Efficacy of cardiac resynchronization in acutely infarcted canine hearts with electromechanical dyssynchrony

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BACKGROUND Patients with acute myocardial infarction (MI), left bundle branch block (LBBB), and marked left ventricular (LV) decompensation suffer from nearly 50% early mortality. Whether cardiac resynchronization therapy (CRT) improves hemodynamic status in this condition is unknown. We tested CRT in this setting by using a canine model of delayed lateral wall (LW) activation combined with 2 hours of coronary artery occlusion-reperfusion.

OBJECTIVE This study aimed to evaluate the acute hemodynamic effects of CRT during and immediately after MI.

METHODS Adult dogs (n = 8) underwent open-chest 2-hour mid-left anterior descending artery occlusion followed by 1-hour reperfusion. Four pacing modes were compared: right atrial pacing, pseudo-left bundle block (right ventricular pacing), and CRT with the LV lead positioned at either the LW (LW-CRT) or the peri-infarct zone (peri-infarct zone-CRT). Continuous LV pressure-volume data, regional segment length, and proximal left anterior descending flow rates were recorded.

RESULTS At baseline, both right ventricular pacing and peri-infarct zone CRT reduced anterior wall regional work by ~50% (vs right atrial pacing). During coronary occlusion, this territory became dyskinetic, and dyskinesis rose further with both CRT modes as compared to pseudo-LBBB. Global cardiac output, stroke work, and ejection fraction all still improved by 11%–23%. After reperfusion, both CRT modes elevated infarct zone regional work and blood flow by ~10% as compared to pseudo-LBBB, as well as improved global function.

CONCLUSION CRT improves global chamber systolic function in left ventricles with delayed LW activation during and after sustained coronary occlusion. It does so while modestly augmenting infarct zone dyskinesis during occlusion and improving regional function and blood flow after reperfusion. These findings support CRT in the setting of early post-MI dyssynchronous heart failure.

KEYWORDS Myocardial infarction; Acute heart failure; Cardiac resynchronization therapy

ABBREVIATIONS **CRT** = cardiac resynchronization therapy; **CS** = cardiogenic shock; **IV** = intravenous; **LAD** = left anterior descending; **LBBB** = left bundle branch block; **LV** = left ventricle/ventricular; **LVEF** = left ventricular ejection fraction; **LW** = lateral wall; **MAP** = mean arterial pressure; **MI** = myocardial infarction; **PIZ** = peri-infarct zone; **RA** = right atrial; **RV** = right ventricle/ventricular

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Introduction

Cardiac resynchronization therapy (CRT) acutely improves hemodynamic status in patients with a low left ventricular ejection fraction (LVEF <40%) and left bundle branch block (LBBB; QRS duration >120 ms).[1,2] However, those who present with acute myocardial infarction (MI) in conjunction with decompensated heart failure are not generally considered for this intervention, as the safety and efficacy of CRT in the immediate post-infarct period remain unknown. Although recently updated appropriate use criteria[3] rated CRT as "may be appropriate" for patients with an LVEF ≤35% from any cause, concurrent use of at least 1 intravenous (IV) inotropic agents, and any QRS prolongation, the acute MI-cardiac failure condition is rarely targeted.[4,5]

At present, only 40%–50% of the patients suffering from both acute MI and cardiogenic shock (CS) survive to hospital discharge.[6–8] Many of these individuals also have or develop LBBB, and if CRT is effective as an urgent means of improving systemic hemodynamics beyond standard treatment (ie, intra-aortic balloon pump and IV inotropic agents), it might improve survival. Ideally, this would lead to either medically managed recovery or definitive cardiovascular therapy, including coronary artery bypass surgery, left ventricular (LV) assist device, or permanent biventricular pacemaker implantation. CRT might provide an added

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advantage in the post-MI ventricle as it can modestly decrease overall myocardial oxygen requirements while augmenting systolic function.[9,10] Support for this was provided in a safety-feasibility study of 15 patients with CS and LBBB, about half of whom had ischemic disease, 3 with acute infarction. In their report, Eitel et al[11] found some benefit from temporary LV pacing with atrioventricular synchrony, with improved mean arterial pressure (MAP), although 2 of 3 patients with acute MI were identified as nonresponders. Svendsen et al[12] studied canine hearts with proximal coronary perfusion that was lowered by 50%–80% to induce regional ischemia and found that this often prevented CRT efficacy. Thus, the role of CRT in the acute ischemia/MI setting remains unclear and, importantly, lacks mechanistic analysis.

From a theoretical standpoint, one can predict effects of CRT on LV function in hearts with acute anterior MI and LBBB that go in either direction. If the anterior wall cannot generate systolic force regardless of when it is activated, that is, is purely passive and dyskinetic,[13] early stimulation of an otherwise late activated lateral wall (LW) would expose the infarct zone to systolic forces sooner, but not likely enhance overall function. In fact, some have suggested that pacing the peri-infarct zone (PIZ) itself, essentially inducing LBBB, could be therapeutic by reducing anterior wall loading and flow requirements.[14,15] However, it is also possible that inefficient global function associated with LBBB would offset these concerns, particularly if the ischemic region was stiffened and/or rendered hypokinetic after reperfusion therapy.[13] In this instance, CRT could improve workload and blood flow in the anterior region.[16]

Given the high risks of any therapy in this critically ill population, we explored the impact and mechanisms for CRT efficacy in an acute animal model. CRT has previously been shown to benefit animals with LBBB and stable (4 weeks) MI,[17] but its impact in the more immediate infarction and post-reperfusion period has not been reported. Here, we show CRT improves chamber systolic function both during coronary occlusion and after reperfusion in hearts with late lateral activation–induced dyssynchrony. This occurs despite CRT amplification of dyskinesis in the infarct zone during occlusion and regional work and blood flow in this region after reperfusion.

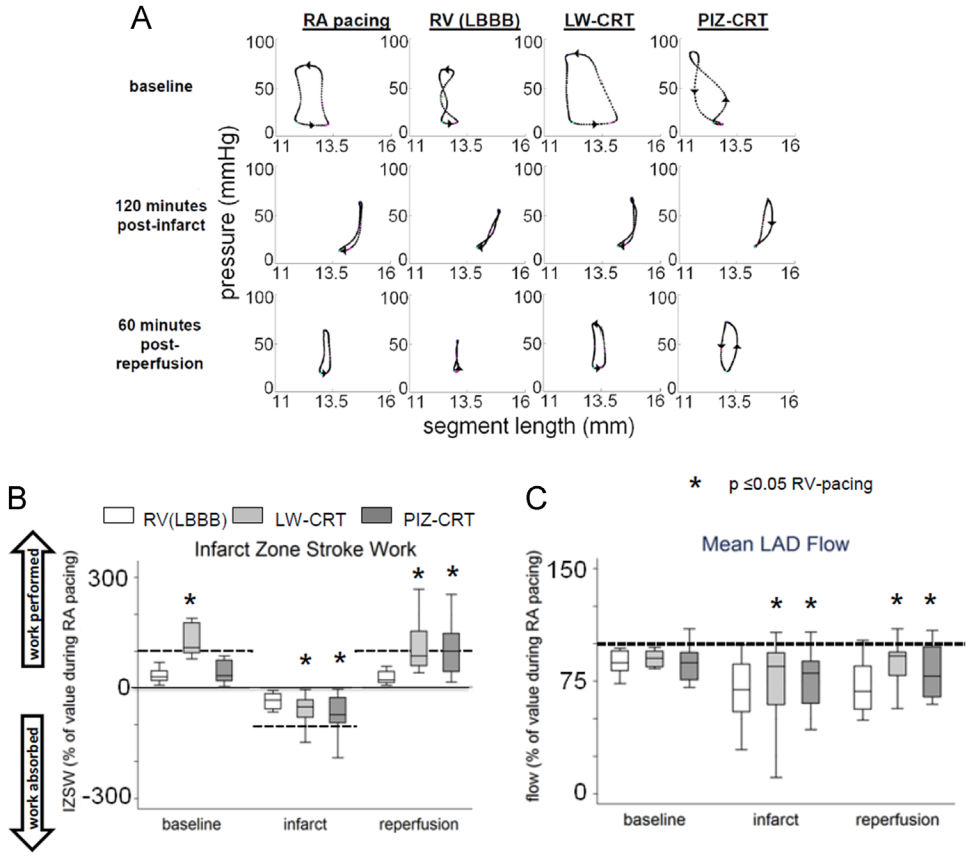

Figure 1 Effect of CRT on regional stroke work and mean LAD flow in the infarction zone. **A:** Example regional pressure-length loops from a single animal are shown (top) using data from sonomicrometer crystals embedded within the distal anterior wall. During ischemia, loops lean leftward (denoting dyskinesis) and encompass a small area, demonstrating loss of regional stroke work. **B:** Group data normalized to RA pacing (dashed line) and displayed as box plots at each time point. At baseline, RV and PIZ-CRT reduced regional work, whereas this was maintained with LW-CRT. During the ischemic period, both forms of CRT increased dyskinesis as compared with RV pacing. After reperfusion, both LW-CRT and PIZ-CRT increased infarct zone stroke work significantly compared to RV pacing. On the y-axis, values greater than zero indicate that work was performed while negative values indicate that work was absorbed (ie, dyskinetic work loss). **C:** Both forms of CRT were associated with significantly increased mean LAD flow as compared to RV pacing during ischemia and after reperfusion. CRT = cardiac resynchronization therapy; IZSW = infarct zone stroke work; LAD = left anterior descending; LBBB = left bundle branch block; LW = lateral wall; PIZ = peri-infarct zone; RA = right atrial; RV = right ventricular.

Methods

The protocol was approved by the Johns Hopkins University Animal Care and Use Committee. Adult mongrel dogs (n = 8) were sedated with propofol (2–8 mg/kg IV), intubated, maintained on isoflurane anesthesia (1%–2.5%), and mechanically ventilated. Anesthesia was monitored using heart rate, eye blink response, and jaw muscle tension. Dogs received a continuous lidocaine drip (100–150 μg/(kg · min) IV) during surgery, as well as 20–40 mg IV boluses as required to suppress ventricular ectopy or nonsustained tachycardia. The chest was opened via lateral thoracotomy and the heart placed in a pericardial cradle. Epicardial leads were attached to the right atrial (RA) appendage, right ventricular (RV) apex, LV-LW, and LV-PIZ. The left anterior descending (LAD) artery just distal to the second diagonal branch was transiently occluded to demarcate the PIZ for LV-PIZ lead placement. Mid-wall sonomicrometers (Sonometrics, London, ON, Canada) were implanted in the distal anterior wall and anterolateral free wall to assess regional motion in infarct and remote zones. A coronary flow probe (model MA-2.5PSB, Transonic Instruments Inc, Ithaca, NY) was placed around the proximal LAD to measure coronary blood flow to the anterior wall. The LV was instrumented with a pressure-volume catheter (model SPR-550, Millar Instruments, Inc, Houston, TX) advanced to the apex, a micromanometer catheter to the ascending aorta, and a balloon-tipped pulmonary artery thermodilution catheter. The instrumentation is shown in Online Supplemental Figure 1.

Experimental protocol

After the completion of instrumentation and stabilization, baseline data were recorded at each pacing mode in random order: (1) RA pacing (normal conduction); (2) RV pacing (pseudo-LBBB); (3) 2 minutes of RV pacing, followed by RV + LV-LW pacing (LW-CRT); and (4) 2 minutes of RV pacing, followed by RV + LV-PIZ pacing (PIZ-CRT). PIZ-CRT was included as prior studies[15,18] reported that wall stress is reduced at the site of the earliest activation (ie, near the pacing lead tip). Thus, PIZ-CRT might provide both CRT efficacy and reduction in load at the injured territory. RA pacing served as the default mode between the other measurements and allowed for heart rate to remain constant. Data were measured after 2 minutes at each final pacing mode to establish steady-state responses.[2] Once baseline data were obtained, the LAD artery was occluded just beyond the second diagonal and hemodynamic data were recorded continuously. Data at each pacing mode (order randomized) were obtained after 30, 60, and 120 minutes of coronary occlusion and then at 30 and 60

Table 1 Comparison of hemodynamic effects between RA or RV pacing to the other modes, and Baseline versus infarction and reperfusion data (all RA paced)

		Stroke work		Stroke volume		LVEF		Cardiac output		MAP	
Groups Compared		Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
RA pacing vs	RV	−35.5%	<0.001	−21%	<0.001	−13.9%	<0.001	−21%	<0.001	−21.8%	<0.001
	LW-CRT	−13.1%	<0.001	−8.4%	.016	−7.1%	.007	−8.4%	.016	−10.5%	<0.001
	PIZ-CRT	−12.1%	.001	−2.9%	.403	−1.1%	.683	−2.9%	.403	−10%	<0.001
RV pacing vs	LW-CRT	22.4%	<0.001	12.6%	<0.001	6.7%	.011	12.6%	<0.001	11.3%	<0.001
	PIZ-CRT	23.4%	<0.001	18.1%	<0.001	12.8%	<0.001	18.1%	<0.001	11.8%	<0.001
Baseline vs	inf+30	−1.8%	.677	1.5%	.714	−15.1%	<0.001	1.5%	.714	−5.6%	.015
	inf+60	−0.1%	.975	6.7%	.112	−17.5%	<0.001	6.7%	.112	−1.8%	.437
	inf+120	−18.9%	<0.001	−10.6%	.011	−24.6%	<0.001	−10.6%	.011	−1%	.655
	reperf+30	−29.7%	<0.001	−21.5%	<0.001	−35.3%	<0.001	−21.5%	<0.001	.5%	.853
	reperf+60	−26.9%	<0.001	−24.4%	<0.001	−35.7%	<0.001	−24.4%	<0.001	5.3%	.030

		dP/dt_{max}		dP/dt_{min}		tau		Infarct zone stroke work		Mean LAD flow	
Groups Compared		Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
RA pacing vs	RV	−27.2%	<0.001	−27.2%	<0.001	27.8%	<0.001	−2.9%	.786	−15.4%	<0.001
	LW-CRT	−9.3%	<0.001	−20.6%	<0.001	17.8%	<0.001	17.3%	.103	−9.6%	<0.001
	PIZ-CRT	−13.1%	<0.001	−20.6%	<0.001	17.5%	<0.001	−3.2%	.766	−11.9%	<0.001
RV pacing vs	LW-CRT	17.9%	<0.001	6.6%	.001	−10%	.034	20.2%	.057	5.7%	.034
	PIZ-CRT	14.1%	<0.001	6.7%	.001	−10.3%	.029	−0.28%	.979	3.4%	.204
Baseline vs	inf+30	−14.2%	<0.001	−14.2%	<0.001	19.9%	<0.001	−128.7%	<0.001	−56%	<0.001
	inf+60	−15.1%	<0.001	−15.7%	<0.001	22.3%	<0.001	−128.5%	<0.001	−51.8%	<0.001
	inf+120	−19.4%	<0.001	−22.2%	<0.001	34.6%	<0.001	−118.5%	<0.001	−55.1%	<0.001
	reperf+30	−23.4%	<0.001	−27.9%	<0.001	51.9%	<0.001	−19.4%	.141	−15.6%	<0.001
	reperf+60	−19%	<0.001	−24.2%	<0.001	47.3%	<0.001	−28.5%	.030	−13.6%	<0.001

Overall, RA pacing consistently performed best while RV pacing performed worst with respect to all measured dependent variables except for infarct zone stroke work. Both LW-CRT and PIZ-CRT significantly improved myocardial performance as compared to RV pacing.

CRT = cardiac resynchronization therapy; inf+X = duration of infarction (min); LAD = left anterior descending; LVEF = left ventricular ejection fraction; LW = lateral wall; MAP = mean arterial pressure; NS = not significant; PIZ = peri-infarct zone; RA = right atrial; reperf+X = duration of reperfusion (min); RV = right ventricular.

P values and coefficients are from multilevel, mixed effects linear regression models.

minutes after reperfusion. Dogs were then euthanized by injection of 50 mL of IV saturated KCl.

Data analysis

Data were analyzed using software developed in our laboratory (WinPVAN). The volume signal was calibrated to match cardiac output by thermodilution. Absolute volumes were not determined, but expressed as relative changes between pacing modes, normalizing to either RA or RV pacing as the comparator. Mean values for each measured variable were obtained by signal averaging at least 10 beats under each pacing mode. Chamber and regional stroke work (pressure-volume loop or pressure-segment-length loop area, respectively), cardiac output, LV ejection fraction, MAP, and LV pressure derivatives were digitally computed.

Each animal served as its own control. To assess overall trends in a given parameter over the full study, data were normalized to baseline RA pacing for each animal and then expressed as percent change ± standard error of mean. These results were analyzed using mixed-effects linear regression that included clustering by dog (STATA 13, StataCorp, College Station, TX). Multiple regression analyses were also performed, in which an interaction term for reperfusion status and pacing was included. Lastly, we compared RV pacing to both CRT modes at each time point in the protocol. To remove the influence of gradual impact from infarction/reperfusion per se, data were first normalized to the RA-pacing value of each animal at each time point rather than at initial baseline. Data were then grouped by perfusion status: baseline, infarct period, and reperfusion. RV pacing was then compared to LW-CRT and PIZ-CRT using a Wilcoxon rank-sum test for each perfusion state. The effects of each pacing mode during and after reperfusion were similarly compared.

Results

Influence of CRT on regional function and LAD flow in the ischemic zone

Figure 1A displays representative pressure-segment length loops from the anterior wall territory at baseline, during coronary occlusion, and after reperfusion. The normal appearance of such loops is shown at the upper left—essentially a rectangular shape that moves counterclockwise with each cardiac cycle. To its right is the regional loop with RV pacing, which shows typical discoordinate motion, shortening early and then stretching later in systole (a "figure-eight" shape). This is pseudo-LBBB, and compared to this, regional stroke work increased by 111.1% ($P = .012$) with LW-CRT. This was not the case with PIZ-CRT, however, as the LV lead was now in the same region where work was being measured, and pre-excitation there combined with RV stimulation left this zone discoordinate.

During LAD artery occlusion, the anterior-apex became essentially passive and dyskinetic, which is shown by the thin curvilinear pressure-length loops that bowed rightward as pressure increased. The extent of this systolic stretch increased further during both CRT modes and was indexed by more negative regional stroke work (LW-CRT: 24.8%, $P = .05$; PIZ-CRT: 34.7%, $P = .015$; Figure 1B and Table 1). After reperfusion, some positive regional work was restored in the infarct zone. This was reduced by RV pacing, but augmented similarly with either CRT mode (all $P < .05$).

Results for mean LAD flow measured just upstream to the site of occlusion are presented in Figure 1C. At baseline, flow was similar with all ventricular pacing modes, whereas during coronary occlusion or after reperfusion, coronary flow was slightly less with RV pacing and significantly increased with either CRT mode. Thus, both CRT modes augmented negative regional work (dyskinesia) during coronary occlusion, but enhanced positive work along with regional blood flow after reperfusion.

Influence of CRT on global function in the ischemic/reperfused heart

Figure 2A displays LV pressure-time recordings after 2 hours of anterior coronary occlusion and 1 hour after reperfusion. Pseudo-LBBB reduced systolic pressure compared to RA pacing under both conditions. This was modestly improved by LW-CRT during coronary occlusion, but more so after reperfusion. Figure 2B displays example pressure-volume loops for all pacing modes and observation

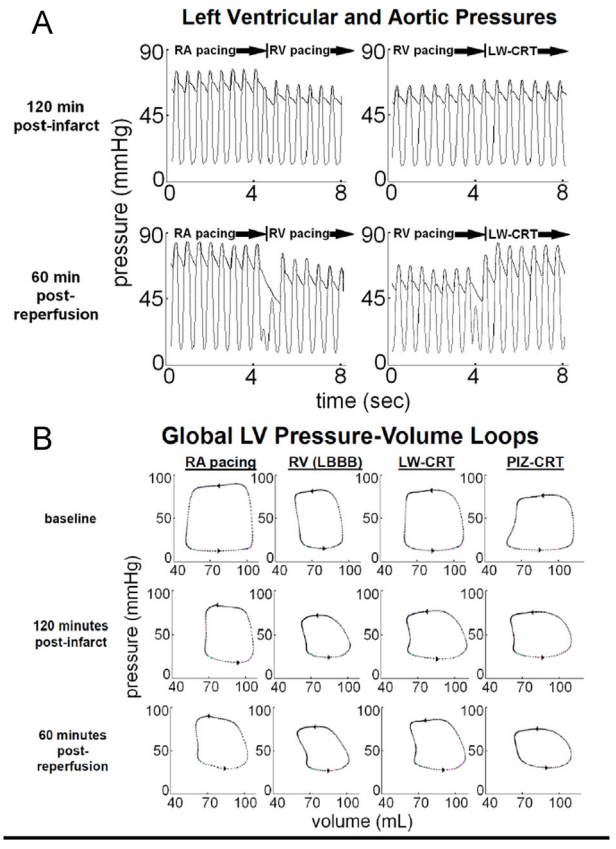

Figure 2 Global hemodynamic effects of CRT. **A:** Example left ventricle with superimposed aortic pressure tracings are shown from a single animal during transitions from RA pacing to RV pacing and from RV pacing to LW-CRT. **B:** Example global left ventricular pressure-volume loops from a single animal demonstrate the effects of LW-CRT and PIZ-CRT at each measurement interval in comparison to RA and RV pacing. Abbreviations as in Figure 1.

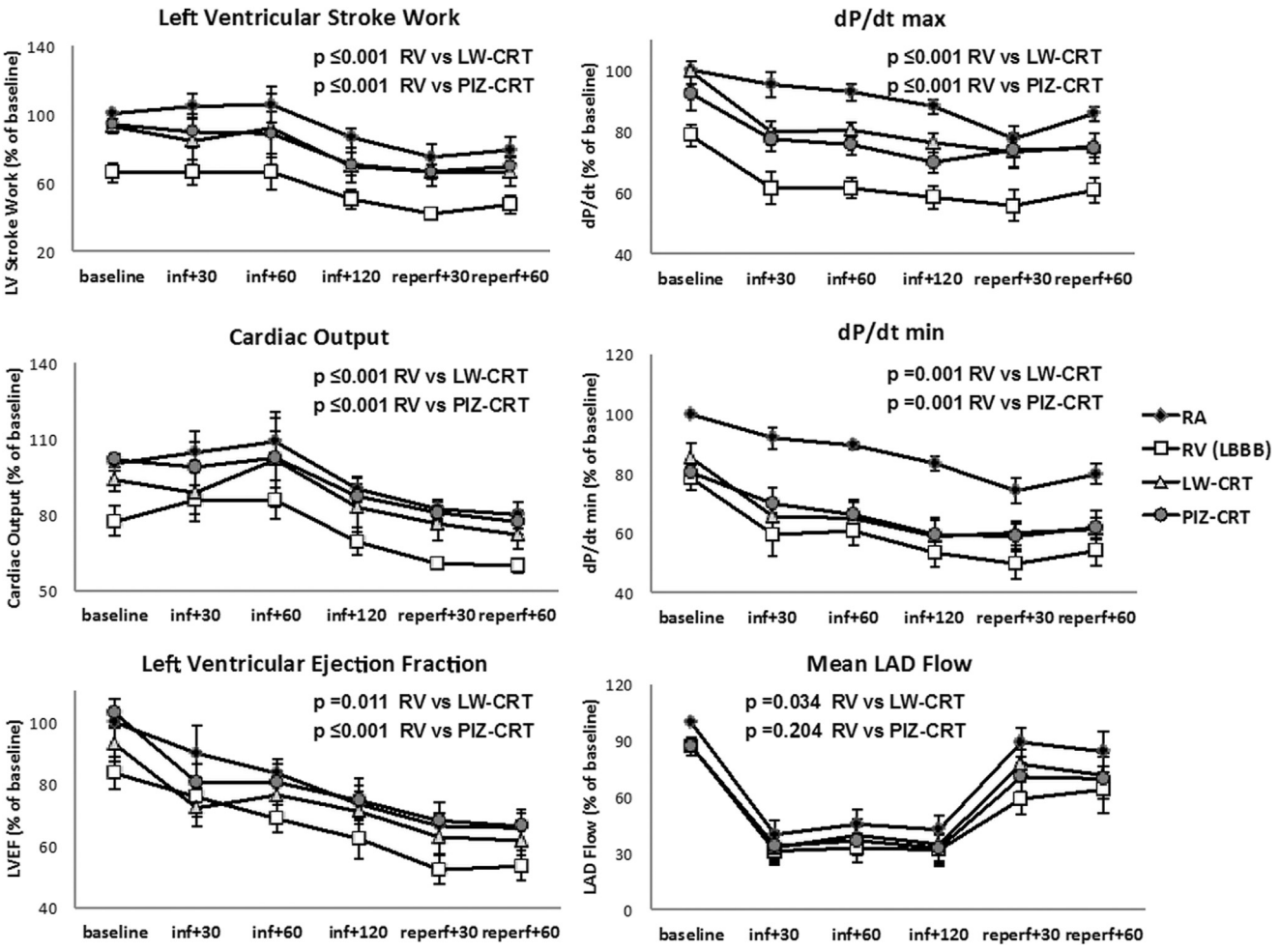

Figure 3 Overall effects of CRT on various measures of cardiac function in the immediate postinfarct period. Line graphs for each measurement variable are normalized to RA pacing before infarction (baseline) in order to demonstrate the overall trend. Mixed-effects linear regression models were used to assess statistical significance (Table 1). *P* values for the overall trend by repeated measures analysis of variance are shown. Abbreviations are as in Figure 1 and Table 1.

points in the study. With distal LAD artery occlusion, chamber stroke work and cardiac output declined by 20% and ejection fraction by 40%. Both declined further with pseudo-LBBB but rose toward RA-pacing levels with either CRT mode at all time points. The impact of the different pacing modes throughout the entire protocol was tested by mixed-effects linear regression (Figure 3 and Table 2). LW-CRT or PIZ-CRT significantly enhanced LV hemodynamics as compared to RV pacing, nearly matching RA pacing for ejection phase parameters such as cardiac output and ejection fraction, but falling below for isovolumic indexes (dP/dt_{max} and dP/dt_{min}). RA pacing augmented mean LAD flow more than that with any of the other pacing modes.

We also compared pseudo-LBBB to each form of CRT (Figure 4 and Table 2), normalizing data to RA pacing at each time point to remove the changes from ischemia/reperfusion per se and grouping the analysis into baseline, coronary occlusion, and reperfusion. For many variables, both modes of CRT generally improved function over pseudo-LBBB regardless of regional perfusion status. The one exception was the time constant of relaxation, which was little affected by either CRT mode.

Discussion

The use of CRT in patients with LBBB and severe acute cardiac decompensation after MI remains limited and largely anecdotal. Our own favorable experience with several patients in the coronary care unit at the Johns Hopkins Hospital originally triggered our interest in this area. Reported clinical data from 15 patients with CS included only 3 patients with MI, and although they fared poorly, the number was too small to make conclusions.[11] Animal data, however, also raised concerns that CRT efficacy might be lost when regional flow was critically reduced.[12] The present study provides the first physiological mechanistic analysis of CRT efficacy in a model of coronary occlusion and reperfusion and yields important new insights regarding its impact on regional function, perfusion, and global hemodynamics that should prove valuable for the future consideration of CRT for this condition.

In the presence of pseudo-LBBB and LAD artery occlusion, the early-activated territory is also the ischemic/infarct zone. By contracting early, loading in the PIZ is reduced,[19] and in prior animal studies, this has benefited post-MI remodeling.[15] Others have applied CRT to the post-

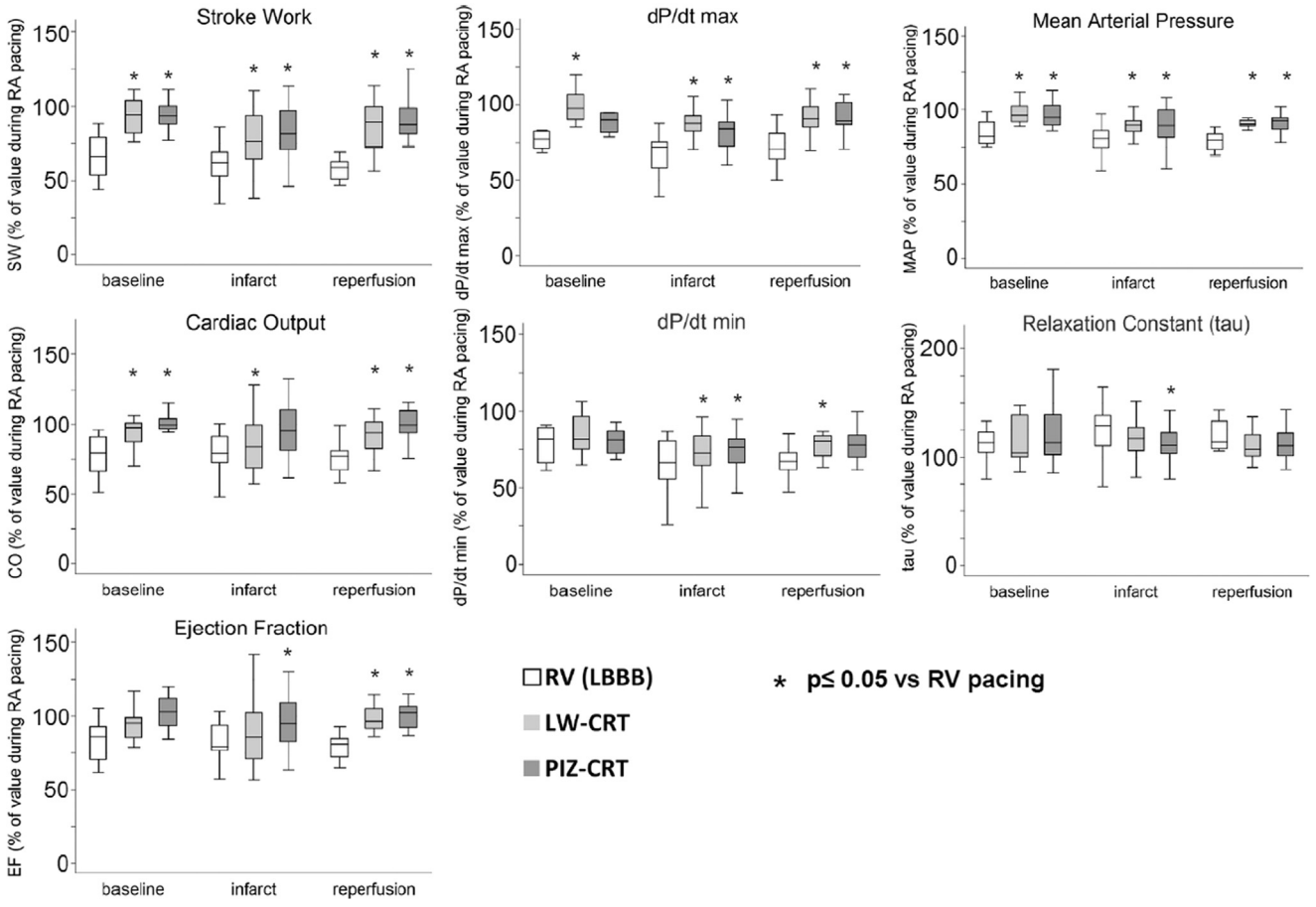

Figure 4 Effects of CRT on various measures of cardiac function, grouped by perfusion status. Box plots for each measurement variable are normalized to RA pacing at each time interval in order to demonstrate differences between pacing sites in the experimental protocol. Aggregate data are shown, grouped by perfusion status. RV pacing was compared to LW-CRT and PIZ-CRT by using the Wilcoxon rank-sum test, with results summarized in Table 2. Significant differences ($P \leq .05$) between RV pacing and each CRT mode are labeled. Abbreviations are as in Figure 1.

MI rabbit heart without any conduction delay and found benefits on chronic remodeling.[20] The use of PIZ-CRT was tested in post-MI patients with a narrow QRS complex,[21] though no effects on 1-year cardiac remodeling or clinical outcomes were found. However, these conditions differ from the present investigation in that we made pseudo-LBBB the baseline state. While both CRT modes augmented PIZ loading and corresponding dyskinesis (reflected by more negative regional stroke work) during coronary occlusion as compared with pseudo-LBBB, the magnitude was small and mostly mediated by the rise in systolic pressures. The net impact on global function remained positive. These positive findings contrast to negative results when regional coronary flow was markedly reduced for 3 minutes into the entire region subtended by the LAD artery or circumflex.[12] In our protocol, the mid-LAD artery was occluded, leaving excitable peri-infarct tissue, and we also examined efficacy after reperfusion. These conditions may provide for more adaptive changes that improve CRT efficacy.

After reperfusion, the infarct zone became less dyskinetic and more hypo- or akinetic, even in the presence of pseudo-LBBB. This decline in dyskinesis likely contributed to greater functional improvement from CRT owing to mechanical advantage offered by a stiffer infarct zone and more viable myocardium.[22] Interestingly, during and after coronary occlusion, both CRT modes were similarly effective as compared to pseudo-LBBB, whereas in the normal heart, LW-CRT increased anterior wall regional work vs pseudo-LBBB while PIZ-CRT did not. The latter may be due to delay in LV conduction in the PIZ with ischemia/infarction, and so the timing of LV and RV mechanical activation becomes similar between the CRT modes. In the healthy heart, conduction through an uninjured anterior wall with PIZ-CRT would be rapid, resulting in some dyssynchrony in a septal to lateral direction and little improvement compared with RV pacing.

Chronic dyssynchrony induces disparities of regional blood flow, with relative increases in the higher-stressed late-activated region[19] and reduced flow in the anteroseptum, and chronic CRT can reverse this.[23,24] This increase is thought to result from rehomogenization of work load.[18,23] In the postinfarct region, coronary flow regulation is likely compromised, and so increases in perfusion pressure (estimated by MAP-LV diastolic pressure) and regional work induced by CRT may both contribute to higher flow rates. This could be clinically useful, so long as the flow more than matches the rise in regional work from CRT. It is worth considering whether CRT would likely provide similar efficacy if the ischemic territory was in the lateral or

inferoposterior walls. Either region would be less common in the context of CS and LBBB, but if viable tissue in the LW were approachable and could be activated, one would see similar efficacy. The CRT mode would resemble PIZ-CRT in this regard, since the LV lead would be in the PIZ.

This study has several limitations. First, we used RV pacing to simulate LBBB. This was chosen so that comparisons to RA pacing with synchronous contraction were possible, and so we could use this as the default mode between RV and LV pacing interventions. Second, a single-chamber impulse generator with a Y adapter was used to provide biventricular stimulation, resulting in loss normal atrioventricular timing delay with all ventricular pacing states (RV, LW-CRT, and PIZ-CRT). Hence, comparisons between RA pacing and the other pacing modes include the effects from loss of atrial timing. However, the key comparisons between ventricular pacing modes would be little affected. Third, we addressed only the acute safety and hemodynamic efficacy of CRT in hearts with dyssynchrony and infarction, and how long such interventions would remain beneficial remains to be determined. However, the condition we envision treating has high short-term mortality, and so even transient CRT might make a difference. Subsequent decisions regarding whether such therapy should be sustained with a chronic implant will likely depend on clinical status, the capacity for enhanced regional load and perfusion in the PIZ that will accompany CRT (even PIZ-CRT), and the extent of global benefit that is observed more acutely.

Table 2 RV pacing vs LW-CRT and PIZ-CRT during each perfusion state

		Stroke work		Stroke volume		LVEF		Cardiac output		MAP	
Perfusion state	Comparison	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*
A: Wilcoxon rank-sum test results: RV vs LW-CRT and RV vs PIZ-CRT											
Baseline	RV vs LW-CRT	27%	.012	16.1%	.050	9.3%	.401	16.1%	.050	13.3%	.025
	RV vs PIZ-CRT	27.5%	.025	23.9%	.012	19.5%	.357	23.9%	.012	12.3%	.036
Infarct	RV vs LW-CRT	19%	<.001	8.4%	.230	7%	.179	8.4%	.230	9.1%	<.001
	RV vs PIZ-CRT	22.1%	<.001	15.5%	<.001	13.1%	<.001	15.5%	<.001	10.5%	<.001
Reperfusion	RV vs LW-CRT	28.2%	.002	16%	.013	15.8%	.006	16%	.013	12.3%	.001
	RV vs PIZ-CRT	32%	.001	22.8%	.001	21.7%	.001	22.8%	.001	12.9%	.002

		dP/dt_{max}		dP/dt_{min}		tau		Infarct zone stroke work		Mean LAD flow	
Perfusion state	Comparison	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*
Baseline	RV vs LW-CRT	20.5%	.012	−12.8%	.327	3.3%	.779	111.1%	.012	.2%	.484
	RV vs PIZ-CRT	13.6%	.093	−17.4%	.161	10.2%	.889	9.7%	.575	−0.5%	.998
Infarct	RV vs LW-CRT	20.1%	<.001	6.2%	.007	−8.6%	.059	−24.8%	.050	7.1%	.018
	RV vs PIZ-CRT	14.9%	<.001	8.2%	<.001	−13%	<.001	−34.7%	.015	6.2%	.008
Reperfusion	RV vs LW-CRT	19.5%	.001	12.2%	.008	−9.5%	.074	82.4%	.005	14.7%	.002
	RV vs PIZ-CRT	19.5%	.002	12.1%	.055	−7.7%	.177	72.8%	.002	10%	.006

B: Wilcoxon rank-sum test results: each pacing state during infarct vs itself after reperfusion

		Stroke work		Stroke volume		LVEF		Cardiac output		MAP	
Pacing site	Comparison	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*
RV	Infarct vs reperfusion	−2.3%	.875	−4.4%	.875	−4.3%	.975	−4.4	.875	.7%	.300
LW-CRT	Infarct vs reperfusion	6.9%	.074	3.1%	.074	4.6%	.096	3.1%	.074	3.9%	.594
PIZ-CRT	Infarct vs reperfusion	7.5%	.030	2.9%	.074	4.3%	.04	2.9%	.074	3.1%	.972

		dP/dt_{max}		dP/dt_{min}		tau		Infarct zone stroke work		Mean LAD flow	
Pacing site	Comparison	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*	Difference	*P*
RV	Infarct vs reperfusion	5%	.875	1.3%	.638	−7.9%	.363	74.2%	.001	2.9%	.778
LW-CRT	Infarct vs reperfusion	4.4%	.551	7.3%	.272	−8.8%	.272	181.4%	.001	10.4%	.177
PIZ-CRT	Infarct vs reperfusion	9.6%	.196	5.2%	.972	−2.7%	.875	181.6%	.001	6.7%	.683

Comparisons between RV pacing and each form of CRT are shown (top, 2A) using the Wilcoxon rank-sum test to establish statistical significance. LW-CRT and PIZ-CRT significantly improved myocardial performance as compared to RV pacing during the infarction period and after reperfusion. Each pacing mode during the infarction period was also compared to itself after reperfusion (bottom, 2B). Snare release was associated with a significant improvement in infarct zone stroke work, particularly with CRT pacing.

CRT = cardiac resynchronization therapy; LAD = left anterior descending; LVEF = left ventricular ejection fraction; LW = lateral wall; MAP = mean arterial pressure; NS = not significant; PIZ = peri-infarct zone; RV = right ventricular.

Conclusion

Our results suggest that the use of CRT in the acutely infarcted heart made worse by LBBB-type dyssynchrony can enhance global cardiac performance. This comes with the requirement that regional work in the PIZ increases. Translation to patients in the coronary care unit is probably best considered on the basis of their individual response to acute CRT, with those gaining more substantial improvement in global performance without evidence of further ischemia becoming candidates for sustained therapy. In practice, acute initiation of CRT would involve temporary coronary sinus pacing after revascularization, ideally with an atrial lead for atrioventricular synchrony (depending on the patient). This approach would allow CRT to act as an adjunctive therapy to an intra-aortic balloon pump and/or IV inotropic agents in patients with CS, poor LVEF, and LBBB. Further studies are needed to determine whether acute CRT can reduce the high mortality in the appropriate high-risk post-MI population.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.05.036.

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