CHAPTER 6

The Cardiac Pacemaker: A Crossroads of Engineering and Medicine

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6.1 INTRODUCTION

Over the past 70 years, the cardiac pacemaker has blossomed into a technology capable of monitoring and treating patients with inappropriate cardiac rhythms. To date, over 600,000 Americans have undergone pacing therapy, with hundreds of thousands more devices implanted each year.[1] The past, present, and future development of cardiac pacing results from an intricate symbiosis between engineering and medicine. To gain an in-depth understanding of the field and perhaps where future innovation may lead, it is important to learn valuable lessons from past innovators. This chapter dives into the rich history surrounding the field of cardiac pacing. It describes the current technology standards, discusses different pacing paradigms, and offers a glimpse into the bright future of cardiac pacemaker therapy.

6.2 LOOKING BACK: A BRIEF HISTORY OF CARDIAC PACING

6.2.1 Lidwill, Hyman, and Zoll: forefathers of cardiac pacing

At its inception, electrical stimulation of the heart was thought only to serve the purpose of resuscitating patients who had experienced a recent sudden cardiac arrest. Interestingly, prior to the late 1920s, cardiac arrest was a relatively common and frequently fatal occurrence in the operating room. Resuscitation attempts centered around delivering epinephrine to prime the heart, coupled with mechanical excitation of the ventricular myocardium. It seemed that after arrest, the threshold for electrical conductivity through the heart was lowered; the prick of a needle was occasionally sufficient to send a sweeping electrical pulse through the myocardium, restoring cardiac rhythm. Lidwill[2] and Hyman,[3] early pioneers of pacing, paired these resuscitation efforts with their basic understanding of the ECG and surrounding electrophysiology. Their efforts centered on electrically stimulating the atrial half of the heart, hoping that upon cessation of a brief external stimulation, the heart would resume a native

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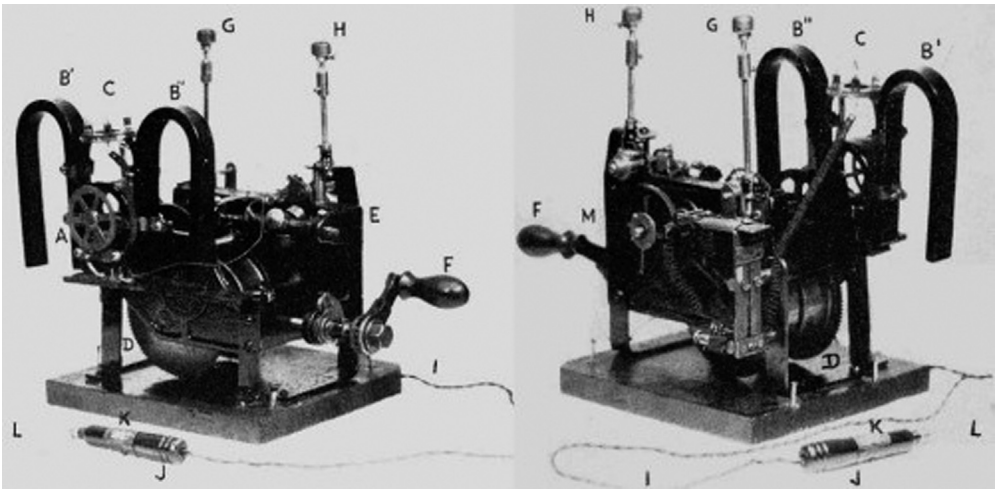

Figure 6.1 Albert Hyman's original device. This "pacemaker" was designed to provide electrical shocks at the turn of a hand crank, revitalizing a stopped heart.

sinus rhythm and begin beating again. The first documented evidence of using electrical stimulation to stimulate the human heart was provided by Lidwill in 1929.[2] Shortly after, in 1932, Hyman[3] published his electrical resuscitation efforts (Fig. 6.1).

Unfortunately, inventions by Lidwill and Hyman did not immediately flourish. The medical community at large was skeptical toward their work, and many physicians could not palate the treatment of cardiac arrest, due to low success rates of resuscitation and the inherent invasiveness of placing a plunged needle electrode into the heart of a patient near death. Unbeknownst to the inventors, cardiac arrest predominantly results from arrhythmia known as ventricular fibrillation, a condition which pacing cannot cure—thus, they ought to have invented the defibrillator! The true promise of cardiac electrical stimulation was not unearthed until the 1950s.

Prior to 1950, the heart was thought to fundamentally drive human emotion; to some, it was the center of the soul itself. There were no methods for conducting external heart surgery and no way to sufficiently oxygenate the brain during surgery. As such, all efforts to surgically repair the heart were made while it remained beating. Any stoppage of blood flow during these procedures could result in damage to the brain; hence, only simple surgeries could be performed on the beating heart.

This thinking began to change when World War II inspired a surge in surgical advances; daily life vs death operations were performed by field surgical teams, spurring rapid innovation. Surgical teams returning from the war were armed with new surgical techniques and an inspired confidence to take on any challenge presented. One of these young war-experienced surgeons, C. Walton Lillehei, returned to the University of Minnesota in 1950 to complete his surgical residency after leading an

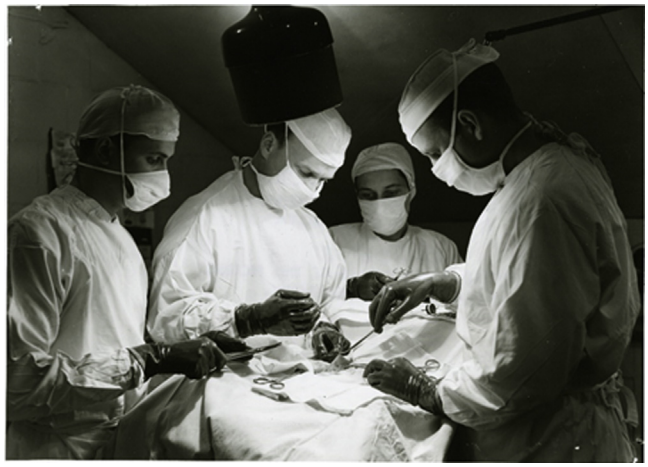

Figure 6.2 C. Walton Lillehei performs open-heart surgery on a patient at the University of Minnesota. Lillehei pioneered many open-heart surgeries and played a pivotal role in bringing pacemakers to mainstream clinical practice.

army surgical field unit in both North Africa and Italy. Lillehei, a maverick, pushed the next level of care for his patients by rebelling against what convention might propose. Notably, Lillehei played a fundamental role in the development of deep hypothermia, cross-circulation, bubble oxygenation, and revolutionary surgical techniques to repair congenital heart defects (Fig. 6.2). Unfortunately, his pioneering surgical work was not performed without complications. Early cardiac surgery pioneers were not in tune with the challenges of working with the human cardiac conduction system. In 10%–20% of Lillehei's early cases, children would develop complete heart block, a fatal consequence at the time. To solve this dilemma, Lillehei looked across the country and drew inspiration from the work of Dr. Paul Zoll.

While Lillehei was pioneering cardiac surgery in Minnesota, Dr. Paul Zoll, a research cardiologist at Harvard Medical School, was laying the groundwork for clinical pacing therapy. Zoll's pacemaker concept strapped two pacing electrodes on opposite sides of the thoracic cavity, such that the generated electric field would pass through both ventricles of the heart.[4] Clinicians could feasibly control the heart rate, effectively eliminating the arrest brought on by heart block. By 1952, Zoll began using his device on human patients. In one 65-year-old patient, Zoll's device was able to maintain a stable heart beat for more than 50 h at a time.[4] Unlike the preceding Lidwill and Hyman techniques, Zoll's approach was noninvasive and used stimulation electrodes placed on the skin, as opposed to plunge electrodes placed within the myocardium. Zoll's method also stimulated the ventricular half of the heart and as such could treat those patients affected by atrioventricular (AV) nodal block. His pioneering

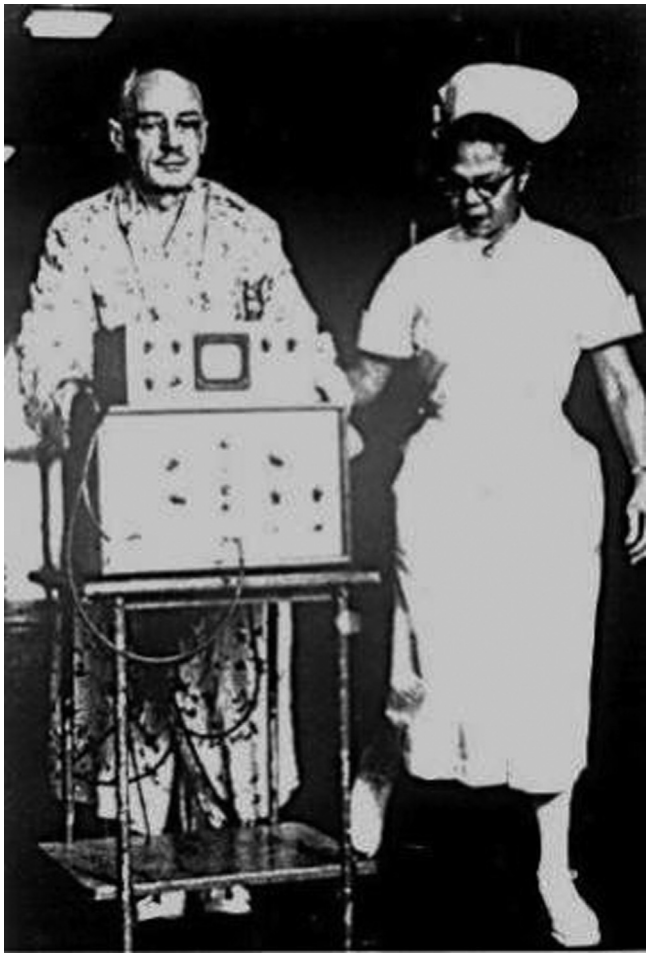

Figure 6.3 A patient outfitted with the Zoll pacemaker. Ambulatory movement required unplugging and replugging the pulse generator as it moved through the corridor. Incidentally, this patient was the first to receive a transvenous pacing lead implanted by Dr. Seymour Furman.

research spurred innovation across the medical community, leading many to consider electrical stimulation as a viable means for treating cardiac ailments (Fig. 6.3).

Lillehei knew about Zoll's successes across the country but was skeptical that the Zoll pacemaker could fit his needs. Zoll's device was designed to pace noninvasively, thus it required large voltages to capture ventricular myocardium through the thorax. Patients often complained the pain of repeated high-voltage electrical stimulation, often capturing thoracic skeletal muscle in addition to cardiac tissue. Lillehei needed an improved concept for his patients.

6.2.2 Earl Bakken and the birth of a medical device industry

Lillehei's surgical pacing approach employed a multistrand, braided stainless steel wire implanted directly into the ventricular myocardium, with the other end brought through the surgical incision and attached to external stimulation. This method of treatment, suggested by Dr. John A. Johnson, a professor of Physiology at the University of Minnesota, required only small magnitude electrical stimuli to effectively control heart rate.[5] The initial pulse generators for Lillehei's pacemakers were plugged into an external wall socket just like those used by Zoll, limiting patient mobility to the length of an extension cord. With a patient population dependent on the functioning device, Lillehei ran the risk of power outages endangering his patient's lives. On October 31, 1957, that is exactly what happened. A sudden city-wide blackout tragically ended the life of an infant patient. Lillehei, again, needed an innovative solution.

At the time, the University Hospital subcontracted with a local electric equipment repair company, Medtronic Inc., to perform maintenance tasks on operating room equipment. At the time, Medtronic was a two-person company—Earl Bakken and his brother-in-law Palmer Hermundslie.[5] Bakken was a trained electrical engineer who received his degree from the University of Minnesota; importantly, he was present during cardiac surgical procedures in the University's operating rooms. Lillehei approached Bakken to see if he was up to the task of designing an improved pacing system.

Bakken[6] began this work in 1957, using a circuit modified (in his words "plagiarized") from a circuit diagram for a transistorized metronome described in a Popular Electronics magazine. In 1958, Bakken brought the pacemaker to the University's

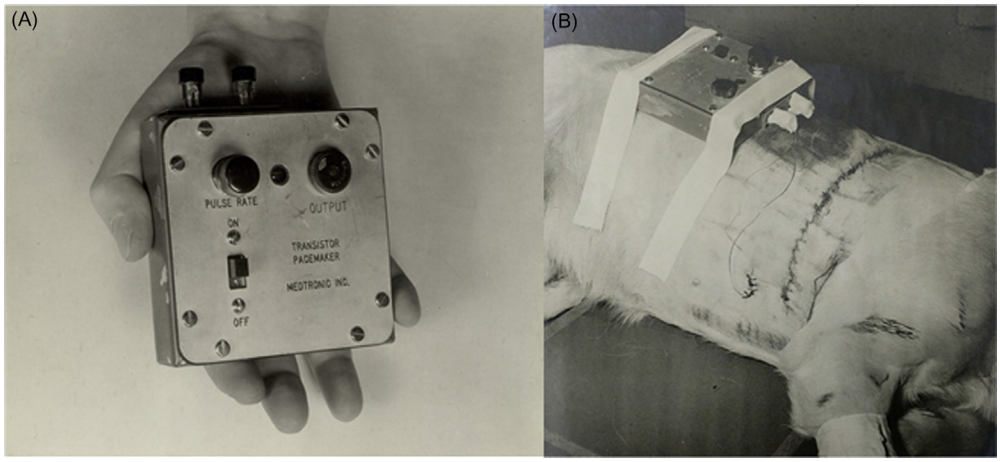

Figure 6.4 Earl Bakken's first transistorized pacemaker was developed over a course of weeks (A), animal tested over a course of hours (B), before first-in-human implantation.

animal laboratories to test the device on a dog (Fig. 6.4). The device functioned as intended, so Bakken returned home for the evening. On April 14, 1958, the "battery-powered, wearable pacemaker" was first used clinically, even though this was somewhat unplanned. In the words of Bakken,[6] "the next day I returned to the hospital to work on another project when I happened to walk past a recovery room and spotted one of Lillehei's patients. I must have done a double take when I glanced through the door. The little girl was wearing the prototype I had delivered only the day before!" Bakken's transistor pulse generator made a miraculous "overnight" transition from preclinical animal testing to clinical use.[7] Bakken commercialized his device, recessing the dials and streamlining the design. Soon he was receiving pacemaker orders from all over the country, and Medtronic became a dedicated pacemaking company, which would eventually blossom into one of the largest medical device companies in the world.

6.2.3 Innovation fuels innovation

The kick start to cardiac pacing was not without obstacles. By wiring an external device through a surgical incision, surgeons created a source for infection, which needed constant monitoring (Fig. 6.5). Several groups considered fully implanted devices to alleviate these problems.

In Europe, Ake Senning and Rune Elmqvist, a Swedish surgeon–engineer pairing, made the first attempt at an implantable pulse generator (IPG). The initial device implant lasted only 3 h, and a second attempt failed after a few weeks. Interestingly,

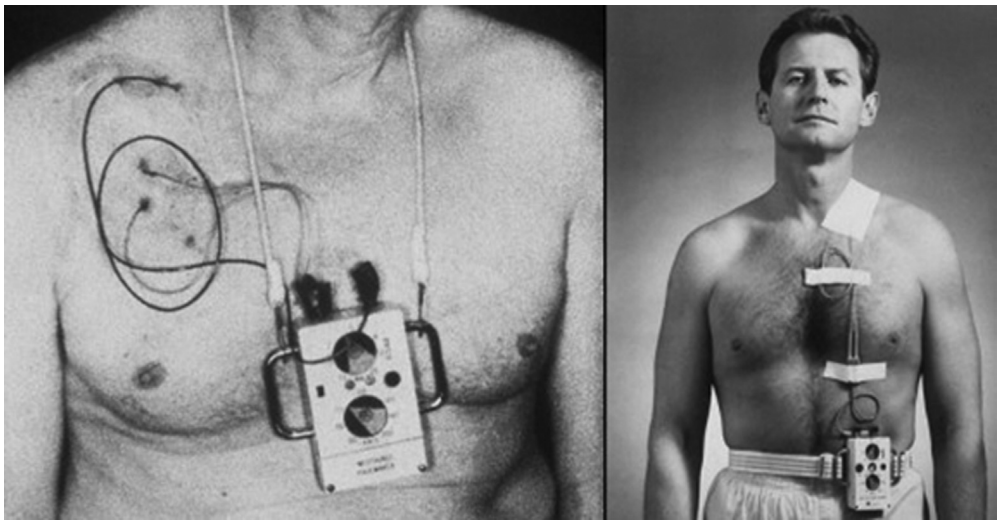

Figure 6.5 A patient wearing a Medtronic model 5800 pacemaker. The first commercialized pacemakers were worn around the neck. There were common clinical complications with the lead entry sites.

the patient who was given this preliminary implantable device lived for another 44 years, receiving over 25 new pacemakers along the way.[8]

Across the Atlantic, unaware of Senning and Elmqvist's efforts, another physician–engineer pairing, Dr. William M. Chardack and Wilson Greatbatch, took a different approach to create an implantable device. Greatbatch created a device with mercury–zinc battery cells and shrunk the device circuitry into a package slightly smaller than a hockey puck (Fig. 6.6).[9] Chardack and Greatbatch's first prototypes suffered from a phenomenon seen in many of the early Medtronic Model 5800 external pacing systems: threshold rise and subsequent greater power consumption. While external pacemakers could simply switch out batteries, rising threshold was a death knell for implanted systems.

Fortunately, for Chardack and Greatbatch, Dr. Samuel Hunter was collaborating with Hunter–Roth, a Medtronic engineer; the duo devised an innovative solution to early pacing threshold challenges (Fig. 6.7). The Hunter–Roth electrode required roughly 70% less current to pace the myocardium than existing electrode technology.[10] The bipolar electrode partially solved Chardack and Greatbatch's power consumption issues, allowing them to license their technology to Medtronic, who manufactured and sold 50 of the devices within the year. The device line remained the most widely used pacemaker throughout the 1960s (Fig. 6.8).

Figure 6.6 The Chardack–Greatbatch pacemaker was licensed by Medtronic in 1960 and quickly became the standard-bearer for implantable pacing devices. The pacemaker can was roughly the size of a hockey puck. Coupled with the Norman Roth electrode, the Chardack–Greatbatch pacemaker was the benchmark pacing technology throughout the 1960s.

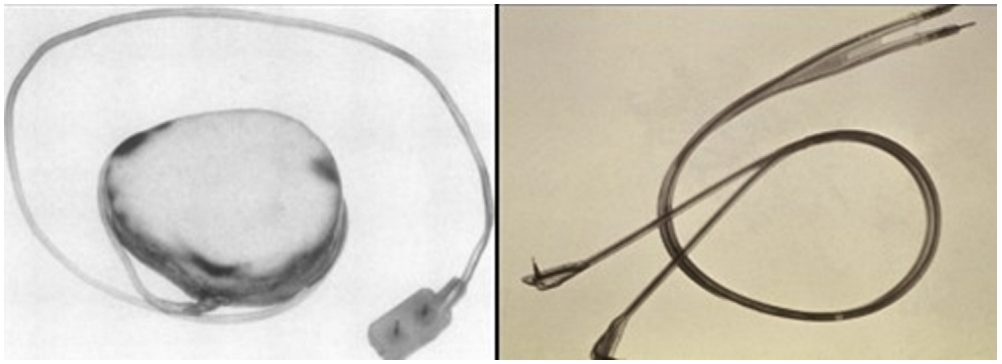

Figure 6.7 Pacing electrodes invented by Dr. Samuel Hunter and Medtronic engineer Hunter–Roth. The stainless steel Hunter–Roth electrode helped to reduce pacing capture threshold.

Figure 6.8 Dr. Samuel Hunger (inset) and adult pacing patient Warren Mauston. Dr. Hunter and Medtronic engineer Norman Roth developed a bipolar electrode that represented a major advance in pacing technology. First implanted in 1959, the Hunter–Roth lead helped add 7 years of life to a Stokes–Adams disease patient, Warren Mauston in 1960.

Around the same time frame, Dr. Seymour Furman was tasked with setting up an open-heart surgical program at New York's Montefiore Hospital; this included, in part, learning the technique of cardiac stimulation pioneered by the Minnesota surgical teams. Concurrently, Furman was learning cardiac catheterization. Furman

connected the dots and began efforts to pace the ventricle via a subclavian catheterization. Furman's second patient, an elderly gentleman of 76 years, was a pivotal success story. By threading a catheter through the left subclavian vein, Furman[11] paced the man's right ventricle (RV) at a threshold of 1.5−3.0 V for 96 days.

Furman's technique resolved many issues that plagued Lillehei's myocardial pacing method. Namely, it did not require a thoracotomy, making the therapy available to sick patients who otherwise could not tolerate the surgery. In addition, pacing capture was achievable at the low voltage and did not appear to suffer from the same rising phenomenon seen in myocardial pacing. In 1965, Medtronic released a pacemaker intended to be used with a transvenous lead, and transvenous pacing rapidly became the standard of care. Still today, the vast majority of pacemaker implants employ a transvenous lead.

In the early days of pacing, systems were marked with rapid improvements on all fronts. Mercuric-oxide−zinc batteries resulted in limited device longevity. At a low pacing capture threshold, these batteries lasted around 2 years. Longer lasting, reliable batteries were needed for successful implantable technologies. Fortunately, in the 1960s and early 1970s, the medical device industry applied research on lithium ion batteries that the military had been studying for years. Wilson Greatbatch, already famous for his work in implantable devices, brought lithium batteries into the medical space in 1971, and only a few years later, the first lithium ion pacemaker hit the medical market. Due to their vastly increased longevity, lithium ion batteries rapidly ascended into prominence, and by 1978, their use comprised a majority of pacemakers on the market.

In the subsequent decades, pacing therapy went through a series of improvements, while maintaining similar core technologies. Transistor-driven pacemakers were replaced by integrated circuits, which eventually were replaced by microprocessors.

6.3 MODERN IMPLANTABLE PACING SYSTEMS

6.3.1 Current pacing systems

Today, implantable pacing systems consist of multiple components working as a unit to deliver effective therapy. Generally, the chronically implanted components of a modern pacing system include the IPG, or pacemaker, as well as the pacing lead or leads. The IPG can is most commonly implanted subcutaneously near the left pectoral region but may be shifted to the right pectoral region if the left subclavian vasculature is unsuitable, if other devices are present, or if there is an overarching patient or physician preference (e.g., left-handed trap shooters may wish to have right pectoral implants to avoid interaction on their shooting shoulder). IPGs may also be placed submuscularly, so to prevent or minimize subcutaneous pocket erosion and/or for cosmetic considerations. In pediatric patients, they are often implanted abdominally.

Currently, pacemaker rates and modes of function can be programmed via telemetry. An external programmer telemeters information to and from the programmable IPG. As such, the cardiac electrophysiologist may change pacing parameters and download electrical information captured by the device without direct access to the IPG.

It should again be noted that early pacing systems utilized plunge electrodes placed through the epicardial wall of the heart. In these systems, it was common to implant the pulse generator in the abdomen, due to the large size of the can and easier access to the epicardial surface. This technique is still used in certain clinical situations (e.g., neonates or individuals with compromised vascular access). However, a transvenous lead approach, as pioneered by Furman, is far more common.

Transvenous pacemaker leads are generally placed via one of two methods: the surgical cephalic cutdown or a subclavian puncture. In a surgical cutdown, the vessel is exposed via careful dissection, and a small incision on the vessel wall allows direct insertion of the lead. In a subclavian puncture, a needle passes into the lumen of the vessel, allowing guidewire introduction. Subsequently, a percutaneous lead-introducing catheter is placed over the wired-rail and into the venous lumen. The guidewire is removed and the lead is then inserted through the catheter and advanced into the right side of the heart, allowing fixation in the right atrium (RA), RV, and/or through the coronary sinus to a cardiac vein on the left side of the heart (all depending on the type of system chosen, single, dual, or biventricular systems). An anchoring sleeve secures the lead at the entry site, preventing external forces from dislodging or displacing the implanted lead(s). The lead terminals are connected to the respective inserts of the IPG. Generally, the IPG will be placed in a subcutaneous pocket near the left or right pectoral. Suturing closes the incision, completing the implantation.

6.3.2 Implantable pulse generators

In a modern pacing system, an IPG is controlled by a small microprocessor computer housed within a hermetically sealed pacemaker housing, typically referred to as the "can." The circuitry is generally powered by a lithium ion battery, which routinely takes up more than half of the can volume. In pacing systems, device longevity varies by utilization (i.e., pacing capture threshold, circuit impedance, and their associated current drains) but commonly exceeds 8–10 years. The internal circuitry is wired to an external connector block which allows the transvenous pacing leads to interface with the internal device circuitry (Fig. 6.9).

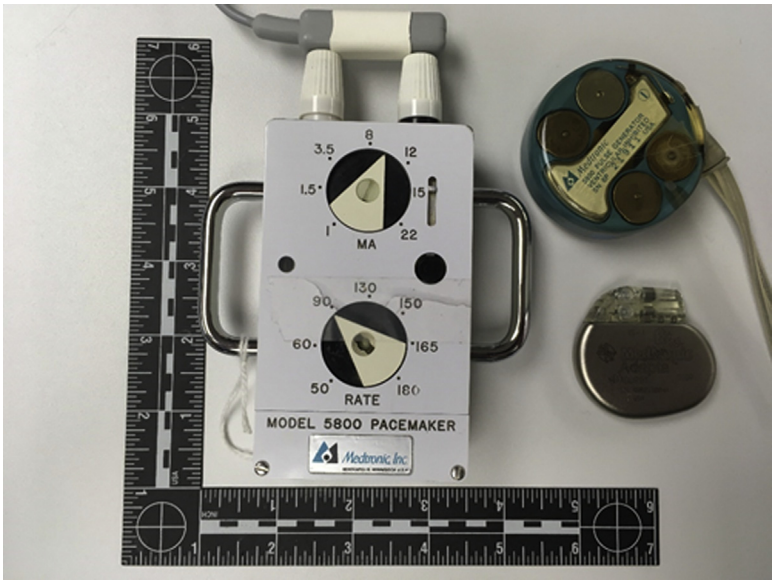

Figure 6.9 Pulse generators have dramatically reduced in size over the years. Pictured here is the Medtronic 5800 (the first commercialized transistorized pacemaker), the Medtronic 5950 (implanted in the late 1970s), and the Medtronic Adapta (currently market-available).

6.3.3 Sensing algorithms

Modern pacing systems have evolved significantly from the basic functionality seen in early pacemaker prototypes. Within the IPG, microprocessors combine to sense electrical activity and deliver timed pulses, programmable based on the desired therapy.

Delivering appropriate therapeutic intervention relies heavily on accurate detection and interpretation of intrinsic electrical signals within the heart. The pacing system will measure a voltage between the bipolar electrode pair on the lead (bipolar lead) or between the lead tip cathode and the IPG (unipolar lead); this signal is known as the cardiac electrogram. Within the IPG, the heart's electrical activity is computationally interpreted by sensing algorithms.

Most rhythm management decisions are based on the patient's detected heart rate. The modern IPG continuously measures the time from one sensed event to the next and compares the interval to the rates and intervals programed by the clinician. For example, if two atrial events occur with a separation of 1500 ms (1.5 s), the heart rate is 40 bpm (HR = 60/measured beat-to-beat interval; 60/1.5 = 40 bpm).

6.3.4 Pacemaker leads

Cardiac pacing leads are the traditional electrical conduit between the IPG and the heart (Fig. 6.10). Leads allow transmission of electrical energy to the heart to

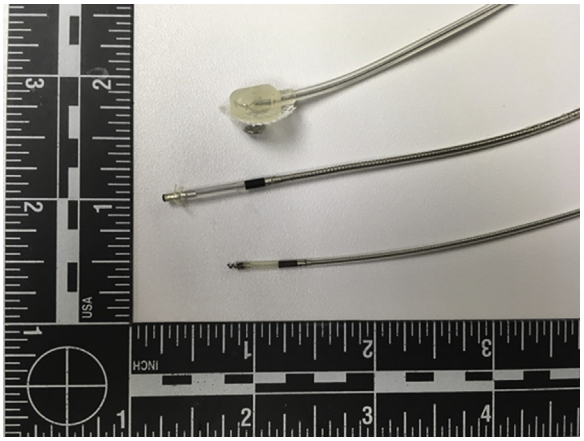

Figure 6.10 Examples of the distal portion of multiple cardiac pacing leads. Pictured here from top to bottom: Medtronic 4968 epicardial pacing lead, Medtronic 4074 passive fixation pacing lead, and Medtronic 5076 active fixation pacing lead.

artificially stimulate contraction and also relay sensed electrical signals back to the IPG for diagnostics and cardiac monitoring. Pacemaker leads commonly traverse through diverse, dynamic vascular and cardiac anatomies. As such, leads must be able to withstand foreign body responses of the human body, anchor securely within myocardium while maintaining the flexibility necessary to navigate through venous and cardiac anatomies, and undergo approximately 400 million cardiac cyclic deformations over a 10-year period without fracture or damage.

Currently, leads are most commonly placed endocardially within the cardiac chambers but may be placed on the heart's external surface "epicardially," depending on the patient's indication, physician preference, and/or anatomic considerations. Endocardial leads generally originate from the IPG in the subcutaneous space, enter the subclavian venous vasculature, travel through the superior venous return, and anchor their distal tips within the myocardium. The vast majority of pacing systems utilize endocardial leads, taking a subclavian venous approach, as originally described by Furman. In contrast, epicardial leads are attached directly to the surface of the heart; these leads are most commonly used when transvenous implantation is not feasible (i.e., in pediatric patients or adults with compromised and/or tortuous venous vasculature).

Modern leads are all constructed with biocompatible polymers and biostable metals. Yet, lead body design is variable based on the number of circuits required, its ultimate size (e.g., diameter or French size and overall length), handling considerations, and manufacturer preferences.

At the distal tip of the pacing lead, an electrode interfaces with cardiac tissue and must provide stable, chronic electrical sensing and stimulation. Electrode configurations also vary across commercially available leads and are designed in both unipolar

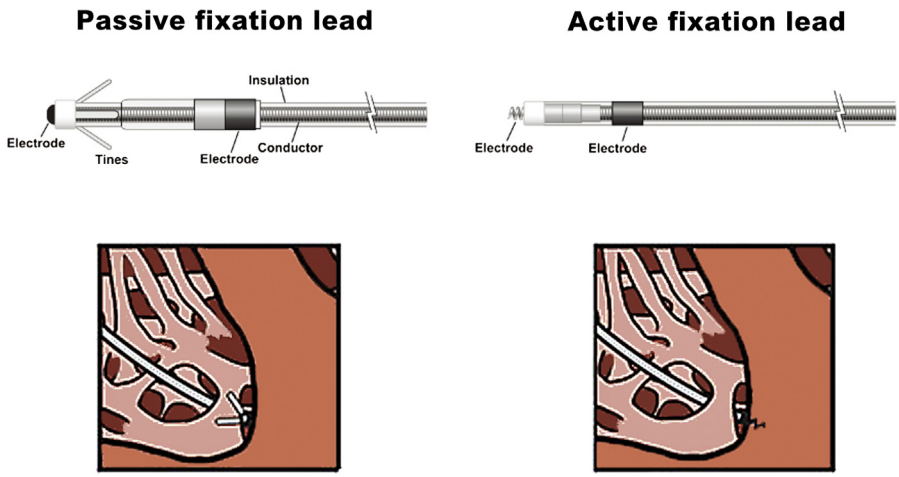

Figure 6.11 Pacing leads come equipped with either passive or active fixation. Shown here are a tined passive fixation and a helical active fixation (corkscrew) mechanism.

and bipolar configurations. Unipolar pacing circuits utilize a single cathodal electrode at the tissue interface, with the IPG serving as the anode. Bipolar pacing systems use an electrode at the tissue interface as a cathode but have a pacing anode positioned on an adjacent section of the distal lead body. Pacing leads commonly use a cylindrical electrode placed along the lead body (ring electrode) as the anode.

To facilitate stable electrical interface at the cathode, pacemaker leads will often utilize an active or passive fixation mechanism at the lead's distal tip (Fig. 6.11). Passive fixation mechanisms do not require active deployment by a clinician, while passive mechanisms commonly include polymeric tines and/or shaped segments along the length of the lead. Conversely, active fixation mechanisms require some active deployment from the clinical implanter, for example, deployment of helices, hooks, or barbs. In addition, some epicardial leads require sutures to maintain a stable position.

Typically, the distal portion of the lead is designed to interface with the cardiac tissue. Thus, in order to optimize chronic electrical performance, the distal lead tip must (1) minimize inflammatory response, (2) provide high capacitance and impedance, and (3) act as a stable fixation mechanism throughout the life of the lead. Most modern cathodic electrodes elute antiinflammatory agents/drugs (e.g., dexamethasone sodium phosphate) to suppress inflammatory responses. This helps to manage acute changes in the cardiac tissue at the implant site, thus stabilizing chronic pacing and sensing performance. Many pacing electrodes are also given coatings to produce a large, highly capacitive surface area; this reduces battery drain and results in small polarization following a pacing pulse, increasing sensing performance. However, the size of the pacing cathode has decreased over time, increasing cathode-tissue

impedance and augmenting system efficiency by reducing the current drain of each pacing impulse.

6.4 CLINICAL PACING CATEGORIES

6.4.1 Bradycardia pacing

Pacemaker therapy is most commonly used for symptomatic bradycardia (abnormally slow heart rate). Typical causes of these bradyarrhythmia are (1) sinus node dysfunction, (2) acquired permanent or temporary AV block, (3) chronic bifascicular or trifascicular block, (4) hypersensitive carotid sinus syndrome, (5) neurocardiogenic in origin, and/or (6) a side effect due to a drug therapy. Pacemaker therapies for symptomatic bradycardia come in a variety of forms, including ventricular pacing, atrial pacing, and dual-chamber pacing. The prescribed therapy is typically dependent on a patient's pathology, age, and previous medical history. For example, a patient with AV nodal block might require ventricular pacing to appropriately time the ventricular contraction with atrial depolarization. Conversely, a patient with sinus node dysfunction, but an otherwise unaffected conduction system, might require only atrial pacing.

In the early 1990s, advances in lead and pulse generator technology led to dual-chamber pacing systems. New polyurethane leads made for easier implantation of multiple leads and allowed RA and RV pacing to be accomplished in the same patient.[12] Further, advanced tined lead designs dramatically reduced atrial lead dislodgements.[13] Similarly, the aforementioned developments in integrated circuits and pacemaker microprocessors led to IPGs with sophisticated algorithms for novel treatments and cardiac monitoring. As such, IPGs may be programed to deliver both atrial and ventricular pacing in patients with chronotropic incompetence that necessitates pacing in both atrial and ventricular chambers of the heart.

6.4.2 Cardiac resynchronization therapy

Cardiac pacing has historically been used to treat bradycardia (delayed or absent activation of the entire ventricle). The conception of cardiac resynchronization therapy (CRT) came from two separate studies. A French clinical research team showed that multisite atrial pacing—one lead in the right atrial body and a second in the coronary sinus—aided in suppressing atrial tachyarrhythmias in patients with an intraatrial conduction delay.[14] This therapeutic innovation led to the development of a dedicated coronary sinus pacing lead: the model 2188 CS lead (Medtronic plc, Minneapolis, MN, United States). In 1994, a patient with severe congestive heart failure (HF) received a four-chamber pacing system utilizing standard right atrial and ventricular leads, the model 2188 CS lead, and an epicardial Medtronic 5071 lead on the left

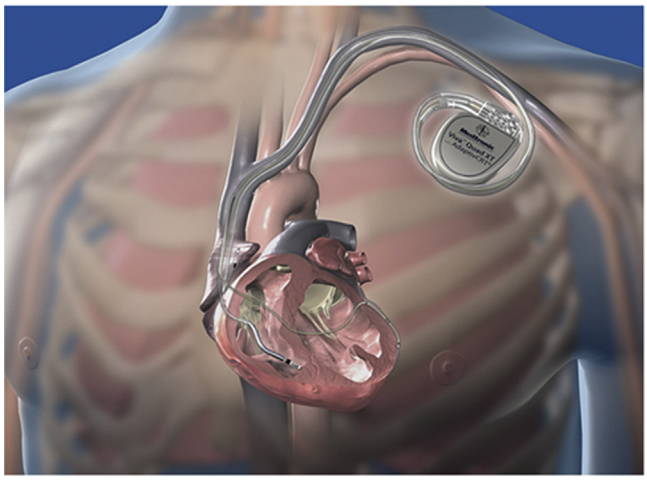

Figure 6.12 A cardiac resynchronization therapy pacing and defibrillation system is shown, with the device can implanted in the left pectoral region. Endocardial leads pace within the right atrial and right ventricular chambers of the heart. The defibrillation lead within the right ventricle allows for defibrillation shocks in the case of abnormal ventricular tachyarrhythmia. The left ventricular lead enters the coronary sinus and wraps around the coronary venous system to pace on the left ventricular epicardium.

ventricular (LV) free wall.[15] The patient's clinical status improved dramatically, showing the feasibility of multichamber resynchronizing pacing.

These original research studies led to the clinical development and use of CRT (Fig. 6.12) to treat HF. At its core, CRT improves cardiac function by restoring coordinated (more physiologic) contraction across the LV. In some cardiac pathologies—commonly left bundle branch block—segments of the LV show marked delay in activation. This results in an inefficient contraction of the ventricles, leading to reduced stroke volume and cardiac output. Broadly, this left-sided delay with respect to the right is termed *dyssynchrony.* Cardiac resynchronization involves pacing a single locus (or multiple loci) within the LV to improve ventricular electrical (and consequently mechanical) coordination. Generally, CRT therapy involves placing a pacing lead through the left coronary venous vasculature, resulting in epicardial pacing of the LV. This lead will provide stimulus nearly simultaneously with a secondary lead placed in the RV. By resynchronizing conduction, immediate acute improvements in a patient's LV hemodynamic function can be observed (i.e., increased ventricular contractility, stroke volume, and ejection fraction).[16,17] In selected HF patient populations, CRT has been shown to be more powerful than traditional pharmacological agents for reversing pathological chamber remodeling, improving ventricular function indices, reducing traditional HF biomarkers, and lowering mortality.[18–20] Yet, successful CRT is considered to be dependent on selecting only patients with ventricular

dyssynchrony as characterized by QRS > 120 or 130 ms. Further, it is critical that the resynchronization lead be placed in the optimal position and the device be programed appropriately to normalize LV conduction.

6.4.3 His bundle pacing

Traditional ventricular bradycardia pacing utilizes leads placed within the endocardial body of the RV. While traditional pacing therapies are effective, RV (apical) pacing inherently causes interventricular dyssynchrony and adverse hemodynamics, as the pacing-induced ventricular depolarization does not utilize the native cardiac conductive system. Some have proposed an alternative therapy: His bundle pacing (Fig. 6.13). The bundle of His is the beginning of the ventricular conduction system. It originates from the distal portion of the AV node and travels through the central fibrous body before bifurcating into the left and right bundle branches. Thus by pacing the bundle of His, the pacing-induced depolarization waves will utilize the native cardiac conduction system to travel through the myocardium, producing theoretically ideal ventricular synchrony. Permanent His bundle pacing was first described in 2000, in a subset of patients with chronic atrial fibrillation and dilated cardiomyopathy.[21] Across 18 patients, investigators saw improvements in cardiac functional indices, indicating that permanent His bundle pacing is a feasible treatment strategy.[21] Yet at that time, it never realized widespread adoption as a therapy. Today, His bundle pacing can be achieved by delivering the Select Secure Model 3830 lead (Medtronic) through specially designed sheaths (C 315 His). His bundle pacing is currently only practiced by a few skilled operators, though there is significant interest in bringing it to the mainstream. As noted above, early studies have shown promising results compared to

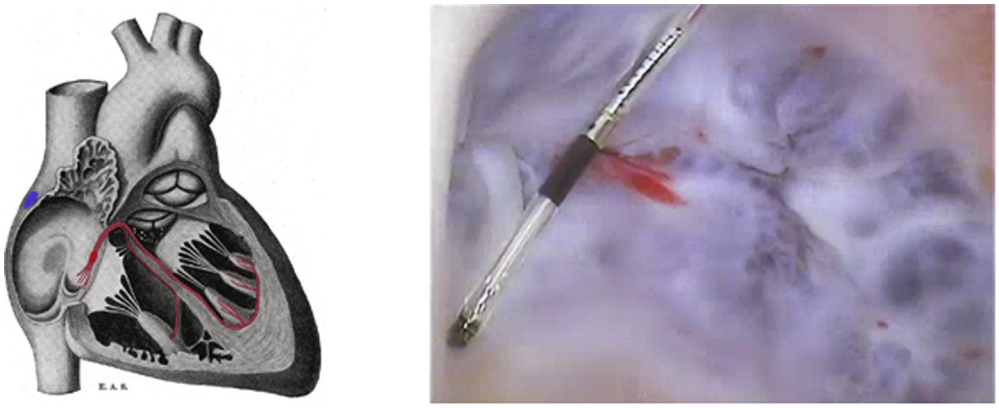

Figure 6.13 (A) The cardiac conduction system is highlighted in red. The bundle of His penetrates through the central fibrous body separating the atrial and ventricular halves of the heart. Shortly after, the bundle of His bifurcates into the right and left bundle branches. (B) A Medtronic 386 lead is shown fixated to the bundle of His in a reanimated swine heart.

traditional pacing paradigms. However, several other studies have observed mixed results comparing permanent His bundle pacing to traditional RV apical pacing.[22–24] Overall acute hemodynamic functional indices appear to improve when pacing the His bundle, but long-term reductions in HF hospitalization and mortality are less clear.[25,26]

Today, though the basis of evidence to replace traditional RV apical pacing with permanent His bundle pacing is not fully formed, small pilot studies suggest that pacing the bundle of His may benefit some patients that are eligible for CRT therapy. When compared to traditional LV leads, His bundle pacing has been hypothesized to improve LV functional indices, normalize LV dimensions, and lower New York Heart Association (NYHA) functional class.[27,28] Yet there is insufficient data to make definitive conclusions about the safety and efficacy of chronic His bundle pacing as a replacement for traditional dual-chamber pacing or traditional CRT pacing. Nevertheless, small early feasibility trials have shown that His bundle pacing may provide significant benefits over other traditional pacing paradigms. These early results, coupled with physiologic intuition, make His bundle pacing an attractive frontier for the future of cardiac pacing therapy.

6.5 FUTURE PACING DIRECTIONS

Pacemakers today are the result of years of innovative ideas combined with extensive clinical expertise. Thus, it follows that the next generation of devices will require more of the same. Our glance into the future of pacing shows multiple promising areas of progress that may revolutionize the way we think about pacing today.[29]

6.5.1 Leadless pacing: an emerging frontier

Major breakthroughs in cardiac pacing therapies are likely to center around leadless technologies. Leadless pacemakers remove Achilles' heel from traditional transvenous systems. The devices that are truly leadless incorporate pacing circuitry, battery, and electrodes, all within a small intracardiac capsule. Thus, by eliminating lead-related and pocket-related complications, to date, leadless pacemakers have reduced implant procedural complication rates to 4%–6.5% from 7.5% to 12.5% in traditional single and dual-leaded systems.[6–33] Of note, the procedural complications associated with leadless implants are likely to diminish as clinicians gain a better understanding of leadless technology and various implant procedures.

Currently, there are two leadless pacing systems available for clinical use: the Medtronic Micra and the Abbott Nanostim (St. Jude Medical/Abbott, St. Paul, MN, United States). The Nanostim LCP received CE mark in the fall of 2013 and is currently awaiting FDA approval for use in the United States. The Medtronic Micra received CE mark in April 2015, and FDA approval 1 year later. Both systems are

capable of delivering single-chamber RV pacing, sensing, and rate response therapies. Both systems are delivered into the right side of the heart via femoral vein catheterization. A deflectable sheath/delivery tool allows the device to be maneuvered through the RA, across the tricuspid valve, and into the desired implant location within the RV of the heart. However, there are differences in device fixation mechanisms, profiles, delivery, and function.

By volume, Micra is the smaller of the two devices (0.8 vs 1.0 cm^3). The Micra device profile is shorter (25.9 mm) with a thicker radial dimension (23 Fr inner diameter introducer), while the Nanostim is longer (42 mm) and thinner radially (18 Fr inner diameter introducer sheath). These devices are significantly smaller than traditional IPG cans. The small size of leadless pacemakers may facilitate the placement of multiple pacing systems within the same heart. In fact, up to three Micra pacing systems can be comfortably placed within the RV of the average human heart.[34]

One of the most critical features of any leadless pacing system is its fixation mechanism. Leadless pacemakers carry the risk of embolization into the lungs or femoral venous system, if they become dislodged. Interestingly, the two currently clinically available devices utilize fundamentally different fixation mechanisms. The Nanostim has a screw-in helix at its distal tip, which anchors the cathode electrode to the ventricular myocardium. In contrast, the Micra transcatheter pacemaker fixes to tissue via four self-expanding nitinol tines (Fig. 6.14). These tines are designed to deploy into the myocardium with minimal tissue damage, while holding the pacing electrode in stable contact with the ventricular myocardium.[35] These variations in fixation mechanism may lead to modest differences in pacemaker functionality; utilization to date has elicited 1.5% pericardial effusion rates in initial clinical studies of both devices.[6,31]

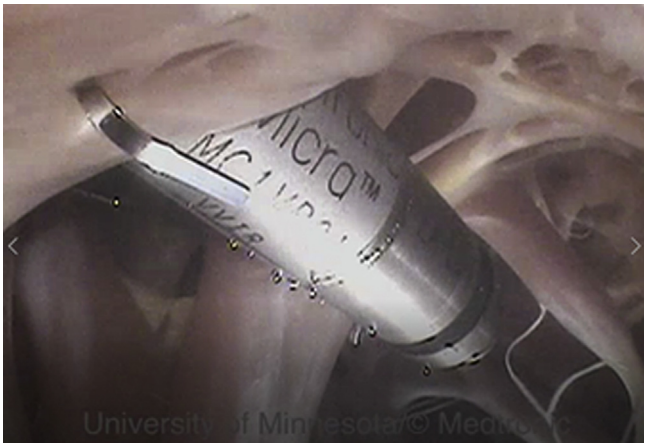

Figure 6.14 Image of a Medtronic Micra implanted within the right ventricular apex of a reanimated human heart at the University of Minnesota's Visible Heart Laboratory.

However, the Micra transcatheter pacemaker has shown zero gross dislodgements,[6] while Nanostim has documented a 2.3% dislodgement rate.[31]

The Nanostim and Micra leadless pacemakers are designed for rate-responsive ventricular pacing; however, the mechanisms for rate response therapies vary between devices. In the Micra pacemaker, an accelerometer senses extracardiac motion and associatively sets the stimulation rates based on the patient's relative activity level. In contrast, the Nanostim device utilizes an incorporated temperature sensor to detect central venous temperatures and then programs an appropriate change in paced rates.[36]

Based on use history thus far, leadless pacing systems have shown significant utility and reduced complication rates, while preserving the major functionality of a standalone ventricular pacing system. The devices do, however, pose significant questions as to appropriate end-of-life decisions. For example, with current battery technology, these leadless systems are designed to provide approximately 10 years of pacing at stable chronic thresholds (estimated 12 years for Micra, 8.5−9.8 years for Nanostim). Patients receiving pacemakers are typically between 60 and 80 years,[1] but a nonninsignificant percentage of patients receive pacing systems much younger. Therefore, the current battery longevity of these leadless systems may necessitate multiple device upgrades and/or revisions in order to provide long-term therapy to younger patients. In addition, should a leadless device become infected or provide ineffective therapy after implant, the device may need to be physically removed. Indeed, early implantations of the Nanostim pacemaker have shown issues with battery failure, necessitating the removal of implanted devices.[37] As such, appropriate consideration must be given to acute and chronic device retrieval.

Fortunately, recent documented clinical outcomes have supported the acute retrievability of leadless pacemakers.[37–39] The Nanostim device has a dedicated retrieval catheter available with either single or tri-loop snares; successful acute and short-term chronic retrievals were accomplished in 94% of the required cases.[38] In contrast, the Micra pacemaker system does not have a dedicated retrieval catheter. To date, retrieval attempts of the Micra device involve passing a large diameter snare through a steerable sheath, although a smaller 7 mm snare may be used in conjunction with the Micra delivery catheter. Direct visualization of leadless pacemaker extraction reveals some of the challenges that face extractors.[40] Any extraction attempt must access the proximal retrieval feature of the leadless device; in a chronic setting, the degree of encapsulation of this retrieval feature is unknown (Fig. 6.15). Clinical retrieval experience of the Micra leadless pacemaker is limited, but the flexibility of nitinol tines has facilitated retrieval of the device without countertraction.[39,41] Neither device has proven long-term chronic extractability, and the chronic encapsulation profile of leadless devices is yet unquantified.

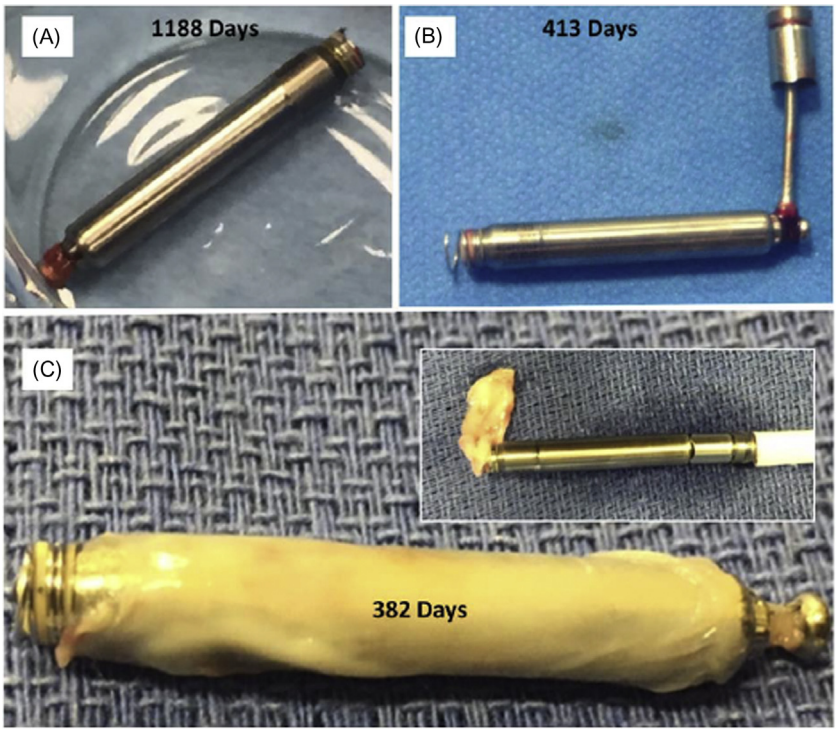

Figure 6.15 Encapsulation on the body of chronically implanted leadless pacemakers varies. Devices may be fully encapsulated within a year of implantation, or completely bare several years postimplant. *Image from Reddy VY, Miller MA, Knops RE, et al. Retrieval of the leadless cardiac pacemaker: a multicenter experience.* Circ Arrhythm Electrophysiol *2016;**9**:e004626.*

Current leadless technologies are approved only for RV—VVI(R)—pacing. To become a truly transformative technology, leadless pacemakers must be adapted for the diverse indications of bradycardia pacing. Namely, leadless pacemakers should be designed for use in both the atria and ventricles, so to allow for atrial only or dual-chamber pacing modalities. For medical device designers, the challenges to creating leadless dual-chamber systems are considerable. To provide effective therapy, the two leadless devices must be able to decipher what the other is doing. Although direct device−device communication is theoretically possible, it must be accomplished with significant consideration to the finite battery life of the employed leadless devices. In addition, designers must account for the substantial differences in tissue biomechanics and hemodynamics across chambers. Simply put, the currently existing ventricular leadless devices are not readily transferable to atrial or dual-chamber pacing applications. Therefore, medical device engineers must critically understand clinical needs to deliver therapies that can maximally benefit patient populations indicated for bradycardia therapy.

6.5.2 Endocardial LV pacing and novel CRT

In addition to bradycardia pacing, the benefits of leadless pacing may be an aid for CRT. Currently, the WiSE-CRT (EBR Systems, Sunnyvale, CA, United States) pacing system utilizes ultrasound technology paired with a "passive" (no battery required) leadless endocardial receiving electrode.[42] The WiSE-CRT system consists of a traditional dual-chamber (RA, RV) and a transmitter/receiver combination that stimulates the LV endocardium. After a traditional lead applies a pacing stimulus to the RV, an ultrasound wave is emitted by a subcutaneous transmitter. A receiver implanted in the LV converts this ultrasound energy into a pacing stimulus. As such, the system delivers LV synchronization pacing through the endocardial LV. Early studies with this leadless CRT system have shown that the device may be able to improve outcomes in patients who do not respond to traditional CRT therapeutic approaches.[42]

Conceptually, multiple device solutions, such as those proposed by WiSE-CRT, can fit a wide variety of clinical needs with these novel technologies. For example, another combination of a leadless pacemaker and a subcutaneous defibrillator may be able to substitute for traditional implantable cardio defibrillator (ICD) leads. Indeed, early studies have aimed to pair the two devices and suggest that leadless pacemaker performance was not affected by a subcutaneous defibrillation shock.[43,44] One limitation of pairing the currently market-available leadless pacemakers with subcutaneous defibrillators is the lack of antitachyarrhythmia pacing capabilities (as can be provided by most ICD leads). It should be noted that Boston Scientific (Minneapolis, MN, United States) has started investigating a new leadless technology that will pair with their market-released subcutaneous defibrillator. In early ovine studies, they have shown feasibility in the design, which would allow device–device communication and leadless antitachyarrhythmia pacing before attempting defibrillation.[45] These up-and-coming technologies may eventually substitute for traditional transvenous ICD coils, providing the benefits of leadless technology without sacrificing functionality.

The WiSE-CRT system actually combines two common regions of interest for next-generation pacing: leadless technology and endocardial LV stimulation. Currently, FDA approved CRT is delivered through epicardial electrodes, generally placed through the venous vasculature. Notably, epicardial LV pacing introduces multiple areas of clinical concern, including (1) nonresponse due to unsuitable coronary venous anatomy, (2) phrenic nerve activation, and/or (3) less physiologic epicardial-to-endocardial activation. By contrast, endocardial LV pacing theoretically allows for pacing from any LV site, perhaps resulting in idealized, more physiologic lead placement. In addition, it has been reported that LV endocardial pacing improves acute hemodynamic functional indices compared to epicardial pacing[46]; however, there are no randomized data demonstrating superior chronic outcomes. Further, with endocardial pacing, there is a diminished risk of phrenic nerve stimulation, a more physiologic

endocardial-to-epicardial activation pattern, and a larger area of myocardial substrate to pace. In future pacing therapies, endocardial LV access might be gained transapically, transmurally, transaortically, or perhaps across the interatrial or interventricular septae. One must consider that any leaded endocardial LV pacing solutions must take care to mitigate the risks of thromboembolism and/or mitral valve regurgitation. Future CRT technologies—whether leaded or leadless—are likely to leverage the benefits of endocardial LV stimulation.

6.5.3 Next-generation CRT: employing multisite pacing

Importantly, contractile dyssynchrony is the underlying substrate for CRT. As such, a recent clinical hypothesis postulates that pacing at multiple LV locations may improve overall resynchronization and thus improve both resting cardiac output (ejection fraction) and clinical outcomes. There are two overarching ideas on how to accomplish this: (1) using multisite pacing with two or more LV leads, each placed within the coronary vasculature; or (2) employing multipoint pacing using a single multipolar lead.

Multisite pacing has been shown to improve acute hemodynamic responses in HF patients,[47,48] but a recent study has shown no benefit over the best single pacing location.[49] While modern CRT systems offer options for delivering multiple point pacing, there have been significant drawbacks to these approaches. Currently, multiple point pacing using two LV leads is accomplished via a Y adapter, thus the additional hardware leaves multisite pacing systems at a higher risk for chronic loss of capture.[50]

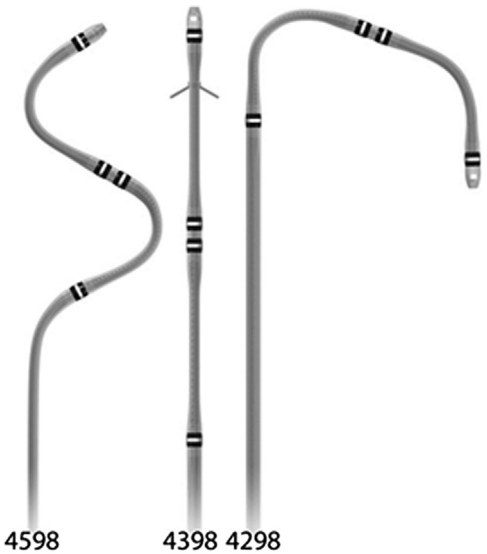

Figure 6.16 Attain Performa quadripolar lead family. *Courtesy of Medtronic.*

Battery depletion also remains a significant issue, as the implanted pulse generator is responsible for delivering therapy through two parallelized leads.[50] Chronic placement of multiple LV leads has yielded mixed results, and chronic studies of multiple point pacing from quadripolar lead have not demonstrated systematic benefit. Nevertheless, multisite pacing remains an active area of interest.

Quadripolar leads have emerged as a viable means for delivering multipoint pacing (Fig. 6.16). In a quadripolar lead, the clinician attains the ability to choose a pacing vector from four electrodes placed on the distal portions of the lead body (e.g., the pacing vector may be programed between electrodes 1−2, or 1−4, or 2−4, etc.). Having the ability to select the pacing vector reduces the probability of phrenic nerve capture during pacing and simultaneously minimizes the chance of high pacing capture threshold (as a separate vector can be selected, should capture threshold rise). Early studies show acute hemodynamic advantages and lower mortality rates with quadripolar leads when compared to bipolar leads.[51,52]

6.5.4 Batteryless pacing

As noted multiple times within this chapter, battery depletion has been a longtime limiting factor in cardiac pacemaker therapy. Whether considering the first IPGs or modern leadless devices, limited battery life remains a significant barrier to advancing pacing therapy. As time has passed, battery chemistry has provided dramatic reductions in battery size (early pacemakers exceeded 60 g mass, while current leadless devices are less than 2 g) while improving battery longevity. An attractive, yet currently clinically unattainable concept is pacing without a battery or with batteries that can be recharged transcutaneously.

The human heart beats an estimated 2−3 billion times during an average lifetime. Each beat of the heart couples electrical wave fronts into mechanical beats. As such, any pacemaker energy source must be inexhaustible in order to replace battery technology. Research efforts have focused on many avenues. Perhaps some of the more promising efforts have centered on the beating of the heart to power pacemakers using either mechanical coupling or piezoelectrics.[53,54] Other attempts have aimed to harvest solar energy to power cardiac pacemakers.[55] These concepts have been tested in animal models but remain in the realm of research.

Other research efforts have focused on generating biological pacemakers using gene or stem cell therapies.[56,57] Biological pacemakers are still early in research phases. There are many challenges to overcome including, but not limited to, engraftment and the significant potential for promoting arrhythmia. Nevertheless, if these problems can be solved, they will have applications to all clinically implanted devices within humans (e.g., deep brain stimulators, or LV assist devices).

6.6 CONCLUSION

This chapter provided an overview of pacemaker technologies, firmly establishing the vibrant history of the device, describing state-of-the-art technologies, and providing a glimpse into the future of this bright field. Throughout the history of the pacemaker, clinical inspiration has driven both ground-breaking research and innovation. The symbiosis between engineering and medicine pivotally shaped the development of these life-saving technologies and will prove to be just as critical moving forward.

LIST OF ABBREVIATIONS

AT atrial tachyarrhythmia
AV atrioventricular
CRT cardiac resynchronization therapy
ICD implantable cardio defibrillator
IPG implantable pulse generator
LV left ventricle/left ventricular
RA right atrium/right atrial
RV right ventricle/right ventricular

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