Review Article

Cardiac Resynchronization Therapy (CRT) —Its History, Indication, Usefulness and Problems—

Kazuo Matsumoto MD
Cardiology Department, Saitama International Medical Center

This report was an overview of pacing therapy for heart failure to explain the usefulness and problems of CRT in broad terms. It is not an exaggeration to say that pacemakers were originally developed to improve cardiac function in patients with heart failure. However, it must be understood that pacing itself is unphysiological, and we should know what pacing does to the heart. Concerning the simple issue of pacing, it is true that there are a lot of matters that we think we understand but actually we do not, such as the effects of the differences in site, output, and frequency. At least, it seems clear that the currently available CRT devices are effective for patients with heart failure and for improving survival. Further improvement in their effectiveness is an important issue we must continue to address.
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Key words: Pacemaker, Heart failure, Resynchronization, Biventricular pacing

1. Introductions

The history of cardiac pacemakers began in 1932 with Hyman’s invention1 of an external cardiac stimulator to electrically stimulate the heart from outside the body using a needle electrode. He named this stimulator the “artificial pacemaker,” and this name is still generally used. In 1958, Furman et al.2 performed endocardial pacing using an external pacing device, and Lagergreen et al.3 developed a prototype of the current VVI (ventricular demand inhibited) pacemaker in 1963. At first, pacemakers were mainly used to treat bradycardia in clinical settings, and the primary challenge was to ensure pacing without any problems, thus technical improvement was promoted. More specifically, there were many advances and improvements in the lead: namely, the development of the epicardial and endocardial leads, improvements in lead material and tip shape, and development of a screw-in lead and a steroid-eluting lead.4 Regarding the pacemaker body, efforts were made to downsize the body and prolong battery life. After these objectives were attained, energy was focused on treatment modalities which were more physiological and implementation of various diagnostic functions. The application of pacemakers was extended to heart failure treatment using bi-ventricular pacing (cardiac resynchronization therapy, CRT), and now, CRT-D (cardiac resynchronization therapy with an implantable cardioverter defibrillator [or ICD] function), effectively preventing sudden cardiac death, are now being used in clinical settings. This report looks back on the history of the use of pacemakers in patients with heart failure to discuss their usefulness and the problems associated with CRT.

Address for correspondence: Kazuo Matsumoto MD, Cardiology Department, Saitama International Medical Center, 1397-1 Yamane, Hidaka City, Saitama, Japan. E-mail: Kazuom@saitma-med.ac.jp
2. Pacemakers for Treatment of Heart Failure

1) Improvement of heart rate

Originally, pacemakers were developed as a therapeutic measure to improve the symptoms of bradycardia, i.e., sudden unconsciousness, vertigo, and breathlessness. It is well known that breathlessness is a symptom associated with heart failure in many cases and that heart failure due to bradycardia, even if not associated with atrioventricular block, can be an indication for pacemaker implantation. Normalization of heart rate was originally seen as being important in improving cardiac function. That is, pacemakers constituted a therapeutic measure for patients with heart failure. The relationship between heart rate and cardiac output has been discussed for many years. Even in VVI (ventricular demand) pacing, cardiac output is increased by increasing the heart rate from 30 beats/min to 60 beats/min in patients with normal contractility. When the heart rate is increased from 80 beats/min to 120 beats/min, the atrial contraction also has an effect, increasing cardiac output and showing the growing importance of atrioventricular synchrony from atrioventricular sequential excitation.5) In 1987, Benditt et al. reported that atrioventricular synchrony became less important for cardiac output and the heart rate was more deeply involved as it increased.6) In addition, VVI pacing in patients with bradycardia and atrioventricular conduction was reported to lower cardiac output to induce pacemaker syndrome.7) These problems were resolved by atrioventricular sequential pacing, which was also referred to as physiological pacing.

2) Improvement of atrioventricular synchrony

As described above, normalization of the heart rate by VVI pacing caused various hemodynamic problems, and the more aggressive atrioventricular sequential pacing using the pacing function, as described by Hochleitner in 19908) and Brecker in 1992,9) became the mainstream treatment for heart failure. They implanted a DDD (dual chamber) pacemaker in patients with dilated cardiomyopathy, and observed improvements in LVEF (left ventricular ejection fraction), CTR (cardiothoracic ratio), hypotension, and NYHA (New York Heart Association) class. In patients with a heart failure condition, such as dilated cardiomyopathy or atrioventricular sequential excitation, sequential contraction is maintained if sinus rhythm is maintained. However, this is a hemodynamic condition in which atrioventricular synchrony is lost. That is, the atrial contraction phase is discordant with that of the ventricular contraction, resulting in a shortened time for blood inflow from the atrium to the left ventricle during ventricular diastole and mitral regurgitation (MR) during presystole (diastole) occurs. This phenomenon is reproduced in first-degree atrioventricular block and observed in heart failure with dilated ventricles when the PQ interval is within a normal range. Shortening of the atrioventricular excitation interval by pacing and improvement of atrioventricular synchrony prolong the diastolic left ventricular inflow time, increasing the inflow, and decreasing the diastolic mitral regurgitant flow, all these consequently improving cardiac function. However, the contribution of DDD pacing to the improvement of heart failure by correcting ventricular asynchrony has its limits.10)

3) Improvement of ventricular wall motion synchrony

There is no doubt that improved ventricular wall motion synchrony was a major goal in the aggressive use of pacemakers to treat heart failure. Meanwhile, it was gradually clarified that the conventional method to pace the ventricle from the right ventricular apex had only a limited effect. In 1991, Xiao et al.11) reported that a widened QRS complex correlated with a decrease in peak dp/dt and the time to reach the peak dp/dt, and that cardiac functions might be improved by narrowing the QRS complex. In 1996, Cazeau et al.12) reported that biventricular pacing showed acute and chronic effects in 8 patients with heart failure. To ascertain the acute effects, temporary pacing was induced on the right ventricular apex or right ventricular outflow tract in combination with the left ventricular wall to examine hemodynamic changes. The results showed no difference between the right ventricular outflow tract and right ventricular apex. The cardiac index was reported to have improved from 1.83 ± 0.30 L/min to 2.25 ± 0.29 L/min (p < 0.006), pulmonary arterial wedge pressure from 31 ± 10 mmHg to 26 ± 9 mmHg (p < 0.01), and v wave amplitude from 36 ± 12.5 mmHg to 26 ± 10 mmHg (p < 0.01), showing an improvement in MR. A pacemaker was implanted in 6 of the 8 patients (one died from heart failure before implantation and the other died during the implantation procedure). A left ventricular lead was implanted thoracoscopically in 5 of the 6 patients, and biventricular pacing was induced in the remaining patient. Four of these patients were followed for 7.7 ± 6.3 months on average. The symptoms were reported to have improved 2 weeks after implantation with an improvement in physical activity from NYHA class IV to class II. The number
of cases reported by Cazeau et al. was small but theirs was the first report that discussed biventricular pacing in detail. At first, the effectiveness of biventricular pacing was considered to be closely related to the improvement in the duration of the QRS complex, but it was later clarified by echocardiography, RI cardioangiography, etc., that synchrony in the interventricular septum and left ventricular free wall as well as mitral regurgitation was improved by pacing.

3. Usefulness of Biventricular Pacing: Evidence

There have been many prospective multicenter studies on the effectiveness of biventricular pacing: namely, PATH-CHF,13) MUSTIC,14) MIRACLE,15) MIRACLE-ICD,16) CONTAK-CD,17) COMPANION,18) and CARE-HF.19) The results showed that biventricular pacing improved the patient’s QOL, NYHA class, motor ability (in 70% of cases), EF (5–15%), etc., and reduced mortality (NNT: 9) (Table 1); thus, biventricular pacing was confirmed to be a relatively safe method. These studies showed that according to ACC/AHA/NASPE guidelines20) class III and class IV dilated cardiomyopathy or ischemic cardiomyopathy with drug resistance and a QRS duration of ≥130 msec, a left ventricular end-diastolic diameter of ≥55 mm, and a left ventricular ejection fraction of ≤35% constituted class IIa indication for biventricular pacing. In Japan,21) class III and class IV chronic heart failure with drug resistance, QRS duration of ≥120 msec and left ventricular ejection fraction of ≤35% constitute class I indication for biventricular pacing. For class III and class IV patients with chronic heart failure and drug resistance and a pacemaker implanted for bradycardia, upgrading of the indication for biventricular pacing (to IIa) has been approved.

Biventricular pacing has also been referred to as CRT (cardiac resynchronization therapy), indicating that synchrony in the cardiac septum and free wall is restored by pacing. In actual clinical practice, left ventricular synchrony is not necessarily restored by only applying biventricular pacing and may require 3-point pacing or left ventricular pacing. Therefore, in a practical sense, biventricular pacing could be referred to as cardiac resynchronization therapy for heart failure.

4. Problems in Application of Cardiac Resynchronization Therapy (CRT)

Pacing involves a mechanism to pace cardiac tissues from the electrode placement site and does not involve any other action. The indication for pacing is determined by examining whether pacing has beneficial or harmful effects on hemodynamics. It should be clearly noted that in vivo a pacemaker is a foreign body and that pacing itself cannot be considered a physiological behavior. Because pacing is used to treat serious heart failure conditions, there are several problems associated with it, including surgery-related death, troubles during implantation, and various complications (Table 2). The problems that are now drawing attention are as follows.

1) QRS complex duration in patients with indications for implantation

There are some patients with an indication for implantation who have a narrow QRS complex and no ventricular synchrony.22) Such patients may not benefit from CRT, even though beneficial effects of CRT are expected under the current criteria. On the contrary, there has been a report of patients with a wide QRS complex with ventricular synchrony. Under the conventional criteria used to decide the indications for implantation, it has been confirmed that the percentage of patients for which CRT has proved effective is 70%, and that it was not effective in the remaining 30% (CRT-ineffective). As the reasons for this, a wide QRS complex without left ventricular dysynchrony or ineffective pacing due to ventricular wall fibrosis was proposed. To solve these problems, use of tissue Doppler method,23) ventricular synchrony evaluation by MRI, and diagnostic imaging have been suggested.

2) Mild heart failure as an indication

Another issue is whether milder heart failure (NYHA class II) is an indication for CRT. What would be the results of CRT implemented at an early stage? The survival rate is expected to increase but this has not been proved so far. How can CRT be effective in patients with originally mild heart failure?24) We cannot overlook whether this indication makes sense economically, and the long-term pacing complications. We are waiting for the results of multicenter studies addressing these issues, such as REVERSE (supervised by Medtronic Co.) and MADIT-CRT (supervised by Boston Scientific Co.).

3) Other issues concerning synchrony

The best way to measure cardiac function is by looking at left ventricular contraction. When left ventricular contraction is reduced, atrial contraction and atrioventricular synchrony greatly affect cardiac output. If it were possible to control left and right
ventricular synchrony, right atrio-ventricular synchrony, left atrio-ventricular synchrony, and left and right atrioventricular synchrony (i.e. synchrony at four sites), the effectiveness of CRT could be further increased. However, the degree of effectiveness and how the phase should be set have not been clarified. These will probably differ from patient to patient.

Table 1  Summary of main multicenter studies conducted so far.

<table>
<thead>
<tr>
<th>Study name</th>
<th>(Number of cases)</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Control patients condition</th>
<th>Principal results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>(47)</td>
<td>2001</td>
<td>randomized cross over</td>
<td>NYHA III, LVEF &lt; 35%</td>
<td>Improvement in 6-minute walk</td>
</tr>
<tr>
<td>PATH-CHF</td>
<td>(42)</td>
<td>2002</td>
<td>single blind randomized cross over controlled</td>
<td>NYHA III/IV, DCM QRS &gt; 120 ms</td>
<td>Improvement in 6-minute walk Improvement in maximum oxygen consumption</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>(453)</td>
<td>2002</td>
<td>prospective randomized double blind parallel controlled</td>
<td>NYHA III/IV, QRS ≥ 130 ms LVDD ≥ 55 mm, EF ≤ 35% 6 min walk &lt; 450 m</td>
<td>Improvement in 6-minute walk Improvement in QOL Improvement in NYHA class</td>
</tr>
<tr>
<td>MIRACLE-ICD</td>
<td>(369)</td>
<td>2003</td>
<td>prospective randomized double blind multicenter parallel controlled</td>
<td>NYHA III/IV, QRS ≥ 130 ms LVDD ≥ 55 mm, EF ≤ 35% Indicated for ICD</td>
<td>No improvement in 6-minute walk Improvement in QOL Improvement in NYHA class</td>
</tr>
<tr>
<td>CONTAK CD</td>
<td>(501)</td>
<td>2003</td>
<td>prospective randomized cross over parallel controlled</td>
<td>NYHA II/III/IV QRS ≥ 120 ms, EF ≤ 35% Indicated for ICD</td>
<td>No significant difference in overall mortality and hospitalization rate Improvements in EF and LVDD were frequently seen in NYHA class II cases.</td>
</tr>
<tr>
<td>COMPANION</td>
<td>(1292)</td>
<td>2004</td>
<td>prospective randomized multicenter controlled</td>
<td>NYHA III/IV, QRS ≥ 120 ms EF ≤ 35%, PR ≥ 150 ms History of hospitalization for heart failure of ≥12 months</td>
<td>CRT reduced the relative mortality risk by 19% and CRTD by 20%.</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>(409)</td>
<td>2005</td>
<td>prospective randomized multicenter controlled</td>
<td>NYHA III/IV, QRS ≥ 120 ms EF &lt; 35%, PEdelay &gt; 140 ms Vtdelay &gt; 40 ms, Ventricular wall dysynchrony</td>
<td>Improvement in overall mortality Improvement in cardiac functions Improvement in motor ability Improvement in QOL</td>
</tr>
</tbody>
</table>

The CRT studies conducted in or before 2004 reported only on the improvement in cardiac function, QOL, and motor ability. In 2005, the CARE-HF study revealed that CRT improved the prognosis of patients with heart failure. The reason for this might be the use of more exact indicators of ventricular asynchrony in the CARE-HF study than in other studies.

Table 2  Incidence of complications in major large-scale studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>CARE-HF</th>
<th>COMPANION</th>
<th>MIRACLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRTP</td>
<td>CRTD</td>
<td>CRTP</td>
</tr>
<tr>
<td>Number of cases</td>
<td>(409)</td>
<td>(617)</td>
<td>(595)</td>
</tr>
<tr>
<td>Unsuccessful lead placement</td>
<td>5%</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Perforation</td>
<td>3%</td>
<td>1.1%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Coronary dissection</td>
<td>2.6%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery-related death</td>
<td>0.5%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker infection</td>
<td>2.7%</td>
<td></td>
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</tr>
</tbody>
</table>

Surgery-related deaths were reported because patients with serious heart failure were involved in the studies. The deaths that occurred within 30 days after surgery were not included. Although there were many complications caused by implantation of the device, the mortality rate decreased. Future technical improvement is expected to reduce complications.
4) Possibility of causing severe ventricular arrhythmia complications

The multicenter studies conducted so far have occasionally reported on individual patients in whom CRT induced severe ventricular arrhythmia, although the relationship has not been clarified by a statistical study. However, it is clear that the heart failure itself is a risk factor of sudden death, and defibrillation must be considered when CRT is conducted. The COMPANION study has shown higher effectiveness of CRT-D (CRT-defibrillation) than CRT-P (CRT-pacing) based on the survival rate.

5) Application of CRT to AF

While atrioventricular resynchronization is not expected to have an effect on atrial fibrillation (AF), the effectiveness of CRT has been expected because synchrony in the ventricular wall, slowed heart rate, and stabilized heart rate can be obtained. The PAVE study found that the use of CRT in ablate and pace therapy for heart failure due to atrial fibrillation with a rapid ventricular response showed improvement of cardiac function in patients with heart failure compared with the conventional pacing method. Selection of the patients with atrial fibrillation for whom CRT is indicated is an issue for future discussion.

In addition, treatment methods other than CRT should also be taken into account, considering the ease and success rate of maintaining or controlling sinus rhythm in atrial fibrillation by catheter ablation.

References

22) Uchiyama T, Matsumoto K, Suga C, et al: QRS width does not reflect ventricular dyssynchrony in patients with...


