Technological and Clinical Challenges in Lead Placement for Cardiac Rhythm Management Devices

Albatat M.[1], J. Bergsland[1], H. Arevalo[2], H. H. Odland[3], P. Bose[1], P. S. Halvorsen[1], I. Balasingham[1,4]
[1] Intervention Center, Oslo University Hospital; [2] Department of Computational Physiology, Simula Research Laboratory; [3] Department of C, Oslo University Hospital; [4] Department of Electronic Systems, Norwegian University of Science and Technology, Norway

Abstract—Cardiac Cardiac disease is a leading cause of death worldwide. Disturbance in the conduction system of the heart may trigger or aggravate heart dysfunction, affecting the efficiency of the heart, and lead to heart failure or cardiac arrest. Patients may require implantable cardiac rhythm management devices (ICRMDs) to maintain or restore the heart rhythm. ICRMDs have undergone important improvements, yet limitations still exist, presenting important technological challenges. Most ICRMDs consist of a subcutaneous control unit and intracardiac electrodes. The leads, which connect the electrodes to the control unit, are usually placed transvenously through the subclavian veins. Various locations inside the heart are used for placement of electrodes, depending on the specific condition. Some of the limitations to effective pacemaker therapy are associated with placement and location of the leads. Various approaches have been developed to overcome these challenges, such as multi-site pacing and leadless solutions. This paper aims to review the state of the art for the selection of placement sites for pacemakers, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy devices (CRT) devices and discuss potential technological advancements to improve the results of ICRMD-therapy including development av leadless technology.

Key words—Pacemaker, ICD, CRT, Electrophysiology

1 INTRODUCTION

Cardiovascular diseases (CVD) is a leading cause of mortality in the Western World, and is responsible for 37.5 % of all deaths in EU [59]. To prolong lives and reduce the social and economic burden from CVD, prevention, early diagnosis and appropriate therapy is essential. Pacemaker therapy, initially developed in the 1960s, have improved quality and quantity of life for certain patients with heart rhythm abnormalities. Remarkable technological developments have occurred, making cardiac rhythm management devices (CRMDs) an option for larger groups of patients, although a number of important challenges still exist.

Disturbance of cardiac rhythm and malfunction of the heart's conduction system is the result of disease processes such as hypertension, coronary artery- and valvular- heart disease or from primary- or secondary- abnormalities of cells of the specialized conduction system. Conduction disorders reduce the heart's functional state by impairing optimal coordination of the contraction of atria and ventricles. CRMDs were developed to maintain, improve or restore heart rhythm. There are three main classes of CRMDs: 1) anti bradycardia- or tachycardia- pacemakers, 2) cardioverter-defibrillators, and 3) cardiac resynchronization therapy devices (CRT). The 5-letter code developed by The Heart Rhythm Society (previously known as the North American Society for Pacing and Electrophysiology and the British Pacing and Electrophysiology Group) classifies pacemakers according to functional capabilities [24]. Anti-bradycardia devices pace the atrium and/or the right ventricle to prevent bradycardia, while anti-tachycardia pacemakers use programmed pacing to terminate tachy-arrhythmias in the atria or ventricles. Most anti-tachycardia devices now include a cardioverter-defibrillator function, which terminate ventricular tachycardia and fibrillation by an electric shock. Unfortunately, there are still no reliable tools to identify all patients at risk for sudden cardiac arrest (SCA) from arrhythmia, which is seriously limiting the ability to decrease SCA in the population. CRT, a newer pacing-modality is effective in a relatively small fraction of patients with systolic heart failure (HF) when the HF is caused by unsynchronized contractions of the right- and the left- ventricles. The incidence of HF is increasing, and CRT has a definite, although limited effect in selected HF patients. CRT have no effect in diastolic HF and only suitable for systolic HF with electrical substrate, which represents around 30 % of the HF population [118].

CRMDs are used on temporary or permanent basis. Temporary devices are used to treat temporary dysfunction of the conduction system after heart surgery or myocardial infarction [23]. In this paper, focus will be on permanently implanted cardiac rhythm management devices (ICRMDs).

ICRMDs typically consist of a subcutaneous pacemaker can containing the control unit (CU) and the energy source. The pacemaker can is connected to single, double, or multiple leads with electrodes at the tip which detect cardiac activity and stimulate the heart to contract when appropriate (Figure 1). The CU communicates with an external programmer during follow-up visits, to obtain stored or real-time records of cardiac and pacing activities. Pacemaker settings such as sensitivity, pacing output and other parameters may be reprogrammed to optimize function and reduce energy-use. Modern CRMDs have at least three functions: 1) **Sensing electric impulses of the heart**, through one or more electrical leads, 2) Processing the information **and prepare future action** by the CU, and 3) **Pacing or defibrillation action**, through the pacing lead(s) or defibrillation coils. The position of the electrodes in the heart is essential for proper functioning of the device. Most leads are presently positioned through the venous system, entering veins in the upper body.

In addition to electronic malfunction of devices, which are relatively uncommon, the leads are weak links in pacemaker systems and may dislodge, break or develop exit block where the voltage required for pacing becomes excessive 175. Leads are foreign bodies that can cause infection and/or thrombosis94. They are subject to mechanical breakdown and

complications may occur during implantation causing tricuspid valve damage and pneumothorax 95, 161. The rate of short-term complications can be as high as 10 % 93. With a yearly implantation rate of more than one million ICRMDs worldwide – which is expected to rise considerably due to the increasing life span and ICRMD indications – around 100 000 complications occur every year. Pocket infection is another risk associated with ICRMDs, which may spread to the bloodstream through the leads and cause endocarditis 93. Infected devices should be extracted immediately, with a reported mortality rate of 12 % to 31 % 35 138.

Reducing current drain by miniaturization of electronics and batteries have made it possible to construct leadless, implantable pacemakers incorporating sensing, stimulation, processing and power supply in a small capsule placed in a heart chamber. Current leadless pacemakers have limited programmability and are presently used exclusively for pacing the right ventricle. This mode of pacing is indicated for elderly patients with intermittent need for pacing. There is a large potential for further innovation by creating devices for multi-chamber leadless pacing.

The goal of this paper is to review the state of the art of ICRMDs – with focus on the placement of the electrodes – and outline a vision of the future of possible technological developments.

The literature search was performed using Pubmed and Google Scholar including only English language publications published within the last 15 years, in addition to some older "flagship" papers. Search criteria included the following terms: Single-chamber pacemakers, atrial pacing, ventricular pacing, dual-chamber pacemakers, leadless pacemakers, cardiac resynchronization therapy, multisite pacing, multipoint pacing, implantable cardioverter defibrillator, subcutaneous ICD. Papers were included after review of abstracts filtering for lead placement. When multiple papers demonstrated similar conclusions, those with higher impact were selected to reduce the overall number of references.

The electrode placement of the three ICRMD devices are reviewed in the three following chapters, followed by the discussion. A short summary table is provided at the end of each chapter.

2 PACEMAKER THERAPY

2.1 Single-Chamber Pacemaker

Single chamber pacemakers are either *atrial* or *ventricular* with function limited to sensing and pacing of the atrium or the ventricle. Such pacers may also have sensors for modifying pacing rates to metabolic demands, so called rate responsive pacing.

2.1.1 Atrial Pacing

Atrial pacing is used for patients with sick sinus syndrome, which is prevalent in 0.1 % of the population above 45 years [86]. Atrial pacing is useful when atrioventricular (AV) conduction is normal and is presently a IIb recommendation according to the latest guidelines due to the long-term risk of AV block [68]. The rate of change from atrial pacing to dual-chamber pacing is 4.5 % per year [32].

Atrial pacing leads are placed in the right atrium transvenously and connected to the control unit. Various lead locations are used. The *right atrial appendage* (RAA) provides ample contact with atrial endocardium, and a stable position for passive fixation leads. RAA pacing is associated with increased risk of atrial fibrillation (AF) in patients with atrial conduction disorders [46].

Active fixation leads, make pacing from the *septal wall* possible, providing simultaneous activation of the left and right atria [134]. As reported by Verlato et al. [178], in patients with SA-node and intra-atrial conduction delay, *low interatrial septum* pacing may be superior to RAA pacing in preventing atrial fibrillation. Pacing the Bachmann's bundle has been associated with lower risk of atrial fibrillation acutely and chronically [19]. Such placements present risk of far-field sensing because septal locations lie close to the tricuspid annulus where leads may sense ventricular signals. The *coronary sinus* (CS) *orifice*, which forms a prominent electrical connection between the atria, has been used as atrial pacing site, but to a limited extent, due to the relatively high rate of perforation and clot formation. It is difficult to place an electrode near the CS orifice. Septal sites in general provide better activation patterns, but are harder to locate/access and associated with far-field sensing, which may result in cross-talk [19, 178].

Another approach to atrial synchronization is pacing two sites simultaneously, one in each atrium (bi-atrial pacing) [142] or two different locations in the RA (dual-site atrial pacing) [51]. This helps synchronize the atria and decrease atrial activation time [51] and prevent tachycardia [140]. Multisite atrial pacing provides shorter atrial activation time, but is rarely used since atrial synchrony has low impact on cardiac output and single-site pacing is more effective in preventing AF [134]. Dual-site atrial pacing requires additional hardware, increasing lead-related risks and the risk of "double- sensing" atrial events, which may result in inappropriate pacemaker behavior.

2.1.2 Ventricular Pacing

In the case of AV block, a ventricular pacemaker, or a dual-chamber (atrium and ventricle) is necessary to ensure that impulses are delivered to the ventricles.

Since the development of the first implantable pacemaker in 1959, the *right ventricular apex* (RVA) has been the commonly used pacing site for ventricular pacing due to accessibility and stability of passive fixation leads positioned in the apical trabeculated area. Leads are inserted trans-venously, through the tricuspid valve to the RVA and the position secured by *passive or active fixation* mechanisms. Studies have shown that RVA pacing may cause impaired pumping function due to late activation of the left ventricle – a response similar to that of a *left bundle branch block (LBBB)*, where activation occurs from right to left instead of the natural left-to-right activation sequence [120]. If pacing is needed occasionally (around 10 % of the time), deleterious consequences of apical RV pacing are limited [166], but extensive pacing from RVA is associated with limited apical motion, remodeling and reduced function of the LV [167, 169]. Patients with normal LV can develop HF from continuoues RV pacing [43].

With the introduction of the *active fixation* electrodes, alternative pacing sites became available. Pacing in the RV from locations closer to the AV-node, such as the *right ventricular septum* (RVS) and *right ventricular outflow-tract*

(RVOT) result in relatively normal conduction and a "*more natural"* contraction pattern [90, 159, 181, 190].

On reviewing the heart's conduction system in Figure 2, the His Bundle may appear to represent an ideal pacing site since it would utilize the Purkinje fibers to activate and synchronize both ventricles. *Direct His bundle pacing* (DHBP), reported by Deshmukh et al. [54] resulted in ventricular activation close to natural, producing normal QRS complexes. The implantation process requires detailed electrophysiological mapping to locate the His bundle, long procedure times (mean 4 hours) and pacing threshold as high as 2.4V at 0.5ms pulse-width, whereas pacing threshold for other RV sites is usually below 1V. The same group, compared DHBP to RVA pacing in 54 patients [55] and confirmed DHBP's safety and effectiveness compared to RVA pacing and encouraged others to investigate DHBP [5, 187, 188]. Zanon et al used a steerable catheter for such implantation and reduced mean procedure time to 75 minutes [188]. The study included 26 patients with a 92 % success rate, but pacing thresholds were relatively high. Detailed review of implantation techniques of DHBP is described by Vijayaraman et al. [179].

2.2 Dual-Chamber Pacemaker

Improvement in electronics and batteries enabled the development of dual chamber pacemakers with leads in the right atrium (usually at the RAA) and the RV (typically at the RVOT, RVA, or RVS). Dual-chamber pacing improves cardiac output compared to single-chamber pacing, maintaining the sequence of atrial and ventricular contractions, allowing better filling of the ventricles. Dual-chamber pacemakers are multi-programmable and operate in various modes to optimize therapy and minimize power consumption. In case of *first or second-degree* AV block, the pacemaker senses the activation in the atrium and paces the ventricle only when a QRS complex is missed after the programmed AV delay. A simplified overview of the existing single- and dual-chamber pacing modes are available on the online resource Deranged Physiology [183].

According to guidelines from the European Society of Cardiology (ESC), dual-chamber pacemakers are recommended except in patients with chronic atrial fibrillation [33]. Even though dual-chamber- is superior to single-chamber-pacing in patients with functioning atrial contraction, it has not completely replaced single-chamber pacing, due to increased risk of infection and lead dislocation [97]. The cost of the hardware and requirements for more frequent follow-up and shorter battery duration are significant factors, especially in older patients and in developing countries. A study from 1992 demonstrated that the use of dual-chamber pacing increase cost by 94 % [144]. Petch [137] speculated that improved functional capacity may not be beneficial for health in older patients. Furthermore, single-chamber pacing is adequate for patients with sick sinus syndrome who only requires pacemaker for occasional bradycardia, as discussed by El Gamal [58].

A dual-chamber pacing system using dual-site atrial pacing was introduced by Stockburger et al. [165]. The RA is simultaneously paced from the RAA and the CS. The ventricular lead is placed in the RVA or RVOT. This type of pacing increases left atrium appendage flow and may prevent *paroxysmal atrial fibrillation.*

2.3 Leadless Pacemaker

Improved electronics and smaller batteries made leadless pacemakers possible. The concept was proposed 40 years ago [162], but only recently became a clinical reality. Two commercial systems are available: Nanostim™ (St. Jude Medical Inc., Minneapolis, USA) and Micra™ (Medtronic Inc. Minneapolis, USA). Nanostim™ was retrieved from the market in 2016 due to battery and communication malfunction [100]. Leadless pacemakers are self-contained and consist of a power generator, sensors, current injector, and an integrated battery unit and are implanted in the right ventricle transvenously [119].

Leadless pacemakers communicate wirelessly with an external programming unit to allow reprogramming. Wireless transmission range is an important challenge for these small devices. The fact that tissues rich in water and salt dampen radiofrequency waves makes the challenge particularly severe in adults and overweight people because the distance between device and body surface is wider. Neither Micra™ or Nanostim™ have a permanent power solution, making battery replacement a technical challenge. This limitation may potentially be overcome by energy harvesting from the body's electrical activities or from energy generated by cardiac motion and vibration [74, 89]. The concept of energy harvesting remains experimental, the main concern is whether enough energy to supply all the components of a pacemaker can be reliably supplied.

Current leadless pacemakers may be superior from a safety perspective, but functionality is limited. At present, they only pace the right ventricle (VVI- or VVI-R pacing) and can only be used for bradycardia patients in whom AV-synchrony and RV-LV synchrony are not considered essential or for patients with chronic atrial fibrillation [68].

3 Cardiac Resynchronization Therapy

3.1 Biventricular Pacing

Heart failure (HF) is a pathological condition affecting the heart's pumping efficiency. HF is a major health and economical problem affecting more than 26 million people increasing in prevelance with increasing age span [151].

About 30 % of HF patients have intra- or inter-ventricular conduction disorders, characterized by low ejection fraction and abnormally wide QRS complexes causing dyssynchronous ventricular contraction and relaxation patterns [118]. Conventional dual-chamber pacemaker cannot correct this dyssynchrony, but might further worsen it by activating the RV ahead of the LV [182]. From a functional point of view, it would be ideal to control the activation of all four chambers of the heart, as shown by Serge Cazeau, who introduced cardiac resynchronization therapy clinically (CRT) [40].

Current CRT devices are similar to dual-chamber pacemaker, but require an additional lead for stimulation of the LV to synchronize inter- and intra-ventricular contraction. Pacing outputs from CRT-devices are adjustable for optimizing pacing and thereby contraction in the cardiac chambers. CRT may improve pumping mechanism, HF symptoms, exercise tolerance, quality of life in mid and end-stage HF patients and reduce hospitalization for- and mortality

from- HF [3, 17, 20, 26, 44]. CRT is indicated for patients with left ventricular ejection fraction of 35 % or less, reduced LV systolic function despite optimal drug therapy, LBBB with a QRS duration of 150 ms or greater, and NYHA class II, III [33]. The effect of CRT is limited to selected patients with systolic HF and has no demonstrable effect in patients with HF caused by diastolic dysfunction.

Several studies investigated the location of LV pacing sites on CRT outcomes [13, 37, 67], while only a few studies evaluated the impact of RV lead location and few clear benefits were reported [63, 102, 125, 146]. Reidlbauchova et al. [146] suggested that mid-septal positioning of the RV lead is better than apical positioning, while Thébault et al. [170] observed no clinical difference between apical, septal and basal positions, preferring apical positions in 78 % of the patients due to optimal stability and pacing thresholds.

3.1.1 Left Ventricular pacing lead

LV- leads for CRT are mostly placed transvenously through the coronary sinus (CS) or alternatively on the epicardium using a small thoracotomy. The position of the LV lead is important for the hemodynamic response and clinical effects [13, 37, 38], and optimal lead position is dependent on various patient factors [7, 135]. Placement of leads for LV stimulation represent a bigger challenge than for other chambers. The CS approach is presently strongly favored since leads placed inside the LV may cause embolization and stroke, and epicardial leads require a surgical procedure.

3.1.2 Coronary Sinus (CS) LV Pacing

The LV lead is typically inserted trans-venously and advanced through the CS to an appropriate coronary sinus branch on the epicardial surface of the LV (Figure 3). Lead placement requires fluoroscopy and angiography to properly select a branch of the CS branch. Gasparini et al. conducted a 3-year study of the CS lead position's impact on the heart-function [67]. No significant difference in outcome parameters related to lead-placements was demonstrated, but only long-term clinical results were reviewed and no comparison between acute and chronic results were made. In 2011, the multicenter MADIT-CRT study indicated that any CS branch could be utilized if it was located in the proximal- to the middle- part of the LV [160]. The study highlighted that apical LV lead positions were unfavorable.

The LV lead should not pace a myocardial scar, which impedes impulse propagation [27, 41, 184]. More than 30 % of patients with indications for CRT, do not respond due to suboptimal LV activation [14] and up to 10 % has a limited venous anatomy [107, 158]. Lead-related complications have decreased in recent years, but lead placement remains an important limitation in ICRMD therapy [94].

Patients with non-ischemic HF have variable response to CRT due to *zones of slow conduction* in the LV [69, 101]. Response may be unpredictable due to the fact that conduction block may vary in the myocardium [65]. Two types of LV activation patterns have been identified: Type I is associated with uniform slow conduction between the septum and the lateral wall, and type II with slow or blocked conduction within a confined area producing a U-shaped activation pattern [12, 149]. Fung et al. verified that type II activation patterns are more responsive to CRT treatment [64]. Patients with Type I activation pattern and/or myocardial scar have an unpredictable response to conventional CRT with standard mid to basal posterolateral CS lead position. Patients not responding to conventional CRT typically have more scar burden than responders, and patients with scar burden of more than 30% rarely respond [184, 185]. The variable and unpredictable response has led to the investigation of alternative methods for determining optimal LV pacing locations.

3.1.3 Multipoint pacing (MPP) and multisite pacing (MSP)

MPP and MSP are used to augment CRT response rates by pacing the LV from multiple locations to improve; 1) chance of finding optimal sites; 2) electro-mechanical synchrony by recruiting more LV muscle 3) optimization using various pacing configuration. Results of these approaches have been summarized by Antoniadis et al. [8].

MPP was recently introduced into the market (MultiPoint™ Pacing [MPP], St. Jude Medical, Inc., Sylmar, CA, USA). In MPP, a quadripolar lead is used to pace the LV simultaneously or sequentially at multiple locations within a single CS vein. MSP involves insertion of an additional LV lead in another CS branch. MPP acutely improved LV function (LV dP/dt_{max}) and hemodynamics [127, 171]. The quadripolar lead inject current between any two of the four electrodes and the RV electrode, providing up to ten different pacing vectors and LV activation configurations. Most MPP studies improve LV synchrony, contractility, activation pattern [8], but other studies achieved similar outcome with optimized single-point pacing [164]. Although adaptive pacing allowing intrinsic activation of the right bundle branch simultaneously with LV pacing may reduce battery drainage [115], the main limitation of MPP pacing is increased power consumption, which reduces the longevity of the device. The programming flexibility of quadripolar leads, allows physicians to limit *phrenic nerve stimulation* (PNS) and improve capture threshold without lead repositioning [117]. With a regular electrode, 20 % of CRT patients experience uncomfortable PNS [25].

Pappone et al. introduced MSP and suggested that it enhances the systolic function compared to single-site pacing in patients with LBBB [135]. Randomized comparison demonstrated increased LV reverse remodeling compared to conventional LV pacing [103]. Padeletti et al. used a special LV lead that could be used both as dual- or single-site leads, providing comparisons in the same patient [133]. It was demonstrated that optimal single-site LV pacing produced similar or better results than dual-site LV pacing. Jackson et al. supported this conclusion [84], but other studies reported improved acute and long-term outcomes with dual site pacing [99, 106]. The main limitation of MSP remains the need for a second lead, which increases lead-related complications, procedure- and x-ray exposure- time. Additionally, some patients may not have two accessible CS branches [130]. Current MSP technique increases the power consumption since the two LV leads are connected to the same port on the can using a Y-connector reducing lead-impedance.

3.1.4 Surgical Epicardial LV Pacing Leads

Conventional CS catheterization is unfeasible in more than 10% of eligible patients, and the choice of pacing sites is limited by anatomy contributing to the 30 % non-respondence rate [6, 37]. LV epicardial leads may be implanted on the surface of the heart through a small surgical intervention [16, 113]. This allows lead-implantation anywhere on the LV and facilitates

pacing by providing improved conductance routes [16]. The best hemodynamics outcomes are achieved when pacing the LV free wall, whereas LV anterior wall pacing produces the least favorable results [15, 37, 122]. Surgical procedures include mini-thoracotomy, video-assisted thoracoscopy, robotically enhanced tele-manipulation and subxiphoid puncture [112, 189]. Such operations require general anesthesia and are *more invasive* than CS approaches, but may improve outcomes and reduce lead-related complications [16, 45, 83, 113]. Daoud et al. [45] showed relatively frequent early-stage complications and mortality from surgical lead placement, due to inadequate medical therapy preoperatively.

3.1.5 Endocardial LV Pacing

Endocardial pacing replicates natural LV-activation, which originates in the endocardium and propagates towards the epicardium. Endocardial LV stimulation produces better CRT outcomes and less dispersion of repolarization, increasing the efficiency of the LV contraction [29, 53, 69, 176]. This has proven advantageous for patients not responding to conventional CS epicardial pacing [42, 91]. In LV endocardial pacing, the lead is inserted transvenously through the right atrium and trans-septally via the left atrium through the mitral valve and then fixed in the basal or middle free wall of the LV. The trans-septal technique was proposed in 1996 for patients not responding to CS pacing [85, 104] enabling alternative placement of the LV lead providing better hemodynamics when CS pacing has failed [66, 132, 163, 176]. Trans-septal placement of LV leads increases the risk of thrombo-embolism despite anticoagulation, and since the lead must cross the mitral valve, regurgitation may occur.

Ginks et al. demonstrated that CRT with multiple endocardial LV pacing sites improves CRT response and is particularly beneficial for patients with type I LV activation pattern and ischemic heart disease [70]. Hemodynamic response was dependent on the underlying activation pattern, but not on total LV activation time, implying that there is a nonlinear relationship between mechanical and electrical resynchronization of the heart chambers.

A new approach for overcoming the limitations of conventional CS LV lead positioning, is wireless stimulation of the LV; Wireless Cardiac Stimulation system (WiC®S-LV (EBR Systems Inc. USA)) [56, 57 145]. The WiC®S-LV system may be implanted with any pacemaker system and consists of a subcutaneous pulse generator and an endocardial, LV electrode. The generator detects the electrical activity from the pacemaker and triggers an acoustic pulse sent to the receiving electrode (Figure 4). The receiving electrode converts the acoustic pulse to an electrical pacing pulse. Initial human trials validated safety and demonstrated short- and mid-term efficacy [11]. Ultrasound mediated LV pacing WiC®S is a promising method to overcome anatomical constrains of CS, but the added complexity of implanting a second device makes the technique less attractive. Around 25 % of all CRT patients are upgraded from dual-chamber pacemakers through implantation of a third lead, which is difficult [77], and has a complication rate of 10 % [177]. The WiC®S-LV technique may reduce implantation-related risks for this subset.

4 IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD)

4.1 Sudden Cardiac Arrest (SCA) and Tachyarrhythmia

Sudden cardiac arrest is a significant cause of mortality [61]. The majority of patients who experience SCA outside hospitals, do not survive [81]. Most SCAs are caused by ventricular tachyarrhythmia or ventricular fibrillation (VF), in which the heart loses pumping efficiency due to multiple reentrant circuits and continuous wavelet formation. A high voltage **defibrillation** shock can restore normal rhythm, by eradicating reentrant circuits. The rate of survival after SCA decreases exponentially with time before restoring heart rhythm, while the permanent damage increases [1]. Brain damage occurs after a few minutes of cardiac arrest, and resuscitation by bystanders frequently comes too late. Implantable automatic defibrillators sense ventricular fibrillation and defibrillate the heart automatically, preventing SCA. During atrially initiated tachyarrhythmias, such as atrial fibrillation or flutter, the heart will work less effectively, but the ventricular activation may still be intact. If a shock is delivered during ventricular repolarization (T wave in ECG) it may induce VF. Therefore the rhythm in these cases is restored by delivering a shock during the ventricular depolarization (R wave in ECG), a method called **cardioversion** [110].

4.2 ICD Therapy

ICDs were initially used only to manage cardiac arrest from VF. Relatively slow ventricular tachycardia (<300 bpm), often preceding VF, could be treated with **anti-tachycardia pacing** (ATP), making defibrillation unnecessary [121]. ATP was introduced in 1980 and became safer when shock was available as a backup treatment [75]. ATP can terminate VT by programmed pacing at a rate close to the tachycardia frequency to overdrive the tachycardia, before gradually reducing the rate until normal rhythm is achieved [48]. ATP reduces the need for shocks – reducing patient discomfort, and increasing device longevity [47, 87, 139, 180].

Modern ICDs have single or dual-chamber pacing functions embedded. When VT is detected, the ICD will apply ATP, but if ATP is ineffective or ventricular fibrillation is detected, the device will deliver a high-energy shock. Dual-chamber ICDs are increasingly used as they provide better discrimination between VT, VF and other arrhythmias, preventing inappropriate shocks. As indications for ICD often overlap indications for CRT, patients may get a CRT device (biventricular pacemaker) with ICD capabilities, called CRT-D, to improve pumping functionality and reduce mortality from SCA [3, 34]. However, there are still not adequate diagnostic criteria for identifying all patients at risk for SCA, limiting the number of lives saved by ICDs.

Conventional ICDs are larger than pacemakers due to the capacitors needed to accumulate enough charge for high voltage shocks. Initially, ICD cans were placed in the abdomen, but miniaturization of electronics has allowed subcutaneous implantation.

ICD leads are similar to pacemaker leads, but may have a large-surface electrode (coil) incorporated in the right ventricular lead for delivery of high-voltage shock (Figure 1). The shock is delivered between the coil and the can casing (active can). Hence, the right ventricular lead is typically

placed in the RVA to ensure that the shock covers the largest possible volume of heart tissue. The atrial lead placement is the same as for pacemakers and enables continuous dual-chamber monitoring and pacing (2.2). For CRT-D therapy, a CS left ventricular lead is used in addition (3.1.2).

Studies from the late 90's proposed an additional coil within the RV lead, positioned in the superior vena cava as shown in Figure 1 [71, 168]. The dual-coil configuration quickly became widely used clinically, because of large surface area, reduced impedance, and lower defibrillation threshold [72]. Even though a larger area is covered with dual-coil configuration, the density of the shock is reduced, decreasing the overall benefit [21, 173]. The extra SVC coils increase complexity, cost, risk of lead failure, and lead removal complications [9, 147, 154], and the dual-coil ICD has become less common.

4.3 Subcutaneous-ICD (S-ICD)

The S-ICD was developed to reduce implantation complexity [22, 49] and does not require transvenous lead insertion. Defibrillation shocks are delivered when VF is sensed by a subcutaneous electrode. This reduces implant-related complications including lead-problems and venous thrombosis [128, 177]. The implantation procedure does not require fluoroscopy or other imaging modalities and uses anatomical landmarks, as shown in Figure 5.

S-ICDs were tested and validated clinically in 2011, and the method was demonstrated to be feasible and safe [2, 39]. S-ICD was included in the 2015 European Society of Cardiology guidelines and recommended as an alternative for patients with indication for ICD when: 1) pacing is not needed; 2) venous access is difficult due to infection; 3) patients are young with long-term need for ICD therapy [141]. Several studies demonstrated considerable limitations of S-ICD, including variable and inadequate sensing [73, 128, 131]. Even though S-ICD reduced acute complication rates from 3.5 % to under 2 % [36], the lack of pacing capability, limits S-ICD to 2.5 % of the market with approximately 20000 S-ICD units implanted yearly [155].

5 DISCUSSION

Indications for implantation of a ICRMD are malfunctions of the cardiac conduction system, or risk of serious arrhythmias. It is speculated that the ultimate treatment for cardiac arrhythmias may be based on replacement or repair of defective cardiomyocytes, using gene therapy or stem cells. Biological pacing has been under investigation for two decades, but is still in an early non-clinical stage [28, 79, 150] leaving implantable electric ICRMDs as the treatment of choice in the foreseeable future.

Complications from ICRMDs are frequently due to the pacing leads and the anatomical limitations of their placement: When selecting placement site, sensing and pacing attributes must be considered. A site providing better sensitivity may have higher pacing threshold or it may lie in a fragile or inaccessible place. In this chapter, we will discuss currently used pacing sites and approaches and try to cast light on future directions. A summary of this review is shown in Table 4.

5.1 Atrial Pacing Site

As mentioned above the RAA is a commonly used site providing natural activation, reliable sensitivity, and anatomy favorable for implantation. Septal sites provide better activation patterns, but are harder to locate/access and associated with far-field sensing, which may result in cross-talk [19, 178].

We believe that micro/nano electronic- pacing of the atrium will be a relatively safe target for new technology, when patients have normal AV conduction. Pacemakers consisting of modified myocytes may become an alternative. However, microelectronic devices incorporating sensing and pacing and the ability to respond to physiologic demands, are more realistic as a short-to intermediate term goal.

5.2 Ventricular Pacing Site

The selection of the appropriate mode of pacing and optimal placement of leads require good understanding of cardiac physiology and anatomy. In general, more data from randomized trials are needed to determine optimal pacing modes, but pacing sites can be optimized for each patient depending on individual response determined prior to- or during implantation [5]. Biological pacing may eventually become a reality, most likely initially for non-critical applications like atrial pacing.

5.3 LV Pacing in CRT

The LV pacing site is even more important in CRT outcomes [160]. Conventionally, leads are inserted in a lateral or posterolateral branch of the CS to achieve positional stability. The MADIT-CRT study [160] implied that LV apical sites should be avoided, while the COMPANION study [153] observed no difference in outcome between apical and basal pacing. Posterolateral- may be more advantageous than anterior- sites [7, 37, 186], but this is not uniformly accepted [53, 62]. It is claimed that results for various LV pacing sites are patient specific and that optimal outcome are achieved by pacing the LV where activation occurs the latest, as long as the site is without scar tissue [7, 52, 53, 124, 163, 186].

MPP pacing showed promising results but increases battery drain. MSP is more effective in CRT, but only a handful of randomized MSP trials including 10-50 patients have been conducted. Dedicated leads and devices are required as well as larger studies to evaluate the full potential of MSP.

Endocardial pacing used for LV pacing results in more natural activation pattern, but increases the complication risks and is used only as an alternative to CS pacing. Placement of leads on the epicardial surface through a thoracotomy is more invasive and is used in children, or when the LV is inaccessible through the CS. There is a need for new, innovative approaches to expand the locations for LV pacing beyond those reachable from CS. An interesting approach could be the use of ultra-thin leads which could be implanted in smaller CS tributaries thereby expanding the possibility for optimization of the LV activation pattern.

5.4 ICD

ICDs are superior to antiarrhythmic drug therapy for prevention of sudden cardiac death [60, 116, 123]. The position of defibrillation coils is not important provided the area between

anode and cathode covers 90 % of the heart tissue with a voltage gradient of more than 5 volts per meter [129]. An ICD delivers pacing therapy when needed, since bradycardia frequently develops immediately after a shock. ICD lead complications can be more severe and lead-extraction harder, due to the caliber and shape of the coils [108, 136]. Lead malfunctioning, changes in patient condition and drug therapy may disturb defibrillation thresholds and prompt inappropriate shocks [87]. Malfunctioning devices require re-programming or replacing, or repositioning the leads [136].

Average life span is increasing globally, resulting in a rapidly increasing number of patients with chronic heart conditions. More than 40 % of ICD patients live for more than 10 years after implantation, and 30 % are less than 60 years old [76, 152]. The rate of lead-related complications may increase with a cumulative increasing number of patients. The rate of ICD lead complications requiring re-intervention is estimated to be 20 % for the average patient over ten years [96]. Device replacement after battery depletion are associated with a 5-fold risk if leads have to be replaced [109]. Due to the formation of fibrotic tissue around the leads, extraction procedures are associated with complications such as major hemorrhage and valve damage [78]. Utilization of improved leads and subcutaneously placed ICD cans will decrease complication rates, and ablation of arrhythmogenic areas in the myocardium may reduce the need for such devices.

5.5 Future Directions

5.5.1 Computational Models to predict optimal pacing site

The target area for pacemaker lead placement may be assessed using Doppler imaging [7, 53], tissue synchronization imaging [124], speckle tracking imaging [52, 92, 186], pressure-volume loops [50] or electrophysiological mapping [101]. All these methods are performed with resting patients, far from everyday life, whereas the actual outcomes and overall effects on the heart are assessed chronically after implantations. Therefore, a reliable and safe methods of predicting outcomes and defining optimal pacing sites are required, especially in CRT where the response rate has remained below 70 %.

The advances in computational medicine resulted in the emergence of new detail heart models [174], with a clear potential for analyzing the effect of ICRMDs non-invasively. Such in silico concepts have been utilized in studying various problems, such as stratifying ICD patients [10] and optimizing CRT [4, 80, 82, 157]. A comprehensive review of the role of computational modeling in CRT was provided by Lee et al. [105]. The main challenge of such models is the ability to simulate patient specific electrophysiological and electromechanical properties. With the diverse anatomy and pathology between patients from cellular to tissue and organ level, patient specific modeling is a complex multi-dimensional problem [126].

5.5.2 S-ICD and Leadless Pacemaker

An alternative approach to prevent lead-related complications is the combination of commercially available S-ICDs and leadless pacemakers, providing single-chamber pacing with defibrillation capability. This concept has been demonstrated clinically [172], but further studies are needed for safety and performance validation. Even though such device(s) may reduce complication rates, the concept will be useful for patients in need of ICD with ventricular pacing. Such patients represent a minority of the ICD population since dual-chamber pacing and CRT-D are increasingly considered necessary since patients who need ICDs frequently suffer from HF as well [98].

5.5.3 The WiBEC Project and Pacing

Inspired by the leadless pacemaker–S-ICD combination, the Wireless in-Body Environment Communication (WiBEC) project [88], aims to overcome the challenges of current ICRMDs by introducing pacemaker-systems containing wireless, multi-node sensor networks. The system will measure regional- and global- cardiac contractility and ventricular volumes and semi-automatically adjust pacer function to adjust cardiac output to metabolic needs. Using sophisticated sensors and current injectors, such devices will optimize overall cardiac status. Electronic capsules located at multiple sites in the heart will improve functionalities such as cardioversion, defibrillation and CRT. To develop reliable and efficient implantable wireless cardiac devices, challenges such as power consumption, miniaturization, communication and safety must be overcome.

The WiBEC project is utilizing a multi-national, multi-sectoral and multi-disciplinary approach and includes two hospitals, three universities and four industrial partners from four different countries, all with unique qualifications and expertise in intra-body communication and sensor technology. The project includes four main themes: 1) *Wireless communication* and establishing communication channels between different nodes, including antenna design and specifications [31 30 143]; 2) *Signal processing*; focusing on new algorithms to increase efficiency, intelligence and cyber security [111 18]; 3) *Energy source development;* aiming at the development of non-invasive energy sources, utilizing *wireless power transfer* technology or *energy harvesting* from heart-motion [148]; 4) *Preclinical testing*; including system integration, minimization of electronics, prototyping, development of testing platforms and simulation software, phantoms and animal models. Detailed description of the various topics is out of the scope of this paper – more information can be found through the project's website [88].

A multi-node wireless pacemaker system may eliminate restrictions caused by leads and broaden the selection of the pacing sites. The nodes should be able to wirelessly communicate with each other and with a subcutaneous or external control units. With CRT-D ability, systems can be configured as single- or dual-chamber pacemakers or CRTs with or without ICD capability. This will unify present modalities of ICRMDs in one system with selective configuration, reducing complexity while increasing practicality.

To provide CRT, the system needs at least three nodes placed in the RA, RV and LV. The RA node in this system may be placed in the right atrial appendage, while the RV node can be placed like commercially available leadless pacemakers (see Section 2.3), or it can be shaped like a patch and placed in the right ventricular septum for better activation pattern. The LV node can either be endocardial and placed through trans-septal puncture, or epicardial and placed through mini thoracotomy, thoracoscopy or subxiphoid puncture or traditional CS approach. Endocardial positions provide better activation patterns, epicardial electrodes are associated with lower embolic risks. Consequently, the size of the epicardial

LV node will not be of a great concern clinically, provided it does not damage the coronary circulation or the movement of the LV. Figure 6 shows one of several conceptional configuration of such system.

The ultimate objective is to participate in the development of capsule-like devices implantable in multiple cardiac locations. Such capsules will have sensing, pacing, communication, and intelligence capabilities able to collectively provide optimal cardiac rhythm management. Although in the relatively short term, nodes will be of electronic character, use of biologically modified cardiomyocytes may eventually provide the treatment of choice for cardiac rhythm management.

6 CONFLICTS OF INTEREST

Dr. Hans Henrik Odland reports personal fees from Abbot, grants from Medtronic, outside the submitted work. The other authors have nothing to disclose.

7 ACKNOWLEDGEMENT

This work was funded by the European Union's H2020: MSCA: ITN program for the "Wireless In-body Environment Communication – WiBEC" project under the grant agreement no. 675353.

8 REFERENCES

1. Abella B. and D. Edelson. Resuscitation errors: a shocking problem. WebM&M: Morbidity & Mortality Rounds on the Web. Rockville, MD: Agency for Healthcare Research and Quality 2007.
2. Abkenari L. D., D. A. Theuns, S. D. Valk, Y. Van Belle, N. M. de Groot, D. Haitsma, A. Muskens-Heemskerk, T. Szili-Torok and L. Jordaens. Clinical experience with a novel subcutaneous implantable defibrillator system in a single center. *Clinical Research in Cardiology* 100: 737-744, 2011.
3. Abraham W. T., W. G. Fisher, A. L. Smith, D. B. Delurgio, A. R. Leon, E. Loh, D. Z. Kocovic, M. Packer, A. L. Clavell and D. L. Hayes. Cardiac resynchronization in chronic heart failure. *New England Journal of Medicine* 346: 1845-1853, 2002.
4. Albatat M., D. R. King, L. A. Unger, H. Arevalo, S. Wall, J. Sundnes, J. Bergsland and I. Balasingham. Electromechanical Model to Predict Cardiac Resynchronization Therapy. *Conf Proc IEEE Eng Med Biol Soc* 2018: 5446-5459, 2018.
5. Albouaini K., A. Alkarmi, T. Mudawi, M. D. Gammage and D. J. Wright. Selective site right ventricular pacing. *Heart* 95: 2030-2039, 2009.
6. Alonso C., C. Leclercq, F. Victor, H. Mansour, C. de Place, D. Pavin, F. Carré, P. Mabo and J. C. Daubert. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. *The American journal of cardiology* 84: 1417-1421, 1999.
7. Ansalone G., P. Giannantoni, R. Ricci, P. Trambaiolo, F. Fedele and M. Santini. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *Journal of the American College of Cardiology* 39: 489-499, 2002.
8. Antoniadis A. P., B. Sieniewicz, J. Gould, B. Porter, J. Webb, S. Claridge, J. M. Behar and C. A. Rinaldi. Updates in Cardiac Resynchronization Therapy for Chronic Heart Failure: Review of Multisite Pacing. *Current heart failure reports* 14: 376-383, 2017.
9. Aoukar P. S., J. E. Poole, G. W. Johnson, R. J. Anderson, A. S. Hellkamp, D. B. Mark, K. L. Lee and G. H. Bardy. No benefit of a dual coil over a single coil ICD lead: evidence from the Sudden Cardiac Death in Heart Failure Trial. *Heart Rhythm* 10: 970-976, 2013.
10. Arevalo H. J., F. Vadakkumpadan, E. Guallar, A. Jebb, P. Malamas, K. C. Wu and N. A. Trayanova. Arrhythmia risk stratification of patients after myocardial infarction using personalized heart models. *Nature communications* 7: 2016.
11. Auricchio A., P.-P. Delnoy, F. Regoli, M. Seifert, T. Markou, C. Butter and C. S. Group. First-in-man implantation of leadless ultrasound-based cardiac stimulation pacing system: novel endocardial left ventricular resynchronization therapy in heart failure patients. *Europace* 15: 1191-1197, 2013.
12. Auricchio A., C. Fantoni, F. Regoli, C. Carbucicchio, A. Goette, C. Geller, M. Kloss and H. Klein. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. *Circulation* 109: 1133-1139, 2004.
13. Auricchio A., H. Klein, B. Tockman, S. Sack, C. Stellbrink, J. Neuzner, A. Kramer, J. Ding, T. Pochet and A. Maarse. Transvenous biventricular pacing for heart failure: can the obstacles be overcome? *The American journal of cardiology* 83: 136-142, 1999.
14. Auricchio A. and F. W. Prinzen. Non-responders to cardiac resynchronization therapy. *Circulation Journal* 75: 521-527, 2011.
15. Auricchio A., C. Stellbrink, M. Block, S. Sack, J. Vogt, P. Bakker, H. Klein, A. Kramer, J. Ding and R. Salo. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 99: 2993-3001, 1999.
16. Auricchio A., C. Stellbrink, C. Butter, S. Sack, J. Vogt, A. R. Misier, D. Böcker, M. Block, J. H. Kirkels and A. Kramer. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *Journal of the American College of Cardiology* 42: 2109-2116, 2003.
17. Auricchio A., C. Stellbrink, S. Sack, M. Block, J. ürgen Vogt, P. Bakker, C. Huth, F. Schöndube, U. Wolfhard and D. Böcker. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *Journal of the American College of Cardiology* 39: 2026-2033, 2002.
18. Awan M., S. Perez-Simbor, C. Garcia-Pardo, K. Kansanen and N. Cardona. Experimental Phantom-Based Security Analysis for Next-Generation Leadless Cardiac Pacemakers. *Sensors* 18: 4327, 2018.
19. Bailin S. J., S. Adler and M. Giudici. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. *Journal of cardiovascular electrophysiology* 12: 912-917, 2001.
20. Bakker P. F., H. W. Meijburg, J. W. de Vries, M. M. Mower, A. C. Thomas, M. L. Hull, E. O. R. de Medina and J. J. Bredée. Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. *Journal of Interventional Cardiac Electrophysiology* 4: 395-404, 2000.
21. Bardy G. H., G. L. Dolack, P. J. Kudenchuk, J. E. Poole, R. Mehra and G. Johnson. Prospective, randomized comparison in humans of a unipolar defibrillation system with that using an additional superior vena cava electrode. *Circulation* 89: 1090-1093, 1994.
22. Bardy G. H., W. M. Smith, M. A. Hood, I. G. Crozier, I. C. Melton, L. Jordaens, D. Theuns, R. E. Park, D. J. Wright and D. T. Connelly. An entirely subcutaneous implantable cardioverter–defibrillator. *New England Journal of Medicine* 363: 36-44, 2010.
23. Batra A. S. and S. Balaji. Post operative temporary epicardial pacing: When, how and why? Annals of pediatric cardiology 1: 120, 2008.

24. Bernstein A. D., J. C. DAUBERT, R. D. Fletcher, D. L. Hayes, B. LüDERITZ, D. W. Reynolds, M. H. Schoenfeld and R. Sutton. The Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-Rate, and Multisite Pacing. *Pacing and Clinical Electrophysiology* 25: 260-264, 2002.
25. Biffi M., C. Moschini, M. Bertini, D. Saporito, M. Ziacchi, I. Diemberger, C. Valzania, G. Domenichini, E. Cervi and C. Martignani. Phrenic Stimulation. *Circulation: Arrhythmia and Electrophysiology* 2: 402-410, 2009.
26. Blanc J.-J., V. Bertault-Valls, M. Fatemi, M. Gilard, P.-Y. Pennec and Y. Etienne. Midterm benefits of left univentricular pacing in patients with congestive heart failure. *Circulation* 109: 1741-1744, 2004.
27. Bleeker G. B., T. A. Kaandorp, H. J. Lamb, E. Boersma, P. Steendijk, A. de Roos, E. E. van der Wall, M. J. Schalij and J. J. Bax. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 113: 969-976, 2006.
28. Boink G. J., L. Duan, B. D. Nearing, I. N. Shlapakova, E. A. Sosunov, E. P. Anyukhovsky, E. Bobkov, Y. Kryukova, N. Ozgen and P. Danilo. HCN2/SkM1 gene transfer into canine left bundle branch induces stable, autonomically responsive biological pacing at physiological heart rates. *Journal of the American College of Cardiology* 61: 1192-1201, 2013.
29. Bordachar P., N. Derval, S. Ploux, S. Garrigue, P. Ritter, M. Haissaguerre and P. Jaïs. Left ventricular endocardial stimulation for severe heart failure. *Journal of the American College of Cardiology* 56: 747-753, 2010.
30. Bose P., A. Khaleghi, M. Albatat, J. Bergsland and I. Balasingham. RF channel modeling for implant-to-implant communication and implant to subcutaneous implant communication for future leadless cardiac pacemakers. *IEEE Transactions on Biomedical Engineering* 65: 2798-2807, 2018.
31. Bose P., A. Khaleghi and I. Balasingham. Wireless Channel Modeling for Leadless Cardiac Pacemaker: Effects ofVentricular Blood Volume. In: *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*IEEE, 2018, p. 3746-3749.
32. Brandt N. H., R. E. Kirkfeldt, J. C. Nielsen, L. S. Mortensen, G. V. H. Jensen, J. B. Johansen and K. Haugan. Single lead atrial vs. dual chamber pacing in sick sinus syndrome: extended register-based follow-up in the DANPACE trial. *EP Europace* 19: 1981-1987, 2016.
33. Brignole M., A. Auricchio, G. Baron-Esquivias, P. Bordachar, G. Boriani, O.-A. Breithardt, J. Cleland, J.-C. Deharo, V. Delgado and P. M. Elliott. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Revista española de cardiología-English Edition* 67: 58e51-58e60, 2014.
34. Bristow M. Comparison of medical resynchronization and defibrillation therapies in heart failure (COMPANION) trial. *Bethesda, Md.: American College of Cardiology* 2003.
35. Brunner M. P., E. M. Cronin, O. Wazni, B. Baranowski, W. I. Saliba, J. F. Sabik, B. D. Lindsay, B. L. Wilkoff and K. G. Tarakji. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. *Heart Rhythm* 11: 419-425, 2014.
36. Burke M. C., M. R. Gold, B. P. Knight, C. S. Barr, D. A. Theuns, L. V. Boersma, R. E. Knops, R. Weiss, A. R. Leon and J. M. Herre. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE Study and EFFORTLESS Registry. *Journal of the American College of Cardiology* 65: 1605-1615, 2015.
37. Butter C., A. Auricchio, C. Stellbrink, E. Fleck, J. Ding, Y. Yu, E. Huvelle and J. Spinelli. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 104: 3026-3029, 2001.
38. Butter C., A. Auricchio, C. Stellbrink, M. Schlegl, E. Fleck, W. Hörsch, E. Huvelle, J. Ding, A. Kramer and P. T. i. C. H. F. I. S. Group. Should stimulation site be tailored in the individual heart failure patient? *The American journal of cardiology* 86: K144-K151, 2000.
39. Cappato R., S. Castelvecchio, P. Erlinger, R. Sanghera, D. Scheck, A. Ostroff, W. Rissmann, C. Gropper and G. H. Bardy. Feasibility of defibrillation and automatic arrhythmia detection using an exclusively subcutaneous defibrillator system in canines. *Journal of cardiovascular electrophysiology* 24: 77-82, 2013.
40. Cazeau S., P. Ritter, S. Bakdach, A. Lazarus, M. Limousin, L. Henao, O. Mundler, J. Daubert and J. Mugica. Four chamber pacing in dilated cardiomyopathy. *Pacing and Clinical Electrophysiology* 17: 1974-1979, 1994.
41. Chalil S., B. Stegemann, S. Muhyaldeen, K. Khadjooi, P. Foley, R. Smith and F. Leyva. Effect of posterolateral left ventricular scar on mortality and morbidity following cardiac resynchronization therapy. *Pacing and Clinical Electrophysiology* 30: 1201-1209, 2007.
42. Chung E. S., A. R. Leon, L. Tavazzi, J.-P. Sun, P. Nihoyannopoulos, J. Merlino, W. T. Abraham, S. Ghio, C. Leclercq and J. J. Bax. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 117: 2608-2616, 2008.
43. Cicchitti V., F. Radico, F. Bianco, S. Gallina, G. Tonti and R. De Caterina. Heart failure due to right ventricular apical pacing: the importance of flow patterns. *EP Europace* 18: 1679-1688, 2016.
44. Cleland J. G., J.-C. Daubert, E. Erdmann, N. Freemantle, D. Gras, L. Kappenberger and L. Tavazzi. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine* 352: 1539-1549, 2005.
45. Daoud E. G., S. J. Kalbfleisch, J. D. Hummel, R. Weiss, R. S. Augustini, S. B. Duff, G. Polsinelli, J. Castor and T. Meta. Implantation Techniques and Chronic Lead Parameters of Biventricular Pacing Dual-Chamber Defibrillators. *Journal of cardiovascular electrophysiology* 13: 964-970, 2002.
46. Daubert J.-C., D. Pavin, G. Jauvert and P. Mabo. Intra-and interatrial conduction delay: Implications for cardiac pacing. *Pacing and Clinical Electrophysiology* 27: 507-525, 2004.
47. Daubert J. P., W. Zareba, D. S. Cannom, S. McNitt, S. Z. Rosero, P. Wang, C. Schuger, J. S. Steinberg, S. L. Higgins and D. J. Wilber. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *Journal of the American College of Cardiology* 51: 1357-1365, 2008.
48. De Maria E., D. Giacopelli, A. Borghi, L. Modonesi and S. Cappelli. Antitachycardia pacing programming in implantable cardioverter defibrillator: A systematic review. *World journal of cardiology* 9: 429, 2017.
49. De Maria E., A. Olaru and S. Cappelli. The entirely subcutaneous defibrillator (S-ICD): state of the art and selection of the ideal candidate. *Current cardiology reviews* 11: 180-186, 2015.
50. Dekker A., B. Phelps, B. Dijkman, T. van Der Nagel, F. van Der Veen, G. Geskes and J. Maessen. Epicardial left ventricular lead placement for cardiac resynchronization therapy: optimal pace site selection with pressure-volume loops. *The Journal of thoracic and cardiovascular surgery* 127: 1641-1647, 2004.
51. Delfaut P., S. Saksena, A. Prakash and R. B. Krol. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single-and dual-site right atrial pacing for arrhythmia prevention. *Journal of the American College of Cardiology* 32: 1900-1908, 1998.
52. Delgado V., R. J. van Bommel, M. Bertini, C. J. W. Borleffs, N. A. Marsan, A. C. Ng, G. Nucifora, N. R. van de Veire, C. Ypenburg and E. Boersma. Relative Merits of Left Ventricular Dyssynchrony, Left Ventricular Lead Position, and Myocardial Scar to Predict Long-Term Survival of Ischemic Heart Failure Patients Undergoing Cardiac Resynchronization TherapyClinical Perspective. *Circulation* 123: 70-78, 2011.
53. Derval N., P. Steendijk, L. J. Gula, A. Deplagne, J. Laborderie, F. Sacher, S. Knecht, M. Wright, I. Nault and S. Ploux.

Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. *Journal of the American College of Cardiology* 55: 566-575, 2010.
54. Deshmukh P., D. A. Casavant, M. Romanyshyn and K. Anderson. Permanent, Direct His-Bundle Pacing A Novel Approach to Cardiac Pacing in Patients With Normal His-Purkinje Activation. *Circulation* 101: 869-877, 2000.
55. Deshmukh P. M. and M. Romanyshyn. Direct His-Bundle Pacing. *Pacing and Clinical Electrophysiology* 27: 862-870, 2004.
56. Echt D., D. Moore, M. Cowan, V. Valli, J. Whitehair and N. Willis. Chronic implantation of leadless pacing electrodes in the left ventricle of a goat model. *Heart Rhythm* 7: S451-452, 2010.
57. Echt D. S., M. W. Cowan, R. E. Riley and A. F. Brisken. Feasibility and safety of a novel technology for pacing without leads. *Heart Rhythm* 3: 1202-1206, 2006.
58. El Gamal M. Atrial pacing, the forgotten pacing mode. *Netherlands Heart Journal* 16: 23-26, 2008.
59. Europace. Cardiovascular Diseases Statistics. [Electronic Article].Date accessed: 15/01/2017. Available: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics#Further_Eurostat_information
60. Ezekowitz J. A., P. W. Armstrong and F. A. McAlister. Implantable Cardioverter Defibrillators in Primary and Secondary PreventionA Systematic Review of Randomized, Controlled Trials. *Annals of internal medicine* 138: 445-452, 2003.
61. Fishman G. I., S. S. Chugh, J. P. DiMarco, C. M. Albert, M. E. Anderson, R. O. Bonow, A. E. Buxton, P.-S. Chen, M. Estes and X. Jouven. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 122: 2335-2348, 2010.
62. Foley P. W., S. Chalil, K. Ratib, R. Smith, F. Prinzen, A. Auricchio and F. Leyva. Fluoroscopic Left Ventricular Lead Position and the Long-Term Clinical Outcome of Cardiac Resynchronization Therapy. *Pacing and Clinical Electrophysiology* 34: 785-797, 2011.
63. Frias P. A., J. S. Corvera, L. Schmarkey, M. Strieper, R. M. Campbell and J. VINTEN-JOHANSEN. Evaluation of Myocardial Performance with Conventional Single-Site Ventricular Pacing and Biventricular Pacing in a Canine Model of Atrioventricular Block. *Journal of cardiovascular electrophysiology* 14: 996-1000, 2003.
64. Fung J. W., J. Y. Chan, G. W. Yip, H. C. Chan, W. W. Chan, Q. Zhang and C.-M. Yu. Effect of left ventricular endocardial activation pattern on echocardiographic and clinical response to cardiac resynchronization therapy. *Heart* 93: 432-437, 2007.
65. Fung J. W., C. Yu, G. Yip, Y. Zhang, H. Chan, C. Kum and J. Sanderson. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. *Heart* 90: 17-19, 2004.
66. Garrigue S., P. Jaïs, G. Espil, J.-N. Labeque, M. Hocini, D. C. Shah, M. Haïssaguerre and J. Clementy. Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure. *The American journal of cardiology* 88: 858-862, 2001.
67. Gasparini M., M. Mantica, P. Galimberti, M. Bocciolone, L. Genovese, M. Mangiavacchi, U. La Marchesina, F. Faletra, C. Klersy and R. Coates. Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy? *Pacing and Clinical Electrophysiology* 26: 162-168, 2003.
68. Gillis A. M., A. M. Russo, K. A. Ellenbogen, C. D. Swerdlow, B. Olshansky, S. M. Al-Khatib, J. F. Beshai, J. M. McComb, J. C. Nielsen and J. M. Philpott. HRS/ACCF expert consensus statement on pacemaker device and mode selection. *Journal of the American College of Cardiology* 60: 682-703, 2012.
69. Ginks M. R., P. D. Lambiase, S. G. Duckett, J. Bostock, P. Chinchapatnam, K. Rhode, M. J. McPhail, M. Simon, C. Bucknall and G. Carr-White. A Simultaneous X-Ray/MRI and Noncontact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in HumansClinical Perspective. *Circulation: Heart Failure* 4: 170-179, 2011.
70. Ginks M. R., A. K. Shetty, P. D. Lambiase, S. G. Duckett, J. Bostock, J. L. Peacock, K. S. Rhode, C. Bucknall, J. Gill and P. Taggart. Benefits of Endocardial and Multisite Pacing Are Dependent on the Type of Left Ventricular Electric Activation Pattern and Presence of Ischemic Heart Disease Insights from Electroanatomic Mapping. *Circulation: Arrhythmia and Electrophysiology* 5: 889-897, 2012.
71. Gold M. R., M. R. Olsovsky, M. A. Pelini, R. W. Peters and S. R. Shorofsky. Comparison of single-and dual-coil active pectoral defibrillation lead systems. *Journal of the American College of Cardiology* 31: 1391-1394, 1998.
72. Gold M. R. and S. R. Shorofsky. Transvenous defibrillation lead systems. *Journal of cardiovascular electrophysiology* 7: 570-580, 1996.
73. Gold M. R., D. A. Theuns, B. P. Knight, J. STURDIVANT, R. Sanghera, K. A. Ellenbogen, M. A. Wood and M. C. Burke. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *Journal of cardiovascular electrophysiology* 23: 359-366, 2012.
74. Goto H., T. Sugiura, Y. Harada and T. Kazui. Feasibility of using the automatic generating system for quartz watches as a leadless pacemaker power source. *Medical & biological engineering & computing* 37: 377-380, 1999.
75. Hammill S. C., D. L. Packer, M. S. Stanton and J. Fetter. Termination and acceleration of ventricular tachycardia with autodecremental pacing, burst pacing, and cardioversion in patients with an implantable cardioverter defibrillator. *Pacing and Clinical Electrophysiology* 18: 3-18, 1995.
76. Hauser R. G. The growing mismatch between patient longevity and the service life of implantable cardioverter-defibrillators. *Journal of the American College of Cardiology* 45: 2022-2025, 2005.
77. Hauser R. G., D. L. Hayes, L. M. Kallinen, D. S. Cannom, A. E. Epstein, A. K. Almquist, S. L. Song, G. F. O. Tyers, S. C. Vlay and M. Irwin. Clinical experience with pacemaker pulse generators and transvenous leads: an 8-year prospective multicenter study. *Heart Rhythm* 4: 154-160, 2007.
78. Hauser R. G., W. T. Katsiyiannis, C. C. Gornick, A. K. Almquist and L. M. Kallinen. Deaths and cardiovascular injuries due to device-assisted implantable cardioverter–defibrillator and pacemaker lead extraction. *Europace* 12: 395-401, 2010.
79. Hu Y.-F., J. F. Dawkins, H. C. Cho, E. Marbán and E. Cingolani. Biological pacemaker created by minimally invasive somatic reprogramming in pigs with complete heart block. *Science translational medicine* 6: 245ra294-245ra294, 2014.
80. Hu Y., V. Gurev, J. Constantino and N. Trayanova. Optimizing cardiac resynchronization therapy to minimize ATP consumption heterogeneity throughout the left ventricle: a simulation analysis using a canine heart failure model. *Heart Rhythm* 11: 1063-1069, 2014.
81. Huikuri H., A. Castellanos, R. Myerburg, B. Pitt, F. Zannad and W. Remme. Sudden death duo to cardiac arrhythmias. *Response to a letter New Engl J Med* 346: 946-947, 2002.
82. Huntjens P. R., J. Walmsley, S. Ploux, P. Bordachar, F. W. Prinzen, T. Delhaas and J. Lumens. Influence of left ventricular lead position relative to scar location on response to cardiac resynchronization therapy: a model study. *Europace* 16: iv62-iv68, 2014.
83. Izutani H., K. J. Quan, L. A. Biblo and I. S. Gill. Biventricular pacing for congestive heart failure: early experience in surgical

epicardial versus coronary sinus lead placement. In: *Heart Surg Forum*2002, p. E1-6.
84. Jackson T., R. Lenarczyk, M. Sterlinski, A. Sokal, D. Francis, Z. Whinnett, F. Van Heuverswyn, M. Vanderheyden, J. Heynens and B. Stegemann. Left ventricular scar and the acute hemodynamic effects of multivein and multipolar pacing in cardiac resynchronization. *IJC Heart & Vasculature* 19: 14-19, 2018.
85. Jais P., H. Douard, D. C. Shah, S. Barold, J. L. BARAT and J. Clementy. Endocardial biventricular pacing. *Pacing and Clinical Electrophysiology* 21: 2128-2131, 1998.
86. Jensen P. N., N. N. Gronroos, L. Y. Chen, A. R. Folsom, S. R. Heckbert and A. Alonso. Incidence of and risk factors for sick sinus syndrome in the general population. *Journal of the American College of Cardiology* 64: 531-538, 2014.
87. Kamphuis H., J. De Leeuw, R. Derksen, R. Hauer and J. Winnubst. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery. *Europace* 5: 381-389, 2003.
88. Kansanen K. Wirless in-Body Environment. 2017.
89. Karami M. A., D. J. Bradley and D. J. Inman. Vibration powered cardiac rhythm devices. *Circulation* 126: A15551-A15551, 2012.
90. Kaye G. C., N. J. Linker, T. H. Marwick, L. Pollock, L. Graham, E. Pouliot, J. Poloniecki and M. Gammage. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *Eur Heart J* 36: 856-862, 2015.
91. Khan F. Z., M. S. Virdee, S. P. Fynn and D. P. Dutka. Left ventricular lead placement in cardiac resynchronization therapy: where and how? *Europace* 11: 554-561, 2009.
92. Khan F. Z., M. S. Virdee, C. R. Palmer, P. J. Pugh, D. O'Halloran, M. Elsik, P. A. Read, D. Begley, S. P. Fynn and D. P. Dutka. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *Journal of the American College of Cardiology* 59: 1509-1518, 2012.
93. Kirkfeldt R. E., J. B. Johansen, E. A. Nohr, O. D. Jørgensen and J. C. Nielsen. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *European heart journal* 35: 1186-1194, 2013.
94. Kirkfeldt R. E., J. B. Johansen, E. A. Nohr, M. Moller, P. Arnsbo and J. C. Nielsen. Risk factors for lead complications in cardiac pacing: a population-based cohort study of 28,860 Danish patients. *Heart Rhythm* 8: 1622-1628, 2011.
95. Kiviniemi M. S., M. A. Pirnes, H. J. K. ErÄNen, R. V. J. Kettunen and J. E. K. Hartikainen. Complications Related to Permanent Pacemaker Therapy. *Pacing and Clinical Electrophysiology* 22: 711-720, 1999.
96. Kleemann T., T. Becker, K. Doenges, M. Vater, J. Senges, S. Schneider, W. Saggau, U. Weisse and K. Seidl. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of> 10 years. *Circulation* 115: 2474-2480, 2007.
97. Klug D., M. Balde, D. Pavin, F. Hidden-Lucet, J. Clementy, N. Sadoul, J. L. Rey, G. Lande, A. Lazarus and J. Victor. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators. *Circulation* 116: 1349-1355, 2007.
98. Kremers M. S., S. C. Hammill, C. I. Berul, C. Koutras, J. S. Curtis, Y. Wang, J. Beachy, L. B. Meisnere, d. M. Conyers and M. R. Reynolds. The National ICD Registry Report. *Heart Rhythm* 10: 2013.
99. Laish-Farkash A., S. Bruoha, V. Khalameizer, C. Yosefy, Y. Michowitz, M. Suleiman and A. Katz. Multisite cardiac resynchronization therapy for traditional and non-traditional indications. *Journal of Interventional Cardiac Electrophysiology* 51: 143-152, 2018.
100. Lakkireddy D., R. Knops, B. Atwater, P. Neuzil, J. Ip, E. Gonzalez, P. Friedman, P. Defaye, D. Exner, K. Aonuma, R. Doshi, J. Sperzel and V. Reddy. A worldwide experience of the management of battery failures and chronic device retrieval of the Nanostim leadless pacemaker. *Heart Rhythm* 14: 1756-1763, 2017.
101. Lambiase P., A. Rinaldi, J. Hauck, M. Mobb, D. Elliott, J. Gill and C. Bucknall. Areas of Slow Conduction in Biventricular Pacing. A non-contact left ventricular endocardial mapping study. *Heart* 90: 44-51, 2004.
102. Leclercq C., S. Cazeau, H. Le Breton, P. Ritter, P. Mabo, D. Gras, D. Pavin, A. Lazarus and J.-C. Daubert. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. *Journal of the American College of Cardiology* 32: 1825-1831, 1998.
103. Leclercq C., F. Gadler, W. Kranig, S. Ellery, D. Gras, A. Lazarus, J. Clémenty, E. Boulogne, J.-C. Daubert and T.-H. S. Group. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *Journal of the American College of Cardiology* 51: 1455-1462, 2008.
104. Leclercq F., F.-X. Hager, J.-C. Macia, C.-J. Mariottini, J.-L. Pasquie and R. Grolleau. Left Ventricular Lead Insertion Using a Modified Transseptal Catheterization Technique: A Totally Endocardial Approach for Permanent Biventricular Pacing in End-Stage Heart Failure. *Pacing and Clinical Electrophysiology* 22: 1570-1575, 1999.
105. Lee A. W. C., C. M. Costa, M. Strocchi, C. A. Rinaldi and S. A. Niederer. Computational Modeling for Cardiac Resynchronization Therapy. *J Cardiovasc Transl Res* 11: 92-108, 2018.
106. Lenarczyk R., O. Kowalski, B. Sredniawa, P. Pruszkowska-Skrzep, M. Mazurek, E. Jedrzejczyk-Patej, A. Woźniak, S. Pluta, J. Głowacki and Z. Kalarus. Implantation Feasibility, Procedure-Related Adverse Events and Lead Performance During 1-Year Follow-Up in Patients Undergoing Triple-Site Cardiac Resynchronization Therapy: A Substudy of TRUST CRT Randomized Trial. *Journal of cardiovascular electrophysiology* 23: 1228-1236, 2012.
107. León A. R., W. T. Abraham, A. B. Curtis, J. P. Daubert, W. G. Fisher, J. Gurley, D. L. Hayes, R. Lieberman, S. Petersen-Stejskal and K. Wheelan. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *Journal of the American College of Cardiology* 46: 2348-2356, 2005.
108. Levine P. and C. Love. Pacemaker diagnostics and evaluation of pacing system malfunction. In: *Clinical Cardiac Pacing and Defibrillation*, edited by K. Ellenbogen, G. Kay, C. Lau and B. Wilkoff. Philadelphia, Pa: WB Saunders, 2000, pp. 827-875.
109. Lovelock J. D., C. Cruz, M. H. Hoskins, P. Jones, M. F. El-Chami, M. S. Lloyd, A. Leon, D. B. DeLurgio and J. J. Langberg. Generator replacement is associated with an increased rate of ICD lead alerts. *Heart Rhythm* 11: 1785-1789, 2014.
110. Lown B. Defibrillation and cardioversion. Elsevier Science, 2002.
111. Lu P., M. Veletić, J. Bergsland and I. Balasingham. On the intracellular signaling of cardiomyocytes for energy efficient leadless pacemakers. In: *Proceedings of the 5th ACM International Conference on Nanoscale Computing and Communication*ACM, 2018, p. 31.
112. Mair H., J.-L. Jansens, O. M. Lattouf, B. Reichart and S. Dabritz. Epicardial lead implantation techniques for biventricular pacing via left lateral mini-thoracotomy, video-assisted thoracoscopy, and robotic approach. *Heart Surgery Forum* 6: 412-417, 2003.
113. Mair H., J. Sachweh, B. Meuris, G. Nollert, M. Schmoeckel, A. Schuetz, B. Reichart and S. Daebritz. Surgical epicardial left ventricular lead versus coronary sinus lead placement in biventricular pacing. *European journal of cardio-thoracic surgery* 27: 235-242, 2005.
114. Marieb E. N. and K. Hoehn. *Human anatomy & physiology*. Pearson Education, 2007.

115. Martin D. O., B. Lemke, D. Birnie, H. Krum, K. L.-F. Lee, K. Aonuma, M. Gasparini, R. C. Starling, G. Milasinovic and T. Rogers. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm* 9: 1807-1814. e1801, 2012.
116. McAnulty J., B. Halperin, J. Kron, G. Larsen, M. Rait, R. Swenson, R. Floreck, C. Marchant, M. Hamlin and G. Heywood. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *New England Journal of Medicine* 337: 1576-1583, 1997.
117. Mehta P. A., A. K. Shetty, M. Squirrel, J. Bostock and C. A. Rinaldi. Elimination of phrenic nerve stimulation occurring during CRT. *Journal of Interventional Cardiac Electrophysiology* 33: 43-49, 2012.
118. Members A. T. F., M. Brignole, A. Auricchio, G. Baron-Esquivias, P. Bordachar, G. Boriani, O.-A. Breithardt, J. Cleland, J.-C. Deharo and V. Delgado. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *European heart journal* 34: 2281-2329, 2013.
119. Miller M. A., P. Neuzil, S. R. Dukkipati and V. Y. Reddy. Leadless cardiac pacemakers: back to the future. *Journal of the American College of Cardiology* 66: 1179-1189, 2015.
120. Mills R. W., R. N. Cornelussen, L. J. Mulligan, M. Strik, L. M. Rademakers, N. D. Skadsberg, A. van Hunnik, M. Kuiper, A. Lampert and T. Delhaas. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. *Circulation: Arrhythmia and Electrophysiology* 2: 571-579, 2009.
121. Mirowski M., P. R. Reid, M. M. Mower, L. Watkins, V. L. Gott, J. F. Schauble, A. Langer, M. Heilman, S. A. Kolenik and R. E. Fischell. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *New England Journal of Medicine* 303: 322-324, 1980.
122. Molhoek S. G., J. J. Bax, L. van Erven, M. Bootsma, E. Boersma, P. Steendijk, E. E. van der Wall and M. J. Schalij. Effectiveness of resynchronization therapy in patients with end-stage heart failure. *The American journal of cardiology* 90: 379-383, 2002.
123. Moss A. J., W. J. Hall, D. S. Cannom, J. P. Daubert, S. L. Higgins, H. Klein, J. H. Levine, S. Saksena, A. L. Waldo and D. Wilber. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *New England Journal of Medicine* 335: 1933-1940, 1996.
124. Murphy R. T., G. Sigurdsson, S. Mulamalla, D. Agler, Z. B. Popovic, R. C. Starling, B. L. Wilkoff, J. D. Thomas and R. A. Grimm. Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy. *The American journal of cardiology* 97: 1615-1621, 2006.
125. Nadurata V., A. Hamer and P. Kertes. Optimizing the site of the right ventricular lead in cardiac resynchronization devices. *Heart Lung Circ* S5, 2004.
126. Niederer S. A., J. Lumens and N. A. J. N. R. C. Trayanova. Computational models in cardiology. 1, 2018.
127. Niederer S. A., A. Shetty, G. Plank, J. Bostock, R. Razavi, N. Smith and C. Rinaldi. Biophysical modeling to simulate the response to multisite left ventricular stimulation using a quadripolar pacing lead. *Pacing and Clinical Electrophysiology* 35: 204-214, 2012.
128. Nordkamp L. R. O., A. A. Wilde, J. G. Tijssen, R. E. Knops, P. F. van Dessel and J. R. de Groot. The ICD for primary prevention in patients with inherited cardiac diseases: indications, utilization and outcome. a comparison with secondary prevention. *Circulation: Arrhythmia and Electrophysiology* CIRCEP. 112.975268, 2012.
129. Noro M., X. Zhu, Y. Enomoto, Y. Oikawa, H. Tatsunami, R. Ishii, Y. Toyoda, M. Asami, N. Sahara and T. Takagi. Decreased defibrillation threshold and minimized myocardial damage with left axilla implantable cardioverter defibrillator implantation. *Circulation Journal* 80: 878-886, 2016.
130. Ogano M., Y.-k. Iwasaki, J. Tanabe, H. Takagi, T. Umemoto, M. Hayashi, Y. Miyauchi and K. Mizuno. Antiarrhythmic effect of cardiac resynchronization therapy with triple-site biventricular stimulation. *Europace* 15: 1491-1498, 2013.
131. Olde Nordkamp L. R., J. L. Warnaars, K. M. Kooiman, J. R. Groot, B. R. Rosenmoeller, A. A. Wilde and R. E. Knops. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. *Journal of cardiovascular electrophysiology* 25: 494-499, 2014.
132. P. J., A. Takahashi, S. Garrigue, T. Yamane, M. Hocini, D. C. Shah, S. S. Barold, I. Deisenhofer and M. H. A. J. Clémenty. Mid-term Follow-Up of Endocardial Biventricular Pacing. *Pacing and Clinical Electrophysiology* 23: 1744-1747, 2000.
133. Padeletti L., A. Colella, A. Michelucci, P. Pieragnoli, G. Ricciardi, M. C. Porciani, F. Tronconi, D. A. Hettrick and S. Valsecchi. Dual-site left ventricular cardiac resynchronization therapy. *The American journal of cardiology* 102: 1687-1692, 2008.
134. Padeletti L., P. Pieragnoli, C. Ciapetti, A. Colella, N. Musilli, M. C. Porciani, R. Ricci, C. Pignalberi, M. Santini and A. Puglisi. Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. *American heart journal* 142: 1047-1055, 2001.
135. Pappone C., S. Rosanio, G. Oreto, M. Tocchi, S. Gulletta, A. Salvati, C. Dicandia, V. Santinelli, P. Mazzone and F. Veglia. Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization. *Italian heart journal: official journal of the Italian Federation of Cardiology* 1: 464-469, 2000.
136. Pavia S. and B. Wilkoff. The management of surgical complications of pacemaker and implantable cardioverter-defibrillators. *Current opinion in cardiology* 16: 66-71, 2001.
137. Petch M. Who needs dual chamber pacing? *BMJ: British Medical Journal* 307: 215, 1993.
138. Polewczyk A., W. Jacheć, A. Tomaszewski, W. Brzozowski, M. Czajkowski, G. Opolski, M. Grabowski, M. Janion and A. Kutarski. Lead-related infective endocarditis: factors influencing early and long-term survival in patients undergoing transvenous lead extraction. *Heart Rhythm* 14: 43-49, 2017.
139. Poole J. E., G. W. Johnson, A. S. Hellkamp, J. Anderson, D. J. Callans, M. H. Raitt, R. K. Reddy, F. E. Marchlinski, R. Yee and T. Guarnieri. Prognostic importance of defibrillator shocks in patients with heart failure. *New England Journal of Medicine* 359: 1009-1017, 2008.
140. Prakash A., S. Saksena, M. Hill, R. B. Krol, A. N. Munsif, I. Giorgberidze, P. Mathew and R. Mehra. Acute effects of dual-site right atrial pacing in patients with spontaneous and inducible atrial flutter and fibrillation. *Journal of the American College of Cardiology* 29: 1007-1014, 1997.
141. Priori S. G., C. Blomström-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, P. M. Elliott, D. Fitzsimons, R. Hatala and G. Hindricks. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Europace* euv319, 2015.
142. R. D. a. G., D. Pavin, C. Leclercq, J. E. Ecke, G. Jauvert, P. Mabo and J. C. Daubert. Long-Term Effects of Biatrial Synchronous Pacing to Prevent Drug-Refractory Atrial Tachyarrhythmia: A Nine-Year Experience. *Journal of cardiovascular electrophysiology* 11: 1081-1091, 2000.
143. Ramzan M., X. Fang, Q. Wang, N. Neumann and D. Plettemeier. Miniaturized Planar Implanted Spiral Antenna Inside the Heart Muscle at MICS Band for Future Leadless Pacemakers. In: *2019 13th International Symposium on Medical Information and Communication Technology (ISMICT)*IEEE, 2019, p. 1-4.

144. Ray S., M. Griffith, S. Jamieson, R. Bexton and R. Gold. Impact of the recommendations of the British Pacing and Electrophysiology Group on pacemaker prescription and on the immediate costs of pacing in the Northern Region. *British heart journal* 68: 531-534, 1992.
145. Reddy V. Y., M. A. Miller, P. Neuzil, P. Søgaard, C. Butter, M. Seifert, P. P. Delnoy, L. van Erven, M. Schalji and L. V. Boersma. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: the SELECT-LV study. *Journal of the American College of Cardiology* 69: 2119-2129, 2017.
146. Riedlbauchová L., R. Ĉihaák, J. Bytešník, V. Vanĉura, P. Frídl, L. Hoškovaá and J. Kautzner. Optimization of right ventricular lead position in cardiac resynchronisation therapy☆. *European journal of heart failure* 8: 609-614, 2006.
147. RINALDI C., R. D. Simon, P. Geelen, S. Reek, A. Baszko, M. Kuehl and J. S. Gill. A randomized prospective study of single coil versus dual coil defibrillation in patients with ventricular arrhythmias undergoing implantable cardioverter defibrillator therapy. *Pacing and Clinical Electrophysiology* 26: 1684-1690, 2003.
148. Rizzo G., V. Loyau, R. Nocua, J. C. Lourme and E. Lefeuvre. Potentiality of magnetoelectric composites for Wireless Power Transmission in medical implants. In: *2019 13th International Symposium on Medical Information and Communication Technology (ISMICT)*IEEE, 2019, p. 1-4.
149. RODRIGUEZ L., C. Timmermans, A. Nabar, G. Beatty and H. J. Wellens. Variable patterns of septal activation in patients with left bundle branch block and heart failure. *Journal of cardiovascular electrophysiology* 14: 135-141, 2003.
150. Rosen M. R., R. B. Robinson, P. R. Brink and I. S. Cohen. The road to biological pacing. *Nature Reviews Cardiology* 8: 656-666, 2011.
151. Savarese G. and L. H. Lund. Global public health burden of heart failure. *Cardiac failure review* 3: 7, 2017.
152. Saxon L. A., D. L. Hayes, F. R. Gilliam, P. A. Heidenreich, J. Day, M. Seth, T. E. Meyer, P. W. Jones and J. P. Boehmer. Long-Term outcome after ICD and CRT implantation and influence of remote device follow-up The ALTITUDE survival study. *Circulation* 122: 2359-2367, 2010.
153. Saxon L. A., B. Olshansky, K. Volosin, J. S. Steinberg, B. K. Lee, G. Tomassoni, T. Guarnieri, A. Rao, P. Yong and E. Galle. Influence of left ventricular lead location on outcomes in the COMPANION study. *Journal of cardiovascular electrophysiology* 20: 764-768, 2009.
154. Schulte B., J. Sperzel, J. Carlsson, T. Schwarz, W. Ehrlich, H. Pitschner and J. Neuzner. Dual-coil vs single-coil active pectoral implantable defibrillator lead systems: defibrillation energy requirements and probability of defibrillation success at multiples of the defibrillation energy requirements. *Europace* 3: 177-180, 2001.
155. Scientific B. CRM Product Performance report. August 2016. Bostonscientific.com: 2016.
156. Scientific B. EMBLEM™ MRI S-ICD System. Implant procedures. 2017.
157. Sermesant M., R. Chabiniok, P. Chinchapatnam, T. Mansi, F. Billet, P. Moireau, J.-M. Peyrat, K. Wong, J. Relan and K. Rhode. Patient-specific electromechanical models of the heart for the prediction of pacing acute effects in CRT: a preliminary clinical validation. *Medical image analysis* 16: 201-215, 2012.
158. Shepard R. K. and K. A. Ellenbogen. Challenges and solutions for difficult implantations of CRT devices: the role of new technology and techniques. *Journal of Cardiovascular Electrophysiology* 18: S21-S25, 2007.
159. Shimony A., M. J. Eisenberg, K. B. Filion and G. Amit. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace* 14: 81-91, 2011.
160. Singh J. P., H. U. Klein, D. T. Huang, S. Reek, M. Kuniss, A. Quesada, A. Barsheshet, D. Cannom, I. Goldenberg, S. McNitt, J. P. Daubert, W. Zareba and A. J. Moss. Left Ventricular Lead Position and Clinical Outcome in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) Trial. *Circulation* 123: 1159-1166, 2011.
161. Sohail M. R., D. Z. Uslan, A. H. Khan, P. A. Friedman, D. L. Hayes, W. R. Wilson, J. M. Steckelberg, S. M. Stoner and L. M. Baddour. Risk Factor Analysis of Permanent Pacemaker Infection. *Clinical Infectious Diseases* 45: 166-173, 2007.
162. Spickler J. W., N. S. Rasor, P. Kezdi, S. Misra, K. Robins and C. LeBoeuf. Totally self-contained intracardiac pacemaker. *Journal of electrocardiology* 3: 325-331, 1970.
163. Spragg D. D., J. Dong, B. J. Fetics, R. Helm, J. E. Marine, A. Cheng, C. A. Henrikson, D. A. Kass and R. D. Berger. Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. *Journal of the American College of Cardiology* 56: 774-781, 2010.
164. Sterliński M., A. Sokal, R. Lenarczyk, F. Van Heuverswyn, C. A. Rinaldi, M. Vanderheyden, V. Khalameizer, D. Francis, J. Heynens and B. Stegemann. In heart failure patients with left bundle branch block single lead multispot left ventricular pacing does not improve acute hemodynamic response to conventional biventricular pacing. A multicenter prospective, interventional, non-randomized study. *PloS one* 11: e0154024, 2016.
165. Stockburger M., R. Bartels, L. Gerhardt and C. Butter. Dual-Site Right Atrial Pacing Increases Left Atrial Appendage Flow in Patients with Sick Sinus Syndrome and Paroxysmal Atrial Fibrillation. *Pacing and Clinical Electrophysiology* 30: 20-27, 2007.
166. Stockburger M., S. Boveda, J. Moreno, A. Da Costa, R. Hatala, J. Brachmann, C. Butter, J. Garcia Seara, M. Rolando and P. Defaye. Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population. *European heart journal* 36: 151-157, 2014.
167. Sweeney M. O., A. S. Hellkamp, K. A. Ellenbogen, A. J. Greenspon, R. A. Freedman, K. L. Lee and G. A. Lamas. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 107: 2932-2937, 2003.
168. Swerdlow C. D., S. Davie, R. M. Kass, P.-S. Chen, C. Hwang, W. J. Mandel, E. S. Gang, S. Raissi and C. T. Peter. Optimal electrode configuration for pectoral transvenous intplantable defibrillator without an active can. *The American journal of cardiology* 76: 370-374, 1995.
169. Thambo J.-B., P. Bordachar, S. Garrigue, S. Lafitte, P. Sanders, S. Reuter, R. Girardot, D. Crepin, P. Reant and R. Roudaut. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 110: 3766-3772, 2004.
170. Thébault C., E. Donal, C. Meunier, R. Gervais, B. Gerritse, M. R. Gold, W. T. Abraham, C. Linde, J.-C. Daubert and R. S. Group. Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. *European heart journal* 33: 2662-2671, 2012.
171. Thibault B., M. Dubuc, P. Khairy, P. G. Guerra, L. Macle, L. Rivard, D. Roy, M. Talajic, E. Karst and K. Ryu. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. *Europace* 15: 984-991, 2013.
172. Tjong F., T. Brouwer, L. Smeding, K. Kooiman, J. de Groot, D. Ligon, R. Sanghera, M. Schalij, A. Wilde and R. Knops. Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety, and performance. *Europace* euv457, 2016.
173. Tomassoni G., K. Newby, S. Deshpande, K. Axtell, J. Sra, M. Akhtar and A. Natale. Defibrillation Efficacy of Commercially

Available Biphasic Impulses in Humans Importance of Negative-Phase Peak Voltage. *Circulation* 95: 1822-1826, 1997.
174. Trayanova N. A. Whole-heart modeling. *Circulation research* 108: 113-128, 2011.
175. Udo E. O., N. P. Zuithoff, N. M. van Hemel, C. C. de Cock, T. Hendriks, P. A. Doevendans and K. G. Moons. Incidence and predictors of short-and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm* 9: 728-735, 2012.
176. van Gelder B. M., M. G. Scheffer, A. Meijer and F. A. Bracke. Transseptal endocardial left ventricular pacing: an alternative technique for coronary sinus lead placement in cardiac resynchronization therapy. *Heart Rhythm* 4: 454-460, 2007.
177. van Rees J. B., M. K. de Bie, J. Thijssen, C. J. W. Borleffs, M. J. Schalij and L. van Erven. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. *Journal of the American College of Cardiology* 58: 995-1000, 2011.
178. Verlato R., G. L. Botto, R. Massa, C. Amellone, A. Perucca, M. G. Bongiorni, E. Bertaglia, V. Ziacchi, M. Piacenti and A. Del Rosso. Efficacy of Low Interatrial Septum and Right Atrial Appendage Pacing for Prevention of Permanent Atrial Fibrillation in Patients With Sinus Node Disease Results From the Electrophysiology-Guided Pacing Site Selection (EPASS) Study. *Circulation: Arrhythmia and Electrophysiology* 4: 844-850, 2011.
179. Vijayaraman P., M. K. Chung, G. Dandamudi, G. A. Upadhyay, K. Krishnan, G. Crossley, K. Bova Campbell, B. K. Lee, M. M. Refaat, S. Saksena, J. D. Fisher and D. Lakkireddy. His Bundle Pacing. *J Am Coll Cardiol* 72: 927-947, 2018.
180. Wathen M. S., P. J. DeGroot, M. O. Sweeney, A. J. Stark, M. F. Otterness, W. O. Adkisson, R. C. Canby, K. Khalighi, C. Machado and D. S. Rubenstein. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. *Circulation* 110: 2591-2596, 2004.
181. Weizong W., W. Zhongsu, Z. Yujiao, G. Mei, W. Jiangrong, Z. Yong, X. Xinxing and H. Yinglong. Effects of right ventricular nonapical pacing on cardiac function: a meta-analysis of randomized controlled trials. *Pacing and Clinical Electrophysiology* 36: 1032-1051, 2013.
182. Yancy C. W., Jr. and B. G. Firth. Congestive heart failure. *Disease-a-Month* 34: 469-536, 1988.
183. Yartsev A. Single and Dual Chamber Pacing Modes. In: *Deranged Physiology*. DerangedPhysiology.com: 2016.
184. Ypenburg C., S. D. Roes, G. B. Bleeker, T. A. Kaandorp, A. de Roos, M. J. Schalij, E. E. van der Wall and J. J. Bax. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *The American journal of cardiology* 99: 657-660, 2007.
185. Ypenburg C., M. J. Schalij, G. B. Bleeker, P. Steendijk, E. Boersma, P. Dibbets-Schneider, M. P. Stokkel, E. E. van der Wall and J. J. Bax. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *European heart journal* 28: 33-41, 2006.
186. Ypenburg C., R. J. van Bommel, V. Delgado, S. A. Mollema, G. B. Bleeker, E. Boersma, M. J. Schalij and J. J. Bax. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *Journal of the American College of Cardiology* 52: 1402-1409, 2008.
187. Zanon F., E. Bacchiega, L. Rampin, S. Aggio, E. Baracca, G. Pastore, T. Marotta, G. Corbucci, L. Roncon and D. Rubello. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. *Europace* 10: 580-587, 2008.
188. Zanon F., E. Baracca, S. Aggio, G. Pastore, G. Boaretto, P. Cardano, T. Marotta, G. Rigatelli, M. Galasso and M. Carraro. A Feasible Approach for Direct His-Bundle Pacing Using a New Steerable Catheter to Facilitate Precise Lead Placement. *Journal of cardiovascular electrophysiology* 17: 29-33, 2006.
189. Zenati M. A., G. Bonanomi, A. K. Chin and D. Schwartzman. Left heart pacing lead implantation using subxiphoid videopericardioscopy. *Journal of cardiovascular electrophysiology* 14: 949-953, 2003.
190. Zhuang L., Y. Mao, L. Wu, W. Niu and K. Chen. Effects of right ventricular septum or His-bundle pacing versus right ventricular apical pacing on cardiac function: A systematic review and meta-analysis of randomized controlled trials. *Journal of International Medical Research* 46: 3848-3860, 2018.

9 Table of Figures and Tables

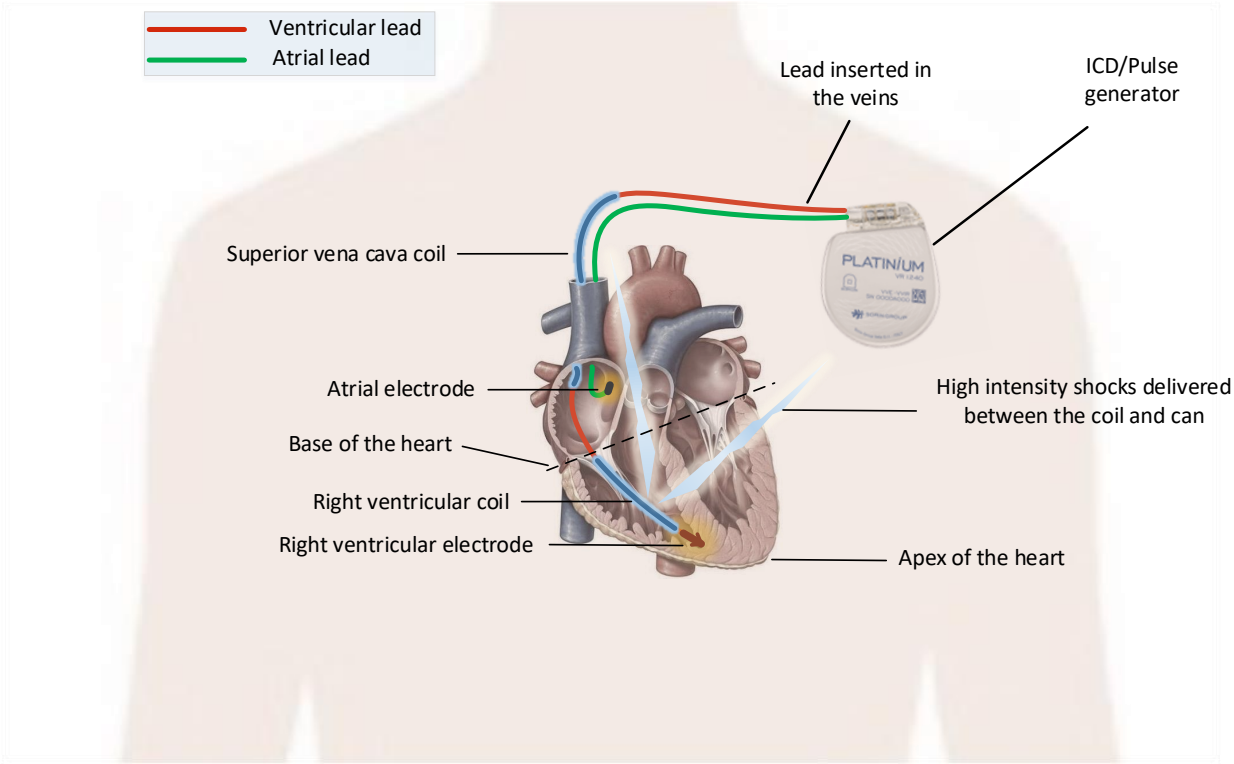

Figure 1 Diagram of conventional ICD with dual-chamber and dual-coil configuration. The pacing pulses are delivered using the electrodes at the tip of the leads, whereas the high intensity shocks are delivered using the coils and the case of the can. [The heart figure has been modified and reprinted with permission of Pearson Education, Inc., New York, New York [114]]. [The images of the devices shown in all figures (Platinium™) are trademark of LivaNova, London, UK]

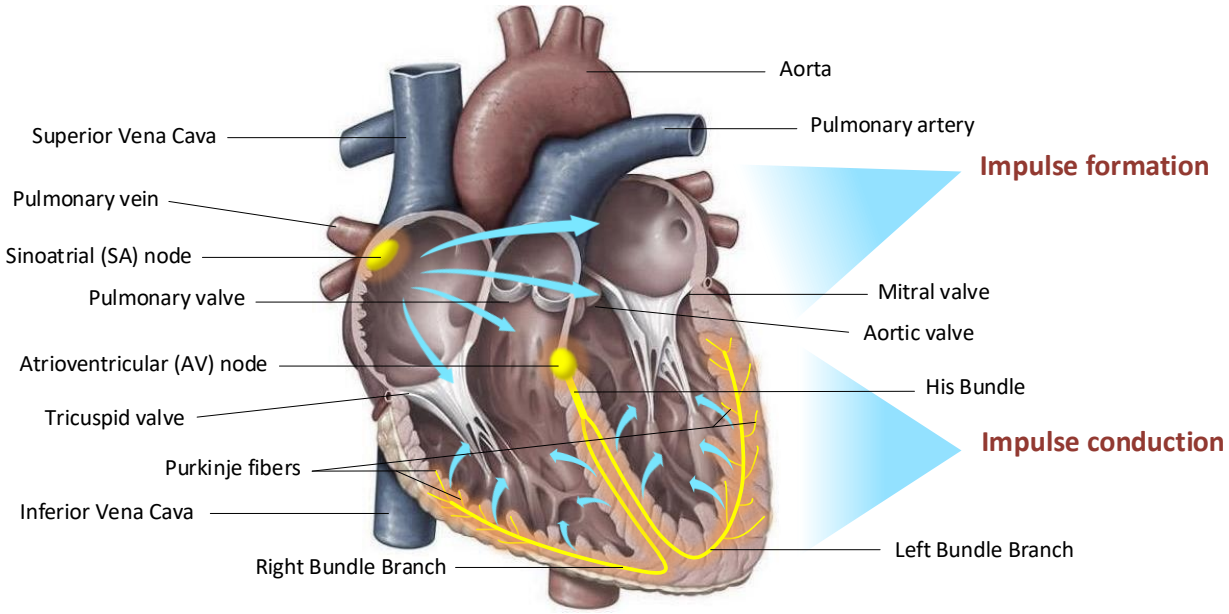

Figure 2 Anatomy of the heart's conduction system. The electrical activity of the heart originates from the SA-node (impulse formation) and spread through the myocardium in a coordinated manner governed by the fast-conducting conducting system (impulse conduction). [The heart figure has been modified and reprinted with permission of Pearson Education, Inc., New York, New York [114]].

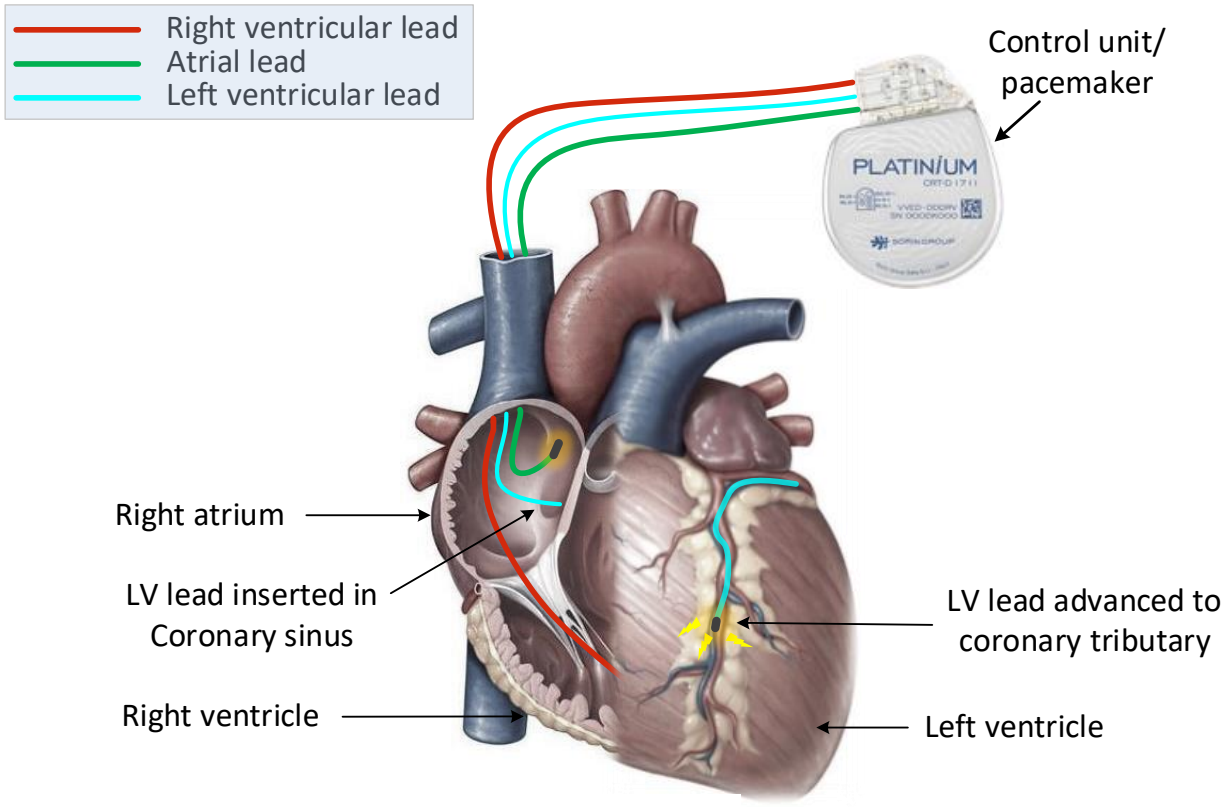

Figure 3 In CRT or Biventricular pacemaker, a left ventricular lead is implanted in addition to the conventional dual-chamber leads, to synchronize both ventricles and improve heart failure. [The heart figure has been modified and reprinted with permission of Pearson Education, Inc., New York, New York [114]]

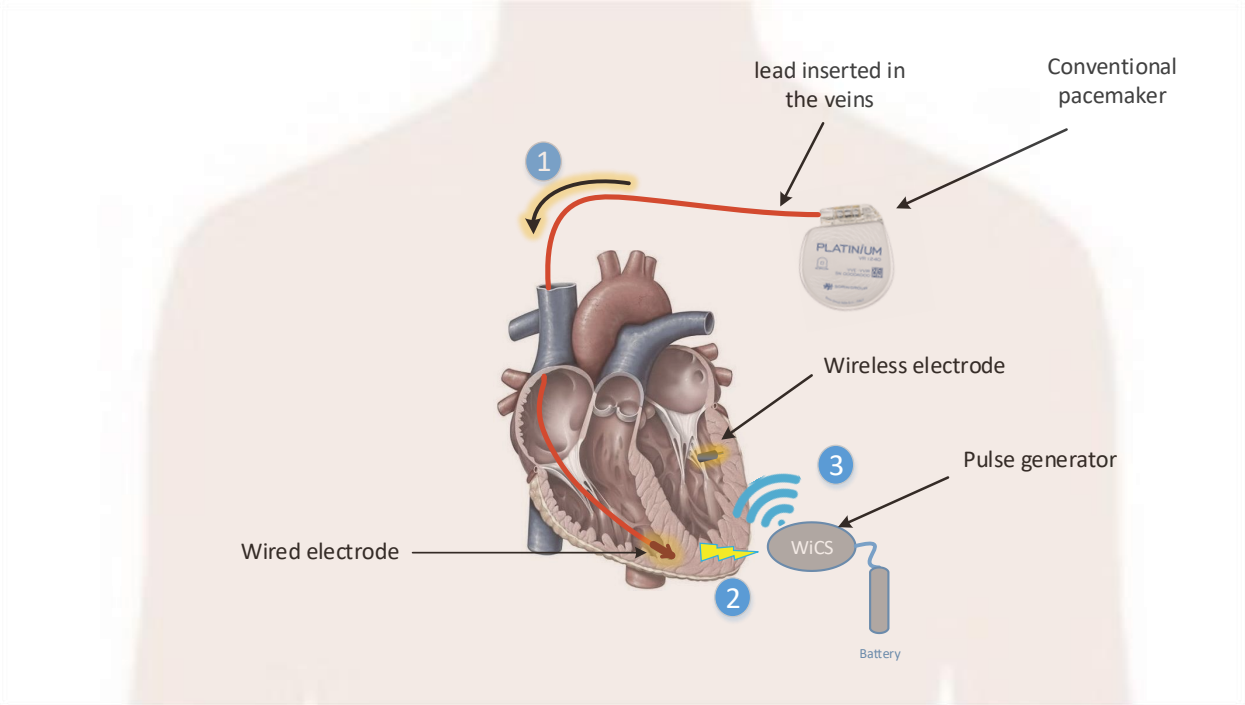

Figure 4 Wireless Cardiac LV-Stimulation (WiCS LV (EBR Systems Inc)) is an alternative approach to stimulate the LV endocardially using ultrasonic pulses. 1) The right ventricle is paced with a conventional pacemaker. 2) The WiCS LV pulse generator, which is implanted subcutaneously in the lateral wall of the abdomen, detects the pacing pulse from the right ventricular electrode. 3) The WiCS LV pulse generator sends an ultrasonic pulse to the wireless electrode, which converts it to an electrical pulse and pace the LV. [The heart figure has been modified and reprinted with permission of Pearson Education, Inc., New York, New York [114]]

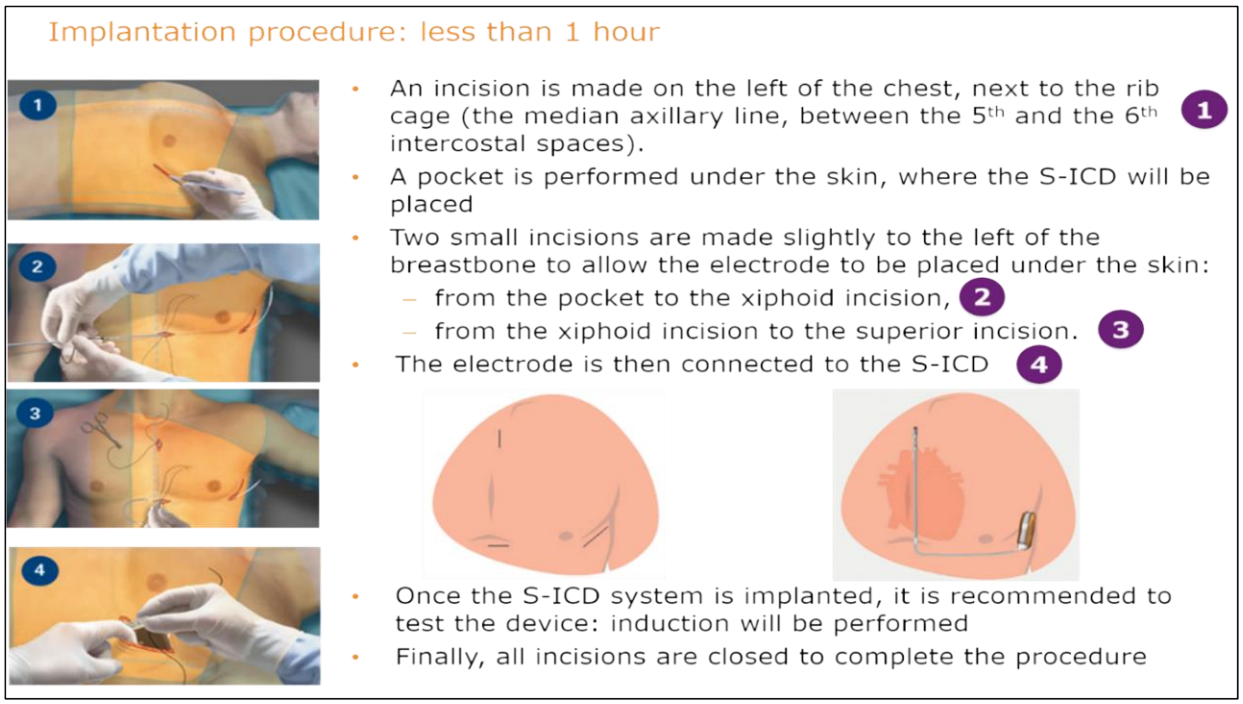

Figure 5 Subcutaneous-ICD implantation procedure [156]

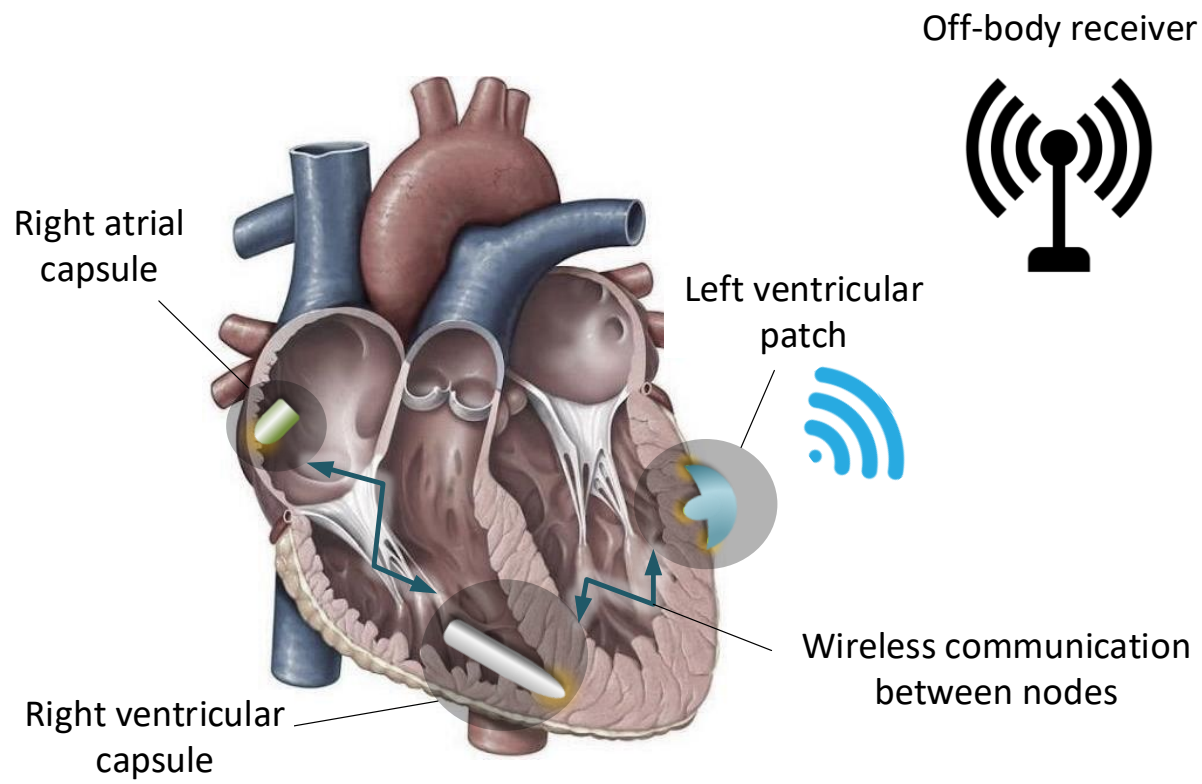

Figure 6 Conceptional multi-nodal ICRMD. Right atrial capsule-like node may be implanted in the right atrial appendage for sensing and pacing the atria. Bullet-like right ventricular apex node may be implanted like current leadless pacemakers to pace the RV. Patch-like left ventricular epicardial node may be implanted via mini-thoracotomy or subxiphoid puncture and provide LV pacing and defibrillation. Wireless channels, such as human body communication or ultrawideband communication, may be used for the communications within the implants and to an outside receiver. Large electronics, such as the defibrillation capacitor and the antenna for the off-body communication, may be contained in the large patch-like LV device. [The heart figure has been modified and reprinted by permission of Pearson Education, Inc., New York, New York [114]]

Technology	*Eligible patients/criteria*	*Advantage*	*Disadvantage*
Single chamber	Patients with sick sinus syndrome or only occasional pacing.	Fewest leads, i.e. lower risk of complications and cost.	No synchrony between atria and ventricle. Can develop.
Dual chamber	All patients with AV conduction disorder.	Well established and recommended.	Leads are the weakest link as they may dislodge or get infected
Leadless pacemaker	Bradycardia patients	Self-contained device. No lead-related complications.	Requires intact AV and VV conduction. No extraction option

Table 1 Summary of pacemaker modalities.

Technology	*Eligible patients/criteria*	*Advantage*	*Disadvantage*
CS LV simulation	All CRT patients with accessible CS vein	Well established and the conventional method.	Limited by CS anatomy contributing to the >30 % non-respond rate
Multipoint	All CRT patients with accessible CS vein	Multiple pacing vector options without the need to relocate	Drain the battery. Uncertain benefits compared to conventional.
Multisite	All CRT patients with two accessible CS veins	Recruit larger area of the LV. Improved hemodynamics.	Limited by CS. Not well studied yet.
WiC®S-LV	Dual chamber patients requiring upgrade to CRT	No CS anatomy constrains. Provides endocardial pacing	Additional device needed. Higher complexity.

Table 2 Summary of CRT modalities

Technology	*Eligible patients/criteria*	*Advantage*	*Disadvantage*
Single coil	All ICD patients	Conventional and recommended	Complicated lead extraction due to shape and size of the coil.
Dual coil	All ICD patients	Larger area of the heart is recruited. Reduced impedance.	Increased complexity and risk of lead failure. No clear benefits obtained.
S-ICD	ICD patients who do not require pacing	Reduced complexity. Reduced implant-related complications.	Lack of pacing capability. Limited to less than 3 % of the ICD market.

Table 3 Summary of ICD modalities

Chamber	*Site*	*Fixation*	*Eligible patients/criteria*	*Advantage*	*Disadvantage*
RA	Right atrial appendage	Passive/active	Most patients	Stable implantation	Synchrony between atria rely on intact conduction pathways
	Septal wall	Active	With or in risk of having atrial fibrillation	Simultaneous activation of atria	Unstable implantation and high rate of perforation
	Multi-site/bi-atrial	Passive/active	With or in risk of having atrial fibrillation	Shorter and more natural atrial activation	Increasing lead-related complications and double sensing
RV	Right ventricular apex	Passive	Unimpaired LV function	Accessibility and stability	Dyssynchronous activation of ventricles
	Right ventricular septum	Active	Impaired left ventricular function	Better activation pattern, shorter QRS	Slightly harder implantation procedure
	Right ventricular outflow-tract	Active	Most patients, unimpaired distal Purkinje system	Better activation pattern, shorter QRS	Minor coronary artery occlusion risk
	Direct His bundle pacing	Active	Unimpaired Purkinje system	Optimal activation pattern	Challenging implantation, higher pacing threshold
LV	Epicardial via coronary sinus	Passive	Standard site, 70 % success rate	Stability, low risk of thrombosis	Dependent on the coronary venous anatomy
	Surgical epicardial	Active	Non-responders to CS LV pacing, high risk of thrombosis	Direct access to any point on the LV wall, higher respond rate	Invasive
	Transvenous endocardial	Active	Non-responders to CS LV pacing	Replicate normal physiology	More invasive, risk of regurgitation and clot formation

Table 4 Summary of the various pacing sites. RA: Right atrium, RV: Right ventricle, LV: Left ventricle.