Indian Pacing and Electrophysiology Journal 16 (2016) 113–114

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Pump up the volume: Cardiac resynchronization therapy to improve renal function

Keywords:
Cardiac resynchronization therapy
Renal failure
Heart failure

In the western population, approximately 40% of heart failure is associated with left ventricular ejection fraction (LVEF) of 0.35 or less. Conduction abnormalities are common in systolic heart failure. A third of the patients with QRS greater than 120 msec have left bundle branch block (LBBB) and 17% have QRS duration ≥150 msec [1]. Delayed atrio-ventricular (AV) and intra-ventricular conduction are associated with cardiac dys-synchrony.

The mechanisms that lead to deteriorating cardiac function in cardiac dys-synchrony are manifold. If prolonged AV conduction delays LV systolic contraction to the point that diastolic LV pressure exceeds atrial pressure, diastolic mitral regurgitation will occur. Loss of ventricular pre-load reduces ventricular contractility based on the Starling mechanism. Ventricular dys-synchrony due to intra and inter-ventricular conduction delay reduces LV contractility, increases myocardial oxygen demand, and decreases cardiac output. Disorganized papillary muscle contraction worsens functional mitral regurgitation. Progressive decline in LV function is compounded by adverse remodeling of the LV that sets off a downward spiraling course in heart failure. Cardiac resynchronization therapy reverses several of these pathophysiological mechanisms. Although the exact beneficial mechanism in any individual patient may vary, the end result is improvement in cardiac output with augmented blood flow and organ perfusion including improved renal function. Over the longer term, reverse remodeling of the LV is often evident by reduced LV volume and improved ejection fraction.

To date, over 7000 patients have been studied in clinical trials of cardiac re-synchronization therapy. These trials showed that in appropriate patients (patients with LVEF ≤ 0.35, NYHA class II to IV on optimal medical therapy, and QRS duration greater than 120 msec), CRT improved heart failure symptoms, reduced hospitalization for heart failure and lead to a reduction in all cause mortality [2–6]. The majority of these trials utilized a defibrillator in combination with resynchronization although CRT-pacing alone has shown similar benefits [4]. It should be remembered that CRT implantation is associated with higher costs and complications. Hence, to maximize benefit from this therapy, judicious selection of patients is critical. Based on post-hoc analysis of the clinical trials of CRT, it is now recognized that CRT is most beneficial in patients with LBBB and QRS duration of 150 msec or greater [7,8]. As a result, the current guidelines include this group as the only Class 1 recommendation for CRT. Benefits of CRT tends to recede as a function of the nature of the underlying disease process and the type of conduction abnormality (Fig. 1) [9].

In this issue of the journal, authors Jeevanantham et al. present data from a single center (University of Kansas Medical Center, MO, USA) on the effect of CRT on renal function [10]. In a cohort of 558 patients who underwent CRT implants at their institution, 80% has mild renal dysfunction (Stage 2 or 3) at baseline. A small proportion (11%) had stage 4 or 5 renal disease. Sixty five percent of patients who underwent CRT were classified as responders based on a finding of greater than 5% increase in LVEF. During a follow up of just over a year, renal function as measured by glomerular filtration rate (GFR) remained unchanged in the majority of patients. However, in patients with stage 4 and 5 renal failure, there was a significant improvement in GFR from a mean of 20–28 ml/min. In multivariate analysis, deterioration of renal function was a predictor of mortality. Limitations of the present study include lack of data to correlate the improvement in renal function to the CRT responder status or the frequency of biventricular pacing as a percentage of heartbeats. In addition, the absence of a control group that was treated with optimal heart failure medications tempers the conclusions of the study. Nevertheless, the finding of improved renal function in severe renal failure is encouraging and underlines the critical interaction between cardiac and renal function. Analysis of the larger CRT trials has implied a similar, incremental benefit from CRT in patients with evidence for renal dysfunction as a result of heart failure.

There are practical issues with implementation of CRT therapy in patients with severe cardio-renal failure. Epicardial LV lead placement by surgical techniques carries a higher early mortality and morbidity that is likely augmented in the face of significant renal dysfunction [11]. Transvenous techniques run the risk of worsening renal function with the use of radiographic contrast used to define coronary sinus anatomy. In the present study [10], the operators used minimal contrast (40–45 cc) to minimize renal damage and utilized hydration and sodium bicarbonate over the 24-hour period around the implantation. Other than maintenance of adequate hydration and maintaining adequate urine flow in the post exposure period, it is unclear whether any other pre-treatment alters the risk of contrast nephropathy. *N*-acetyl cysteine

Peer review under responsibility of Indian Heart Rhythm Society.

http://dx.doi.org/10.1016/j.ipej.2016.11.005

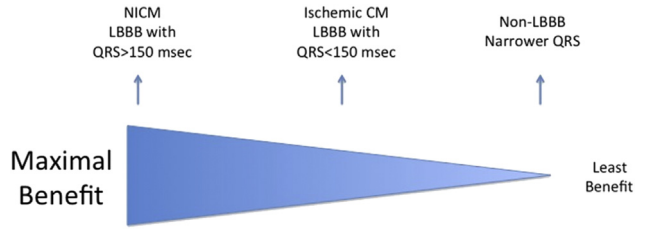

Fig. 1. Magnitude of benefit from Cardiac resynchronization therapy. Adapted from Ref. [9]. NICM = non-ischemic cardiomyopathy, LBBB = left bundle branch block.

was recently shown to reduce serum creatinine levels in normal individuals not exposed to contrast. Hence, the role of this drug in preserving glomerular filtration (as opposed to just maintaining serum creatinine levels steady) after contrast exposure has been called to question. The maintenance of hydration prior to CRT in a patient with chronic heart failure is not simple and may require invasive measures of filling pressure, a procedure that increases the risk of infection in a newly implanted device. Fortunately, in the majority of cases, CRT can be implemented with the minimal use of contrast (5–10 cc). When one encounters a situation of difficult coronary venous anatomy and need for higher contrast volume, serious consideration has to be given to benefit of proceeding versus the risk of precipitating the need for dialysis.

The relation between cardiac function and renal failure has been long recognized and studied. Deteriorating renal function portends a poor outcome in heart failure patients and inability to tolerate angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or beta-blockers is associated with a higher mortality. The predominant mechanism of renal deterioration in heart failure is reduced cardiac output; declining GFR is however, likely due to a combination of reversible and irreversible renal injury. CRT by improving renal perfusion allows reversal of a significant component of the renal failure. In addition, successful CRT results in a higher blood pressure that in turn permits gradual reintroduction and escalation of doses of heart failure medications that improve cardiac function. Thus, the present study, like others that have defined the role of CRT in cardio-renal failure, once again underlines the importance of “pumping up the volume” by increasing cardiac output to preserve renal function.

References

[1] Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail 2007;9:491–501.
[2] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al., MIRACLE Study Group, Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
[3] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, DeMarco T, et al., Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
[4] Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al., Cardiac Resynchronisation–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronisation on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
[5] Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834–43.
[6] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al., MADIT-CRT Trial Investigators. Cardiac resynchronisation therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
[7] Gold MR, Thebault C, Linde C, Abraham WT, Gerritse B, Ghio S, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012;126:822–9.
[8] Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012;163:260–7.
[9] The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2013;34:2281–329.
[10] Jeevanantham V, Shanberg D, Reddy M, Atoui M, Daubert JP, Dawn B, et al. Cardiac resynchronization therapy prevents progression of renal failure in heart failure patients. Indian J Pacing Electrophysiol 2015 (in this issue).
[11] Miller AL, Kramer DB, Lewis EF, Koplan B, Epstein LM, Tedrow UB. Event-free survival following CRT with surgically implanted LV leads versus standard transvenous approach. Pacing Clin Electrophysiol 2011;34:490–500.

Roy M. John*
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

* Cardiac Arrhythmia Service, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115, United States.
E-mail address: rjohn2@partners.org.

Available online 9 November 2016