**Cardiac Resynchronization Therapy for Heart Failure**

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**ABSTRACT**

Heart failure is the final common pathway of all heart diseases and is the major cause of morbidity and mortality. Approximately 1/3rd of patients with heart failure have wide QRS causing ventricular dyssynchrony which results in various mechanical consequences aggravating the heart failure. This can be addressed by a biventricular pacing device which can rectify that problem. Cardiac Resynchronization Therapy (CRT) is the simultaneous pacing of the left and right ventricles following atrial contraction using a biventricular pacemaker to restore ventricular contraction synchrony in patients who have heart failure accompanied with ventricular dyssynchrony. Numerous trials have shown that such therapy has improved the symptoms and decreased mortality in conjunction with optimal medical treatment.

**INTRODUCTION**

Heart failure is a clinical syndrome resulting from a structural and functional disorder of the heart that impairs the ability of the ventricles to fill with or eject blood to fulfil the demands of the body, or does so in expense of increased filling pressures. The major manifestations of heart failure are: dyspnoea, fatigue, palpitations, fluid retention and decreased exercise tolerance. Heart failure is the final common pathway of all heart diseases and is the major cause of morbidity and mortality. Heart failure is estimated to afflict more than 22 million people worldwide with an estimated 2 million new cases diagnosed annually. According to the American Heart Association, heart failure affects nearly 5.7 million Americans of all ages. It is responsible for more hospitalizations than all forms of cancer combined. It accounts for 34% of cardiovascular-related deaths and about 670,000 new cases are diagnosed each year. Approximately 15 to 30% of the patients with heart failure have wide QRS duration of ≥ 120 msec in the surface Electrocardiogram (ECG). This width of QRS is being used to identify patients with dissynchronous ventricular contraction which is associated with increased mortality.

**BASIC SCIENCE**

The mechanical consequence of ventricular dyssynchrony includes suboptimal ventricular filling, reduction in the rate of rise of ventricular contractile force, prolongation of mitral regurgitation and paradoxical septal motion. Ventricular dyssynchrony is associated with increased mortality in patients with heart failure. Dyssynchronous contraction can be addressed by electrically activating right and left ventricle in synchronous manner with a biventricular pacemaker device known as Cardiac Resynchronization Therapy (CRT). This approach to heart failure with biventricular device may enhance ventricular contraction and reduce the degree of secondary mitral regurgitation. Short term use of biventricular device has been associated with improvement of cardiac function and hemodynamics including rate of rise of LV pressure (dp/dt), increase in pulse pressure, left ventricular stroke work, cardiac index and decrease in pulmonary capillary wedge pressure. Remarkably CRT improves ventricular function without increasing myocardial oxygen consumption in contrast to inotropic agent such as Dobutamine. In addition CRT may reverse left ventricular remodelling over time.

**HOW A CARDIAC BIVENTRICULAR PACEMAKER DEVICE IS IMPLANTED?**

The procedure is similar to implantation of a dual chamber pacemaker. A pacing lead is placed in right atrium and another in right ventricular apex. Then coronary sinus is cannulated and a third lead is placed preferably in postero-lateral vein of coronary sinus (CS) which serves as a Left Ventricular (LV) lead. Right atrium is paced with short Atrio Ventricular delay to insure consistent pacing of both ventricles.

**Complications of the procedure**

In addition to the complications of a pacemaker implantation the most common complication is trauma to coronary sinus which is 2 to 4%. Perforation of CS causing cardiac tamponade is rare and occurs in <1%. CS lead dislodgement occurs in 1 to 3% and diaphragmatic stimulation in 1 to 4% which is reduced by the use of bipolar leads.

**Human Studies**

Studies have shown that for the entire heart failure population about one third have a wide QRS. Left Bundle Branch Block (LBBB) was present in 8% of those with preserved LV systolic function (diastolic heart failure), in 24% of those with left ventricular ejection fraction less than 50% (p<0.001) and 38% of those with severe heart failure. There is increased one year mortality with presence of complete LBBB (QRS > 140 ms). Havranek and colleagues studied the charts of 800 Medicare patients per (US) state, or 40,000, who were hospitalized with a principle diagnosis of heart failure. A totla of 34,587 were left after excluding those less than 65 years old and various other reasons, and of those 32,270 had ECG data available. 15.3% of those were identified as having LBBB.

Although mechanical dysynchrony is more prevalent in patients with wide QRS group it is not uncommon in patients with normal QRS, estimated around 50%. Approximately 30 – 40% of patients with wide QRS do not have demonstrable dysynchrony and 25 – 30% with dysynchrony demonstrated by echocardiogram do not have wide QRS of more than 120 ms.

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msec. Acute data have suggested that patients with QRS width of 120 – 130 msec had less increase or no change in cardiac contractility and stroke volume compared to patients with a QRS width of 150 msec or more.²

A study done by Iuliano et al on 669 heart failure patients (ischemic or non ischemic cardiomyopathy, NYHA II-IV heart failure) with median follow up of 45 months, prolonged QRS was associated with increase in mortality (49.3% vs. 34.0%) and sudden death (24.8% vs. 17.4%). LBBB was associated with worse survival but not sudden death.³ The VEST Study demonstrated QRS duration was found to be an independent predictor of mortality. Patients with wider QRS (>200 ms) had five times greater mortality risk than those with the narrowest (< 90 ms).¹⁰ In the first closed chest study of CRT, in 27 subjects with heart failure and QRS delay, Blanch and associates¹¹ demonstrated improvements in systolic blood pressure, pulmonary capillary wedge pressure and V wave amplitude with left ventricular or biventricular stimulation in comparison with baseline or right ventricular pacing.

Initial trials assessed only measures of heart failure, functional status, LV systolic function and LV remodeling (LV end – systolic and diastolic dimensions). The later, larger studies targeted mortality and hospitalization endpoints. Initial trials showed improvement of heart failure, increased functional capacity and improvement in quality of life. Several prospective, randomized trials have been performed to evaluate the effectiveness of CRT. In most of the trials transvenous left ventricular leads was use where as only two early trials used epicardial left ventricular leads, placed via limited thoracotomy for LV stimulation.¹²,¹³ The pacing Therapies for Congestive Heart Failure (Path I and II– CHF) European studies were ground breaking in that chronic device programming was based on acute hemodynamic measures of cardiac performance. They enrolled patients with NYHA III or IV heart failure, sinus rate higher than 55 beats per minute and QRS duration longer that 120 msec showed improvement in functional status and a decrease in LV dimensions at 6 months.¹⁴

The Multicentre InSync Randomized Clinical Evaluation (MIRACLE) study group a double blind study of bi ventricular pacing in patients with moderate to severe congestive heart failure. All 453 patients was randomly assigned to “CRT on” or “CRT off” status for a period of 6 months. The patients who had CRT turned on had increased 6 minutes walk test, maximal oxygen consumption and increased quality of life. It is interesting to note that neither baseline QRS duration nor type of bundle branch block influenced response to CRT. Improvements in LV end – diastolic volume and ejection fraction (EF) were two fold greater in patients with non ischemic cardiomyopathy.¹⁵

Concurrent with MIRACLE trial enrollment, two large – scale trials of CRT – D for patients with heart failure and either primary or secondary indications for an ICD were also enrolling subjects. These were Multicentre InSync ICD randomized Clinical evaluation (MIRACLE ICD) and the CONTAK ICD Biventricular Pacing Study. Sixty one percent and 75% of patients had ischemic cardiomyopathy respectively. Both studies demonstrated improvements in functional measures of heart failure status in patients with NYHA class III to IV. Neither study showed a difference in the incidence of treated episodes of VT / VF with CRT on or off, indicated a neutral effect of CRT on the arrhythmia substrate early after device implantation. There was improvement in LV ejection fraction and ventricular size and dimension and degree of mitral regurgitation were noted.¹⁶,¹⁷

The Multisite Stimulation in Cardiomyopathy (MUSTIC) Trial provided the first long term controlled trial data on the efficacy of CRT. In this single – blinded crossover study Bi ventricular pacing with transvenous systems, compared with an inactive pacing mode was associated with improvements in six minute walk distance, peak oxygen consumption, and Quality of Life scores in patient with severe heart failure, LV systolic dysfunction and electrical conduction abnormalities.¹⁸

A reduction in the risk of heart failure events in patients treated with CRT plus an ICD over that of individuals treated with ICD alone was demonstrated in the Multicenter Automatic Deﬁbrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT – CRT) a randomized trial included 1820 patients with an EF of 30% of less, a QRS duration of 130 msec or more and NYHA class I or II symptoms.¹⁹ During an average follow – up of 2.4 years, death from any cause or a nonfatal heart failure event
occurred in 17.2% of patients in the CRT – ICD group versus 25.3% of patients in the ICD only group. There was 41% reduction in the risk of heart failure events in patients in the CRT group, which was evident primarily in patients with a QRS duration of 150 msec or more. CRT was associated with a significant reduction in LV volume and improvement in the EF. No significant difference occurred between the two groups in the overall risk of death. In the follow up women seemed to achieve a better response to CRT than men, with a significant 69% reduction in heart failure alone with echocardiographic evidence of reverse cardiac remodeling.20

The Cardiac Resynchronization – Heart Failure (CARE – HF) study, enrolling 813 patients at 82 European centers, compared CRT only with optimal medical therapy in patients with NYHA class III or IV heart failure due to LV systolic dysfunction and ventricular dyssynchrony. Over a mean follow up of 29 months, CRT resulted in significant reductions in the primary composite endpoints of death or cardiovascular hospitalization. Additionally secondary endpoint of mortality was achieved. The relative risk reduction in death was 36% with biventricular pacing (P = 0.002) when compared to optimal medical treatment. This trial also demonstrated that the advantages of CRT over best medical management appear to increase over time.21

In Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) have demonstrated that CRT with or without defibrillation has decreased all cause mortality and hospitalization by 20%. It was conducted in patients with NYHA class III or IV heart failure due to ischemic or non ischemic cardiomyopathies and a QRS interval of at least 120 msec. The addition of a defibrillator to biventricular pacing incrementally increased the survival benefit, resulting in a substantial 36% reduction in the risk of death compared with optimal pharmacologic therapy.22 In both CARE – HF and the COMPANION studies, mortality was largely due to reduction in sudden cardiac death.21,22 The 2010 Heart Failure Society of America (HFSA) guidelines indicates that device therapy is an integral part of the treatment of heart failure.

CONCLUSION

Cardiac resynchronization is a safe and the treatment option in patients with NYHA class III, IV (ambulatory). The earlier trials showed improvement in symptoms only but CARE – HF trial has shown additional mortality benefit. The AHA/ACC and European has incorporated in their guidelines for heart failure the implantation of CRT as a class I indication in patients with NYHA class III, IV (ambulatory) heart failure with QRS width of 120 msec or more with optimal medical treatment. Still there are difficulties with CRT, as only 10 – 15% of heart failure patients qualify for CRT. There is problem of non responders, which range from 20 – 30%. Nevertheless CRT has provided a hope for heart failure patients who are symptomatic despite optimal medical management.

REFERENCES

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**ANSWER**

**Formalin poisoning**

The UGI endoscopy done at the time of presentation had shown that the patient might have ingested some corrosive substance. On reviewing the history again, it was found that the patient had ingested 50 ml of formalin (40% solution of formaldehyde in water). The patient was treated conservatively with bowel rest, intravenous (IV) nutrition supplement, IV proton pump inhibitor, IV antibiotic and blood transfusion. The serum creatinine level, white blood cell and hemoglobin returned to normal range after 3 days of treatment. This is a case of formalin poisoning with the strange endoscopic finding, which was unusual in the sense that there was completely normal esophagus, but the presence of severely burnt gastric mucosa. The UGI endoscopy was repeated after 4 weeks of treatment with a full bowel rest to the patient. The repeat endoscopy after 4 weeks was normal (figure 3) with no traces of burn injury to the mucosa. Gastric outlet obstruction has been described as the late complication of formaldehyde ingestion.\(^1\) In our case, after a follow up of 12 weeks, the patient was doing well and did not develop any features of gastric outlet obstruction or other late complication.

![Figure 3. Stomach (normal mucosa, after four weeks of treatment)](image)

Formaldehyde poisoning has been described previously by some authors.\(^2,3\) The few signs and symptoms that develop following the ingestion of formaldehyde are severe abdominal pain, retching, development of seizures, hypotension and difficulty in breathing. To our knowledge, this is the first report of formalin poisoning presenting with hematemesis, having the finding of normal esophagus, but severely burnt gastric mucosa, which returned to completely normal condition after a 4 week of bowel rest and other conservative treatment.

**REFERENCES**