Cardiac Resynchronization Therapy in Heart Failure Management

Hilman Zulkifli Amin, Siska Suridanda Danny

Heart failure (HF) is a worldwide health problem with high prevalence rate. The prevalence is over 23 million worldwide. It is a chronic disease characterized by the inability of the heart to pump an adequate amount of blood to achieve the demand of the different organ systems and/or doing so at increased filling pressures. Despite many recent advances in medication, the rate of people with HF is rising. This health challenges need to be answered properly. One of the new important treatment for HF is cardiac resynchronization therapy (CRT). Many patients with HF also have an abnormality of the heart’s electrical system resulting in asynchronous contraction pattern of heart muscle.

The ultimate goal of CRT is to restore synchrony of the heart rhythm in HF patients. CRT implantation in heart failure patients with proper indications like wide QRS complexes, low left ventricular ejection fraction (LVEF), and left bundle branch block (LBBB) has been proved to reduce morbidity, mortality, and also improve symptoms and quality of life (QoL).

(J Kardiol Indones. 2015;36:227-36)

Keywords: heart failure, cardiac resynchronization therapy
Terapi Resinkronisasi Jantung pada Penanganan Gagal Jantung

Hilman Zulkifli Amin, Siska Suridanda Danny


Tujuan utama dari TRJ ialah mengembalikan sinkronisasi ritme jantung pada pasien GJ. Pemasangan TRJ pada pasien GJ dengan indikasi yang tepat dan sesuai seperti kompleks QRS yang lebar, ejeksi fraksi ventrikel kiri yang rendah, dan blok berkas cabang kiri telah terbukti dapat menurunkan angka morbiditas, mortalitas, dan juga meningkatkan kualitas hidup serta memperbaiki gejala.

Kata kunci: gagal jantung, terapi resinkronisasi jantung

HF is a worldwide health problem with high prevalence rate. The prevalence is over 23 million worldwide. This disease carries substantial risk of morbidity and mortality. Over 2.4 million patients are hospitalized and nearly 300,000 deaths annually are directly attributable to HF. There is a dramatic increase in the prevalence of HF. The growing prevalence of HF might reflect increasing incidence, an aging population, improvements in the treatment of acute cardiovascular disease and HF, or combination of these factors. Since then, medications are the mainstay therapy for patients with HF.

Medications help rid the body extra fluid, strengthen the heart's contraction, and ease the heart's workload by relaxing the blood vessels and reducing...
of this electrical delay on an electrocardiogram (ECG) is widening of the QRS complex.

**Cardiac Resynchronization Therapy (CRT)**

The ultimate goal of CRT is to restore synchrony of the heart rhythm in HF patients. It is a unique type of cardiac pacemaker. Pacemakers usually being used to prevent symptoms associated with symptomatic slow heart rates. The patient’s heart rate is continuously monitored by the pacemaker. The heart rate is stimulated by the pacemaker by delivering a tiny electrical charge when necessary. Common pacemakers have 2 leads, one in the right atrium and one in the right ventricle, in order to keep the normal pump function relationship between bottom and top of the heart. These leads are connected to a pulse generator placed under the skin in the upper chest.

CRT is a specialized type of pacemakers, that have a third lead which is positioned in a vein on the outer surface of the left ventricle, in addition to the 2 leads used by common pacemakers. This allows a synchronous pumping action of left and right ventricle.

There are two types of CRT, a CRT pacemaker and a combination CRT pacemaker with defibrillation therapy (CRT-D). Both help to coordinate the heart pumping action and improve blood flow. In CRT-D, it also has the ability to detect and treat malignant heart rhythms, which some individuals with a damaged heart muscle may be at risk for developing. The decision of which device to use depends on the physician.
Indications and Benefits of CRT in Heart Failure Management

Many conclusive evidences of CRT benefits in HF from several randomized clinical trials (RCTs). The inclusion criteria used in the most RCTs was, New York Heart Association (NYHA) functional class III-IV in sinus rhythm (SR), low left ventricular ejection fraction (LVEF) < 35%, and duration of QRS interval > 120 ms. The Cardiac Resynchronization in Heart Failure (CARE-HF) trials with 813 patients evaluated all-cause mortality, hospitalization, NYHA functional class, and quality of life (QoL). This study was double-blinded and randomized trial. The result was CRT proved to reduce all-cause mortality, hospitalization, improved NYHA functional class, and QoL. Other study showing similar result was Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. This study even has larger subjects which was 1520 patients. The result was also the same that CRT could reduced all-cause mortality or hospitalization. Other studies like Multisite Stimulation in Cardiomyopathy (MUSTIC), Pacing Therapies in Congestive Heart Failure (PATH-CHF), and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trials also showed superiority of CRT in HF patients. These studies proved that CRT could improved QoL, NYHA functional class, 6-minutes walk distance (6MWD), LVEF, and peak VO2.

However, in accordance to the low number of subjects enrolled in RCTs, the evidence in HF patients with NYHA functional class IV was limited (from 7 to 15%). Ambulatory HF patients functional class IV showed a significant reduction in the combined primary endpoint of time to all-cause mortality and hospitalization as shown in a sub-study of COMPANION trial. The summary of the RCTs of CRT benefit in HF patients with NYHA functional class III-IV, sinus rhythm, poor left ventricular ejection fraction (LVEF), and prolonged QRS interval (≥120 ms) will be shown on the table below.

Other topic related to the CRT benefit in HF patients was the impact of QRS duration on the efficacy of CRT. Subgroup analysis, in a recent meta-analysis from COMPANION and CARE-HF trials, evaluating the impact of QRS duration on the efficacy of CRT, has shown that, in NYHA functional class III-IV HF patients, CRT significantly reduced all-cause mortality or hospitalization in patients with QRS duration ≥ 150 ms. The effect and benefit of CRT declined with shorter QRS duration. These studies also supported by Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial. It showed that patients with a QRS duration ≥ 150 ms, has a most benefit effect from CRT and suggested that it might not effective in patients with QRS < 150 ms. In addition, most patients in the RCTs had LBBB morphology, which was associated, with a more pronounced benefit, compared with non-LBBB patients. It was shown in the MADIT-CRT, Resynchronization-Defibrillation for Ambulatory Heart Failure (RAFT), and Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) trials, and a meta-analysis of COMPANION, CARE-HF, MADIT-CRT, and RAFT. Patients with complete LBBB, showed a greater benefit on the composite of morbidity and mortality from CRT, compared with patients with non-specific IVCD or RBBB. However, patients with LBBB had longer QRS duration, and therefore analyses by morphology may be confounded by QRS duration. On the other hand, the MADIT-CRT trial showed that non-LBBB patients did not derive clinical benefit from CRT (statistically not significant 24% increased risk). Other trials also showed consistent results that indicated clinical benefit of CRT in LBBB patients. Based on this evidence, current class I recommendations were restricted to patients with complete LBBB. The relationship between QRS duration and morphology requires further research.
### Table 1. Summary of Randomized Clinical Trials

(Evaluating CRT in HF patients and Sinus Rhythm)

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Patients</th>
<th>Design</th>
<th>NYHA Functional Class</th>
<th>LVEF</th>
<th>QRS</th>
<th>Primary Endpoints</th>
<th>Secondary Endpoints</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC-SR</td>
<td>58</td>
<td>Single-blinded, crossover, randomized CRT vs OMT, 6 months</td>
<td>III</td>
<td>&lt;35%</td>
<td>≥150 ms</td>
<td>6MWD</td>
<td>NYHA class, QoL, peak VO2LV volumes, MR hospitalizations, mortality</td>
<td>CRT-P improved 6MWD, NYHA class, QoL, peak VO2, reduced LV volumes and MR and reduced hospitalizations</td>
</tr>
<tr>
<td>PATH-CHF</td>
<td>41</td>
<td>Single-blinded, crossover, randomized RV vs LV vs BiV, 12 months</td>
<td>III-IV</td>
<td>NA</td>
<td>≥150 ms</td>
<td>Peak VO2, 6MWD</td>
<td>NYHA class, QoL hospitalizations</td>
<td>CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>453</td>
<td>Double-blinded, randomized CRT vs. OMT, 6 months</td>
<td>III-IV</td>
<td>≤35%</td>
<td>≥130 ms</td>
<td>NYHA class, 6MWD, QoL</td>
<td>Peak VO2 LVEDD, LVEF, MR clinical composite response</td>
<td>CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF</td>
</tr>
<tr>
<td>MIRACLE-ICD</td>
<td>369</td>
<td>Double-blinded, randomized CRT-D vs. ICD, 6 months</td>
<td>III-IV</td>
<td>≤35%</td>
<td>≥130 ms</td>
<td>NYHA class, 6MWD, QoL</td>
<td>Peak VO2 LVEDD, LVEF, MR clinical composite response</td>
<td>CRT-D improved NYHA class, QoL, peak VO2</td>
</tr>
<tr>
<td>CONTAK-CD</td>
<td>490</td>
<td>Double-blinded randomized CRT-D vs. ICD, 6 months</td>
<td>II-IV</td>
<td>≤35%</td>
<td>≥120 ms</td>
<td>NYHA class, 6MWD, QoL</td>
<td>LV volume, LVEF composite of mortality, VT/VF, hospitalizations</td>
<td>CRT-D improved 6MWD, NYHA class, QoL, reduced LV volume and increased LVEF</td>
</tr>
<tr>
<td>MIRACLE-ICD II</td>
<td>186</td>
<td>Double-blinded randomized CRT-D vs. ICD, 6 months</td>
<td>II</td>
<td>≤35%</td>
<td>≥130 ms</td>
<td>Peak VO2 VCO2, NYHA, QoL, 6MWD, LV volumes and EF,</td>
<td>All-cause mortality or hospitalization</td>
<td>CRT-D improved NYHA, VE/C02 and reduced LV volumes and improved LVEF</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1520</td>
<td>Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months</td>
<td>III-IV</td>
<td>≤35%</td>
<td>≥120 ms</td>
<td>All-cause mortality or hospitalization</td>
<td>All-cause mortality, cardiac mortality</td>
<td>CRT-P and CRT-D reduced all-cause mortality or hospitalization</td>
</tr>
<tr>
<td>Trial</td>
<td>No</td>
<td>Study Design</td>
<td>Follow-up</td>
<td>LV EDV %</td>
<td>LV EF</td>
<td>Primary Endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>--------------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE-HF</td>
<td>813</td>
<td>Double-blinded randomized OMT vs. CRT-P</td>
<td>29.4 months</td>
<td>≥35%</td>
<td>≥120 ms</td>
<td>All-cause mortality or hospitalization, NYHA class, QoL CRT-P reduced all-cause mortality and improved NYHA class and QoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVERSE</td>
<td>610</td>
<td>Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months</td>
<td>I-II</td>
<td>≤40%</td>
<td>≥120 ms</td>
<td>% worsened by clinical composite endpoint LVESV index, heart failure hospitalizations and all-cause mortality CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>1820</td>
<td>Single-blinded, randomized CRT-D vs. ICD, 12 months</td>
<td>I-II</td>
<td>≤30%</td>
<td>≥130 ms</td>
<td>All-cause mortality or heart failure hospitalizations All-cause mortality and LVESV CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV. CRT-D did not reduced all-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAFT</td>
<td>1798</td>
<td>Double-blinded, randomized CRT-D vs. ICD 40 months</td>
<td>I-II</td>
<td>≤30%</td>
<td>≥120 ms</td>
<td>All-cause mortality or heart failure hospitalizations All-cause mortality and cardiovascular death CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CARE-HF (Cardiac Resynchronization-Heart Failure); CONTAK-CD (CONTAK-Cardiac Defibrillator); COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure); CRT-D (Cardiac Resynchronization therapy with Defibrillator); CRT-P (Cardiac Resynchronization Therapy Pacemaker); LV (Left Ventricular; LVEDD (Left Ventricular End-Diastolic Dimension); LVEF (Left Ventricular Ejection Fraction); LVESV (Left Ventricular End-Systolic Volume); MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy); MIRACLE (Multicenter InSync Randomized Clinical Evaluation); MIRACLE-ICD (Multicenter InSync Implantable Cardioverter Defibrillator trial); MR (Mitral Regurgitation); MUSTIC (Multisite Stimulation in Cardiomyopathies); No (Number of Patients); NYHA (New York Heart Association); PATH-CHF (Pacing Therapies in Congestive Heart Failure Trial); QoL (Quality of Life Score); RAFT (Resynchronization Defibrillation for Ambulatory Heart Failure Trial); VE/VCO2 (Minute Ventilation/Minute Volume Carbondioxide Production); VF (Ventricular Fibrillation); VO2 (Volume of Oxygen); VT (Ventricular Tachycardia); 6MWD (6-min Walk Distance)
In HF patients with NYHA functional class I-II, sinus rhythm, LVEF \( \leq 30\text{-}40\% \) and QRS duration \( \geq 120\text{-}130 \) ms, four RCTs which were MADIT-CRT, RAFT, REVERSE, and Multicenter InSync Implantable Cardioverter Defibrillator (MIRACLE-ICD) trials have demonstrated that CRT improves LV function, all-cause mortality and HF hospitalizations.\(^6\) However, improvement in functional status or quality of life among patients randomized to CRT were not too significant. Most patients enrolled had NYHA functional class II; only 15% in Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) and 18% in Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) were in NYHA functional class I. CRT did not reduce all-cause mortality of HF events among NYHA functional class I patients. Therefore, the recommendation is restricted to patients in NYHA functional class II.

Finally, there is no evidence of benefit in patients with HF and QRS \(< 120 \) ms. In the Cardiac Resynchronization Therapy In Patients with Heart Failure and Narrow QRS (RethinQ) trial, CRT did not improve peak oxygen consumption (primary endpoint) or QoL in the subgroup of patients with QRS \(< 120 \) ms and evidence of echocardiography dyssynchrony.\(^6,16\)

**Table 2. Indications for CRT in HF Patients and Sinus Rhythm**\(^6\) (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) LBBB with QRS duration (&gt;150 ) ms. CRT is recommended in chronic HF patients and LVEF (\leq 35% ) who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.(^d)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2) LBBB with QRS duration (120\text{-}150 ) ms. CRT is recommended in chronic HF patients and LVEF (\leq 35% ) who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.(^d)</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

**Figure 3.** Benefit Scale of CRT Based on Clinical Factors\(^6\) (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org)
Other randomized and double-blind study named Evaluation of Resynchronization Therapy for Heart Failure in Patients with a QRS Duration Lower Than 120 ms (LESSER-EARTH) was prematurely stopped due to safety concerns.\(^6,17\)

### CRT In Heart Failure Management With Atrial Fibrillation (AF)

There are two ways of considering CRT for AF patients, first, AF patients with moderate to severe HF with a hemodynamic indication for CRT. Second, patients with a fast ventricular rate with HF or LV dysfunction justifying a strong rate control strategy with an AV junction ablation.\(^6\)

In the first way of considering CRT for AF patients were described in Multisite Stimulation in Cardiomyopathies (MUSTIC) AF trial.\(^6,18\) There was a slight but significant improvement in functional status in patients with NYHA functional class III, low LVEF, AF rhythm, and QRS \(\geq\) 120 ms at 6-month and 1-year follow-up. In the Ablate and Pace in AF (APAF) trial, in the patients with low LVEF, NYHA functional class \(\geq\) III, AF rhythm, and QRS \(\geq\) 120 ms, CRT significantly reduced the primary endpoint, including death, hospitalizations or worsening of HF, as well as beneficial effect on LV reverse remodeling.\(^6,19\)

Second way, combination of AV junction ablation and CRT in uncontrolled heart rate of AF patients provided highly efficient rate control, regularization of the ventricular response, and also improved symptoms.\(^6\) Hence, CRT may prevent the potential LV asynchrony. The multi-center, randomized, and prospective APAF trial with 186 patients studied about CRT implantation followed by AV junction ablation.\(^6,19\) During a median follow-up of 20 months, CRT significantly decreased the primary composite endpoint (of death due to HF, hospitalization or worsening due to HF) by 63\% in the overall population. The effects and efficacy of CRT were significantly consistent in patients who had EF \(\leq\) 35\%, NYHA functional class \(\geq\) III, and QRS width \(\geq\) 120 ms, thus meeting the requirement of the guidelines.

### Conclusion

The prevalence of HF is still high. This disease carries substantial risk of morbidity and mortality. Over 2.4 million patients are hospitalized and nearly 300,000 deaths annually are directly attributable to HF. HF is characterized by the inability of the heart to pump an adequate amount of blood to achieve the demand of the different organ systems and/or doing so at increased filling pressures. The most common abnormality...
conduction in HF patient is left bundle branch block (LBBB). Because of this block, the right ventricle made an earlier contraction than the left ventricle, instead of simultaneously. The result is an asynchronous contraction of the ventricles. Eventually, cardiac pump will lose its efficiency. Almost 40% of HF patients have an asynchronous ventricular contraction caused by electrical delay, most often LBBB. CRT, a specialized and unique pacemaker, plays an important new role as a novel treatment in HF patients, despite many recent advances in medication. HF patients with proper and right indications like wide QRS complexes, low left ventricular ejection fraction (LVEF), LBBB, SR with conduction delay, and permanent AF have shown improvement of symptoms and QoL. Thus, CRT have been proven to reduce morbidity and mortality in HF patients.

References

11. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DC, Packer M, Clavell AL, Hayes DL, Ellestad...


