Cardiac Resynchronization Therapy for Congestive Heart Failure

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Abstract: Congestive heart failure (CHF) is a leading cause of morbidity and mortality worldwide. Many CHF patients have intraventricular conduction delays such as right or left bundle branch block or non-specific QRS widening on the body surface ECG. Intraventricular conduction delays cause dyssynchrony of the ventricles, leading to regional movement abnormalities and worsening of cardiac function. Recent clinical trials have indicated that cardiac resynchronization therapy improves cardiac function class, exercise tolerance, maximum oxygen consumption and quality of life in patients with moderate to severe heart failure. It is also associated with a significant reduction in mortality and hospital admissions for heart failure. [Life Science Journal. 2006;3(1):1-4] (ISSN: 1097-8135).

Keywords: heart failure; cardiac resynchronization therapy; cardiac electrophysiology

1 Introduction

Congestive heart failure (CHF) is a common cardiovascular disease and a leading cause of morbidity and mortality around the world. Despite major advances in pharmacological therapy in the past 2 decades, CHF is still associated with a high morbidity and mortality rate (The CONSENSUS Trial Study Group, 1987; Bristow, 2000). Recently, the effects of cardiac resynchronization therapy, or biventricular pacing, on heart failure have been investigated in a number of clinical trials (Leclercq, 1998; Alonso, 1999; Auricchio, 1999; Gras, 1998; Leclercq, 2000; Etienne, 2001; Lau, 2000; Cazeau, 2001; Braunschweig, 2000; Abraham, 2002 ; Higgins, 2003; Bristow, 2004; Cleland, 2005). The rationale for the resynchronization therapy is that many of the heart failure patients have intraventricular conduction delays, leading to poor coordination of ventricular contraction and relaxation (dyssynchrony) and worsening cardiac function (Farwell, 2000; Aaronson, 1997; Shenkman, 2002; Xiao, 1992; Littmann, 2000).

Results from major clinical studies have demonstrated that cardiac resynchronization therapy provides significant improvement in cardiac function, exercise tolerance and quality of life (Leclercq, 1998; Alonso, 1999; Auricchio, 1999; Gras, 1998; Leclercq, 2000; Etienne, 2001; Lau, 2000; Cazeau, 2001; Braunschweig, 2000). MIRACLE trial, one of the largest clinical trials on cardiac resynchronization therapy, presents some convincing evidence on the efficacy of cardiac resynchronization therapy in treating moderate to severe CHF (Abraham, 2002). However, no clear benefits on short-term mortality are observed in the study. Two recent trials, the COMPANION (Bristow, 2004) and CARE-HF (Cleland, 2005), have demonstrated that cardiac resynchronization therapy, with or without implantable defibrillator, not only improves patient's quality of life but also reduces the mortality in short- and medium-term. The primary aims of this paper are to review the most recent landmark clinical trials and evaluate the therapeutic effects of cardiac resynchronization on CHF.

2 Rationale of Cardiac Resynchronization Therapy

Intraventricular conduction delays, such as right or left bundle branch block (RBBB or LBBB), or non-specific wide QRS complex, occurs in more than 20% of patients with CHF (Farwell, 2000; Shenkman, 2002). Such conduction delays are the primary causes of dyssynchrony of the ventricles. They have a negative impact on the failing heart to eject blood and are major contributors of worsening clinical symptoms. QRS duration is closely related to the level of ejection fraction, the wider the QRS duration, the lower the ejection fraction (Shenkman, 2002). LBBB alone is associated with a 13% increase in the left ventricular end-systolic diameter and 40% reduction in left ventricular ejection fraction. Left ventricular dyssynchrony also enhances the severity of the mitral regurgitation in CHF patients (Xiao, 1992; Littmann, 2000; Saxon, 1998; Kerwin, 2000).

Furthermore, intraventricular conduction de-

lays have been found to correlate with an increased risk of death in CHF patients (Xiao, 1996; Shamim, 1999; Hesse, 2001). The highest 5-year mortality has been found in those with QRS duration between 120 – 140 ms (Shenkman, 2002). Both LBBB and RBBB are associated with elevated and equal all-cause mortality rates in a general population (Hesse, 2001).

The current indications for cardiac resynchronzation therapy are that patients are in New York Heart Association class Ⅲ or Ⅳ despite standard pharmacological therapy, with a left ventricular ejection fraction of less than 35 per cent and left ventricular end-diastolic dimension of at least 30 mm (Cleland, 2005). The duration of QRS complex must be more than 120 ms. Additional criteria to be met are an aortic pre-ejection delay of more than 140 ms, an interventricular mechanical delay of more than 40 ms or delayed activation of the posterolateral left ventricular wall (Higgins, 2003; Bristow, 2004; Cleland, 2005).

Currently, resynchronization is achieved by pacing or sensing the right atrium, pacing the right and left ventricles. This involves the positioning of pacing leads into the right atrium, right ventricle and the left ventricle, respectively (Wang, 2003). The positioning of left ventricular pacing lead is the key for a successful resynchronization therapy. This is achieved by inserting a pacing lead into one of the distal coronary venous branches where the left ventricle is paced from the epicardium. The pacing locations for the best hemodynamic outcomes are the lateral or posterolateral left ventricular walls (Wang, 2003).

There is a considerable variability in the presence, diameter, angulation and tortuosity of coronary veins (Meisel, 2001). For this reason the coronary veins must be studied by injecting contrast media into the coronary sinus before the positioning of left ventricular lead. Overall, the success rate for implantation of left-sided leads ranges from 75% to 93% (Leclercq, 1998; Alonso, 1999; Auricchio, 1999; Gras, 1998; Leclercq, 2000; Etienne, 2001; Lau, 2000; Cazeau, 2001; Braunschweig, 2000; Abraham, 2002; Higgins, 2003; Bristow, 2004; Cleland, 2005).

Color tissue Doppler imaging (TDI) has emerged as a noninvasive tool for selection of proper left ventricular pacing sites and for evaluation of myocardial contraction synchrony. TDI has been proven useful in detecting quantitatively the regional systolic and diastolic times and velocities within the myocardium (Hatle, 2000). TDI is able to accurately identify the ventricular site of most delayed activation (Ansalone, 2002). Pacing from these most delayed sites results in the greatest improvement in ventricular resynchronization and ventricular function (Ansalone, 2002).

Cardiac resynchronization therapy is generally well tolerated by patients. However, implantation and maintenance of biventricular pacing devices are associated with greater risks than a conventional pacing device. Apart from the common adverse effects seen in a pacemaker implantation, a very small proportion of patients (<0.1%) undergoing cardiac resynchronization procedure develop complete heart block that requires permanent cardiac pacing, or progressive hypotension or asystole during the procedures (Abraham, 2002).

Other major adverse effects include coronary sinus dissection (4%) and cardiac vein or coronary sinus perforation (2%) (Abraham, 2002). After implantation, approximately 6% – 11% of the patients require repositioning or replacement of the left ventricular lead due to lead dislodgement during long-term pacing (Abraham, 2002; Alonso, 2001). However, this complication does not result in the discontinuation of treatment in any patient.

3 Effects of Cardiac Resynchronization Therapy

The primary goals of any heart failure treatment are to improve the length or quality of the patient's life. Trials of cardiac resynchronization therapy have shown improvements in functional status of the heart, the distance patients can walk in 6 min, and hospital admission for heart failure (Braunschweig, 2000; Abraham, 2002; Higgins, 2003; Bristow, 2004; Cleland, 2005). Cardiac resynchronization therapy also reduces left ventricular end-systolic diameter, and increases stroke volume and thus, cardiac output and ventricular systolic function (Leclercq, 1998; Alonso, 1999; Auricchio, 1999; Gras, 1998). There is also an increase in the systolic and pulse pressure, and a decrease in pulmonary wedge pressure (Leclercq, 1998; Alonso, 1999; Auricchio, 1999; Gras, 1998). The acute hemodynamic benefits of the cardiac resynchronization are largely due to improved septal contribution to ventricular ejection, increased diastolic filling times, and reduced mitral regurgitation. Another important and unique benefit of resynchronization therapy is that biventricular pacing acutely enhances systolic function but modestly lowering myocardial oxygen consumption (Nelson, 2000). Most other heart failure therapy, however, increase energy cost of the myocardium while enhancing systolic function.

MUSTIC study (Linde, 2002) was a randomised, crossover clinical trial where patients un-

derwent 3 months' active pacing then switched to a non-pacing period of three months. It was found that patients' exercise capacity improved only during active pacing period, with a more than 23% increase in 6-min walking distance. The clinical symptoms were improved by 32% during active treatment and the maximal oxygen consumption was up by 8%.

MUSTIC study (Linde, 2002) also investigated the long-term effects of cardiac resynchronization therapy in patients with sinus rhythm and those with atrial fibrillation. At the end of the 12-month active pacing period, there was a significant improvement in 6-min walk distance, peak oxygen consumption and the quality of life. The NYHA class improved by 25% – 27% and the ejection fraction was up by 4% – 5% (Linde, 2002). Mitral regurgitation in these patients was almost halved at the end of the trial. These data indicate the clinical benefits of cardiac resynchronization can be maintained for at least 12 months.

MIRACLE trial randomized 228 patients to biventricular pacing therapy and 225 to a placebo control arm for six months (Abraham, 2002). All patients were in normal sinus rhythm and had an ejection fraction of less than 35%. Compared with the control group, patients assigned to cardiac resynchronization experienced an improvement in the distance walked in 6 min, NYHA functional class and quality of life (Abraham, 2002). The time on the treadmill exercise testing and the ejection fraction were also improved during active pacing periods. Furthermore, patients treated with cardiac resynchronization required less hospitalisation or intravenous medication for heart failure (Abraham, 2002). However, the clinical benefits were observed on only about two thirds of the patients received the resynchronization therapy. Furthermore, although the overall cardiac event rate was 40% lower in the cardiac resynchronization group, the mortality rate was similar between the pacing and control groups in the first 6 months of therapy (Abraham, 2002).

The CARE-HF trial is the largest trial so far, to assess the effect of cardiac resynchronization therapy on mortality rates in short- and medium-term (Cleland, 2005). A total of 813 patients were enrolled and followed for more than 29 months. At the end of the study, the mortality rate in the cardiac resynchronization therapy and medication group was 20% and 30%, respectively, indicating that resynchronization reduces mortality more than 2 years after the treatment. As compared with medical therapy, cardiac resynchronization reduced the interventricular mechanical delay, the end-systolic volume index and the area of the mitral regurgitant jet (Cleland, 2005). There was also a greater increase in ejection fraction, improvement in quality of life and symptoms in the resynchronization group (Cleland, 2005).

Another major trial, COMPANION, compared the effect of drug therapy, cardiac resynchronization, and cardiac resynchronzation plus implantable defibrillator on mortality and hospital admission in 1,250 patients (Bristow, 2004). Compared with the drug therapy group, the risk of the combined end point of death or hospitalization for heart failure was reduced by 34 percent in the resynchronization group and by 40 percent in the resynchronization-defibrillator group (Bristow, 2004). These results suggest that a combination of resynchronization therapy and implantable defibrillator offers further survival benefits for patients with severe CHF.

4 Conclusions

Cardiac resynchronization therapy offers a new approach for treating patients with ventricular dyssynchrony and moderate to severe heart failure. Clinical trials have demonstrated that this new therapy improves patient's symptoms, quality of life and short- to medium-term survival. However, up to 30% of patients who receive resynchronization devices will not show clinically significant responses to this therapy. Given the significant costs associated with the therapy, it is important to have further studies to establish measures of identifying the non-responders before the therapy is implemented.

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Received November 1, 2005