Introduction

Hypertrophic cardiomyopathy (HCM) is a member of the inherited cardiac disease family, which affects approximately one in 500 people in the world population [7]. It is caused by mutations in cardiac sarcomeric genes that control cardiac muscle contraction. So far, more than 84 genes have been identified to be correlated with this disease [7]. HCM is one of the most common causes of sudden cardiac death in young adults [8]. Additionally, it can also cause chronic complications and disabilities that impair patients’ productivity and limit their daily activities. These complications range from angina to heart failure, cardiac arrhythmias to embolic stroke [9]. Clinical diagnosis of HCM can be made by detecting left ventricular hypertrophy without explainable cause during echocardiography or cardiac MRI. Patients with HCM are usually asymptomatic and are diagnosed accidentally during examination of other diseases or HCM complications [9].

One of the serious complications of HCM is cardiac conduction disturbance [8]. The degree of severity of this conduction disorder can vary from mild to severe. Atrioventricular block (AVB) is one form of these disorders. Types and electrocardiographic features of AVB can be seen in Figure 1. In the first-degree AVB, despite the occurrence of PR interval prolongation (PR interval more than 200ms), every impulse is propagated to the ventricle. Second-degree AVB is described as conduction disturbance, in which one or more impulses from the atrium are not propagated to the ventricle. In complete/third-degree AVB, no impulse from the atrium is propagated through the ventricle. As a result, ventricles are conducted by ‘escape’ rhythms (either junctional or ventricular ‘escape’ rhythm).

Complete AVB in HCM was reported to cause life-threatening complications such as acute pulmonary congestion and subsequent cardiac standstill [8]. Clinical presentation of patients with AVB varies according to the type and severity of the AVB, from asymptomatic to syncpe and cardiac arrest. Based on this potentially life-threatening condition, lots of modalities were developed many years ago including drug therapies and device therapy (i.e. pacemaker) to support patients’ conditions [10,11]. Drugs, such as anticholinergic agents (i.e. atropine) could be beneficial in acute conditions. However, these drugs cannot be used in the long-term because of side effects that may appear
during drug administration. Until now, long-term management of AVB relied on the device therapy, which is believed to be one of the best approaches to control impaired cardiac conduction system [11].

**Indications of Pacing in Atrioventricular Block**

Lots of studies report improvement in survival rates among patients with third-degree AVB who are using permanent cardiac pacemakers [11-17]. However, in the first-degree AVB, the indication of pacing is controversial. Some researchers suggest that pacing is only recommended for symptomatic patients; but others argue that pacing should be started earlier, regardless of symptoms, to improve survival especially for AVB that occurs diurnally [11]. Another study showed that marked first-degree AVB (PR ≥ 0.30s) can cause similar symptoms to the pacemaker syndrome without any existence of higher degree AVB [18]. To solve this controversy, uncontrolled trials of pacing in marked first-degree AVB were carried out. The results showed that the patients’ condition was improved with dual chamber pacing, specifically in patients with normal ejection fraction [18].

Some of these AVBs can also be avoided and treated by stopping certain drugs or improving certain medical conditions that act as trigger factors. Recommendations of pacing from European Society of Cardiology (ESC) can be seen in Figure 2 below.

**Leadless Cardiac Pacemaker (LCP) as a new minimal invasive modality**

More than 55 years ago, the first cardiac pacemaker was implanted in the heart [19]. Since then, this device has been developed into a more reliable device by adding battery lifetime, improving lead performance and enhancing device capability (i.e. adding new software). However, main components of current pacemakers are still the same of the first cardiac pacemaker type, such as a pulse generator and one or more transvenous leads. This design usually causes some short-term and long-term complications (in approximately 10% of patients) [4,20]. The subcutaneous pocket is very prone to local infections and often causes skin erosion and hematoma inside the implantation region [20]. In addition, implantation procedures of this regular pacemaker also have several risks. In the short-term, it can cause mobility limitations, pneumothorax, cardiac tamponade and upper limb Deep Vein Thrombosis (DVT). [3,4,6,19]. A study showed that up to six out of ten patients with regular pacemakers developed mobility limitations in the shoulder region, where the pulse generators were implanted [6]. In the long-term, transvenous leads are associated with the majority of complications in regular pacemakers [19]. Those transvenous leads can potentially cause obstructions in the vena cava, and they are prone to insulation breaks, conductor fractures, lead dislodgements and even a systemic infection [3,20,21]. For these reasons, researchers now are developing a new design of pacemakers, which eliminates such leads. It is called the Leadless Cardiac Pacemaker (LCP) [3,4].

There are two main types of Leadless Cardiac Pacemaker: the multicomponent leadless pacemaker and the single component leadless pacemaker. A multicomponent LCP or non-self-contained LCP contains two parts, a subcutaneous pulse generator and a small receiver electrode (as seen in Figure 3). It uses ultrasound energy to propagate the impulse. However, this system might trigger some problems, such as the use of a receiver electrode, long-term ultrasound exposure and environmental interference to the device performance that tends to cause unintended adverse effects. In some cases, implantation of multicomponent LCP (endoluminal left ventricle position) can cause thromboembolic events. Additionally, ultrasound energy drains the battery faster and causes shorter battery life. Based on this fact, an LCP that uses induction technology is being developed. This type of

**Figure 1.** Electrocardiographic Findings in AVB. There are differences in the pattern of PR interval and appearance of non-captured beats in higher degree of AVB. (Cited from: Zimmerman F. 2015)

**Figure 2.** ESC Recommendation of Permanent Pacing in Atrioventricular Block. For chronic symptomatic 3rd or 2nd degree AVB, a permanent pacemaker implantation is strongly indicated and recommended (Class I, LOE C). However, for asymptomatic 1st degree AVB, pacing should be avoided (Class III, LOE C). (Cited from: Vardas PE et al. European Heart Journal. 2007)
multicomponent LCP uses electromagnetic fields rather than ultrasound energy to propagate the impulse. However, clinical trials for this LCP should be commenced. So far, this device was only tested on animal models [3].

The second type of LCP is single-component or fully self-contained. In this LCP, the pulse generator is combined with electrodes in a single device (Figure 4). In other words, it eliminates transvenous leads, the pectoral surgical pocket and intra-system connections [22]. Single-component LCP is preferable to the previous types because it has a simpler, smaller design and also because of the absence of transvenous leads. Details of the single-component LCP will be discussed below.

Implantation Procedures of LCP
The device is delivered to the right ventricle of the heart by a transvenous catheter through the femoral vein [3,23]. After placing the delivery sheath in the femoral vein, the device is delivered to the RV by a delivery catheter with an extendable sleeve to protect the fixation parts (the helix). Once located, the sleeve is retracted, and the device is undocked from the delivery catheter while a tethered connection is retained to allow device measurement and assess stability [4]. Procedures of implantation can be seen in figure 5 and repositioning procedure can be seen in figure 6.

Both Micra™ TPS and Nanostim™ LCP are using nitinol tines as fixations to the right ventricle (figure 7A and 7B). However, there is a difference in the fixation part. On the one hand, Nanostim™ LCP uses a distal non-retractable single turn screw-in helix fixation unit as the primary fixation with three angled nitinol tines perpendicular to the helix as secondary fixations [3,22,24]. At the centre of the fixating helix, there is a steroid-eluting disc which acts as a tip electrode [20]. On the other hands, Micra™ TPS uses four self-expanding nitinol tines to attach to the myocardium with a steroid-eluting cathode in the distal part of the device [3,20].

Clinical Efficacy of LCP
From the very first clinical studies (LEADLESS Trial and Micra TPS Study), this device has been indicated for single chamber RV pacing (VVI-R) candidates [4,6]. In LEADLESS trial, those included atrial fibrillations with AVB, normal sinus rhythm with 2nd or 3rd-degree AVB with a low level of physical activity, sinus bradycardia with infrequent pauses, and undefined syncope with EP findings [4]. The exclusion criteria of LEADLESS trial were pulmonary hypertension, pacemaker dependent patients, prosthetic valve and Inferior Vena Cava (IVC) filter users, and patients who had a pacemaker or ICD leads in their heart [4,6]. In this trial, no major complications were recorded for both acute and chronic period (1-year after implantation) [3]. Overall, based on LEADLESS trial, complication-free rate was about 94 percents [4]. Recently, this LCP was put into a longer duration study called LEADLESS II trial, which covered larger multi-centred participants (670 patients) around US, EU and Canada [6,25]. The purpose of this study was to evaluate the performance and potential complications of the device six months after implantations.

On the other hands, Micra TPS study is a prospective, single-arm, non-randomised study of 780 patients. Those eligible for this study were patients who had indication class I and II for single chamber pacemaker implantation [3]. Aims of this study are to evaluate the long-term performance and safety of Micra™ TPS as a single chamber pacemaker. This study is still ongoing, but in the interim result that was released, there were no major complications at one and three months after implantation [6,26].

The biggest benefit of these LCP devices is obviously the absence of transvenous leads. In the absence of those leads, most of the

Figure 3. Leadless Endocardial Left Ventricular Pacing System. A) Anteroposterior projection of chest X-ray (CXR) B) Lateral Projection of CXR. In this type of LCP, a small receiver / pacing electrode is present. (Cited from: Miller et al, JACC. 2015; 66(10))

Figure 4. A) Micra™ Transcatheter Pacing System LCP (TPS) B) Nanostim™ LCP. Micra™ TPS was founded in Minneapolis, Minnesota by Medtronics and it is the newest type of LCP in the market now. Nanostim™ LCP was founded by St.Jude Medical in St. Paul, Minnesota. Both are containing generator and sensing electrodes. They are also eliminating transvenous leads and pectoral surgical pocket. (Cited from: Miller et al, JACC. 2015; 66(10))

Figure 5. Left Anterior Oblique (LAO) View A) Micra™ Transcatheter Pacing System LCP (TPS) B) Nanostim™ LCP. Micra™ TPS was founded in Minneapolis, Minnesota by Medtronics and it is the newest type of LCP in the market now. Nanostim™ LCP was founded by St.Jude Medical in St. Paul, Minnesota. Both are containing generator and sensing electrodes. They are also eliminating transvenous leads and pectoral surgical pocket. (Cited from: Miller et al, JACC. 2015; 66(10))
complications related to them (i.e. lung injury, pneumothorax, leads dislodgement) can be diminished. In the longer term, the absence of the leads can mitigate chronic venous occlusion incidence. Furthermore, the combination of intra-system connection inside the device helps to reduce complications such as connection error. The transcatheter procedure, which is minimal invasive intervention, reduces surgical risk such as local infection and inflammation. Battery life of this device has been tested, and researchers suggest that LCPs’ battery life is much longer than standard transvenous pacemaker (approximately 15.0 ± 6.7 years) [3,28,29]. Some studies reported that implantation duration of fully self-contained LCP is shorter than the implantation duration of regular single chamber pacemaker (20-45 minutes for Nanostim™ LCP and 43 minutes for Micra™ TPS vs. 60 minutes for regular pacemaker). It also reported a shorter hospitalisation period and earlier recovery times [28-30]. Both Nanostim™ LCP and Micra™ TPS are also safe to be used with magnetic resonance imaging (MRI) because of their lack of ferrous components.

**Limitations of LCP Implantation**

This new form of pacemakers can work flawlessly in certain conduction disturbances that need a single chamber RV pacing (VVIR). However, in diseases that need a dual-chamber pacing device (i.e. sinus node dysfunction ~ sick sinus syndrome), this new LCP is not useful. Moreover, the risk of device embolization cannot be disregarded. The fixation part of the device is the key to “anchor” an LCP to the myocardium, so if this part is not strong enough to attach to the myocardium, the device will ‘fly’ away and obstruct the outflow tract or pulmonary arteries [3-5].

In the LEADLESS trial, one significant complication was reported because of cardiac perforation and tamponade suddenly after repositioning of the LCP. Then, CABG was done to fix the perforation in RV apex. However, this patient died after 18 days because of ischemic stroke and progressive cerebral oedema [4]. Presumably, this complication happened because of the size of the delivery catheter. Although LCP’s size is smaller than the standard pacing device, a fairly big size delivery sheath and a delivery catheter are generally used to deliver the LCP. These items may cause problems during the implantation procedure [3]. In an animal model, hematomas occurred at the site of venous access. Although this condition was resolved without any additional intervention, the hematomas, which may be related to the size of the delivery catheter and sheath, would have needed additional consideration [23,24]. In another patient in the LEADLESS trial, a fixation problem occurred. The LCP was implanted in the RV apex, but then in ventriculography, it was found in LV. After the investigation, the cause of this problem was a patent foramen ovale (PFO) that allowed migration of the device to the left side of the heart [4]. Descriptions and frequencies of complications that were encountered in LEADLESS and LEADLESS II trial could be seen in Figure 8.
In MicraTPS study, from 140 patients, one case of pericardial effusion without tamponade, four patients with transient AVB, two patients with VT and one with Vfib were reported at the time of the interim. No significant complications have been reported in this study including procedure-related death or unanticipated serious adverse events [3].

Besides the technical and procedural limitations of LCP, the cost issue remains challenging. The price of the new type of LCP is assumed to be three times higher than regular pacemaker (around €11,500) [6]. However, so far, LCP’s limitations do not exceed its benefits. Essentially, the limitations outlined above can be avoided with advanced training and a higher level of interventional skills [5].

**Encapsuluation phenomenon in long-term LCP implantation**

Alongside the complications and limitations described above, there is an additional problem that may occur. It is the risk of encapsuluation of the LCP. In order to investigate the encapsuluation phenomenon of this new form of pacemaker and its effects on surrounding tissues, a case study was published recently. This post-mortem study30 examined an 80-year-old man with LCP (because of a brady-tachy syndrome), who died because of cholangiocarcinoma. An LCP was placed 19 months before he died (Figure 9). It was reported that the LCP performance was stable, and no device-related complications...
occurred during his life. The post-mortem autopsy found that the LCP was covered by a thin layer of myofibrous tissue. This tissue made a capsule that surrounded the LCP with a firm base and a fragile roof. The histological examination of that capsule showed alpha smooth muscle actin immunostainable myofibroblasts without any confirmed endothelium lining [30].

Full encapsulation of an LCP device has both a benefit and a risk. The benefit is that the encapsulation may lower the risk of infection in the existence of bacteraemia; whereas the risk is the retrievability of the device. It would be difficult to withdraw an LCP that is attached very tightly to the surrounding myocardium by this myofibrous capsule (Figure 10) [5]. LEADLESS II trial reported that LCPs were successfully retrieved without any problem at 160±180 days (median=100, min=1, max=413) [25]. However, there is no study to date that reports the retrievability of this device more than 1-year after implantation [25]. For that reason, further and longer duration studies are needed [21,30].

**Discussion & Conclusion**

The Leadless Pacemaker is a relatively new cardiac pacemaker, which resembles the function of a single chamber pacemaker. This device has greater benefits compared to a regular single chamber pacemaker, such as minimal intervention during implantation, less complication for both short and long term of use and longer battery lifetime. Additionally, the absence of transvenous leads in LCP minimises potential long-term complications of implantation. However, there are several limitations reported so far, such as the size of the delivery catheter and delivery sheath, possibility of device embolization and the most important one, retrievability of the device. This issue of retrievability is questioned, particularly in the case of full encapsulation that may occur in the longer period. On one hand, encapsulation may be beneficial to reduce the risk of infection, specifically when LCP is surrounded by endothelium. Nevertheless, this encapsulation can become a big issue when the time to change the battery comes because it would be difficult to extract the “buried” device beneath the myofibrous capsule without causing any damage or injury to the myocardial tissues. The research of LCPs (Nanostim™ LCP and Micra™

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**Figure 10.** A) Gross appearance of LCP implant site and Histopathology staining of surrounding tissues three months after implantation (Animal Model). Mild endocardial fibrosis was reported at the site of implantation. B) In histopathological examination, fibrous tissues were found around the helix. Granulomatous reaction was also reported in 10/10 animals and small stabilised thrombi adjacent to RV apex – interface with LCP in 9/10 animals C) Fully Encapsulated Micra™ TPS in RV Apex (Cited from: Koruth et al. J Cardiovasc Electrophysiol. 2015;26:322-328, Krypta A, et al. Clin. Res Cardiol 2016; 105(94))

**Figure 11.** Future Applications of Leadless Pacemaker. In the future use of this pacemaker, the LCP can be functioned as a dual chamber pacemaker to treat sinus node disorder and combined with Implantable Cardiac Defibrillator (ICD). (Cited from: Miller et al, JACC. 2015; 66(10))

**Figure 12.** TBX-18 based Genetic Reprogramming of Cardiomyocyte into Pacemaker-like cell. This figure shows the resemblance of TBX-18/GFP expressing cardiomyocyte with Sinoatrial Nodal (SAN) cell. A) Fluorescence Microscopy view, B) Immunohistochemistry view. (Cited from: Boink et al, Trend in Cardiovascular Medicine. 2015; 25)
TPS) is still ongoing, and further improvements are being made to increase the safety and performance of these devices. In the near future, LCP devices are expected to be used in all conduction disturbances, which are indicated for pacing, including sinus node disorders (as dual chamber pacemaker) and congestive heart failure (as LV endocardial pacing). They are also expected to be used together with Implantable Cardiac Defibrillator (ICD) in patients with high risk of sudden cardiac death (Figure 11) [3]. Furthermore, development of the leadless cardiac pacemaker has entered a new level in translational medicine. Nowadays, cardiomyocytes can be converted into fully functional pacemaker cells through genetic reprogramming techniques. They are called biological pacemakers. There are lots of studies on these futuristic pacemakers, including the involvement of T-box transcription factor-18 (TBX-18) gene, TBX-3 gene, and Hyperpolarisation-activated Cyclic Nucleotide (HCN) gated channels (as seen in Figure 12) [6,34,35,36].

Finally, development and improvement of the latest cardiac pacemaker technology will create a new insight into cardiac pacing. It will also create a better understanding of the intrinsic cardiac pacemaker. Hopefully, pacemaker-related problems can be fixed so that the mortality of cardiac conduction disturbances can be reduced.

Declaration of Interests
The authors have no conflicts of interest to disclose.

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