

Are Electronic Cardiac Devices Still Evolving?

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Summary

Objectives: The goal of this paper is to review some important issues occurring during the past year in Implantable devices.

Methods: First cardiac implantable device was proposed to maintain an adequate heart rate, either because the heart's natural pacemaker is not fast enough, or there is a block in the heart's electrical conduction system. During the last forty years, pacemakers have evolved considerably and become programmable and allow to configure specific patient optimum pacing modes. Various technological aspects (electrodes, connectors, algorithms diagnosis, therapies, ...) have been progressed and cardiac implants address several clinical applications: management of arrhythmias, cardioversion / defibrillation and cardiac resynchronization therapy.

Results: Observed progress was the miniaturization of device, increased longevity, coupled with efficient pacing functions, multisite pacing modes, leadless pacing and also a better recognition of supraventricular or ventricular tachycardia's in order to deliver appropriate therapy. Subcutaneous implant, new modes of stimulation (leadless implant or ultrasound lead), quadripolar lead and new sensor or new algorithm for the hemodynamic management are introduced and briefly described. Each times, the main result occurring during the two past years are underlined and repositioned from the history, remaining limitations are also addressed.

Conclusion: Some important technological improvements were described. Nevertheless, news trends for the future are also considered in a specific session such as the remote follow-up of the patient or the treatment of heart failure by neuromodulation.

Keywords

Implantable device, leadless sensor, management of hemodynamic, subcutaneous implantable device, quadripolar lead

Yearb Med Inform 2014;128-34

<http://dx.doi.org/10.15265/IY-2014-0021>

Published online August 15, 2014

1 Introduction

Pacing has been used for nearly 40 years to correct or prevent excessive bradycardia. Starting from the asynchronous ventricular pacing, bradycardia pacing evolved progressively leading to sophisticated single or dual chamber pacemakers, serving one or more sensors. These high performance devices are adapted to the specific and changing needs of each patient and have dramatically improved the patient comfort. The "market" for bradycardia pacing is currently estimated at 50000 units per year in France, 250000 in Europe and 600000 in the world.

Within the last twenty past years, major evolutions were observed in the technology leading to decrease in the size of the pacemakers or Implantable Cardiac Defibrillator (ICD). The major evolutions were related to:

- The battery technology, even if it did not evolve significantly, the reduction in the size was linked to the microelectronic improvements and the consumption of the circuit.
- The evolution of the capacitors with the flat cap technology.
- The dramatic increase in the memory capacities opening new directions for device and patient management including the remote-monitoring system.

In the same time, new fields of application were proposed which were promising, requiring new technologies, often much more complex. These fields are:

Prevention of Rebels Arrhythmias

Despite encouraging experimental and pilot studies, the dream of the eighties to

prevent atrial or ventricular arrhythmias using specific pacing configurations was not validated by the large prospective trials with disappointing results. This is the case for example of synchronous bi-atrial stimulation evaluated in a European multi-center study (study SYNBIAPACE¹). New research's are still carried out in the field and may lead in the future to new positive therapies requiring clinical validation.

The Functions of Cardioversion and Defibrillation

The first ventricular defibrillators were implanted in humans 30 years ago. Their role is to detect and stops automatically, by an electric shock or by a pre-programmed sequence of antitachycardia pacing, malignant ventricular arrhythmias (ventricular tachycardia and fibrillation). Their effectiveness in the prevention of sudden cardiac death in patients with a history of documented arrhythmias (secondary prevention) has been widely demonstrated in prospective randomized studies (AVID and CASH studies). Controlled trial, MADIT², MADIT II, SCDHeft³ and more recently MUSST study also showed a dramatic improvement in survival in ischemic or no ischemic cardiomyopathy patients considered to be at "high risk" of sudden death in

¹ http://www.allacronyms.com/cat/7/SYNBIAPACE/synchronous_biatrial_pacing_therapy/1378867

² <http://www.bostonscientific.com/cardiac-rhythm-resources/clinical/madit-trial.html>

³ <http://www.medscape.com/viewarticle/471461>

the absence of malignant arrhythmias previously documented (primary prevention). The concept of the automatic cardioversion of atrial arrhythmias was also developed in the nineties due to the high prevalence of this arrhythmia. Despite successful technological developments, the clinical validation fails to demonstrate a long-term efficacy. Finally, the major evolution in the treatment of atrial fibrillation was brought by ablation technic.

Hemodynamic Treatment

The case of cardiomyopathy and refractory heart failure is remarkable because it is the first clinical application where the stimulation is used no longer to correct an abnormal heart rhythm, but to improve the mechanics of the heart by modifying its electrical activation sequence. This approach was first evaluated (PIC Study and MPathy study) for the treatment of hypertrophic obstructive cardiomyopathy with the objective of functional improvement by decreasing the left ventricular outflow track obstruction.

Much more common are dilated cardiomyopathies and much more important in terms of public health is the problem of Heart Failure (HF) with an annual incidence of 15000 new cases and strong growth in France. Patients with cardiomyopathies have two main risks: 1) heart failure, when it becomes refractory to medical therapy may require the use of non-pharmacological alternatives, mainly heart transplantation, 2) sudden death whose origin is often arrhythmia (tachycardia or ventricular fibrillation). Active implantable devices play an important role in this disease. These encouraging results have been first validated in the international multicenter study MUSTIC [1], key trial for the development of the Cardiac Resynchronization Therapy (CRT).

These works made 15 years ago with "first generation" devices directly from the conventional dual chamber pacing have highlighted the limitations of current technology. The goal today, to further increase the benefit provided by multisite pacing, is to optimize in real time the dif-

ferent stimulation parameters. Such goals require the development of new tools to better understand the hemodynamic status, continuously and automatically. The achievement of these objectives is possible not only by improving lead positioning, but also by means of multimodal observations using auto-adaptive principles and parameter integration. Various technological aspects (electrodes, connectors, algorithms diagnosis, therapies, ...) are far from being controlled. By combining multimodal observations and multisite pacing and defibrillation functions, these active devices of the future should also contribute to reducing the risk of sudden death in these particularly vulnerable populations. Expected outcomes in this area concern the miniaturization of device, increased longevity, coupled with efficient pacing functions, including multisite pacing modes, leadless pacing and also a better recognition of supraventricular or ventricular tachycardias in order to deliver appropriate therapy. Although a major step was accomplished, a continuous and sustained effort aimed at improving therapies must be maintained. This is the goal of the paper to review some important issues occurring during the past year.

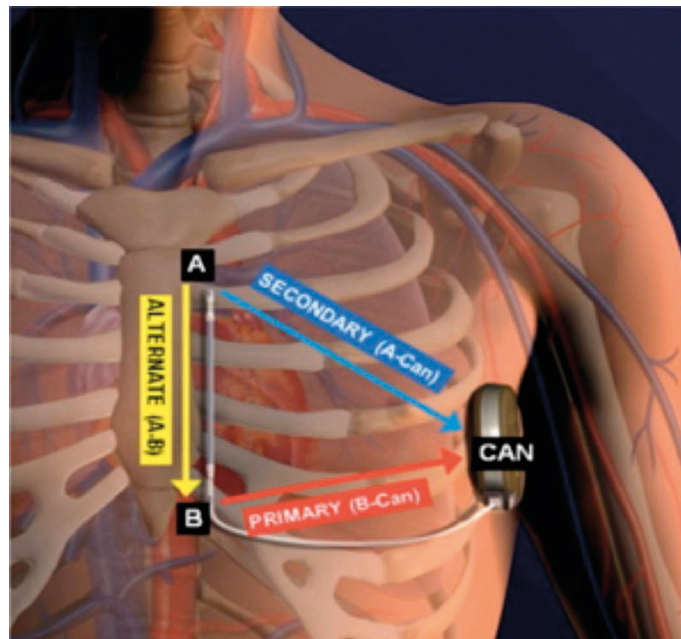


Fig.1 Anatomic locations of S-ICD components with sensing vectors. The sensing vector can be selected from the proximal electrode B-CAN (primary), the distal electrode A-CAN (secondary), or the distal to proximal electrode A-B (alternate) (from *Circulation: Arrhythmia and Electrophysiology* June 2012 vol. 5 no. 3 587-593)

2 Subcutaneous Implantable Cardioverter Defibrillator

Introduced to clinical practice in 1980, the ICD protects patients against sudden cardiac death [2]. Multicenter studies have shown a reduction in total mortality of up to 54% and an arrhythmic mortality reduction of 50% to 70%. Despite its clinical success, close to 300000 patients implanted in the world, implantation of the ICD still remains a gagure [3].

The goal of developing a Subcutaneous-ICD (S-ICD) - which consist in locating pulse generator and electrode on the thorax (Figure 1) - was to fulfil three major objectives:

- First accurate arrhythmias detection and discrimination,
- Defibrillation of Ventricular Fibrillation (VF) with acceptable level of energy,
- Pacing the ventricle to prevent bradycardia or reduce Ventricular Tachycardia (VT) using Anti-Tachycardia Pacing (ATP)

The technical progress was able to achieve the two first objectives but unfortunately, until now, the ventricular capture was not yet possible transcutaneously with conventional energy delivery.

Designing S-ICD was also to overcome the problems (failure to achieve vascular access, intravascular injury and lead failure) that are associated with transvenous leads in conventional ICDs. Additional potential benefits include the preservation of venous access for other uses and the avoidance of radiation exposure during implantation, which is required for transvenous ICD lead implantation.

The initial feasibility, safety, and effectiveness of subcutaneous defibrillation were established in earlier human studies of the S-ICD System [3, 4, 5]. More recent studies sought to establish the safety and effectiveness of the S-ICD System for the treatment of life-threatening VT/VF in a larger patient cohort [6]. In an effort to minimize lead complications and to evaluate the effectiveness and safety of a totally S-ICD, Weiss designed a specific trial [7]. The results show that the primary effectiveness and safety end points were met, demonstrating a good termination rate of induced ventricular tachyarrhythmias and an acceptably low complication rate. Moreover, the defibrillation efficacy is stable over time for both spontaneous and induced arrhythmias. The device effectively withholds shocks for most supraventricular arrhythmias, particularly if the conditional zone is activated for discrimination. The results of the reported study indicate that the subcutaneous implantable cardioverter-defibrillator is a viable alternative to transvenous systems among patients who do not require pacing therapy for heart failure, bradycardia, or ventricular tachycardia.

The present commercially available device need further development especially reduction in the size of the can and increase of battery longevity which remains a compromise due to the battery technology. A technological rupture is still waiting in that field.

3 Endocardial Leadless Pacing

Implantable cardiac pacemakers have been highly correlated with innovations in device operation and implantation techniques, progress in miniaturization and substantial enhancement of system reliability. Nevertheless, as already mentioned, the lead remains

an Achille's heel. In that sense, to propose a device eliminating the pacemaker lead is a real challenge. Review of Patent related to the subject of wireless cardiac pacing revealed a high activity. Several issues have been proposed in the recent past years [8], [9], [10], among them the use of ultrasound (US) or totally implanted system.

The development of US leads to the first clinical trial in the field of CRT (Wireless Stimulation Endocardially for CRT, WiSE-CRT) with the objective of safety and feasibility evaluation. WiSE-CRT was planned to enrol 100 patients in Europe. Unfortunately, the trial was prematurely stopped due to embolic complications. Nevertheless, several potential advantages of an alternative approach of delivering left ventricular endocardial leadless pacing (LEVP) has been stressed in the study reported by [11]. In summary, LVELP shows promise for improving CRT efficacy. It enables Left Ventricular (LV) pacing to be established even if coronary sinus anatomy is unfavourable. It allows a greater choice of LV pacing sites, respects the physiological electrical activation from the endocardium to the epicardium, may be less arrhythmogenic, may be more efficient to resynchronize the LV because of a more rapid activation and may reduce lead-related complications. All these points explain that further developments are still needed to demonstrate that US energy delivery is a commercially viable choice for pacemaker applications [12].

Totally implantable system with total integration of the battery, the electronic circuits and the transfer energy to the heart system has been recently developed (Figure 2). Two systems are now implanted in human the St. Jude medical Nanostim leadless pacemaker (Figure 3) which receives CE mark and the Medtronic Micra leadless implant (Figure 4). The implantation feasibility of the Nanostim system was shown in the LEADLESS study in 33 patients while the Medtronic implant is undervaluation in the Micra TPS study. These totally intracardiac devices are implanted through venous femoral approach with a system delivery and the entire system is screwed into the ventricle and may be repositioned if needed (Figure 2). The device is also theoretically removable which was validated in animal models. Nevertheless, the long-term removability is still questionable, critical in

case of infection. Only a single ventricular pacing is now proposed which represents a limit of the system. Even if, the exceptive longevity of the battery is about 9 years, battery size remains a limitation for dimension reduction of the can and innovative energy harvesting system has to be proposed [13].

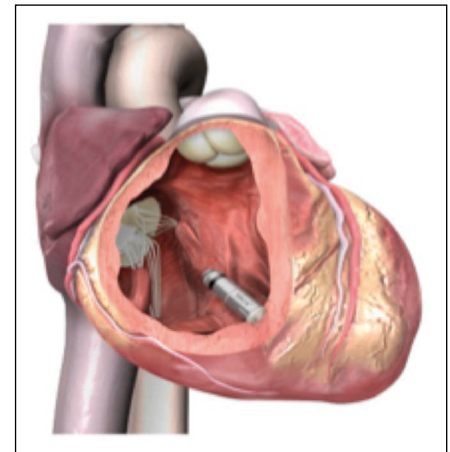


Fig. 2 Schematic implantation of a leadless pacemaker



Fig. 3 The St. Jude medical Nanostim leadless pacemaker



Fig. 4 The Medtronic Micra TPS leadless wireless pacemaker

4 Management of Hemodynamic Aspects

Management by single prosthesis hemodynamic and rhythmic aspects, both in terms of prevention and treatment, justifies reliable information on the hemodynamic status and robust rhythm recognition. Despite the worldwide success of the CRT, the weak point of the technic remains the 30% patients non-improved after implantation also called “non-responders” patients. One way to minimize the rate of non-responders would be to personalize the pacing parameters, particularly the atrioventricular (AV) and interventricular (VV) activation delays, since these parameters have a significant impact on the cardiac function (ventricular contractility, cardiac output, transmitral flow, LV filling, etc.) and their optimal configuration is patient specific [14, 15] and variable other time in one given patient.

Currently, the optimization of these pacing parameters involves an echo-Doppler acquisition to evaluate the ventricular mechanical function while scanning different values for AV and VV delays. An interesting alternative to this in-hospital echocardiography has been proposed based on mechanoacoustic signals. Cardiac mechanoacoustic signals, such as the phonocardiogram (PCG), have been largely studied for the evaluation of the mechanical function of the heart, including the analysis of the effect of different CRT pacing configurations on systolic time intervals [16, 17]. Recently, a piezoelectric microaccelerometer inserted into the tip of an endocardial pacing lead (Figure 5) was proposed.

Initially developed for pacing rate adaptation, it was recently adapted as an “hemodynamic sensor”. This sensor provides an endocardial microacceleration signal that may be useful for the continuous optimization of the delivered CRT [18, 19]. In a previous work, an external version of the SonR signal was proposed with a method to estimate the mitral and aortic valve closure instants [20]. This method was clinically evaluated in the context of CRT optimization with data from 75 heart failure patients, under different pacing configurations [21].



Fig. 5 Example of the SonR Fix atrial lead embedded a microaccelerometer

It was shown that satisfactory systolic/diastolic time interval estimations can be obtained from the SonR signal. An improvement of the original method, integrating an optimal combination of different detector configurations, in an algorithm switching approach [22] was then proposed to extract a set of features, such as the systolic and diastolic time intervals, that can be used as control variables for an adaptive closed-loop AV and VV delay optimization. The proposed method has been quantitatively evaluated using data from a population of

31 patients suffering from chronic HF and implanted with a biventricular pacemaker, so as to estimate the systolic period for different pacing configurations, through the analysis of a cardiac microacceleration signal. This approach would simplify and generalize the application of the AV and VV delay optimization stage, reducing medical burden, and would provide a better CRT delivery under different physiological conditions (rest, exercise, etc.).

The same technology may be used at the implantation time of the device to better select the lead configuration. The SonRMap Station recently proposed (Figure 6) was designed to achieve this objective.

Another way to optimize the CRT delivery is the development of new automatic pacing algorithms. This was the purpose of the novel adaptive cardiac resynchronization therapy aCRT algorithm [23] developed by Medtronic with the aim to provide only left ventricle pacing when the atrioventricular conduction is normal or biventricular pacing otherwise. The algorithm determines the pacing method (left ventricular or biventricular pacing) based on the intrinsic conduction assessment, the heart rate and the left ventricle capture.



Fig. 6 The SonRmap platform, designed by Sorin, to assist the implantation of the device based on the microaccelerometer sensor

5 Quadripolar Left Ventricular Lead

Although advances in technology and improving expertise have increased the success rate for biventricular system implantation, the placement of a Coronary Sinus (CS) lead is still a technically challenging procedure owing to variable vein anatomies and lead stability remains problematic. In addition to difficulties related to device implantation, the procedure has its own complications mainly represented by Phrenic Nerve Stimulation (PNS) and Left Ventricular lead dislodgment with loss of capture.

Recently, a quadripolar LV lead (Quartet 1458Q, St. Jude Medical, Sylmar, CA) has been designed in order to provide more options for LV pacing. This new lead integrates 4 pacing electrodes that give the implant more choices in device programming as compared with the ones available with traditional bipolar LV leads. The hope is to reduce the need for lead revision at implant or during follow-up and to find a pacing configuration with minimal energy consumption (Figure 7).

Indeed, flexible LV pacing configurations are a useful feature of CRT systems for preventing high LV pacing thresholds and PNS [24], [25]. A lead with multiple pacing electrodes increases the possibility to find the best pacing site available among different bipolar and unipolar pacing configurations and is a potential alternative to invasive adjustment of the lead or discontinuing CRT when PNS occurs. Results of early clinical evaluations suggest that CRT with the quadripolar LV lead is associated with a high implant success rate, low rates of dislocation and PNS. However, data on the quadripolar lead are few in the literature and follow-up data are limited. Recently, Forleo [26] proposed, over a period of 21 months, to prospectively enrol 154 consecutive patients scheduled for CRT implantation with a quadripolar LV lead, very interesting results were observed:

- Implanted patients with quadripolar leads have an enhanced possibility to avoid subsequent PNS,

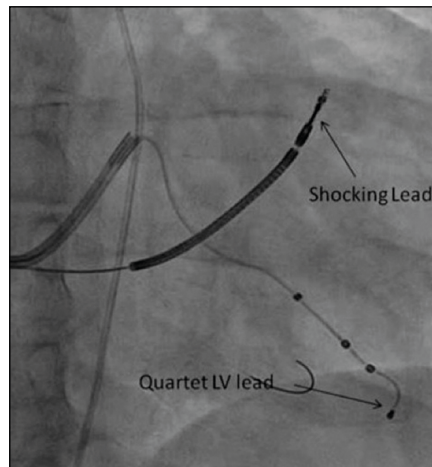


Fig. 7 Fluoroscopic appearance of the quadripolar left ventricular lead with 3-ring electrodes distant 20, 30 and 47 mm from the tip electrode allowing 10 programmable pacing configurations

- Lead stability was also observed. Few reoperations occurred in this study (2.7%), which is relatively low compared to previous studies [27], [28].
- The implant success rate was very high and somewhat surprising, given that many centers had no previous experience and were at the beginning of their individual learning curves.

This study represents the largest cohort and the longest follow-up of CRT patients implanted with a quadripolar LV lead. Nevertheless, some potential limitations still remain: mean follow-up was limited to 15.3 months after implantation and further follow-up data beyond 24 months are needed to confirm the reliability of this lead. This long-term follow-up is important to demonstrate that the diminution of “non-responders” is effective when using quadripolar technology, which is the objective of the on-going MORE-CRT⁴ trial. In parallel, these new electrodes technology requires new connectors configurations, in addition to the new DF4 technology developed for ICD lead with integration in only one port of the sensing and defibrillating leads.

⁴ <http://clinicaltrials.gov/show/NCT01510652>

6 Towards New Paradigms

Due to space limitation, we are aware that some important technological improvements were forbidden here such as the remote follow-up of the patient. Professional practice guidelines recommend that device recipients be followed regularly [29, 30]. A recent studies, the French randomized, multicenter ‘COMPARative follow-up Schedule with home monitoring’ (COMPAS) [31] trial confirmed that remote monitoring is not a substitute for an emergency system but safely eliminated unnecessary follow-up visits and allowed the early detection of events. The observations made in this trial might soon set a new standard of care for the follow-up of pacemaker recipients. The development of these new technologies needs to propose in parallel new economic models for manufactory and healthcare provider.

A second issue is related to the treatment of heart failure by neuromodulation. Preliminary clinical experiences on neuromodulation to treat heart failure show great potential of these therapies. Heart failure is a progressive condition that develops gradually, leading to a cascade of neurohormonal compensatory mechanisms. These phenomena, beneficial in a short-term period, become over time deleterious to the heart pump (vicious circle). These mechanisms include an over-activity of the sympathetic system that may be controlled by the beneficial effect of beta-blocker [32, 33, 34]. The reduced activity of the parasympathetic nervous system is associated with excess mortality in patients with heart failure. The vagus nerve is the main component of the parasympathetic system and in the absence of drug, stimulating the vagus nerve seems legitimate. Its potential in the treatment of heart failure has recently been explored. In three different experimental models of heart failure, improved left ventricular performance [35, 36, 37] and a reduction in mortality was demonstrated by stimulation of the vagus nerve. The beneficial effects of vagal neuromodulation in heart failure would include: a reduction in heart rate, increased heart rate variability and anti-arrhythmic effects. The encouraging

results of the first clinical phase II studies published recently support the interest of such stimulation [38]. All these facts underline the highest activity in this sense by all the industrial leaders of the domain and making neuromodulation probably as a very important challenging issue.

Other directions are also under investigation as renal denervation, baroreceptor stimulation or spinal chord stimulation.

We are at the early phase of new exciting developments with the hope to observe the same “success stories“ as for ICD and CRT within the last twenty past years.

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