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Efficacy of Cardiac Resynchronization in Acutely Infarcted Canine Hearts with Electro-mechanical Dyssynchrony

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Abstract

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

Objective—To evaluate the acute hemodynamic effects of CRT during and immediately after myocardial infarction.

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

Results—At baseline, both RVP and PIZ-CRT reduced anterior wall regional work by ~50% (versus RA 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% over pseudo-LBBB, and improved global function.

Conclusion—CRT improves global chamber systolic function in chambers with delayed lateral wall activation during and following sustained coronary occlusion. It does so while modestly augmenting infarct-zone dyskinesis during occlusion and improving regional function and blood-flow upon reperfusion. These findings support CRT in the setting of early post-MI dyssynchronous heart failure.

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Keywords

myocardial infarction; acute heart failure; cardiac resynchronization therapy

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 >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 criteria³ rated CRT as “may be appropriate” for patients with an LVEF < 35% from any cause, concurrent use of at least one intravenous inotrope, and any QRS prolongation, the acute MI-cardiac failure condition is rarely targeted.^{4, 5}

At present, only 40–50% of patients suffering both acute MI and cardiogenic shock (CS) survive to hospital discharge.^{6–8} Many of these individuals also have or develop a LBBB, and if CRT is effective as an urgent means of improving systemic hemodynamics beyond standard treatment (i.e. intra-aortic balloon pump and intravenous inotropic drugs), it might improve survival. Ideally, this would lead to either medically-managed recovery or definitive cardiovascular therapy, including coronary artery bypass surgery, left ventricular assist device, or permanent bi-ventricular pacemaker implantation. CRT might provide an added 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 al¹¹ found some benefit from temporary LV pacing with atrioventricular synchrony, with improved mean arterial pressure, although two of the three acute MI patients were identified as non-responders. Svendsen et al¹² studied canine hearts with proximal coronary perfusion that was lowered by 50–80% to induce regional ischemia, and found 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 a LBBB that go in either direction. If the anterior wall cannot generate systolic force regardless of when it is activated, i.e. is purely passive and dyskinetic¹³, early stimulation of an otherwise late activated lateral wall 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 itself, essentially inducing a 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 the LBBB would offset these concerns, particularly if the ischemic region was stiffened and/or rendered hypokinetic after reperfusion therapy¹³. In this instance, CRT could improve workload and blood flow in the anterior region¹⁶.

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 been previously shown to benefit animals with a LBBB and stable (four weeks) myocardial infarction¹⁷, 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 following 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 following reperfusion.

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, placed 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 g/kg/min IV) during surgery, and 20–40 mg IV boluses as required to suppress ventricular ectopy or non-sustained tachycardia. The chest was opened via lateral thoracotomy, and the heart placed in a pericardial cradle. Epicardial leads were attached to the right atrial appendage (RA), right ventricular apex (RV), left ventricular lateral wall, and left ventricular peri-infarction zone (LV-PIZ). The left anterior descending artery (LAD) just distal to the second diagonal branch was transiently occluded to demarcate the peri-infarct zone for LV-PIZ lead placement. Mid-wall sonomicrometers (Sonometrics; London, ON) 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; 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; Houston, TX) advanced to the apex, micro-manometer catheter to the ascending aorta, and balloon-tipped pulmonary artery thermodilution catheter. The instrumentation is shown in Supplemental Fig. 1.

Experimental Protocol

After 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) two minutes of RV-pacing, followed by RV + LV-lateral wall pacing (LW-CRT); and 4) two minutes of RV-pacing, followed by RV + LV-PIZ pacing (PIZ-CRT). PIZ-CRT was included as prior studies^{15, 18} reported wall stress is reduced at the site of earliest activation (i.e. 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 responses². Once baseline data were obtained, the LAD was occluded just beyond the second diagonal and hemodynamic data continuously recorded. Data at each pacing mode (order randomized) was obtained after 30, 60, and 120 minutes of coronary occlusion, and then at 30 and 60 minutes following reperfusion. Dogs were then euthanized by injection of 50 mL of IV saturated KCl.

Data analysis

Data were analyzed using custom developed software (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, mean arterial pressure, 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 $\pm$ SEM. These results were analyzed using mixed-effect linear regression clustered by dog (STATA 13, StataCorp; College Station, TX). Multiple regression analysis was 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 following reperfusion. The normal appearance of such loops is shown at the upper left – essentially a rectangular shape that moves counter-clockwise 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 the pseudo-LBBB, and compared to this, regional stroke work increased +111.1% ($p=0.012$) 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 occlusion, the anterior-apex became essentially passive and dyskinetic, 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%, $p=0.05$; PIZ-CRT: +34.7%, $p=0.015$; Figure 1B, Table 1). Following re-perfusion, some positive regional-work was restored in the infarct zone. This was reduced by RV-pacing, but augmented similarly with either mode of CRT (all $p<0.05$).

Results for mean LAD flow measured just upstream to the site of occlusion is shown 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 following 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 points in the study. With distal LAD occlusion, chamber stroke work and cardiac output declined by 20%, and EF by 40%. Both further declined with pseudo-LBBB but rose towards 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, Table 2). LW-CRT or PIZ-CRT significantly enhanced LV hemodynamics when 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 (Table 2, Figure 4), 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 impacted by either CRT mode.

DISCUSSION

The use of CRT in patients with a LBBB and severe acute cardiac decompensation following myocardial infarction remains limited and largely anecdotal. Our own favorable experience with several patients in the coronary care unit at Johns Hopkins Hospital originally triggered our interest in this area. Reported clinical data from 15 patients with cardiogenic shock included only three subjects with infarction, and while they fared poorly, the number was too small to make conclusions¹¹. Animal data, however, also raised concerns that CRT efficacy might be lost when regional flow was critically reduced¹². 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 a pseudo-LBBB and LAD occlusion, the early-activated territory is also the ischemic/infarct zone. By contracting early, loading in the peri-infarct region is reduced¹⁹, and in prior animal studies, this has benefited post-MI remodeling¹⁵. Others have applied CRT to the post-MI rabbit heart without any conduction delay, and found benefits on chronic remodeling²⁰. The use of PIZ-CRT was tested in post-MI patients with a narrow

QRS²¹, 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 dyskinesia (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 or circumflex¹². In our protocol, the mid-LAD was occluded leaving excitable peri-infarct tissue, and we also examined efficacy following reperfusion. These conditions may provide for more adaptive changes that improve CRT efficacy.

Upon reperfusion, the infarct zone became less dyskinetic and more hypo- or akinetic, even in the presence of the pseudo-LBBB. This decline in dyskinesia likely contributed to greater functional improvement from CRT due to mechanical advantage offered by a stiffer infarct zone and more viable myocardium²². Interestingly, during and after coronary occlusion, both CRT modes were similarly effective when compared to pseudo-LBBB, whereas in the normal heart, LW-CRT increased anterior wall regional work versus pseudo-LBBB while PIZ-CRT did not. The latter may be due to delay in LV conduction in the PIZ with ischemia/infarction, so the timing of LV and RV mechanical activation become more 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 region¹⁹ and reduced flow in the antero-septum, and chronic CRT can reverse this^{23, 24}. This increase is thought to result from re-homogenization of work-load^{23, 25}. In the post-infarct region, coronary flow regulation is likely compromised, 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 infero-posterior walls. Either region would be less common in the context of cardiogenic shock and a LBBB, but if viable tissue in the lateral wall were approachable and could be activated, one should see similar efficacy. The mode of CRT would resemble PIZ-CRT in this regard, since the LV lead would be in the peri-infarct zone.

This study has several limitations. First, we employed RV-pacing to simulate a LBBB. This was chosen so comparisons to RA-pacing with synchronous contraction were possible, and so we could use this as the default mode between RV/LV pacing interventions. Second, a single chamber impulse generator with a Y-adapter was utilized to provide bi-ventricular stimulation, resulting in loss normal AV timing delay with all ventricular pacing states (RV, LW-CRT, and PIZ-CRT). Hence, comparisons between RA pacing with the other pacing modes includes the effects from loss of atrial timing. However, the key comparisons are between ventricular pacing modes, would be little impacted. Third, we only addressed 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 very high short-term mortality, so even transient CRT might make a difference. Subsequent decisions regarding whether such therapy should be sustained with a chronic implant will likely depend upon clinical status, the capacity for enhanced regional load and perfusion in the PIZ that will accompany CRT (even PIZ-CRT), and extent of global benefit that is observed more acutely.

CONCLUSION

In summary, our results suggest that 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 acute coronary care patients is probably best considered based on 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 following revascularization, ideally with an atrial lead for A-V synchrony (depending on the patient). This approach would allow CRT to act as an adjunctive therapy to an intra-aortic balloon pump and/or intravenous inotropic agents in patients with cardiogenic shock, poor LVEF, and LBBB. Further studies are needed to determine if acute CRT can reduce the high mortality in the appropriate high risk post-MI population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AV	atrio-ventricular
CRT	cardiac resynchronization therapy
CS	cardiogenic shock
EF	ejection fraction
IV	intravenous
LAD	left anterior descending
LBBB	left bundle branch block
LV	left ventricle

LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MI	myocardial infarction
PIZ	peri-infarct zone
RA	right atrium
RV	right ventricle

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Figure 1. Effect of CRT on regional stroke work in the infarction zone and mean LAD flow
Panel 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 dyskinesia) and encompass a very small area, demonstrating loss of regional stroke work. **Panel B:** A box plot normalized to RA-pacing (dashed line) at each time point demonstrates an increase in dyskinesia with both forms of CRT during the ischemic period, when compared to RV-pacing. Following reperfusion, both LW-CRT and PIZ-CRT increased infarct zone stroke work significantly versus RV-pacing. On the y-axis, values greater than zero indicate that work was performed, while negative values indicate that work was absorbed (i.e. dyskinetic work loss). **Panel C:** Both forms of CRT were associated with significantly increased mean LAD flow when compared to RV-pacing during ischemia and following 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.

Figure 2. Global hemodynamic effects of CRT

Panel A: Example left ventricular with superimposed aortic pressure tracings are shown from a single animal during transitions from RA- to RV-pacing, and from RV-pacing to LW-CRT. **Panel 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 post-infarct period

Line graphs for each measurement variable are normalized to RA-pacing prior to infarction (baseline), in order to demonstrate overall trend. Mixed-effects linear regression models were utilized to assess statistical significance (Table 1). P-values for the overall trend by repeated measures ANOVA are shown. Abbreviations are as in Figure 1.

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 using the Wilcoxon rank sum test, with results reported in Table 2. Significant differences ($p < 0.05$) between RV-pacing and each mode of CRT are labeled. Abbreviations are as in Figure 1.

Table 1

Results from multi-level, mixed-effects linear regression models

	Stroke Work			Stroke Volume			LVEF			Cardiac Output			MAP		
	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%	0.016		-7.1%	0.007		-8.4%	0.016		-10.5%	<0.001	
	PIZ-CRT	-12.1%	0.001	-2.9%	NS		-1.1%	NS		-2.9%	NS		-10%	<0.001	
RV pacing vs.	LW-CRT	+22.4%	<0.001	+12.6%	<0.001		+6.7%	0.011		+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%	NS	+1.5%	NS		-15.1%	<0.001		+1.5%	NS		-5.6%	0.015	
	inf+60	-0.1%	NS	+6.7%	NS		-17.5%	<0.001		+6.7%	NS		-1.8%	NS	
	inf+120	-18.9%	<0.001	-10.6%	0.011		-24.6%	<0.001		-10.6%	0.011		-1%	NS	
	reperf+30	-29.7%	<0.001	-21.5%	<0.001		-35.3%	<0.001		-21.5%	<0.001		+0.5%	NS	
	reperf+60	-26.9%	<0.001	-24.4%	<0.001		-35.7%	<0.001		-24.4%	<0.001		+5.3%	0.030	
	dP/dt max			dP/dt min			tau			Infarct Zone Stroke Work			Mean LAD Flow		
	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%	NS		-15.4%	<0.001	
	LW-CRT	-9.3%	<0.001	-20.6%	<0.001		+17.8%	<0.001		+17.3%	NS		-9.6%	<0.001	
	PIZ-CRT	-13.1%	<0.001	-20.6%	<0.001		+17.5%	<0.001		-3.2%	NS		-11.9%	<0.001	
RV pacing vs.	LW-CRT	+17.9%	<0.001	+6.6%	0.001		-10%	0.034		+20.2%	NS		+5.7%	0.034	
	PIZ-CRT	+14.1%	<0.001	+6.7%	0.001		-10.3%	0.029		-0.28%	NS		+3.4%	NS	
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%	NS		-15.6%	<0.001	
	reperf+60	-19%	<0.001	-24.2%	<0.001		+47.3%	<0.001		-28.5%	0.030		-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 when compared to RV-pacing. CRT, cardiac resynchronization therapy; LAD, left anterior descending; LVEF, left ventricular ejection fraction; LW, lateral wall; MAP, mean arterial pressure; PIZ, peri-infarct zone; RA, right atrial; RV, right ventricular.

Table 2

RV-pacing versus LW-CRT and PIZ-CRT during each perfusion state.

A: Wilcoxon signed rank sum test results, RV versus LW-CRT and RV versus PIZ-CRT													
perfusion state	comparison	Stroke Work		Stroke Volume		LVEF		Cardiac Output		Mean Arterial Pressure			
		difference	p-value	difference	p-value	difference	p-value	difference	p-value	difference	p-value		
baseline	RV vs LW-CRT	+27%	0.012	+16.1%	0.050	+9.3%	NS	+16.1%	0.050	+13.3%	0.025		
	RV vs PIZ-CRT	+27.5%	0.025	+23.9%	0.012	+19.5%	NS	+23.9%	0.012	+12.3%	0.036		
infarct	RV vs LW-CRT	+19%	<0.001	+8.4%	NS	+7%	NS	+8.4%	NS	+9.1%	<0.001		
	RV vs PIZ-CRT	+22.1%	<0.001	+15.5%	<0.001	+13.1%	<0.001	+15.5%	<0.001	+10.5%	<0.001		
reperfusion	RV vs LW-CRT	+28.2%	0.002	+16%	0.013	+15.8%	0.006	+16%	0.013	+12.3%	0.001		
	RV vs PIZ-CRT	+32%	0.001	+22.8%	0.001	+21.7%	0.001	+22.8%	0.001	+12.9%	0.002		
perfusion state	comparison	dP/dt max	p-value	dP/dt min	p-value	tau	p-value	Infarct Zone Stroke Work	p-value	Mean LAD Flow	p-value		
baseline	RV vs LW-CRT	+20.5%	0.012	-12.8%	NS	+3.3%	NS	+111.1%	0.012	+0.2%	NS		
	RV vs PIZ-CRT	+13.6%	NS	-17.4%	NS	+10.2%	NS	+9.7%	NS	-0.5%	NS		
infarct	RV vs LW-CRT	+20.1%	<0.001	+6.2%	0.007	-8.6%	NS	-24.8%	0.050	+7.1%	0.018		
	RV vs PIZ-CRT	+14.9%	<0.001	+8.2%	<0.001	-13%	<0.001	-34.7%	0.015	+6.2%	0.008		
reperfusion	RV vs LW-CRT	+19.5%	0.001	+12.2%	0.008	-9.5%	NS	+82.4%	0.005	+14.7%	0.002		
	RV vs PIZ-CRT	+19.5%	0.002	+12.1%	NS	-7.7%	NS	+72.8%	0.002	+10%	0.006		
B: Wilcoxon signed rank sum test results, each pacing state during infarct versus itself following reperfusion													
pacing site	comparison	Stroke Work		Stroke Volume		LVEF		Cardiac Output		Mean Arterial Pressure			
		difference	p-value	difference	p-value	difference	p-value	difference	p-value	difference	p-value		
		RV	infarct vs reperfusion	-2.3%	NS	-4.4%	NS	-4.3%	NS	-4.4	NS	+0.7%	NS
LW-CRT	"	+6.9%	NS	+3.1%	NS	+4.6%	NS	+3.1%	NS	+3.9%	NS		
PIZ-CRT	"	+7.5%	0.030	+2.9%	NS	+4.3%	0.04	+2.9%	NS	+3.1%	NS		
pacing site	comparison	dP/dt max		dP/dt min		tau		Infarct Zone Stroke Work		Mean LAD Flow			
		difference	p-value	difference	p-value	difference	p-value	difference	p-value	difference	p-value		
RV	infarct vs reperfusion	+5%	NS	+1.3%	NS	-7.9%	NS	+74.2%	0.001	+2.9%	NS		

B: Wilcoxon signed rank sum test results, each pacing state during infarct versus itself following reperfusion											
pacing site	comparison	Stroke Work		Stroke Volume		LVEF		Cardiac Output		Mean Arterial Pressure	
		difference	p-value	difference	p-value	difference	p-value	difference	p-value	difference	p-value
LW-CRT	"	+4.4%	NS	+7.3%	NS	-8.8%	NS	+181.4%	0.001	+10.4%	NS
PIZ-CRT	"	+9.6%	NS	+5.2%	NS	+2.7%	NS	+181.6%	0.001	+6.7%	NS

Comparisons between RV-pacing and each form of CRT are shown (top, 2A), using the Wilcoxon signed rank sum test to establish statistical significance. LW-CRT and PIZ-CRT significantly improved myocardial performance when compared to RV-pacing during the infarction period and following reperfusion. Each pacing mode during the infarction period was also compared to itself following reperfusion (bottom, 2B). Snare release was associated with 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; PIZ, peri-infarct zone; RA, right atrial; RV, right ventricular.