ABSTRACT

The idea of the pacemaker without lead (leadless) mentioned earlier, in hopes of becoming a solution to the problem - a problem associated mounting leads transvenous leads and stability. The success of the first installation of an external pacemaker system by Alber S. Hyman in 1932, then, in 1958 Rune Elmquist and Ake Senning did successfully epicardial pacemaker implantation, and in the same year, Seymour Furman managed using transvenous system for the first time, since the development of the pacemaker tends to stagnate in transvenous system. Although implantation of PPM classified as a minimally invasive procedure, there is a potential risk of complications. The concept of leadless pacemaker be the answer to the problems associated with pacemaker implantation, particularly in complications related to the existence and stability of the pocket, and transvenous lead. There are two systems available nowadays that can fully implanted in RV, either Nanostim or Micra. Another concept LP delivered through the ultrasound media by WICSTM or WISE system (Wireless Cardiac Stimulation; EBR Systems, Sunnyvale, CA, USA). The system is designed to modify the dual chamber conventional pacemaker to be cardiac resynchronisation therapy (CRT).

Keywords: leadless, pacemaker, implantation, right ventricle


INTRODUCTION

Since more than 50 years, permanent pacemaker has been used for the treatment of symptomatic bradycardia. Until now, installation of a pacemaker using the conventional system is still the standard procedure; the system uses an electric generator that contains modules and a battery implanted in the subcutaneous pockets and one or more transvenous leads that connect the generator with a pacing focus or with an alternative epicardial lead when veins cannot be used. Electrical transduction of a pacemaker system comprises an electric generator which is connected to one or more transvenous leads that deliver electrical stimulus to the heart. Although this installation is effective in treating symptomatic bradycardia, about 10–12.5% of the users experienced complications related to procedure of inserting leads and generators, such as hematoma, infection, and hematopneumothorax, as well as complications associated with the lack of stability and position of leads, such as infections, endocarditis, and vascular obstruction. These complications lead to pacemaker interruption and increases incidences of hospitalization and mortality. Implantation of permanent pacemaker (PPM) was estimated to be 1 in 50 in individuals aged above 75 years in 2005, and in2009 the data showed the number of new pacemaker implantations reached 900 per million in Europe and this number is expected to steadily increase along with the increase in life expectancy and an increase in degenerative diseases. Other data sources showed 80% of PPM implantation is performed on patients aged above 70 years.

The idea of the pacemaker without lead (leadless) as mentioned earlier came to received wider attention among researchers given the advantages it may possess to help avoid the complications arising from using pacemakers with leads and insertions, more specifically problems associated with mounting transvenous leads and the lack of stability of leads to stay in position. The development of technology, particularly with regard to developing smaller components of the battery and thus a smaller battery occupying lesser space, became essential to allow for an overall smaller design of pacemaker is small enough to implant intracardially. This idea was first implemented in a trial using a dog and findings were reported in 1991. Leadless pacemaker (LP) has been going through continuous development, specifically the transition to transvenous pacemaker from the conventional epicardial pacemaker system.

PACEMAKER HISTORY

The external pacemaker system was first successfully installed by Alber S. Hyman in 1932, and then, in 1958, Rune Elmquist and AkeSenning successfully carried out epicardial pacemaker
implantation; in the same year, Seymour Furman successfully used a transvenous system for the first time to install pacemaker, since the development of the pacemaker tends to stagnate in transvenous system. Technological advances, especially in the circuit and the battery, has allowed the pacemaker to be retained for periods as long as 7–10 years, which was also made possible with the use of multiple leads and pacemaker program modules. Transvenous pacemaker implantation requires a minor surgical procedure, there is also the risk of complications and perioperative adverse events. Approximately 10–12.5% of complications are associated with the installation of a pacemaker, for example, hematoma, infection, skin erosion, and associated errors, and lead position, for example, pneumothorax, hematothorax, cardiac perforation, and release lead. 4

In 1970, miniature batteries and circuits were first developed and introduced in the field and demonstrated that the concept of pacemaker implantation can be completed without a lead in the right ventricle (RV); this was proven by Spickler et al., but there were restrictions such as size, battery life, and fixation. Different types of batteries have been tested, including nuclear batteries. Although the development of technology at that time took place relatively quickly, the intra-cardiac pacemaker was yet to be developed and implemented in a clinical setting. 5

Along with this, an attempt to diminish the leads is also being made. Transmission of energy wirelessly to the receiver intracardially is the basis of this idea, for example, ultrasound energy. Ultrasound allows intracardiac tissue penetration; this energy is then converted into electrical energy by the intracardiac receiver. This concept was introduced by Kathy L. Lee et al. in patients undergoing electrophysiological study, with the hope of implementing the pacemaker without a surgical procedure; in conducting this study they did find, however, that energy transfer was inefficient due to the ultrasound beam only about 12:06% of the energy was captured by the receiver, but with a better energy transfer and utilization the procedure can be successfully carried out. Another obstacle is also the lack of capability of intra-cardiac media implantation. 6 7

The biological pacemaker concept was introduced with the aim to replace the electronic pacemakers; with modifications in gene therapy and stemcell therapy, this concept has been tested 15 years later, and the gene modification using the adenovirus-based protein media is expected to increase the expression amount of the β-adrenergic receptors. If overexpression increases the inflow into the cells in a resting state. Expression of these proteins have a limited period, up to four weeks, which is another limitation in studying or arriving at clinical implications. The alternative for this concepts using cell-based platform. Currently, there are some investigations about the two approaches used: (a) cell-based, mesenchymal stem cells and (b) pluripotent stem cells that can be air-differentiated into heart cells with endogenous pacemaker activity. The concept of biological pacemaker is still in clinical studies, so there are no data with regards to their use in humans. 8

Complications associated with conventional pacemaker

Although the implantation of PPM is classified as a minimally invasive procedure, there is a potential risk of complications (Table 1). Pacemaker implantation complications at the time of installation can be either acute (post-implantation up to 30 days) or chronic.

Generally, it can be divided into complications related to venous access, positioning and complications associated with lead generator pocket, while based on the etiology it can be a complication of implantation or a system failure. Data showed the incidence of acute complication is about 4-5% and chronic complications is about 2.7%, but the expectation of this figure is greater due to the difficulty of identifying complications in a variety of studies, especially in asymptomatic cases. The most frequent

| Table 1 Most frequently occurring complications in pacemaker implantations and cardiac resynchronization therapy |
|---|---|
| Related to venous access | • Pneumothorax |
| Lead related | • Hemorrhax |
|  | • Brady/tachyarrhythmias |
|  | • Cardiac perforation |
|  | • Cardiac tamponade |
| • Coronary sinus dissection/ perforation |
| • Dislodgement |
| • Diaphragmatic stimulation |
| • Lead malposition |
| • Venous thrombosis |
| Pocket related | • Hematoma |
| Infection | • Wound pain |
|  | • Pocket infection without bloodstream infection |
|  | • Pocket infection with bloodstream infection |
|  | • Device-related endocarditis |
complications associated with the implantation procedure, for example, are lead dislodgement and pneumothorax.

Lead dislodgement is the release of transvenous lead or the lead's move from the initial position, even out of the early heart room. It should be suspected when a wire lead appears too tight or loose. This dislodgement can occur between the first few days and few weeks after the implantation. Dislodgement of lead can increase the pacing threshold, pacing, and sensing failure. Twiddler's syndrome or Reel syndrome may underlie the lead position changes associated with the shift or rotation of the generator. Twiddler syndrome is usually found in obese women with loose subcutaneous tissue, and generator rotation occurs on the longitudinal axis, whereas the Reel syndrome occurs in the transverse axis. In this condition especially, Twiddler syndrome can occur in addition to lead dislodgement due to lead fracture; the clinical presentation of this syndrome is strongly influenced by its dependence on a pacemaker patient or ICD.10,11 These complications can be reduced with the use of both active and passive lead fixations, but the use of active fixation is also associated with an increased risk of perforation incidence of insulator heart leads.10 Although rare, abrasion of lead insulator has also become one of the complications associated with transvenous leads presence; this condition is caused by the body’s inflammatory response to the lead insulation material that can lead to lowering barriers that affect the life of the pacemaker lead and result in lead failure.12

Vein thrombosis (VT) quite often occurs in about 30% of cases; the old data even showed the incidence VT reaches about 50% of cases, as an acute or chronic complication post-implantation of a pacemaker. Venous thrombosis is associated with the number of leads attached, use of hormone therapy, use of temporary pacemaker before PPM, upgrade of ICD, and use of lead dual VT chamber.13 Clinical presentation is usually asymptomatic, due to the growth of collateral, but some cases showed acute thrombosis and vena cava superior syndrome.14,15

Hematoma as a part of complications associated with generator pocket are quite common (2.9–9.5%). Hematomas are more common in patients with concomitant use of antiplatelet and antiagulant therapy who also received pre-procedural therapy bridging.16 Infection is an extremely feared complication after pacemaker implantation; in a cohort study Johansen et al. found 4.8 incidences of infection per 1000 pacemaker implantations in the first year, and 1 event per 1000 pacemakers thereafter. The incidence of infection is more commonly found in PPM reimbursement.17 Clinical presentation of post-implantation infection can be an infection in the generator pocket (69%) and endocarditis (23%). Tricuspid valve vegetation that most frequently manifests is tricuspid valve regurgitation which sometimes causes secondary pulmonary embolism.10

Major complications can be mortality, approximately 0.3%, and mechanical complications, such as coronary sinus dissection, cardiac perforation, pericardial effusion, and pneumothorax or hematothorax in 3.2% of the cases.18 Complications associated with PPM implantation of the dual chamber are more complex and get severe with the addition of lead. Lead dislodgement, pneumothorax, infection, and bleeding/hematoma are also the most common. Lead dislodgement is more common in atrial lead than in lead ventricle.9 Overall, there was a greater magnitude of complication in a flashlight with fewer implantations; it is due to differences in the technology and experience of the operator. National Registry of Denmark reported a 60% greater risk of complications, especially in the flashlight; however, the number of cases is less than 25 per year.16

**Leadless pacing system**

The concept of leadless pacemaker can be the answer to the problems associated with pacemaker implantation, particularly in complications related to the existence and stability of the pocket, and transvenous lead. Although there are limitations to using leadless pacemaker implantations with VVIR system, by putting the system fully in RV complications can be minimized and even eliminated. LP complete implant systems on RV first materialized in 2012, when Nanostim leadless pacemaker (St. Jude Medical, Sylmar, CA, USA) was first introduced, followed one year later by the Transcatheter MicraTM MicraTM Pacing System (Medtronic, Minneapolis, MN, USA).

In addition to cosmetic advantages, this pacemaker system does not require a surgical procedure related to the manufacture of a subcutaneous pocket as in a conventional pacemaker, so with this design complications associated with conventional pacemaker implantation are expected to eliminated.3

**Leadless system for right ventricular pacemaker**

There are two systems available nowadays that can fully implanted in RV, either Nanostim (Figure 2) or Micra (Figure 3); it has the same system of electro energy transmission and the size is small enough for implantation in RV, and the difference
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There is another difference in how sensors respond to rate changes between the two systems: Nanostim uses temperature, and the Micro uses accelerometer. In both systems, the part tip in contact with the endocardial pacemaker is coated with steroid (dexamethasone) with the aim to reduce risk of inflammation at the endocardial implant area. Although this tool is significantly smaller than a conventional pacemaker, it can be retained for up to 10 years.

The second proximal part of this system is equipped with a release mechanism for repositioning or replacement of pacemakers, if necessary; however, up to now there are no data related to the release of the system in old cases. The installation procedure is generally the same in each system; using the femoral venous access, pacemaker modules are sent to the RV with fluoroscopic assistance through the inferior vena cava and right atrium and then the pacemaker is positioned on the Apiko-septal area and fixed. After fixation, pacemaker is separated (undocked) from the sender system (Figure 4) but is still connected with the fastener (tethers). At this stage, pacing threshold measurements, sensing amplitude, and impedance are calculated. Pacemaker can still be repositioned at this stage, and if necessary a tug test is performed with fluoroscopy to ensure fixation has been adequate. When the entire system has certainly been good, the pacemaker can be removed from fastener.

There were studies that evaluated the initial performance of Micra; for example, Ritter et al. reported 100% successful implantation in 140 patients and further reported that during the monitoring period of 1.9 ± 1.8 months there were only 30 events related to complications in the dysrhythmias femoral but no serious events related to implantation itself. Pericardial effusion without tamponade occurred in 1 patient. Against the 60 patients who could be followed for 3 months, the average pacing threshold was V 0.51 ± 0.22; there was no threshold that exceeded 2 V, and the average R-wave was 16.1 ± 5.2 mV and impedance was 650.7 ± 130 ohms.

Reynolds et al.'s (2015) study reported about the same system (Micra) but with a longer monitoring period; they observed and reported a 99.2% success rate of the implantation procedure; in as many as 719 patients who were managed there were only 28 events in 25 patients; Kaplan–Meier curves showed freedom from major complications at about 96%. Complications consisted of 11 cases of cardiac injuries, 5 cases of femoral arterial puncture-related complications, 2 cases of thromboembolism, 2 cases related to pacing, and 8 other complications, for

(Table 2) between the two systems is the mechanism of fixation in RV, where Nanostimuses primer fixation “Screw-in helix” and secondary fixation “Nylon tines,” with a longer size, whereas Micrauses “Self-expanding nitinol tines” fixation and the diameter is larger.

![Figure 1](https://heart-rhythm-center.com/2013/10/14/dont-be-a-twiddler-atrial-lead-dislodgement-from-twiddlers-syndrome/)

**Figure 1** Conventional pacemaker complication - Lead dislodgement caused by Twiddler’s syndrome. (Quoted from https://heart-rhythm-center.com/2013/10/14/dont-be-a-twiddler-atrial-lead-dislodgement-from-twiddlers-syndrome/)

![Figure 2](https://www.stjude.com/)

**Figure 2** St. Jude Medical NanostimTM leadless pacemaker. (Quoted from St. Jude Medical Inc)

**Table 2** Specification Differences between the Two Leadless Pacemaker Right Ventricle Systems

<table>
<thead>
<tr>
<th>Specification</th>
<th>NanostimTM leadless cardiac pacemaker (Volume (cm³))</th>
<th>MicraTM transcatheter pacing system (Weight (g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cm³)</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>41.4</td>
<td>25.9</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Introducer size (French)</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Primary fixation mechanism</td>
<td>Screw-in helix</td>
<td>Self-expanding nitinol tines</td>
</tr>
<tr>
<td>Secondary fixation</td>
<td>Nylon tines</td>
<td>-</td>
</tr>
<tr>
<td>Pacemaker mode</td>
<td>VVI/VVIR</td>
<td>VVI/VVIR</td>
</tr>
<tr>
<td>Rate response sensor</td>
<td>Temperature</td>
<td>Accelerometer</td>
</tr>
<tr>
<td>Battery</td>
<td>Lithium carbon-monofluoride</td>
<td>Lithium silver vanadium oxide/carbonmonofluoride</td>
</tr>
<tr>
<td>Battery time</td>
<td>9.8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>100%/2.5 V/0.4 ms/60 b.p.m.</td>
<td>100%/1.5 V/0.24 ms/60 b.p.m.</td>
</tr>
<tr>
<td>Device retrieval option</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Telemetry</td>
<td>Conductive</td>
<td>Radio frequency</td>
</tr>
</tbody>
</table>

Quoted from Reynolds et al., 2016.

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example, pacemaker syndrome, acute myocardial infarction, heart failure, syncope/presyncope, and metabolic acidosis. One death was associated with metabolic acidosis. Of the 297 patients included in the primary efficacy evaluation, 98.3% had adequate pacing status for up to 6 months with a mean threshold of 0.63 V at 0.24 ms pulse width of implantation and 0.54 V at 0.24 ms pulse width at 6 months. No changes were reported in the position of pacemaker (dislodgement).

Leadless pacemaker studies were conducted in 2012–2013, studying patients over 18 years with indications of pacemaker VVIR and the exclusion criteria were pacemaker dependency, valve prosthesis tricuspid, pulmonary hypertension, a history of the installation of a pacemaker or ICD, or inferior vena cava filter. Evaluation of implantation was performed before a subject becoming an outpatient and at weeks 2, 6, and 12. Safety has become a top priority in this study, and the second measurement of the level of success and performance of the pacemaker took place at 90 days post-procedure.

A total of 33 patients (97%) underwent successful implantation procedure without the need for pacemaker repositioning. There were no complications reported in approximately 94% of the cases; however, there were two serious adverse events related to the procedure: a patient experienced cardiac tamponade during the procedure and ischemic stroke on the 5th day after the procedure, and there was one incident of installation failure; that is, the pacemaker was inadvertently connected to the left ventricle through the foramen ovale, and in this case the pacemaker was taken in a moment and returned; pacemaker implantation was supposed to have been done only in the right ventricle in this procedure. Three patients were rehospitalized, one patient for increased international normalized ratio (INR), one for exacerbation of chronic obstructive pulmonary disease, and one for syncope with monomorphic ventricular tachycardia (VT) originating from the scar in LV. In the case of patients with syncope cases, the pacemaker and ICD were withdrawn. With an average of 8.3 mV R wave amplitude, pacing threshold 0.80 V / 0.4 ms, and 773 Ohms impedance the implant was successfully installed and remained stable in the outpatient during evaluation week 12. There were no disturbances either on batteries or interference-sensing and pacing in evaluation.

A recent study on Nanostim Leadless II conducted in 2015 with a larger sample (524 patients) reported 95.8% (504 patients) success rate of implantation; 300 patients met the primary evaluation criteria, 90% of them (95% CI: 86.0–93.2, \( p = 0.007 \)) met the primary efficacy targets, and 93.3% (95%CI: 89.9–95., \( p < 0.001 \)) met the main target of safety. During the 6-month monitoring of adverse events related to implantation it was found that 6.7% of the subjects experienced adverse effects; events requiring dislodgement were reported in 1.7% of the cases, 1.3% needed cardiac perforation, and an increase in pacing-threshold requiring percutaneous retrieval and replacement pacemaker was observed in 1.3% of the patients.

These data are sufficient to support the use of LP as a promising alternative for conventional pacemaker system. Nevertheless, long-term evaluation of the use of the LP is still necessary in connection with the battery status, thromboembolic events, and pacemaker stability in conditions where endocardial activation may result in right ventricular infarction. Other data related to withdrawal or replacement of pacemaker in chronic cases is still limited, and the available data on the sheep model 5 months post-implantation reported no difficulty with the pacemaker withdrawal procedure. Currently, the only LP that has received approval from the FDA is Micra; the approval was granted in April 2016; with
calendar notes Micra reveals important contraindications in patients with a history of installation of other devices and carrying a risk of disruption either on the device or on LP, severe obese patients, or patients who have intolerance to material from the LP and or heparin. Other contraindication is patients whose vein is not wide enough to accommodate the introducer sheath with 7.8-mm thickness or LP. Overall data derived usage studies on LP show similar levels of success with transvenous pacemaker that in comparison carries a smaller proportion of risks and complications.

Leadless system for left ventricular pacemaker

Another concept with which LP is implanted is through ultrasound media’s wireless cardiac simulation (WiCSTM or WISE; EBR Systems, Sunnyvale, CA, USA). The system is designed to modify the dual-chamber pacemaker in conventional cardiac resynchronization therapy (CRT). The system (Figure 5) works via a module transmitter that is implanted on the left side of pectoralis subcutaneous. The transmitter can detect potential activity on RV, which in turn gives impulse to delay 3 ms on the electrode receiver (receiver) on the endocardial LV through ultrasound signals, where the signal is converted to an electrical potential that is delivered to the endocardial LV; the transmission of ultrasound nevertheless requires a good acoustic window. Biventricular pacing or conventional CRT still has limitations in clinical setting; as much as 30–40% in the study sample were categorized as non-responders, which is mostly associated with the position of the lead in the coronary sinus. In addition, data showed lead failures in LV occurred in up to 10% of the cases. In the anatomy of the left ventricle (LV) limitations were observed in achieving optimal pacing and laying leads of LV in a highly dependent profile of the coronary sinus. The other approach to laying LV leads, either through the transseptal atrial or using the interventricular method, also has limitations in terms of procedural difficulties and long-term risks such as thromboembolism resulting from the lead position in LV. WiCSTM Systems allowed for this constraint to retain, as an alternative to endocardial pacing in LV, where energy is delivered through ultrasound transmission. The system is also designed to reduce the limitations in the current CRT system that provides stimulation outside of LV, and direct stimulation of endocardial LV’s biventricular systolic function is believed to provide a more physiologically ideal solution, and the system also increases the ease with which the location of the lead can be determined. Thus, the WiCSTM system is very useful in patients who had already had CRT implantation performed on them, particularly in those cases where lead installation had failed.

A multicenter prospective study of WiSE-CRT was carried out for the first time in patients with an indication for CRT; the study was conducted to assess the safety (in 24 hours and 30 days post-implantation) and performance (effectiveness of biventricular pacing in 1 month). The study was conducted on 17 patients (14 men), and the majority of the patients had experienced ischemic cardiomyopathy, 7 patients had conventional CRT installation failures, and 8 patients had a pacemaker or ICD. The mean of ejection fraction was 26% and the mean QRS duration was 176 ms and the average relatively functional class was class 3 (NYHA). This system was successfully implanted in 76% of patients (13 patients), and in 4 patients implantation was not successful due to pericardial effusion associated with the procedure as well as device in 3 patients and difficulty experienced with maneuvering in 1 patient. The study was terminated for safety concerns.

Within 30 days of the analysis it was found that about 83% of patients had effective biventricular

Figure 5  The WiCS-LV technology, CRT concept with LV pacing without lead (wireless) through ultrasound media. (Quoted from EBR Systems, Inc,http://www.ebrsystemsinc.com)
pacing. On average, patients had at least two intercostal space areas with a good acoustic window, and the area between the intercostal 5 was found to be the most suitable for all patients. In 6 months, it was found that 92% of patients achieved effective biventricular pacing, which is significantly associated with an increase in ejection fraction; clinical improvement included improvement of functional class, better survey, and higher composite clinical scores. Analysis in the group of non-responders with conventional pacemaker therapy showed excellent results in terms of performance and efficiency and a higher success rate, above 90%. However, further investigations are still required about the safety aspect of this method. Events like perforation, pericardial effusion, and tamponade still call for more rigorous attention given the likelihood of occurrence of cardiac injuries with these procedures. The FDA in the US has approved just one system (Micra). Thus, data based on long-term research into leadless pacemaker profile characteristics are still needed for clinical purposes.

**CONCLUSION**

We estimate that over 1 million pacemaker implantations are carried out every year all around the world for the management of symptomatic bradycardia with or without cardiac block. Conventional pacemaker applications are still a routine procedure, which may lead to complications related arising from lead insertion, lead position, and generator pocket. Pacemaker implantation will continue to increase because of the increase in survival rate and a rise in degenerative diseases, across the globe, including in developing countries. Because of the complications associated with conventional pacemaker implantation, the leadless pacemaker may be a good choice. So far, three novel pacemaker systems have come to be actively used in the field: two systems for right ventricle, which is totally leadless and is indicated for VVIR mode, and one system for CRT mode with conventional system modifications. A short-term study of these three systems showed excellent results in terms of performance and efficiency and a higher success rate, above 90%. However, further studies are still needed for clinical purposes.

**REFERENCES**

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