Cardiac resynchronization therapy in congestive heart failure: The state of the art and future perspectives

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Congestive heart failure (CHF) is one of the leading causes of morbidity and mortality worldwide. Up to 50% of CHF patients have intraventricular conduction disturbances such as left bundle branch block or nonspecific wide QRS complex on the body surface ECG. Intraventricular conduction delays cause dyssynchrony of the ventricles which in turn leads to regional movement abnormalities and worsening of cardiac function. Recent clinical trials have indicated that cardiac resynchronization therapy or biventricular pacing in CHF patients with left bundle branch block or wide QRS complex improves cardiac function class, exercise tolerance, maximum oxygen consumption and quality of life within the first 12 months of therapy. The number of hospitalizations and the use of intravenous medications for worsening heart failure are also reduced by this new therapy. Apart from the short to medium term clinical benefits, cardiac resynchronization therapy has not been shown to reduce overall cardiac mortality. The present article reviews the pathophysiology of ventricular dyssynchrony and evaluates the results of recent clinical trials on resynchronization therapy.

Key Words: Biventricular pacing; Cardiac function; Cardiac resynchronization; Congestive heart failure

PATHOPHYSIOLOGY OF VENTRICULAR DYSSYNNCHRONY

Intraventricular conduction delay, such as right or left bundle branch block (RBBB or LBBB, respectively), or nonspecific wide QRS complex, are seen in up to 50% of CHF patients (13-15). Such conduction delays often lead to dyssynchrony of the ventricles which in turn cause worsening of clinical symptoms. In the case of LBBB, asynchronous ventricular contraction makes the left ventricular lateral wall contract much later than the interventricular septum. There is also a right ventricle-left ventricle asynchrony with the right ventricle contracting earlier than the left.

Intraventricular conduction disturbances have a negative impact on the ability of the failing heart to eject blood. A recent large-scale clinical survey (15) identified a linear relationship between increased QRS duration and decreased ejection fraction. RBBB alone leads to a 13% increase in the left ventricular end-systolic diameter and a 40% reduction in left ventricular ejection fraction. LBBB alone leads to a 13% increase in the left ventricular end-systolic diameter and a 40% reduction in left ventricular ejection fraction. LBBB and RBBB are associated with elevated and equal all-cause mortality rates in a general population (22).
TECHNICAL CONSIDERATIONS ON CARDIAC RESYNCHRONIZATION

A QRS duration more than 150 ms with class 3 or 4 CHF and low left ventricular ejection fraction is an accepted indication for biventricular pacing therapy. However, those with QRS duration greater than 120 ms are also responding to resynchronization. The first clinical applications of cardiac resynchronization therapy occurred between 1990 and 1992, when two separate groups of investigators reported that pacing with a dual chamber pacemaker at right atrium and right ventricle with a programmed short atrioventricular delay improved clinical symptoms in severe CHF patients waiting for heart transplantation (23,24). Currently, resynchronization is achieved by pacing or sensing the right atrium, and pacing the right and left ventricles.

The key for a successful resynchronization procedure is the positioning of the left ventricular pacing lead. Under local anesthesia, a pacing lead is placed via the coronary sinus into one of the distal coronary venous branches where the left ventricle is paced from the epicardium. The insertion of the left ventricular leads follows the same conventional central-stylet technology, with curves being fashioned to negotiate the variability in cardiac vein anatomy.

There is a considerable variability in the presence, diameter, angulation and tortuosity of coronary veins (25). For this reason, the coronary veins are first studied by contrast injections with a balloon-inflated catheter within the coronary sinus. The left ventricular lead is subsequently placed. Overall, the success rate for implantation of left-sided leads ranges from 75% to 93% (3-12).

The pacing site in the left ventricle is of major importance for maximal improvement of left ventricular function. Pacing at a suboptimal site can even deteriorate left ventricular contractility. The ideal left ventricular pacing sites are the lateral or posterior ventricular walls where the best hemodynamic outcomes are expected (26,27). The increase in pulse pressures and dP/dt are maximal at the mid-lateral epicardial pacing sites compared with other regions of the left ventricle (26). These locations can be reached through the left marginal vein (for the lateral wall) or posterior veins (for the posterior wall). Pacing within the great cardiac vein (interventricular sulcus) should be avoided because the improvement in hemodynamics from pacing these locations are suboptimal.

Colour tissue Doppler imaging (TDI) has emerged as a noninvasive tool for the selection of proper left ventricular pacing sites and for evaluation of myocardial contraction synchrony. TDI is useful for quantitatively detecting the regional systolic and diastolic times and velocities within the myocardium (28). TDI is able to accurately identify the ventricular site of most delayed activation (29). Pacing from these most delayed sites results in the greatest improvement in ventricular resynchronization and ventricular function (29).

CLINICAL OUTCOMES OF CARDIAC RESYNCHRONIZATION

Several studies have indicated that cardiac resynchronization reduces left ventricular end-systolic diameter and increases stroke volume and, thus, cardiac output and ventricular systolic function (3-6). There is also an increase in the systolic and pulse pressures, and a decrease in pulmonary wedge pressure (3-6). The acute hemodynamic benefits of 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 lowers myocardial oxygen consumption (30). Most other heart failure therapies, however, increase energy cost of the myocardium and enhance systolic function.

Randomized clinical trials have shown that cardiac resynchronization enhances exercise performance (eg, maximal oxygen consumption) during active pacing periods.

The Multisite Stimulation in Cardiomyopathy (MUSTIC) study (31) was a randomized, cross-over clinical trial where patients underwent three months of active pacing and then were switched to a nonpacing period for three months. The study found that patients’ exercise capacity improved only during the active pacing period, with a more than 23% increase in 6-min walking distance. Clinical symptoms improved by 32% during active treatment and maximal oxygen consumption increased by 8%.

The MUSTIC study also investigated the long term effects of cardiac resynchronization in patients with sinus rhythm and 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 quality of life. The New York Heart Association (NYHA) class improved by 25% to 27% and the ejection fraction increased 4% to 5% (31). 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.

The recently completed MIRACLE trial (32) is the largest study on biventricular pacing to date. This six-month trial randomized 228 patients to biventricular pacing therapy and 225 patients to a placebo control arm. 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 (32). The time on the treadmill and the ejection fraction also improved during active pacing periods. Furthermore, patients treated with cardiac resynchronization required less hospitalization or intravenous medication for heart failure (32). Although the overall event rate was 40% lower in the cardiac resynchronization group, the mortality rate was similar between the pacing and control groups in the first six months of therapy (32).

COMPLICATIONS

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 (less than 0.1%) undergoing cardiac resynchronization procedure develop complete heart block that requires permanent cardiac pacing, or progressive hypotension or asystole during the procedures (32).

One of the problems associated with biventricular pacing is that in about 8% of patients, left ventricular lead insertion failed (32). Other major adverse effects include coronary sinus dissection (4%) and cardiac vein or coronary sinus perforation (2%) (32). After implantation, approximately 6% to 11% of
the patients required repositioning or replacement of the left ventricular lead due to lead dislodgement during long-term pacing (32,33). However, this complication did not result in the discontinuation of treatment in any patient. When all possible reasons for technical failure were considered, about 8% of participating patients were unable to receive and be maintained on resynchronization therapy (32).

The success rates for left ventricular lead placement and the rate of acute or delayed left ventricular lead dislodgement are closely related to the operators’ experience. In a single centre that has conducted 116 resynchronization procedures over a six-year period, the success rate of left ventricular lead insertion increased from 61% early on to 98%, and left ventricular lead dislodgement decreased from 30% in the early years to 11% (33).

LIMITATIONS AND FUTURE PERSPECTIVES

All current clinical trials on cardiac resynchronization therapy in CHF are based on short or medium term observations. It is unclear whether the benefits in clinical outcomes during the first six to 12 months of active pacing are sustained over the following months or years. The benefits of cardiac resynchronization on overall cardiac mortalities remain to be seen.

The criteria for patient selection need to be further defined. Apart from the current electrocardiography (ECG) criteria, new methods examining regional wall motion and generating a dysynchrony index may improve the current indirect ECG methods for patient selection.

Furthermore, there is uncertainty as to whether cardiac resynchronization is useful in CHF patients with chronic atrial fibrillation. The current practice with these patients is ablation of the atrioventricular node followed by cardiac resynchronization. This requires rate-responsive generators for atrial and ventricular pacing, and activation of both lower chambers. Although recent trials suggest that cardiac resynchronization offers significant clinical benefits in terms of cardiac function and quality of life within 12 months of therapy (31,34), more investigations on a larger scale are needed to clarify the benefits of cardiac resynchronization in these patients.

CONCLUSIONS

Cardiac resynchronization therapy, or biventricular pacing, has presented a new dimension for heart failure management. Current evidence suggests that in CHF patients with intraventricular conduction delay or wide QRS complex on surface ECG, cardiac resynchronization improves exercise tolerance and cardiac function, and reduces the need for hospitalization. The long-term effects of cardiac resynchronization and its impact on the overall cardiac mortalities remain to be seen.

REFERENCES