Historical Overview of Cardiac Implantable Electrical Devices

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Since its approval for reimbursement in 1974 in Japan, the artificial pacemaker (PM) for the treatment of bradycardia has come into wide clinical use. In the years that have followed, remarkable structural and functional progress has been made with PMs and the associated lead systems, and the reliability of the PM as an implanted artificial device has been established. In 1996, the implantable cardioverter-defibrillator (ICD) became the next reimbursed device, approved as a therapy for fatal ventricular arrhythmias. ICD have contributed to improved prognosis in patients with these arrhythmias through preventing sudden cardiac death. Cardiac resynchronization therapy (CRT) was recognized as the next effective modality for drug-refractory chronic heart failure. CRT became reimbursable in 2004, followed by CRT with defibrillator function in 2006. Large-scale randomized trials and meta-analyses have confirmed the reduced overall mortality with CRT. Currently, these implanted devices are essential therapeutic modalities, collectively known as cardiac implantable electrical devices (CIEDs), for indications from symptomatic bradycardia and fatal ventricular tachyarrhythmia to severe chronic heart failure. As CIEDs continue to evolve, we should always be updating relevant knowledge and ensuring appropriate indications for CIED implantation.

Key words: pacemaker, implantable cardioverter–defibrillator, biventricular pacing

Introduction

More than 60 years have passed since the pacemaker (PM) became an approved implantable device for patients with symptomatic bradycardia. In that interval, modern technological developments have made it the most reliable artificial implant device in terms of both structure and function. Implantable cardioverter–defibrillators (ICDs) then appeared, leading to improved prognosis for patients with ventricular tachyarrhythmia by preventing sudden cardiac death (SCD). The next target of device therapy was drug-refractory severe chronic heart failure with desynchronization between the right and left ventricles. To improve the disadvantageous hemodynamics and extend the lives of these patients, cardiac resynchronization therapy with or without defibrillator function (CRT, CRT–D) was developed.

Currently, these devices are collectively known as cardiac implantable electrical devices (CIEDs), and they are essential therapeutic modalities for various indications (Table-1). Modern CIEDs can even allow for MRI scanning under certain conditions, and the new category devices such as leadless PM and subcutaneous ICD (S–ICD) have recently appeared in clinical practice. In addition, the evolution of electronic communication has made possible the remote monitoring of a device system and patient condition.

Here, we provide a historical overview of the continuously evolving CIED therapy.
Progress of PM

PM is recognized as the most advanced artificial device and is implanted worldwide as the only reliable therapy for patients with symptomatic bradycardia. Advances in technology related to its structure and function have led to the currently used PM system. Major advances have included its miniaturization and much improved battery longevity. In addition, integrated electrical circuits that can be incorporated into the PM have contributed to size reduction. The batteries initially were made of mercury, followed by nickel–cadmium, and even plutonium at one point to yield durable, lifelong use. However, these components in the cell were toxic to human body, so that these devices ultimately were withdrawn from the commercial market. The highly stable lithium–iodine battery has now become the mainstream component and yields acceptable longevity. Recently, new batteries using a lithium and a silver vanadium oxide electrode have also been introduced. At present, despite minor differences in size and design, current PMs are all well accepted.

From the perspective of functional advancement, the most noteworthy progress has been the establishment of physiological pacing, which maintains the sequence of atrio-ventricular (AV) contraction. Additional features are the emergence of PMs that allow for the performance of MRI and leadless PMs.

1. Physiological pacing

Physiological pacing is defined as the maintenance of the sequence of AV contraction (AV synchronization). The initial PM was aimed only at maintaining the heart rate, which was achieved with a fixed ventricular rate. The lack of AV synchronization and accompanying marked changes in blood pressure were disadvantageous in terms of hemodynamics. After PM implantation, blood pressure could fluctuate, so that vertigo symptoms, or the so-called "pacemaker syndrome," were often a complication. Because of these drawbacks, modalities to support synchronous AV pacing were needed. Although fixing the atrium using initial type of pacing leads proved difficult, the emergence of a tined type lead and a screw-in type lead has made stable atrial pacing possible. In addition, the development of steroid–eluting electrodes has contributed to suppression of the acute and chronic threshold rise, so that physiological pacing can be rapidly and widely applied. A typical physiological pacing mode is the DDD mode, in which the ventricle is paced in synchronization with the atrial contraction (Figure-1).

In terms of heart rate, a fixed-rate pacing in PM-dependent patients is not physiological because heart rate does not increase in response to exercise. To solve this problem, a "rate-responsive pacemaker" has been developed so that the pacing rate increases in response to the intensity of body movement and/or to change in respiration rate during exercise. Because the rate response function is incorporated into the AV synchronous pacing, more physiological condition can be achieved (Figure-2). Modern PMs are equipped with a rate-responsive function with dual sensors of body activity level and respiration rate. The responsive reaction can be programmed into appropriate step depending on the individual activity.

2. MRI-conditional PMs

If MRI is performed in a patient implanted with a conventional PM, various pacing troubles can arise because of the static magnetic field, gradient magnetic fields, and radiofrequency (RF) magnetic fields. RF magnetic fields may generate pacing failure from the threshold rise caused by heat-induced myocardial necrosis. In addition, the noise in the gradient magnetic field also causes ventricular fibrillation or inappropriate shock in ICD patients, along with sudden loss of output. Other defects, such as the stack of a programmer

<table>
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<tr>
<th>Table 1 Cardiac Implantable Electrical Devices (CIEDs)</th>
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<td>Indication</td>
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<tr>
<td>Bradycardia</td>
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<td>VT/VF</td>
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<td>Drug-refractory HF</td>
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<td>CRT</td>
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VT: Ventricular tachycardia
VF: Ventricular fibrillation
HF: Heart failure
PM: Pacemaker
ICD: Implantable cardioverter defibrillator
CRT: Cardiac resynchronization therapy
CS: Coronary sinus
S-ICD: Subcutaneous ICD
operation or an abnormal battery depletion, have also been observed\[^2\]
\[^{10}\]. However, in PM-implanted populations, the need for MRI scans is relatively high, so specific filters and internal components have been developed to prevent the influence of the magnetic field. A heat-resistant filter also has been incorporated at the tip of the lead electrode. The current PMs are compatible with MRI under certain conditions. The relationship between CIED and MRI scan is always changing, so that information must be constantly updated\[^1\]\.[

3. Leadless PM

Although the conventional PM implantation technique is well established, system-specific complications would often arise during the intra- or post-operative period. Particularly, during lead insertion through the subclavian puncture method, pneumothorax or arterial injury is a risk. Furthermore, in the process of lead fixation, myocardial perforation is a possibility. The generator, which is usually implanted in the subcutaneous pocket at the left or right anterior chest, can cause such cosmetic problems, hematoma formation and postoperative pocket infection. In addition, lead fracture is a concern during long-term follow-up. According to reports, the incidence of complications in transvenous leads was 8% after 5 years of follow-up and 11% with respect to a subcutaneous pocket\[^{12}\].

To avoid such lead-related complications, a leadless PM has been designed. In Japan, the currently available leadless PM is 1 ml in body volume, 1.75 g in weight, and 25.9 mm in length (The Transcatheter Pacing System, Medtronic plc, MN, USA). A delivery catheter is inserted into the right ventricle through the femoral vein and placed at the septal area of the right ventricle. The main body has four metal projections, and if it can be confirmed that at
least two of them are fixed to the myocardium, the
placement is completed (Figure–3). Clinical results
in the United States and Europe indicated a success
rate of 99.2% with 725 implants, 96% without
complications, no dislodgement or infection, and a
good stimulation threshold of 93.8%\(^1\). In Japan,
implant numbers have gradually increased but
have not yet yielded a sufficient accumulation of
data. In fact, serious complications, including
cardiac perforation, have been observed in 1.56% to
date\(^1\). Complications during leadless PM are often
serious, so careful selection of patients with
appropriate indications is a must.

**Advances in ICDs**

ICD is a reliable treatment for ventricular
tachycardia (VT) and ventricular fibrillation (VF).
In the early era of ICD, it was to be implanted at the
abdomen and the lead system placed on the
epicardium. Therefore, a cardiac surgeon could
perform this procedure only by an open-chest
approach. Later, with technical advances, body size
reduction, and the invention of intravenous shock
leads, transvenous implanting procedures became
possible.

Since reimbursement was approved in 1996 in
Japan, the number of implanted ICDs has increased
year over year and more than 6,000 implantations
are carried out annually. Modern ICDs also are
equipped not only with a PM and a defibrillator
function but also for remote monitoring for early
detection of device failure and deterioration of heart
failure.

The efficacy of ICDs in preventing SCD has been
confirmed in many meta-analyses for both second-
dary and primary prevention\(^1\). In the MADIT II
study, in patients with a history of myocardial
infarction and left ventricular ejection fraction (LVEF) less than 30%, the mortality rate in the ICD
treatment group was significantly lower than in the
drug treatment group, regardless of the presence of
VT (Figure–4)\(^1\). The SCD–Heft trial targeting
non-ischemic heart disease also indicated improve-
ment in prognosis for the ICD group\(^1\). These
results expanded the indication for ICD to primary
prevention. Despite abundant evidence of the
efficacy of ICD in improving prognosis, the fre-
cquency of appropriate shock delivery and
anti-tachycardia pacing (ATP), and even inappro-
priate shock delivery worsened the prognosis of
some patients\(^1\). Considering these results, the
current ICDs have been programmed to reduce
shock delivery and ATP initiation as much as
The transvenous shock lead also has been adjusted to handle more easily. The conventional lead (DF-1) was designed to have the pacing electrode and the coil electrode for shock arranged on the right ventricle and/or superior vena cava position. Therefore, the connecting portion was divided into three prongs, which meant that the lead loop from the generator bore most of the burden of bending and compression. During the implantation procedure, a large ICD and four-point connection to the lead make the procedure very complicated. To ameliorate this disadvantage, a simpler and more compact lead (DF-4) has been developed. Pacing and shock-conducting wires have been incorporated into the one lead, and the overall length of the connecting portion has also been minimized. Eventually, the implantation has become easier and a largely stress-free procedure could be achieved (Figure-5).

S-ICD

Transvenous ICD leads often carry a risk for complications during venous access and lead insertion. In addition, if an infection occurs, the device system must be removed completely. To avoid these outcomes, S-ICD was developed (EMBLEM™ MRI S-ICD System, Boston Scientific, MA, USA). This device is a simple and single-unit ICD system that can be implanted subcutaneously, including the shock lead (Figure-6). Before S-ICD implantation, the screening of the sensing vector confirms that it is appropriate. Three electrodes are placed on the top and bottom of the parasternal position and left lateral position where the S-ICD is to be placed. If one or more sensing vectors are accepted in two positions (supine, standing, etc.), implantation can move forward. Screening during exercise is also recommended to prevent T wave oversensing, particularly in Brugada syndrome or hypertrophic cardiomyopathy. However, S-ICDs have no pacing function except with 30-s trans-thoracic pacing immediately after shock delivery. If patients require pacing for bradycardia or ATP for sustained VT, S-ICD is not recommended. Although the indication for S-ICD is limited, clinical trials have yielded favorable results for preventing
The conventional type (DF-1) of ICD lead consists of three individual prongs at the connecting site for pacing and sensing, SVC, and right ventricular coil electrode. In contrast, a new type (DF-4) is improved by reduction of the prong through incorporation of a shock wire into the lead body.

**Figure 5** Improvement of the ICD Lead

**Figure 6** Subcutaneous ICD Implantation

(A) Subcutaneous lead position and device. (B, C) The implantation technique. (D) After the implantation.
SCD\textsuperscript{19,20} and the number of S-ICDs in use, including for primary prevention, has increased since approval of these devices for reimbursement in 2016.

**Advances in CRT**

Intraventricular conduction disturbance (IVCD) or left bundle branch block (LBBB) are commonly observed in patients with chronic severe heart failure. The left ventricular contraction in LBBB delays the right ventricular contraction and causes synchronization loss. This condition affects the hemodynamics, and heart failure would worsen because of hypotension or reduced cardiac output\textsuperscript{21}. Right ventricular apical pacing also shows LBBB pattern and similar hemodynamics. It has been reported that cardiac function deteriorates over a long period of time on right ventricular apical pacing (Figure–7). We previously reported a significant correlation between the paced-QRS width and LVEF. With paced-QRS width over 180 ms, LVEF decreased in patients with right ventricular apical pacing\textsuperscript{22}.

The lateral wall is the most delayed area in the left ventricle, and the pacing from this site experienced the maximum effects of CRT\textsuperscript{23}. The left ventricular lead via a coronary sinus is usually targeted to the lateral branch. If re-synchronization can be achieved, the QRS width would be shortened and hemodynamic improvement expected (Figure–7, 8). The CRT candidates have already led to reduced LVEF and lethal ventricular arrhythmias are common. To improve the prognosis of these patients, the necessity of defibrillation functions has been highlighted. Gras et al followed-up 108 patients with CRT for 1 year, 21 of whom (19.4%) died during follow-up. Almost half of the deaths were the result of SCD\textsuperscript{24}. To prevent SCD and produce a better outcome, a defibrillating function is mandatory, and reimbursement for CRT (2004) and CRT-D (2006) was approved one after the other in Japan. To date, the clinical effectiveness of CRT has been established in large-scale randomized trials and meta-analyses suggesting improvement in overall mortality\textsuperscript{25}. Meanwhile, approximately 30% to 40% of patients with CRT do not respond and are designated as “non–responders”\textsuperscript{26}. A major

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<th>Normal</th>
<th>IVCD</th>
<th>RV pacing (Apex)</th>
<th>Biventricular pacing</th>
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<td><img src="image1" alt="Normal" /></td>
<td><img src="image2" alt="IVCD" /></td>
<td><img src="image3" alt="RV pacing (Apex)" /></td>
<td><img src="image4" alt="Biventricular pacing" /></td>
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**Figure–7** Concept of CRT (Cardiac resynchronization therapy) and Relation with QRS Width

Normally, atrio–ventricular (AV) conduction passes simultaneously through the left and right ventricles with no contraction delay, and the ECG shows a narrow QRS. If patients have intraventricular conduction disturbance (IVCD) or LBBB, the conduction wave toward the left ventricle is blocked and passes through the right ventricle. Then left ventricular contraction would be delayed, and a wide QRS would be depicted. Right ventricular apical pacing also yields a wide QRS (LBBB type) because the right ventricular contraction would precede the left ventricular contraction. The concept of CRT is simultaneous biventricular pacing from the left and right ventricles so that both ventricles contract at the same time, generating a narrow QRS complex.
**Figure 8** The Efficacy of CRT in a Patient with Severe Heart Failure
A representative case of a CRT responder. Before CRT, chest X-ray showed marked cardiomegaly and pleural effusion. After CRT, the cardiac silhouette had improved, and pleural effusion disappeared.

**Figure 9** Advancement of CS (Coronary sinus) Lead
(A) Comparison of bipolar (①, ②; electrodes) and quadripolar lead (①-④). (B, C) Various shapes and designs of quadripolar leads. A quadripolar lead (distal to proximal: ① to ④) is depicted.
RV, right ventricle; LV, left ventricle.
reason for this outcome is the lack of predictors for evaluating CRT efficacy before implantation. The QRS morphology and width (>150 ms, LBBB) are the only predictive parameters in CRT. Other factors are mostly anatomical issues, including 1) no appropriate branch vessel as the target site, leading to ineffective CRT; 2) a strongly bent or tortuous vessel that hinders fixation of the appropriate branch vessel in the target site; 3) dislodgement because of incompatibility between lead shape and vessel size; and 4) a high threshold or phrenic nerve stimulation even in the appropriate fixation. To reduce these anatomical obstacles, several improvements have been made to the CS lead. A bipolar electrode has been changed to quadripolar, and the lead shape has also been changed from straight to sigmoid or spiral shapes to allow for proper adjustment to the target vessels. In addition, device companies have developed the lead with different interelectrode distances. The quadripolar lead enables an optional stimulus vector selection up to more than 10 combinations and contributes to avoiding phrenic nerve stimulation; alternatively, the threshold rises with a change in electrode selection (Figure-9). The use of a quadripolar versus bipolar lead has been reported to improve life expectancy 27. The novel concept of dual point pacing using four electrodes on the left ventricle (multipoint- or multisite-pacing) also has been developed for increased interventricular synchrony by broader capture of the myocardium. Using multipoint pacing has yielded favorable clinical results 28. As noted, how to reduce the number of “non-responders” remains an issue, and various efforts are still in progress regarding factors related to both hardware and software.

Conclusion

Starting with artificial PM, CIEDs therapy has made dramatic progress in the last 60 years of clinical use. Currently, these devices are applied for the treatment of bradycardia, fatal ventricular arrhythmias, and even severe heart failure and contribute to improved prognosis. The number of patients with CIEDs is increasing steadily, so updated knowledge about these devices and confirming the appropriate indication before implantation are mandatory.

Conflict of interest

The author has no conflicts of interest directly relevant to the content of this manuscript.

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