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Advances in piezoelectric nanogenerators for self-powered cardiac care

Shumao Xu, Xiao Wan, Farid Manshaii, Ziyuan Che, Jun Chen *

Department of Bioengineering, University of California, Los Angeles, Los Angeles, CA 90095, USA

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ABSTRACT

Piezoelectric nanogenerators have emerged as a pivotal platform technology in bioengineering, advancing cardiac healthcare. Unlike common pacemakers, these devices capitalize on the mechanical energy derived from cardiac movements to power themselves, presenting a sustainable alternative to the battery constraints faced by current implantable cardiac devices. This review explores the advances in piezoelectric nanogenerators for cardiac monitoring and therapy, highlighting their capabilities to not only track cardiac activity but also provide therapeutic interventions and reliable energy for pacemakers. It also discusses the electrical stimulation effects and biocompatible integration with human biology, positioning piezoelectric nanogenerators at the forefront of healthcare solutions. This enhances the effectiveness, durability, and personalization of cardiac care.

1. Introduction

As the global population ages, the focus on improving cardiac healthcare through soft bioelectronics that continuously monitor heart rhythms in real time and detect early signs of cardiac events has intensified [1-15]. According to the World Health Organization, cardiovascular diseases account for an estimated 17.9 million deaths each year. The widespread impact of these diseases highlights the critical need for advances in monitoring and therapeutic methods [9,11,14]. Typical battery-operated cardiac devices, despite their effectiveness, are plagued by the need for periodic battery replacements, which introduce infection risks and elevate healthcare costs [1-5]. The convergence of the Internet of Things (IoT), 5G communication, and biotechnologies ushers in a new era of personalized healthcare, spotlighting the role of piezoelectric effects in cardiac monitoring and modulation [16-34].

Piezoelectric nanogenerators (PENGs) leverage biomechanical energy from heartbeats, estimated to produce between 0.3 to 1 W, providing a sustainable power source for cardiac devices such as pacemakers and implantable cardioverter-defibrillators (ICDs), thereby eliminating the need for batteries [35-45]. This advancement reduces device size and weight while lowering the risks associated with battery replacements [35-42]. Furthermore, the development of compact, lightweight cardiac implantable electronic devices (CIEDs), which autonomously monitor and provide therapeutic interventions, has been facilitated by the high-power conversion efficiency and miniaturization capabilities of PENGs [46-50]. Recent advances in flexible PENGs, tailored to the heart's unique mechanical properties, ensure they conform comfortably to the cardiac surface without impeding natural heart functions [47,51,52], aligning with sustainable and patient-centric healthcare solutions [42,52-61]. This seamless integration is vital for long-term monitoring and therapeutic application, offering a continuous energy supply and functional support devoid of the mechanical failure or infection risks associated with typical battery-operated devices. The development of self-powered PENGs not only aligns with the shift towards sustainable and patient-centric healthcare solutions [40,62,63] but also reduces the environmental impact of battery disposal and enhances patient mobility and quality of life by eliminating the need for frequent medical interventions [64-70].

This review delves into the transformative potential of piezoelectric effects in cardiac healthcare, with a special emphasis on their role in enabling self-powered monitoring and therapeutic options in CIEDs. By transforming the heart's mechanical energy into electrical energy, these devices propose a sustainable alternative that could eliminate the need for battery replacements, thereby reducing the risks and expenses associated with cardiac care practices. Further adoption of PENGs in clinical settings is poised to enhance patient outcomes and streamline healthcare services, marking a pivotal shift towards personalized, proactive, and sustainable approaches to managing cardiovascular diseases.

2. Cardiac system and its biomechanical activities

Recording arterial pulse waveforms is crucial for cardiac monitoring, providing critical insights into cardiovascular health [38,71-73]. Employing piezoelectric effects for this purpose enables the sensitive

* Corresponding author at: Department of Bioengineering, University of California, Los Angeles, Los Angeles, CA 90095, USA.
E-mail address: jun.chen@ucla.edu (J. Chen).

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detection of arterial pulses at various body sites, providing distinct data indicative of cardiac function [61,71,74,75]. This technique is beneficial due to its capacity to distinguish subtle variations in pulse waveforms from different arterial locations, influenced by factors such as proximity to the heart, arterial elasticity, and the artery's depth beneath the skin.

The clinical significance of recording arterial pulse waveforms lies in their direct correlation with the mechanical and circulatory status of the cardiovascular system [72,73]. PENGs enhance the accuracy and reliability of this recording by providing high-fidelity capture of biomechanical signals generated by blood flow, even at low amplitudes that conventional electrocardiograph (ECG) devices fail to detect [11]. Moreover, PENGs' sensitivity to minor pressure changes makes them excellent for detecting early signs of arterial stiffness, a predictor of cardiovascular events [11,14]. Their ability to operate without external power sources reduces artifacts and noise that can compromise the quality of waveform data [76], ensuring clear and consistent readings for cardiovascular assessment.

PENGs can be implanted or attached to cardiac tissue through various methods. Flexible PENGs can be laminated onto the heart's surface, often involving placement on the epicardial surface and securing them with biocompatible adhesives, such as medical-grade silicone or other polymer-based glues, ensuring stable contact without causing tissue irritation [77-83]. PENGs can also be integrated into existing CIEDs such as pacemakers or defibrillators to harness biomechanical energy from heart movements to power or enhance the functionality of these devices [46,84,85]. To protect the PENGs and ensure long-term stability, encapsulation materials including biocompatible polymers and hydrogels are used to create a protective barrier around the device [86-88], preventing direct contact with bodily fluids and tissues while allowing mechanical energy transfer.

2.1. Cardiac monitoring at different arterial locations

The heart, as the central pump of the cardiovascular system, initiates a series of biomechanical activities crucial for understanding systemic health. It generates pulse waves that propagate through the arterial network, with characteristics that vary across different anatomical sites [44,89,90]. Near the heart, the carotid artery displays waveforms with higher magnitudes and pronounced features such as the dicrotic notch, which mirrors the aortic pressure during the diastolic phase of the cardiac cycle [39] (Fig. 1a,b). In contrast, peripheral sites like the radial or dorsal pedis arteries show attenuated waveforms due to greater distances from the heart and the dampening effects of the arterial system's biomechanical properties [91-99]. These variations in pulse wave characteristics across measurement sites provide a comprehensive overview of the mechanical behavior of the cardiac system and indicate the health of the cardiovascular system.

The deployment of PENG sensors has revolutionized cardiac monitoring by harnessing these biomechanical signals. PENGs convert mechanical energy from heartbeat-induced arterial deformations into electrical signals, offering a less obtrusive, continuous monitoring solution [62,71,100-113]. By capturing detailed, site-specific arterial waveforms, these sensors enable clinicians to assess cardiovascular risk accurately and customize therapeutic interventions based on dynamic biomechanical data [114-117]. The real-time monitoring capability of PENGs aligns with a responsive and personalized approach to cardiac care, adapting to physiological changes or therapeutic interventions, thereby enhancing patient management through direct biomechanical feedback.

2.2. Therapeutic electrical stimulation for cardiac healthcare

Cardiovascular disease, particularly ischemic heart disease (IHD), remains a major global health challenge, necessitating therapeutic treatments including pharmacotherapy (beta-blockers, statins, and antiplatelet agents), percutaneous coronary interventions (angioplasty and stent placement), coronary artery bypass grafting (CABG), and regenerative medicine (stem cell therapy and tissue engineering) to reduce risk factors, manage symptoms, and repair or replace damaged heart tissue [40,64,107,118-128]. Among these strategies, therapeutic electrical stimulation emerges as a promising technique to advance cardiac healthcare [129,130]. This approach, often leveraging piezoelectric self-powered devices, converts mechanical energy from body movements into electrical signals, using the body's natural bioelectric phenomena for non-invasive, continuous cardiac care and directly influencing heart function [44,61,69,131].

Therapeutic electrical stimulation facilitated by PENGs introduces a novel modality in cardiac care, providing targeted and controlled electrical impulses to the heart tissue. Integration of PENGs into existing therapeutic strategies such as pacing and defibrillation offers several potential benefits over typical battery-powered methods. The self-powered nature of PENGs provides a consistent energy supply,

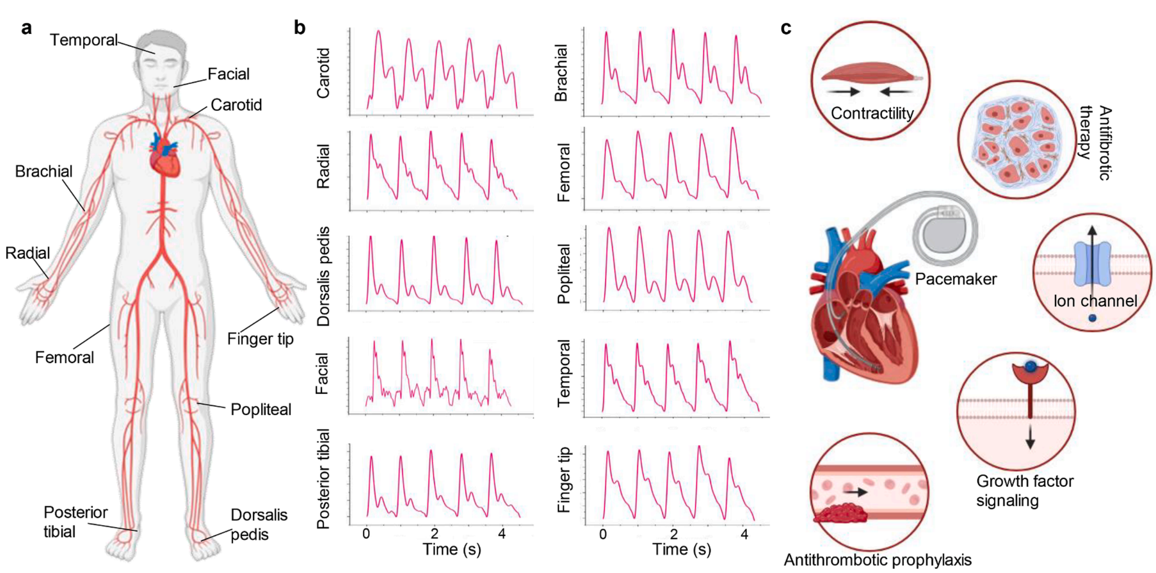

Fig. 1. Cardiac system and its biomechanical activities. a, Major arterial pulse points for measurement. b, Typical recording of arterial pulse waveforms at key arterial locations [39]. Copyright (2019) WILEY–VCH GmbH. c, Cardiac stimulation therapy, highlighting its benefits: enhancing contractility, promoting angiogenesis, regulating ion channels, facilitating growth factor signaling, and supporting antithrombotic prophylaxis.

reducing reliance on battery life and enabling consistent, long-term therapy without the need for invasive battery change procedures. Furthermore, the miniaturized and flexible design of PENGs may lead to less invasive implantation, improved patient comfort, and the potential for precise localization of therapeutic electrical stimuli. These advances could translate into effective management of arrhythmias and ischemic conditions, enhancing patient outcomes and quality of life.

The study of bioelectric activity dates back to the 19th century, but recent advances in molecular biology have expanded our understanding of its therapeutic potential [132]. Electrical stimulation is now recognized for its capacity to elicit profound changes, from subcellular organization to cellular behavior and even tissue functionality [133-136]. This method holds relevance for managing IHD, characterized by pathophysiological alterations such as coronary artery stenosis and myocardial ischemia [137]. In cardiac treatment, electrical stimulation utilizes electrical impulses to improve myocardial contractility with ion channel regulation and promote angiogenesis, influencing growth factors and other signaling pathways [138] (Fig. 1c). Electrical stimulation enhances myocardial contraction by increasing the synchronized permeability of ion channels and subsequent calcium influx into cardiomyocytes through channels and T-tubules. Such processes aid in both action potential propagation and harmonized sarcomere contraction, thereby improving heart pump efficiency—a crucial factor in heart failure management—and stabilizing heart rhythms, mitigating the risk of arrhythmias [139]. Additionally, electrical stimulation has demonstrated potential for promoting angiogenic factors like vascular endothelial growth factor (VEGF), improving blood flow to ischemic tissues, and aiding in cardiac repair and regeneration [140].

Moreover, electrical stimulation aids in activating signaling pathways crucial for cellular survival and proliferation, supporting the repair of heart tissue. Utilizing piezoelectricity for arterial pulse waveform recording provides valuable insights into cardiovascular dynamics, revealing the efficacy of electrical stimulation therapies [47,51,136]. This multifaceted approach not only enhances immediate cardiac function but also promotes long-term heart health and resilience, establishing it as a comprehensive and adaptable treatment strategy in cardiac healthcare.

3. Working principles of piezoelectric nanogenerators

PENGs, which generate an electric charge under mechanical stress, can be utilized to monitor the subtle nuances in pulse waveforms [39, 56]. Their ability to detect even minor deflections on the skin surface caused by arterial pulses renders them invaluable for unobtrusive, continuous monitoring [52,54,141]. These devices can be strategically placed at various arterial sites, enabling versatile monitoring without compromising waveform data quality. PENGs' sensitivity to slight waveform variations offers a detailed view of the pulse wave's propagation from the heart to peripheral areas [91,93,95,97]. This feature is useful in evaluating pulse wave velocity (PWV) and other cardiovascular parameters essential for diagnosing and monitoring conditions like arterial stiffness and peripheral arterial disease.

3.1. Piezoelectric materials

PENGs utilize various types of piezoelectric materials. Common inorganic piezoelectric materials include piezoelectric ceramics like lead zirconate titanate (PZT) and barium titanate ($BaTiO_3$), which offer high piezoelectric coefficients and stability. Piezoelectric semiconductors such as ZnO and GaN combine semiconducting and piezoelectric properties. Common organic piezoelectric polymers include polyvinylidene fluoride (PVDF) and its copolymers, known for their flexibility and biocompatibility, and polytetrafluoroethylene (PTFE), recognized for its chemical resistance and superior mechanical properties. Piezoelectric composite fabrication can be categorized into 0–3 type, where piezoelectric particles are dispersed in a non-piezoelectric matrix, and 1–3 type, where piezoelectric fibers are embedded in a polymer matrix [142-145]. These composites provide flexibility and enhanced mechanical properties, combining the advantages of ceramics and polymers to enhance performance through tailored microstructures. They can be customized for specific applications, ranging from wearable health monitors to implantable medical devices, ensuring efficient energy harvesting and reliable performance.

At the core of PENGs' functionality is the direct piezoelectric effect, where mechanical deformation induces an electric field in materials with non-centrosymmetric crystal structures, such as the wurtzite structure of ZnO [14]. This property enables the conversion of mechanical energy into electrical energy, which is critical for energy-harvesting applications in wearable and implantable bioelectronics. ZnO-based PENGs harness the piezoelectric properties of ZnO's wurtzite crystal structure [14,146] (Fig. 2a), where the alignment of Zn^{2+} and O^{2-} ions introduces an inherent asymmetry essential for their function. Applying mechanical stress along the *c*-axis of ZnO displaces ions across the crystal lattice and generates a piezoelectric potential, which, when connected to an external circuit, can power devices or transmit signals.

To enhance sensitivity and accuracy in energy conversion, materials with high piezoelectric coefficients, such as PZT, PVDF-based copolymers, and their composites [147-149], are preferred. These materials have piezoelectric coefficients in the range of 200–500 pC N^{-1} [149], which is significantly higher compared to typical quartz piezoelectric materials (2–3 pC N^{-1}). This high coefficient allows PENGs to convert mechanical energy to electrical energy efficiently. Flexible and biocompatible materials, such as polydimethylsiloxane (PDMS) integrated with piezoelectric nanoparticles, polylactic acid [150], and polyurethane (PU) [151,152], ensure that the device conforms to the dynamic movements of the heart without causing discomfort or damage, making them ideal for long-term implantation. Further microstructural designs, such as aligning nanowires or nanoribbons, are essential for increasing surface area and improving mechanical-electrical energy conversion efficiency [86,153-155]. Achieving this alignment includes techniques like electrospinning [86,155], which can produce highly oriented nanofibers, and template-assisted synthesis [40,156,157]. This ensures the uniformity and alignment of nanostructures. These aligned nanostructures facilitate efficient stress distribution and charge accumulation, enhancing PENGs' overall sensitivity.

3.2. PENG configurations

Device configurations, including thin film materials, surface structures, device structure designs, and interdigitated electrodes, can be tailored for specific applications to optimize performance and medical care. Thin film structures involve depositing a thin layer of piezoelectric material onto a flexible substrate, such as PDMS or polyethylene terephthalate (PET) [39,128,158,159]. These films are advantageous for their flexibility, lightweight properties, and ability to conform to various surfaces. Thin film PENGs can be used in wearable devices that adhere to the skin for continuous monitoring of physiological signals or in implantable patches that adhere to the heart's surface. They can also be integrated into endovascular devices for monitoring blood pressure or flow within the arteries. For PENG textiles, a piezofabric generates electricity through pressing and releasing movements [160] (Fig. 2b). Initially, the charge centers of cations and anions coincide, resulting in no polarization. When a pressing force is applied, the deformation of the piezofabric creates a negative strain, separating charge centers and forming electrical dipoles. This separation results in a piezopotential that drives electrons through an external circuit, converting mechanical energy into electrical energy. Maximum compression achieves the highest polarization density, and releasing the force allows electrons to flow back, rebalancing the charge. Continuous reciprocating strain produces a steady pulse current, with output voltage and current reversing when the system is reversed. To further explain the PENG

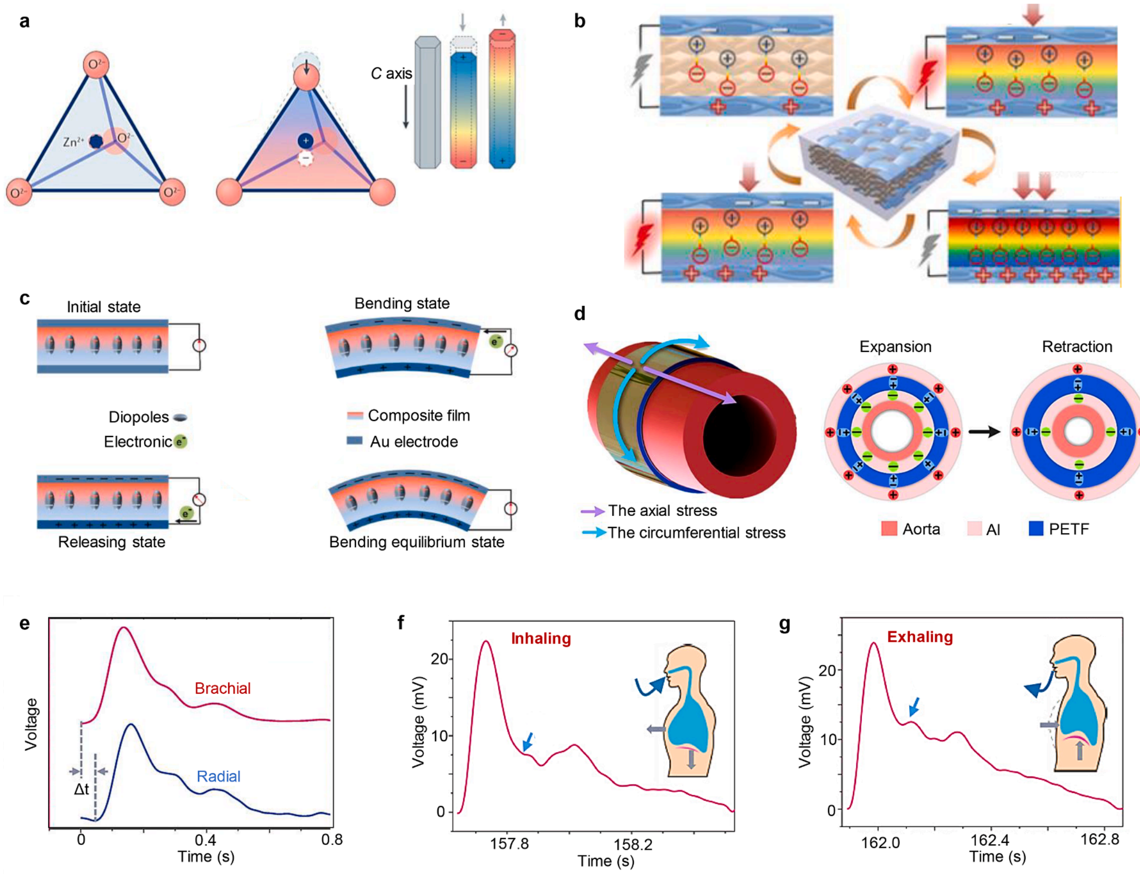

Fig. 2. PENGs working principles. a, Operation of a ZnO PENG, focusing on the tetrahedral alignment of Zn^{2+} and O^{2-} ions and the induced dipole formation from external stress applied along the *c*-axis, leading to a piezoelectric potential through dipole superposition [14]. Copyright (2021) Springer Nature. b, Mechanisms of textile-based PENGs [160]. Copyright (2020) WILEY–VCH GmbH. c, PENGs working principles [161]. Copyright (2021) Elsevier. d, Circumferential tension in dilated aortic walls and the resultant charge distribution during expansion and retraction phases [158]. Copyright (2016) Elsevier. e, Pulse waveform analysis from brachial to radial arteries for PWV estimation [39]. f,g, Inhalation and exhalation signal monitoring [39]. Copyright (2019) WILEY–VCH GmbH.

power generation mechanism, no electrical output is observed initially as charge centers coincide [161] (Fig. 2c). Material deformation causes electric dipoles to unbalance, increasing the potential gradient and deflecting the ammeter pointer. The pointer stabilizes when deformation stops and then deflects in the opposite direction as the material returns to its original state, maintaining charge balance. This cyclic deformation generates periodic alternating current signals.

When a piezoelectric thin film device is wrapped around the aorta [158] (Fig. 2d), it encounters unique operational dynamics due to the aorta's dilation. This process applies circumferential and axial stresses to the thin film. As the aorta expands, compressive stress affects the outer surface of the thin film, while tensile stress acts on the inner surface. The alignment with the d_{33} piezoelectric mode promotes charge generation through mechanical deformation parallel to the electric field's direction. Electron movement from the thin film's outer to inner surface during expansion, and vice versa during retraction, generates an alternating current. This current is capable of powering external circuits, such as a blood pressure monitoring system, providing battery-free operation. Notably, this setup not only gauges the mechanical stress induced by the aortic pulse but also facilitates a visual representation of blood pressure levels based on the voltage output from the device, leveraging a battery-free system like a liquid crystal display (LCD). Incorporating such devices around critical anatomical structures like the aorta enables real-time, self-powered monitoring of cardiovascular health. In cardiovascular diagnostics, analyzing pulse waveforms is pivotal for estimating PWV, a key marker of arterial stiffness [39] (Fig. 2e). Thin-film flexible piezoelectric pulse sensors excel in detecting subtle changes in pulse waveforms throughout the respiratory cycle, including phases of deep inhalation and exhalation [39,128,159] (Fig. 2f,g). Inhalation causes the chest cavity to expand, creating a vacuum that facilitates lung inflation and also expands the heart and aorta. This expansion leads to a diminished tidal wave and introduces a shoulder peak in the pulse waveform. Conversely, exhalation results in chest cavity contraction and a pronounced tidal wave. The ability of these sensors to detect such physiological nuances highlights their utility in non-invasively providing comprehensive insights into cardiac and respiratory health, showcasing the potential of piezoelectricity in medical diagnostics.

Device structures could be designed to twist and stretch with the heart's movements [162,163] (Fig. 3a), maximizing energy harvesting by maintaining continuous mechanical deformation. This design is well-suited for implantable devices that need to adapt to the dynamic movements of the heart. Layered composites combine multiple piezoelectric layers with alternating directions of polarization [2,164,165] (Fig. 3b), which can capture multi-directional strains and convert them into electrical energy effectively. This configuration is beneficial for both surface-mounted and implanted devices, enhancing energy conversion efficiency.

Interdigitated electrodes consist of comb-like structures with interlocking fingers of conductive material [166] (Fig. 3c). These electrodes enhance the electric field distribution and sensitivity of the device, making them ideal for applications requiring precise spatial resolution. By adjusting the finger width, spacing, and material properties, interdigitated electrodes can be tailored for precise spatial resolution, suitable for detecting minute changes in arterial pulse waveforms. They can be integrated into surface-mounted devices for skin contact to continuously monitor physiological signals, such as heart rate and blood

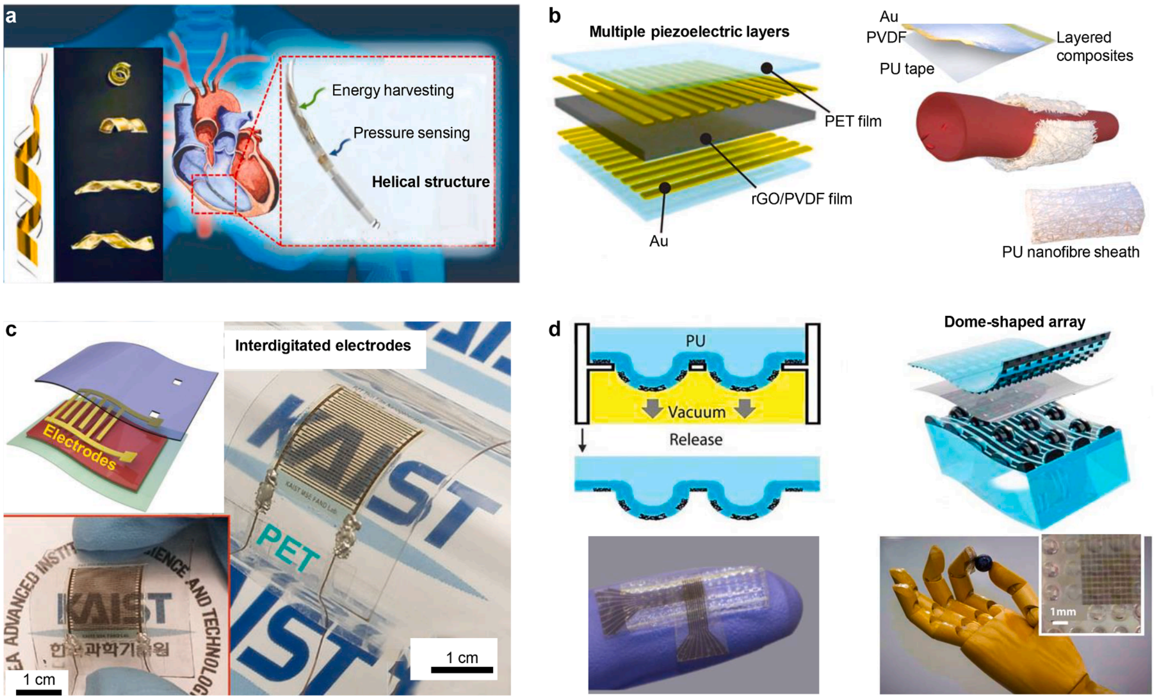

Fig. 3. PENGs Device Configurations. a, Helical structure [163]. Copyright (2020) WILEY–VCH GmbH. b, Multiple piezoelectric layers (layered composites). Left, [164]. Copyright (2015) Science, under a CC BY-NC 4.0 license. Right, [165]. Copyright (2024) WILEY–VCH GmbH. c, Interdigitated electrodes [166]. Copyright (2014) WILEY–VCH GmbH. d, Dome-shaped arrays [167]. Copyright (2018) Science.

pressure, or implantable patches for internal cardiovascular monitoring, such as blood flow and arterial pressure. Dome-shaped arrays consist of hemispherical structures that conform to curved surfaces like the heart or blood vessels [167,168] (Fig. 3d). These arrays maximize contact area and mechanical deformation with high energy conversion efficiency, making them well-suited for applications where conformability and flexibility are crucial, such as monitoring the dynamic movements of the heart or detecting pulse waves on the skin surface. They can be surface-mounted or used in minimally invasive inserted devices.

3.3. Back-end signal processing

Further enhancements in sensitivity and accuracy can be achieved through back-end signal processing, including signal amplification, noise reduction techniques, and others. Charge amplifiers convert the charge generated by the piezoelectric material into a proportional voltage, enhancing the output signal without adding significant noise [169,170]. These amplifiers boost the weak signals generated from minor pulse waveforms. Low-noise preamplifiers are designed to amplify small signals while introducing minimal additional noise, optimized to work with high-impedance PENGs. When used in conjunction with charge amplifiers, they further enhance signal strength before processing.

To reduce noise and artifacts, differential signal processing involves comparing the signal from the PENGs to a reference signal, ideally a noise signal common to the environment but not correlated with the desired signal [171]. By subtracting the reference signal from the primary signal, common noise can be reduced, which is useful in environments with high electromagnetic interference. Adaptive filtering dynamically adjusts its parameters to minimize the difference between the filtered signal and a reference noise signal, learning and adapting to noise characteristics for filtering out motion artifacts and other varying noise sources in real-time cardiac monitoring [172-174].

Kalman filtering is an optimal estimator that processes a series of measurements over time, containing statistical noise and other inaccuracies. It estimates the true signal by predicting future states of the system and correcting predictions with new measurements [175]. This technique is useful in processing signals from PENGs in dynamic environments during physical activity or varying heart rates. Wavelet transforms, a mathematical tool that decomposes a signal into different frequency components [176], can enhance PENG signals by filtering out noise components and reconstructing the signal, identifying and retaining important features of the pulse waveforms. By locking onto the reference frequency, lock-in amplification can extract signals even when they are smaller than the noise [177]. This method is effective for detecting periodic signals from PENGs, allowing for accurate measurement of heartbeats amidst a noisy environment. By integrating these advanced signal amplification and noise reduction techniques, the sensitivity and accuracy of PENGs in detecting arterial pulse waveforms can be improved. These enhancements ensure that PENGs provide reliable and precise data for cardiovascular monitoring and therapy.

4. PENGs for self-powered cardiac monitoring

In cardiac monitoring, the advent of PENGs marks a leap forward in measuring and recording heart mechanics with high precision [5]. These devices utilize their distinctive material properties and design to transform mechanical stresses, such as heartbeats, into electrical signals, allowing for continuous health monitoring.

Wearable PENGs are ideal for monitoring pulse, heartbeat, and other subtle physiological signals. Their ability to detect minor deflections on the skin surface caused by arterial pulses makes them invaluable for unobtrusive, continuous monitoring [160,178-185]. These devices can be strategically positioned at various arterial sites, offering versatile monitoring options without compromising data quality.

Implantable PENGs focus on monitoring internal parameters such as blood pressure, blood flow rate, and heartbeat [186-188]. These devices can continuously track cardiovascular health by converting mechanical stresses within the body into electrical signals, enabling real-time and self-powered monitoring. This approach ensures comprehensive cardiac monitoring, enhancing both preventive and diagnostic healthcare capabilities.

The integration of PENGs with wireless communication shows potential in offering real-time cardiac monitoring that transcends the limitations of stationary healthcare [189,190]. This wireless capability not only facilitates continuous ambulatory monitoring but also ensures that healthcare providers receive instantaneous data for immediate intervention, reducing response times in critical cardiac events. The advantage of this integration is pronounced in telemedicine and remote healthcare services, where distance and access to healthcare facilities can impede timely cardiac care. Typically made from ultrathin PZT nanoribbons, these devices are crafted into stretchable networks that function as mechanical actuators and sensors. They attach to the skin or directly to the heart's surface through soft, reversible lamination, enabling rapid, quantitative assessments of the heart tissue's viscoelastic moduli [191] (Fig. 4a). The dynamic output voltage and current of the piezoelectric transducer were measured using a compression stage simulating heartbeats. Under loading forces of 0.6 N at 1 Hz, the open-circuit voltage remained consistent with force, while the short-circuit current varied with frequency [192] (Fig. 4b). Analyzing blood pressure waveforms against the devices' voltage outputs [158] (Fig. 4c) reveals their potential as non-invasive yet accurate blood pressure monitors, crucial for tracking cardiovascular health and the impact of therapeutic interventions over time.

A battery- and leadless heart-worn PENGs-based pacemaker system, including a piezoelectric transducer, pacing probe, pulse generator circuit, and external encapsulation, was developed [192] (Fig. 4d) to address challenges of energy generation and leadless pacing through piezoelectric energy scavenging and exocardial pacing. The piezoelectric component includes piezoelectric, metal, and polymer layers, with $Pb(Mg_{1/3}Nb_{2/3})O_3$–$PbTiO_3$ (PMN-PT) chosen for its high electromechanical coupling. The flexible structure improves energy harvesting, and PDMS and parylene-*C* encapsulation ensure biocompatibility. Connected to a data acquisition system, the PENGs transducer, Ag/Sm-doped PMN-PT/P(VDF-TrFE), records real-time ECG and blood pressure [192] (Fig. 4e). At 140/100 mmHg and 100 bpm, it achieves a peak open-circuit voltage of 8.1 V and a short-circuit current of 30 μA. Another test shows improved performance with a maximum voltage of 83.5 V and current of 1.2 μA [161] (Fig. 4f). The enhancement could be attributed to Ag creating a conductive path during poling, increasing the electric field applied to ceramic particles.

For implantable biomedical devices, it is essential to integrate vital sign sensing with data transmission. However, the power demands of wireless communication can shorten battery life, leading to frequent and risky battery replacement surgeries, which are especially detrimental to elderly patients [193,194]. The integration of PENGs with wireless communication could mitigate these issues by offering a sustainable, self-powered alternative. A promising solution is converting

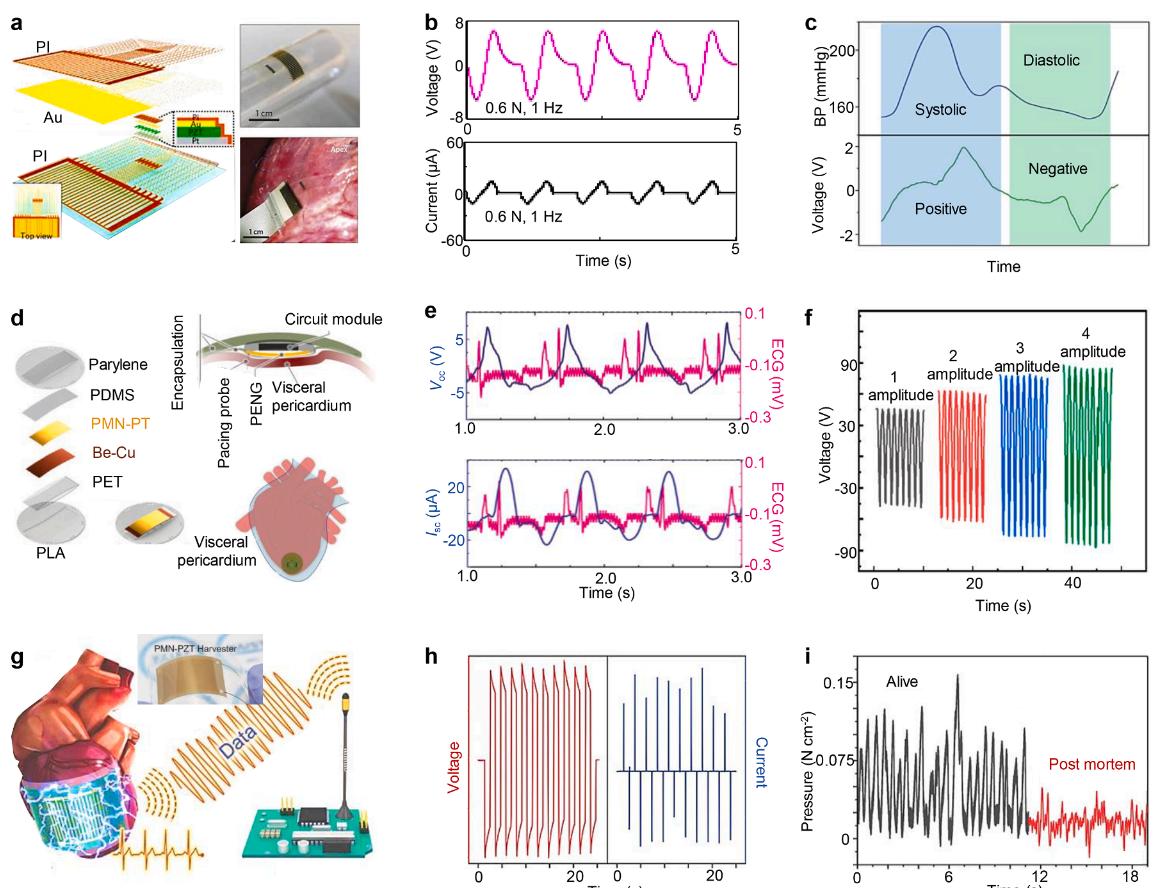

Fig. 4. PENGs for self-powered cardiac monitoring. a, Schematic and images of piezoelectric devices, showing adhesion to a tube and heart [191]. Copyright (2015) Springer Nature. b, Open-circuit voltage and short-circuit current under peak loading forces of 0.6 N at 1 Hz [192]. Copyright (2020) WILEY–VCH GmbH. c, Comparative analysis of blood pressure waveforms and device output voltage [158]. Copyright (2016) Elsevier. d, Schematic of the leadless and batteryless heart-worn piezoelectric pacemaker [192]. Copyright (2020) WILEY–VCH GmbH. e, Real-time open-circuit voltage and short-circuit current measurements with corresponding electrocardiograph (ECG) and blood pressure (BP) signals [192]. Copyright (2020) WILEY–VCH GmbH. f, Output voltages of Ag/Sm-doped $Pb(Mg_{1/3}Nb_{2/3})O_3$–$PbTiO_3$/P(VDF-TrFE) device at 1 Hz with varying amplitudes [161]. Copyright (2021) Elsevier. g, Schematic of a flexible piezoelectric energy harvester on a heart for wireless data transmission [195]. h, Output voltage and current from the flexible energy harvester during bending and unbending motions [195]. Copyright (2017) WILEY–VCH GmbH. i, Force signal data from an implanted sensor in a mouse at active (black) and euthanized states (red) due to anesthetic overdose [196]. Copyright (2018) National Acad.

biomechanical energy into electrical energy using flexible piezoelectric energy harvesters, which offer advantages over triboelectric harvesters, including superior flexibility and stability within the human body. The development of single-crystalline $Pb(Mg_{1/3}Nb_{2/3})O_{3-x}Pb(Zr,Ti)O_3$ with Mn doping (PMN-PZT-Mn) for attachment to the porcine heart [195] (Fig. 4g) mitigates the need for battery replacements and enhances the functionality and integration of implantable medical devices in ubiquitous healthcare settings, requiring robust, self-powered solutions. These devices demonstrate a high piezoelectric charge coefficient and electromechanical coupling factor, making them efficient at converting the heart's mechanical movements into energy, which is crucial for powering wireless data transmission systems through the heart's natural actions. Fig. 4h showcases the electrical performance of these energy harvesters under mechanical stress [195], as evidenced by their performance during bending and unbending motions. These devices generate substantial open-circuit voltage and short-circuit current, showcasing their adeptness at converting mechanical energy into electrical energy. This capability is crucial for the long-term monitoring and stability of device operation, as verified by rigorous fatigue testing that confirms the harvester's durability against repetitive mechanical stress. An implanted PENG in a mouse model, designed to detect physiological force signals, serves to monitor respiratory functions [195,196] (Fig. 4i). By comparing the sensor's signals before and after administering an anesthetic overdose, valuable insights are gained into the sensor's reactivity to changes in biological states. This demonstration of sensitivity not only indicates its potential for cardiac applications but also its capability to serve as an early-warning system for various respiratory conditions, further affirming its role in a comprehensive cardiac and respiratory monitoring strategy.

While PENGs hold promise for cardiac monitoring, several challenges need to be addressed for their effective clinical implementation. One major challenge is sensor sensitivity, ensuring that the PENGs can detect and decode the subtle mechanical signals of the heart and blood vessels. Another crucial challenge is balancing high piezoelectric performance with flexibility to conform to the body's movements and contours without causing discomfort or compromising functionality. Addressing these challenges is essential for optimizing the performance and reliability of PENG-based cardiac monitoring devices.

5. PENGs for self-powered cardiac modulation

Implantable cardiac devices, like pacemakers and defibrillators, are vital for treating various heart disorders [159,197-220]. Specific heart disorders that could benefit from PENG-based treatments include bradyarrhythmia, where pacemakers regulate the heart rate, and tachyarrhythmias, where defibrillators can correct abnormal rapid rhythms [14]. The adaptation of PENGs in these devices could enhance therapeutic outcomes by providing a stable and sustainable energy source, ensuring continuous operation without interruption due to power depletion. These devices typically depend on lithium-ion batteries [196,

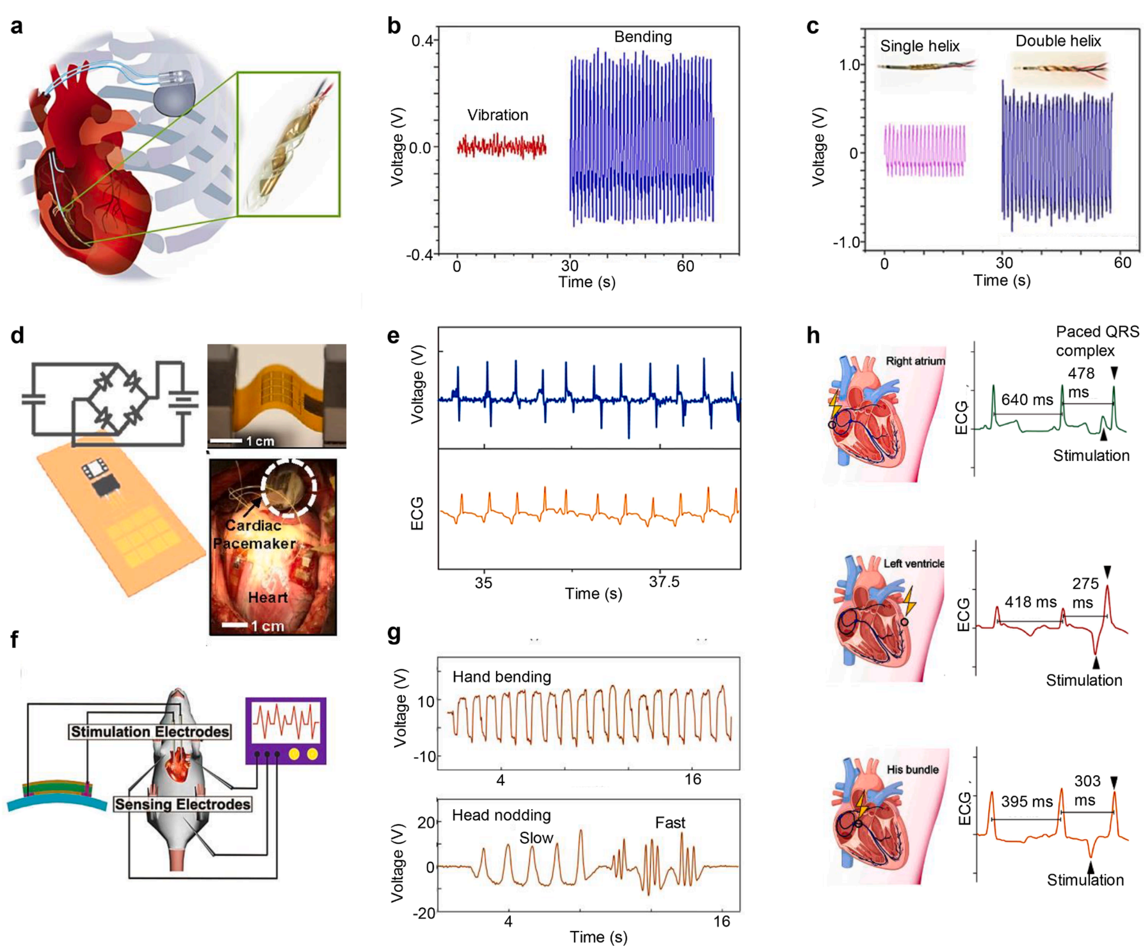

Fig. 5. PENGs for self-powered cardiac modulation. a, Schematic of a helical piezoelectric energy harvester, self-wrapped around a pacemaker to charge its battery [51]. b, Voltage output responses to vibration and bending motions of the pacemaker lead [51]. c, Open-circuit voltage from single- and double-helix devices [51]. Copyright (2019) Elsevier. d, Schematic and photo of a PENG with a rectifier and microbattery [2]. Copyright (2014) National Acad Sciences. e, In vivo open-circuit voltage of the PENG and ECG recordings [42]. Copyright (2022) Elsevier. f, Artificial cardiac pacemaking scheme powered by a flexible piezoelectric energy harvester [7]. Copyright (2014) WILEY–VCH GmbH. g, Output voltage from optimal PENG during hand bending and head nodding [42]. h, Representative ECGs of effective pacing at the right atrium, left ventricle, and bundle [42]. Copyright (2022) Elsevier.

221-234], which, due to their finite energy capacity, require periodic replacements through surgical procedures. Such operations carry the risk of infection and generate substantial healthcare costs. Recent advances in PENGs introduce a transformative solution by offering a renewable power source, eliminating the need for battery replacements and the associated surgical interventions.

Harvesting energy from the body's ambient biomechanical movements, such as heartbeats and arterial pulsations, presents a compelling alternative to conventional power sources [212,235-240]. A typical design is the helical piezoelectric energy harvester, which adapts to the complex motions of the pacemaker lead. This bioinspired design captures mechanical energy, transforming it into electrical energy through direct heart contact. A flexible harvester, employing porous piezoelectric thin films, wraps around the pacemaker to capture kinetic energy from its movements during cardiac cycles [51] (Fig. 5a). This energy is converted into electrical power, recharging the pacemaker's battery, and exemplifying a sustainable approach to powering implantable medical devices. The device's performance, assessed under simulated conditions, reveals that its voltage output responds to the bending motions of the pacemaker lead [51] (Fig. 5b), mimicking the heart's dynamic beating. These results highlight the device's capacity to utilize energy from natural physiological movements. The scalability is evidenced by configurations of single and double-helix devices connected in series to increase the voltage output [51] (Fig. 5c). This adaptability proves that these energy harvesters can meet diverse energy needs by altering their structural designs, paving the way for their broad application in self-powered medical devices.

PENGs combined with a rectifier and microbattery not only capture but also convert and store mechanical energy from physiological movements. This functionality makes them suitable for powering medical implants and other compact, energy-reliant devices [2] (Fig. 5d). Fig. 5e illustrates the integration of PENGs with ECG recordings [42]. This synchronization of PENGs' output with the cardiac cycle ensures a real-time, self-powered energy supply that aligns directly with the heart's rhythmic movements without the need for external power sources. Furthermore, an external flexible PENG powers artificial cardiac pacemaking, using the immediate electrical output from the harvester to stimulate the heart [7] (Fig. 5f), introducing a novel method for self-powered cardiac pacing. Additionally, PENGs responsive to simple body movements like hand bending and head nodding can generate high voltage outputs [42] (Fig. 5g), showcasing potential beyond cardiac care and extending to various applications in biomechanical energy harvesting.

Beyond harvesting energy from the body's movements, PENGs can also utilize external energy sources such as ultrasound. This method involves converting ultrasonic energy into electrical energy, enhancing the versatility and applicability of PENGs. For instance, ultrasound energy can wirelessly power implanted devices, ensuring continuous operation without battery replacements [241-243]. This integration of internal and external energy sources maximizes the potential of PENGs for comprehensive and sustainable energy harvesting solutions. These developments hinge on the principle of post-extrasystolic potentiation (PESP), an inherent feature of cardiac muscle that enhances the contractility of subsequent beats after spaced depolarizations. The phenomenon, driven by changes in Ca^{2+} dynamics within cardiac cells, is crucial for the piezoelectric-based cardiac pacing mechanism. Following an extrasystole, the sarcoplasmic reticulum's (SR) calcium uptake remains relatively unchanged, but the premature beat prevents complete calcium release by the SR, reducing the contraction force. However, this results in a higher calcium load in the SR, leading to a stronger contraction in the next beat. This leverages the heart's natural reaction to improve pacing efficiency. ECG signals from various cardiac sites, including the right atrium, left ventricle, and bundle, demonstrate the PENGs' versatility in supporting different pacing modes and their adaptability to the heart's complex electrical structure [42] (Fig. 5h).

By harnessing biomechanical energy from cardiac movements to generate electricity, PENGs eliminate the need for battery replacements, reducing the frequency of surgical interventions and lowering the risk of infection and complications. This sustainable power source allows PENGs to be small and light, improving patient comfort and making them less invasive for pediatric and elderly patients. Meanwhile, PENGs can integrate with sensors to provide real-time monitoring of cardiac activity, enabling immediate therapeutic interventions and improving patient outcomes by detecting subtle variations in pulse waveforms and responding promptly to cardiovascular events.

Compared with typical triboelectric nanogenerators (TENGs), which are less efficient at converting the subtle mechanical energy generated by cardiac movements into electrical energy [119,244,245], PENGs provide a consistent and sustainable power source for cardiac devices. This high conversion efficiency ensures reliable device performance and longevity, reducing the need for frequent medical interventions. Additionally, PENGs are sensitive to minor mechanical changes, allowing for precise modulation of cardiac activity, which is crucial for effective therapeutic interventions.

Despite their promises, PENGs face several challenges in therapeutic applications. Ensuring biocompatibility is crucial to avoid adverse immune responses and tissue damage when devices are implanted in the body. Surface engineering, including the addition of bioactive coatings that release anti-inflammatory agents or growth factors and the use of nanostructured surfaces that mimic the natural extracellular matrix, can enhance cell adhesion and tissue integration without causing fibrosis or encapsulation. Biodegradability should also be considered, as it can reduce the need for surgical removal once the device is no longer needed. Meanwhile, miniaturization is essential for integrating PENGs into compact, implantable devices without compromising their performance or causing discomfort to the patient. Addressing these challenges is vital for advancing the use of PENGs in widespread therapeutic applications.

6. Concluding remarks and future perspectives

As the global population ages, there is an escalating need for efficient cardiac bioelectronics that cater to the increasing demand for remote and wireless cardiac health management. These innovations seek to enhance the quality of life for patients by minimizing hospital visits and reducing healthcare costs through a shift from reactive to preventive care. PENGs emerge as versatile and intelligent solutions for pioneering treatment systems, promoting healthcare advances by improving minimally invasive surgeries and reducing surgical interventions. This approach not only extends the longevity and functionality of implantable devices but also supports consistent, at-home heart monitoring (Fig. 6). This monitoring could decrease hospitalization rates for heart failure patients and pave the way for proactive healthcare management.

Within cardiovascular healthcare, the adoption of self-powered PENGs holds great promise, especially in the IoT and the growing demand for personalized healthcare. These devices play a critical role in minimizing invasive procedures, heralding new avenues for biodegradable electronics, and proposing sustainable medical treatment solutions. While bioresorbable electronics are designed to degrade over time and may be suitable for temporary therapeutic applications, PENGs provide a permanent solution, reducing the need for repeated surgeries and minimizing the risk of complications associated with device degradation. The exceptional properties of PENGs, including high output performance and successful in vivo applications, pave the way for the development of next-generation pacemakers that harvest energy from the body's movements, smart implants that monitor and respond to physiological changes in real time, and biocompatible sensors that provide continuous health data.

However, to integrate piezoelectric effects within healthcare, several challenges and considerations must be addressed. There is a pressing need for long-term studies to evaluate the biocompatibility and durability of these devices within the human body. Exploring new

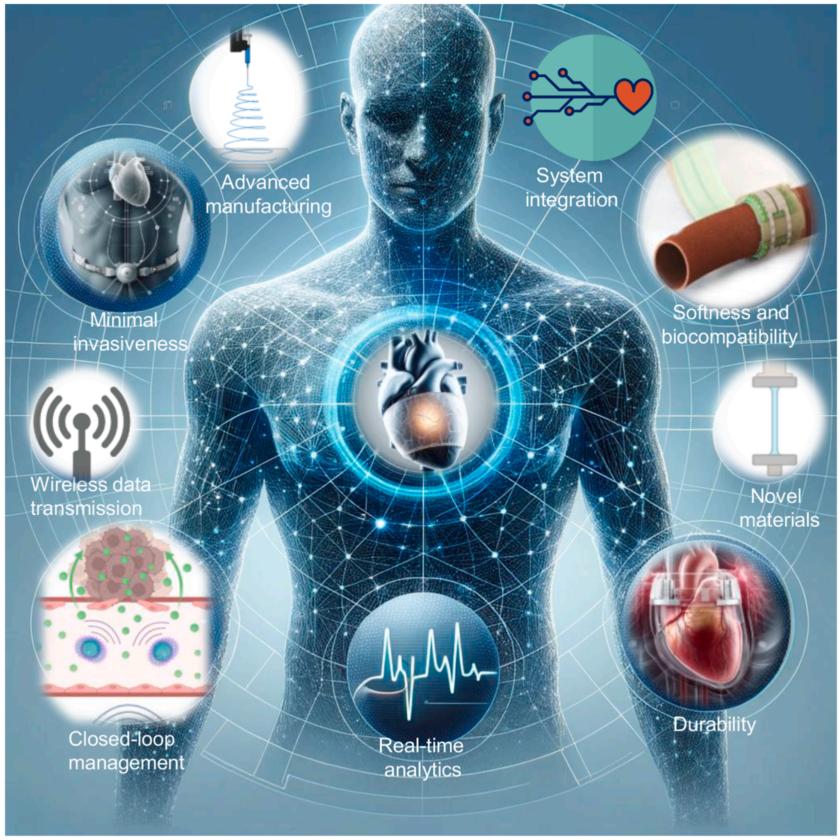

Fig. 6. Perspective on the contribution of PENGs as a platform technology for cardiac health monitoring and modulation, highlighting their role in promoting minimal invasiveness, enabling wireless data transmission, and supporting real-time analytics for continuous heart monitoring, through enhanced stability and durability, material engineering, and effective system integration. Flexible PENGs [73], Copyright (2019) Springer Nature.

piezoelectric materials or composites that combine biocompatibility with energy-harvesting efficiency, along with surface bioactive coatings to promote cell adhesion and tissue integration while reducing the risk of immune rejection, is crucial for improving the long-term integration and functionality of these devices [112,201,246,247]. Scalability for widespread application remains a significant challenge [248]. Advancing manufacturing processes could enable large-scale production and accessibility.

The potential for real-time analytics and precise therapeutic interventions powered by PENGs promises to revolutionize treatment modalities [249]. PENGs can reliably detect abnormalities such as premature ventricular contractions or atrial fibrillation by collecting heart rate, rhythm, and pulse waveforms, which is critical for early intervention and identifying early signs of cardiovascular issues such as arrhythmias and ischemic events. Wireless data transmission capabilities are essential for their seamless integration into health management systems [196,200,250-252]. Developing flexible PENGs is vital to accommodate body dynamics without compromising patient comfort or mobility [73].

In conclusion, incorporating PENGs into cardiac healthcare represents an innovative shift toward managing heart conditions in a self-powered working manner. With continued research and development, these technologies can improve patient care and drive innovations in biomedical engineering, paving the way for flexible, reliable, and efficient solutions to cardiac monitoring and modulation.

Outstanding questions

What advancements in the miniaturization and energy efficiency of piezoelectric materials are necessary to ensure the seamless integration of PENGs within the cardiovascular system without altering heart biomechanics?

How can structural design and implantation strategies address the challenges of long-term biocompatibility and functional stability of these devices in vivo?

With the convergence of IoT and personalized healthcare on the horizon, what technological developments are crucial for ensuring the robust wireless integration of PENGs with healthcare monitoring ecosystems?

In self-powered cardiac modulation, how can we optimize PENGs to support and potentially augment the body's electrophysiological signals with minimal artifacts for heart disorder treatments?

Glossary terms

Piezoelectric Nanogenerator (PENG): A small-scale piezoelectric transducer designed to harvest energy from minute mechanical movements, such as heartbeats or arterial pulsations.

Cardiac Monitoring: The continuous observation and recording of heart activity, typically using devices like ECGs, to detect cardiac conditions or monitor cardiac health in real time.

Self-Powered Cardiac Systems: Cardiac monitoring or therapeutic devices that generate their power from bodily movements or biological functions, eliminating the need for external power sources like batteries.

Implantable Cardioverter-Defibrillators (ICDs): Medical devices implanted in the body to monitor heart rhythms and provide necessary electrical stimulation to correct arrhythmias.

Cardiac Implantable Electronic Devices (CIEDs): A broad category of electronic devices implanted in the heart or chest to regulate or monitor heart function, including pacemakers and ICDs.

Pacemakers: Devices that send electrical impulses to the heart to maintain a normal heart rate and rhythm, commonly used to treat bradyarrhythmia.

Schottky Barrier: A junction formed at the interface between a metal and a semiconductor, affecting electrical properties and device performance, often manipulated in piezoelectric devices.

Pulse Wave Velocity (PWV): A measure of arterial stiffness, determined by the speed at which blood pressure pulses travel through the circulatory system.

Field-Effect Transistors: Semiconductors that control electrical behavior using an electric field, fundamental components in digital circuits.

Post-Extrasystolic Potentiation (PESP): A cardiac phenomenon where increased efficiency in heart contractions occurs following a premature contraction, potentially useful in enhancing cardiac pacemaker function.

Wurtzite Structure: A specific crystal structure that exhibits strong piezoelectric properties, often used in ZnO-based PENGs to generate electrical charge under mechanical stress.

CRediT authorship contribution statement

Shumao Xu: Writing – original draft. **Xiao Wan:** Writing – review & editing. **Farid Manshaii:** Writing – review & editing. **Ziyuan Che:** Writing – review & editing. **Jun Chen:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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