Cardiac Pacemakers: Past, Present and Future

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Pacemakers were the first active implantable devices. Being so commonly known nowadays, their use has been integrated to our daily lives, like the use of the aspirin or antibiotics. Only 60 years ago, people with heart diseases would have a very poor life quality or even died but ever since the use of pacemakers several heart diseases are not life threatening anymore. In this article, I present basic concepts about the physiology of the heart, the history of the development of cardiac pacemakers, and the characteristics of today's pacemaker designs.

Basic Concepts of the Electrical Behavior of the Heart and the Ideal Pacemaker

The heart, conformed by four chambers of two atriums and two ventricles, is an organ which pumps blood to provide oxygen and nutrients to all the cells of the body. Fig. 1 shows a simplified diagram of the blood circulation.

The heart's electrical system can be explained in the following simplified manner. Under normal conditions, the heart's electrical activity is originated in the sinoatrial (SA) node (Fig. 2) in a rhythmic and spontaneous manner, travelling through the rest of the heart by specialized channels that enable an orderly and sequential activation of the heart chambers, assuring maximum mechanical efficiency.

The SA node is, under normal conditions, the structure that generates the electrical impulse that activates the whole heart, being the primary natural pacemaker of the heart. It is located in the upper part of the wall of the right atrium near the entrance of the superior vena cava.

The group of cells from the SA node, as other excitable cells of the human body, present under resting conditions an electrical potential difference of +90 mV if measured from the outside relative to the inside of the cell. This means the cells are polarized.

Cells in the SA node can spontaneously depolarize – this means inverting temporarily the charge polarity of the inside in relation to the outside of the cell – generating an action potential. This action potential propagates from one cell to the next (reminiscent of a row of dominoes) along the left atrium and towards the ventricles producing depolarization on each of the cells reached and contraction as a consequence.

The synchronous and efficient contraction of the heart's four chambers is achieved because the signal transmission is optimal to reach the correct timing during the contraction of all cardiac cells. Therefore, the transmission from the SA node to both of the atria happens almost simultaneously.

Once the propagation reaches a place between the right atria and the right ventricle called the atrioventricular (AV) node, the propagation inside the AV is slow enough to produce a delay between the atrial and ventricular contraction making the heart's output greater. The delay between atrial and ventricular contraction can be up to 200 ms in a healthy heart.

Pacemakers act on a low rhythm heart, restoring the synchronization and heart rate that a healthy heart would have. Therefore, if the patient's problem is that the sinoatrial node in the heart does not generate the proper rate, the ideal pacemaker should generate a rate with a frequency suitable for the patient's needs. If a patient's heart has conduction problems

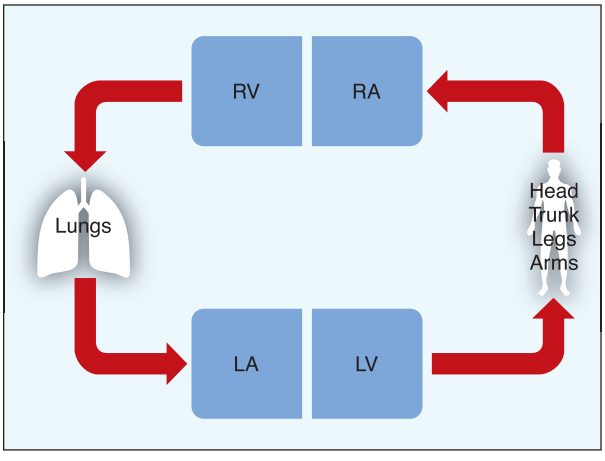

Fig. 1. Diagram of the flow of the blood. Non-oxygenated blood enters the right atrium, goes to the right ventricle and it is pumped to the lungs. Oxygenated blood from the lungs enters the left atrium, goes to the left ventricle and it is pumped to all the body.

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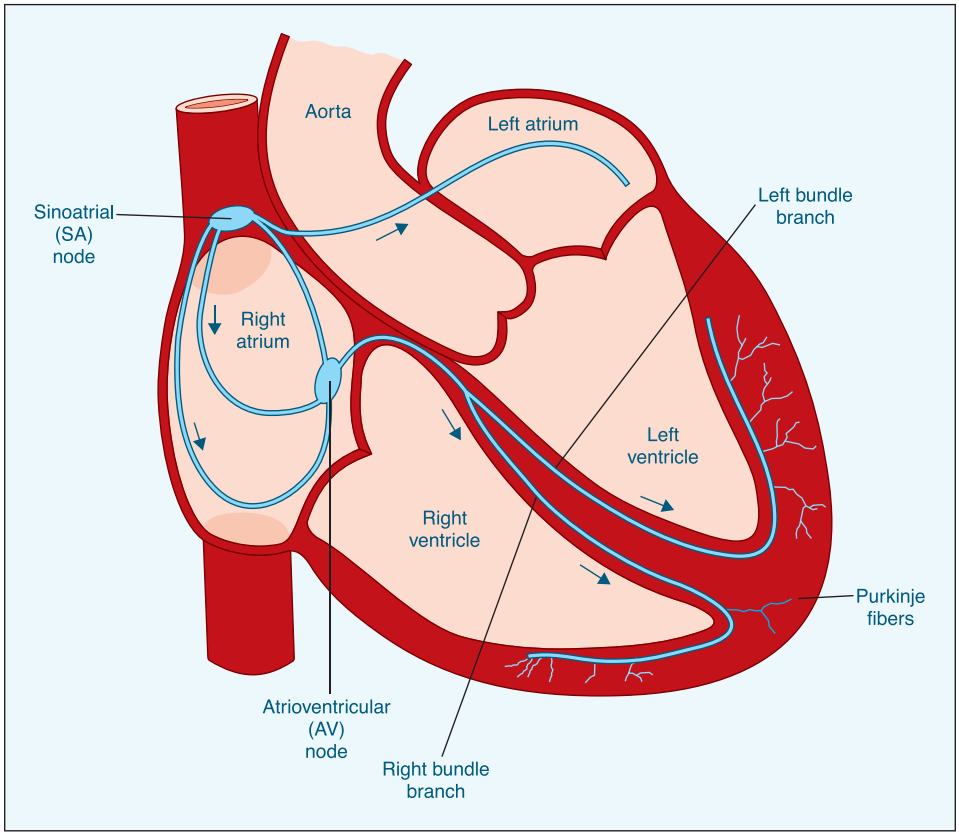

Fig. 2. Diagram of electrical conduction in the heart. (© 2005 J. Wiley & Sons, Inc., D. Prutchi and M. Norris, *Design and Development of Medical Electronic Instrumentation*, reproduced with permission.)

in the atrioventricular node, the ideal pacemaker should sense the atrial signal and stimulate the ventricle with a delay optimal for the patient's frequency.

The First Pacemakers

Up until the 1960s, patients suffering with severe bradycardia (low cardiac rate) or cardiac arrest episodes did not have any other medical alternative rather than the use of external devices developed by Dr. Zoll. They were connected to the mains and therefore, attached by a cable to an outlet. In Sweden, on October 8, 1958, the first pacemaker was implanted. It was developed by the doctor that became an engineer, Rune Elmqvist and implanted by Dr. Ake Senning in Karolinska Hospital, Solna. Arne Larsson was the patient [1]. Unfortunately, this first totally implantable pacemaker lasted only eight hours and a second device implanted the next day, only two days. A little more than a year after, on February 3rd, 1960, in Montevideo, Uruguay, Dr. Orestes Fiandra and Dr. Roberto Rubio implanted the first implanted pacemaker that successfully worked in a human being [2] (Fig. 3).

The first pacemakers designed in Sweden had elemental electronics capable of stimulating the ventricle with fixed frequency, amplitude, and pulse width. They had a cylindrical shape, a diameter of 52.5 mm and a 17.5 mm thickness. The power supply was three nickel-cadmium batteries that could be recharged with a 25 cm diameter external coil, which transferred energy to a 50 mm diameter coil placed in the implantable device. The electronics were covered by epoxy. The lead with the cathode electrode came directly out of the pacemaker body without a connector. The stimulation cathode in the distal extreme of the lead was a 9 mm diameter platinum disk covered on one side with epoxy resin. It had two holes to attach it to the myocardium.

Figs. 4 and 5 show images of the pacemaker with its electrode and the complete system including the charger, respectively. The stimulation anode was a 10 mm wide metal ring surrounding the pacemaker. Once implanted, they had to be charged once a week for twelve hours. The electrodes of these two pacemakers, as well as the ones that came after them shortly (the first one of these being the one from Greatbatch, implanted in Buffalo, New York, USA in April, 1960), were connected to the heart by open-heart surgery. The cathode electrode was sutured to the heart using the fixing holes.

Fig. 3. Dr. Orestes Fiandra and Dr. Roberto Rubio in CCC del Uruguay in September1999, almost 40 years after the first implant of a pacemaker in a human being in the Americas. The showcase at their side has the pacemaker they implanted in 1960, which was developed in Sweden (up at the left) and some pacemakers models manufactured by CCC del Uruguay in the 1970s (at the bottom).

Fig. 4. Picture of the first pacemaker implanted in the Americas. The electrode has two small holes to be sutured to the epicardium. The lead (broken in the figure), exits the pacemaker directly without any connector.

Fig. 5. Picture of the first pacemaker system implanted in the Americas. The big device is the external charger that had to be connected to the mains. The big white ring is the external rechargeable coil to charge the implantable pacemaker (in the center of the figure) once a week.

Pacemaker Developments

From the time of those basic pacemakers from the 1960s, much water had gone under the bridge until a reliable pacemaker was achieved. The leads with the electrodes came to be connected to the pacemaker in order to be able to change the pacemaker without having to replace the cables as well. Titanium became the main enclosing material although epoxy resin was still used as the material of the pacemaker connector block. The batteries came to be non-rechargeable and very reliable, using lithium iodine chemistry. The electronics became highly reliable and the consumption was reduced to make devices that would last years. The implanting technique was improved as well. The epicardial electrodes that had to be sutured to the heart by a complicated surgery were replaced by endocardial electrodes introduced through the veins to the heart by a simple surgery under local anesthesia.

Along with the developments described before, pacemakers gradually introduced new functions. In the early 1960s, the sensing of the cardiac signal was introduced to stimulate only when the heart did not depolarize spontaneously.

Dual chamber pacemakers were developed. The use of electrodes in the ventricle and atrium provided an optimal rhythm and a correct synchronization between the atrial and ventricular contractions. This was a more physiological action in relation to the unicameral stimulation.

Subsequently, it was possible to adjust the pacemaker's operation after being implanted, adapting them to the patient's conditions. Pacemakers' terminology uses the word *program* to refer to the selection of parameters to be used by the device. In the beginning, the changes required one to have access to the device by puncturing the patient with needles to move little presets. Wireless communication with the device was achieved later. The first and more extended way to wirelessly program the pacemakers was by magnetic coupling, which continues to be used in our days. Initially, only a few parameters could be changed (like the stimulation frequency, amplitude, and pulse width) but gradually, it was possible to program all the relevant parameters. The relevant parameters include the pacing mode, the atrial to ventricular delay, the sensitivities for sensing atrial and ventricular events, and the period of time that shall pass after an event before the sensing of atrial and/or ventricular events takes place again (refractory or blanking periods). In the present, they also include the programming of several algorithms that can be enabled or disabled, and also frequently customized through the selection of some parameters that are used in it. The dynamic AV delay that changes the time between an atrial and a paced ventricular event - taking into account the time between two atrial events - is an example of this kind of parameter.

The next step was the real time automatic adjustment of the stimulation frequency according to the patient's needs, which is useful for patients with certain diseases where the use of the SA node rhythm is not an option. Pacemakers with rate responsiveness were developed. Many different methods and measurements were used to detect the patient's needs, for example activity sensors, the minute ventilation measurement, the QT interval time, body temperature, pH value, and the intracardiac impedance [3]. Some of those were ignored later on as they required a special lead.

The idea of rate responsive pacemakers is to find a sensor of which the output can be used for determining the heart rate that a patient would have if in full health. In order to understand the idea of rate adaptation, we will provide a couple of examples: the minute ventilation and the QT interval.

The Minute Ventilation

Minute ventilation is the amount of air that enters to the lungs each minute. The minute ventilation is used because during exercise, heart rate and minute ventilation are pretty proportional. To calculate the minute ventilation, it is necessary to measure the respiratory rate and the tidal volume. Both values require measuring the transthoracic impedance several times per cardiac cycle, as transthoracic impedance allows determining the volume of the lungs. By taking the impedance versus time curve, it is possible to know the number of respiratory cycles and the volume of air during inhalation. The respiratory rate is the frequency of this signal and the tidal

volume is related to the area below the breathing curve during inhalation. There are different variations for measuring the transthoracic impedance but in general, they apply subthreshold constant current pulses between well-spaced points in the thorax and measure its voltage amplitude. Subthreshold pulses are those for which amplitude and pulse width are too small to stimulate the heart. The energy of the used pulses is 1–10% the energy necessary to stimulate. Aside from minute ventilation, there are other parameters related to respiration used for calculating the pacing rate, for example the respiration rate alone.

The QT Interval

The QT interval is the period of time between the start of the QRS complex (heart depolarization) and the T wave (repolarization). It was demonstrated that the QT interval following a ventricular stimulus is shorter while the patient is active, and longer when the patient is at rest even if the pacing rate is constant [3]. For this reason, the period is used for determining the pacing rate. A great advantage of a sensor that utilizes this measurement is that only the ventricular signal has to be sensed by the device, so to measure the QT interval the only modification to a standard circuit would be to have an amplifier filter with a pass-band able to detect the T wave.

One of the first explored sensors, the accelerometer, used to measure the patient's physical activity resulted in the most widely used method to adapt the stimulation frequency to the patient's needs. Most of the modern pacemakers include more than one sensor.

The fast development of digital circuits along with the possibility of developing integrated circuits for specific uses and, finally, the possibility of using powerful low consumption micro-controllers, enabled the use of more complex algorithms for countless things. As a simple example, the frame of time between the atrial event and the ventricular event in dual chamber devices became dependent on if the atria event was spontaneous or caused by pacemaker stimulation. There was also an option for the AV delay, if selected by the physician, of automatically adjusting it with the interval between two atrial events.

Other important progresses were triggered by the use of analog to digital converters and the inclusion of significant amounts of memory. This allowed, for example, improvements on the battery status indicator in order to enable safe use of stimulators until shortly before battery depletion as well as lead impedance measurements, which allowed identifying of certain faults.

Different statistical information storage was added, enabling the physician to evaluate the pacemaker's behavior within selected parameters and providing important information on how to change those parameters if necessary. The current devices memory size enables them to have a large event log saved as well as specific electrocardiographic parts taken from between the electrodes. These records are automatically stored according to the criteria established by the physician. This allows further adapting as much as possible the pacemaker behavior as well as diagnosing different types of heart diseases. These records act in some ways as a permanent Holter, although they cannot store all the events throughout the device's life. Having a record of events with a big memory space is important for monitoring patients with different pathologies (e.g., cardiac arrhythmias). They have also been used for miscellaneous applications, e.g., to determine the time of death of a patient that had a pacemaker and had been a victim of assault at their home [4].

Current Situation

At the end of the last century, the pacemakers' technology reached full maturity. Fig. 6 shows a simplified general diagram of a DDDR pacemaker, in accordance with the NASPE/BPEG (NBG) generic pacemaker code. In this case, it refers to a pacemaker with pacing and sensing in atrium and ventricle, and rate adaptation functionality. It has one pacing and one sensing circuit for each cardiac chamber, a communication circuit, an acceleration measurement circuit (it could be substituted by one or more alternative circuits for calculating the pacing rate in function of the patient needs), a battery measurement circuit, and a circuit for detecting the presence of a magnet. These circuits are commanded by one or two microcontrollers. The need for two microcontrollers could be determined by the need for backup pacing or the concurrence of different events that could not be performed with just one microcontroller. Regarding the second item, it depends generally on the circuits that the microcontroller needs to control. Most of the blocks that are shown in the diagram are normally integrated in a single ASIC, thus reducing the size of the circuit board. Some discrete components will still be necessary because it is not possible to integrate them in the circuit, i.e., big capacitors or front-end protection components.

Pacing circuits typically implement pacing pulses of amplitude varying between 0.1 V and 7.5 V and pulse widths between 0.1 ms and 1.5 ms. Sensing circuits usually allow sensitivities from 0.1 mV or 0.2 mV to a value in between 6.0 and 8.0 mV. The sensitivity of a pacemaker channel is the minimum signal amplitude, with a standard shape, that the device is able to sense. If it is programmed too low, it could sense noise. If it is programmed too high, it could not sense adequately the patient signal. It has to be programmed in the higher value that assures the patient signal sensing. The polarity of pacing and sensing are also programmable parameters, so sensing or pacing could be performed between electrodes that are connected to the heart (A- and A+ or V- and V+) or between one electrode connected to the heart (A- or V-) and the CASE of the pacemaker.

The communication circuit is implemented in most cases by magnetic coupling but some of the new pacemaker models implement it using RF and it is very likely for this to be a trend for the coming years. The term RF here does not refer to the technical definition to the band from 3 kHz to 300 GHz but to a standard method of communication of implantable devices alternative to magnetic coupling. There is a specific band for communication of implantable devices which is denominated

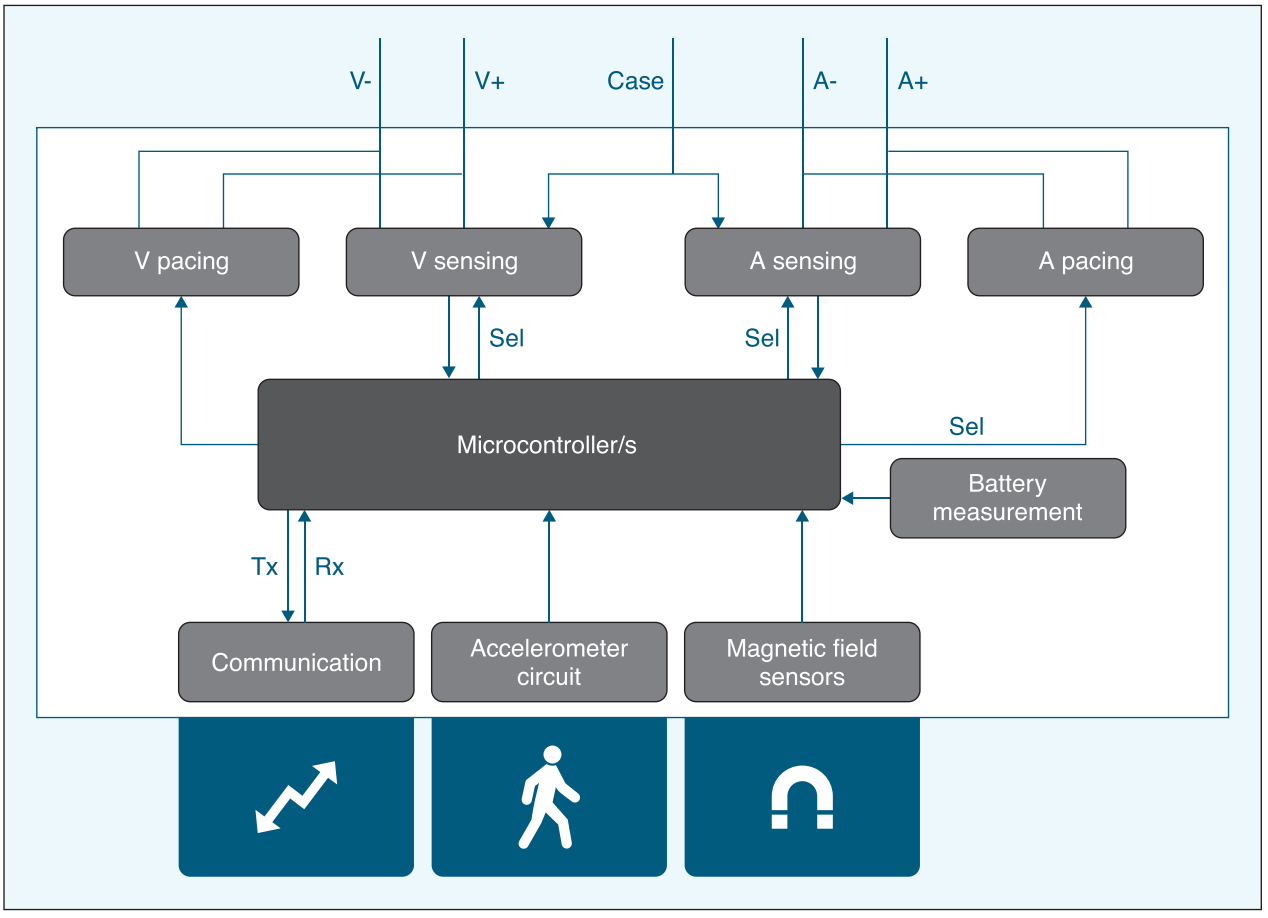

Fig. 6. Simplified diagram of a DDDR pacemaker. V- and V+ are the outputs that are connected to the ventricular electrodes, cathode. and anode respectively. A- and A+ are the outputs that are connected to the atrial electrodes, cathode and anode respectively. CASE corresponds to the can of the pacemaker.

Medical Implant Communication Service (MICS) and which frequency ranges from 402 MHz to 405 MHz. Devices using MICS are able to communicate in a range of two meters typically while standard magnetic coupling has a communication range of some centimeters.

Battery measurement circuits always measure the battery voltage but in some cases, depending on the chemistry used, they also measure the battery output impedance. The circuit for detecting a magnet is used mainly for having a quick mean of diagnosing the status of the device without the need of using a pacemaker programmer. It allows knowing if the device is working well or not and if the battery is near its end of life or depleted. For doing that, the microcontroller changes the pacing rate and operation mode in presence of a magnet and selects the pacing rate depending on the battery status. Modern pacemakers have a volume in the range of 10 to 14 cc and a mass between 20 g and 30 g for a DDDR pacemaker.

The lithium iodine batteries are the power source of most of the implanted pacemakers but the new models frequently use lithium carbon monofluoride or lithium silver vanadium oxide hybrid batteries. These chemistries are widely used in other implantable devices. They are not new, but they are relatively new in the pacemaker world. These chemistries have two main advantages: they have much less output impedance, which is very important to be able to use higher currents temporarily, and they have a higher density of energy per unit of volume and per unit of mass. Lithium iodine batteries have an output impedance that varies from some hundreds of Ohms at the beginning of life to more than 10 kOhms at end of life. The alternative batteries have output impedance so low as 10 Ohms at beginning of life and lower than 100 Ohms at end of life. The longevity of a pacemaker varies depending on its use. Modern pacemakers' lifespans are in the range of 6 to 10 years for nominal settings.

The surgery for implanting a pacemaker is very simple, it lasts about half an hour, and it is performed with local anesthesia. The last data reported by the FDA in 2001 showed a 1% failure rate for every 1000 implanted pacemakers in a year [5]. With no objective data to demonstrate it, the author is convinced that this failure rate has decreased since the mentioned study. The conviction is based in the maturation of the technology and the electronic components used and in confidential information obtained from people that works or worked in the main pacemaker companies.

In our opinion, during this century, the new pacemaker models that the leader companies constantly introduce to the market do not present relevant innovations from the point of view of the safety and comfort of the patients. The main new characteristics are related to marketing most of all: shape and size have improved, not being a real advantage for the

Fig. 7. The Nanostim leadless pacemaker is less than a 10% of the size of a conventional pacemaker.

Fig. 8. The Micra TPS, with a size of about a tenth of a conventional pacemaker, was implanted for the first time in a human being in Austria in December 2013.

patients, and more memory has been added for event records which only in a very few cases provides a clinical advantage. Programming possibilities increased but medical practice shows that most of the programmable parameters are used in a very small percentage of patients.

The Future

2013 has been the year of the leadless pacemakers. In October, St. Jude announced that Nanostim device obtained the CE mark [6]. During the review of this article, in February 2014, St. Jude announced the first U.S. implant in the company's LEADLESS II pivotal trial designed to evaluate the Nanostim leadless pacemaker for FDA approval (Fig. 7).

In December, Medtronic announced the first in-human implant of the World`s smallest pacemaker, the Micra TPS [7] (Fig. 8).

Leadless pacemakers are implanted directly into the heart via a minimally invasive surgery. They do not require to surgically create a *pocket* for the pacemaker. At the moment, the leadless pacemakers that are commercialized in Europe or in clinical studies are unicameral. The advantages of being leadless and the simplified implant procedure are clear. However, it is too soon to know if the use of leadless pacemakers will evolve to gain a substantial part of the market or not, or if the implant procedure has associated risks during the implant or explant and how easy it will be to correct the position of the device in the heart. It is also too soon to know if the longevity of these devices (that use new battery technologies) will be as long as expected. According to the manufacturer, the Nanostim device is expected to have an average lifespan of more than nine years at 100% pacing, or more than 13 years at 50% pacing.

An interesting question for the future is if new technologies in the power supplies of the pacemakers will work to avoid replacing the devices. The improvements can be related to new battery technologies or renewable energy. Recently, there have been several attempts of using the energy of the heart's own beat to power the pacemakers: a study presented in the American Heart Association's Scientific Sessions 2012 reported an experimental device that could convert energy from a beating heart to provide enough current to power a pacemaker [8]. In the study, researchers tested an energy-harvesting device that uses *piezoelectricity*, electrical charge generated from motion.

In the future, it is possible that pacemakers will be automatically programmed according to the patients' physiological needs. Probably, also, their behavior will be remotely monitored when the patients are at home, and they would need to visit the physician just when any problem is detected. This would not been just a future possibility because a part of this journey has already been done.

Some parameters of the pacemakers are automatically adjusted. The first and more important of these is the stimulation amplitude. To do so, modern pacemakers after delivering a pulse, sense the signals in the paced chamber to know if it was effective or not. If the pulse was effective, they will sense the wave corresponding to the depolarization of the stimulated chamber (QRS complex in the case of the ventricle, P wave in the case of the auricle) and if it was not effective, they will not sense that wave. Then, they increase or decrease the stimulation amplitude in order to get near 100% of effective stimulation using the least energy possible. This is very important because with no automatic adjustment, the physician has to select a stimulation amplitude much higher than necessary to make sure that any change in the stimulation threshold of the patient will not affect the effectiveness of the device, which greatly increases the power consumption and consequently greatly reduces the longevity of the device.

Home monitoring of pacemakers is already possible and implemented by the main pacemaker companies. However, it is yet far from being universal and they require the analysis of the data by specialized health care personnel. The introduction of pacemakers with RF communication make the automatic transmission of information much easier because it is enough to have a communication device at the bed side table to assure the communication of the information every night via internet or cell phone service.

Pacemaker technology has improved the quality of life of people with severe bradycardia. The technology is mature and

the failure rate is low enough to be considered a very safe therapy. The maximum discomforts of pacemakers in the life of people are related to the periodic controls and the surgery for replacing them.

The people that require pacemakers are mostly elder people. In the United States, people receiving pacemakers in 2009 were on average 75.4 or 80.1 years old depending on the type of pacemaker they received [9]. For that reason, the need of periodic controls and replacement surgery are very important issues. Both disturbances could be eliminated in the medium term with the use of renewable energy and home monitoring.

The growth of the leadless pacemakers will be determined by the real advantages that this new technology could demonstrate in the field.

References

[1] B. Larrson, H. Elmqvist, L. Ryden, and H. Schüller, "Lessons from the first patient with an implanted pacemaker," *PACE*, vol. 26, pp. 114–124, Jan 2003.

[2] O. Fiandra, "The first pacemaker implant in America," *PACE*, vol. 11, issue 8, pp. 1234–1238, Aug. 1988.

[3] S. Furman, D. L. Hayes and D. R. Holmes, Jr, *A Practice of Cardiac Pacing*, Futura Publishing Company, Inc., 1993, Ch. 11.

[4] H. G. Mond, B. C. Valentine, D. Randall, R. Kelsall, and M. Gregory, "Anatomy of a murder: telemetric footprints," *PACE*, vol. 25, no. 9, pp. 1406–1408, Sept. 2002.

[5] W. H. Maisel, M. O. Sweeney, et al., "Recalls and safety alerts involving pacemakers and implantable cardioverter-defibrillator generators," *JAMA*, vol. 286, no. 7, pp. 793–799, Aug. 2001.

[6] St Jude Medical, Inc., (Oct. 2013). St. Jude medical announces acquisition and CE mark approval of world's first leadless pacemaker. *News Release* [Online]. Available: http://www.sjm.com/~/media/SJM/corporate/Media%20Kits/nanostim/NanostimAquisition_CEMarkApproval_FINAL_WEB.ashx.

[7] Medtronic. (Dec. 2013). Medtronic announces first human implant of world's smallest, minimally invasive cardiac pacemaker, *Press Release* [Online]. http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle_Print&ID=1883208&highlight=.

[8] M. A. Karami, D. J. Bradley, and D. J. Inman, (Nov. 2012). New device could allow your heartbeat to power pacemaker, *American Heart Association [Online]*. http://newsroom.heart.org/news/new-device-could-allow-your-heartbeat-239558.

[9] A. J. Greenspon, J. D. Patel, et al., "Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures," *J. American College of Cardiology*, vol. 60, no. 16, pp. 1540–1545, Oct. 2012.

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