Review

PHYSIOLOGICAL STIMULATION OF THE HEART – HISTORY AND THE PRESENT

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The possibility of electrical stimulation of the heart has fascinated researchers and doctors since the Age of Enlightenment until the 21st century. Cardiac pacing strategies have evolved from epicardial and myocardial to stimulation of the cardiac conduction system. Despite progress, many issues remain unresolved, including intraoperative determination of the optimal site for stimulation and pre- and postoperative assessment of left ventricular ejection fraction to select optimal patients and evaluate the treatment dynamics.

Literature review was performed to evaluate the evolution of electrical myocardial stimulation, its modern methods, advantages and disadvantages.

The evolution of electrical cardiac pacing has gone through stages from non-selective stimulation of the left and right ventricular myocardium to biventricular pacing and the latest milestone – the pacing of the conduction system – the bundle of His or its left bundle branches.

Cardiac conduction system stimulation is today’s most physiological method of permanent cardiac pacing. However, it is not without some drawbacks, in particular, the need to perform the intraoperative evaluation of the effectiveness of myocardial resynchronization to have methods of objective assessment of left ventricular systolic function before and after resynchronization therapy in patients with significantly reduced ejection fraction. It is necessary for the selection of optimal patients for biventricular pacing, or stimulation of the conduction system of the heart, and prediction of possible outcomes.

Keywords: physiological cardiac pacing, heart failure, Simpson’s method, performance index, resynchronization therapy, His bundle pacing, biventricular cardiac pacing, left bundle branch pacing.
Electrical stimulation of the heart is based on a well-known concept – reflex muscle contraction in response to electric current application. The study of this process has been going on for several centuries and has gone through stages from questioning to the explosive development of this concept over the past 50 years [1]. One of the first experimental external cardiac stimulations was performed by Danish physicist Nickolev Abildgaard in 1775, who placed electrodes on the head of a chicken and applied an electric discharge that led to the animal’s clinical death. After that, he used another electric shock to the chicken’s chest, which “came to life.” He probably achieved fibrillation and defibrillation of heart ventricles [1].

Marie Francois Xavier Bichat (1800-1802) and Nysten described experiments on decapitated human bodies in which heart contractions were induced by the application of electric current, and they did not lack experimental materials during the French Revolution [1].

An ideal opportunity for a clinical and scientific experiment appeared in 1882. A 46-year-old woman was admitted to the Hugo Von Ziemssen clinic. She was an uneducated laborer from Upper Silesia (then Prussia), Kateryna Serafin. A tumor localized on her chest was removed, along with part of the chest wall (ribs and soft tissues). As a result, the heart became accessible for observation and manipulation through a thin layer of skin [1]. Von Ziemssen stimulated her heart with an electric current and changed her heart rate at will. The recordings clearly demonstrate ventricular activity caused by electrical impulses applied to the surface of the heart, a fascinating but potentially fatal study [1].

The Hyman device, described in 1932, was powered by a dynamo and described by its developer, Hyman, as an “artificial pacemaker,” a term still used today. The electric current from this dynamo was delivered to the right atrium through a bipolar needle-electrode, which was inserted through the intercostal space. Stimulation could be performed with a frequency of 30, 60, or 120 pulses per minute.

Pacemakers powered by household electricity were developed in the early 1950s and were large boxes with vacuum tubes (lamps), which made it impossible to implant them. They were transported by carts and connected to household AC power sources, so they were conditionally portable, as they could only be transported to the next “outlet.”

All these, and many subsequent systems, operated only in asynchronous mode, which led to “R on T”-induced ventricular fibrillation. In 1956, at St. George’s Hospital (London), Aubrey Leatham and Geoffrey Davies created an external stimulator that helped resuscitate a patient with A-V block and asystole.

At that time, the results of the first studies on external cardiac stimulation were reported by Paul Zoll (Boston). But Zoll’s external pacemaker system was “fixed” without the ability to work “on demand,” which led to the phenomenon of “R on T” and the induction of VF. In 1956, the first pacemaker that could function “on-demand” was created in the same St. George’s Hospital [1].

The rapid evolution of cardiac surgery gave impetus to the development of pacemaking, in particular Lilley, who intensively introduced innovative methods of treating heart defects using artificial circulation. Thus, one out of ten operated patients had iatrogenic complications in the form of cardiac conduction or automaticity disorders. This situation was not radically resolved by atropine, epinephrine, or the recently discovered isoprenaline, nor by the percutaneous (external) cardiac stimulation technique proposed by Zoll, as its use was painful, and it took several days to restore the function of the conduction system (under favorable circumstances). Lilley and colleagues developed a Teflon-insulated myocardial electrode that was sutured to the myocardium at one end and brought out through a puncture in the skin to the outside and connected to a modified external pacemaker developed by Grass, which was used in animal models. The stimulation threshold of 1.5 V and the possibility of prolonged electrode stay in the patient’s body allowed for waiting for the restoration of the cardiac conduction system function without discomfort, and the electrode could be easily removed from the patient’s body. The first such electrode was implanted on January 30, 1957, in a 3-year-old girl after correction of tetralogy of Fallot. This technique of temporary cardiac pacing has survived to the present day, almost unchanged [1].

The problems of portability and electrical power were obvious. They were solved at the same Lilley Clinic, thanks to the already wide availability of transistors (at that time), in the form of the first portable external battery-powered pacemaker that could be carried and was put into mass production by Medtronic.

In 1958, for the first time, temporary electrical stimulation of the heart was successfully performed using a transvenous electrode located in the right ventricular outflow tract in a patient with third-degree AV block during surgery for an intestinal tumor.
October 8, 1958, was a truly historic day, as it was the first time that a system of permanent cardiac pacing was fully integrated into the human body. This took place at the Karolinska Institute (Solna, Sweden). The model used was designed by Rune Elmqvist and surgeon Ake Seneng and was connected to electrodes fixed to the myocardium through a thoracotomy. The device failed after 8 hours. The second device, which was implanted instead of the first, worked much longer. This world’s first patient with an implanted cardiac pacemaker, Arne Larsson, suffered from Morgagni-Adams-Stokes attacks 20 to 30 times a day (he had a documented third-degree AV block). The prognosis for his life was poor, and the only chance for salvation was to agree to a new method of treatment, which was experimental and not yet tested on humans. The only (and ineffective) alternative at the time was intensive therapy in the form of a combination of atropine, epinephrine, penthymal, isoprenaline, caffeine and whiskey. This patient underwent more than 20 implantations of various pacemaker systems during his life. He died in 2001 at the age of 86 and ironically outlived both the device’s inventor and his surgeon. An interesting feature of this device was the wireless (inductive) charging of the battery, which had to be done during 12 hours once a week [1].

In addition to the evolution of cardiac pacemaker (CPM) batteries – from zinc and isotope batteries to lithium batteries, and the evolution of electrodes – from epicardial to endocardial with active fixation, the “on-demand” function was added to pacemakers during the 1970s. In the late 1970s, the first two-chamber CPM was developed, able to detect and stimulate the atria and ventricles, with functions for changing the atrioventricular (AV) delay and the first sensors of frequency adaptation that appeared later. These technical inventions gradually brought cardiac pacemakers closer to the conventionally physiological pacing of the heart.

However, some problems remained unresolved for a long time. Stimulation of the right ventricular apex provoked the appearance of the complete left bundle branch block (LBBB) pattern. Only in 2013, Chen S. and colleagues proved that an expansive QRS complex that occurs during apical pacing predicts myocardial dysfunction, a decrease in left ventricular ejection fraction (LVEF) and the development of heart failure [2].

In 2014, Khurshid and colleagues linked the pattern of LBBB due to permanent cardiac pacing to the development of the so-called pacemaker-induced cardiomyopathy [3].

Right ventricular (RV) stimulation is also a proven predictor of atrial fibrillation [4].

Not all patients with heart failure and severely reduced left ventricular ejection fraction (LVEF) have the technical and anatomical feasibilities for implantation of a three-chamber resynchronization device due to the lack of target veins for implantation of the left ventricular electrode or a high threshold of stimulation [5].

Poor efficacy of resynchronization therapy has been proven in patients with a narrow QRS complex and mechanical LV dyssynchrony – the results of the PROSPECT study [6]. The results of the same study showed that mechanical dyssynchrony cannot be an isolated indication for LV electrical resynchronization.

The key to a potential solution or avoidance of the described problems and complications was the work of Onkar S. Narula (1970), where he demonstrated the disappearance of the LBBB pattern during the stimulation of the His bundle (HB) zone from the right heart. The researcher concluded that the lesion of the left bundle branch is located mainly in the bundle of His before its division into left and right branches. This can explain the narrowing of the QRS complex to normal duration during stimulation more distally than the lesion point.

The Mode Selection Trial (MOST) in patients with sinus node dysfunction demonstrated that at least 40% of RV stimulation is associated with an increased risk of heart failure (HF) or more frequent hospitalizations for atrial fibrillation [7].

Another study by Kurshid and colleagues showed that the percentage of RV stimulation, even less than 40%, leads to a decrease in LV EF from 62.1% to 36.2% over 3.3 years. This condition is clearly associated with an increase in the duration of the QRS complex and is a pacemaker-induced cardiomyopathy [8]. Therefore, RV stimulation is not physiological, although it is still considered typical in many clinics and, unfortunately, is widely used empirically in practice [9].

Great expectations were placed on the continuous stimulation of the interventricular septum from the RV. It was believed that this was more physiologic than apical stimulation of the RV. However, since 2013, two randomized trials have been conducted that demonstrated the lack of clinically significant results of this concept [10, 11]. Another study showed a lower risk of heart ventricular perforation in the group of patients with septal RV pacing [12]. Achieving true septal RV pacing is not always easy, and the effects obtained are more positive than negative compared to apical
RV pacing [13]. Therefore, there is no solid evidence to recommend septal RV pacing as a routine procedure for all patients and to include this technique in mandatory clinical guidelines.

In 2000, Deshmukh and colleagues described the first, relatively successful, use of a permanent bundle of His stimulation in 18 patients with dilated cardiomyopathy, permanent atrial fibrillation with rapid heartbeat, normal QRS complex duration (< or =120 ms), reduced LVEF and clinical manifestations of HF. In 12 patients, it was possible to establish reliable intraoperative continuous pacing of a bundle of His using fixed-drill electrodes. After that, patients underwent destruction of the AV node. However, in the early postoperative period, most of these patients experienced technical complications in electrode dislocation and a significant increase in stimulation thresholds, which required repeated surgical correction. These issues were related to the mismatch between the anatomy of the HB zone and the design of permanent transvenous electrodes and introducers. However, the result, in the form of an improvement in patients’ LVEF and functional class of HF, confirmed the potential value of this method. Three randomized trials proved the superiority of biventricular stimulation over the right ventricular stimulation in patients with moderately or significantly reduced LV systolic function who required cardiac stimulation due to bradycardia to improve the quality of life, symptoms of HF and achieve positive echocardiographic changes [14].

In the BLOCK HF trial, which compared biventricular and right ventricular pacing, 691 patients with A-V node dysfunction and indications for implantation of a CPM with moderately reduced LVEF (<50% by inclusion criteria, mean 42.9% in patients in the CPM group) were randomized to biventricular pacing (with or without implantation of a cardioverter-defibrillator) and followed for an average of 37 months. The primary outcome was death from any cause, emergency care for HF requiring IV medications, or more than a 15% increase in LV end-systolic volume index. Patients in the biventricular pacing group were less likely to have the primary outcome described compared with the right ventricular pacing group (hazard ratio, 0.74; 95% confidence interval, 0.60 to 0.90). Complications associated with the left ventricular electrode occurred in 6.4% of patients [15, 16].

There is no doubt about the significant positive effect – a combination of an increase in LVEF of more than 15% and a decrease in LV end-systolic volume, a decrease in hospitalization for HF, and a decrease in mortality – in patients with cardiac resynchronization therapy (CRT). A positive clinical effect was obtained in response to CRT in many patients with LV systolic dysfunction and the expected high percentage of RV stimulation. In patients with normal or preserved EF, data on the positive effect of CRT contradict the frequency of hospitalizations, and there is no advantage in reducing mortality [17, 18, 19].

Nevertheless, several studies have demonstrated that negative cardiac remodeling due to RV pacing was prevented by biventricular pacing, especially in the long term [20, 21].

Another single-center study showed that >20% of RV stimulation was associated with significant negative LV remodeling in patients with AV block and preserved LV EF [21].

A new milestone in electrophysiology was the stimulation of the cardiac conduction system, particularly the bundle of His and its left bundle branch (LBB). HB stimulation can be used not only to treat patients with severe heart failure in the setting of complete LBBB but also routinely in patients with compromised cardiac conduction systems and a high predicted percentage of RV stimulation [22].

On the other hand, technical difficulties in the process of implanting an electrode for HB stimulation – the need for separate vascular access for an electrophysiological catheter, variability in the anatomy of the HB zone, high stimulation thresholds, a relatively higher percentage of electrode dislocations, and a long learning curve for the doctor – prompted the search for other techniques for stimulating the conduction system of the heart, in particular, stimulation of the LBB zone.

This technique has demonstrated its comparative technical simplicity and comparable positive clinical outcomes versus RV stimulation [23], both in patients with intact cardiac conduction system function and in patients with LBBB [24, 25].

A significant advantage of HB or LBB pacing is its lower cost compared to biventricular stimulation [26]. The typically higher thresholds for HB pacing compared to LBB pacing are also a known drawback [27]. With infrahis LBBB, effective HB pacing is impossible; such a limitation is not present in the case of stimulation of the LBB zone [28].

Before implanting a biventricular resynchronization device, one should consider its higher cost and the percentage of possible complications compared to the direct cardiac conduction system stimulation [29].
The issue of an objective assessment of LVEF as the main criterion of the effectiveness of cardiac resynchronization remains unresolved. There is a lack of a strong correlation between mechanical and electrical LV dysynchrony, which complicates the selection of prognostically optimal patients, finding a place in the heart for implantation of an endocardial electrode, assessing the dynamics of treatment effectiveness and patient’s dynamic monitoring [30]. Simpson’s method remains the standard and is generally recommended for measuring LVEF. It has tangible disadvantages; for example, a diagnostician must be experienced in clearly registering optimal images and identifying the edges of the endocardium. The latter is sometimes impossible for many patients due to the a priori lack of high-quality images. In practice, the edges of the endocardium could be clearly visualized in less than 50% of patients, especially with an apical approach. The measurements take a lot of time. The phenomenon of “left ventricular foreshortening” is also known when measurements are obtained that do not correspond to the longest axis of the LV, which leads to distortion of the EF results [31]. As a consequence, the result of measuring LVEF by the Simpson method can give an error of +/- 7%, which potentially does not allow it to be used as a reference for assessing the effectiveness of CRT in the dynamics, especially in the group of patients with significantly reduced baseline LV systolic function and electrical myocardial dys synchrony. This makes scientists and doctors look for alternative methods and approaches [32].

The main intraoperative criteria for effective CRT are the narrowing of the QRS complex and the disappearance of the LBBB block pattern [33]. However, the problem of the accurate assessment of this parameter remains. More accurate figures for the width of the QRS complex can be obtained by using an electrophysiological station, which allows for obtaining high signal quality and amplitude and accurately determining the moment of onset of myocardial depolarization. Still, such equipment is not widely available, so this method cannot be routinely used [33].

In conclusions:

1) The most physiological method of permanent electrical cardiac pacing today is stimulating the heart’s conduction system – the bundle of His or its left bundle.

2) Stimulation of the cardiac conduction system is almost always an alternative to biventricular resynchronization therapy with similar efficacy and significantly lower cost.

3) The problem of assessing LVEF in patients who qualify for myocardial resynchronization therapy and accurate assessment of this parameter to monitor the effectiveness of treatment in a group of patients with significantly reduced LV systolic function remains unresolved. A possible alternative to the Simpson method for assessing LV systolic function may be the “performance index”.

4) Intra- and postoperative assessment of the effectiveness of electrical resynchronization of the myocardium remains problematic since the available methods for its determination are not widely available (electrophysiological station), and the analysis of a conventional ECG gives a significant error. Therefore, searching for new methods to accurately and quickly assess this parameter continues.

References


