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EcoMat FUNCTIONAL MATERIALS FOR GREEN ENERGY AND ENVIRONMENT WILEY

REVIEW

Power supplies for cardiovascular implantable electronic devices

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Abstract

The use of cardiovascular implantable electronic devices (CIEDs) has proved to be the most successful device-based therapy to reduce morbidity and mortality of cardiovascular disease over decades. The evolution of power supplies always promotes the development of CIEDs from historical perspectives. However, with the increased demands of therapy energy, modern CIEDs still face huge challenges in terms of longevity, size, and reliability of power supplies. Recent advances in batteries and novel energy devices have provided promising approaches to improve power supplies and enhance the therapeutic capabilities of CIEDs. In this review, we will summarize the therapy energy in different types of CIEDs tailored to specific cardiovascular diseases and discuss the design criterion of implantable batteries. After overviewing the evolution of batteries, we will discuss emerging cutting-edge power technologies, including new battery systems, wearable power management platforms, wireless energy transfer, and leadless and unsealed devices.

KEYWORDS

cardiovascular electronic device, implantable, battery, implantable, wearable

1 | INTRODUCTION

Since the first implantable pacemaker was invented in 1958,[1,2] the enormous development of cardiovascular implantable electronic devices (CIEDs) has been made over the past few decades.[3] Nowadays, the application of CIEDs becomes one of the most important therapeutic technologies to reduce morbidity and mortality of cardiovascular diseases (Figure 1A). More than 1.7 million CIEDs are implanted per year in worldwide[4] to save millions of patients' lives by continuously and precisely monitoring and managing cardiac rhythm. Classified by the function or purpose, one class of clinical-adopted CIEDs is cardiovascular rhythm management devices, which are used to regulate abnormal cardiac rhythm, including pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices (Figure 1B). The other is implantable cardiac monitoring devices, which are implanted for the continuous or intermittent observation of cardiac activity, including implantable loop recorders and cardiac hemodynamic monitors (Figure 1C).

Power supply is the most important component in the CIEDs. From historical perspective, the evolution of CIEDs was always accompanied with the development of power sources.[5] The capacity of power sources determines the application scenarios in clinics and the safety for patients. With the recent advances in electrochemical cells, modern CIEDs can not only provide electrical

stimulation, but sensing and regulation capabilities with improved longevity and biosafety.[6] However, the applications of CIEDs still suffer from limited battery life, insufficient and unreliable long-term functionalities, the relatively large size of devices, device malfunctions, and/or device-induced infections.[7] To date, many research advances offered emerging technologies and promising energy solutions to solve the abovementioned challenges.[3,8–11] In this review, we discuss the therapy energy demands of different CIEDs in clinic scenarios and the principal design criterion of implantable batteries. We review the evolution and emerging energy solutions for CIEDs, and outlook some promising and cutting-edge technologies for the next-generation CIEDs.

2 | ENERGY DEMANDS

2.1 | Cardiovascular rhythm management devices

The application of electronic pacemakers is the most well-known device-based therapy for electrical conduction abnormalities (Figure 1D). For normal cardiac activity, cells in the sinus node undergo spontaneous generation of action potentials, and the electrical wave spread across atria, atrioventricular node, and ventricular, depolarizing tissues, causing atrial and ventricular contraction[12,13] (Figure 1A). When intrinsic cardiac conduction integrity fails, pacemakers can provide periodic electrical stimulation to restore or maintain normal heartbeat. Cardiac pacing has been used as the standard of care for bradycardia (slow heart rhythms), which is generally defined as a heart rate of <60 beats per minute (bpm).[14] The typical electrical stimuli for cardiac pacing are direct current pulses with a fixed duration and a fixed pacing rate. The applied electrical stimulus generates an electric field that initiates cardiac excitation as a result of transmembrane potential. The electric field strength needs to exceed a certain value (~1.5 V/cm) to initiate a self-propagating wave of depolarization (captures the heart).[15] The minimal energy required to activate the myocardium is the capture threshold, which is the interaction of stimulus intensity and the duration of the pulse. From a clinical standpoint, the sites, parameters, and modes of cardiac pacing vary for different cardiovascular diseases. Generally, single-chamber cardiac pacing requires relatively low energy (<0.1 mJ) in each pulse for stimulation of the heart, such as ventricular pacing for the treatment of bradycardia and atrial pacing to

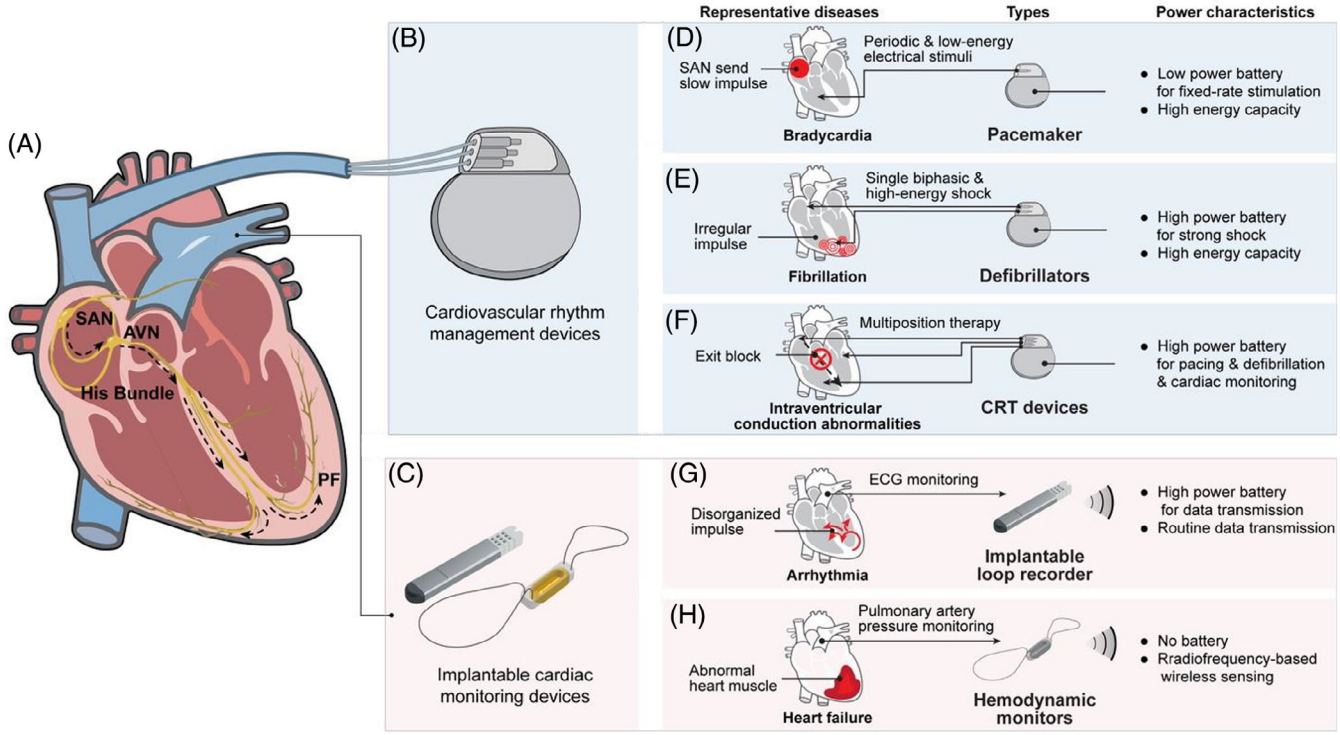

FIGURE 1 Existing cardiovascular implantable electronic devices and their clinical applications. (A-C) Schematic illustration of the anatomy and electrophysiology of the cardiac conduction system with existing cardiovascular rhythm management devices and implantable cardiac monitoring devices. (D-H) Summary of different implantable cardiovascular electronic devices, their clinical applications for representative diseases, and their power characteristics. SAN, sinoatrial node; AVN, atrioventricular node; PF, Purkinje fibers; CRT, cardiac resynchronization therapy. ECG, electrocardiogram.

avoid abnormal ventricular activation. Typically, the impulse of current is less than 10 mA with a pulse duration of 0.3–0.5 ms, and the charge for a delivered pacing stimulus is the product of current and pulse duration.[15,16] Given a fixed energy capacity of the battery in implantable pacemakers, minimizing the amount of energy for each impulse is an important determinant of longevity. Because the design factors of pacing electrodes,[17] and physiologic and pharmacologic factors[18] that affect the capture threshold have been extensively summarized, we will focus on the design criterion of power sources.

ICDs are another type of CIEDs powered by the implantable batteries. ICDs provide shock therapy and become the gold standard treatment for tachycardia, atrial fibrillation, and ventricular fibrillation, preventing sudden cardiac death[19] (Figure 1E). Different from low-energy stimulation therapy provided by pacemakers, a strong shock (>100 J) is delivered by ICDs on the heart to terminate the arrhythmia. Typically, an electric field strength of 6 V/cm is required to achieve ventricular defibrillation.[16] The current amplitude of the shock should approximately reach 10 A, which means the current required for defibrillation is around 1000 times required for cardiac pacing. Despite single biphasic shock therapy being the gold standard, higher performance of power sources is needed because of the development of new shock therapies, including multiple pulse or multistage therapies,[20] a combination of ICDs with pacing therapy for heart failure,[21] and frequent monitoring of heart failure.[22] Given the greater power consumption of ICDs in comparison with that of pacemakers, increasing longevity becomes a priority.[22,23] Many effects have been made on understanding the mechanism and optimization of the shock to achieve an effective and low-energy treatment.[24,25]

With the understanding of cardiac physiology and increasing clinical demands, the use of cardiac pacing has been significantly extended. Cardiac resynchronization therapy (CRT), known as biventricular pacing, has become an established therapy for patients with heart failure and intraventricular conduction abnormalities[22,26,27] (Figure 1F). More than one pacing sites are applied in a simultaneous or sequential order. Given the fact that some patients do not show improved cardiac functions with CRT, other pacing modalities have been developed, such as dual-chamber pacing and multipoint pacing. In addition, CRT requires advanced sensing capabilities to maximize cardiac efficiency. On the one hand, the increased number of pacing sites and the complex monitoring requirements in these advanced pacing modalities create higher demands for the power source. On the other hand, advances in miniaturization and optimized algorithms allow automatic adjustment of pacemaker stimulation output correlated with continuously monitoring capture thresholds, prolonging the longevity of CRT devices.

2.2 | Implantable cardiac monitoring devices

The implantable loop recorder (ILR) is a classic example of cardiac monitoring devices, which is subcutaneously implanted for the detection of cardiac arrhythmias[28] (Figure 1G). Modern pacemakers and ICDs are capable of continuous monitoring of basic cardiac rhythm, and built-in algorithms have been integrated into dual-chamber pacemakers and ICDs for monitoring supraventricular arrhythmias. Those sophisticated monitoring functions and resultant requirements of frequent data transmission typically consume more energy and decrease the longevity of cardiac rhythm management devices. For patients who do not yet have an indication for intervention and have a risk of arrhythmia, implantation of stand-alone monitors is a well-established therapy with valuable insights into incidence, mechanism, and consequences of arrhythmia.[29–31] Routine data transmission is necessary for further diagnosis, and the longevity significantly depends on the frequency of data transmission. ILR should provide relatively high-power output for frequent data transmission. Given the size of ILR is smaller than pacemakers and ICDs, the expected longevity of ILR is generally 3 years. With a deceased frequency of data transmission, the longevity can be extended to 5–6 years.[32]

Implantable cardiac hemodynamic monitors are another class of ICMDs, which are adopted for the detection of heart failure by measuring filling pressure, heart rate, core temperature, pulmonary fluid, and intracardiac electrograms[33,34] (Figure 1H). The recorded data need to be uploaded by a patient-activated advisory module for diagnosis and appropriate adjustment of drug therapy. The benefits of implantable heart failure monitoring devices will be maximized only when the data are measured and evaluated frequently (at least daily).[35] Although the monitoring has been beneficial from telemonitoring features,[35] and some monitors remove internal power sources and use ultrasound-activated or radiofrequency-based wireless pressure sensing, cardiac hemodynamic monitors still tend to have multiparametric monitoring to reflect heart failure status and understand the pathophysiology of heart failure. In addition, incorporating heart failure diagnostic monitors in cardiac pacemakers and defibrillators becomes an attractive feature for specific patients. Coupling with the routine frequent data transmission and multiparametric monitoring requirement, the design of ideal power sources for implantable cardiac monitoring devices becomes essential.

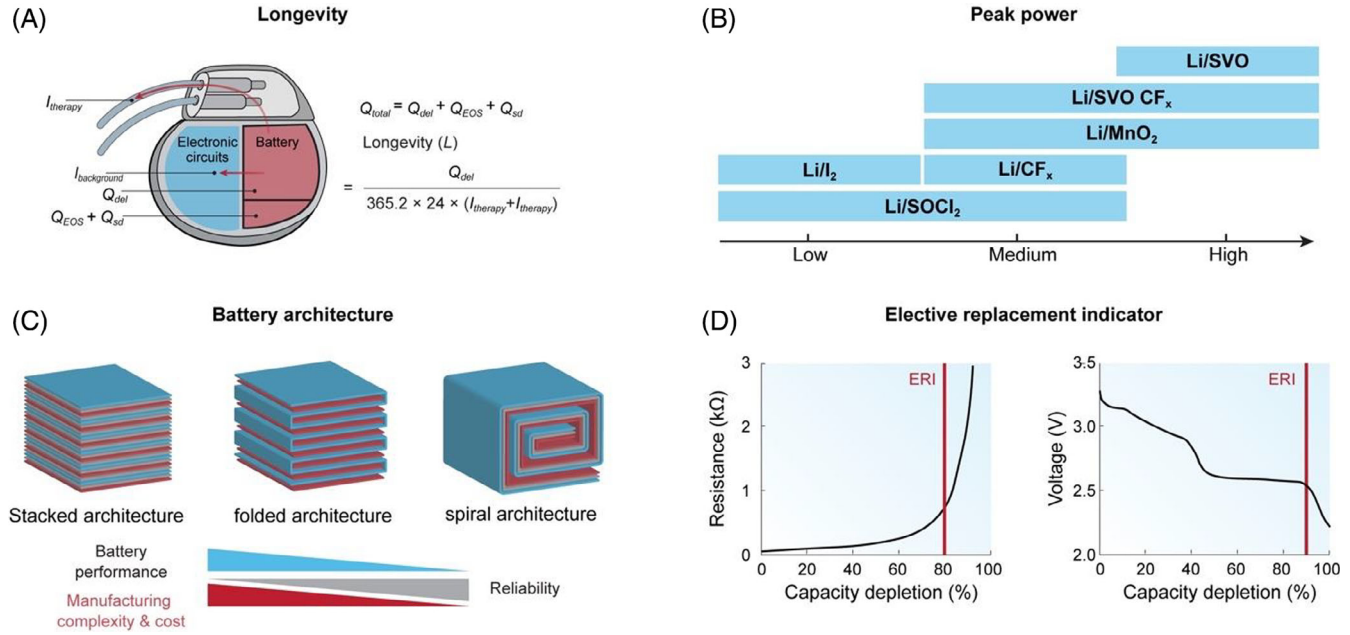

FIGURE 2 The principal design criterion of power supplies for CIEDs. (A) Influence parameters associated with the longevity of power supplied. $I_{therapy}$, average therapy current drain; $I_{background}$, average background current drain; L, longevity; Q_{del}, the energy capacity of the battery; Q_{sd}, self-charging energy; Q_{EOS}, extra energy for end-of-service. (B) Peak power of different power supplies in existing clinical-adopted CIEDs. (C) Typical battery architecture in CIEDs and their comparisons in terms of battery performance, reliability, manufacturing complexity, and cost. (D) Typical impedance-based (left) and voltage-based (right) curves with elective replacement indicator.

3 | DESIGN CRITERION OF POWER SUPPLIES

3.1 | Longevity

The longevity of the devices depends on the battery capacity and therapy energy (Figure 2A). The energy consumption rate depends on many factors, including the number of leads, telemetry transmission, background current, pacing parameters, and electrode-tissue interface.[36] Although the different therapeutic parameters can substantially change the longevity from patient to patient, the longevity for a specific battery can be calculated from the average current needed for a certain therapeutic condition. The following equation can be used to calculate the longevity.

$$L = \frac{Q_{\text{del}}}{8766 I_{\text{ave}}} \quad (1)$$

L (year), the longevity of the pulse generator; Q_{del} (mAh), the energy capacity of the battery; I_{ave} (mA), the average current drain. The constant 8766 (365.25 days per year × 24 h per day) converts the expression of longevity into years. Note that the average current drain includes the average therapeutic current (I_{therapy}) and the average background current drain ($I_{\text{background}}$), which is used to run the electronic circuitry for data logging and powering microprocessors, etc. The therapeutic current typically is in a range from 3 to 10 μA, and the background current is lower than 1 μA. For example, the average current drain for dual-chamber pacemakers is 7 μA, and the longevity of the pacemakers with a 1200 mAh power source is around 20 years.[5] The actual longevity must be lower than the theoretical/calculated longevity because the internal self-discharging of the battery consumes additional energy (Q_{sd}) and extra energy (Q_{EOS}) must be included after the end-of-service indicator for safety consideration.

3.2 | Peak power

Peak power requirement is another important parameter that needs to be considered for different device-based therapies (Figure 2B). Power is the product of output voltage and current ($P = \text{I} \times V$). For bradycardia therapy, small amounts of energy are delivered by pacemakers in each electrical pulse, which is on the order of 15 μJ within 1 ms or less. The pacing rate is usually set between 70 and 80 beats per minute. For ventricular fibrillation or tachycardia, ICDs generally deliver more than 40 J in a defibrillation shock within about 10 s, which is very different from cardiac pacemakers. For example, the lithium/iodine battery widely used in pacemakers can provide adequate

voltage for continuous pacing, while it cannot provide such a high-power output for defibrillators. For high-degreed cardiac dysfunctions that require both bradycardia pacing and defibrillation, power sources with high energy, and power density are desirable to meet the requirements of longevity and peak power output simultaneously. Up to now, lithium anode batteries are the dominant power sources for CIEDs, and different cathode materials are adopted to balance the longevity and peak power requirements. With the increasing demands of data logging, telemetric communication, multisite pacing, and the integration of novel biosensors, it is highly desirable yet challenging to design better batteries with both high power and energy densities.

3.3 | Battery architecture

Battery architecture needs to be considered to balance against volume, shape, and mass. In lithium anode batteries, the lithium metal is rolled into a thin sheet or pressed onto current collectors. The cathode materials, in the form of paste or slurry, are coated or compacted onto current collectors with binders. The total volume is one important factor for biosafety concerns, particularly in pediatric patients. The volume of the battery also must be constant in the application lifespan. The electrode expansion or gas production in the hermetically sealed battery can result in severe accidences. Note that the battery generally occupies one-third of the volume in an ICD and half of the volume in a pacemaker, and the circuitry and capacitors fill the remaining volume. To maximize the power capacity and energy density of batteries, the area-to-volume ratio is an important factor to be optimized. Currently, three configurations, namely stacked plate, folded plate, and spiral wound, are the typical battery architectures used in modern CIEDs[36] (Figure 2C). In a battery with a fixed volume, the increasing area-to-volume ratio of the electrodes can enhance current capacity, subsequently resulting in high power output. For example, defibrillator batteries generally use long, thin anode and cathode to increase the total electrode areas. Such a design can provide high power to quickly charge the capacitors in the defibrillator. In addition, the high space efficiency can also enhance energy density. On the other hand, the increased area-to-volume ratio can also cause more concerns of reduced reliability, high manufacturing complexity, and high cost.

3.4 | Elective replacement indicator

Elective replacement indicator has been incorporated into all implantable pulse generator designs nowadays to alert physicians to battery depletion.[37–39] Implanted power sources should provide some measurable parameters, such as impedance or voltage, to estimate the remaining battery life (Figure 2D). The battery voltage or impedance can be telemetered to the programming device in clinics. Generally, this indicator should be detected at least 3 months before the power sources no longer support the critical functions. Different battery chemistries can result in totally different voltage or impedance characteristics during discharging, which requires the clinicians to select the specific method or procedure to estimate the remaining battery life for each model of implantable devices. For example, the lithium/silver vanadium oxide (SVO) battery shows two clear voltage plateaus, and the battery voltage drops very quickly after 2.6 V following the second plateau. Therefore, the voltage indicator is ideal for these power sources to estimate the remaining service life. For the lithium/iodine batteries, the voltage maintains constant through most of the lifespan, while the impedance keeps increasing. The speed of impedance enhancement is especially rapid when it approaches to the end of the lifespan. Thus, impedance is an ideal indicator for lithium/iodine batteries. Another method for monitoring the remaining battery life is to calculate the total charge removed from the battery. In actual clinic situations, more than one method is commonly used together to increase the accuracy of estimation.

3.5 | Encapsulation

The encapsulation of electronics is typically required for existing implantable batteries, and the sealing materials generally have the following features. First, hermetic sealing is necessary to prevent any interchanges between the inside of the batteries and the surroundings. Hermetically welded containers can isolate lithium batteries from external moisture and foreign contaminants. The leak rate for a test gas, usually helium, needs to be less than 1×10^{-7} cm^3 s^{-1} difference between the inside and the outside of the battery at one-atmosphere pressure.[16] Electrical feed-throughs are used to make the electrical connection, allowing transferring energy from the sealed battery chamber. Second, sealing materials are inert to electrolytes and biological tissues. With the feature of high corrosion resistance to electrolytes, sealing materials can maintain consistent environments in the batteries during their lifespan. In addition, inert sealing materials can prevent acute adverse tissue responses, device-induced infections, and complications associated with the exposure to biological tissues. Typically, a series of biological evaluations, such as cytotoxicity, systemic toxicity, and degradation, need to be conducted to confirm

biocompatibility.[40] Third, lightweight and low-density encapsulation are always desirable for energy devices to maximize energy density. Conventional and clinically approved technologies rely on titanium or ceramic materials, which are generally bulky and heavy. Several emerging materials have been developed as alternative encapsulation methods for medical implants with the features of mechanical flexibility, conformability, and electrical insulation.[41] These emerging encapsulation materials include inorganic thin-film coatings of Al_2O_3,[42,43] HfO_2,[44] SiO_2,[45] and SiC[46] as well as organic polymers such as polyimide,[47] parylene,[43] silicone elastomer,[48] etc. However, these emerging alternatives have not been proven to be as hermetic as traditional methods yet, which requires additional examinations before adopting to medical implants.

3.6 | Biocompatibility

Improving the biocompatibility of electrode and electrolyte are definitely beneficial to eliminate the concerns of potential exposure of battery materials to surrounding tissues. Due to the poor biocompatibility of the cathode, the anode, and the electrolytes in the existing medical batteries, complete encapsulation is necessary to prevent biosafety issues at the current stage.[49] In order to be fully biocompatible, several nontoxic and biocompatible battery systems have been developed. For example, two promising anodic materials are Mg[50,51] and Zn,[52] since they have high theoretical energy density (Mg: 2200 mAh g^{-1}, Zn: 820 mAh g^{-1}) and relatively high daily allowance (Mg: 350 mg day^{-1}, Zn: 40 mg day^{-1}). Since cathodic materials in conventional Mg or Zn-based batteries are generally toxic, biocompatible metals such as Fe, W, or Mo can serve as substitutes for conventional cathodic materials. The biocompatible aqueous solution, such as $MgCl_2$ solution or physiological fluids can serve as the electrolyte.[53,54] In addition, solid electrolytes with reduced risk of leakage, high robustness and flexibility, and low flammability can further increase the biosafety and biocompatibility of the medical batteries.[49] Although fully biocompatible battery systems show many advantages, they are still in the early stage and rigorous evaluations should be conducted prior to clinical translation.

4 | EVOLUTION OF IMPLANTABLE POWER SUPPLIES

In 1958, the first fully implantable pacemaker was placed in Sweden.[55] A rechargeable nickel–cadmium battery with an output voltage of 1.25 V and a capacity of 190 mAh provided the energy for the first pacemaker to support the patient's heart rhythm for 3 h. Due to the difficulty of recharging and very short longevity, this type of secondary battery was rapidly replaced by series-connected mercury-zinc batteries in the 1960s. However, gas generation during discharging and unpredictable battery life sufficiently increased the possibility of electrical shortcuts and device failure, which severely limited the usage of mercury-zinc batteries. To solve the limitation of short longevity in previous implantable electronics, nuclear batteries were adopted successfully to provide a remarkable lifespan. The first isotope-based (^{238}Pu) pacemaker was implanted in the 1970s,[56] which enabled it to provide reliable cardiac pacing for over 30 years. However, nuclear-based pacemakers became obsolete with the obvious safety concerns and the development of lithium batteries. With the rapid development of lithium-based batteries in the 1970s, lithium primary batteries became the standard power source for modern pacemakers. Lithium served as an anode, and many different cathode materials were gradually developed and used in the primary batteries of pacemakers (Figure 3A).

One successful and well-investigated energy system is lithium/iodine (Li/I_2) battery, in which iodine is mixed with poly-2-vinyl pyridine, and the mixture is served as a cathode.[57] Since the first Li/I_2–battery-based pacemaker was implanted in 1972, the Li/I_2 battery has sustained the pacemaker industry for five decades.[58,59] This type of cell is still the preferred power source for many implantable pulse generators because of its high reliability and biosafety. The reliable feature is attributed to the solid lithium iodide electrolyte. The crystalline electrolyte is gradually formed at the interface of the anode and the cathode during the initial self-discharge. The solid electrolyte results in an extremely low self-discharge rate and high impedance. Since the current requirement in modern pacemaker circuits is very low, the relatively high impedance has not limited the basic functions of cardiac pacing. Coupling with the feature of no gas generation during the reaction, the solid electrolyte allows the whole cell being completely sealed. The output voltage of 2.8 V is very stable during most of the lifespan, and it gradually drops to 1.8 V when the battery is about to exhaust (Figure 3B). This discharge curve allows us to estimate the battery life and determine the proper time for the replacement of the pulse generator. With continuous improvement in cell design and materials innovation, the energy capacity of the Li/I_2 battery increases from 2 to 3.5 Ah with a smaller size. With the invention of the Li/I_2 battery, other types of lithium-based batteries, such as lithium-bromine cells, lithium-lead iodide cells, and lithium-copper sulfide cells, fade out of the market.[5,57] Until now, over 15 million Li/I_2-powered pacemakers have been implanted.[60]

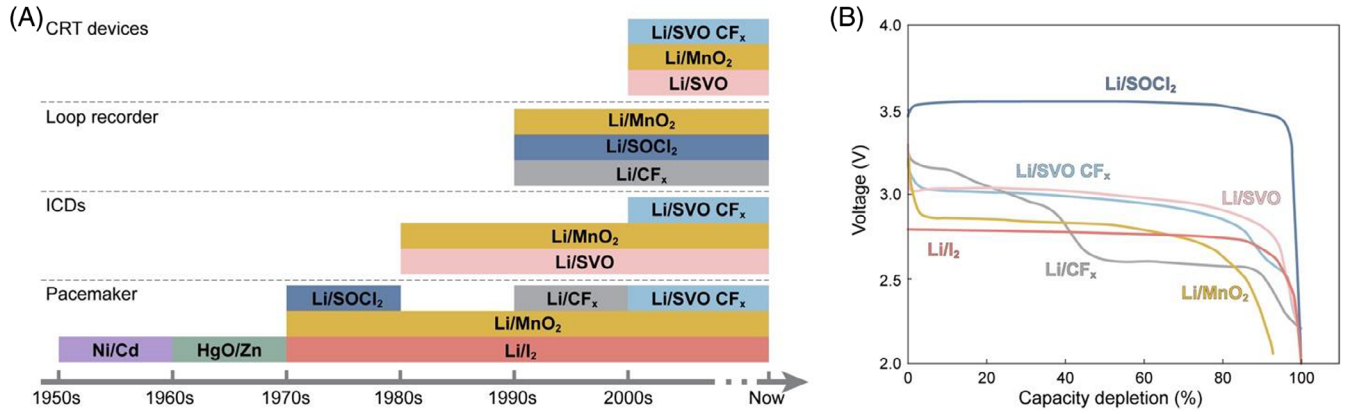

FIGURE 3 The evolution of power supplies in different types of CIEDs. (A) Timeline of battery chemistries for different types of CIEDs. (B) Discharge curves for different batteries that are in use currently.

With the increasing demands of advanced functions, such as electrogram storage, telemetric communication, multisite cardiac pacing, and defibrillation, the requirements of high-power output are beyond the capacity of Li/I_2 cells. Several new battery systems with high power densities are developed to support these features. Lithium/thionyl chloride ($Li/SOCl_2$) was developed in the 1970s as a high-energy density power source for pacemakers. Thanks to its high energy density, the size of the battery for pacemakers is similar with that of a standard AA battery, conforming to the trend of miniaturization. However, the sudden decreased voltage shown in the discharge curve results in unexpected device failure (Figure 3B), which limited its use in the devices with life-support features. As another medium power source, lithium/carbon monofluoride (Li/CF_x) batteries can provide significantly higher power density and similar energy density in comparison to Li/I_2 cells. It was first proposed for pacemakers in 1996. Suffering from the same challenge of determining the elective replacement time, the applications of these two types of batteries have been limited to cardiac monitoring devices.

Lithium/manganese dioxide (Li/MnO_2) battery was developed in the 1970s, and become the most common battery for consumers and the military nowadays.[61] High-power lithium/manganese dioxide battery allows strong energy output in a short duration of time, which has a long history for the applications of photoflash. With similar power requirements, it gradually developed to be the power source for ICDs. For battery constructions, coiled or stacked thin electrodes can effectively increase the electrode area and subsequently maximize the power capacity. The operating voltage is very stable at around 3 V over the first half of the battery life, and then it gradually slopes down. This electrochemical characteristic allows clinicians to estimate the battery depletion. Combined with high power capacity and reliable discharging performance, lithium/manganese dioxide power source can be used for pacemakers, ICDs, CRT devices, and implantable loop recorders by different manufacturers nowadays.

Lithium/silver vanadium oxide (Li/SVO) battery was the dominant power source in the early development of ICDs, providing high energy and power densities to address the limitations in previous power sources. The discharge curve of Li/SVO battery has two flat voltage plateaus, followed by a sharp decline toward the end of the lifespan. The reliable stepped discharging curve makes it easy to monitor the longevity and determine elective replacement. Some modern ICDs and CRT devices still contain Li/SVO batteries as power sources. However, it is gradually replaced by a new battery system with dual or hybrid cathode of SVO and CF_x.[62] By taking the advantages of the best features of two cathode materials, SVO and CF_x, Li/SVO-CF_x battery was developed in 1999, showing a synergetic effect. SVO contributes most of the energy for shock therapy or high voltage discharges, while CF_x provides a high gravimetric energy density. Two cathode materials can be constructed in a laminated structure or a mixture, with a large electrode area-to-volume ratio. Both of these two battery structures show similar power capabilities. The discharge curve shows initial and terminal characteristics associated with SVO, which is ideal for end-of-service indication, and the middle portion that is characteristic of CF_x. Li/SVO-CF_x battery has been widely adopted for most cardiac rhythm management devices. Table 1 summarizes the characteristics of different types of primary batteries used in CIEDs.

5 | EMERGING TECHNOLOGIES

Several cutting-edge technologies are extensively explored in academia, and serve as important supplements to existing primary batteries. They have the

TABLE 1 Characteristics of primary batteries for CIEDs.

Type of battery	Capacity (Ah)	Operating voltage (V)	Longevity (year)	Energy density (Wh kg^{-1})
Li/I_2	2.0–3.5	2.8	>10	210–270
Li/MnO_2	1.0–2.0	2.9	>10	230–270
Li/CF_x	2.0	3.0	5–10	440
Li/SVO	0.9–2.0	2.4–2.8	5–10	270
Li/SVO CF_x	1.7–2.0	3.0	5–10	400

potential to address the challenges of current implantable power supplies including limited battery life and power output, large device size, and associated complications. For example, new battery systems and wearable power management platforms are promising to extend the longevity of implants, especially for high-power-consuming functions. Wireless energy transfer technologies and leadless devices provide opportunities to miniaturize or even eliminate the energy devices in the CIEDs. We will introduce these emerging technologies in the following section.

5.1 | New battery systems

The adoption of rechargeable batteries in the implantable electronic devices has a long history. The first implantable pacemaker contained a single rechargeable nickel-cadmium battery, although it was soon abandoned. The interest of replacing primary batteries with rechargeable battery increased with the development of new-generation rechargeable batteries, since rechargeable lithium-ion batteries were introduced to consumer electronics in 1991.[63–65] Lithium-ion batteries commonly use lithium-intercalated compounds as cathodes, such as $LiCoO_2$, $LiFePO_4$, $LiMn_2O_4$, and $LiNiMnCoO_2$. Most of them are more stable than pure lithium electrode. Extended longevity is one obvious advantage for CIEDs with secondary batteries. Moreover, several electrochemical characteristics in lithium-ion batteries are also favorable for medical implants, including high energy density, similar operating voltage with existing lithium primary batteries, and low self-discharge. However, the primary batteries continue to dominate the power source for medical devices (Figure 4A), due to the biosafety concerns of existing rechargeable lithium-ion batteries.[66,67]

New battery systems were extensively investigated in order to overcome the intrinsic biosafety concerns or promote the capacity of primary batteries (Figure 4B). One promising direction is to develop nonlithium battery systems.[68] Alkali metals and alkaline earth metals have been proposed as alternative electrodes to lithium. Currently, sodium-ion batteries,[53,69] potassium-ion batteries,[70] and calcium-ion batteries[71] show great potential due to their high energy densities and relatively high safety. Another series of new battery systems are metal–air electrochemical cells, which have the highest energy densities among all commercial batteries.[72,73] Because an external cathode of ambient air and an aqueous or aprotic electrolyte are typically used in metal–air electrochemical cells, they show reduced flammability and toxicity. For example, zinc–air batteries have been used for hearing aids and in the external units of cochlear implants.[74–76] However, the lack of continuous oxygen flow inside the body limited the applications of these batteries. Another promising direction is to develop new electrolytes. Gel or solid electrolytes are nonflammable, thermally robust, reduced toxicity, and electrochemically stable.[77] A great number of new gel or solid electrolytes have been invented, which has been summarized otherwise. The evaluation of stability in structure, composition, and performance for gel or solid electrolytes in human body environments is an important next step toward practical applications. In addition, new electrolytes were continuously invented to boost the energy capacity of traditional Li-primary batteries, although this field is quite mature with few fundamental innovations. For example, one advanced catholyte has been developed that successfully exploits the wide oxidation state window of S in nonmetal-containing and lightweight reactants, significantly boosting the gravimetric energy of Li primary batteries by 20%.[78]

5.2 | Wearable power management platforms

Wearable power transfer platform is another practical solution to provide high power and high energy to implantable electronic devices.[79] For example, existing ventricular assist devices require relatively high energy input that is beyond the capability of implanted primary batteries (Figure 4C). External batteries are necessary for the sustained operation of these implants. Increasing the integrability of the external power systems with the human body is attractive, because

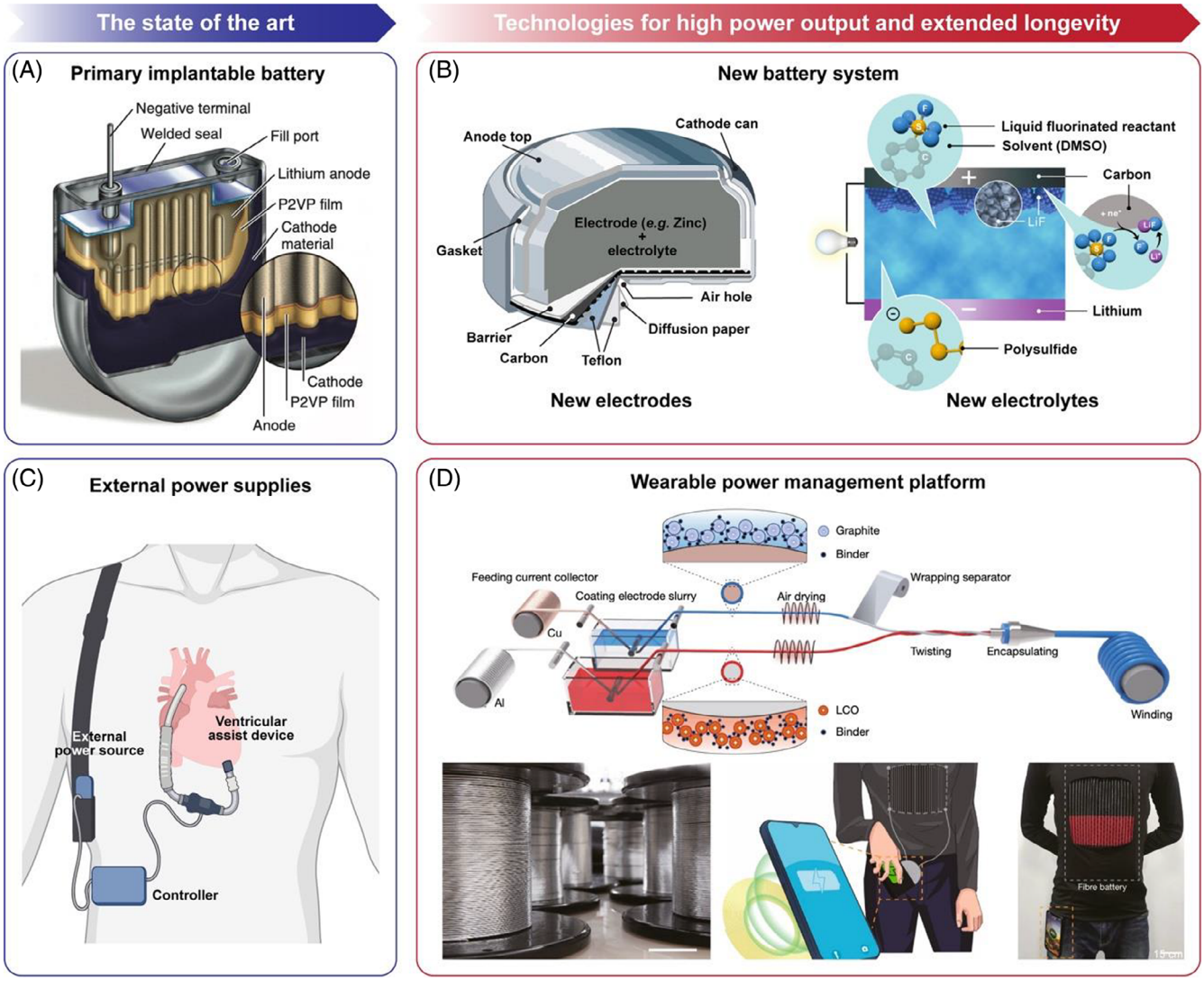

FIGURE 4 Emerging technologies for high power output and extended longevity. (A) Schematic illustration of primary implantable battery for CIEDs, demonstrating the state of the art. Reproduced with permission.[16] Copyright 2011, Elsevier. (B) Schematic illustration of a new battery system, including new electrodes and new electrolytes. Reproduced with permission.[78] Copyright 2022, National Academy of Sciences. (C) Schematic illustration of the external power supplies for existing ventricular assist device. (D) Schematic illustration and representative images of wearable power management platform, enabled by wearable lithium-ion battery textiles. Reproduced with permission.[82] Copyright 2021, Springer.

they can power implants in a convenient way. Wearable power textiles are the most representative and emerging examples.[80,81] With the combination of new scientific understandings and traditional textile technologies, scalable manufacturing of wearable power textiles can also be achieved. They can be manufactured in a form of continuous fibers and subsequently woven into textiles, such as clothes or medical bandages.[82,83] Such wearable power platforms are flexible, breathable, and portable, thus providing on-demand energy input at a relatively low current continuously without tissue overheating or damage (Figure 4D).

Wearable battery systems need to be recharged constantly for long-term treatment in existing ventricular assist devices. With the increased energy demands in new long-term therapies, frequent telemetry for sensing and regulation, and total artificial hearts, wearable power management platforms that consists of energy harvesting devices and energy storage devices would be beneficial from a reduction in recharge times. A variety of wearable energy harvesting devices have been invented and integrated with wearable energy storage devices to support implanted devices. One class of wearable energy harvesting devices is solar cell systems, which help to extend longevity and reduce the size of batteries.[84] Harvesting kinetic energy from cardiac and pulmonary motion by the triboelectric and piezoelectric devices is another

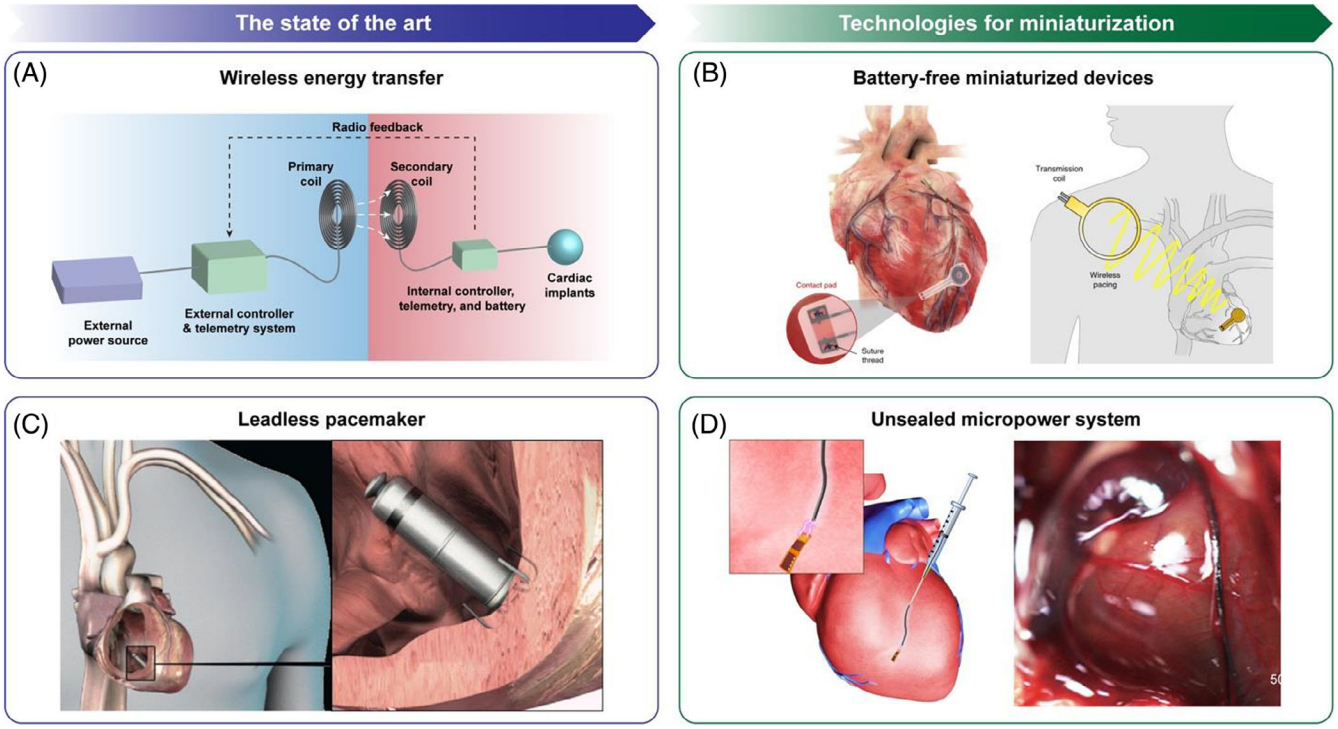

FIGURE 5 Emerging technologies for miniaturization of power supplies. (A) Schematic illustration of a transcutaneous energy transfer system. (B) Schematic illustration and representative image of a battery-free miniaturized pacemaker. Reproduced with permission.[88] Copyright 2021, Springer. (C) Schematic illustration of leadless pacemaker. Reproduced with permission.[16] Copyright 2011, Elsevier. (D) Schematic illustration and representative photograph of unsealed micropower system enabled by biocompatible battery fibers. Reproduced with permission.[98] Copyright 2021, RSC.

potential candidate technology.[8] However, controlled or predictable failure mechanisms and the method of energy transfer from the site of power generation to the site of therapy are unclear, which limits them to be used as the only power source for implantable devices, especially for high-power-level cardiovascular implants. Although the devices have been evaluated in large animal models,[85] these challenges, associated with insufficient practicality and reliability, make these energy-harvesting technologies unattractive from the clinical perspective. The promising direction for energy harvesters or generators is to combine with wearable batteries and serve as important supplements in wearable power management platforms, in order to provide higher power and longer service life to CIEDs.

5.3 | Wireless energy transfer

Wireless energy transfer technologies are attractive for charging the implanted batteries and miniaturizing the implants. Energy transfers across the skin without a direct electrical connection, avoiding potential infection and complexity associated with wire connection[86] (Figure 5A). Various wireless power transfer technologies have been developed over decades, such as inductive coupling power transfer, far-field radio frequency, magnetic resonant coupling, and mid-field wireless power transfer. In general, the primary coil is connected to the external controller and external power source, and the current in the primary coil produces a magnetic field and subsequently induces current in the secondary coil. This system can also integrate wireless telemetry to provide close-looped regulation of power. The speed and power transfer efficiency of recharging depends on the relative position of the primary and secondary coils, antenna designs, and frequencies. These non-invasive power transfer strategies not only alleviate the risks of lead-associated infections and dislodgement by eliminating the need for percutaneous hardware, but facilitate the miniaturization of implants by reducing the size of batteries. Battery-free technology is an extreme example of miniaturization, exploiting wireless energy transfer[87,88] (Figure 5B). The internal energy storage devices are completely deducted. Battery-free cardiac pacemakers are invented, consisting the flexible extension electrodes and a wireless receiver, which can receive power and control commands through wireless inductive power transfer.

Although wireless energy transfer technologies have the potentials to ultimately address the issues associated with battery depletion, they are still in the early stage in

clinics and several limitations require further investigations. The main hurdle comes from the unreliability of energy transfer. The energy transfer efficiency is greatly influenced by the alignment and distance between coils. The resultant unsuccessful charging, overcharging, and charging-induced localized overheating can potentially cause severe clinical issues, particularly for life-support implantable cardiac monitoring devices. The overheating of surrounding tissues is also a common issue for transcutaneous energy transfer at a high current.[89] The development of low-temperature energy transfer systems is a promising direction to avoid overheating and traumatic outcomes. Additional medical supervision for recharging is another obstruction to the application of rechargeable batteries. Decreasing the recharging time under supervision or increasing the safety and reliability of self-manageable recharging will facilitate the widespread adoption of secondary batteries. Despite these challenges associated with recharging, rechargeable batteries have been used in high-power, nonlife-support implantable electronics, including endovascular stimulators,[90] spinal cord stimulators, and deep brain stimulators.[91]

5.4 | Leadless and unsealed devices

With the advancements in low-power electronic technology that decreased the background current, fully self-contained, leadless pacemakers have been developed to prevent potential pocket infection and lead damage.[92,93] The leadless pacemakers that contain batteries, electronics, and electrodes can be directly implanted into the femoral vein via a minimally invasive manner (Figure 5C). The batteries in the leadless pacemaker are significantly smaller than those in the traditional pacemaker.[94] Therefore, they only can provide single-chamber low-power ventricular pacing to patients who require infrequent pacing. Leadless pacemakers lack the capabilities of defibrillation and dual-chamber pacing due to the limitation of battery.[95] By reducing the high-power consuming functions, the theoretical longevity of the leadless pacemakers can still reach 5–15 years. In addition, another distinguishing feature of leadless pacemakers is that the battery is not completely encapsulated in the device case. Internal batteries and electronics can partly contact with the body fluids in such a semi-enclosed configuration.

These advanced features in leadless pacemakers are premature, which can potentially cause a high incidence of battery malfunction. For example, a clinical trial reported that up to 40% of devices failed within 3 years.[96] A detailed analysis of retrieved devices showed reduced electrolytes within the Li/CF_x battery, resulting in a high internal resistance and subsequent device failure. Generally, electrolytes in existing implanted batteries are the non-biocompatible, organic solution, and the leakage of electrolytes puts patients at risk. To construct the semi-enclosed or unsealed micropower system, the usage of aqueous electrolytes and biocompatible electrode materials is a potential solution. The biocompatible electrodes need to be stable in the body fluids, and the unsealed batteries can maintain stable discharge. Recent studies have demonstrated the proof-of-concept unsealed micropower systems on heart[97–99] (Figure 5D). The unsealed batteries used biofluid or hydrogel as electrolytes and were fabricated in a form of flexible fiber. Sharing a similar fiber configuration with catheter and transvenous leads, the fiber batteries were capable to be implanted atraumatically. Although the long-term reliability of the biocompatible fiber batteries needs to be further investigated in clinical-relevant setups, a new trend of developing unsealed biocompatible micropower systems will provide attractive power supplies for future cardiovascular micro-devices.

6 | PERSPECTIVES

The application of primary batteries is still the mainstream approach to provide energy to CIEDs.[100] We outlook the power supplies for CIEDs will keep upgrading along the following three principal characteristics in the near future (Figure 6).

i. Extended longevity. Future power supplies with extended longevity can ultimately solve the main issue associated with battery replacement. The innovations of high-performance electrode materials and electrolytes in new battery systems will keep contributing to the extension of longevity. We envision some of the new batteries that currently are not desirable for medical implants will gradually be adopted in implants without life-support features

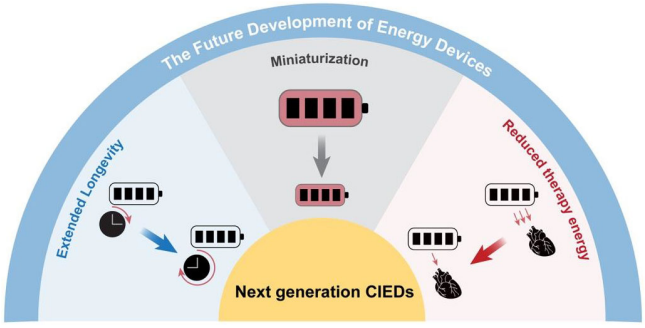

FIGURE 6 Perspectives of the future development of energy devices for next-generation CIEDs.

after systematic and rigorous evaluations in clinical trials. Wearable power transfer platforms will become a strong supplement for high-energy demanded implants, such as multi-chamber assist devices or artificial hearts. To clinically adopt and boost the applications of external wearable supplements, the seamless and noninvasive interconnection between external power sources and internal implants requires further innovations.

ii. Miniaturization. The development of miniaturized power supplies will continue to be the main direction for next-generation cardiac implants due to the need for improved safety. Leadless pacemakers have shown advantages in eliminating complications in comparison with traditional pacemakers. Although leadless pacemakers can only be used in low-energy therapies at the current stage, significant benefits in the reduction of invasiveness will promote leadless device technology. More derivate leadless devices will be invented with enhanced pacing capabilities. Moreover, battery-free and in-situ energy harvesting technologies could be the ultimate energy solutions for medical implants. Nonetheless, more rigorous and long-term validations in large animal models are necessary to ensure reliability and biosafety before any of these technologies are adopted.

iii. Reduced therapy energy. An additional interesting direction is to develop new biological therapies to reduce energy requirements. Given gene therapy technologies or stem cell therapies can enhance cardiac automaticity[101] via biological pacemakers, the energy demands for cardiovascular disease treatment might be completely changed. While the development of biological pacemakers is still at a very early stage, it is hard to predict the process and outcomes for the clinical translation of this technology. As our understanding of cardiovascular diseases continues to deepen, new precise treatments might decrease the therapy energy. The improved management of therapy energy might further extend the longevity of the devices and in turn, provides extra energy for more complex monitoring and therapeutic functions.

AUTHOR CONTRIBUTIONS

Jue Deng: Visualization, Writing - original draft. **Xuemei Sun:** Writing - review & editing. **Huisheng Peng:** Supervision, Writing - review & editing, Project administration, Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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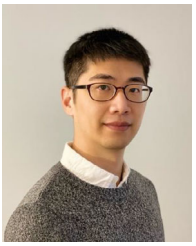

Jue Deng works on the development of bioelectronic devices seamlessly and imperceptibly integrated on/in the human body for advanced diagnostic and therapeutic applications. He obtained his PhD degree in Polymer Physics and Chemistry at Fudan University, where his doctoral work focused on electronic textiles for power supplies and biosensing. He received postdoctoral training at Massachusetts Institute of Technology and explored the applications of bioadhesive electronics in cardiovascular diseases. He is now interested in the development of minimally invasive interventional medical devices.

Huisheng Peng is University Professor at the Department of Macromolecular Science and Laboratory of Advanced Materials at Fudan University. He and his coworkers have explored a new family of fiber-shaped energy-harvesting devices including perovskite solar cells and fluidic generators, fiber-shaped energy storage devices including lithium-ion batteries, lithium–sulfur batteries, and metal–air batteries, fiber-shaped light-emitting devices, and fiber-shaped sensors; thus, a new direction of fiber electronics is started. He is now interested in the development of fiber electronics.

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