The Influence of Right Ventricular Afterload in Cardiac Resynchronization Therapy: A CircAdapt Study

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Abstract

The individual response to cardiac resynchronization therapy (CRT) remains difficult to predict, and some research has focused on right ventricle (RV) dysfunction parameters in an effort to shed light on this problem. In a recent clinical study, researchers investigated the interaction of the RV with the pulmonary system. In this article, we analyze this issue by performing a computer simulation with the established CircAdapt model. Our results indicate that RV afterload at baseline is highly correlated with positive acute CRT response in terms of positive stroke volume (SV) and RV ejection fraction (EF) change.

1. Introduction

CRT is a widely accepted and successful treatment for heart failure (HF) occurring in combination with electrical conduction delay, i.e. left bundle branch block (LBBB). Large clinical studies have shown that CRT improves left venctricular (LV) function and affects long-term survival. However, the response of any given individual to CRT response is difficult to predict for reasons that are not completely understood. Analysis of RV fractional area change (FAC) and tricuspid annular plane excursion have shown that right ventricle (RV) function is an important predictor of echocardiographic and clinical outcomes following CRT. Studies of the relationship of these non-invasive parameters to CRT response have yielded conflicting results, however [1]. To clarify this issue, a recent study [2] of invasive criteria measured RV pressure volume (PV) loops and concluded that RV-pulmonary arterial coupling ratio - specifically, RV afterload - can indeed predict a given individual's response to CRT.

Several studies have elaborated the acute CRT response due to various conditions via the multipatch module of CircAdapt [3,4], a well-established tool that allows rapid simulation of the heart and circulatory system [5,6]. Recently, CircAdapt was also used in this context to test both mechanical dyssynchrony and RV contractility [7]. In this article, we also use CirAdapt to examine in silico the results of the aforementioned study. We first simulate RV afterload variations in terms of pulmonary hypertension (PH), increased arterial stiffness, and dilated cardiomyopathy (DCM) - all based on an HF setting. Then, we conduct a specific simulation for two representative patients. In both cases, we evaluate the acute CRT response.

2. Methods

2.1. Patient data

Magdeburger cardiologists included 111 patients with standard CRT indications in their study. Data collection was performed via echocardiography, as well as left- and right-heart catheterization including RV conductance catheterization (PV loop measurement). Table 2.1 gives an extract of mean patient data (response defined as LV end systolic volume (LVESV) remodeling $\geq 15\%$ after six months). See [2] for further details.

	Responder	Non-responder
LV EF (%)	33	29
LV EDP (mmHg)	19	24
LV ESP (mmHg)	131	123
RV EF (%)	47	39
RV EDP (mmHg)	7	9
RV ESP (mmHg)	27	42
CO (l)	4.8	4.3
Ea (mmHg/ml)	0.38	0.62
Ees (mmHg/ml)	0.35	0.34
PA-C (ml/mmHg)	3.3	2.1
PVR (dyn)	137	195

Table 1. Study data, with end-diastolic pressure (EDP), end-systolic pressure (ESP), cardiac output (CO), arterial elastance (Ea), end-systolic elastance (Ees), pulmonary artery compliance (PA-C), pulmonary vascular resistance (PVR).

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2.2. CircAdapt and simulation of HF with CRT

The CircAdapt model consists of several modules that permit realistic simulation of cardiovascular mechanics and hemodynamics. It features 29 ordinary differential equations, and thus justifies the label 'phenomological'. For brevity's sake, we skip the details and refer the interested reader instead to [3,4]. Using the already established algorithm, we simulated HF with LBBB for our mean responder patient. Using a reference simulation, we incorporated a heart rate of 71 beats/min and adjusted blood volume and mean aortic pressure to meet both CO as well as LV and RV volume data. As in [6], we applied adaptation protocols before inducing HF. This involved decreasing contractility and dividing the ventricles into patches with LBBB-like atrioventricular (220 ms) and intraventricular (135ms) activation delays. We then varied the RV afterload by means of three simulations - pulmonary artery stiffness, DCM, and PH. We also examined increased and decreased contractility. For the contractility and DCM simulations, we changed the right ventricular parameters $A_{\mathrm{m,Ref}}$, $\sigma_{\mathrm{f,Act}}$. Similarly, we adjusted the nonlinear stiffness exponent k and PH parameter $p_{0\mathrm{AV}}$ to meet different pressure conditions. This resulted in a total of about 80 combinations, for each of which we applied a homoestatic pressure-flow regulation algorithm [5] before performing the CRT ventricular activation pattern from [6]. The acute CRT response was observed by running 20 heart cycles without pressure-flow adaptation. To consider RV afterload independently of other factors, LV dysfunction was kept constant for all simulations.

2.3. Afterload evaluation

For brevity we skip units in this section. The wave impedance $\mathrm{R_{wave}}$ and the cross-sectional compliance at the arterial entrance C_{art} were deduced in [8] as a priori model parameters:

$$\mathrm{R_{wave}} = \sqrt{\frac{\rho(k/3-1)p_{\mathrm{art}}}{A_c(A_c+0.5\cdot A_w)}}, \qquad C_{\mathrm{art}} = \frac{L_c(A_c+0.5\cdot A_w)}{(k/3-1)p_{\mathrm{art}}},$$

where ρ is the blood density, p_{art} is the PA pressure, and A_c and A_w are the cross-sectional pulmonary cavity and wall area, respectively. A posteriori, we decided to rely on clinical driven afterload criteria: mean PA pressure PAP_{mean}, together with

$$\mathrm{TPG} = \mathrm{mean}(p_{\mathrm{art}} - p_{\mathrm{LA}}), \qquad \mathrm{Puls} = \frac{\max A_c - \min A_c}{\min A_c/100},$$

$$\mathrm{PVR} = \frac{80\cdot TPG}{CO}, \qquad \text{PA-C} = \frac{SV}{\max p_{\mathrm{art}} - \min p_{\mathrm{art}}},$$

$$E_a = \frac{ESP}{SV}, \qquad \mathrm{Cap} = \frac{\max A_c - \min A_c}{\max p_{\mathrm{art}} - \min p_{\mathrm{art}}},$$

where Puls denotes the pulsatility, Cap is the capacitance, and TPG is the transpulmonary gradient. In this study, we calculated ESP as peak ventricular pressure divided by volume.

2.4. Patient specification

We performed a global sensitivity analysis to identify sensitive right ventricular volume parameters. On the basis of the obtained insights, we were able to manually adapt the parameters $A_{m,ref}$, V_{Wall}, TR, $\sigma_{\mathrm{f,Act}}$, $p_{0\mathrm{AV}}$, and k in order to represent the patient's PV loop data. We selected a typical patient with a triangle-shaped RV-PV loop and another patient with a reverse triangle curved RV-PV loop. Triangle-shaped loops indicate low afterload and, therefore, a high likelihood of CRT response; reverse triangular curved loops imply the opposite. The previously-described CRT algorithm was then performed for both cases.

3. Results

After electrical synchronization is induced, an immediate improvement in SV and RV EF generally appears in the simulated heart. The relationship between the change in RV afterload and the change in SV and RV EF is illustrated in fig. 1. PH and artery stiffness strongly correlate (negatively) with both criteria. Elevated DCM shows also a negative effect on CRT response, but not as intense as the others. The response behavior to varied contractility, which appears even with a nonlinear correlation to SV and RV EF, is also depicted for comparison purposes. Altogether, ΔSV is between -10.8% and 8.4%, while ΔRV EF is between -11.2% and 10.3%. For all four parameter groups, the trend of SV change is in line with the trend of RV EF.

Table 2 summarizes computed Pearson correlation coefficients for the introduced afterload criteria at baseline to Δ SV and Δ RV EF. The strongest (negative) correlation appears for E_a, which confirms the results in [2]. The a priori indicators $\mathrm{R_{wave}}$, and C_{art} predict slight CRT changes. Changes of afterload criteria from pre- to post-CRT are also analyzed with respect to ΔSV and ΔRV EF. Interestingly, PAP_{mean} and TPG correlate positively with both ΔSV and ΔRV EF. The effect of increasing PAP_{mean}, however, is insignificant compared to the effect of increasing SV, as indicated by the strong association of ΔE_a and ΔPVR to ΔSV.

Figure 2, illustrates simulated patient specific PV loops. Their simulated CRT reaction is shown in table 3, where patient "triangular" outperforms patient "reverse triangular".

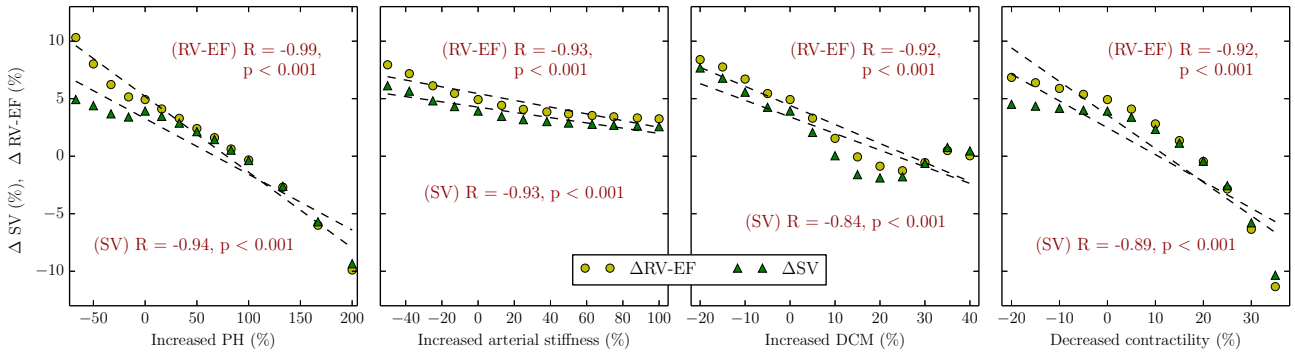

Figure 1. Acute CRT response in relation to RV afterload and contractility parameter variation.

	R_{wave}	C_{art}	PAP_{mean}	E_a	ESP	PVR	PA-C	TPG	Puls	Cap
R of Δ SV to baseline AC	-0.01	0.27	-0.77	-0.82	-0.81	-0.73	0.31	-0.72	0.52	0.26
R of Δ SV to Δ AC	-0.46	-0.45	0.9	-0.97	0.49	-0.88	0.67	0.82	-0.21	0.61
R of Δ RV-EF to baseline AC	-0.03	0.28	-0.84	-0.89	-0.89	-0.78	0.34	-0.78	0.54	0.27
R of Δ RV-EF to Δ AC	-0.47	-0.5	0.94	-0.95	0.43	-0.92	0.81	0.7	-0.42	0.71

Table 2. Pearson correlation coefficients of SV and RV-EF CRT change to baseline afterload criteria (AC) and CRT changes of afterload criteria, respectively.

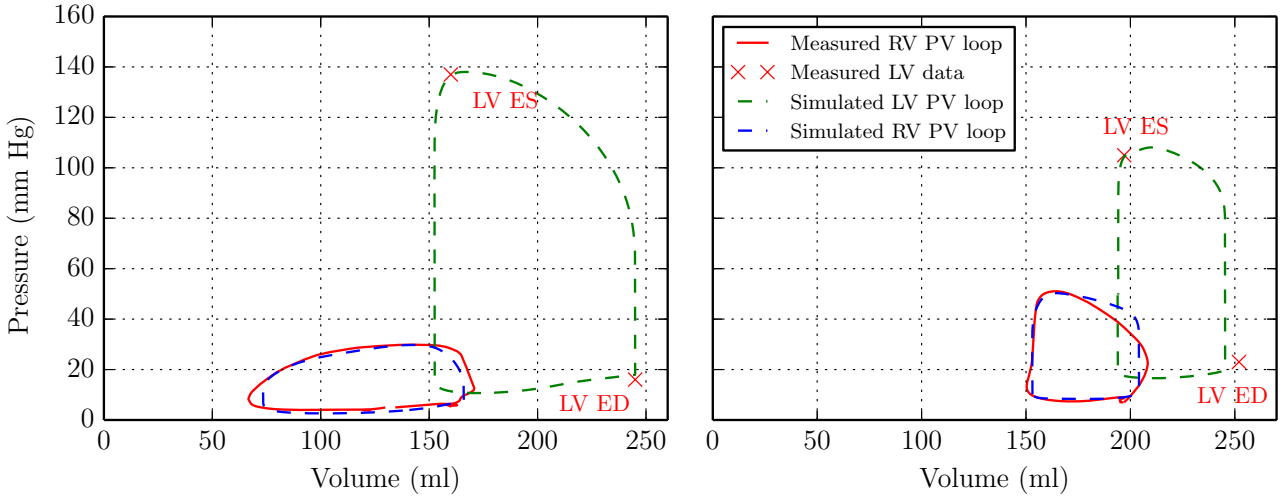

Figure 2. Simulated baseline PV loops, patient with triangular loop (left) and reversed shaped patient (on the right).

	Baseline data						**Simulated CRT**	
	LV-EF	RV-EF	SV	RV ESP	PVR	PA-C	Δ SV	Δ RV-EF
Patient T	35 %	48 %	86 ml	22 mmHg	163 dyn	4.04 ml/mmHg	8.2 %	10.8 %
Patient RT	22 %	27 %	55 ml	57 mmHg	201 dyn	1.15 ml/mmHg	5.2 %	7.2 %

Table 3. Simulated CRT response with baseline data of triangular (T) and reverse triangular (RT) patient.

4. Discussion

The results of this computational study indicate that RV afterload correlates negatively with CRT response. While studies so far [7] focussed on RV function by analyzing contractility, we demonstrate an examination of PH, arterial stiffness and added DCM in the HF-LBBB setting. In

[7], septal systolic rebound stretch as mechanical dyssynchrony parameter and RV FAC as function parameter were used to elaborate associations with acute CRT response. Our study neglects mechanical dyssynchrony parameters, but deals with clinical parameters and includes also other influences apart from contractility.

Schmeisser et al. [2] identified afterload in terms of E_a as main contributing factor to RV PA coupling ratio, so that our in silico analysis is justified. As a first case study, we see afterload as influencing factor - independent of its cause. We evaluated the acute response in terms of SV change, as experienced in clinical practice. Stolfo et al. [9] found acute RV FAC changes to be a predictor of LVESV long-term remodelling in CRT. In our study, we used RV EF as correlate for RV FAC to interpret acute CRT response in CircAdapt. ΔRV EF appeared to be in accordance with ΔSV and affirms therefore the hypothesis of negative correlation of RV afterload and CRT success. We conjecture that high RV afterload hinders an increase of SV and therefore also LV remodeling.

5. Limitations

In this computational study, we have included only a limited number of the factors affecting RV afterload. The heart, with its two circulatory systems, is very interactive and, for this reason, features such as LV dysfunction have been neglected. The authors in [2]] conjectured that, in many cases, weak LVs were the main cause for low RV pulmonary artery coupling values. Hence, increased RV afterload appeared as secondary effect. Non-responders in the clinical study had larger right ventricles and higher LV dysfunction at baseline. We incorporated this only indirectly into our simulations.

As a phenomenological model, CircAdapt is highly simplified and features only acute CRT response, without capturing the crucial remodeling process. We induced afterload changes solely by means of pressure-flow regulation and did not adapt the system to altered load. Finally, the Pearson correlation coefficient as a statistical tool supports only a very rough and linear notion of relations.

6. Conclusion

Computer simulations indicate that RV PV loops (particularly RV afterload) should be carefully considered in making CRT decisions. Future research might focus on a more sophisticated analysis of RV pulmonary-artery coupling factors and causes in LBBB-HF patients.

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