Chapter 3

The Impact of Cardiac Resynchronization Therapy in the Treatment of Heart Failure

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Additional information is available at the end of the chapter

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Abstract

The number of patients who suffer from heart failure is rapidly increasing. In about one-third of heart failure patients, conduction delays cause dyssynchronous left ventricular contractions, which leads to reduction in left ventricular function, adverse cardiac remodelling and finally increased mortality. Cardiac resynchronization involves simultaneous pacing of both ventricles, and improves left ventricular contractile function. Although resynchronization does not restore myocardial function, multiple studies have shown that cardiac resynchronization therapy improves quality of life, exercise capacity, symptoms of heart failure, left ventricular ejection fraction, morbidity and mortality. The use of cardiac resynchronization therapy has increased significantly, since its initial approval in 2001, in patients with advanced heart failure.

Keywords: heart failure, cardiac resynchronization therapy, electrophysiologist, left bundle branch block, left ventricular function

1. Introduction

The number of patients who suffer from chronic heart failure is rapidly growing. According to the 2016 update on heart disease and stroke statistics reported by the American Heart Association, an estimated 5.7 million Americans ≥20 years of age have a diagnosis of heart failure and projections show that the prevalence of heart failure will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with heart failure [1]. In the year of 2013, heart failure was the underlying cause in >65,000 deaths and contributed to the death of >300,000 people [1]. In the same report, there is an estimate that a total cost of over $30 billion was used for the treatment of heart failure in 2012 [1]. Direct medical costs attributed to 68% of this total amount. The lifetime risk of developing heart failure is 20% for adults at the

age of 40 years and goes up with age. Acute heart failure consists of one of the most common reasons for hospitalization, attributing to over 1 million discharges annually and high 30-day readmission rates (up to 25%) and 1 year (up to 60%) [1]. The prognosis for heart failure is poor, with an estimated mortality rate of 50% within 5 years of diagnosis.

2. Cardiac resynchronization therapy (CRT)

2.1. Advent of CRT

An intraventricular conduction delay is found in approximately 20–30% of patients with symptomatic heart failure. Conduction delay causes dyssynchronous left ventricular contractions, which lead to left ventricular dysfunction, adverse cardiac remodelling and eventually high mortality [2–4]. Conduction delay may also lead to mitral valve regurgitation, thus increasing symptoms of heart failure. The prevalence of left ventricular dyssynchrony in heart failure has been shown to increase with reduced left ventricular ejection fraction and with increased QRS width [5–7].

Cardiac resynchronization therapy (CRT), which was first introduced for clinical use in 1996, attempts to restore ventricular synchrony in patients who suffer from dilated cardiomyopathy with a widened QRS complex to improve the mechanical efficiency of left ventricular contraction. Since U.S. Food and Drug Administration (FDA) approval, the use of CRT has steadily increased [8]. Sridhar and colleagues showed a trend in CRT device implantation in the United States [9] (**Figure 1**).

2.2. Mechanism of CRT

Janaswamy et al. listed the studies which demonstrated that the presence of a bundle branch block or other intraventricular conduction delay can worsen heart failure due to systolic dysfunction by causing ventricular dyssynchrony [10] (**Table 1**). The rationale for CRT is based upon these findings. These acute mechanical benefits of CRT can be accompanied with more chronic adaptations that lead to long-term benefit in the patient who suffers from heart failure [11].

Nowadays, it has been reported that CRT improves quality of life, exercise capacity, symptoms of heart failure by [12–16] left ventricular ejection fraction [17, 18], morbidity and mortality [18] in patients with moderate to severe left ventricular dysfunction with a wide QRS complex. The benefit of CRT in mild to moderate heart failure has also been demonstrated by several studies [19–23]. Long-term beneficial effects on left ventricular function were shown by positron emission tomography evaluations, and CRT enhances myocardial forward work efficiency at rest in patients with dilated cardiomyopathy and heart failure [24, 25].

CRT improves left ventricular contractile function in patients with heart failure associated with left bundle branch block. Improved efficiency from resynchronization pacing is unlikely due to the alterations in intrinsic myocyte function. The improvement of ventricular function is the result of improved efficiency of the work performed by different regions of the wall. Nelson et al. demonstrated that pressure-volume loops display an increase in loop area and width (stroke work and volume, respectively) and a decline in end systolic volume with

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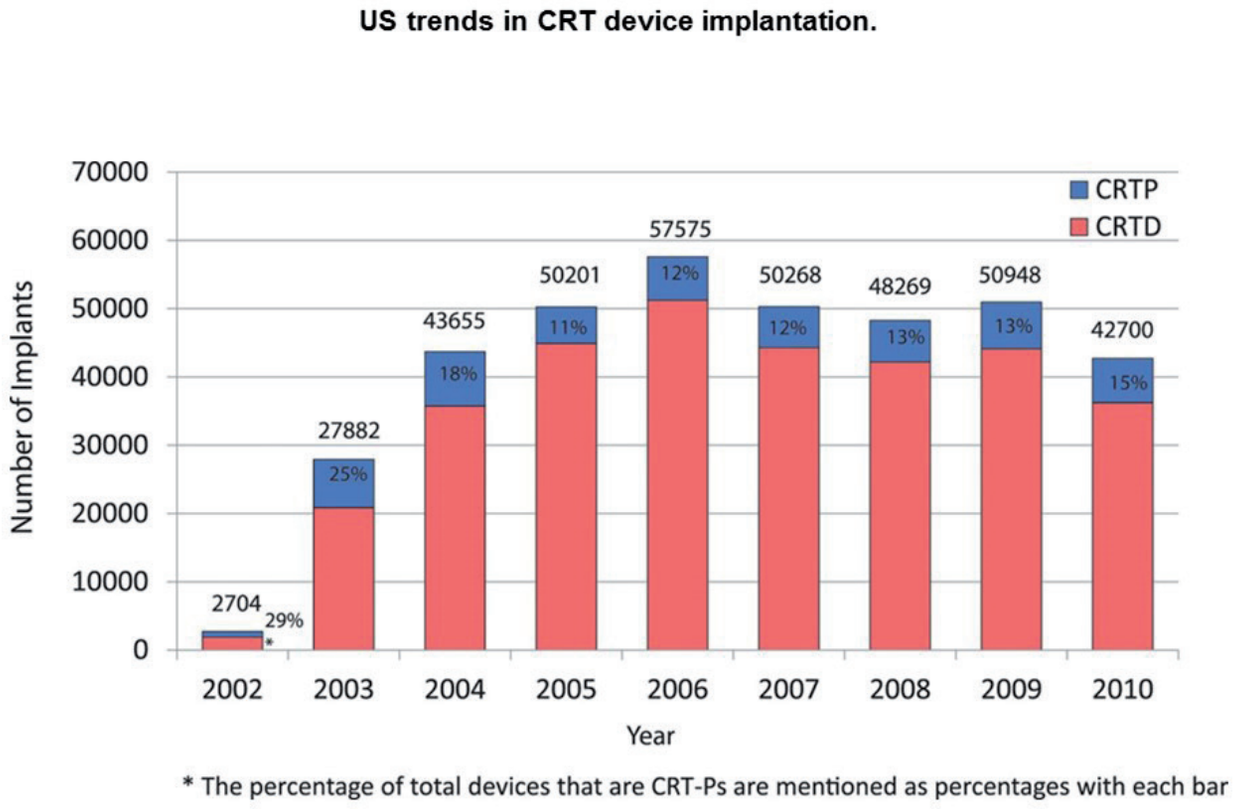

Figure 1. The number of CRT device implantation in the United States.

pacing [25]. In spite of improvements in systolic function, myocardial oxygen consumption decreases due to a slight fall in coronary flow as well as transcardiac oxygen gradient.

2.3. U.S. trends in CRT

CRT is now recommended for patients with heart failure due to systolic dysfunction combined with intraventricular delay. CRT is also recommended in addition to guideline-directed medical therapy, such as angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonist therapy and implantable cardioverter defibrillators (ICDs) when indicated for primary or secondary prevention of sudden cardiac death.

Sridhar et al. used the Nationwide Inpatient Sample database to identify all patients who underwent CRT implantation during 2002–2010 [9]. The overall trends in CRT device implantation, patient characteristics and outcomes were studied in detail and comparisons among demographic subgroups were performed. They found that an average of 41,578 CRT device implantations was performed per year. There has been a significant increase in the percentage of CRTs implanted in patients with advanced age (≥85 years). There were significant differences in CRT utilization favouring male and whites compared with female and black patients, respectively, in spite of adjustments for rates of heart failure. The highest numbers of implants were found in the patient group with moderate comorbidity (48%), followed by mild comorbidity group (39/7%). The overall number of CRT implantations in the severe comorbidity group was the lowest (12.3%). However, in the recent years, there has been a significant increase in the number of CRT implantation in this category (**Figure 2**).

Trial	Inclusion criteria	Primary end point	Follow-up	Results/conclusion
MIRACLE [12]	QRS duration ≥130 ms, an LV end diastolic diameter ≥55 mm by echocardiography and ejection fraction (EF) ≤0.35	NYHA symptom class, quality of life (Minnesota Living with heart failure questionnaire) and exercise capacity	6 months	Significant reductions in LVEDV ($P < 0.001$) and LVESV ($P < 0.001$) at 3 months, and continued to 6 months, in the CRT group compared with the control group. Significant improvement in EF compared with the control group at 3 months (2.3 vs. 0.6%; $P < 0.01$) and 6 months (3.6 vs. 0.4%; $P < 0.001$). Significant decrease in severity of MR at 3 months (-2.1 vs. 0.1 cm^2 jet area; $P < 0.01$) and at 6 months (-2.5 vs. 0.5 cm^2 jet area; $P < 0.001$). Increase in cardiac index from baseline to 6 months (0.11 L · min-1 · m-2; $P < 0.05$).
PATH-CHF [13]	NYHA functional class III or IV, dilated cardiomyopathy of any etiology, sinus rhythm ≥55 beats/min, a QRS complex duration ≥120 ms in at least two surface electrocardiographic (ECG) leads and a PR interval ≥150 ms	Primary end points: oxygen uptake at peak exercise, oxygen uptake at the anaerobic threshold and the 6-min walking distance. The secondary end points were changes in NYHA functional class and quality of life.	12 months	Oxygen uptake during bicycle exercise increased from 9.48 to 10.4 ml/kg/min at the anaerobic threshold ($P = 0.03$) and from 12.5 to 14.3 ml/kg/min at peak exercise ($P < 0.001$) with the first treatment. From 10.0 to 10.7 ml/kg/min at the anaerobic threshold ($P = 0.2$) and from 13.4 to 15.2 ml/kg/min at peak exercise ($P = 0.002$) with the second treatment. Increase in maximal exercise capacity from 12.6 to 15.6 ml/kg/min. Increase in 6-min walk performance from 357 to 466 m. 2/3 of patients improved to NYHA functional class I or II.
MUSTIC [14]	Severe HF with EF < 0.35 as measured by radionuclides and an LV end diastolic diameter >60 mm NYHA functional class III. The 6-min walking distance <450 m. QRS duration >150 ms. AF > 3 months. QRS duration >200 ms	6-min walking distance, the peak VO2 by cardiopulmonary exercise test, quality of life, NYHA class, systolic and diastolic blood pressure (BP), body weight, 12-lead surface electrocardiogram (ECG), 24-h Holter monitoring and Doppler echocardiography	1 year	Significant improvement in 6-min walk distance of 20% compared with baseline at 6, 9 and 12 months. Peak VO2 at 12 months had increased by 1.7 ml/min/kg or 11% in the SR group and 1.1 ml/kg/min or 9% in the AF group compared with baseline. Reduction in the Minnesota score of 17 points or 36% in the SR group and of 14 points or 32% in the AF group. The NYHA class improved by 0.7 in the SR group and 0.8 in the AF group.

Trial	Inclusion criteria	Primary end point	Follow-up	Results/conclusion
MIRACLE ICD [16] Combination with ICD	Cardiac arrest due to VF or VT, or spontaneously sustained ventricular tachyarrhythmia, or inducible ventricular fibrillation or sustained ventricular tachyarrhythmia, NYHA III or IV LVEF ≤ 0.35 QRS duration ≥130 ms LVEDD ≥55 mm	Primary end points: NYHA functional class, quality-of-life score and distance covered during the 6-min walking test.	1, 3 and 6 months.	Significantly higher median improvement in quality of life, NYHA functional class and distance during 6-min walk in the CRT group compared with the control group.
RAFT [19] ICD + CRT	NHYA class II or III, EF <0.30, an intrinsic QRS duration of 120 ms or more or a paced QRS duration of 200 ms or more, sinus rhythm or permanent AF or flutter with a controlled ventricular rate (≤60 beats per minute at rest and ≤90 beats per minute during a 6-min walk test) or planned atrioventricular-junction ablation after device implantation), and planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death	Primary outcome: death from any cause or heart failure leading to hospitalization	The mean (±SD) follow-up period was 40 ± 20 months for all patients and 44 ± 18 months for surviving patients	Prolonged time to the occurrence of the primary outcome in the ICD–CRT group (hazard ratio, 0.75; 95% confidence interval [CI], 0.64–0.87; $P < 0.001$). The time until death was significantly prolonged (relative risk reduction, 25%) in the ICD–CRT group (hazard ratio, 0.75; 95% CI, 0.62–0.91; $P = 0.003$).
COMPANION [29] Pharmacologic therapy alone, pharmacologic + CRV with pacemaker, pharmacologic + CRT+ pacemaker defibrillator	NYHA class III or IV HF, LVEF of 0.35 or less, QRS interval of at least 120 ms and a PR interval of more than 150 ms, sinus rhythm, no clinical indication for a pacemaker or ICD, and a hospitalization for the treatment of heart failure or the equivalent in the preceding 12 months.	primary end point: composite of death from any cause or hospitalization for any cause	Median duration of follow-up for the primary end point: 11.9 months in the pharmacologic therapy group, 16.2 months in the pacemaker group and 15.7 months in the pacemaker defibrillator group	12-month rate of death from any cause or hospitalization for any cause was 68% in the pharmacologic therapy group as compared with 56% in the pacemaker group (hazard ratio for the primary end point: 0.81) and 56% in the pacemaker defibrillator group (hazard ratio, 0.80)

Trial	Inclusion criteria	Primary end point	Follow-up	Results/conclusion
MADIT-CRT [30] ICD and CRT	Ejection fraction of 30% or less, a QRS duration of 130 ms or more, and NYHA class I or II symptoms	Death from any cause or nonfatal heart failure events, whichever came first	Follow-up of patients in the trial averaged 2.4 years	34% reduction in the risk of death or nonfatal heart failure (whichever came first) among patients in the CRT–ICD group, as compared with those in the ICD-only group. CRT–ICD therapy was associated with a greater benefit in women (hazard ratio, 0.37; 95% confidence interval [CI], 0.22–0.61) than in men (hazard ratio, 0.76; 95% CI, 0.59–0.97; $P = 0.01$ for interaction) and in patients with a QRS duration of 150 ms or more (hazard ratio, 0.48; 95% CI, 0.37–0.64) than in those with a QRS duration of less than 150 ms (hazard ratio, 1.06; 95% CI, 0.74–1.52; $P = 0.001$ for interaction).
REVERSE [31]	QRS ≥120 ms and LV ejection fraction ≤0.40, active 55-mm or wider LV end diastolic diameter, measured by echocardiography	Primary end point: HF clinical composite response	Patients were followed at 1, 3, 6, 12, 18 and 24 months	Worsening of the HF clinical composite response in 34 of the 180 patients (19%) assigned to CRT ON compared with 28 of the 82 patients (34%) assigned to CRT OFF ($p = 0.01$). LVESVi decreased by a mean of 27.5 ± 31.8 ml/m2 in the CRT ON compared with 2.7 ± 25.8 ml/m2 in the CRT OFF group ($P < 0.0001$). Rates of HF hospital stay was 14 of 82 (17.1%) in CRT OFF patients and 13 of 180 (7.2%) CRT ON patients

Table 1. Summary of studies of CRT.

2.4. Outcomes of CRT implantation

The in-hospital mortality rates associated with CRT implantation is shown in **Figure 3**.

For an elective CRT procedure, the mean length of stay was 2.81 days and the median was 1.00 day. The overall in-hospital mortality following CRT implantation was 0.87%, which has decreased significantly from 2003 to 2010 (1.08 in 2003 to 0.70% in 2010; $P = 0.03$). Mortality following elective CRT implantation was 0.4% compared with 1.0% with non-elective CRT implantations. The mortality was higher in male (0.93%) compared with female (0.71%), and decrease in mortality was observed in both male and female. The mortality rate in advanced age group (≥85 years) was significantly higher compared with younger population (<85 years). However, the mortality rate in the ≥85-year group has significantly decreased in recent years. Patients with

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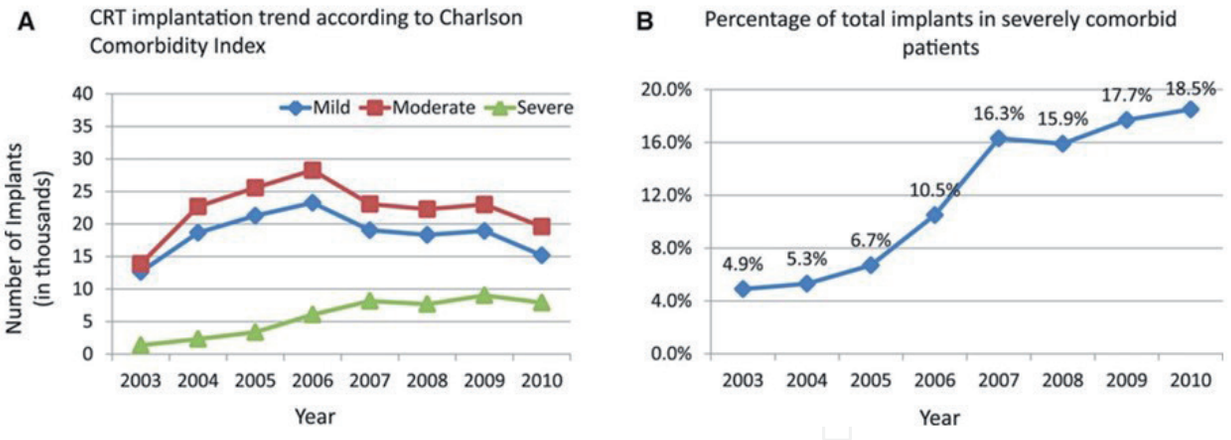

Figure 2. Patient comorbidities and CRT implantation. (A) CRT implantation trends stratified according to comorbidity categories. (B) CRT devices implanted in patients with severe comorbidities, expressed as a percentage of total CRT implants in the United States in each year.

severe comorbidities had significantly higher overall mortality (1.5%) compared with those with moderate (0.8%) or mild (0.7%) comorbidities ($P < 0.001$). However, mortality in all three comorbidity groups has decreased in recent years, most notably in the severe comorbidity group.

In terms of complications associated with CRT implantation, pericardial effusion was found in 0.2%, pneumothorax was found in 1.4% and hematoma was found in 3.0% of all CRT implantation procedures.

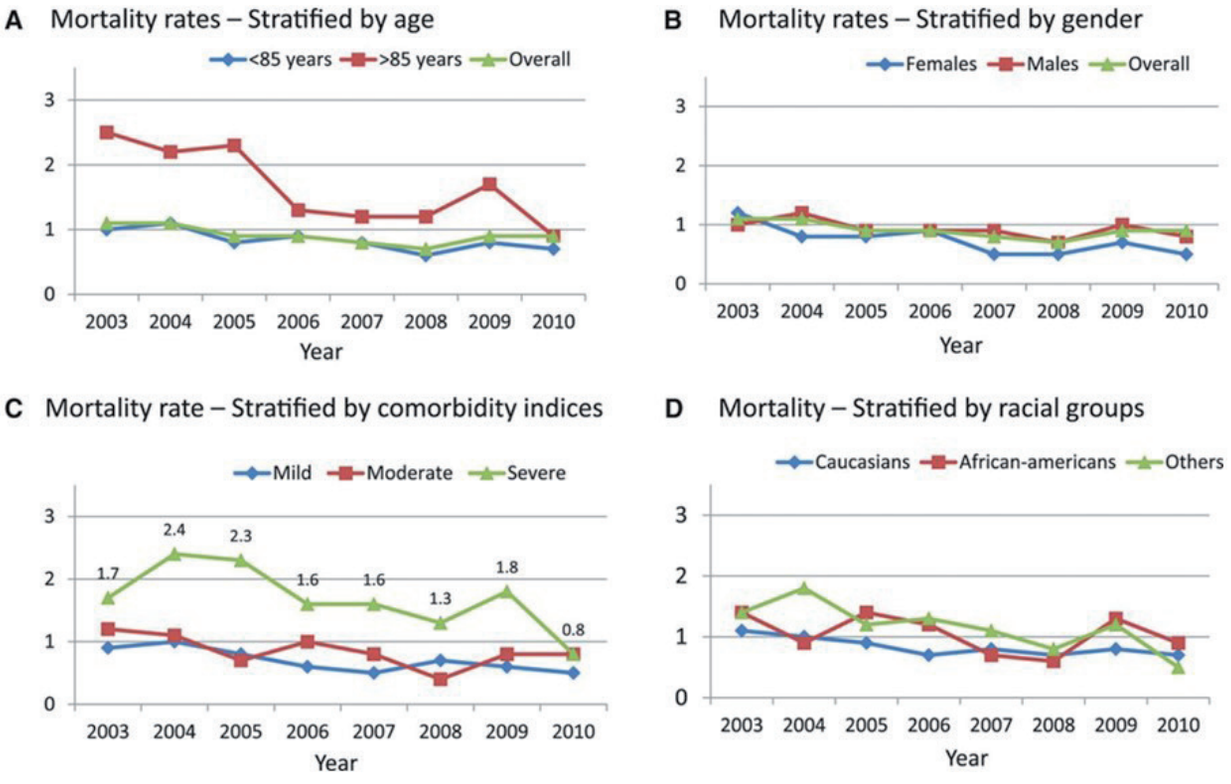

Figure 3. In-hospital mortality rates associated with CRT implantation stratified by patient characteristics.

The overall mean hospital charges accompanied with CRT implantation were reported to be $129,098 per implant. Of note, hospital charges for CRT implantation have dramatically increased from $111,197 in 2003 to $154,297 in 2010 ($P < 0.001$). Charges accompanied with CRT implantation were higher in male sex, ≥85-year group, and higher comorbidities compared with female sex, <85-year group, and lower comorbidities, respectively.

2.5. Implantation technique of CRT

Electrophysiologists are the main players for the CRT implantation. The CRT implantation requires the placement of a left ventricular pacing lead, which is fed onto the epicardial surface through a venous branch of the coronary sinus (**Figure 4**). Difficulty with coronary sinus cannulation, challenging anatomy of coronary sinus venous tributaries, unacceptable pacing and sensing thresholds, unavoidable phrenic nerve pacing and lead dislodgement have resulted in a 10–20% failure rate associated with left ventricular lead placement [16, 26]. When a transvenous lead implantation at desired sites is not achievable, epicardial left ventricular leads can easily be placed surgically directly on the lateral or posterolateral wall. Garikipati et al. performed a randomized study and reported no difference in the echocardiographic and clinical outcomes comparing a conventional transvenous approach versus surgical epicardial left ventricular lead placement for CRT [27]. Therefore, surgical approaches are a viable alternative when a transvenous procedure has failed or is not feasible.

Zhang et al. reported that advanced age, male sex, ischemic cause, end-stage heart failure, inadequate electrical delay and absence of mechanical dyssynchrony are regarded as non-modifiable risk factors for CRT non-responders [28]. However, efforts should be made to correct modifiable factors, such as suboptimal medical therapy, uncontrolled atrial fibrillation, left ventricular lead dislodgement or inappropriate location, loss of biventricular capture and lack of device optimization.

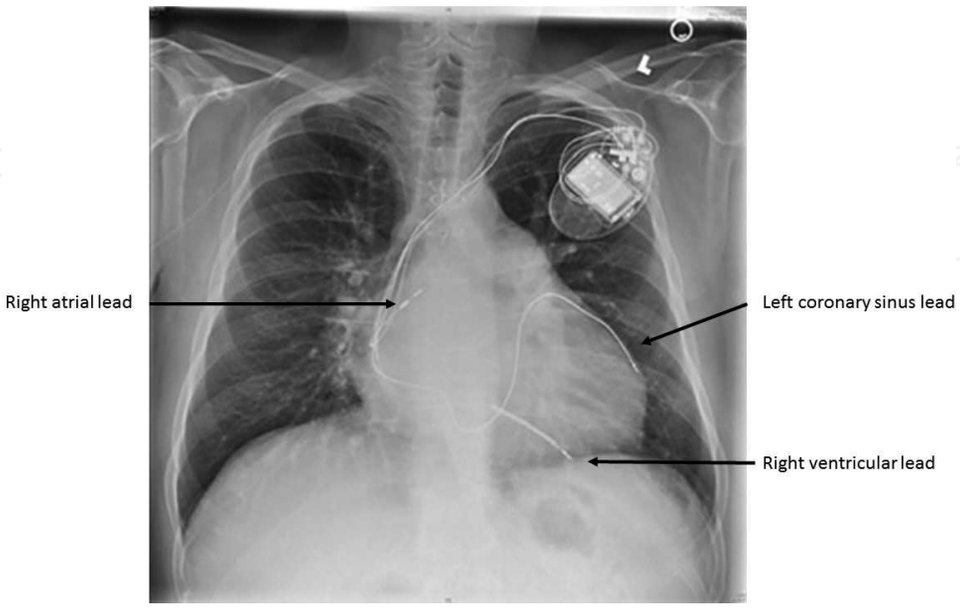

Figure 4. A chest X-ray after a successful CRT implantation.

3. Conclusions

CRT implantation is a safe procedure that has become safer in higher risk patients. With the increase of heart failure patients, CRT plays more and more role in the treatment of heart failure. Electrophysiologists should understand the indication, outcomes and procedure technique of CRT implantation.

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