

Gradually increasing interventricular activation delay resulted in increasing early systolic septal- and RV free wall shortening and concomitant increasing stretch in the LV lateral wall, which demonstrated a direct relationship (Figure 5).

Isolated pacing of the LV lateral wall

Isolated pacing in the LV lateral wall in animals without LBBB resulted in left-to-right activation, opposite of right-to-left activation during LBBB. LV pacing induced LV lateral wall early systolic shortening and reduced regional work (-6±22 vs. 47±39 mm*mmHg, P<0.05) (Figure 6). The corresponding early systolic stretch of septum resulted in increased septal work compared to normal electrical conduction (141±41 vs. 72±32 mm*mmHg, P<0.01). Similarly, RV free wall work was also increased (36±18 vs. 27±18 mm*mmHg, P<0.01). LV short axis work was higher during LV pacing compared to normal electrical conduction (316±177 vs. 232±150 mm*mmHg, P<0.01), indicating increased septal contribution to the LV. RV short axis work, however, decreased (18±22 vs 45±12mm*mmHg, P<0.05).

Discussion:

This study demonstrates that LBBB and subsequent application of CRT have instantaneous mechanical effects on RV function (Central Illustration and Figure 2). In LBBB patients, there was an abnormal early systolic shortening in the RV free wall, which coincided and correlated with early systolic septal shortening. In the animal study identical findings were seen and allowed us to study the underlying mechanisms in detail. It demonstrated how the abnormal septal motion in LBBB reduced RV free wall workload. Furthermore, CRT was shown to improve LV and RV contractions, resulting in increased work in the RV free wall.

RV function during LBBB

LBBB is an electrical conduction disturbance in the LV whereas conduction in the RV remains unaffected. We have, however, demonstrated that LBBB causes significant changes in the contraction pattern in the RV. This is in accordance with previous computer simulations (8,17). Hence, changes in contraction pattern must have other reasons than the electrical activation delay per se. During normal electrical conduction, experimental studies have demonstrated that septal contraction facilitates RV ejection (23), and that LV contraction accounts for up to 40% of RV systolic pressure (16). Septal shortening in LBBB, however, is abnormal and septal contractile function is reduced as shown by lower myocardial work (24). Thus, septal contraction during LBBB is not optimal for supporting RV function. This is demonstrated by the present experimental study, where leftward septal motion during early systole caused prolonged RV pressure rise. The delayed pressure rise in early systole led to RV free wall contraction against lower pressure and thereby reduced regional work, even though total shortening was unchanged (Table).

Despite reduced septal contraction during LBBB, the LV still supports the RV by pushing the septum rightwards driven by the late, but enhanced contraction in the LV lateral wall. The early systolic septal shortening causes a systolic pre-excitation stretch of the late-activated LV lateral wall (Central Illustration), which increases regional preload on this wall (14,25). Subsequent vigorous contraction of the LV lateral wall causes a systolic rightward shift of septum. This is evident as increased RV short axis work (Table and Figure 4).

The rightward shift of the septum is dependent of the function in the LV lateral wall as demonstrated by a recently published experimental study from our group (26). When regional ischemia was induced in the LV lateral wall, the delayed contraction in this wall was reduced, followed by a concomitant reduction in the rightward septal motion.

The direct mechanical connection between RV free wall and LV lateral wall

The RV free wall shortening in early systole during LBBB, may contribute directly to the stretching of the LV lateral wall due to the continuum of the epicardial fibers between the two ventricles (27). This contraction in RV would have resulted in a considerable increase in RV pressure if not the septum moves leftwards. Our results demonstrated that the RV pressure rise in fact was slowed, in accordance to a leftward motion of the septum as also seen in the traces in Central Illustration. Previously, we have demonstrated that the early systolic septal leftward motion is an active contraction (14). Therefore, the direct mechanical connection between RV free wall and the LV lateral seems to be of less importance than the early septal shortening during LBBB for slowing the RV pressure rise and reduces the RV free wall work.

RV function during CRT

CRT counteracts the delayed activation of the LV lateral wall, attenuates abnormal septal motion and improves RV pressure rise. Hence, the opportunity to contract against low pressure in the RV free wall and septum is reduced, and thereby reducing both septal and RV free wall early systolic shortening (Central Illustration). In patients, this effect was seen shortly after CRT implantation. In animals it was shown to be a beat-to-beat response, demonstrated by pacing with increasing interventricular delay (Figure 5). By this approach we confirmed the direct mechanical interaction between the LV and the RV, as LV end-diastolic pressure was unchanged (Table). The demand on the RV free wall increased (Figure 4), which was demonstrated by increased workload due to a rightward- and upward shift of the early systolic part of the pressure-dimension relation. As also seen in Figure 4, CRT reduced short axis work due to the support of the LV lateral wall on the RV free wall mediated by the septum.

Early vs late activation of the ventricular walls

We analyzed additional experiments to further explore the concept that the earliest activated ventricular wall decreases its work with a corresponding increase of work in the latest activated wall. With LV-only pacing in ventricles with normal electrical activation the pacing induced left-to-right activation as opposed to right-to-left activations as in LBBB. A corresponding opposite effect on distribution of regional work was also demonstrated. During early activation of the LV lateral wall, it became less effective and performed less work, as more of its contraction occurred against lower pressure (Figure 6). The relatively later activated septum and RV free wall increased their work. Taken together, our two sets of experimental studies show that septal motion contributes to the earliest activated ventricle and that the latest activated region supports the early activated regions mediated through septum. These results are in line with previous studies (17,18,25,28).

Limitations:

The experimental study was designed to demonstrate hemodynamic mechanisms. Anesthesia and surgery may modify pressure levels and ventricular function. Insertion of catheters through the RV free wall could potentially alter its contraction, however, a similar contraction pattern was found in patients. Furthermore, the anesthetic protocol was changed to propofol/ fentanyl to improve rate of successful experiments. As each animal serve as its own control during the interventions, and this paper focuses on the relative changes make this change in anesthetic protocol less important.

This study accounted for acute hemodynamic changes when CRT was applied, and was not designed to analyze long-term responses to LBBB or CRT. In addition, the animal experiments were performed in non-failing ventricles that may not always reflect the clinical setting where CRT is applied. Thus, there may be differences in the hemodynamic response depending on the type and design of study. In the clinical study we investigated patients with

a relatively preserved RV function and further studies should be performed in LBBB patients in RV failure.

Valvular events in the RV are not accounted for and therefore it is not possible to determine how much of the shortening in early systole was prior or after ejection. However, in the animal model shortening was measured at fifty percent of pressure rise. This allowed us to measure shortening during early systole regardless of valvular events. Furthermore, this is during low pressure and shortening in this period contribute less to the total work than shortening during higher pressure.

LBBB and pacing influences the atrioventricular coupling which also may affect ventricular filling and hence preload. We used the longest possible atrioventricular delay, but with still adequate capture, to minimize this effect. No changes were observed in the ventricular end-diastolic pressures, indicating no major effects on preload.

There is a risk of type II error in the clinical study as it was a pilot study without pro forma power calculation. However, the minor changes in RV GLS, which can achieve statistically significance with a larger number of patients, do not have any clinical significance. In patients with RV-failure this may be more important.

Conclusions:

LBBB reduces RV free wall work and, instead, RV systolic function is supported by abnormal rightward septal motion during early systole due to exaggerated contraction in the late-activated LV free wall. CRT reduces the abnormal septal motion, which increases workload on the RV free wall. Future studies should evaluate if CRT may be harmful in patients with LBBB and RV failure.

Perspectives:

Competency in Medical Knowledge: LBBB and CRT influences RV systolic function by altering contraction pattern in the RV free wall.

Competency in Patient Care: The increased demand on the RV free wall during CRT could be of importance to clinicians, especially in patients with borderline RV function or in RV failure. These patients may not be able to increase their RV work.

Translational Outlook: Future studies should investigate if RV free wall work determines response and prognosis in CRT recipients, and whether contraction pattern in the RV free wall adds further value in prediction of CRT response in heart failure patients with LBBB.

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Figure legends

Figure 1. Schematic illustration to demonstrate placement of ultrasound crystals in the experimental study.
Closed circles indicate the crystals in the RV free wall, septum and the LV lateral wall. These crystals were used to assess regional longitudinal deformation (vertical arrows) and short axis diameters (horizontal arrows). In combination with invasive RV or LV pressure, regional and short axis work was calculated. LV; left ventricle, RV; right ventricle.

Figure 2. Right ventricular and septal shortening in patients during left bundle branch block and cardiac resynchronization therapy.
RV free wall strain traces in LBBB patients demonstrated a distinctive contraction pattern with a steeper early systolic shortening (red) that coincided with the inefficient early systolic septal shortening (red). This was followed by a plateau before it continued to shorten. Please confer similar findings in the animals given in the Central Illustration. CRT decreased this early systolic shortening. Aortic valve opening (AO) and closing (AC) is marked on the ECG. CRT; cardiac resynchronization therapy, LBBB; left bundle branch block, RV; right ventricle.

Figure 3. Line plot of regional work.
Individual data from ten animals demonstrating regional longitudinal work from RV free wall, septum and LV lateral wall at baseline and the interventions. *Left panel:* During LBBB the regional work in RV free wall was reduced and then increased by CRT. *Mid panel:* Regional work in septum changed similarly as in RV free wall (except in one animal). *Right panel:* The work in LV lateral wall increased during LBBB and was reduced during CRT, opposite to RV free wall and septum. See table for mean data and P-values. LBBB; left bundle branch block, CRT; cardiac resynchronization therapy, RV; right ventricle, LV; left ventricle.

Figure 4. Regional- and short axis work in the right ventricle.
Left panel: Pressure-segment length loops from the RV free wall during LBBB (blue line) and CRT (black line). CRT increased regional work in the RV free wall illustrated by the shading, due to less inefficient shortening against low pressure during early systole. *Right panel:* The effect of septal motion on the RV function was indicated by RV short axis work. From the LBBB loop (blue) one can see leftward septal motion during early systole (increasing diameter) during low pressure followed by rightward septal motion (shortening of diameter) at higher pressure. This increases RV diameter work as seen as the shaded area. It was a result of the delayed contraction in the LV lateral wall and the work transferred by the septum. During CRT, RV short axis work was reduced due to reduced contribution of the LV lateral wall to the right ventricular work. Thus, RV “lost” its help from the LV lateral wall mediated by the septum during CRT, and RV free wall increased its regional work as seen by the shading in left panel (see central illustration for the separate ultrasonic traces). CRT; cardiac resynchronization therapy, LBBB; left bundle branch block, RV; right ventricle, RVP; right ventricular pressure.

Figure 5. Relationships between early systolic shortening in RV free wall, early systolic shortening in septum and early systolic stretch in left ventricle during gradually increased dyssynchrony.
The figure demonstrates similar response to biventricular pacing, at different interventricular conduction delays in two animals. Squares and circles correspond to each separate animal.

Darker shades of blue indicate increasing activation delay of the lateral wall (4ms, 16ms, 32ms and finally left bundle branch block (dark blue), respectively). Immediate beat-to-beat responses were seen when altering the interventricular delay. *Panel A*: The increases in early systolic shortening in RV free wall and septum corresponded significantly. *Panel B:* Concomitant changes were seen between the LV lateral wall early systolic stretch and RV free wall early systolic shortening. *Panel C*: There was equivalent correlation between LV lateral wall early systolic stretch and early systolic shortening in septum. LV; left ventricle, RV; right ventricle, VV; Ventriculo-ventricular.

Figure 6. Differences in regional work during left bundle branch block and left ventricular lateral wall pacing.
Pressure-segment length loops, representing regional work, at LBBB (Animal A) and LV lateral wall pacing (Animal B). Please note the opposite directed changes in workload during the two interventions. The latest activated regions had increased workload due to initial lengthening compared to the early activated regions, which had early systolic shortening. RV; right ventricle, LBBB; left bundle branch block, LV: left ventricle, LVP: left ventricular pressure, RVP: right ventricular pressure.

Central Illustration. Regional segment length traces and diameter traces by sonomicrometry during left bundle branch block and cardiac resynchronization therapy.
Representative findings from an animal experiment during LBBB and CRT. During LBBB, the early systolic shortening in the RV free wall and septum coincided with the abnormal septal motion (LV- and RV short axis diameter traces), and the early systolic stretch in the LV lateral wall (all highlighted red). CRT reduced the early systolic shortening in the RV free wall. The concomitant early systolic septal shortening and the LV lateral wall early systolic stretch were also reduced. Furthermore, septal flash and rebound stretch were minimized as seen in both RV and LV diameter traces. In the ECG, aortic valve opening (AO) and closing (AC) as were seen in the aortic pressure curves (not given). CRT; cardiac resynchronization therapy, LBBB; left bundle branch block, LV; left ventricle, RV; right ventricle, RVP; right ventricular pressure, SL; segment length.

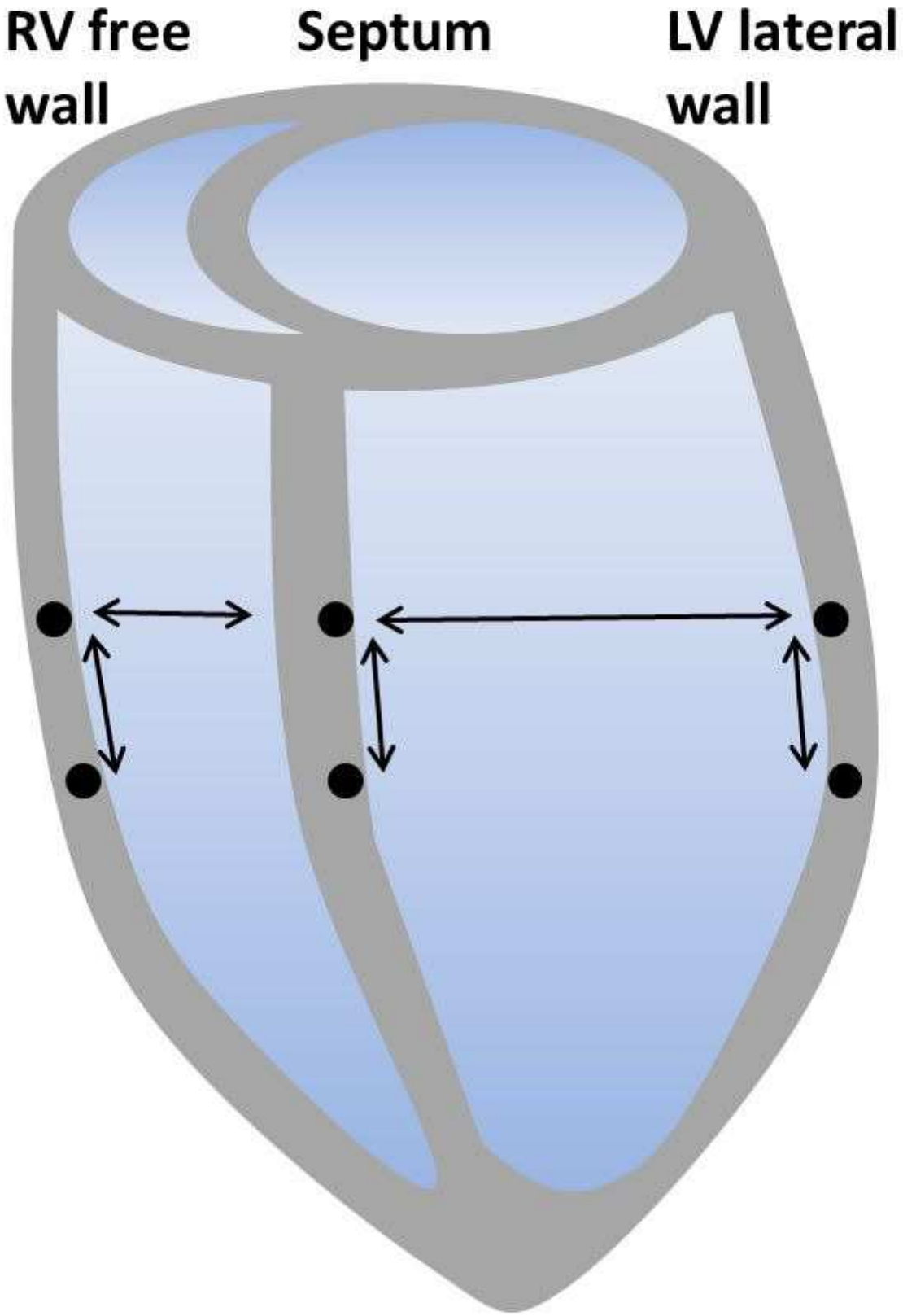
Table: Animal data from Baseline, LBBB and CRT (N=10)

				p Value			
Parameter	**Baseline**	**LBBB**	**CRT**	**ANOVA**	**LBBB vs. baseline**	**CRT vs. LBBB**	**CRT vs. baseline**
RV peak systolic pressure (mmHg)	23 ± 2	27 ± 4	26 ± 3	0.09	-	-	-
LV peak systolic pressure (mmHg)	99 ± 10	86 ± 15	88 ± 17	0.006	0.003	1	0.024
RV end-diastolic pressure (mmHg)	6 ± 3	8 ± 4	7 ± 4	0.071	-	-	-
LV end-diastolic pressure (mmHg)	8 ± 4	8 ± 4	8 ± 4	0.220	-	-	-
QRS duration (ms)	50 ± 3	108 ± 9	75 ± 14	0.000	0.000	<0.000	0.001
Heart rate (beats/min)	103 ± 21	115 ± 13	113 ± 14	0.173	-	-	-
RV dP/dt_{max} (mmHg/s)	283 ± 69	301 ± 62	326± 71	0.078	-	-	-
LV dP/dt_{max} (mmHg/s)	1301 ± 230	985 ± 154	1136 ± 204	0.001	0.001	0.000	0.079
RV free wall work (mm*mmHg)	36 ± 15	23 ± 14	36 ± 15	0.001	0.010	0.001	1
Septum work (mm*mmHg)	96 ± 52	16 ± 61	92 ± 48	0.001	0.001	0.016	1
LV lateral wall work (mm*mmHg)	118 ± 89	194 ± 111	82 ± 68	0.003	0.004	0.003	0.304

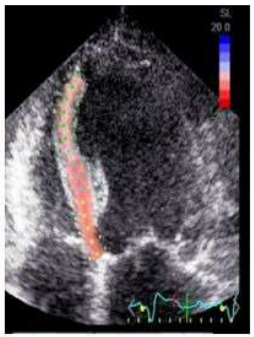
LV short axis work (mmHg*mm)	306 ± 140	114 ± 109	180 ± 97	0.000	0.001	0.006	0.027
RV short axis work (mmHg*mm)	41 ± 19	65 ± 25	32 ± 29	0.001	0.002	0.002	0.338
RV free early systolic strain (%)	-2 ± 1	-4 ± 1	-2 ± 2	0.000	0.000	0.000	1
RV free wall total strain (%)	-10 ± 4	-8 ± 3	-8 ± 3	0.057	-	-	-
Time from end-diastole to P_{50} (ms)	57 ± 13	70 ± 11	54 ± 17	0.000	0.001	0.000	0.908

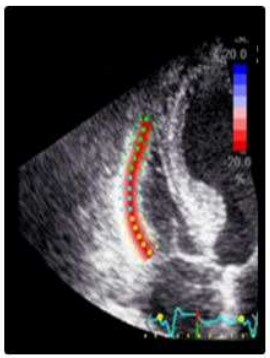
Values are mean±SD

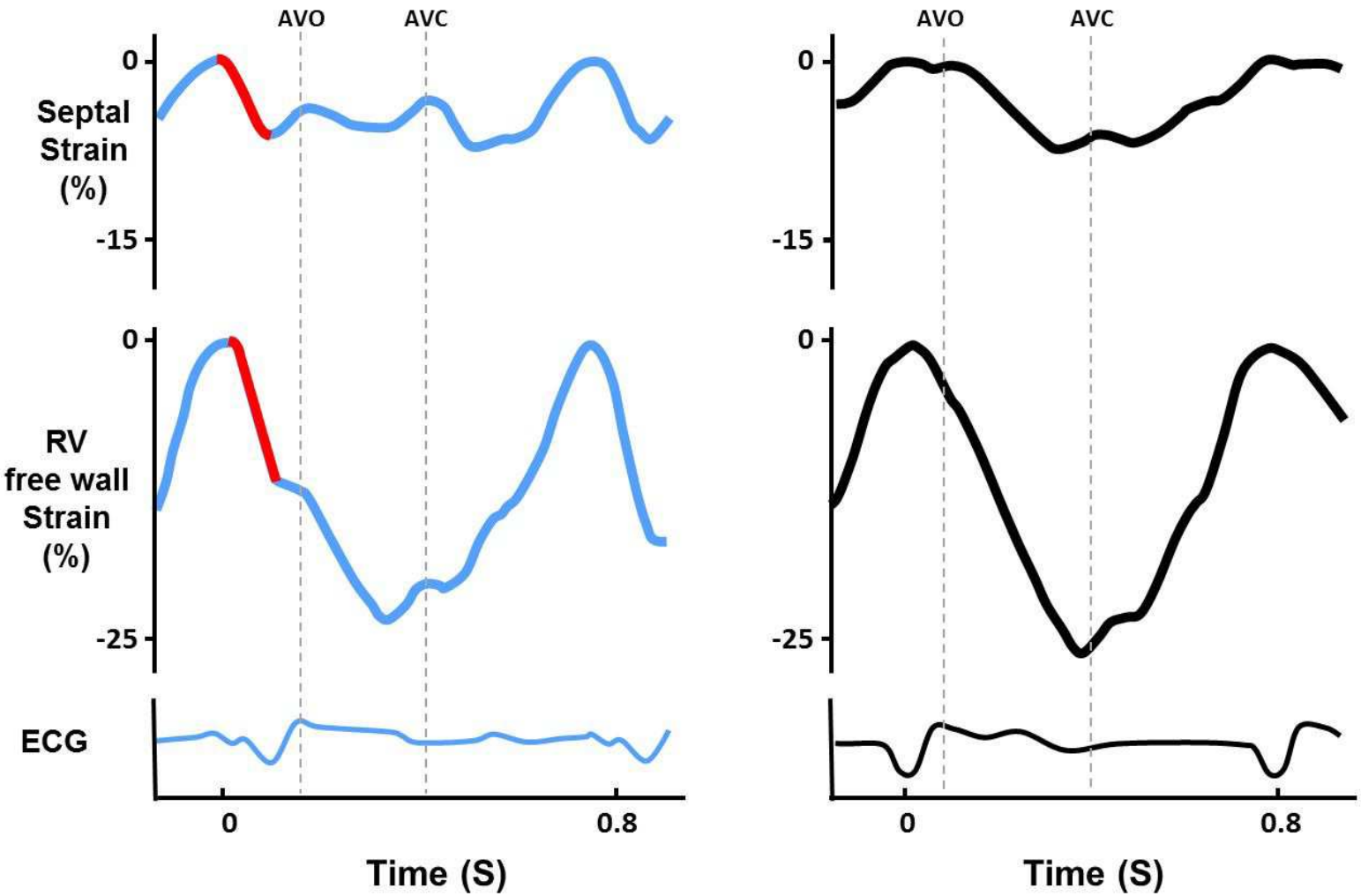
One-way repeated measures analysis of variance (ANOVA) was used to compare baseline, left bundle branch block (LBBB) and cardiac resynchronization therapy (CRT). Post-hoc tests with Bonferroni adjustment were done when ANOVA showed significance. LV; left ventricle, RV; right ventricle, dP/dt_{max}; maximal rate of pressure rise, P_{50}: Fifty percent of RV pressure rise from end-diastolic pressure to peak systolic pressure.

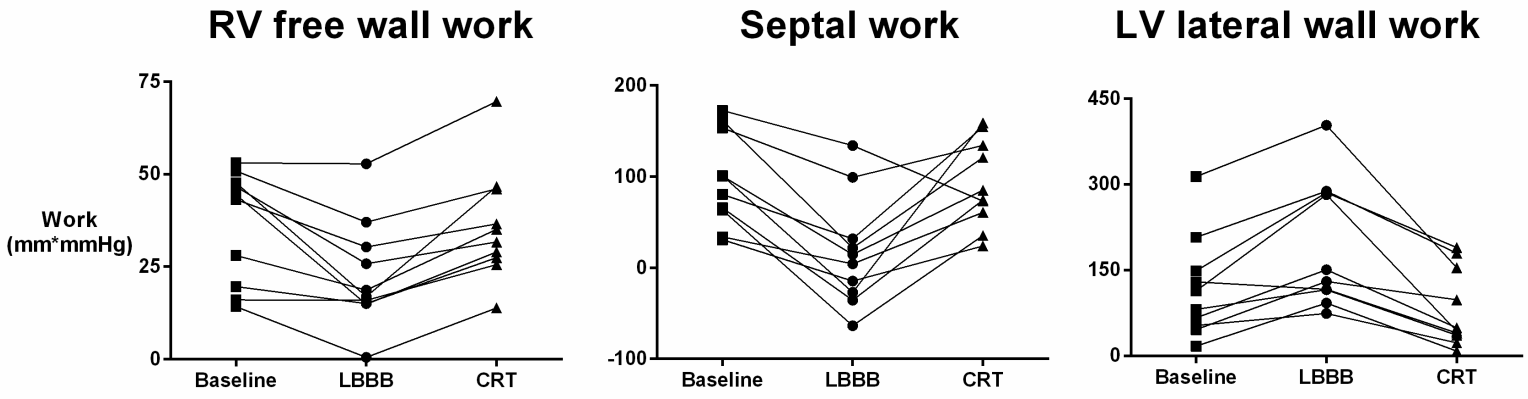

RV free wall
Septum
LV lateral wall

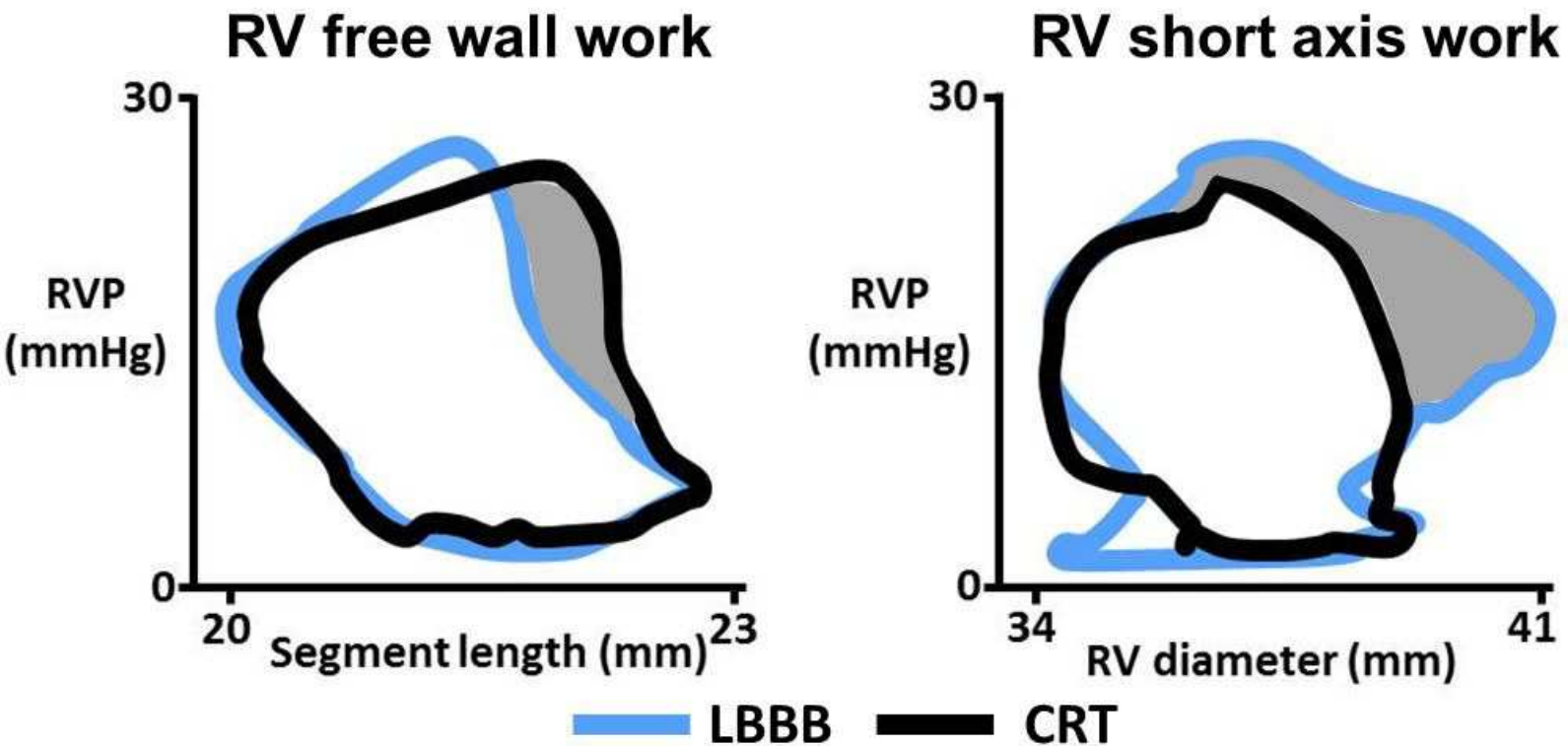
Clinical study

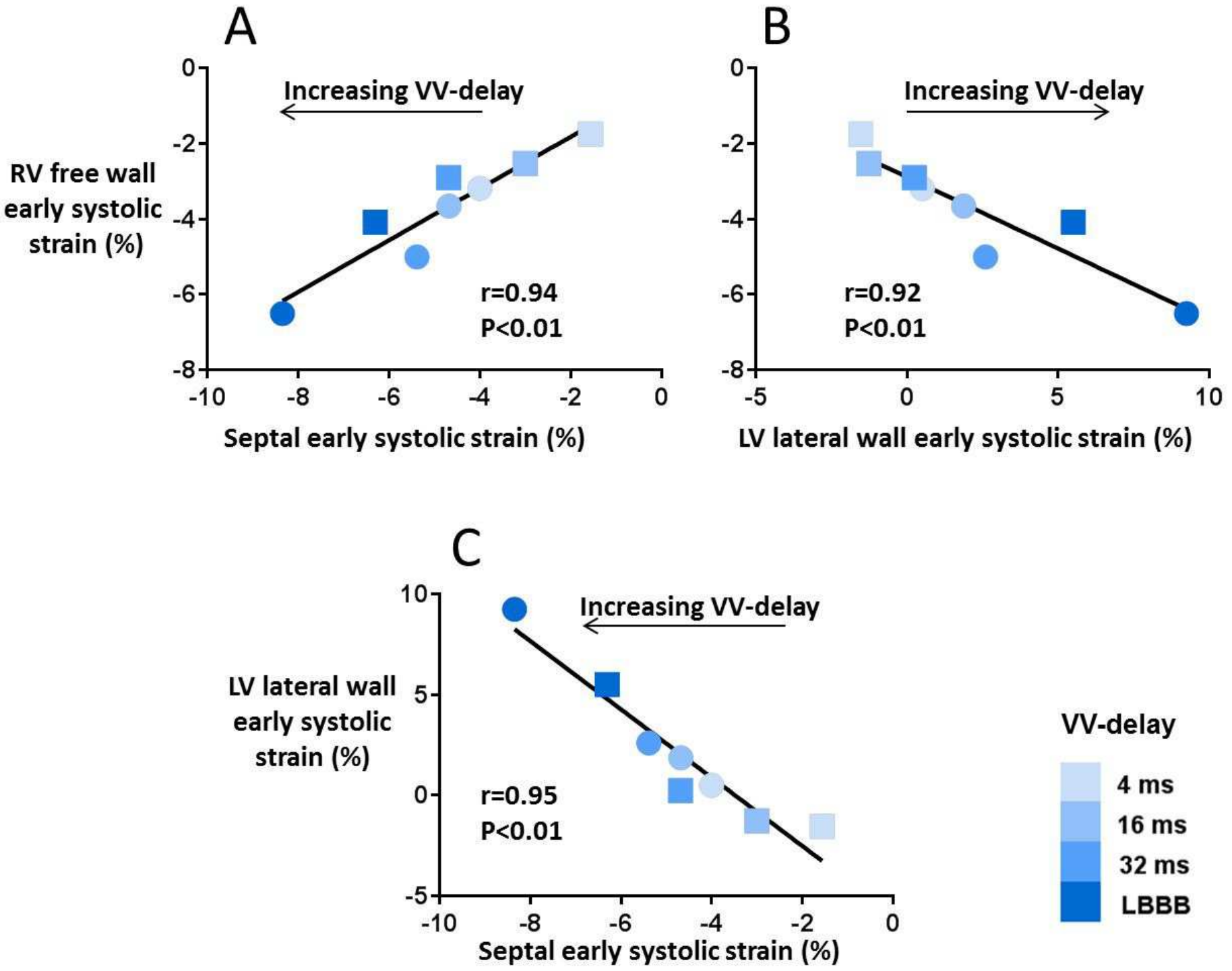


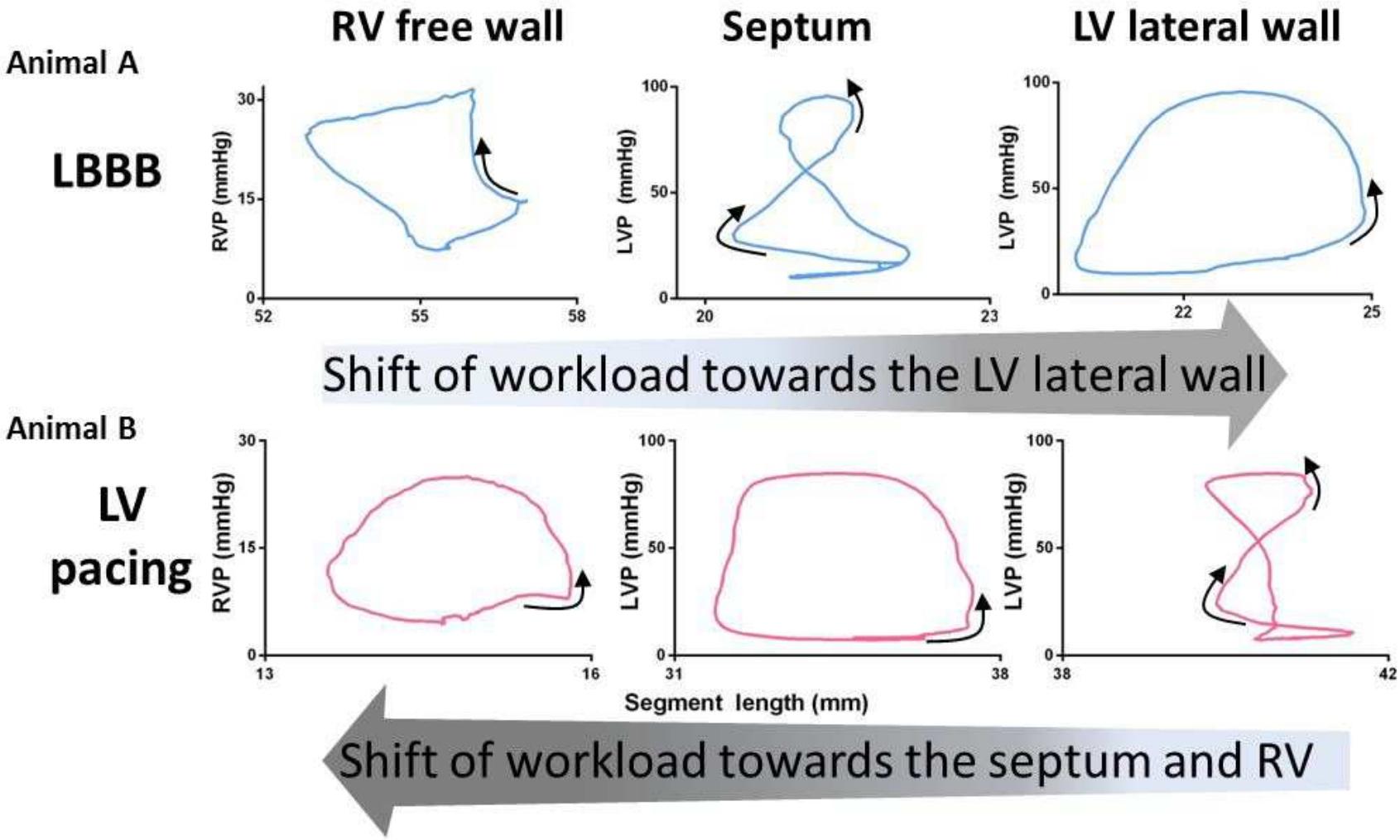


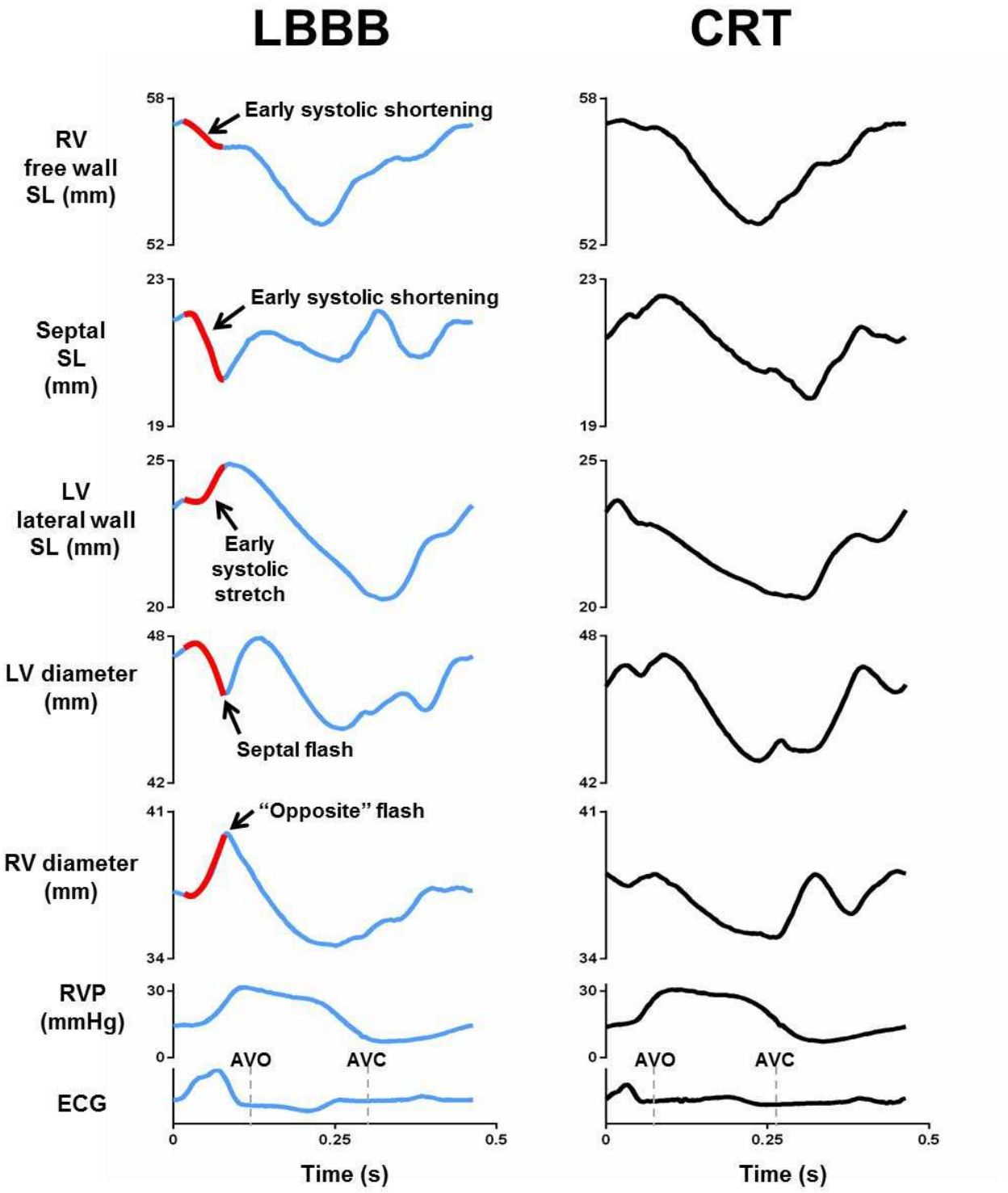



RV free wall work
Septal work
LV lateral wall work
Work
(mm*mmHg)
75
50
25
0
200
100
0
-100
450
300
150
0
Baseline
LBBB
CRT
Baseline
LBBB
CRT
Baseline
LBBB
CRT


RV free wall work
30
RVP
(mmHg)
0
20
Segment length (mm)
23
RV short axis work
30
RVP
(mmHg)
0
34
RV diameter (mm)
41
LBBB
CRT


A
Increasing VV-delay
RV free wall early systolic strain (%)
0
-2
-4
-6
-8
-10
-8
-6
-4
-2
0
r=0.94
P<0.01
Septal early systolic strain (%)
B
Increasing VV-delay
0
-2
-4
-6
-8
-5
0
5
10
r=0.92
P<0.01
LV lateral wall early systolic strain (%)
C
Increasing VV-delay
LV lateral wall early systolic strain (%)
10
5
0
-5
-10
-8
-6
-4
-2
0
r=0.95
P<0.01
Septal early systolic strain (%)
VV-delay
4 ms
16 ms
32 ms
LBBB


RV free wall
Septum
LV lateral wall
Animal A
LBBB
RVP (mmHg)
LVP (mmHg)
LVP (mmHg)
30
15
0
100
50
0
100
50
0
52
55
58
20
23
22
25
Shift of workload towards the LV lateral wall
Animal B
LV pacing
RVP (mmHg)
LVP (mmHg)
LVP (mmHg)
30
15
0
100
50
0
100
50
0
13
16
31
38
38
42
Segment length (mm)
Shift of workload towards the septum and RV


LBBB
CRT
RV free wall SL (mm)
58
52
Early systolic shortening
Septal SL (mm)
23
19
Early systolic shortening
LV lateral wall SL (mm)
25
20
Early systolic stretch
LV diameter (mm)
48
42
Septal flash
RV diameter (mm)
41
34
"Opposite" flash
RVP (mmHg)
30
0
AVO
AVC
ECG
0
0.25
0.5
Time (s)

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Manuscript number: JIMG062619-0783DR

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Corresponding author's printed name: Helge Skulstad

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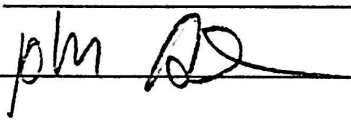
Signature: 

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Manuscript number: JIMG062619-0783D

Corresponding Author: Mr. Skulstad

Corresponding author's printed name: Skulstad

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