Echocardiographic Prediction of Cardiac Resynchronization Therapy Response Requires Analysis of Both Mechanical Dyssynchrony and Right Ventricular Function

Echocardiographic Prediction of Cardiac Resynchronization Therapy Response Requires Analysis of Both Mechanical Dyssynchrony and Right Ventricular Function: A Combined Analysis of Patient Data and Computer Simulations

Wouter M. van Everdingen, MD, John Walmsley, PhD, Maarten J. Cramer, MD, PhD, Iris van Hagen, MD, Bart W. L. De Boeck, MD, PhD, Mathias Meine, MD, PhD, Tammo Delhaas, MD, PhD, Pieter A. Doevendans, MD, PhD, Frits W. Prinzen, PhD, Joost Lumens, PhD, and Geert E. Leenders, MD, PhD, *Utrecht and Maastricht, The Netherlands; Luzern, Switzerland; and Pessac, France*

Background: Pronounced echocardiographically measured mechanical dyssynchrony is a positive predictor of response to cardiac resynchronization therapy (CRT), whereas right ventricular (RV) dysfunction is a negative predictor. The aim of this study was to investigate how RV dysfunction influences the association between mechanical dyssynchrony and left ventricular (LV) volumetric remodeling following CRT.

Methods: One hundred twenty-two CRT candidates (mean LV ejection fraction, 19 ± 6%; mean QRS width, 168 ± 21 msec) were prospectively enrolled and underwent echocardiography before and 6 months after CRT. Volumetric remodeling was defined as percentage reduction in LV end-systolic volume. RV dysfunction was defined as RV fractional area change < 35%. Mechanical dyssynchrony was assessed as time to peak strain between the septum and LV lateral wall, interventricular mechanical delay, and septal systolic rebound stretch. Simulations of heart failure with an LV conduction delay in the CircAdapt computer model were used to investigate how LV and RV myocardial contractility influence LV dyssynchrony and acute CRT response.

Results: In the entire patient cohort, higher baseline septal systolic rebound stretch, time to peak strain between the septum and LV lateral wall, and interventricular mechanical delay were all associated with LV volumetric remodeling in univariate analysis ($R = 0.599$, $R = 0.421$, and $R = 0.410$, respectively, $P < .01$ for all). The association between septal systolic rebound stretch and LV volumetric remodeling was even stronger in patients without RV dysfunction ($R = 0.648$, $P < .01$). However, none of the mechanical dyssynchrony parameters were associated with LV remodeling in the RV dysfunction subgroup. The computer simulations showed that low RV contractility reduced CRT response but hardly affected mechanical dyssynchrony. In contrast, LV contractility changes had congruent effects on mechanical dyssynchrony and CRT response.

Conclusions: Mechanical dyssynchrony parameters do not reflect the negative impact of reduced RV contractility on CRT response. Echocardiographic prediction of CRT response should therefore include parameters of mechanical dyssynchrony and RV function. (J Am Soc Echocardiogr 2017;30:1012-20.)

Keywords: Cardiac resynchronization therapy, Dyssynchrony, Echocardiography, RV function, Interventricular interaction, Computer simulations

From the University Medical Center Utrecht, Utrecht (W.M.v.E., M.J.C., I.v.H., M.M., P.A.D., G.E.L.), and the CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands (J.W., T.D., F.W.P., J.L.); Kantonsspital Luzern, Luzern, Switzerland (B.W.L.D.B.); and L'Institut de Rythmologie et Modélisation Cardiaque, Université de Bordeaux, Pessac, France (J.L.).

This work was supported by a personal grant within the Dr. E. Dekker framework of the Dutch Heart Foundation to J. Lumens (grant 2015T082). Dr. Prinzen has received research grants from Medtronic, Boston Scientific, St. Jude Medical, LivaNova, Biosense Webster, and EBR Systems and is an adviser to Medtronic.

Drs. van Everdingen and Walmsley contributed equally to this work.

Reprint requests: Wouter M. van Everdingen, MD, Department of Cardiology, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands (E-mail: *w.m.vaneverdingen@umcutrecht.nl*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.06.004

Abbreviations

2DS-RV = Right ventricular free wall peak strain

CRT = Cardiac resynchronization therapy

LBBB = Left bundle branch block

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

NYHA = New York Heart Association

RV = Right ventricular

RVFAC = Right ventricular fractional area change

SRSsept = Septal systolic rebound stretch

Strain-SL = Time to peak strain delay between the septum and the lateral wall

TRPG = Tricuspid regurgitation peak gradient

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure and evidence of electrical conduction delay.[1,2] Despite the success of CRT in large clinical trials, predicting CRT response in individual patients remains challenging. Response prediction is difficult because the mechanisms through which CRT response occurs are still not completely understood. An important mode of action of CRT is the correction of mechanical dyssynchrony caused by an electrical conduction delay, resulting in improvement in myocardial efficiency.[3] Attempts to predict outcome after CRT by identifying such electrical or mechanical substrates have yielded variable results, however.[4]

Right ventricular (RV) function is an important predictor of echocardiographic and clinical outcomes following CRT.[5] The impact of RV function on prognosis has been demonstrated in both observational studies and in landmark CRT trials.[5-7] RV dysfunction is strongly associated with more advanced heart failure.[8,9] Moreover, changes in RV function and loading can lead to mechanical dyssynchrony through ventricular interaction, even without underlying electrical dyssynchrony.[10] Whether RV function directly affects mechanical dyssynchrony and CRT response, and how this relates to the association with more advanced heart failure, remains unclear.[5-7,10,11] We therefore used echocardiographic deformation imaging to investigate whether RV dysfunction affects baseline mechanical dyssynchrony indices in a CRT population. We also investigated how these indices related to CRT response (i.e., volumetric remodeling). CRT response was defined as the reduction in left ventricular (LV) end-systolic volume 6 months after CRT. We further hypothesized that RV dysfunction could directly influence both mechanical dyssynchrony and CRT response, independent of LV condition. Because determining causation in the interaction between RV and LV myocardial dysfunction and mechanical dyssynchrony using patient data is challenging, we also performed computer simulations. Simulations were performed with the multiscale CircAdapt model of the human heart and circulation to isolate and explain the effects of RV and LV myocardial dysfunction on both mechanical dyssynchrony and CRT response.[12]

METHODS

Study Population and Protocol

The study population consisted of a cohort of prospectively enrolled patients undergoing CRT because of medication-refractory heart failure (New York Heart Association [NYHA] classes II–IV, LV ejection fraction [LVEF] $< 35\%$) and evidence of conduction disturbances (QRS width ≥ 120 msec) with a left bundle branch block (LBBB)–like morphology on surface electrocardiography. Patients were excluded from the analysis if they had poor echocardiographic image quality ($n = 20$). Echocardiographic and clinical characteristics were prospectively assessed in all patients before and 6 months after CRT. Care was taken to optimize heart failure medication before the implantation of a CRT device. The execution of the study complied with the principles outlined in the Declaration of Helsinki on research in human subjects and with the procedures of the local medical ethics committee. In compliance with Dutch law, the requirement to obtain written informed consent was waived by the local medical ethics committee, as all echocardiograms and CRT implantations were part of standard clinical care.

Echocardiographic Protocol

All echocardiographic data were obtained using a Vivid 7 ultrasound machine (GE, Chicago, IL). A minimum of three loops were acquired at breath hold and analyzed offline (EchoPAC version 6.0.1; GE). In patients with atrial fibrillation, all parameters are averages over five representative beats.

Two-Dimensional Echocardiography and Doppler Imaging. LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were measured using the biplane Simpson method.[13] Reverse remodeling after CRT was defined as the percentage of reduction in LVESV between echocardiographic examination before and 6 months after CRT implantation. Response was defined as a reduction in LVESV of $\geq 15\%$.

Mitral regurgitation effective regurgitant orifice was quantified by the proximal isovelocity surface area method. RV measurements were performed in the apical four-chamber view. RV end-diastolic and end-systolic areas were traced and were used to calculate RV fractional area change (RVFAC). RV dysfunction was defined as RVFAC $< 35\%$.[13] Tricuspid annular plane systolic excursion and transtricuspid pressure gradient were also measured. RVFAC was chosen to define RV dysfunction, as we expected that RVFAC would provide the most adequate estimation of RV function in the presence of mechanical dyssynchrony.[14]

For offline deformation imaging, additional narrow-sector single-wall images of the septum, lateral wall of the left ventricle, and free wall of the right ventricle were prospectively acquired from the standard apical views at 51 to 109 Hz. The onset of the QRS complex was taken as the zero reference for timing and strain measurements. Systole was defined using mitral valve closure and aortic valve closure, derived from Doppler flow patterns. Interventricular mechanical delay was assessed as the delay between pulmonary and aortic valve opening.

Deformation Analysis. Dedicated speckle-tracking software (EchoPAC 2DS version 6.1; GE) was used to derive longitudinal strain curves. The region of interest was placed from base to apex and adapted to match wall thickness. Tracking was visually checked and the region of interest adjusted if necessary. Global longitudinal deformation was calculated over the entire length of the wall. To assess LV dyssynchrony, time to peak strain delay between the septum and the lateral wall (Strain-SL) was calculated. Septal systolic rebound stretch (SRSsept) was determined by summing all systolic stretch following prematurely terminated shortening in the septum, as previously described (Figure 1).[15,16] Septal strain patterns were also categorized as type I (double-peaked), type II (predominant stretch during ejection), and type III (pseudonormal), as previously described (Figure 1).[17]

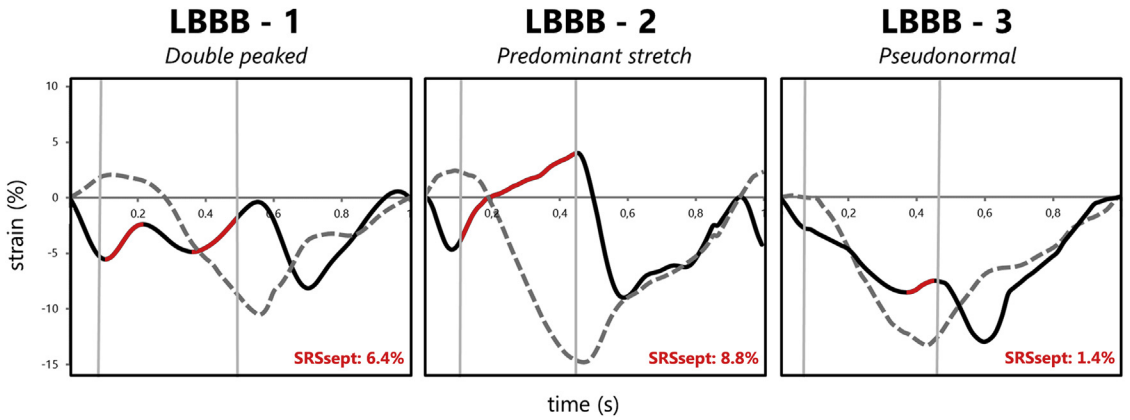


Figure 1 Examples of septal strain patterns and SRSsept. Three septal strain patterns (*solid black curves*) are displayed: LBBB-1, double-peaked shortening; LBBB-2, predominant stretch during ejection phase; and LBBB-3, pseudonormal shortening. SRSsept (*red*) is indicated in the *lower right corner* of each panel and is determined as all systolic stretch following prematurely terminated shortening in the septum. Lateral wall strain is displayed as a *dashed gray curve*. *Horizontal solid gray lines* represent the ejection phase (mitral valve closure to aortic valve closure).

Device Implantation

Implantation was performed under local anesthesia. RV and atrial leads were placed transvenously at conventional positions. The LV lead was aimed at a tributary of the coronary sinus overlying the LV free wall. Leads were connected to a CRT defibrillator in all patients.

Computer Simulations

The CircAdapt computational model of the human heart and circulation (www.circadapt.org) was used to simulate local ventricular myofiber mechanics and global pump function in the hearts of virtual patients with different degrees of LV and RV contractile weakness and LV conduction delay.[12,17,18] More detailed descriptions of both the CircAdapt model and simulations we performed are provided in the Supplemental Methods (available at www.onlinejase.com).

Simulation of LV and RV Failure at Baseline. The starting point for all simulations of heart failure and CRT was a computer model representing normal healthy adult physiology obtained as described previously.[17] We produced a virtual patient with heart failure and LBBB by imposing a cardiac output of 3.1 L/min, on the basis of the mean value in the patient data (Table 1), with a heart rate of 70 beats/min and mean arterial pressure of 92 mm Hg. We reduced RV and LV myocardial contractility, being the intrinsic ability of myocardial tissue to generate active stress following cross-bridge formation, to 60% of the contractility value in healthy myocardium. LV and RV unloaded wall areas were expanded by 10% to represent eccentric remodeling. An activation delay was imposed within the left ventricle to represent LBBB-like activation (Supplemental Figure 1, available at www.onlinejase.com). The resulting LVEF and RV ejection fraction were 22% and 41%, respectively.

Beginning with the initial virtual patient with heart failure and LBBB, further worsening of RV or LV myocardial contractile weakness was simulated through further reductions in either the contractility of the RV or LV free wall from 60% down to 20% of the original healthy contractility in nine steps. This protocol resulted in nine virtual patients with varying degrees of LV myocardial dysfunction causing a decrease in LVEF to a minimum of 10% and nine virtual patients with varying degrees of RV myocardial dysfunction causing a gradual decrease in RV ejection fraction to a minimum of 24%. Cardiac output, heart rate, and mean arterial pressure were sustained through homeostatic control mechanisms in each virtual patient. The average myofiber strain from the septal wall segments was used to calculate SRSsept for each simulation.

Simulation of CRT. CRT was simulated in each virtual patient using an activation pattern representing preexcitation of the RV apex and the LV lateral wall, as shown in Supplemental Figure 1 (available at www.onlinejase.com). When simulating the acute effects of CRT, homeostatic control was turned off to allow changes in stroke volume to occur. We defined the acute response to CRT in the simulations as the percentage change in stroke volume after initiation of CRT once a new hemodynamic steady state was reached.

Statistical Analysis

Statistical analysis was performed using SPSS (SPSS, Chicago, IL). Values are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Continuous data were compared using the paired or unpaired *t* test as appropriate. Categorical data were compared using the χ^2 or Fisher exact test. Correlations between parameters were expressed using Pearson or Spearman correlation coefficients as appropriate. Univariate analysis of parameters of LV function, RV function, and dyssynchrony was performed to determine their relation to CRT response. The single best performing parameter for each aspect (i.e., LV function, RV function, and dyssynchrony) was used in a stepwise, forward selection, multivariate model. Three models were used to test whether baseline RV function affected the prediction of reverse remodeling independent of baseline LV function (i.e., LVEDV, LVESV, or LVEF) and mechanical dyssynchrony. One model incorporated the best performing dyssynchrony and LV function parameter, one incorporated the best performing dyssynchrony and RV function parameter, and one incorporated all three. A P value $< .05$ was considered to indicate statistical significance for all analyses.

Measurement Variability. Last, measurement variability of key echocardiographic parameters and dyssynchrony parameters was analyzed by a second observer in 20 randomly selected patients and compared using the intraclass correlation coefficient. Intraclass

Table 1 Baseline characteristics

Parameter	RVFAC ≥ 35% (*n* = 83)	RVFAC < 35% (*n* = 39)	*P*
Age (y)	65 ± 11	64 ± 12	.716
Male	52 (63)	33 (85)	.019
Rhythm			
Sinus rhythm	76 (92)	30 (77)	.041
Atrial fibrillation	7 (8)	9 (23)	
NYHA class			
II	8 (10)	0 (0)	.005
III	70 (84)	30 (77)	
IV	5 (6)	9 (23)	
Medication			
β-blocker	71 (86)	25 (64)	.010
ACE inhibitor or ATII antagonist	76 (92)	37 (95)	.717
Diuretics	75 (90)	38 (97)	.269
Aldosterone antagonist	42 (51)	23 (59)	.440
Lead position			.606
(Postero)lateral	68 (82)	32 (82)	
Anterolateral	7 (8)	5 (13)	
Posterior	8 (10)	2 (5)	
QRS width (msec)	170 ± 25	167 ± 20	.517
LBBB	57 (69)	23 (59)	.313
Ischemic etiology	44 (53)	11 (28)	.012
LVEDV (mL)	237 ± 65	290 ± 107	.006
LVESV (mL)	188 ± 59	247 ± 101	.001
LVEF (%)	21 ± 6	16 ± 5	<.001
Cardiac output (L/min)	3.1 ± 1.0	3.1 ± 1.2	.902
Left atrial size (mm)	48 ± 8	54 ± 7	<.001
MRERO (mm^2)	8 ± 7	14 ± 8	.001
SRSsept (%)	5.2 ± 3.5	3.3 ± 2.9	.003
Septal strain pattern			.017
1 (double-peaked)	27 (33)	5 (13)	
2 (predominant stretch)	28 (34)	11 (28)	
3 (pseudonormal)	28 (34)	23 (59)	
Strain-SL (msec)	276 ± 143	230 ± 145	.099
IVMD (msec)	47 ± 26	47 ± 26	.983
RVEDA (cm^2)	14 ± 5	20 ± 5	<.001
RVESA (cm^2)	7 ± 4	15 ± 4	<.001
RVFAC (%)	49 ± 10	25 ± 6	<.001
TAPSE (mm)	19 ± 5	14 ± 4	<.001
2DS-RV (%)	−20.4 ± 5.6	−14.3 ± 4.4	<.001
TRPG (mm Hg)	30 ± 8	35 ± 9	.009

ACE, Angiotensin-converting enzyme; *ATII*, angiotensin receptor II; *IVMD*, interventricular mechanical dyssynchrony; *MRERO*, mitral regurgitation effective regurgitant orifice; *RVEDA*, RV end-diastolic area; *RVESA*, RV end-systolic area; *TAPSE*, tricuspid annular plane systolic excursion.
Data are expressed as mean ± SD or as number (percentage).

correlation coefficient values were as follows, 0.98 for LVEDV, 0.97 for LVESV, 0.77 for LVEF, 0.83 for RV end-diastolic area, 0.90 for RV end-systolic area, 0.93 for RVFAC, 0.91 for interventricular mechanical delay, 0.75 for Strain-SL, and 0.92 for SRSsept.

RESULTS

Patient Study

Study Population. Table 1 shows baseline characteristics of patients with and without RV dysfunction. Patients with RV dysfunction had more advanced heart failure with more pronounced RV and LV dilatation, lower LVEFs, larger left atria, more severe mitral regurgitation, and higher NYHA functional class. These patients were also more often male, more often had atrial fibrillation, had higher transtricuspid pressure gradients, and less often had an ischemic etiology of heart failure. Of all dyssynchrony parameters, only SRSsept was significantly lower in patients with RV dysfunction.

CRT Response. In total, nine patients died (four patients without RV dysfunction and five with RV dysfunction), and three underwent LV assist device implantation or heart transplantation (two patients without RV dysfunction and one with RV dysfunction) before the 6-month follow-up visit. NYHA class decreased by two levels in nine patients (7%), decreased by one level in 65 patients (53%), remained stable in 33 patients (27%), and had missing data in 15 patients (12%). NYHA class decreased significantly compared with baseline values in the subgroup without RV dysfunction. However, there was no statistically significant difference in change of NYHA class between the two subgroups (Table 2). LV volumes could not be quantified at 6-month follow-up in three patients. In the remaining population, CRT reduced LVEDV (from 256 ± 84 to 227 ± 96 mL) and LVESV (from 208 ± 80 to 174 ± 92 mL) and improved LVEF (from 20 ± 7% to 26 ± 11%) at 6 months ($P < .001$ for all). RV free wall peak strain (−18.2% to −21.1%, $P < .001$), RV end-systolic area (10 ± 6 to 9 ± 4 cm^2, $P < .05$), and transtricuspid pressure gradient (33 ± 9 to 29 ± 9 mm Hg, $P < .05$) showed a significant improvement after CRT, whereas RVFAC and tricuspid annular plane systolic excursion did not. Table 2 shows responses in patients with and without RV dysfunction. Patients with RV dysfunction showed less LV reverse remodeling and less improvement of LVEF, but improvements in RV parameters were greater in these patients. There were nine volumetric responders (28%) in the subgroup with RV dysfunction, compared with 45 (60%) in the subgroup without RV dysfunction ($P < .01$).

Association of Baseline Parameters with CRT Response. In the entire patient cohort, SRSsept showed the strongest association with volumetric response ($R = 0.599$, $P < .001$), while traditional dyssynchrony parameters also showed correlations ($R = 0.410$ for interventricular mechanical delay and $R = 0.421$ for Strain-SL, $P < .001$ for both). SRSsept had an even stronger association with volumetric response in the subgroup of patients with preserved RV function ($R = 0.648$, $P < .001$; Figure 2). However, neither SRSsept nor any of the other dyssynchrony parameters correlated with volumetric response in patients with RV dysfunction.

All RV function parameters showed significant associations with LV reverse remodeling (Table 3). The association between baseline RVFAC and LV reverse remodeling was strongest out of all of the RV function parameters. Of the baseline parameters reflecting LV

Table 2 CRT response in patients with and without RV dysfunction

Parameter	RVFAC ≥ 35% (*n* = 83)	RVFAC < 35% (*n* = 39)	*P*
ΔLVEDV (%)	−17 ± 19*	−3 ± 16	<.001
ΔLVESV (%)	−24 ± 23*	−7 ± 18*	<.001
ΔLVEF (percentage points)	8 ± 8*	4 ± 7*	.006
Δ2DS-RV (percentage points)	−2.3 ± 6.0*	−4.4 ± 4.7*	.082
ΔRVEDA (%)	8 ± 31	−15 ± 34*	.001
ΔRVESA (%)	18 ± 44	−25 ± 30*	<.001
ΔRVFAC (percentage points)	−4 ± 11*	9 ± 11*	<.001
ΔTRPG (mm Hg)	−2 ± 9	−5 ± 7*	.343
ΔTAPSE (mm)	−1 ± 4*	2 ± 4*	<.001
ΔNYHA class			
0	24 (32)*	9 (28)	.913
−1	45 (60)*	20 (63)	
−2	6 (8)*	3 (9)	

RVEDA, RV end-diastolic area; *RVESA*, RV end-systolic area; *TAPSE*, tricuspid annular plane systolic excursion.
Data are expressed as mean ± SD or as number (percentage).
*Significant change compared with baseline.

condition, both LVEDV and LVESV were associated with reverse remodeling. There was no significant association between baseline LVEF and reverse remodeling. LVEDV showed the best correlation with LV reverse remodeling. Although changes in the R^2 value were small, addition of LVEDV or RVFAC to SRSsept improved the prediction of LV reverse remodeling in multivariate regression (Table 4). However, when both were included in the model, LVEDV no longer had significant independent predictive value on top of SRSsept and RVFAC. This indicates that LV reverse remodeling after CRT was more strongly associated with baseline RVFAC than with baseline LVEDV and that RVFAC is additive to mechanical dyssynchrony parameters in their ability to predict response to CRT.

Simulations

Effect of LV and RV Contractile Parameters on SRSsept. The baseline virtual patient with heart failure and LBBB produced a characteristic type II LBBB myocardial deformation pattern that was similar to LV strain patterns observed in the patients (Figures 3B and 3C, *left*) with an SRSsept of 9.3%. Virtual patients with decreased LV contractility had qualitative changes in their septal strain patterns (Figure 3B, *middle and right*). These changes in septal strain were accompanied by a decline in SRSsept to 2.7% (Figure 4A). In contrast, virtual patients with decreased RV contractility did not have qualitative changes in their septal strain patterns (Figure 3C, *middle and right*). They also had only a small change in SRSsept (Figure 4A), which reduced from 9.3% in the baseline heart failure with LBBB simulation to 8.6% at an RV contractility of 20% of healthy tissue.

Effects of LV and RV Contractility on CRT Response. In the virtual patients, reductions in both LV and RV contractility affected CRT response when an LBBB-like activation pattern was present at baseline (Figure 4B). Deteriorating LV contractile function led to a decrease in the acute response to CRT from a 9.1% change in stroke volume with 60% LV contractility down to 0.7% when LV contractility was 20%. Comparable decreases in acute response were also seen in the simulations as RV contractility deteriorated, from a 9.1% change in stroke volume with RV contractility at 60% of normal down to 2.2% with an RV contractility of 20%. Comparing Figure 4A and 4B, a mismatch between SRSsept and acute response occurred when RV contractility was low, despite the presence of an appropriate LV substrate for CRT.

DISCUSSION

This study demonstrates that commonly used mechanical dyssynchrony parameters are not associated with CRT response when RV dysfunction is present. Incorporating RV function (i.e., RVFAC) with mechanical dyssynchrony in multivariate analysis improved the association with CRT response. Computer simulations demonstrated that both LV and RV myocardial dysfunction could reduce acute response to CRT. However, whereas LV contractility changes had congruent effects on dyssynchrony and CRT response, RV contractility changes hardly affected mechanical dyssynchrony. This discrepancy potentially creates a mismatch between mechanical dyssynchrony and CRT response. Therefore, response prediction using mechanical dyssynchrony parameters should be approached cautiously in patients with a dysfunctional RV. These findings emphasize the complexity of predicting CRT response and may have important implications for improvements in patient selection for CRT.

Interaction of LV and RV Function and Their Effects on CRT Outcome

In the present study population, worse baseline LV and RV function was associated with less reverse remodeling following CRT. The effects of LV and RV function on outcome are likely to be both independent effects and effects interacting with CRT. LV function was more severely reduced in patients with RV dysfunction compared with patients with preserved RV function. RV dysfunction is known to be an important predictor of adverse prognosis in patients with both moderate and advanced heart failure.[8,9] The same adverse prognostic effect has also been demonstrated for CRT patients with advanced (i.e., NYHA classes III and IV) heart failure,[5] although a recent meta-analysis showed no effect of RV function parameters on changes in LVEF.[14] In a meta-analysis by Sharma *et al.*,[14] RVFAC remained the strongest RV function metric for predicting volumetric response after CRT as measured by change in LVEF and was only borderline statistically nonsignificant. The use of LVEF as an outcome parameter might be a cause for discrepancy with our results. Although both LVEF and LVESV reflect changes in volumes, LVESV might have a different relation with RVFAC. The evidence is also inconclusive for CRT patients with mild heart failure.[6,19]

The computer simulations support the hypothesis that a very weak left ventricle is intrinsically less able to benefit from resynchronization despite the presence of an appropriate LV conduction delay.[17,20] In the clinical situation, severe adverse remodeling of the left ventricle, which may be irreversible, may compound this effect. The computer simulations also highlight a potential role for reduced RV contractility in limiting CRT response. In LBBB, LV myofiber work

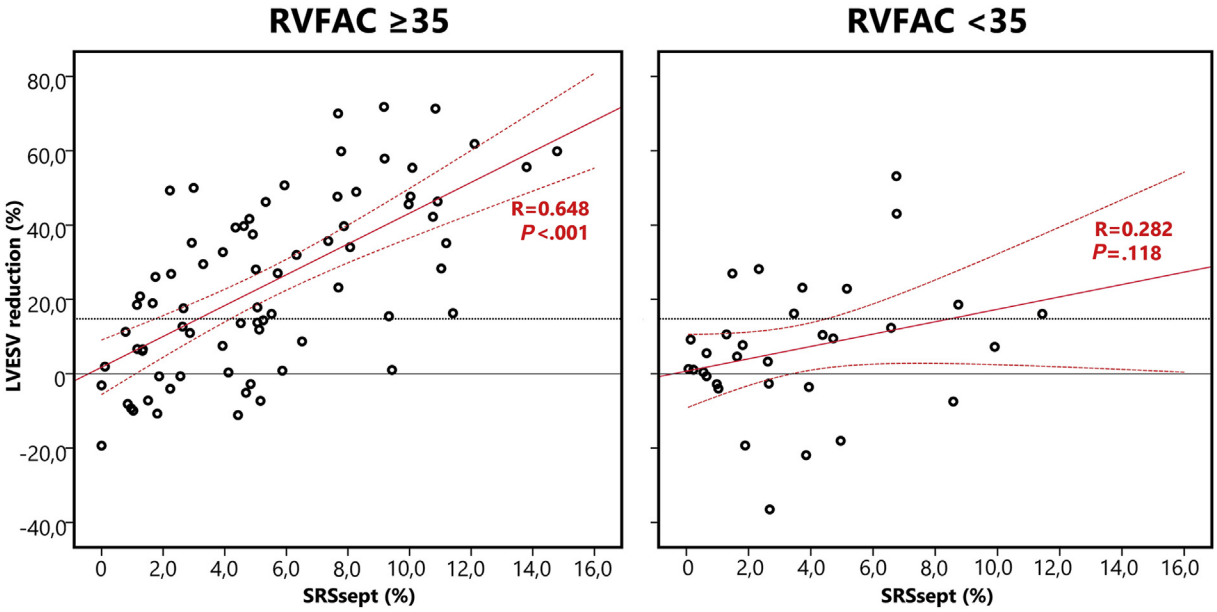


Figure 2 Relation of SRSsept and LV reverse remodeling in patients with and without RV dysfunction. Patients with low RVFAC (<35%) had a weaker and statistically nonsignificant relation between LVESV reduction and SRSsept (*right*). Those with preserved RVFAC (≥35%) (*left*) had a strong and statistically significant relation between LVESV reduction and SRSsept. The *dotted horizontal line* indicates the response cutoff of 15% reduction in LVESV.

Table 3 Univariate relation of baseline LV and RV parameters with LV remodeling

	ΔLVESV (%)	
Parameter	*R*	*P*
LVEDV	−0.291	.002
LVESV	−0.274	.004
LVEF	0.120	.220
TAPSE	0.342	<.001
RVEDA	−0.242	.012
RVESA	−0.354	<.001
RVFAC	0.430	<.001
2DS-RV	−0.218	.024

RVEDA, RV end-diastolic area; *RVESA*, RV end-systolic area; *TAPSE*, tricuspid annular plane systolic excursion.

Table 4 Predictive value of LV and/or RV function on top of dyssynchrony

	ΔLVESV (%)				
Parameter	Model R^2	*B*	SE	β	*P*
Model 1					
SRSsept*	0.36	3.67	0.50	0.57	<.001
LVEDV*	0.39	−0.06	0.02	−0.20	.010
Model 2					
SRSsept*	0.36	3.32	0.53	0.51	<.001
RVFAC*	0.41	38.75	12.87	0.24	.003
Model 3					
SRSsept*	0.36	3.32	0.53	0.51	<.001
RVFAC*	0.41	38.75	12.87	0.24	.003
LVEDV†				−0.15	.062

*Parameter in the model.
†Parameter not in the model.

makes a large contribution to RV pump work through ventricular interaction, and CRT redistributes myofiber work from the LV free wall to the septum and right ventricle.[11] As shown by our simulations, reduced RV contractility leads to reduced mechanical support from the right ventricle after CRT and reduces LV filling, resulting in less improvement in LV stroke volume. It is probable that a combination of the LV and RV effects described above is responsible for the reduction in response observed in the RV dysfunction patient subgroup. The adverse effect of pacing on RV function may also be more significant in an already enlarged right ventricle because of increased RV desynchronization following CRT.[21]

After 6 months of CRT, mean RV size increased and RV function slightly decreased in patients with relatively preserved baseline RV function. The increase in RV volume may represent a mild RV dysfunction induced by RV pacing. Conversely, RV function parameters tended to improve in patients with RV dysfunction, which may indicate a chronic reduction in RV afterload following resynchronization that is not represented by our acute simulations.[22] Consequently, RV function following CRT in the long term is likely to be a balance between induced myocardial dysfunction and reduced afterload.

Why Does RV Dysfunction Complicate Response Prediction? The dyssynchrony parameters we studied were not associated with reverse remodeling within the RV dysfunction subgroup. RV dysfunction can affect the association between CRT response and mechanical dyssynchrony parameters through two potential mechanisms, as found by the computer simulations. First, RV

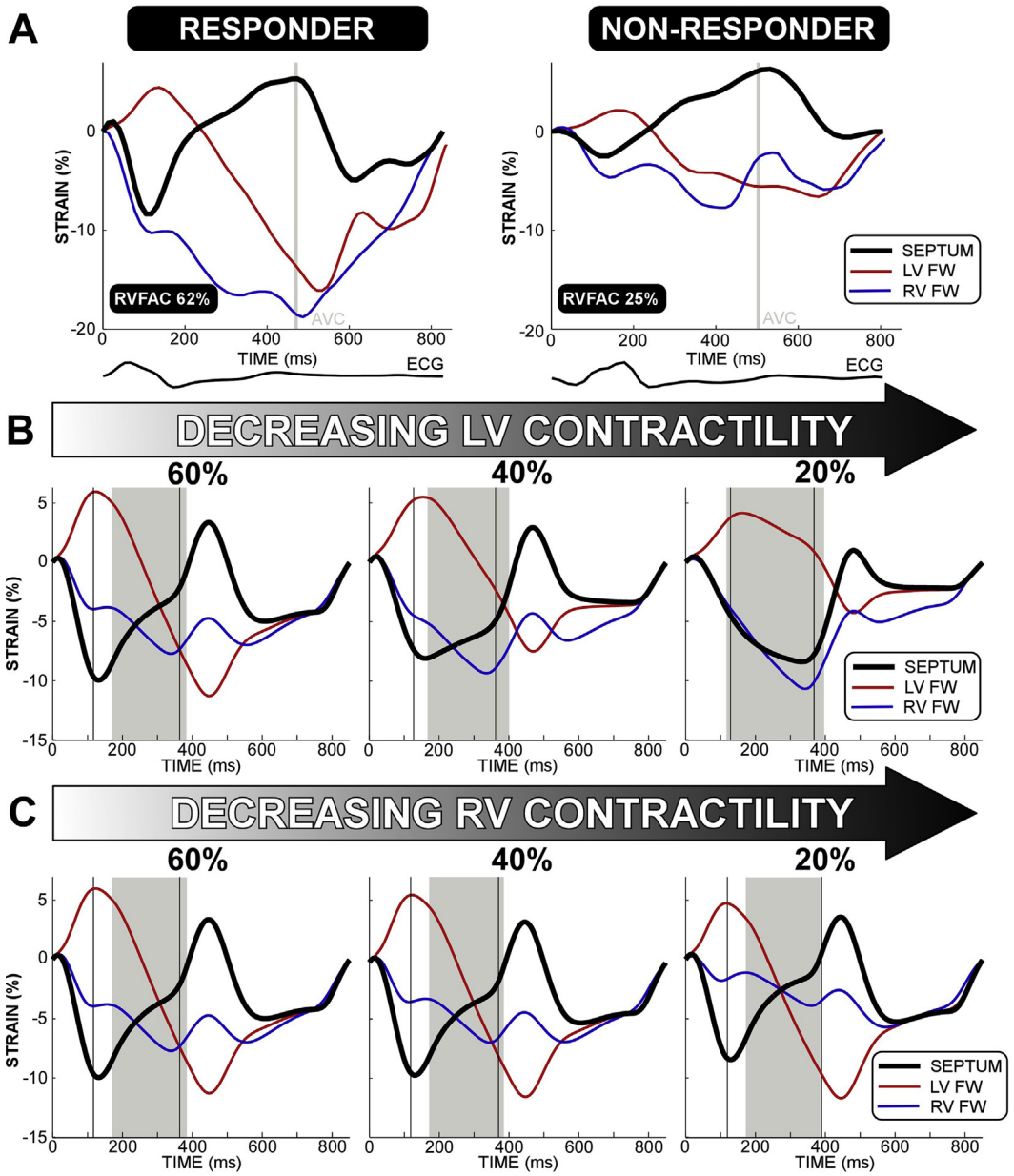


Figure 3 Effects of LV and RV contractility on strain patterns. **(A)** Septal (*black line*), LV free wall (*red line*), and RV free wall (*blue line*) strain patterns from a CRT responder (*left*) and a nonresponder (*right*) with RV dysfunction. Responder: RVFAC 72.4%, SRSsept 13.8%, LVEF 14%, ΔLVESV −55.6%; nonresponder: RVFAC 24.6%, SRSsept 8.6%, LVEF 12%, ΔLVESV 7.5%. **(B,C)** Septal (*black lines*), LV (*dashed lines*), and RV (*dotted lines*) strain patterns from virtual patients with reduced LV **(B)** or RV **(C)** contractility. The corresponding LV or RV contractility for each virtual patient is shown above the strain pattern. Septal strain patterns were sensitive to decreases in LV but not RV contractility. *Arrows* denote direction of decreasing contractility. *AVC*, Aortic valve cosure; *FW*, free wall.

failure can be aggravated by severely reduced LV function through pulmonary congestion and increases in RV afterload. In this situation, both CRT response and mechanical dyssynchrony parameters will be reduced despite an LV conduction delay, producing a correct prediction of reduced response. The declining response to CRT with reduced LV contractility despite a constant conduction delay emphasizes the importance of LV mechanics for determining CRT response.[17,23,24] However, in cases in which RV myocardial function is compromised, CRT response may be reduced in a manner that is not reflected by the mechanical dyssynchrony parameters we tested. Second, severely reduced RVFAC in CRT candidates is a marker of both severe RV and LV dysfunction. Accordingly, we observed lower values of SRSsept in the patients with RV dysfunction, reflecting the associated reduction in LV function in these patients. The higher prevalence of type III deformation patterns in this subgroup supports this relationship as this pattern indicates reduced LV contractility because of weakness of the lateral wall preventing septal stretch from occurring during systole (Figure 3B).[17,25] We did not observe a reduction in the other dyssynchrony parameters, emphasizing the ability of SRSsept to reflect LV contractility. The association of SRSsept with CRT response was comparable with earlier studies[15,17] and strongest in patients without RV dysfunction. However, because CRT response is multifactorial and influenced by, for example, implantation technique, therapy delivery, etiology of heart failure,

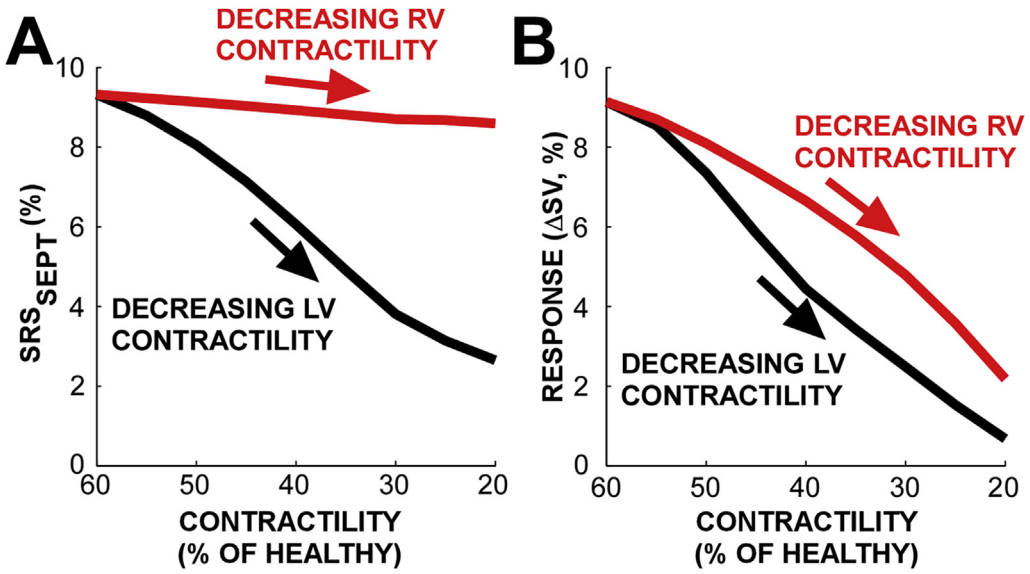


Figure 4 Effects of LV and RV contractility on mechanical dyssynchrony parameters in all virtual patients. **(A)** SRSsept decreased in the virtual patients with decreased LV contractility (*black line*) but not in the virtual patients with decreased RV contractility (*red line*). **(B)** Both the virtual patients with decreased LV (*black line*) and RV (*red line*) contractility had a decreased response to CRT. A mismatch can be observed between SRSsept and CRT response in virtual patients whose RV contractility is low (*red lines*). *SV*, Stroke volume.

and comorbidities, a considerable amount of scatter is still visible in the association between SRSsept and LVESV reduction (Figure 2). Simulations suggest that the fact that all dyssynchrony parameters lost their association with CRT response in patients with RV dysfunction reflects the inadequate representation of reduced RV contractility by these parameters. Therefore, the association with response was improved by adding a parameter influenced by RV contractility (i.e., RVFAC). Because the effects of RV function on CRT outcomes are likely to be more prominent in patients with relatively preserved LV function, adding information on LV function also improved the association with response, but to a lesser extent.

Clinical Implications

Our results indicate that RV function should be routinely quantified in all patients before CRT. If baseline RV function is reduced (RVFAC < 35%), less LV remodeling should be expected after CRT. If RV function is significantly reduced, prediction of CRT response by the mechanical dyssynchrony parameters evaluated in this study should be interpreted cautiously. Although patients with RV dysfunction can benefit from CRT,[5] our simulations suggest that the idea of refraining from CRT in some patients with severely impaired RV contractility merits further investigation. The study was underpowered to define a specific threshold for RV dysfunction to predict CRT response, and further clinical studies are needed to address this issue prospectively. As RV dysfunction is present in a considerable number of CRT candidates, our findings also clarify some of the difficulties of incorporation of mechanical dyssynchrony measurements into daily clinical practice. Our findings should lead to more effective implementation of dyssynchrony parameters. Further research on the underlying mechanisms should improve understanding and implementation of existing parameters.

Limitations

We used only longitudinal strain, as of three myocardial strain directions (i.e., circumferential, radial, and longitudinal), it is the only suitable direction for assessment of RV function. Moreover, longitudinal strain has been standardized recently and is therefore most reproducible.[26] Although a segment-based approach might incorporate additional information, the present approach of global wall strain was chosen because it provides a more robust measurement and introduces less noise in the analyses.[27] The choice of RVFAC as the clinical parameter to reflect RV function was beneficial, because it had the strongest association with LV remodeling (Table 3). However, echocardiographic measurement of RV function is complicated, and it is unclear which parameter best reflects RV function in the presence of dyssynchrony. Dyssynchrony might influence functional parameters such as tricuspid annular plane systolic excursion and to a lesser extent RVFAC and RV strain, as apical rocking due to dyssynchronous LV contraction may also influence RV displacement. Our patient and simulated strain data (Figure 3) are consistent with this hypothesis, as both demonstrate abnormal RV free wall strain patterns in dyssynchronous hearts. The present study was also an exploratory study, and numbers were too small to perform subanalyses to identify factors that determine response in patients with RV dysfunction. Multivariate analysis was limited to a subset of the best-performing parameters because of the population size. The study was underpowered to investigate the effect of smaller subgroups, such as the presence of atrial fibrillation. The findings should therefore be confirmed in larger prospective studies.

Computer simulations were performed with global contractility reduction in either the right or left ventricle. Regional variations in myocardial properties that may arise because of scarring or regional ischemia were not considered.[18] Mitral regurgitation, which can exacerbate backward failure, was not included in the simulations. CRT response in the simulations was assessed by acute hemodynamic changes, as opposed to long-term structural remodeling, as was used in the patient population. Acute hemodynamic response does not capture all of the potential mechanisms through which CRT exerts its longer term benefits on cardiac structure, metabolism, and function.[28] Furthermore, patients with RV dysfunction had worse heart failure and more severe comorbidities than patients without RV

dysfunction. Consequently, we do not exclude the possibility that other factors than RV and/or LV myocardial function limit response in these patients. Because measuring intrinsic RV function remains challenging, our simulation results must be considered as hypothesis generating only.

CONCLUSIONS

Commonly used mechanical dyssynchrony parameters are not associated with volumetric response in CRT patients with RV dysfunction, because these parameters do not adequately reflect the impact of RV dysfunction on CRT response. RV function parameters should therefore be incorporated when predicting CRT response on the basis of mechanical dyssynchrony.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2017.06.004.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, DeLurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
3. Prinzen FW, Vernooy K, De Boeck BW, Delhaas T. Mechano-energetics of the asynchronous and resynchronized heart. Heart Fail Rev 2011;16:215-24.
4. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008;117:2608-16.
5. Damy T, Ghio S, Rigby AS, Hittinger L, Jacobs S, Leyva F, et al. Interplay between right ventricular function and cardiac resynchronization therapy: an analysis of the CARE-HF trial (Cardiac Resynchronization-Heart Failure). J Am Coll Cardiol 2013;61:2153-60.
6. Kjaergaard J, Ghio S, St John Sutton M, Hassager C. Tricuspid annular plane systolic excursion and response to cardiac resynchronization therapy: results from the REVERSE trial. J Card Fail 2011;17:100-7.
7. Tabereaux PB, Doppalapudi H, Kay GN, McElderry HT, Plumb VJ, Epstein AE. Limited response to cardiac resynchronization therapy in patients with concomitant right ventricular dysfunction. J Cardiovasc Electrophysiol 2010;21:431-5.
8. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143-53.
9. de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloux G, et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol 1998;32:948-54.
10. Lumens J, Arts T, Broers B, Boomars KA, van Paassen P, Prinzen FW, et al. Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: a computer simulation analysis. Am J Physiol Heart Circ Physiol 2009;297:H2196-205.
11. Lumens J, Ploux S, Strik M, Gorcsan J 3rd, Cochet H, Derval N, et al. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure: electrical resynchronization versus left-right ventricular interaction. J Am Coll Cardiol 2013;62:2395-403.
12. Walmsley J, Arts T, Derval N, Bordachar P, Cochet H, Ploux S, et al. Fast simulation of mechanical heterogeneity in the electrically asynchronous heart using the MultiPatch module. PLoS Comput Biol 2015;11:e1004284.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.
14. Sharma A, Bax JJ, Vallakati A, Goel S, Lavie CJ, Kassotis J, et al. Meta-analysis of the relation of baseline right ventricular function to response to cardiac resynchronization therapy. Am J Cardiol 2016;117:1315-21.
15. De Boeck BW, Teske AJ, Meine M, Leenders GE, Cramer MJ, Prinzen FW, et al. Septal rebound stretch reflects the functional substrate to cardiac resynchronization therapy and predicts volumetric and neurohormonal response. Eur J Heart Fail 2009;11:863-71.
16. Leenders GE, De Boeck BW, Teske AJ, Meine M, Bogaard MD, Prinzen FW, et al. Septal rebound stretch is a strong predictor of outcome after cardiac resynchronization therapy. J Card Fail 2012;18:404-12.
17. Leenders GE, Lumens J, Cramer MJ, De Boeck BW, Doevendans PA, Delhaas T, et al. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: analysis of patient data using a computer model. Circ Heart Fail 2012;5:87-96.
18. Lumens J, Tayal B, Walmsley J, Delgado-Montero A, Huntjens PR, Schwartzman D, et al. Differentiating electromechanical from non-electrical substrates of mechanical discoordination to identify responders to cardiac resynchronization therapy. Circ Cardiovasc Imaging 2015;8:e003744.
19. Campbell P, Takeuchi M, Bourgoun M, Shah A, Foster E, Brown MW, et al. Right ventricular function, pulmonary pressure estimation, and clinical outcomes in cardiac resynchronization therapy. Circ Heart Fail 2013;6:435-42.
20. Vidal B, Delgado V, Mont L, Poyatos S, Silva E, Angeles Castel M, et al. Decreased likelihood of response to cardiac resynchronization in patients with severe heart failure. Eur J Heart Fail 2010;12:283-7.
21. Varma N, Jia P, Ramanathan C, Rudy Y. RV electrical activation in heart failure during right, left, and biventricular pacing. JACC Cardiovasc Imaging 2010;3:567-75.
22. Stolfo D, Tonet E, Merlo M, Barbati G, Gigli M, Pinamonti B, et al. Early right ventricular response to cardiac resynchronization therapy: impact on clinical outcomes. Eur J Heart Fail 2016;18:205-13.
23. Lumens J, Leenders GE, Cramer MJ, De Boeck BW, Doevendans PA, Prinzen FW, et al. Mechanistic evaluation of echocardiographic dyssynchrony indices: patient data combined with multiscale computer simulations. Circ Cardiovasc Imaging 2012;5:491-9.
24. Tayal B, Sogaard P, Delgado-Montero A, Goda A, Saba S, Risum N, et al. Interaction of left ventricular remodeling and regional dyssynchrony on long-term prognosis after cardiac resynchronization therapy. J Am Soc Echocardiogr 2017;30:244-50.
25. Marechaux S, Guiot A, Castel AL, Guyomar Y, Semichon M, Delelis F, et al. Relationship between two-dimensional speckle-tracking septal strain and response to cardiac resynchronization therapy in patients with left ventricular dysfunction and left bundle branch block: a prospective pilot study. J Am Soc Echocardiogr 2014;27:501-11.
26. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28:1171-81.
27. Lumens J, Prinzen FW, Delhaas T. Longitudinal strain: "think globally, track locally". JACC Cardiovasc Imaging 2015;8:1360-3.
28. Prinzen FW, Auricchio A. The "missing" link between acute hemodynamic effect and clinical response. J Cardiovasc Transl Res 2012;5:188-95.

SUPPLEMENTAL METHODS

Healthy Control Simulation

In this study, we used the CircAdapt contraction model from Leenders *et al.*,[1] with the addition of the ability to subdivide the ventricular walls into patches as described by Walmsley *et al.*[2] All of our simulations began from a baseline healthy situation with no reduction in contractility or conduction delay. This healthy situation was arrived at through the adaptation of size, mass, and passive tissue stiffness of the vascular and cardiac walls. The adaptation process normalizes the local mechanical load on cardiac and vascular tissue to tissue-specific physiologic levels.[3,4] In normal, healthy physiology, the cardiovascular system is not operating at its maximum capacity during rest but instead remodels in response to load under challenges such as exercise. Adaptation is therefore performed in a state of moderate exercise. We assumed a resting heart rate of 71 beats/min. At rest, a cardiac output of 5.1 L/min and mean arterial pressure were maintained at 92 mm Hg through alterations in systemic vascular resistance and circulating blood volume. During the adaptation process, moderate exercise was simulated by tripling the cardiac output and doubling the heart rate, with mean arterial pressure maintained at 92 mm Hg. The methodology used for adaptation of tissue is described in detail by Arts *et al.*[4] No further tissue adaptation was performed during the heart failure simulations. Only hemodynamic changes due to homeostatic control at rest to maintain cardiac output and mean arterial pressure are shown in those simulations.

Simulation Code

The version of the CircAdapt model presented by Walmsley *et al.*[2] is freely available to download from www.circadapt.org. To reproduce the results in this study using the downloadable version, you will need to change the following lines in the file SarcEf2Sf.m before adaptation in order to use the contraction model from Leenders *et al.*[1]:

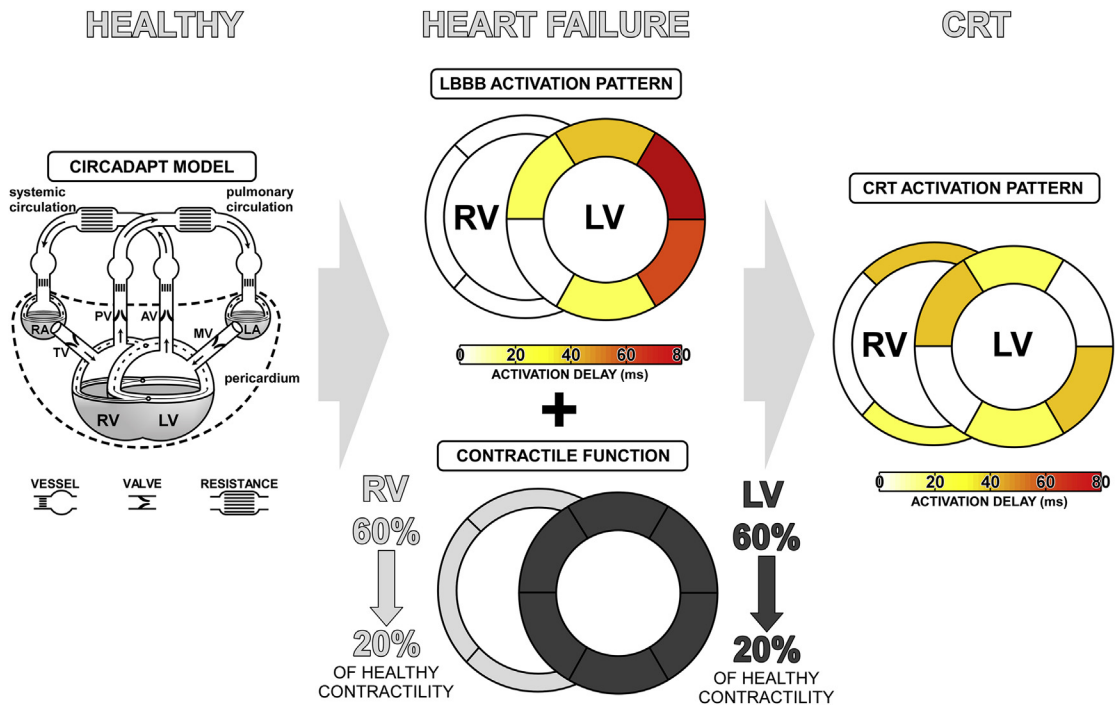
Line 36: $tA = (0.74 + 0.3 \times L) \times \text{TimeAct}$;
Line 37: $tR = 0.45 \times TR \times \text{TimeAct}$;
Line 38: $tD = 0.3 \times TD \times \text{TimeAct}$;

The parameter tA represents the duration of myocardial contraction in the CircAdapt model. This line determines the dependence of this duration on the extension of the sarcomeres.

tR is a time constant that scales the time taken for a ventricular segment to reach maximum activation.

tD is a time constant that scales the time taken for a ventricular segment to relax from maximum activation.

In the file PRef.mat, the parameter SfAct should be changed from 100 kPa to 120 kPa in the ventricular wall segments only (see the field P.Patch.SfAct). The parameter SfAct represents the contractility referred to in the main article and Supplemental Figure 1. Further description of the sarcomere model in CircAdapt can be found in Walmsley *et al.*[2] and the accompanying supplemental material.



Supplemental Figure 1 Background information on the CircAdapt simulations. Overview of the CircAdapt model (HEALTHY), consisting of the systemic and pulmonary circulations, mechanically interacting ventricles, atria, and the cardiac valves. The activation pattern and global contractility patterns used for the virtual patients (HEART FAILURE) are shown in the *middle*. The LV and RV cavities were also dilated by 10% to represent eccentric remodeling. The ventricular activation pattern used when simulating CRT is shown on the *right*. *AV*, Aortic valve; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *PV*, pulmonary valve; *RA*, right atrium; *RV*, right ventricle; *TV*, tricuspid valve. The *left-hand panel* is modified from Lumens J, Delhaas T, Kirn B, Arts T. Three-wall segment (TriSeg) model describing mechanics and hemodynamics of ventricular interaction. Ann Biomed Eng 2009;37:2234–2255.

SUPPLEMENTAL REFERENCES

1. Leenders GE, Lumens J, Cramer MJ, De Boeck BW, Doevendans PA, Delhaas T, et al. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: analysis of patient data using a computer model. Circ Heart Fail 2012;5:87-96.
2. Walmsley J, Arts T, Derval N, Bordachar P, Cochet H, Ploux S, et al. Fast simulation of mechanical heterogeneity in the electrically asynchronous heart using the MultiPatch module. PLoS Comput Biol 2015;11:e1004284.
3. Arts T, Delhaas T, Bovendeerd P, Verbeek X, Prinzen FW. Adaptation to mechanical load determines shape and properties of heart and circulation: the CircAdapt model. Am J Physiol Heart Circ Physiol 2005;288:H1943-54.
4. Arts T, Lumens J, Kroon W, Delhaas T. Control of whole heart geometry by intramyocardial mechano-feedback: a model study. PLoS Comput Biol 2012;8:e1002369.