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

Grant V. Chow, MD, Michael G. Silverman, MD, Richard S. Tunin, MS, Albert C. Lardo, PhD, Saman Nazarian, MD, PhD, FHRS, David A. Kass, MD

From the Division of Cardiology, Johns Hopkins Medical Institutions, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

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.

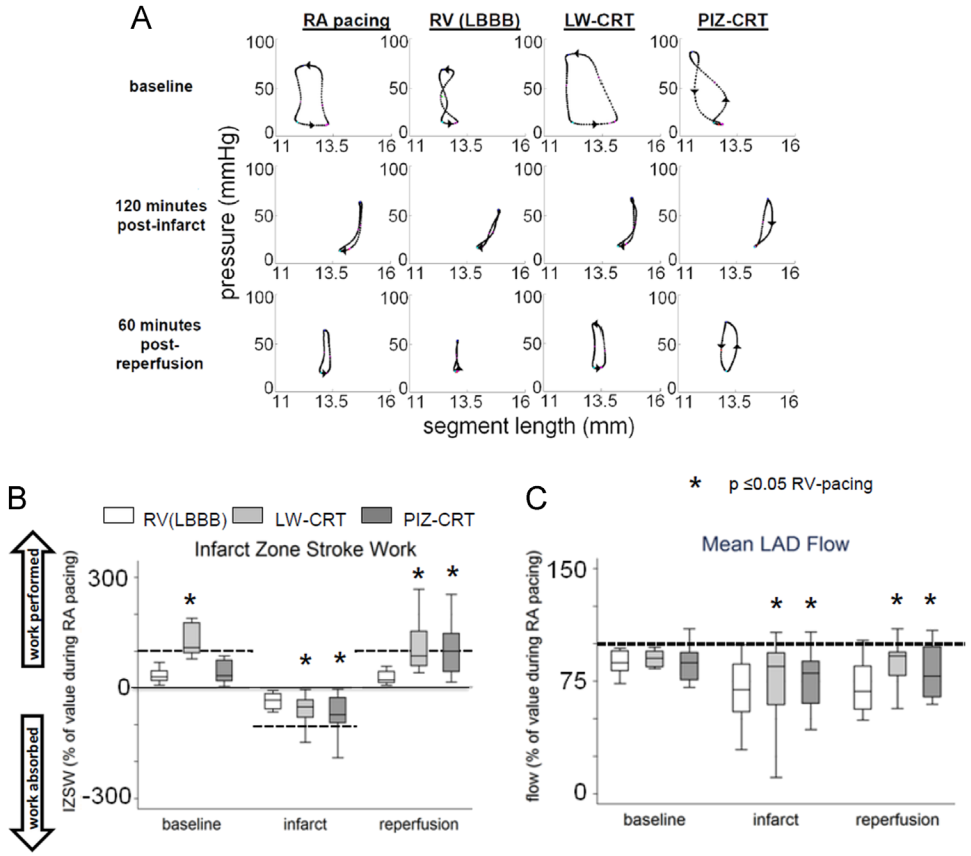

Figure 1 Effect of CRT on regional stroke work and mean LAD flow in the infarction zone. **A:** Example regional pressure-length loops from a single animal are shown (top) using data from sonomicrometer crystals embedded within the distal anterior wall. During ischemia, loops lean leftward (denoting 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.