The first cardiac implantable electronic device (CIED), the electronic pacemaker, maintains cardiac contraction during bradycardia. The implantable cardioverter-defibrillator (ICD) manages ventricular tachycardia (VT) or fibrillation (VF) and saves lives primarily through the use of high-energy shocks. The cardiac resynchronization therapy (CRT) device restores interventricular and intraventricular dyssynchrony in patients with heart failure (HF). Despite >50 years of pacing and 40 years of ICD therapy, the lead remains the weakest link between the device and the patient. Although CRT reduces mortality and morbidity in HF, it is applicable only to those patients with systolic left ventricular (LV) dysfunction and wide QRS complex, especially left bundle-branch block. At best, only 70% of such patients respond, and the majority of patients without left bundle-branch block or with nonsystolic HF derive no benefit from CRT. Early detection of worsened HF with implantable sensors enables corrective therapy to avert acute decompensated HF. Implantable cardiac monitors (ICMs) allow monitoring of arrhythmias such as atrial fibrillation (AF). Despite their efficacy at eliminating the risk of sudden cardiac death (SCD) in the highest-risk patient, ICDs currently have a limited role in reducing the overall burden of SCD, and ICM has the potential for early identification of asymptomatic subjects at risk of SCD to derive benefit from ICD. An increasing cause of SCD is pulseless electric activity (PEA), and alternative management other than defibrillation will be required. This review addresses the recent exciting development of CIEDs in response to these unmet clinical needs such as leadless and endocardial pacing, subcutaneous ICD (S-ICD), low-energy multistage electrotherapy for VT and AF, intermediate-strength stimulation for PEA, early detection of VT, sensors for HF monitoring, and novel therapies for arrhythmias and HF.

**Cardiac Pacing and Resynchronization Therapy**

**Limitations of Cardiac Pacing With Current Pacemakers and CRT**

Despite the significant improvements in device longevity, reliability, size/profile, and ease of implantation over the last 50 years, implanting a pacemaker or CRT currently requires a surgical procedure to create a pocket and venous access to deliver 1 or more transvenous leads. Patients are concerned about device failure and longevity, the cosmetic effect of the pocket, environmental interference, and compromised lifestyle and mobility. In addition to patient discomfort, the surgical pocket is associated with the risk of infection and bleeding, especially in patients prescribed antithrombotic therapy, and patients are exposed to vascular access complications and lead dislodgement (Table 1). Such complications increase with the number of leads involved and the need for device replacement or upgrade. Moreover, long-term clinical problems after implantation include pocket and lead infection and lead interaction with cardiac structures. Lead fracture is a major concern. The global increase in patient longevity will increase the incidence of lead-related problems. Among all components, the pacing leads are the weakest link between patients and CIEDs. Finally, the optimal sites of pacing to preserve or enhance heart function remain unclear or cannot be achieved with existing transvenous leads. As a result, alternative approaches to achieve cardiac pacing are being investigated.

**Leadless Pacing**

The concept of a leadless pacing or pacemaker has been developed that uses either a totally self-contained intracardiac pacemaker, which is now undergoing clinical trials, or pacing from an external energy source, which remains experimental at this time.

**Totally Self-Contained Intracardiac Pacemaker**

In 1970, Spickler et al4 reported the implantation of a totally self-contained leadless intracardiac pacemaker (18x8 mm) through a transvenous sheath (Figure 1), which was limited by an unreliable battery. This concept has now been revisited by several manufacturers. In a sheep study, Bonner and Eggen5 used a 1-in-long steroid-eluting bipolar capsule pacemaker for pacing and sensing in the right ventricle (RV). This device was fixed with metal tines, could last for 7 years, and had bidirectional telemetry. The problems of a totally implanted intracardiac pacemaker are related to the stability and durability of pacing and sensing function, extraction, and replacement and to a size that is at present too large for use in other cardiac chambers. Other similar systems of a smaller size have been developed.
those measurements made by transthoracic echocardiography. This window was sufficient for subcutaneous implantation of the ultrasound generator, even after accommodating changes with respiratory movement and body positioning. Based on these findings, an implantable leadless pacing system using ultrasound (WiCS, EBR Systems) has been developed and is designed for use with either a dual-chamber pacemaker or an ICD as a coimplant. The receiver electrode is small and embedded in the endocardium without any dislodgement, and complete endothelialization has been demonstrated in animal studies. The first human attempts were made in 2011.

There are concerns about the long-term safety and feasibility of continuous ultrasound stimulation and other leadless technologies (Table 2). For example, efficiency of energy transfer, interference from ubiquitous environment sources, sensing of intrinsic cardiac activities, and most important, a reliable, easy-to-use, low-risk delivery system are crucial for the acceptance of this technology.

Electric pulses transformed from an alternating magnetic field have also been tested in swine for leadless cardiac stimulation. A parallel receiver axis with the induced magnetic field provides the most efficient energy transfer, at present 15 to 20 times higher than the power used in a conventional pacemaker. Because of an alternating induction current, only a nonrectangular pulse is generated, but it provides pacing efficiency in animals similar to that of a standard square-wave pulse. This alternative power source is interesting, although the external energy source is bulky and issues similar to those for ultrasound energy apply (Table 2).

or that are capable of being retrieved and replaced are under investigation.

**Externally Powered Leadless Pacemaker**

In an externally powered device, smaller electrodes can be made for implantation via either an endocardial or an epicardial approach. Energy can be harvested from intrinsic electric activities or by using mechanical energy from cardiac motions to convert to electric energy for cardiac stimulation. Vibrations from cardiac contractions captured by a piezoelectric crystal have been estimated to generate sufficient electric energy for cardiac stimulation. The concern about this approach is whether sufficient and durable energy can be attained, especially if implanted endocardially and in the setting of impaired LV function. This concept remains experimental.

Acoustic energy induced by ultrasound is another potential energy source that could drive a remotely positioned electrode for cardiac stimulation without any histological evidence of myocardial damage. In the first-in-humans acute study, ultrasound-mediated pacing could be achieved in the right atrium, RV, and LV and at the coronary sinus via an electrode mounted on a transvenous catheter (Figure 2). A maximum of 2.16±1.10 V was induced by ultrasound at a transmitter-to-receiver distance of 11.3±3.2 cm. The mechanical index, a measure of potential tissue trauma, was well within the recommended safety level. A subsequent study in HF patients also confirmed the feasibility of ultrasound-mediated pacing. In these patients, the acoustic window measured by computed tomography was 39.6±18.2 cm² and correlated with

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CRT indicates cardiac resynchronization therapy; and MRI, magnetic resonance imaging.

Figure 1. Implantation of a totally self-contained intracardiac pacemaker. A, Internal jugular (or femoral) venous access is used to deliver the device to the right ventricle. B, The device is attached by a fixation mechanism, and the pacing and sensing parameters are tested while still connected to the catheter. C, After achieving satisfactory electric parameters and stability, the device is deployed and the sheath is withdrawn. D, The device can be extracted with the use of a wire loop to snare the connecting mechanism at the free end of the implanted intracardiac pacemaker.
Alternative Approaches for LV Pacing

Even in experienced hands, postoperative complications of CRT have been reported in 8.6% to 11.9% of cases, and 8% of patients may require reoperation to manage coronary sinus lead dislodgement, high pacing threshold, phrenic nerve stimulation, or infection. Although implantation success is improving, an optimal response is not achieved in 30% of patients.

Echocardiographic Doppler- and electrogram–based AV and VV optimization, including pacing synchronized to intrinsic RV activation, may enhance the supine hemodynamics and compensate for the variability of the LV lead site in individual patients. However, routine AV programming is not superior to fixed AV programming. Using echo speckle tracking to guide LV lead positioning to the latest site of mechanical contraction free from scar, Khan et al showed a significantly improved volume responder rate from 55% to 70% compared with standard CRT (P<0.03). Retrospective analysis also suggests that pacing at the site with the longest local coronary sinus electrogram delay to the onset of QRS may improve clinical response. However, an optimal site may not always be achievable because of the constraints of coronary sinus anatomy, and lack of an optimal site is associated with suboptimal CRT response.

An alternative approach for LV pacing is surgical epicardial lead placement via video-assisted thoracoscopy or a mini-thoracotomy, which are currently used if coronary sinus lead placement has failed or during concomitant surgical procedures. Moreover, the LV pacing sites can be further optimized by a pressure-volume loop during implantation. Percutaneous placement of novel epicardial pacing lead over LV epicardium via a nonsurgical subxiphoid puncture is under clinical evaluation. This method is simpler and safer than existing surgical approaches, but the long-term stability and feasibility of a percutaneous LV epicardial lead require further investigations.

Compared with epicardial pacing, endocardial LV stimulation simulates normal cardiac activation with more rapid intraventricular and transmural conduction, which may have greater hemodynamic benefits. In a canine model of left bundle-branch block with or without ischemic cardiomyopathy, endocardial pacing achieved better electric resynchronization and improved LV hemodynamic parameters, including LV dP/dT max and stroke work, compared with epicardial pacing. In HF patients with ischemic cardiomyopathy, acute LV endocardial pacing achieved a better hemodynamic response than the best epicardial coronary sinus pacing. Optimal LV endocardial sites were not always the latest mechanical activation site as determined by tissue Doppler echocardiography, and hemodynamic mapping of the best endocardial site may be required. Several investigators have used either standard pacing or active fixation lumenless leads to pace the LV endocardium with the use of transseptal puncture from either the subclavian or femoral veins. These preliminary attempts suggest that endocardial LV pacing is feasible, but general clinical application is uncertain because of the risk of lead dislocation, wound hematoma, interference with mitral valve function by leads, strokes, and lifelong anticoagulation requirement. Thus, as mentioned, leadless pacing is an obvious alternative approach to achieve endocardial LV pacing.

Implantable Cardioverter-Defibrillator

Subcutaneous ICD

An entirely S-ICD was initially targeted at a particular patient population in whom placement of transvenous leads or
epicardial patches was not practical or was associated with a significant risk of morbidity and mortality. The S-ICD may provide certain advantages over the conventional ICD system by avoiding the short- and intermediate-term complications of transvenous leads, including pneumothorax, hemothorax, pericarditis, vein thrombosis, cardiac perforation, infection, and tricuspid valvular dysfunction (Table 1). More important, the high failure rates (20%–40% over 8–10 years) of transvenous defibrillation leads are a major concern because failure can cause inappropriate shock and ICD failure and thus require lead revision or extraction procedures that are associated with substantial morbidity and mortality, which the S-ICD may address.

During short-term human testing, the vector with the lowest defibrillation threshold (32.5±17.0 J) consisted of a left lateral subcutaneous pulse generator with an 8-cm defibrillation coil (between 2 sensing electrode) positioned at the left parasternal margin. Three different sensing vectors are used: the proximal ring to distal tip electrode, the distal tip to proximal ring electrode. These electrode configurations provide an ultra–far-field signal that closely mimics the surface ECG with good specificity (98%) for the discrimination of supraventricular tachycardias compared with a conventional ICD.

The detailed operation and function of the currently available S-ICD (Boston Scientific) have been described. In brief, the S-ICD automatically selects the optimal vector for rhythm detection without double counting of QRS or T-wave oversensing. A template based on up to 41 points of the QRS complex is then stored for morphological discrimination. The S-ICD includes a rhythm detection algorithm with up to 2 zones of detection and defibrillation (80 J) for VT/VF. In the initial pilot human study, S-ICD had 100% sensitivity to detect VF, in which 98% of patients were successfully converted at 65 J. Then, S-ICD was implanted in 55 patients, 3 of whom developed 12 episodes of spontaneous VF and were successfully defibrillated by S-ICD after a mean of 10 months of follow-up.

Several subsequent reports of the clinical experiences of S-ICD are available (Table I in the online-only Data Supplement). A total of 274 patients have been included in these trials. In the earlier reports, the majority of implantations were in younger patients for primary prevention. Subsequently, more devices were implanted in patients for secondary prevention, and there was a higher prevalence of prior transvenous ICD failure or infection. The S-ICD implantation success rate was high, with only a few failures and an infrequent need to exchange for transvenous ICD for high defibrillation threshold or frequent/incessant VT/VF. The procedure-related complications, including wound erosion and infection, appeared to be higher in younger patients, and the most common cause of inappropriate shocks was T-wave oversensing, which resolved with device reprogramming. There are some potential concerns about the lack of pacing capability for bradycardia or antitachycardia pacing. Nevertheless, recent results from the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) provide reassuring data on simple device programming of transvenous ICD with 1 to 2 shock zones without antitachycardia pacing. Implementation of this concept in S-ICD may be expected to reduce inappropriate therapies and to improve survival in patients for primary prevention. Currently, the potential candidates for S-ICD include patients with no access to the venous system or ventricle (eg, those with mechanical heart valves or complex congenital heart) and patients at high risk of lead-related complications (active young patients, those with an existing indwelling catheter, immunocompromised patients, patients with prior device infection). As primary prevention, S-ICD can be considered for those with a low risk of recurrent VT or bradycardia, for example, inherited channelopathies, idiopathic VF, and hypertrophic cardiomyopathy. S-ICD may not be suitable for patients with a high risk of recurrent VT/VF, those with bradycardia requiring pacing, or patients in whom CRT is indicated. With appropriate patient selection, S-ICD is an effective alternative to transvenous ICD as device therapy for primary and secondary prevention of SCD and addresses the main long-term concern about lead fracture in conventional ICD.

The S-ICD is now clinically available. However, further improvement in the size of the device and in battery longevity and the incorporation of future device technologies such as leadless pacing and remote monitoring are required. Comparative clinical studies of its safety and efficacy with conventional ICDs in their current indications are essential. If such requirements are met, it is likely that S-ICD will become a mainstream therapy for SCD, especially for primary prevention. Because of the relative ease and safety of implantation and the freedom from long-term lead-related issues, the use of S-ICD may be investigated in populations at risk of SCD such as those with major cardiac risk factors who are not included in current ICD trials.

Low-Energy Multistage Electrotherapy for Atrial and Ventricular Tachyarrhythmias

Both appropriate and inappropriate defibrillator shocks are associated with adverse long-term outcomes and negative psychological impact for many patients. Similarly, discomfort-related high-energy shocks also limit the patient’s acceptance of device therapy for AF. Although the number of ICD shocks can be minimized by device programming, it is desirable to have alternative electric therapies for atrial and ventricular tachyarrhythmias that require significantly lower energy for defibrillation and thus reduce patient discomfort, battery consumption, and possibly myocardial damage. In vitro experimental studies suggested that multiple low-energy shocks maintain an area of myocardium refractory to reentry and terminate arrhythmias. Multistage electrotherapy using multistage biphasic shocks delivered between the left and right atrial vectors significantly reduce atrial defibrillation threshold to <1 J (0.19–0.51 J) in a canine model of induced AF. Multistage electrotherapy using monophasic shocks delivered between transvenous RV and coronary sinus coils within a single VT cycle length significantly reduced the mean ventricular defibrillation threshold for antitachycardia pacing–refractory monomorphic VTs to nearly 80-fold lower energy that a biphasic shock (0.03±0.05 versus 2.37±1.20 J; P<0.001). Moreover, at a peak shock amplitude of 20 V, multistage electrotherapy was significantly more effective than biphasic shock in terminating VT (91.3% versus 10.5%;
Medium-Voltage Electric Therapy for PEA

In patients implanted with ICD, a significant proportion (25%–60%) died of SCD with PEA as the initial arrhythmia or after defibrillation.\(^43,44\) The incidence of VF SCD has decreased, whereas non-VF SCD has increased over time,\(^45\) possibly as a result of defibrillation, the use of β-blockers, and changing disease pattern. Patients with postshock PEA rarely survive because of the lack of immediately effective therapy except cardiopulmonary resuscitation. Prior experimental studies showed that trains of electric stimulation, called medium-voltage electric therapy, applied via trans-thoracic or intracardiac electrodes can augment coronary and cerebral perfusion during VF or PEA.\(^46,47\) Although the mechanism remains unclear, it has been proposed that medium-voltage electric therapy causes thoracic (skeletal) and myocardial muscle contractions that promote blood flow much like mechanical chest compression. Two different pulse train protocols have been tested: a very short pulse width of 0.15 milliseconds delivered at 14 pulses per train and a long pulse width of 7.5 milliseconds at 7 pulses per train to induce thoracic (skeletal) and myocardial muscle contractions.\(^48\) In a large-animal model of VF, both skeletal-based and cardiac-based medium-voltage electric therapy significantly increased the coronary perfusion pressure compared with control, which was comparable to that generated by manual chest compression. Among different stimulation parameters, increasing the pulse train width from 50 to 200 milliseconds and the train rate from 60 to 120 trains per minute further improved the efficacy of medium-voltage electric therapy.\(^46\) This novel electric cardiopulmonary resuscitation technique can potentially be implemented in the transvenous ICD or S-ICD via transvenous or subcutaneous electrode. Nevertheless, the application of this technology requires integration with an external\(^49\) or internal\(^50\) blood pressure sensor for the detection of PEA to trigger the medium-voltage electric therapy. Moreover, the potential interaction of the medium-voltage electric therapy and ICD, especially noise sensing during medium-voltage electric therapy, remains a major concern. Medium-voltage electric therapy remains in the experimental stage.

Device-Based Monitoring of HF and Arrhythmias

HF Monitoring

Hospitalization for HF is costly and associated with significant morbidity and mortality.\(^51\) Thus, prevention of HF hospitalization can have significant prognostic benefit for the patient and can reduce the cost of HF management. Unfortunately, traditional signs and symptoms of HF such as dyspnea and weight changes either are inaccurate or become evident only late in the course of disease.\(^52\) As CIEDs have been increasingly used in HF patients, incorporation of implantable sensors in such devices may provide an alternative to monitoring, particularly when coupled with Internet-based data transmission.

Acute decompensated HF occurs with initial changes in mechanical cardiac function and/or volume and pressure changes. Impaired tissue perfusion results in compensatory neurohormonal changes that are reflected by biochemical changes such as reduced mixed venous oxygen saturation and sympathovagal activities as reflected by heart rate variability. Ultimately, pulmonary congestion occurs and precipitates dyspnea, hyperventilation, and reduced patient activity. Such changes are detected by electric, biochemical, hemodynamic, or contractility sensors (Figure 3). The collected information is currently accessible by patients, physicians, or both for an intervention. A closed system is envisaged in which an automatic feedback mechanism can affect the volume or pressure status such as the use of automatic drug injection pump. Furthermore, novel stimulation such as neuromodulation therapy may counteract the decrease in cardiac contractility that triggers cardiac decompensation. To be effective, the sensors should have good sensitivity and specificity for HF worsening and antedate clinical HF sufficiently early for intervention.

Figure 3. Concept for heart failure development and the role of heart failure monitoring. Starting with a change in cardiac contractility or a volume-pressure change, neurohormonal compensation will set in. When such compensations are insufficient, the onset of clinical heart failure with congestion follows. These sequences of events are associated with changes in hemodynamic, biochemical, electric, and other parameters. At present, the detected changes are sent to either the patient or the physician using remote patient monitoring, or automatic advice is given to the patient for corrective measures. In the future, an automatic feedback loop can avert the triggers and other heart failure changes such as the use of automatic drug injection pump or neurohormonal modulation pacing.
Electric Sensors
Activity sensing with accelerometers is an accurate reflection of exercise performance.51 The absence of activity usually signifies that the patient is at rest and allows other measurements such as respiratory parameters to be determined. In CIEDs, heart rate variability can be measured as a standard measure of the variability of the atrial cycle length of sensed atrial beats or as a graphic presentation (Foot-print, Boston Scientific).54 However, heart rate variability is not feasible during atrial pacing or AF and can be affected by the use of cardiovascular medications. Both activity and heart rate variability are now standard parameters in most CIEDs but have a limited role in predicting HF.

Changes in the ST segment of an ECG can be monitored by a virtual ECG recorded from the unipolar RV intracardiac electrogram. This type of intracardiac electrogram recording may allow early detection of myocardial ischemia55 and the development of HF and VT/VF. Nevertheless, ST-segment monitoring is not feasible in patients with preexisting bundle-branch pattern or those who require ventricular pacing or CRT, and the current algorithm requires further improvement in sensitivity and specificity for the detection of acute ischemic events.56

Impedance Sensor for Pulmonary Edema and Cardiac Contractility
Dyspnea caused by lung congestion is the most common presenting symptom of acute decompensated HF. Through the use of nonstimulating currents delivered between bipolar electrodes from defibrillation/pacing leads and the CIED casing, a drop in transthoracic impedance could be monitored to detect pulmonary congestion before the onset of dyspnea and subsequent hospitalization.57 An intrathoracic impedance sensor algorithm, for example, Optivol (Medtronic), has been implemented in CIEDs for HF monitoring. However, a recent randomized, controlled trial in class II to III HF patients58 showed that the use of Optivolt with an audible alert did not reduce the number of deaths or hospitalizations and that the number of outpatient visits may be increased compared with conventional therapy, RV pressure–guided HF therapy showed only a nonsignificant 21% reduction (P=0.33) in either HF hospitalization or the need for intravenous diuretics.66 One of the advantages of an RV pressure sensor is the ability to track right-sided volume status, which may be important for edema occurrence of false-positive alerts as a result of other pulmonary conditions such as pleural effusion and pneumonia that may also decrease impedance is of concern. The use of multivector detection may reduce the false-positive detection rate from 0.74 to 0.56 per patient-year61 but requires clinical testing.

Unipolar impedance injected from the RV apex to the CIED casing samples a small region in the cardiac apex. This results in a signal called closed-loop stimulation (Biotronik), reflecting regional contractility.62 Injected nonstimulating currents flowing between different intracardiac electrodes (RV, LV, and right atrium) and the CIED casing allow assessment of LV contractile function as impedance drops with decreased LV volume.61 This sensor has been suggested to be useful for detecting the increase in cardiac contractility before vasovagal syncope.62 Despite its availability for some time, the value of this sensor in HF monitoring has not been clearly defined.

Biochemical Sensors
Although measurement of venous saturation with a specialized lead is feasible and has good correlation with standard invasive assessment, the lack of reliable sensing over time has limited the use of this sensor.63 Other biochemical sensors have been suggested, but none has yet been successfully implemented in CIEDs (Figure 4).

Pressure Sensors
An accelerometer has been incorporated into the tip of a pacing lead to detect peak endocardial acceleration, although this has not found widespread application in HF monitoring.64 Pulmonary arterial (PA) pressure and PA wedge pressure monitoring can provide tailored therapy for patients admitted with advanced HF.65 Ambulatory monitoring of RV pressure to derive PA diastolic pressure has been achieved with the use of a piezoelectric crystal incorporated into the tip of a pacing lead positioned at the RV outflow region. Compared with conventional therapy, RV pressure–guided HF therapy showed only a nonsignificant 21% reduction (P=0.33) in either HF hospitalization or the need for intravenous diuretics. One of the advantages of an RV pressure sensor is the ability to track right-sided volume status, which may be important for edema.
or cardiorenal syndrome. However, the use of a combined ICD and RV pressure–sensing lead was limited by the high risk of lead failure, and RV pressure measurement may be affected by pathological conditions such as mitral valve disease, tricuspid regurgitation, and high pulmonary vascular resistance.

A PA pressure transducer (Champion, CardioMENS, Atlanta, GA) that can be deployed in a branch of the PA for continuous PA pressure monitoring has been developed. In a randomized study, standalone PA pressure monitoring in patients with class III HF resulted in a 28% (P=0.0002) and 39% (P<0.0001) reduction in HF-related hospitalization at 6 and 15 months of follow-up, respectively, compared with conventional therapy.

A direct method to measure LV filling pressure is left atrial (LA) pressure monitoring. The HeartPOD LA pressure monitoring device (St. Jude Medical) comprises an implantable pressure–sensing lead w...
diagnosis and early recognition of cardiac arrhythmias and possibly extended to monitor other cardiac disorders and to identify subjects at risk of SCD. At present, early detection of AF by CIED, often in combination with remote monitoring, allows the physician to intervene early to avoid the adverse consequences of AF, including HF and thromboembolic events. In hypertensive patients without documented AF who received a CIED, device-detected atrial high-rate episodes defined by an atrial rate ≥190 bpm as short as 6 minutes increased the risk of stroke and peripheral embolism by 2.49-fold and the development of clinical AF by 5.56-fold in 2.5 years.78 However, whether the use oral anticoagulation therapy based on the presence or absence of atrial high-rate episodes detected by CIED reduces thromboembolic events awaits prospective trials.77

Subcutaneously implanted ICM for surface electrogram is currently used to evaluate the cause of explained syncope. This is now developed for the detection of AF after ablation79 and as a cause of cryptogenic stroke.78 As a result of the low subcutaneous amplitude of atrial electrogram for its direct detection, the current ICM algorithm based on the irregularities of RR intervals has a moderate efficacy in predicting AF but has excellent negative predictive accuracy.80 Moreover, ICM has been tested in patients with LV dysfunction after myocardial infarction,81,82 In these studies, detection of AF ≥30 seconds increased cardiac events by 3-fold as a result of progressive HF, reinfarction, and cardiovascular death. The occurrence of nonsustained VT ≥16 beats also increased cardiac death by 2-fold. Recently, pressure-measuring ICM implanted over the femoral artery has been developed for monitoring blood pressure in hypertensive patients.83 Given that a large proportion of subjects presenting with SCD have only risk factors rather than manifest HF or arrhythmias, integrated pressure- and electrogram-measuring ICM with automatic remote activation of an emergency medical system49 may facilitate early resuscitation in these subjects. AF surveillance devices are now miniaturized, and implantation is minimally invasive. If proven clinically effective, they will become the norm for most patients with documented AF and possibly for individuals with risk factors for AF for early AF detection and preventive intervention to avert strokes.

Novel Therapies for Cardiac Rhythm and HF

Biological Pacemakers

Although CIEDs are effective, they are palliative measures associated with significant limitations and thus prompt the quest for alternatives. Lead-related issues and finite battery longevity are the 2 major concerns of CIEDs. In the last 2 decades, different biological approaches using gene- or cell-based therapies have been investigated to induce pacemaker activity (Table II in the online-only Data Supplement). Although these approaches are feasible, overexpression of wild-type channels alone, for example, hyperpolarization-activated cyclic nucleotide–gated channels, has failed to induce sufficient automaticity in quiescent ventricular cardiomyocytes because of the complex interaction between native ion channels.83,84 This hurdle can be partially overcome by protein engineering to modify the ion channel structure and thus provide more favorable biophysical properties.85,86 Although conceptually attractive, technical and safety concerns have restricted the successful clinical application. Specifically, the long-term efficacy of these biological alternatives has yet to be demonstrated. In all cases, the transgene expression is only transient (plasmid-based or adenoviral-based gene delivery), typically over a period of weeks, and thus is not comparable to their electronic counterparts. Furthermore, although a certain level of adrenergic responsiveness has been demonstrated in the engineered HCN channels,87 the genuine neurohumoral responsiveness remains to be demonstrated. The overall phenotypic shift is a function of the transgene expression and the intrinsic electrophysiological properties of the recipient cardiomyocytes.

In addition to an ion channel–based gene approach, use of pacemaker cells derived from human embryonic stem cells87 or transdifferentiated from terminally differentiated cardiomyocytes using different transcription factors88 has been explored to develop biological pacemaker. Overexpression of Na channels in human embryonic stem cell–derived cardiomyocytes has also been investigated as a novel approach to restore or improve conduction slowing or block in the myocardium.89 However, the long-term safety and feasibility of these cell-based or combined gene- and cell-based approaches require further evaluation. Moreover, because the long-term stability of these biological therapies remains a major concern, they are likely to be used as a hybrid approach with CIEDs such as leadless pacemakers to provide backup pacing support but to reduce the battery consumption for those devices (Figure 5).

Neuromodulation Therapy for HF

In patients with myocardial ischemia and systolic HF, dysregulation of the autonomic nervous system with increased sympathetic tone and decreased parasympathetic tone plays an important role in the pathogenesis of VT/VF and in the progression of LV dysfunction.90,91 Thus, novel therapeutic approaches that modulate the autonomic nervous system to restore this imbalance between the sympathetic and parasympathetic nervous systems may improve symptoms or clinical outcome. Currently, 3 device-based neuromodulation therapies are being investigated in phase I/II clinical trials for HF.

Vagal Stimulation

Direct activation of the parasympathetic nervous system via vagal nerve stimulation has been shown to improve LV function in small- and large-animal models of HF.92 A programmable implantable neurostimulator system (CardioFit model 5000, BioControl Medical Ltd) has been developed for vagal nerve stimulation. This device senses the heart rate (via an intracardiac electrode) and delivers stimulation at a fixed delay (70 milliseconds) from the R wave to the vagus nerve to avoid excessive bradycardia (<55 bpm) induced by vagal stimulation. Pilot clinical studies93 in 32 patients with class II to IV HF demonstrated that direct right cervical vagal nerve stimulation with the CardioFit system significantly improved the functional class, quality of life, 6-minute walk test, and LV ejection fraction and systolic volumes.94 However, serious adverse events were observed in 40.6% of patients in this initial study,95 and
the long-term safety and efficacy of direct vagal stimulation in HF are being evaluated in an ongoing clinical study.94

**Carotid Baroreceptor Stimulation**

Indirect suppression of the sympathetic nervous system, particularly the renal sympathetic tone, can be achieved by long-term carotid baroreceptor stimulation with an implantable carotid sinus stimulator (Rheos System, CVRx, Inc) for the treatment of hypertension.95 In a pilot study in 45 patients with drug-refractory hypertension, long-term carotid baroreceptor stimulation sustainably reduced blood pressure by 21/12 mm Hg in refractory hypertensive subjects.96 The enthusiasm for this modality for the neuromodulation of the sympathetic nervous system led to ongoing studies of the effect of long-term carotid baroreceptor stimulation in patients with HF: Baroreflex Activation Therapy in Heart Failure (www.clinicaltrial.gov, NCT01484288), Barostim Neo System in the Treatment of Heart Failure (NCT01471860), and Rheos® Diastolic Heart Failure Trial (NCT00718939).

**Spinal Cord Stimulation**

Spinal cord stimulation (SCS) is a clinical technique widely used to treat chronic pain syndromes and refractory angina. Activation of the parasympathetic nervous system with inhibition of the sympathetic nervous system with SCS thus offers a potential novel therapeutic approach to prevent arrhythmias and progressive LV dysfunction in ischemic HF. In a canine model of ischemic HF, prior studies demonstrated that short-term97 and long-term98 thoracic SCS reduced the incidence of spontaneous and ischemia-induced VT/VF. In addition, in a porcine model of ischemic HF, short-term SCS has been demonstrated to improve LV contractile function by decreasing intraventricular dyssynchrony and myocardial oxygen consumption without elevation of serum norepinephrine level.99 These potential clinical benefits of SCS in systolic HF are currently being investigated in 3 phase I/II human clinical trials: Spinal Cord Stimulation for Heart Failure as a Restorative Treatment (SCS Heart; www.clinicaltrial.gov, NCT01362725), Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (Defeat-HF; NCT0112579), and Trail of Autonomic Neuromodulation for Treatment of Chronic Heart Failure (TAME-HF; NCT01820130).

**Cardiac Contractility Modulation for HF**

Cardiac contractility modulation delivers nonexcitatory signals to the myocardium during the absolute refractory period. Previous animal and pilot human studies showed that cardiac contractility modulation improves myocardial contraction without increasing myocardial oxygen consumption in HF. Although the mechanism remains unclear, it has been shown that cardiac contractility modulation enhances the expression of gene and proteins involved with calcium cycling and the myocardial contractile machinery. In a recent randomized, clinical trial (Evaluation of the Safety and Efficacy of the OPTIMIZER System in Subjects With Heart Failure), cardiac contractility modulation had no effect on the primary end point of anerobic threshold in HF patients with narrow QRS and LV ejection fraction ≤35%, but it improved exercise tolerance as measured by peak oxygen consumption and quality of life.100 The role of cardiac contractility modulation therapy in the treatment of systolic HF remains undefined.

**Futuristic Implantable Device for Cardiac Rhythm Management**

An ideal CIED should restore normal automaticity and conduction state (Figure 6). This will require multiple chamber sensing and pacing, preferably with a leadless approach. Considerations should be given to optimizing cardiac hemodynamics, including the use of His bundle pacing. Such intracardiac electrode implants are either powered from external sources or self-powered with regenerating energy. Hybrid gene therapy may be usefully incorporated, not only for conserving battery but also for repairing and exploiting residual native conduction system. They are connected to an external, probably subcutaneous central station that also serves as a power source. Should defibrillation be necessary, the external station can provide an adequate high-energy shock or medium-voltage stimulation for PEA. Because many patients with cardiac arrhythmias have underlying LV dysfunction, this futuristic system should be able to incorporate CRT, have reliable pressure and biochemical sensors for HF monitoring, and have remote telemetry capability and possibly implantable injectable pumps for medication. To avert mechanical dysfunction, to improve HF, and to reduce VT/VF occurrence, a neuromodulation device can also be incorporated into such a system. The safety, effectiveness, and durability of each component remain to be tested. An important development that needs to be realized is effective communication between the components that is also energy efficient and immune to interference. Although the central station remains similar, individual components can be added as other medical conditions develop. Remote patient monitoring of such information and remote programming or automatic feedback are essential for this device.

**Disclosures**

Dr Tse received a research grant and consultant fees from St Jude Medical, Boston Scientific, and Medtronic. The other authors report no conflicts.
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![Image of a document page]


failure device identifies patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. J Am Coll Cardiol. 2010;55:1803–1810.

**Key Words:** arrhythmias, cardiac — cardiac resynchronization therapy — defibrillators, implantable — heart failure — pacemaker, artificial
Future of Implantable Devices for Cardiac Rhythm Management
Chu-Pak Lau, Chung-Wah Siu and Hung-Fat Tse

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The Future of Implantable Devices for Cardiac Rhythm Management

Chu-Pak Lau, M.D.; Chung-Wah Siu, M.D., Hung-Fat Tse, M.D., PhD;
### Supplemental Table 1. Clinical Experiences of S-ICD

<table>
<thead>
<tr>
<th></th>
<th>Dabiri et al\textsuperscript{1}</th>
<th>Jarman et al\textsuperscript{2}</th>
<th>Olde Nordkamp et al\textsuperscript{3}</th>
<th>Kobe et al\textsuperscript{4}</th>
<th>Aydin et al\textsuperscript{5}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>31</td>
<td>16</td>
<td>118</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>53±16</td>
<td>20 (10-48)</td>
<td>50±14</td>
<td>46±16</td>
<td>42±15</td>
</tr>
<tr>
<td><strong>Primary/Secondary prevention, %</strong></td>
<td>67/33</td>
<td>100/0</td>
<td>60/40</td>
<td>59/41</td>
<td>42/58</td>
</tr>
<tr>
<td><strong>Prior transvenous ICD implant, n (%)</strong></td>
<td>2 (6.5)</td>
<td>0</td>
<td>13 (11)</td>
<td>9 (13)</td>
<td>10 (25)</td>
</tr>
<tr>
<td><strong>Etiologies</strong></td>
<td>- Congenital heart disease, n (%)</td>
<td>-</td>
<td>4 (25)</td>
<td>1 (0.8)</td>
<td>3 (4)</td>
</tr>
<tr>
<td></td>
<td>- Inherited cardiac diseases, n (%)</td>
<td>2 (6.5)</td>
<td>10 (62)</td>
<td>15 (13)</td>
<td>14 (20)</td>
</tr>
<tr>
<td></td>
<td>- Idiopathic VF</td>
<td>5 (16)</td>
<td>2 (12.5)</td>
<td>15 (13)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>- Ischemic cardiomyopathy, n (%)</td>
<td>18 (58)</td>
<td>-</td>
<td>45 (38)</td>
<td>11 (16)</td>
</tr>
<tr>
<td></td>
<td>- Dilated cardiomyopathy, n (%)</td>
<td>4 (25.5)</td>
<td>-</td>
<td>22 (19)</td>
<td>25 (36)</td>
</tr>
<tr>
<td></td>
<td>- Other cardiomyopathy, n (%)</td>
<td>2 (6.5)</td>
<td>-</td>
<td>8 (6.8)</td>
<td>17 (25)</td>
</tr>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td>286 days</td>
<td>9 months</td>
<td>18 months</td>
<td>217±138 days</td>
<td>229 days</td>
</tr>
<tr>
<td><strong>Appropriate shock</strong></td>
<td>- Patients</td>
<td>4 (13)</td>
<td>3 (19)</td>
<td>8 (6.8)</td>
<td>3 (4)</td>
</tr>
<tr>
<td></td>
<td>- VT/VF episodes</td>
<td>8</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>First shock efficacy, %</strong></td>
<td>NA</td>
<td>NA</td>
<td>98</td>
<td>NA</td>
<td>57.8</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>- Wound</td>
<td>1 (3.25)</td>
<td>3 (19)</td>
<td>2 (1.7)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td></td>
<td>- Lead</td>
<td>1 (3.25)</td>
<td>-</td>
<td>3 (2.5)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td></td>
<td>- Infection</td>
<td>-</td>
<td>-</td>
<td>7 (5.9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td></td>
<td>- Device</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dislodgement</td>
<td>-</td>
<td>-</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Battery depletion</td>
<td>-</td>
<td>-</td>
<td>2 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Inappropriate shock</strong></td>
<td>5 (16)</td>
<td>4 (25)</td>
<td>15 (12.7)</td>
<td>5 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>- 2 (6.5): T wave over-sensing</td>
<td>- 4 (25): T wave over-sensing</td>
<td>- 9 (7.6): T wave over-sensing</td>
<td>- 3 (4.3): T wave over-sensing</td>
<td>- 1 (2.5): T wave over-sensing</td>
</tr>
<tr>
<td></td>
<td>- 1 (6.7): supraventricular tachycardia</td>
<td>- 1 (6.7): supraventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exchange to transvenous ICD</strong></td>
<td>-</td>
<td>-</td>
<td>1 frequency VT</td>
<td>1 failed implant</td>
<td>2 failed ICD therapy</td>
</tr>
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</table>
### Supplemental Table 2. Experimental Gene-based Approach to Develop Biological Pacemaker

<table>
<thead>
<tr>
<th>Genes</th>
<th>Mechanisms</th>
<th>Vectors</th>
<th>Animal models</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_2$ adrenergic receptor gene overexpression$^6$</td>
<td>Enhancing cardiac chronotropy (but not inducing pacemaker activity) by over-expressing $\beta_2$ adrenergic receptors thereby increasing the cytosolic cAMP.</td>
<td>Plasmid</td>
<td>Right atrium of swine</td>
</tr>
<tr>
<td>Kir-2.1 gene down-regulation$^7,8$</td>
<td>Suppressing the intrinsic repolarizing inward rectifier current, $I_{K_1}$, using a dominant negative construct, Kir2.1AAA</td>
<td>Adenovirus</td>
<td>Guinea pig left ventricle</td>
</tr>
<tr>
<td>Mutated HCN2 gene overexpression$^9$</td>
<td>Increasing the pacemaker current ($I_f$) using a mutant HCN2 channel with a point mutation E324A resulting in positive shift of $\sim$20 mV</td>
<td>Adenovirus</td>
<td>Canine model of complete atrio-ventricular block</td>
</tr>
<tr>
<td>Mutated HCN1 gene overexpression$^{10}$</td>
<td>Increasing the pacemaker current ($I_f$) using a mutated HCN1, HCN1-ΔΔΔ with deletion of amino acid residues, EVY235-7, resulting in a shortened S3-S4 linker favoring channel opening with a positive shift of $V_{1/2}$ of $\sim$5 mV</td>
<td>Adenovirus</td>
<td>Guinea pig left atrium and ventricle, Porcine model of sick sinus syndrome</td>
</tr>
<tr>
<td>Dual gene (Kir2.1AAA/HCN2) approach$^{11}$</td>
<td>Promoting automaticity by simultaneously increasing pacemaker current ($I_f$) by overexpression of HCN2 channels and suppressing the intrinsic repolarizing inward rectifier current ($I_{K_1}$) with using a dominant negative construct, Kir2.1AAA</td>
<td>Adenovirus</td>
<td>Porcine model of atrio-ventricular heart block</td>
</tr>
</tbody>
</table>
Supplemental References


