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Review

Flexible sensors and machine learning for heart monitoring

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ABSTRACT

Cardiovascular disease is the leading cause of death worldwide. Continuous heart monitoring is an effective approach in detecting irregular heartbeats and providing early warnings to patients. However, traditional cardiac monitoring systems have rigid interfaces and multiple wiring components that cause discomfort when continuously monitoring the patient long-term. To address those issues, flexible and comfortable sensing devices are critically needed, and they could also better match the dynamic mechanical properties of the epidermis to collect accurate cardiac signals. In this review, we discuss the principles of the major mechanisms of heart monitoring approaches as well as traditional cardiovascular monitoring devices. Based on key challenges and limitations, we propose design principles for flexible cardiac sensing devices. Recent progress of cardiac sensors based on various nanomaterials and structural designs are closely reviewed, along with the fabrication methods utilized. Moreover, recent advances in machine learning have significantly implemented a new sensing platform for the multifaceted assessment of heart status, and thus is further reviewed and discussed. Such strategies for designing flexible sensors and implementing machine learning provide a promising means of automatically detecting real-time cardiac abnormalities with limited or no human supervision while comfortably and continuously monitoring the patient's cardiac health.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death, causing an estimated 32% of deaths worldwide [1]. According to the World Health Organization (WHO), an estimated 17.9 million people die annually from CVDs, and around 80% of those deaths come from heart attacks and strokes [1]. Continuous heart monitoring is an effective approach in detecting irregular heartbeats and providing early warnings, especially since people may not be able to distinguish some symptoms of cardiovascular diseases on their own. Traditional cardiac monitoring systems, such as Holter monitors and cardiac event recorders, are portable devices that measure the heart's electrical activity in and outside a hospital setting, which could be 24 h or longer [2]. By using certain mechanisms to interpret the collected cardiovascular data, healthcare workers can evaluate patients for their cardiac-related health. Of the various mechanisms available for interpretation, electrocardiogram (ECG) and seismocardiogram (SCG) are the most commonly used and effective methods for monitoring the heart, and this review primarily focuses on those two mechanisms. ECG-based cardiac monitoring approach is one of the most effective methods in detecting the heart's electrical activity in a hospital setting [3,4]. The process is simple, fast, and non-invasive. Despite the effectiveness of ECG machines, patients still require continuous cardiac monitoring outside the hospital setting due to the infrequency of irregular or abnormal heartbeats. Doctors can prescribe portable cardiovascular monitoring systems such as the Holter monitors or cardiac event recorders that can be taken outside the hospital for the patient's ECG to be recorded for 24–48 h. However, such devices are bulky and utilize wiring to attach electrodes to the chest to record ECG as patients go about their daily activities. For the Holter monitor, six to ten wires are attached to the patient and showering is not advised throughout the monitoring period since wet electrodes may provide inaccurate results [5,6]. Skin irritation may also occur through the electrode attachment; thus, long-term continuous monitoring beyond the 48 h would not be feasible. Another non-invasive effective method of diagnosing CVDs is SCG, and it has also been widely used in clinical settings. SCG measures the heart's mechanical activity such as the vibrations induced by the heartbeat [7,8]. Accelerometers or gyroscopes are placed on the patient's chest to collect the SCG data. However, placement of the device on the human chest matters significantly and motion artifacts can greatly affect SCG data if the patient moves around. Furthermore, the devices are either taped or strapped to the human chest, increasing discomfort the longer they are attached.

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While both ECG and SCG methods provide sufficient cardiac information, those heart monitoring devices have limitations: they consist of various hard-wired, rigid interfaces that provide discomfort to the patient during long-term, continuous usage, and they typically rely on batteries to operate. Additional equipment and measurement methods are often required to further evaluate physiology processes. Due to those limitations, flexible cardiac sensing devices designs are critically needed for long-term, continuous monitoring of the heart by excluding rigid interfaces and wiring. Various flexible sensors have been developed in the field to extract the patient's real-time cardiovascular signals, heart rate, blood pressure, respiratory rate, or sleep patterns with ease of access and comfortability to the patient [9–25]. In this review, different design strategies of cardiac sensing innovations are discussed in terms of structural layouts, material development, and fabrication methods. An ideal cardiac sensing device is flexible, conformable, biocompatible, and has an extended or unlimited battery life to enhance its sensing capabilities and to provide a safe and comfortable experience for continuous cardiac monitoring.

Recently, advances in machine learning (ML) have significantly implemented a new sensing platform for the multifaceted assessment of heart status. This is another key challenge for continuous cardiovascular monitoring, which is analyzing real-time sensing data on the patient's cardiac activity outside the hospital setting. Monitoring and analyzing the cardiac data in real-time help healthcare professionals diagnose CVDs early on and provide early warnings to their patients. In recent years, various ML strategies have been employed to provide automatic abnormal cardiac detection [10, 26–31]. ML is a subset of artificial intelligence that can solve complex problems without being explicitly programmed to do each step [32,33]. ML algorithms in cardiac monitoring applications include convolutional neural network (CNN), binarized neural network (BNN), Hidden Markov Model (HMM), and Random Forest. The most commonly employed algorithm is CNN, which operates on a grid-like structure to process data such as images to automatically identify a hierarchy of features such as amplitudes and wavelengths of cardiovascular signals [34–36]. Essentially, CNN can take raw cardiovascular signals and categorize them into normal sinus rhythm or abnormal rhythm, such as atrial fibrillation, different types of arrhythmias (supraventricular ectopic beats and ventricular ectopic beats), and more. By incorporating ML strategies to cardiovascular sensors, minimum human supervision is required to discover and annotate abnormalities in the collected cardiovascular signals.

There have been various comprehensive reviews on sensing devices that have focused on structural designs [37–39], materials development [39,40], and different biomedical applications [11,35,39,41,42]. By contrast, this review focuses on flexible cardiac sensors and machine learning in cardiac monitoring applications. We begin by discussing the principles of the two major mechanisms of heart monitoring: ECG and SCG. Then, traditional cardiovascular monitoring devices currently employed in and outside a hospital setting are discussed, along with their key challenges and limitations. Next, we explore the design principles of cardiac sensors that take several considerations into account, such as the sensitivity, flexibility, conformability, biocompatibility, and battery life of the device. The structure and material designs are also carefully examined, along with the fabrication methods utilized. Then, we further discuss various ML strategies that have been implemented to automatically categorize cardiovascular signals into normal sinus rhythm and various abnormal rhythms. Lastly, we conclude by providing a summary of perspectives in this field.

2. Mechanisms of heart monitoring

CVD is a prevalent disease worldwide and takes up to a estimated 17.9 million lives every year [1]. Examples of such disease include coronary heart disease, cerebrovascular disease, rheumatic heart disease, heart attacks, and other potentially fatal conditions. Those with highest risk of CVDs should be identified early on so that they can be notified of any feasible changes to their lifestyle or receive suitable treatment to prevent premature death. Continuous heart monitoring is an effective approach in detecting irregular heartbeats and providing early warnings. As is shown in Fig. 1, this review primarily focuses on the most commonly used and effective methods for heart monitoring: ECG and SCG approaches.

2.1. The ECG-based cardiac sensing approach

The body naturally produces electrical impulses that correspond with heart contractions that keep the blood flowing. The ECG-based approach is to measure electric potentials induced on the human skin as the stimulation of the cardiac muscle changes the electrical activity of the heart [3, 48–51]. The cardiac signals from the electrical activity have small amplitudes ranging from 110 μV to 4 mV in the low frequency range of 0.05–100 Hz [51,52]. Those ECG signals provide insight to the heart activity, such as the pace of the heart beating, regular or irregular rhythm of the heart, electrical impulse strength, and electrical impulse timing. Clinical and hospital-grade ECG-based devices, such as Holter devices (Fig. 1 top), use adhesive patches as electrodes to detect the heart's electrical impulses, which are then graphed to represent several waves that repeat with each heartbeat [53,54]. One normal cycle of an ECG waveform in Fig. 2A contains waves, intervals, segments, and one complex [4]. The cycle consists of the P wave, R wave, S wave, Q wave, T wave, and the U wave. Certain elements of an ECG wave are closely examined to determine any heart conditions [4,48,50,55] (Fig. 2B). Those elements include the time interval between two ECG events, such as the PR, QRS, QT, and the RR intervals. The combination of various waves grouped together, such as the QRS complex, is observed for any abnormalities, and the lengths between two points that are located on the baseline amplitude, depicted as the PR, ST, and the TP segments, are closely analyzed [4,55]. Comprehension of these elements of ECG waves is significant because any observed abnormalities to the ECG waves would notify healthcare professionals of any issues with the heart, and it could help them easily diagnose medical conditions from the ECG results without any surgeries. For example, a prolonged QT interval may indicate medication or electrolyte abnormalities, such as hypocalcemia, hypomagnesemia, hypokalemia, or other diseases like intracranial hemorrhage. However, certain patient factors, such as patient gender, may affect the diagnosis from the ECG results, as women and those with lower heart rates typically have longer QT intervals. A wide QRS complex heart rhythm could indicate ventricular tachycardia, which is a condition of having a rapid heart rate. A long RR interval or P wave that precedes every QRS complex with a ventricular rate of less than 60 beats per minute may indicate sinus bradycardia, which refers to a slow heart rate. A variation of the PP interval of at least 120 ms may indicate sinus arrhythmia, or an irregular heart rate, which could be indicative of a more serious condition for those who are not young. Moreover, PR intervals longer than 200 ms may indicate a first degree of heart blocking, whereas a PR interval shorter than 120 ms may indicate pre-excitation syndrome [50]. With an explicit understanding of the ECG waveform and its structure, early diagnoses of cardiac conditions can be achieved.

ECG-based cardiac sensing approaches are also considered non-invasive. Hospital-grade ECG instruments conventionally have 12 leads (10 electrodes), leading to increased sensitivity and accuracy when compared to personal-use ECG monitors, which typically use less leads [53]. While the electrodes can be easily and quickly placed on the human body with gel, they may bring discomfort when the gel dries, and thus long-term monitoring with the existing ECG instruments is not preferred. Each electrode is connected to a lead, or wiring, which connects all of them to an ECG machine displaying ECG wave patterns that characterize the heart's rhythm on a screen. Therefore, multiple electrodes would increase the amount of wiring, leading to discomfort and overall difficulty in maneuvering for the patient during long-term monitoring, especially considering some leads are placed not only on the torso but also on the patient's limbs [53]. In addition, changes to

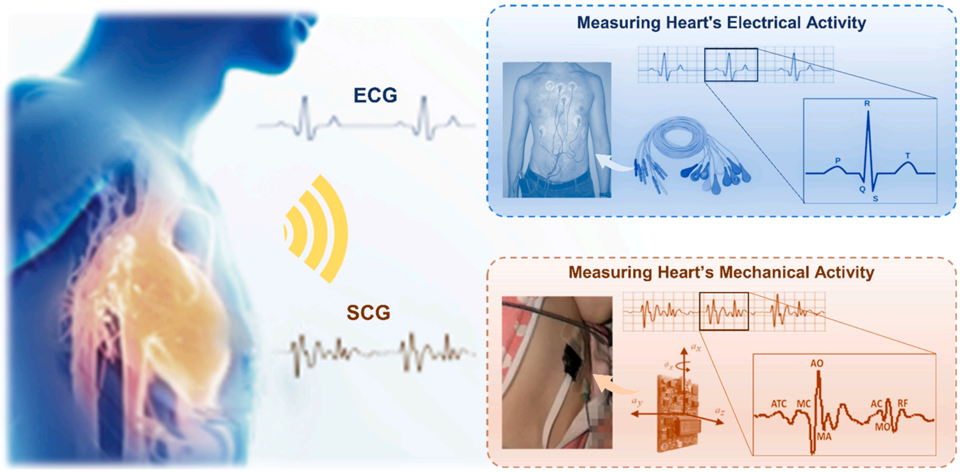

Fig. 1. An overview of two typical heart monitoring strategies and conventional sensing devices: ECG to detect the heart's electrical activity (top) [43,44] and SCG to detect the heart's mechanical activity (bottom) [28, 45–47].

ECG results could be affected by bodily movements, and electrodes are also sensitive to placement on the patient. Certain patient factors, such as patient gender and weight, should also be considered when examining the results for any issues, as they provide differing results [55].

2.2. The SCG-based Cardiac Sensing Approach

The SCG-based approach is to measure the local vibrations caused by the contractions and relaxations of the heart and blood pumping through the heart by using miniature gyroscopes and accelerometers attached to the chest (Fig. 1 bottom) [7,8]. During every cardiac cycle, chest vibrations are produced when the heart twists forward and touches the chest wall [56]. The vibrations of the heart consist of both axial and rotational motion, and SCG signals are measured in the low frequency range of 0.5–100 Hz with amplitudes around 10 mg [48, 57–60]. Accelerometers (in a range of $\pm$ 1 g or $\pm$ 2 g) and gyroscopes can determine the cardiac acceleration in rotational and axial directions [7,60]. Such approach enables the sensing devices to give information about local heart vibrations on the chest wall while also providing a non-invasive technique to evaluate cardiac activity. Using accelerometers or gyroscopes, a typical SCG waveform is measured and recorded, with the peaks of the signals corresponding to specific cardiac events [7, 8,60] (Fig. 2C). Comprehension of these prominent maximum and minimum points of SCG waves is important. Any observed abnormalities to the structure of the waveform can instantly notify healthcare professions to any cardiac-related issues. This enables doctors to quickly provide a diagnosis from the evaluation of these abnormalities without any surgical procedures. For example, certain cardiac mechanical activities can be monitored from SCG cycles [48,50,56,61,62]. The top graph of Fig. 2D displays normal SCG cycles, which show the feature point AO (aortic valve opening) having a higher amplitude compared to other feature points. Abnormal SCG cycles, such as the ones shown on the bottom graph of Fig. 2D, show the feature point with a lower amplitude, which is indicative of a patient who might be suffering from a cardiovascular-related disease or condition [48,56,61,62]. For example, a low amplitude of point AO can indicate a decreased coronary blood flow, which can be associated with coronary artery stenosis or ischemia [61]. Furthermore, the distance between other SCG feature points and point AO can be estimated to calculate the normal range of time intervals of healthy subjects, which can then be used to compare with the range of unhealthy subjects [48]. Those changes or abnormalities of SCG signals can indicate cardiac-related diseases and conditions. Examples include myocardial ischemia, indicating an obstruction of the blood flow to the heart muscle with the buildup of plaques; myocardial infarction, suggesting a cellular response to the rupturing of the built-up plaques; and arrhythmia, referring to an irregular heart rate [48,50,63].

One major benefit of measuring SCG in a clinical setting is that it is an entirely non-invasive and inexpensive technique due to its non-inclusion of any surgical elements. To sense the beating heart and the blood pumping through the arteries, accelerometers and gyroscopes are placed on the human chest at specific locations for easy detection of SCG signals [7, 8, 50, 58–60]. The cardiac muscle, or the myocardium, relaxes and contracts with each heartbeat and the SCG monitoring devices record the dorsoventral acceleration of the chest induced by the cardiac activity [49,61]. Moreover, SCG monitoring devices are not significantly affected by changes in the magnetic field [49]. SCG signals provide information on the heart's mechanical activity, not the heart's electrical activity, so lightweight accelerometers and gyroscopes are compatible with high magnetic fields, such as 3 T or 7 T [58]. During cardiac magnetic resonant imaging (CMRI), data on the heart's electrical activity is distorted by high magnetic fields greater than 3 T, thus making that form of cardiac monitoring unfavorable during CMRIs. Therefore, SCG monitoring can be utilized under those conditions to provide better resolution of the signals. However, there are certain constraints that should be considered when attaching the SCG-based monitoring devices to the human chest wall. One such constraint is that the SCG sensing would be sensitive to motion artifacts, and thus could influence the results [7,8,59]. Motion artifacts from SCG signals include the posture of the human subject, bodily movements, and even respiration. Another constraint of the SCG sensing approach is that the positioning of SCG-based devices relative to the heart would also influence the clarity of the measured SCG waves [7,49]. All those limitations have the capacity to affect SCG results; therefore, additional measurement may be used together with this heart monitoring mechanism to further evaluate cardiac-related health issues.

2.3. Summary of cardiac sensing approaches

As a way to diagnose CVDs, ECG monitoring has been widely used over the years to primarily diagnose cardiac-related health issues [1]. Traditional cardiac monitoring systems like Holter monitors and cardiac event recorders have the ability to measure the heart's ECG in and outside a hospital setting and provide a diagnosis for different cardiac conditions. Holter monitors can continuously monitor a patient's ECG for more than 24 h outside the hospital due to the relatively small, portable recording device [2]. However, those traditional devices have their own disadvantages, such as causing patient discomfort with the electrode attachment and lasting for a short duration outside the hospital when longer periods of observation are required to accurately diagnose cardiac conditions [65]. In recent years, doctors and researchers

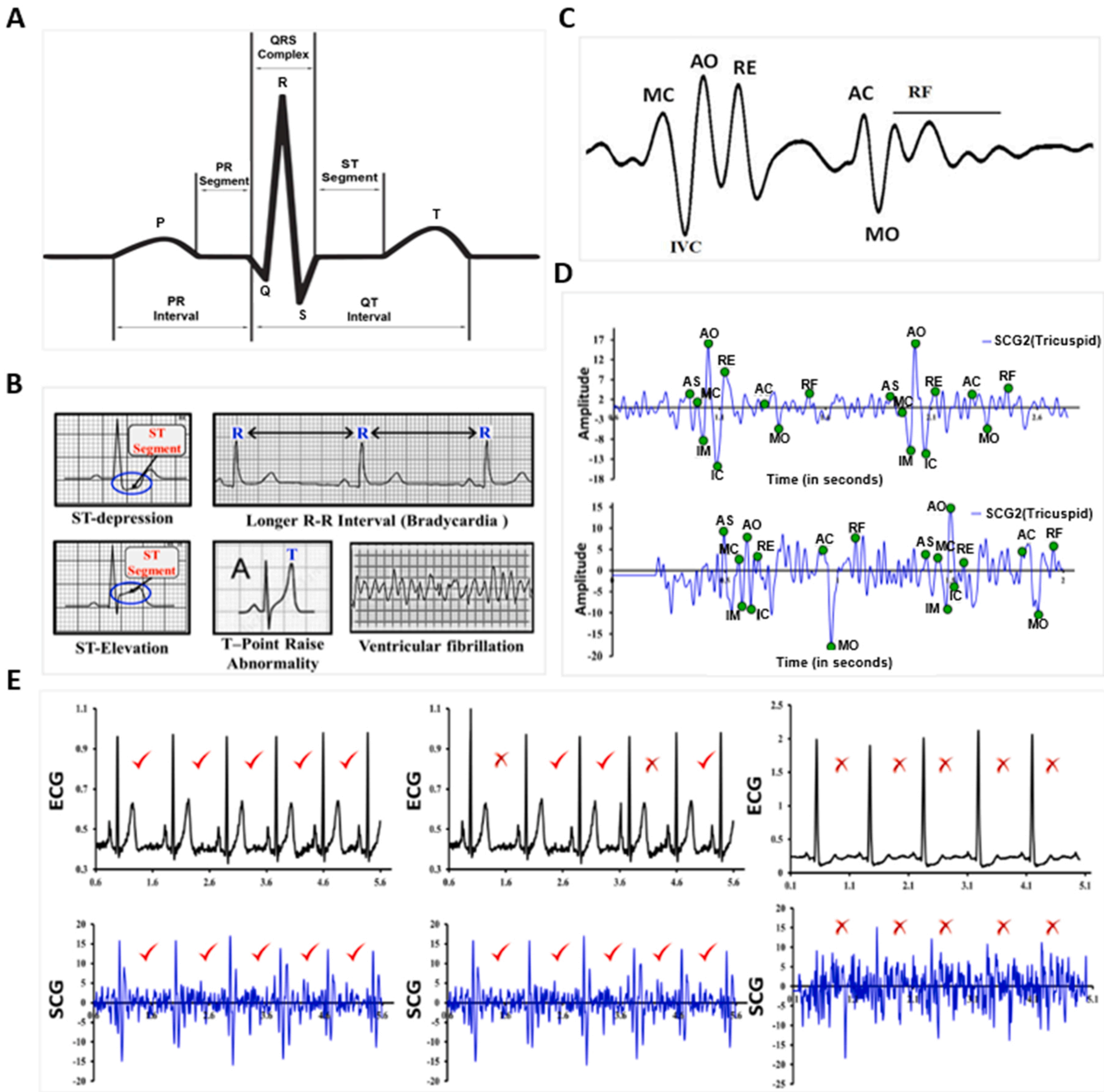

Fig. 2. Typical ECG and SCG waveforms: (A). Waveform of an ECG signal [64]. (B). Various abnormalities from ECG waveforms [50]. (C). Waveform of an SCG signal [8]. (D). Comparison of normal SCG cycles (top) versus abnormal SCG cycles (bottom) [48]. (E). Combined analysis of ECG and SCG approaches with detection of normal ECG and SCG morphologies (left), detection of abnormal ECG morphology and normal SCG morphology (middle), and detection of abnormal ECG and SCG morphologies (right) [48].

have developed an interest in collecting and measuring SCG data alongside ECG data due to its non-invasive and inexpensive method of monitoring the heart's mechanical activities and providing further analysis of the heart to aid in diagnostic tests [8]. ECG monitoring alone may not be able to provide enough insight on the patient's cardiac activity. Thus, a combined analysis of multiple heart mechanisms could provide a more comprehensive and reliable evaluation of the patient's cardiac-related health while also increasing the validity of observed abnormalities [48]. As shown in Fig. 2E, the leftmost graph displays both normal ECG and SCG morphology while the middle graph displays normal SCG morphology with abnormal ECG morphology with atypical R and P amplitudes. Both the left and middle graphs in Fig. 2E used normal subjects for data analysis. According to the authors, that could indicate an issue with the ECG monitor since the SCG data does not show any abnormalities [48]. The rightmost graph in Fig. 2E, which used an abnormal subject, presents an abnormal R-wave in the ECG waveform with a high voltage amplitude compared to the normal ECG readings with corresponding abnormal SCG readings as well. With a dual display of abnormal ECG and SCG morphology, it could be indicative of a cardiac issue since both heart mechanisms validate the existence of abnormalities. Along with an increased validation of cardiovascular diagnoses, a combined analysis of the heart mechanisms could also improve the accuracy of the diagnosis and rule out external noises and motion artifacts that might be affecting one heart mechanism detection and not the other [48].

In general, the analysis of any abnormalities from ECG signals are considered the standard practice with diagnosing the patient, but SCG signals can further complement the analysis. The addition of SCG monitoring alongside ECG monitoring provides a more inclusive analysis for the patient due to the examination of not only the heart's electrical activity but also the heart's mechanical activity. To compare both approaches, Table 1 lists the advantages and disadvantages of both SCG and ECG-based cardiac sensing approaches. For the two cardiac sensing approaches, the most advantageous feature is that they both provide non-invasive methods to detect cardiovascular signals. However, for the SCG-based approach, the disadvantages are that the monitoring devices, such as accelerometers and gyroscopes, are very sensitive to motion artifacts and device placement on the human body. For the ECG-based

Table 1
Comparison of ECG and SCG-based cardiac sensing approaches.

Type	ECG-based Approach	SCG-based Approach
Working Mechanism	Electrical potential of the muscle fibers produced by the stimulation of the cardiac muscle[3]	Chest vibrations induced by the heart twisting forward and tapping the chest wall during every cardiac cycle[56]
Frequency (Hz)	0.05 – 100[51,52]	0.5 – 100[48,57]
Amplitude Range	0.110 μV – 4 mV[51]	~ 10 mg[58–60]
Advantages	1. Non-invasively records electrical activities of the heart. 2. Measures signals from various locations on the body, not just from the human chest, to increase accuracy of the readings. 3. Standard practice of monitoring cardiac activity. 4. Technology for continuous monitoring is possible.	1. Non-invasively records mechanical activities of the heart. 2. Monitoring devices (accelerometers and gyroscopes) are relatively small, compact, and inexpensive. 3. Not easily affected by changes in the magnetic field.
Disadvantages	1. Sensitive to device placement on the patient. 2. Typically requires rigid interfaces and multiple wiring. 3. Sensitive to changes in the magnetic field.	1. Sensitive to motion artifacts. 2. Sensitive to device placement on the patient. 3. Sensor placement has to be relatively close to the patient's heart to record the vibrations and sounds of the heart.

approach, the monitoring devices are also sensitive to device placement. Moreover, the traditional monitoring devices have many rigid interfaces and wiring that can provide discomfort to the patient.

Even though ECG and SCG are the two most standard heart mechanisms that are utilized to diagnose patients for any cardiac-related issues, other mechanisms for heart monitoring approaches are still used to examine patients for any issues regarding their cardiovascular health. The approaches include monitoring the patient's pulse waves, respiration rates, heart rates, and blood pressure. One specific approach called photoplethysmogram (PPG) provides a person's cardiac information by measuring reflection-mode measurements from the base of the patient's foot [9]. Another common approach called phonocardiography (PCG) provides a graphic representation of auscultation from the heart [66]. Alongside ECG and SCG-based cardiac sensing approaches, those mechanisms also assist in providing early diagnoses to the patient.

3. Design strategies of cardiac sensing devices

While both ECG and SCG methods provide sufficient cardiac information, they have major disadvantages that make continuous monitoring challenging. For example, due to the rigid interface and multiple wiring components of traditional monitoring devices, vigorous movement and exposure to water from the patient would affect the quality of the cardiovascular signals. Therefore, flexible cardiac sensing devices are critically needed for long-term, continuous monitoring of the heart by excluding rigid interfaces and wiring. Furthermore, the devices should have enhanced sensing capabilities that allow the patients to go about their daily activities without any restrictions in order to improve their quality of life. In this section, different design strategies of flexible cardiac sensors in the field are discussed [9–25].

3.1. Key challenges and design principles

Traditional heart monitoring devices suffer from various challenges that limit their ability to monitor cardiovascular signals comfortably and long-term while restricting the patient's range of movements. Recently, flexible cardiac sensors have been designed to address the key challenges in order to provide solutions to patients that improve continuous monitoring safely and innovatively. Non-invasive, traditional ECG monitoring devices, such as the Holter monitor, utilize rigid electrodes that use multiple leads to attach to the human body, causing discomfort and chafing during long-term usage (Fig. 3A) [2]. Furthermore, as shown in Fig. 3B [67], accelerometers and gyroscopes are taped or strapped to the chest for traditional SCG monitoring [7,8]. Fig. 3C shows another example of a cardiovascular monitoring device, where various rigid wiring of the polysomnography (PSG) sensors are attached to a subject to measure ECG, electroencephalogram (EEG), electrooculogram (EOG), and pressure transducer air flow measurements [10]. In Fig. 3D, conventional measurement hardware is attached to a life-sized neonate doll to measure blood oxygenation, skin temperature, heart rate, heart rate variability, and respiratory rate [9]. Vigorous movement is not advised, and the patients would be aware of the various attachments on their bodies as they go about their daily activities. Especially for neonates, approximately 300,000 of them in the United States are brought to the neonatal intensive care units (NICUs) every year since a majority have delicate health due to premature birth and low birth weight [9]. In the NICU, current monitoring systems utilize rigid electrodes and sensors that are attached to the skin using adhesives and are connected to the base units through wiring. Adhesives can greatly irritate and even cause scarring to the neonates' fragile skin, and the wiring components make it difficult to turn them from prone to supine, a commonly done task for neonates. Therefore, creating epidermal electronic systems, which removes rigid components and incorporates materials that complement the mechanical properties of the human epidermis, would improve the patient's quality of life.

Strategies of skin-like cardiac sensing devices have been intensively

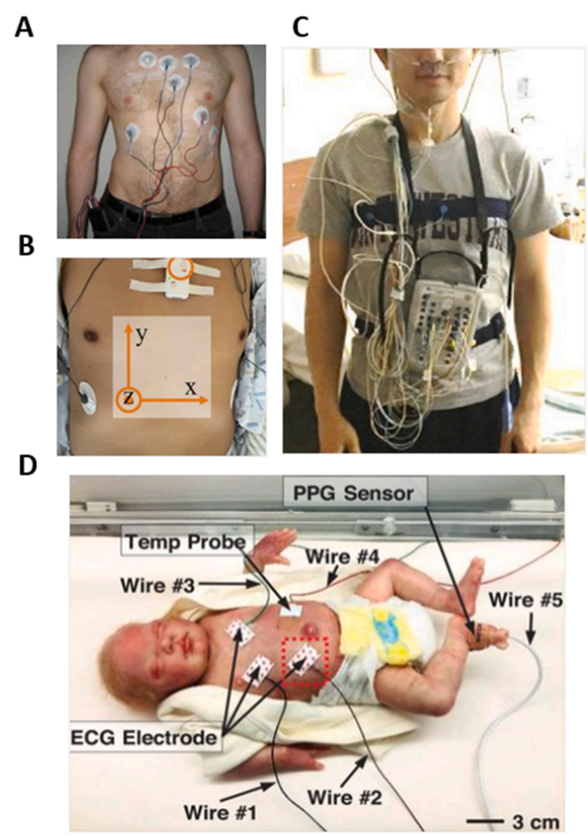

Fig. 3. Traditional heart monitoring devices: (A). Holter monitor with electrodes and leads to measure ECG [44]. (B). IMU taped to a patient's chest to measure SCG [67]. (C). PSG sensing device with various wiring to measure ECG, EEG, EOG, and pressure transducer air flow measurements [10]. (D). Conventional measurement hardware to measure blood oxygenation, skin temperature, heart rate, heart rate variability, and respiratory rate [9].

developed; however, there are still certain challenges to ultimately address. An overview of key challenges of traditional heart monitoring devices and design principles of flexible cardiac sensors is shown in Fig. 4. To design cardiac sensing devices, the sensitivity, conformability, flexibility, biocompatibility, and battery life of the devices are critical considerations that should be focused on in order to optimize the device's performance toward clinical translation (Fig. 4 right). The sensing capability of a cardiac sensor is a significant parameter to maximize since the measurements of the electrical activity and the vibrations of the heart register on a miniscule level. To correctly diagnose the patient with a heart defect or condition, healthcare professionals need to work with accurate readings that filter out background noise and diminish motion artifacts since those artifacts could be intentional and unintentional movement from the patient that can significantly affect image acquisition [10,11,68]. Researchers have employed various materials and structural designs to expand the sensing capabilities of cardiac sensing devices [9–24, 39]. For example, Nayeem *et al.* developed electrospun nanofiber layers for their cardiac sensing device that measured the vibrations of the heart. The device demonstrated a high sensitivity level of 10,050.6 mV/Pa in a low frequency range of less than 500 Hz [12]. Bongrain *et al.* designed a flexible sensor using a piezoelectric material that measured pulse waves, in which different structural designs (annular, disk, and serpentine annular) provided varying sensitivity levels [13]. The annular design achieved the highest sensitivity of 0.805 mV/μL, while the other designs achieved sensitivity values of 0.257 mV/μL and 0.312 mV/μL respectively.

Rigid devices and interfaces increase motion artifact and cause discomfort by creating interfacial gaps between the sensor and human skin and irritating the epidermal layer of the skin especially when continuously monitoring the heart's electrical activity for long-term applications. Therefore, flexibility and conformability are important considerations for cardiovascular sensor designs. Soft materials are being developed to better handle the overall device flexibility [9–14, 16–24, 39]. Due to the outstanding flexibility, polymer-based materials are commonly used in cardiac sensing designs. For example, polyvinylidene fluoride (PVDF) and its co-polymer poly(vinylidene fluoride-trifluoroethylene) (P(VDF-TrFE)) are favorable for biomedical applications due to their excellent flexibility, biocompatibility, and processability with microstructures for designs, and they have been developed in various energy harvesting and sensing applications [39, 69–79]. AlMohimeed *et al.* developed an ultrasonic sensor that incorporated a double-layered film of PVDF to measure cardiac tissue motion [14]. The integration of PVDF allowed it to be a wearable sensor, which reduced patient discomfort and introduced the potentiality of their device to continuously monitor cardiovascular signals in long-term studies. Furthermore, Sun *et al.* developed a strain sensor that was designed to be a wearable or implantable sensor [15]. The researchers chose PVDF as the main functional layer due to its natural flexibility. Hesar *et al.* also incorporated PVDF to the SCG sensing cardiac patch [23], along with Nayeem *et al.*, who electrospun PVDF nanofibers to design a SCG-based cardiac sensor [12]. Other polymer-based materials such as ecoflex, parylene, and more have been used as substrates or encapsulate layers for flexible and conformable cardiac sensors [13,22]. For example, Liu *et al.* encapsulated their entire device with Silbione and ecoflex, both low-modulus silicone, to cover the circuitry of their sensor and to provide conformability that prevented patients from feeling the rigid components [22]. The use of the silicone materials permitted their design to mechanically isolate the electronics, which reduced motion artifacts and improved conformability on the skin without any alterations to the device application. Essentially, those flexible sensors are designed to conform to the dynamic mechanical properties of the human skin, thus increasing patient comfortability.

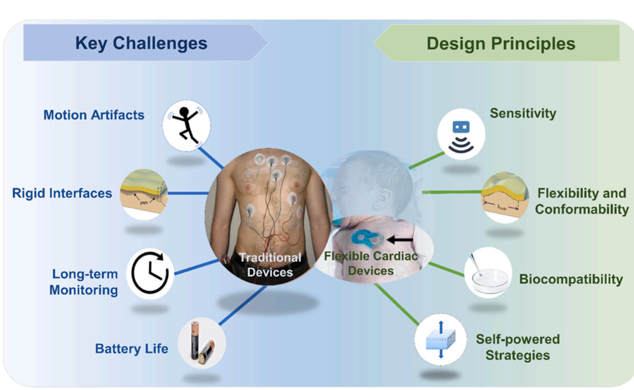

Fig. 4. An overview of key challenges of traditional heart monitoring devices and design principles of flexible cardiac sensors [9,26,44].

Cardiovascular sensors intimately interact with the human skin in order to minimize motion artifacts since the artifacts may disrupt the sensing capabilities of the cardiac monitors, and thus may provide incomplete and even misleading results [10]. Meanwhile, sensing devices are also expected to continuously measure cardiac activity, so they are required to be biocompatible to provide a safe user experience especially for long-term usage. From a design perspective, no toxic materials would be utilized during the fabrication process, and no debilitating or allergic reactions should occur to the patient. So far, various biocompatible materials, such as PVDF, polyimide (PI), ecoflex, parylene, polyurethane (PU), polyethylene terephthalate (PET), hydrogel, and polydimethylsiloxane (PDMS), have been incorporated into the design of the devices to make them biosafe [13,20,23,39,42,72,80,81]. Furthermore, strategies of encapsulating the overall device with biocompatible materials have been developed to effectively prevent the exposure of devices and ensure the safety of the patients. Xu *et al.* incorporated silver nanowire (AgNW) and graphene oxide (GO) into their material composition to create an ECG monitoring device [21]. Since AgNW is not a biocompatible material, they sandwiched the material between the PET substrate and the GO layer to prevent direct contact with the skin. With the encapsulation method, they achieved 24 continuous hours of monitoring while directly pasting their sensor on the human skin and recorded no allergic reaction or skin irritation from the patient after the removal of their sensor. To further prove the biosafety of the cardiac sensing and energy harvesting devices, different biocompatibility tests have been conducted [15,19,22,80,82]. For example, Sun *et al.* conducted a cell viability test on their PVDF strain sensor to confirm biocompatibility with the human skin through live/dead staining of COS7 cells that were cultured on the samples of the sensor [15]. Moreover, Liu *et al.* designed an epidermal mechano-acoustic sensing device that measured both ECG and SCG signals [22]. To test the biosafety of their device, they conducted a cytotoxicity test by culturing mouse embryonic fibroblasts on the device surface, and they observed no signs of apoptosis or necrosis. For those cardiac sensing devices to intimately interface with the epidermis, the biocompatibility of the materials should first be ensured by administering biocompatibility tests or encapsulating the device with biocompatible materials to guarantee the safety of the patient, especially when considering long-term usage of the cardiovascular devices [15,21].

In addition, traditional heart monitoring devices have limited battery life, which reduces the effectiveness of the monitoring devices due to periodic battery replacements [2,39,83,84]. For example, Holter devices utilize batteries that need continuous replacements. For short-term usage, Holter devices can be worn for 24–48 h without replacing batteries, whereas for long-term usage, battery replacement is required to allow the Holter device to be worn for as long as two weeks [2]. The optimization of the battery life of cardiac devices could reduce the number of battery replacements or ultimately remove the use for an external battery supply. Self-powered sensing strategies provide practical and promising power solutions for cardiac devices. One of the most common transduction mechanisms makes use of the direct piezoelectric effect. The piezoelectric effect is the ability of the generation of electric charges on the material surface in response to applied mechanical strain or stress [39,85]. Nayeem *et al.* designed a nanofiber-based cardiac sensing device, whose middle layer consisted entirely of PVDF, to induce the piezoelectric effect [12]. Due to the application of the piezoelectric effect to sense self-sustainably, the cardiac sensor did not require a separate, external battery supply while collecting SCG information. Additionally, Hesar *et al.* designed a piezoelectric sensor that measured SCG signals [23]. They also utilized PVDF as their choice of material, but the device was not able to sense self-sustainably due to the low voltage signals. As an augmentation to their device's battery life, they incorporated near-field communication (NFC) technology to deliver power and also transmit data wirelessly in order to produce a battery-free, contactless cardiovascular sensor. Other strategies besides piezoelectric designs that optimize battery life include using miniaturized rechargeable batteries or utilizing other transduction mechanisms. For example, the triboelectric energy harvesting strategies convert mechanical energy into electrical energy through the movement of electrical charges between two materials that create an electrical potential difference [10,18,39,86].

While taking into account the limitations that affected traditional cardiovascular monitoring systems, other issues should also be considered. Sometimes, to optimize one parameter might negatively affect another. For example, to ensure the biocompatibility of a sensor, it might require the overall device to be encapsulated by an additional biocompatible material, such as PDMS, which would increase the total thickness of the device and impede the sensor's sensitivity by increasing motion artifacts. Therefore, researchers need to carefully contemplate the structures of the device designs, material choice, and appropriate fabrication methods depending on the cardiac sensing mechanism by taking all above considerations and design principles into account.

3.2. Structural and material designs

To address the existing limitations of current cardiac monitoring devices, the rapid advancement in structural designs, material development, and fabrication methods has encouraged diverse innovations in cardiac monitoring device designs. In ECG sensing, flexible materials that have high conductivity are employed to measure the human body's electric potential. To sense SCG signals, various structural layouts are employed to measure the miniscule movements of heart vibrations while simultaneously filtering out motion artifacts. Some designs measure other mechanisms besides ECG and SCG, such as pulse waves, respiration rate, heart rate, and blood pressure, but they are still categorized as cardiovascular signals. With a difference in mechanism approach, various strategies for structural layouts, material development, and fabrication methods are discussed in this section, as shown in Fig. 5.

In recent years, the structures of cardiovascular monitoring devices have evolved beyond Holter devices and cardiac event recorders, which essentially utilize electrodes and leads. For example, Anwar *et al.* created a cantilever sensor from PVDF to measure SCG, pulse rate, and the respiratory cycle [87]. The cantilever structure was affixed to the patient's body with a belt that wrapped around the upper sternum so that the SCG signals could be collected from the left side of the sternum. Moreover, Panahi *et al.* designed a piezoelectric sensor that incorporated PVDF in a double triangle structure to monitor breath rate specifically for COVID-19 patients [88]. The piezoelectric sensor, which was either taped directly to the chest or placed inside a vest and tightened around the chest with a belt, measured the breathing vibrations of the patient through displacement of the chest during respiration, much like a cantilever. The triangle design consisted of three layers, with the PVDF layer sandwiched between two layers of PDMS, which was incorporated due to its ability to prevent moisture and sweat accumulation and act as an insulator for electronics. Takahashi *et al.* developed a piezoelectric plate sensor that incorporated lead zirconate titanate (PZT) to detect pathologic heart sounds and murmurs in patients with hereditary heart defects [89]. The circular plate design consisted of the ceramic PZT plate

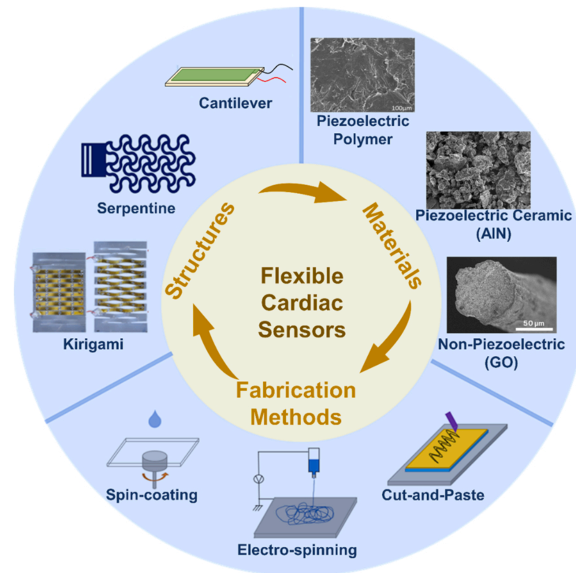

Fig. 5. Summary of the various strategies for structural layouts, materials, and fabrication methods to design a flexible cardiac sensor [15, 23, 109–111].

(diameter of 14 mm), which was attached to a copper plate (diameter of 20 mm) and a plastic plate (diameter of 100 mm). To avoid direct skin contact with neonates, a towel (thickness of ~5 mm) was placed between the skin and the plate sensor while the neonates were placed in a prone position to ensure less signal noise. Using those piezoelectric materials, various structures, such as cantilevers [69, 87, 88, 90–93], plates, patches and membranes [89, 94–103], beams [42, 94, 104–106], and helical structures [72,107,108], have been developed to implement sensing and energy harvesting applications. Essentially, these cantilever and plate devices expand beyond gel-based electrodes that are connected to the patient's body through leads by incorporating piezoelectric materials or other structural components that remove the use of batteries [87–89]. Despite the progression from traditional cardiovascular monitoring devices, these devices have maintained their rigid structural designs that limit their stretchability, flexibility, and conformability to the human skin.

Flexibility and stretchability play an important role in expanding the sensing capabilities of cardiac devices by allowing the devices to conform to the human epidermis without degradation to the device performance [37]. Conventional cardiovascular sensing devices typically have limited flexibility and stretchability that hinder their ability to consistently and accurately sense cardiovascular signals. As shown in Fig. 6, two typical strategies can be employed to enhance the flexibility and stretchability of cardiac sensing devices: implement new structural designs for conventional materials or use new materials with conventional structures. New structural designs can include wavy, island-bridge, and Origami/Kirigami layouts designed to enhance the stretchability of functional materials that have otherwise limited flexibility [37,38]. For the material designs for conventional, rigid structures such as planar configurations, cantilevers, and plates, flexible functional materials and substrates can be used to design a flexible cardiac sensor.

From a structural design perspective (Fig. 6 left), new structural layouts are proposed to integrate with conventional, non-stretchable materials such that they can absorb applied load and strain to augment the flexibility and stretchability of the devices [37,38]. When using non-stretchable materials, three structural layouts are mainly developed in the field: wavy, island-bridge, and Origami/Kirigami [37]. The first design utilizes wavy, wrinkled designs that support the device in absorbing strain and preventing fractures. Such wavy design allows for buckling during the deformation of the device, which permits the buckled structure to freely move out of the plane and thus reduce the

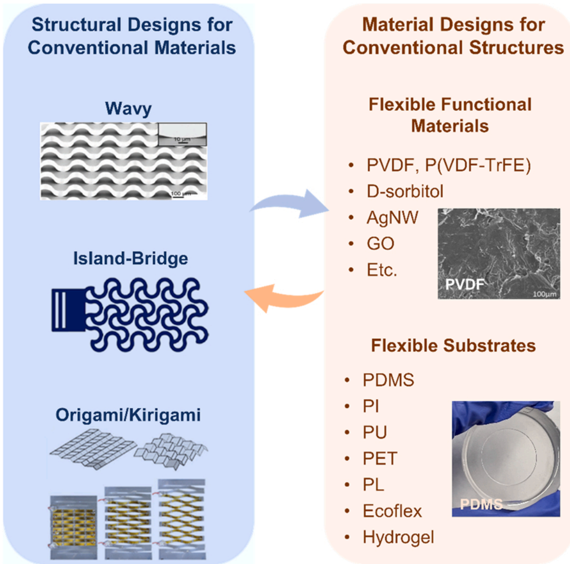

Fig. 6. Two strategies that enhance the stretchability and flexibility of cardiac sensing devices: structural designs for conventional materials (left) [15,23,37] and material designs for conventional structures (right) [109].

chances of fracturing. The wavy design is generally employed for systems that have achieved less than 20% stretchability. Implementation of this design varies the amplitude and wavelengths of the waves to adjust for varying levels of applied strain [37]. The second design structure utilizes island-bridge designs to connect circuitry ("islands") with each other mostly through electrode interconnects ("bridges"). The overall design can then retain rigid circuitry components without fractures or permanent deformations while focusing on enhancing device flexibility and conformability. One of the most commonly used strategies for island-bridge designs is the serpentine structure [9,10,13,16,22,23]. Other strategies include arc-shaped, 2D spiral, and 3D spiral structures [112–114]. Implementation of the island-bridge designs can improve the stretchability of certain materials from 100% up to even 1000% [37]. For example, Ha *et al.* used a filamentary serpentine network of electrode interconnects that acted as the "bridge" [16]. This permitted the use of circuitry components while the filamentary serpentine network of interconnects enabled the overall functionality of the device to stretch and conform to the surface of the human skin. A stretchability of more than 110% was achieved by implementing the serpentine network into their structure. The third type of structural designs utilizes Origami or Kirigami structures, which take inspiration from the art of paper folding and cutting. For Kirigami designs, strain is reduced at the points where cuts are made. The load is then being uniformly distributed throughout the entire Kirigami-inspired design, which helps the device induce lateral buckling or out-of-plane bending to avoid fracturing [37]. Implementation of this design enables high levels of stretchability while also providing breathability for the human skin. For example, Sun *et al.* employed such structural layout for a Kirigami-based cardiovascular sensing device [15]. Along with the intersegment pattern of the electrodes, the network of patterned cuts onto the PVDF film improved the stretchability and electrical performance of the piezoelectrical material. For the Kirigami-based device, cuts have been made to create various strips on the piezoelectric film. Each strip buckles out-of-plane as the device stretches, which induces the piezoelectric effect to generate electrical charges. To test the possibility of the device as an implantable device, researchers placed it on a deforming balloon with tie constrains to simulate the conditions of the heart. Under the same balloon inflation conditions, researchers achieved a maximum strain of 0.2 on the balloon with the Kirigami pattern while the planar configuration of the device without any cut patterns produced a higher strain of 0.47, displaying the device's ability to absorb strain [15]. In addition, researchers also placed it on the human knee where large deformations normally take place. The patient was asked to go through a series of exercises, such as cycling, running, and climbing. Different voltage cycles were produced for each individual exercise, allowing for researchers to differentiate the types of motion. With the application of these structural design strategies such as wavy, island-bridge, and Origami/Kirigami layouts, researchers have successfully utilized conventional, non-stretchable materials to fabricate flexible and stretchable cardiovascular sensing devices. Such structural layouts are designed to absorb applied load and strain and prevent fractures. Especially for high stiffness, non-stretchable materials, without utilizing these structural layouts, there are large interfacial gaps between the skin and the device and thus can create significant motion artifacts that deteriorate the quality of the obtained cardiovascular signals [26]. Mechanistic exploration on the conformability of thin layer devices on soft bio-tissues (such as the human skin) has been developed to quantify the contact area and conformability of epidermal electronics [37,38,115]. Increased adhesion strength between the device and the human skin can be achieved by improving conformability of the device to facilitate signal transfer, and thus increase the sensor sensitivity. Since the human skin is not completely smooth due to having crevices and dips, the design of epidermal electronics should be carefully considered to improve the human-device interface, and thus further enhance sensor sensitivity.

From a materials design perspective, highly flexible and biocompatible materials are developed and integrated into the design of cardiovascular sensors (Fig. 6 right). For example, a commonly used polymer-based material of PVDF has been preferred in various sensing and energy harvesting biomedical applications [39, 75–79, 108]. In addition to the strategies of structural layouts, researchers have evolved advanced materials through engineered micro and nano structures to enhance the cardiac sensing performance [17,69,72,78,108,116,117]. For example, the engineered microporous structures of polymeric piezoelectric materials allow for high compressibility, and thus enable the design of novel piezoelectric polymers with high mechanical-electrical conversion for cardiac sensing and energy harvesting applications [69,72,108]. Piezoelectric nanoarrays are another nanostructure applicable for cardiac sensing and energy harvesting applications due to the excellent piezoelectric performance of aligned nanorods [117]. Engineered polymeric nanofibers also have large surface area to volume ratio to complement the induction of the piezoelectric effect [12,116]. For example, Nayeem *et al.* created an all-nanofiber-based gas-permeable mechano-acoustic SCG-based sensor by electrospinning PU nanofibers and a middle layer of PVDF nanofibers (Fig. 7A) [12]. Scanning electron microscopy (SEM) allowed visualization of individual nanofibers, and they were able to measure average fiber diameters of 250–450 nm. Such electrospinning process involves the use of a high voltage electric field that produces electrically charged jets or streams of the PU or PVDF materials, which are then collected on a flat surface that is oppositely charged [118]. The sensing signals come from both piezoelectricity (the maintained contact between the soft layers even with the air gaps) and triboelectricity (the PVDF layer that oscillates between the top and bottom nanofiber layers), which allowed their sensor to achieve a sensitivity as high as 10,050.6 mV/Pa. Those ultrathin, ultralight nanofibers had higher sensing capabilities, and also assisted in increasing the piezoelectric conversion efficiency, with decreasing PVDF diameters further increasing the efficiency. Outside of micro and nano structures, AlMohimeed *et al.* created a wearable, ultrasonic sensor that used double-layer PVDF films to monitor cardiac tissue motion at a depth of 30 mm [14]. In that work, researchers applied an equal electric potential to each individual PVDF layer to increase the acoustic output power. They obtained the M-mode ultrasonic measurement of the cardiac tissue motion, which corresponded with the reference signals of ECG. Sun *et al.* created a PVDF strain sensor, which could function as a wearable or implantable sensor, with a Kirigami-patterned component (Fig. 7B) [15]. Such design provided a

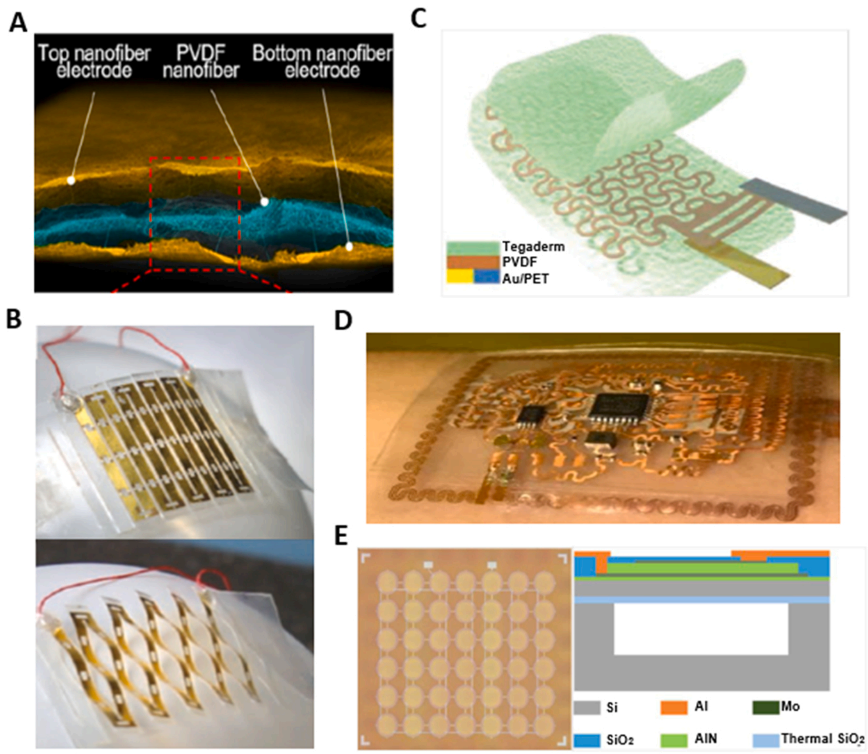

Fig. 7. Reported flexible cardiac sensors using piezoelectric materials. (A). PVDF-based nanofiber SCG sensor [12] (B). PVDF-based Kirigami-patterned strain sensor [15]. (C). PVDF-based e-tattoo ECG and SCG sensor with serpentine network of interconnects [16]. (D). PVDF-based SCG sensor with serpentine designs interconnects and circuitry including NFC technology [23] (E). AlN-based PCG sensor with a 6-by-7 membrane array [24].

solution for materials to further match the dynamic strain of human skin. In addition, Ha *et al.* created an epidermal electronic PVDF-based e-tattoo that sensed ECG signals along with SCG signals [16]. Using a "cut-and-paste" method, they fabricated the ultra-thin, flexible device with a filamentary serpentine network of gold interconnects, enabling the sensor to achieve increased stretchability and skin comfortability (Fig. 7C). The fabrication method utilized a mechanical cutter plotter to pattern and cut out the serpentine network mesh onto the PVDF film, which was previously placed on adhesive transfer tape. To avoid thermal stress in the PVDF film, a weak adhesive transfer tape of Tegaderm was used as a temporary support instead of thermal release tape (TRT). Tegaderm was also used to encapsulate the patterned PVDF film to prevent direct contact with the human skin. Hesar *et al.* also created a wireless, battery-free, PVDF sensor that provided a contactless measurement of SCG signals using NFC technology [23]. A PVDF sheet was metalized with screen-printed silver, and a "cut-and-paste" method was used to fabricate serpentine designs on the PVDF with a mechanical cutter (Fig. 7D). The material was patterned with a serpentine structure that eliminated air gaps between the human skin and the sensor, and further lessened global inertia motions. Due to the serpentine structure, a circuit layer was attainable, which consisted of the NFC chip tag, microcontroller unit, and a voltage regulator. Essentially, the Kirigami and serpentine structural layouts are applied to design non-stretchable materials such that they can absorb applied strain without fracturing [15,16,37]. These design structures also complement piezoelectric materials since the stretchability and flexibility of the devices are enhanced to induce the piezoelectric effect without hindering device performance.

Despite the intrinsic flexibility of polymer-based materials, other piezoelectric materials are also utilized to allow for passive cardiac sensing. In the case of Bongrain *et al.*, researchers used aluminum nitride (AlN) to create a thin, flexible, piezoelectric sensor that measured micro-deformations, which translated into cardiac pulse wave measurement [13]. AlN has properties that are favorable in sensing applications, such as good oxidation resistance and low dielectric constant [119,120]. Since it is a piezoelectric material, AlN can also generate electric charges as a self-powered sensor. Qu *et al.* created a low-cost, light, piezoelectric heart sound MEMS sensor [24]. The device was fabricated by using a 6-by-7 AlN membrane array to sense phonocardiography (PCG) in order to distinguish and diagnose heart diseases (Fig. 7E). Researchers demonstrated the stability of the device by filtering out environmental noises and maintaining the quality of the collected heart sounds a month after the fabrication of their device. Their results showed an observable difference in normalized amplitude graphs for normal heart sounds and various abnormal heart sounds such as patent ductus arteriosus, mitral regurgitation, mitral stenosis, aortic insufficiency, and aortic stenosis. Peng *et al.* created a flexible ultrasound blood pressure sensor using a piezoelectric material PZT-5A and polymer matrix PDMS as the filler material [17]. AgNW based electrodes were deposited to provide increased stretchability and conductivity when compared to conventional electrodes to prioritize non-invasiveness and convenience for the patient. Ultimately, the inherent property of piezoelectric materials makes them favorable for sensing applications by converting the mechanical stress into electrical charges.

In addition to applications of passive sensing, these discussed piezoelectric materials have also been utilized in cardiac energy harvesting applications. The inclusion of materials, such as PVDF and PZT, in the design of implantable medical devices (IMD) allows the devices to power themselves by harvesting biomechanical energy from the heart [39, 69–74]. Current IMDs like pacemakers require surgery for battery replacement every 7–10 years, and an early battery depletion can require emergency surgery as early as 3 years [39,83]. With piezoelectric materials harvesting energy from the human body, longevity of IMDs that utilize these materials can increase so that the likelihood of requiring additional surgeries to replace depleted IMD batteries greatly decreases.

Piezoelectric materials have great potential for various biomedical applications due to their ability to incorporate various approaches to design self-sustainable and biocompatible devices. Other sensing strategies utilize conductive materials to create flexible and stretchable cardiovascular sensors. For example, Zhang *et al.* created a fully-organic, self-adhesive, stretchable dry electrode to measure ECG, electromyography (EMG), and EEG for wet and dry skin conditions (Fig. 8A) [20]. They used the solution processing method to combine poly(ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) with waterborne polyurethane (WPU) and D-sorbitol to increase the conductivity of the dry polymer electrode (Fig. 8B). The fabrication method processed all three solutions together by mixing them and then drop-casted the blend solution into a mold, which would then dry into the blend adhesive film. Peng *et al.* created a flexible pressure sensor that was able to detect heart rate, respiration rate, and blood pressure (Fig. 8C) [18]. Researchers fabricated the device by using printing technology with porous graphene (Fig. 8D). They utilized a printing head to print GO onto the electrodes, which was later sprayed with foaming reagents of aqueous N_2H_4. The device was able to achieve a resolution of less than 0.3 kPa, with a detecting range of 0.3 kPa to 1.0 MPa and repeatability by withstanding 1000 cycles. A high sensitivity of a maximum gauge factor of 53.99/MPa had been reached [18]. Xu *et al.* created an ECG monitoring device (Fig. 8E) that incorporated AgNW-based electrodes and GO using screen printing (Fig. 8F) [21]. Here, they utilized a desktop screen printer with a patterned screen mesh. AgNW was dispersed onto the screen mesh, which was placed on top of a PET substrate. The overall device showed good biocompatibility and stability by going through thermal oxidation and exhibiting a resistance change of less than 1% increase after 1500 bending cycles. It also exhibited excellent optical properties with the transmittance of 83.5% at a wavelength of 55 nm, as well as excellent electrical properties with the sheet resistance of 11.9 Ohm/sq. Kim *et al.* also incorporated AgNW networks into the wearable strain and ECG epidermal sensor (Fig. 8G) [19]. Researchers fabricated adhesive and transparent electrodes by spin-coating a solution mixture of adhesive PDMS (a-PDMS) and Triton X, a nonionic surfactant, on top of the AgNW layer (Fig. 8H). Triton X was included into the solution to effectively embed the AgNW network into the PDMS matrix by creating heterogeneously cross-linked networks of polymer chains, which enabled the fabrication of the highly conformable and stretchable electrodes. No residue remained after removal of their sensor. Moreover, cell viability tests were conducted to validate the biocompatibility of the sensor, which achieved a cell viability of around 90% over three days. Overall, flexible piezoelectric materials are commonly used for cardiac sensing due to the piezoelectric effect. For SCG-based sensors, piezoelectric materials are widely used to convert the heart's mechanical activity into electrical activity. Especially such transduction mechanism allows for energy conversion to self-power and further extend the lifetime of these sensing devices for long-term continuous cardiac monitoring [39, 69–79]. Graphene oxide is also commonly used for the design of epidermal electronics, such as ECG-based sensors, due to their excellent conductivity, high surface area, and nanoscale size [18,121]. Additionally, another biocompatible material that has been recently used in the cardiac sensing field is the hydrogel. It is a biocompatible, hydrophilic polymer that mimics the human tissue with a high-water content, and has been utilized in bioelectronic applications [81,122]. For example, Liu *et al.* designed a hydrogel bioelectric wearable strain sensor [81]. They custom-designed microfluidic channels to encapsulate liquid metal, which was favorable due to its biodegradability and large conductivity. Researchers fabricated the strain sensor by combining a laser-engraving method for the hydrogel microchannel and a crosslinking mechanism for the double network hydrogels. This hydrogel bioelectric strain sensor was able to distinguish various levels of volume and spoken letters with high signal-to-noise ratio.

By taking into consideration of different structural layouts, materials design, and fabrication methods, researchers have successfully developed innovative flexible and biocompatible cardiac sensors with comparable or even increased sensitivity, flexibility, and conformability. For both ECG and SCG-based sensing, flexible cardiac sensors can easily and comfortably obtain the cardiovascular signals outside the hospital setting. Particularly for ECG-based sensors, essentially only conductive materials such as AgNW [17,21] and PEDOT:PSS [20] are needed to act as electrodes to sense the heart's electrical activity. This allows for the facile fabrication of flexible ECG-based sensors since the functional material basically consists of the electrodes. These electrodes are thinner and lighter when compared to the electrodes used in traditional cardiac monitoring systems, such as the Holter device. Therefore, those flexible sensors allow for easy manipulation of the shape of the electrodes to complement the design and adhere to the skin for a longer time by removing any bulky components. However, for ECG-based sensors, care should also be taken to cover those electrode materials if they are not biocompatible. Further design strategies such as encapsulation methods should be considered to prevent exposure to the skin. For SCG-based sensors, piezoelectric materials are commonly used to convert the heart's mechanical activity into electrical activity. This allows for the sensors to be self-sustainable due to the piezoelectric effect without using additional batteries. Other designs include circuitry (such as accelerometers) for SCG-based sensing in order to collect the heart's mechanical activity [7,8,22]. Encapsulation methods can also be utilized for implementation of soft and flexible materials to prevent any rigid components from making direct contact with the human skin.

3.3. Summary of flexible cardiac sensing devices

Traditional cardiovascular monitoring systems can detect and monitor cardiovascular signals through non-invasive means, but the rigid interfaces and wiring ultimately bring discomfort to patients especially during long-term, continuous monitoring outside the hospital setting. Electrodes are attached to the human body with gel to monitor the patient's ECG. When the gel dries over a period of time, it could irritate the human skin. For accelerometers and gyroscopes, instead of gel, they are taped or strapped to the patient's chest. Thus, to address those limitations of existing cardiac sensing devices and improve the quality of life for patients, there is a need for epidermal electronic sensors that have high sensitivity, excellent conformability, outstanding flexibility, verified biocompatibility/biosafe methods, and an extended battery life. The most significant parameter to consider is the sensing capability of the flexible cardiac sensor. Since the heart's mechanical and electrical activity register on a miniscule scale, the sensors should be able to capture the cardiovascular signals without being affected by environmental noise or motion artifacts. Flexibility and conformability are also vital parameters to consider for clinical translation. Soft materials such as polymers provide the cardiac sensors the ability to be flexible and conformable on the epidermis without causing patient discomfort. A long-term usage of cardiac sensors also requires a safe user experience. Using biocompatible materials such as PVDF, PI, and PDMS for device fabrication and encapsulation methods could create biosafe sensors. To further ensure the safety of the devices, biocompatibility tests such as cytotoxicity tests and cell viability tests could be conducted in laboratory settings. Lastly, traditional cardiovascular devices are typically hindered by limited battery life. Strategies of the power solutions include making the cardiac devices self-sustainable through the use of the piezoelectric effect, utilizing miniaturized rechargeable batteries, or employing wireless charging such as NFC technology. Overall, many factors should be taken into consideration to make these cardiac sensors reliable, comfortable, and sensitive to minor changes on the human skin.

To design a flexible cardiac sensor, the structure and material should be carefully considered. Structural layouts such as wavy, island-bridge, and Origami/Kirigami can be integrated into the design to absorb applied load and strain, thus enhancing the flexibility and stretchability of the sensor. The wavy design is generally used for systems that have achieved less than 20% stretchability [37]; the island-bridge can improve the stretchability by up to 1000% for certain materials [16,23]; and a Kirigami layout can absorb applied load by inducing out-of-plane bending, which also provides breathability to the skin [15]. From a

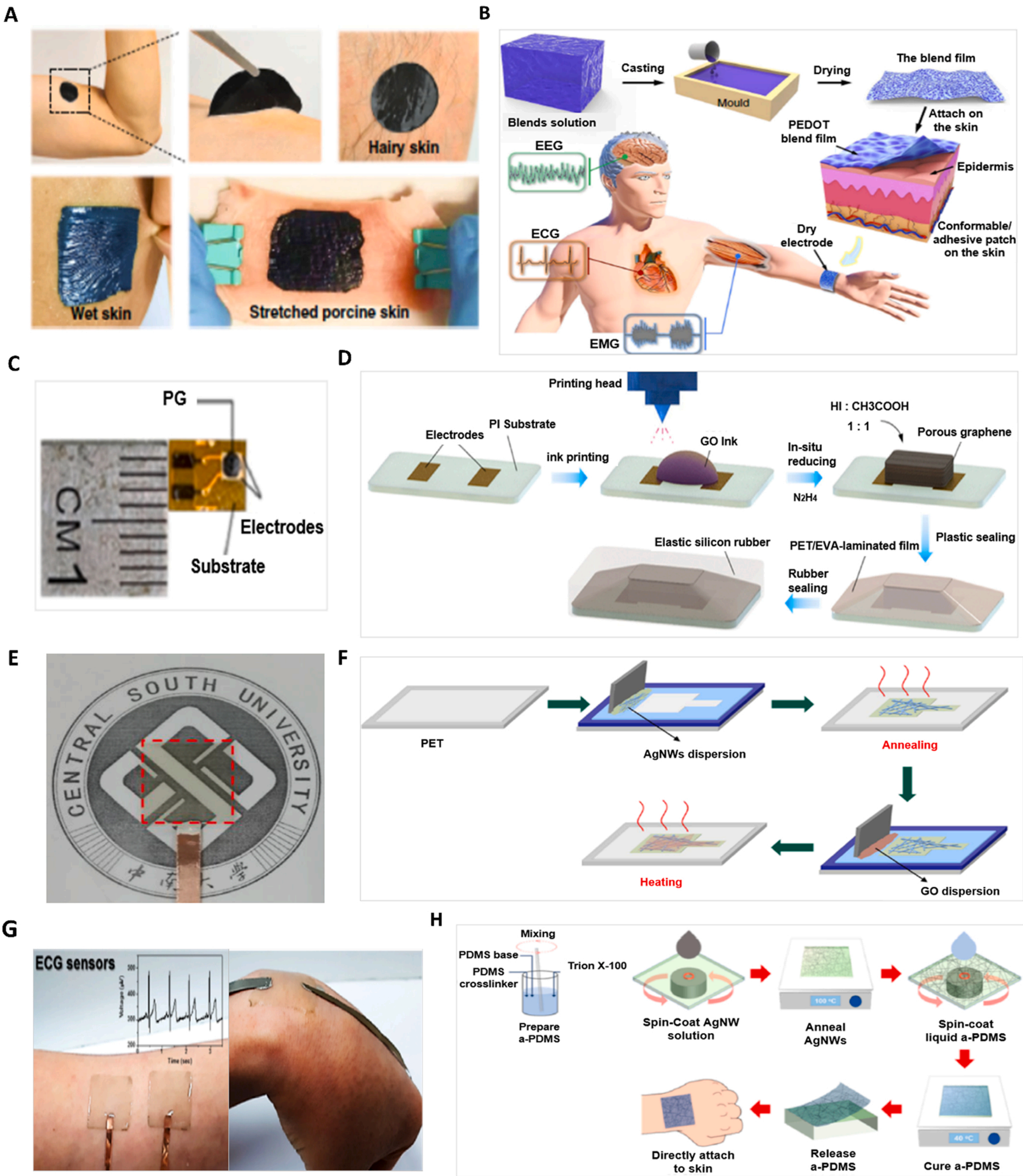

Fig. 8. Reported flexible cardiac sensors and fabrication methods using non-piezoelectric materials. (A). Stretchable dry electrode sensor created with PEDOT:PSS to sense ECG, EMG, and EEG [20]; (B). Fabrication of the sensor using the solution processing method [20]; (C). Pressure sensor created with porous graphene and GO to sense heart rate and respiration rate [18]; (D). Fabrication of the porous graphene and GO sensor using printing technology [18]; (E). ECG sensor created with AgNW and GO [21]; (F). Fabrication of the AgNW and GO sensor using the screen printing method [21]; (G). AgNW-based strain and ECG sensor mixed with PDMS and Triton-X [19]; (H). Fabrication of the AgNW and PDMS sensor using the spin-coating method [19].

material design perspective, piezoelectric materials such as PVDF [12, 14–16, 23], AlN [13,24], and PZT [17,19] can generate electrical charges in response to mechanical stress or strain and are desirable in not only sensing applications but also energy harvesting applications [39, 69–75, 78]. Other non-piezoelectric materials [18,20,21] are also used to create cardiac sensors that are highly flexible, conductive, and biocompatible.

Researchers have developed innovative cardiovascular sensing devices by combining structural layouts, specific materials, and fabrication processes to evolve sensors from traditional cardiovascular monitoring systems and to exceed the limitations hindering traditional cardiovascular devices. A summary of the traditional cardiac monitoring systems and flexible cardiac sensing devices discussed in this review is provided in Table 2. Other heart mechanisms besides ECG and SCG monitoring include blood pressure, respiration rate, strain, PCG, and more. Numerous fabrication techniques were utilized to design flexible cardiac sensors that enhanced favorable properties of certain materials or provided cost-effective methods of fabrication. Also, various metrics for the sensitivity levels of the sensors were reported, which were reliant on the heart mechanism that researchers were analyzing [12,13,15,16,18,20]. Biosafety of the devices was proven by using biocompatible materials. Furthermore, researchers presented promising longevity of devices for long-term usage, with some reporting periodic usage over a span of a month and 24 h of continuous monitoring without any allergic or negative reactions [20,21]. In future works, long-term studies are still needed to further validate the biocompatibility of the sensors and the effects of devices on people's regular physical activity. Additionally, designing a cardiac sensor that combines both SCG and ECG monitoring along with other heart mechanisms could provide an extensive examination to the patient's cardiovascular health. Moreover, certain cardiac sensors discussed here need to be connected to a computer to transfer raw cardiovascular signals for further analysis [12–14, 16–18, 20, 24, 87–89]. Wiring components can disrupt the patient's daily activities and make it problematic for long-term monitoring. Other methods of cardiovascular data transmission utilize NFC technology or Bluetooth to wirelessly transfer data, but that also requires further work to provide real-time analysis and to automatically detect cardiac abnormalities [9, 15,21,23]. If the sensor had the ability to wirelessly transfer raw cardiovascular data and analyze the real-time data without human supervision, healthcare professionals and patients themselves would be able to easily and quickly monitor cardiac health. This would be an effective time-saving cardiac monitoring strategy, since it could provide early warnings to cardiac-related issues, and thus could prevent further cardiac complications or even death.

In terms of the traditional cardiac sensing systems, Holter devices provide amplitudes of $\pm$ 5.0 mV for frequencies up to 40 Hz for ECG monitoring while commercial accelerometers provide a range of $\pm$ 1 g or $\pm$ 2 g for frequencies up to 1 kHz for SCG monitoring [60,123]. As mentioned in Section 2.1, hospital-grade ECG instruments have 12 leads (10 electrodes) that are placed on the patient's chest and limbs. The increased leads, and thus increased skin coverage of the electrodes, provide heightened sensitivity and accuracy at the expense of the patient's comfortability and the instruments' long-term usage. On the other hand, for the flexible cardiac sensors, different metrics for the reported sensitivity levels of the devices were considered based on the heart mechanism that the researchers were analyzing. Especially, the performance evaluations of those reported cardiac sensors (such as sensitivity) are various provided by the researchers based on their own test protocols. For example, Nayeem *et al.* reported a sensitivity value of up to 10,050.6 mV/Pa device in the low frequency range of below 500 Hz [12] and Bongrain *et al.*'s best structural design provided a sensitivity value of 0.805 mV/μL [13]. Furthermore, many varying levels of sensitivity were reported due to the various consideration of certain factors, such as biocompatibility, self-sustainability, and reduced skin coverage, while also utilizing different fabrication methods and structural layouts into the design process of the sensors [15–18, 20, 21, 24]. Fabrication methods such as electrospinning can increase the sensitivity levels of sensing devices by creating aligned nanofibers that are ultrathin, ultralight, and have a high surface area-to-volume ratio [12,116]. Furthermore, structural designs such as wavy, island-bridge, and Origami/Kirigami provide enhanced stretchability to otherwise rigid materials and designs, leading to better conformability to the human skin and thus increased sensing capabilities [37,38]. By testing their sensors, most researchers compared the heart signals obtained by their sensors with those obtained by commercial devices to successfully establish a correlation. For example, Peng *et al.* compared their blood pressure values (mean diastolic pressure of 65.38 mmHg and systolic pressure of 97.15 mmHg) with the values from a commercial upper arm blood pressure monitor (mean diastolic pressure of 64.40 mmHg and systolic pressure of 95.15 mmHg) for the same subject and observed reasonable agreement between the two results [17]. Another example shows Ha *et al.* validating their e-tattoo sensor by comparing their SCG signals with that from a commercial accelerometer and achieving comparable waveforms with peaks that were well-aligned for S1 and S2 heart sounds [16].

4. Machine learning algorithms for cardiac monitoring systems

Cardiac monitoring systems have interfaces and wiring that collect raw physiological data to be analyzed by healthcare professionals. For example, ECG electrodes measure the heart's electrical impulses and the leads transfer the electrical activity to a monitor, which then graphs out ECG waveforms for observation. Essentially, the raw physiological data is collected and converted to accessible signals that are categorized depending on their physiological mechanism, such as ECG, SCG, heart rate, respiratory rate, blood pressure, systolic time intervals, and more. To improve the ease of access provided by cardiac sensors, machine learning has been developed and employed for automatic detection of cardiac abnormalities (Fig. 9). Patient conditions would then be effortlessly available to healthcare professionals outside the hospital setting since those cardiac monitoring systems have the cognitive ability to automatically learn independently or with minimum human supervision [32,126].

4.1. Principles of machine learning

Machine learning is an analytical model that solves complex problems by executing a specific task without explicitly programmed to do so [32,33]. The machine is interfaced with human-like cognitive abilities that allow it to generate patterns, answers, predictions, rules, recommendations, or similar outcomes. The machine is given input data ($X = \{x_1, x_2, x_3, \ldots, x_N\}$) and labeled data ($Y = \{y_1, y_2, y_3, \ldots, y_N\}$), in which it learns a function f(X) from the input X. The machine can then make informed choices on a new dataset by utilizing the function it learned from the training dataset. There are three types to machine learning: supervised learning, unsupervised learning, and reinforcement learning [32,33,127]. For supervised learning, the machine generates relationships and patterns based on what it derived from a given training dataset. With the data points intended for training, it can extract relevant features and build its model. Once the machine is trained, it applies the pattern and relationship it derived to the test dataset for identification (classification) or numerical prediction (regression) purposes. For unsupervised learning, no such reference or training is applied to the machine for it to build its model. Instead, the machine determines structural information that is of interest on its own, such as grouping elements together based on similar properties (clustering). For reinforcement learning, a goal is defined and a list of constraints is applied. The machine then goes through the reiterative process of achieving its goal with a reward-based learning. It uses a trial-and-error based operation, in which the ML model maximizes the reward in order to achieve its goal. These three categories of ML demonstrate the ability of machines to execute specialized tasks with limited human dependency such

Table 2
Summary of traditional cardiac monitoring systems and flexible cardiac sensing devices [12, 13, 15–18, 20, 21, 24, 25, 50, 58, 60, 123–125].

Ref.	Traditional Methods		[20]	[21]	[12]	[16]	[18]	[13]	[15]	[24]	[17]
	Holter Device	Accelerometer	ECG and SCG Signals				Other Cardiovascular Signals				
Heart sensing mechanisms	ECG	SCG	ECG	ECG	SCG	ECG and SCG	Respiration rate, heart rate, blood pressure	Pulse wave	Surface strain and knee flexion	PCG	Blood pressure
Materials	Ag/AgCl Electrodes [124]	Semiconductors	PEDOT:PSS	AgNW, graphene NWs	PVDF nanofiber	PVDF film	GO, porous graphene	AlN	PVDF film	AlN	PZT-5A, AgNW
Fabrication methods	–	–	Drop-casting	Screen printing	Electrospinning	Cut-and-paste	Ink printing	Deposition	Laser engraving (patterning)	Casting	Dice-and-fill[25, 125]
Continuous monitoring/ testing period (power sources)	24–48 hrs (battery-powered)	Up to 24 hrs [50,58, 60] (battery-powered)	1 hr (battery-powered)	24 hrs (battery-powered)	10 hrs (self-powered)	N/A (self-powered)	N/A	N/A (self-powered)	N/A (self-powered)	30 s over 30 days (self-powered)	N/A (self-powered)
Sensitivity	±5.00 mV 0.05–40 Hz [123]	±1 or ±2 g Up to 1 kHz[60]	V_{pp} = 1.84 mV	–	Up to 10,050.6 mV/Pa (<500 Hz)	0.4 mV/με (Sensor) 12 mV/με (PVDF)	53.99/MPa	0.805 mV/μL (Annular) 0.257 mV/μL (Disk) 0.312 mV/μL (Serpentine annular)	V_{open} = 18.4 V	–	–
Biocompatible material (BioM)/ Biosafety test	FDA Approved	FDA Approved	BioM	No allergic reaction after 24 hr	BioM	BioM	Sealed by PI and PET/EVA	Sealed by PL	Live/dead staining of COS7 cells, encapsulation by PDMS	Sealed by PLA-based silicone	BioM
Positions	Chest, limbs	Chest	Left and right inner wrists	Left and right forearms	Chest	Chest	Arm and wrist	Carotid, wrist, clavicular	Knee	Chest	Right arm
Thickness	–	–	20 μm (decreases to 15 μm at 30% strain)	40–90 nm (AgNW diameter)	2.5 μm	122 μm	–	~1.0 mm[a])	–	–	350 μm

[a] Estimated data from the reference.

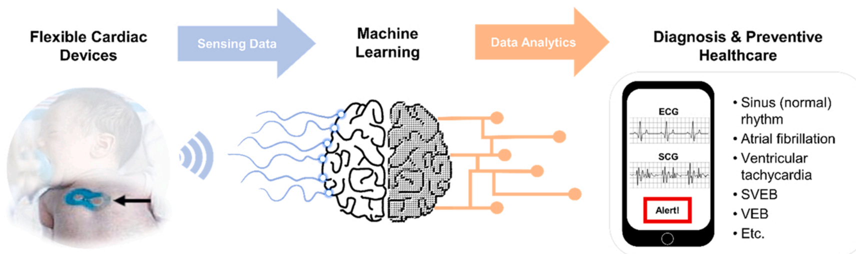

Fig. 9. A schematic of ML implementation in the cardiac sensing field to provide early warnings to healthcare professionals [9,28].

that automation is possible. In the cardiac sensing field, supervised learning has been implemented for automatic classification of specific cardiac conditions from the collected cardiovascular signals. For a more complex performance of machine learning, the machine can identify the features and classify them on its own by using deep learning (Fig. 10A) [34,35]. Many reported cardiac sensing processing approaches applied deep learning algorithms [10, 26–31]. Deep learning simulates the brain's neural network in order to create data representation architecture using multi-layer learning models. By comparing with traditional ML, deep learning does not require some of the data pre-processing and thus can utilize unstructured input data. The initial layers extract low-level features, and the last layers extract high-level features to eventually classify input data such as images. Additional layers help to refine the accuracy of the classification. Specifically for the cardiac sensing field, feature extraction becomes an automatic process while minimizing human dependency. In this section, the major machine learning algorithms for cardiovascular sensing signals including CNN, HMM, Random Forest, and BNN are discussed.

One of the deep learning algorithms utilized for cardiovascular monitoring is the convolutional neural network (CNN). CNN is one of the most commonly employed algorithms especially in the field of speech processing, face recognition, computer vision, and more since it can process data in a grid-like form that allows the machine to automatically identify a hierarchy of features and classify them into the proper category (Fig. 10B) [34–36]. CNN consists of three main layers that allow it to identify and classify features without human supervision:

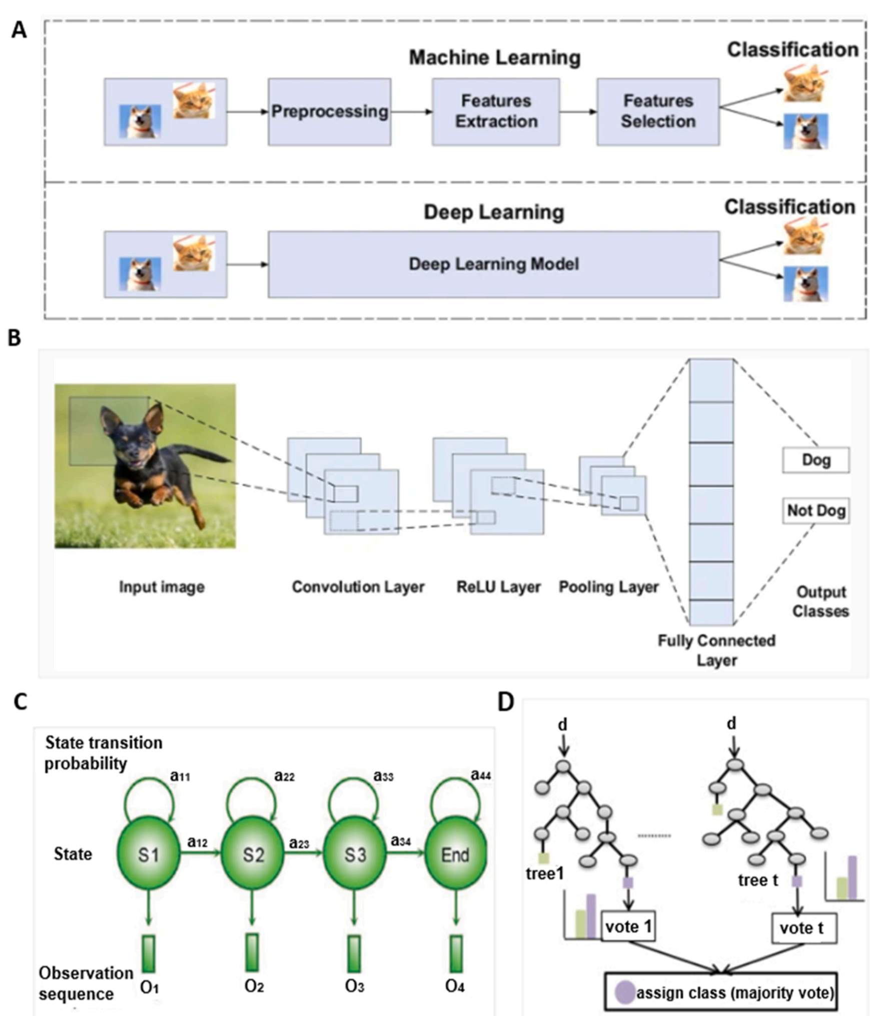

Fig. 10. Machine learning algorithms in the cardiac sensing field: (A). Comparison of the machine learning and deep learning structures [34]; (B). Structure of the CNN model [34]; (C). Structure of the HMM model [35]; (D). Structure of the Random Forest model [130].

convolution (hidden), pooling, and fully connected layer. The input, such as an image that is represented as N-dimensional metrics, is sent to the convolutional layers, which extract feature maps from the image with kernels (filters) that act as pattern detectors. The feature maps are then down-sampled by the pooling layers, where max pooling is the most common method. The down-sampling process reduces network parameters, which decreases computational power and time spent on the training process. Non-linear activation functions are employed to allow the model to apply complex functional mappings between the input and output data. The most common activation functions are ReLU, sigmoid, tanh, Leaky ReLU, and PReLU. Lastly, the fully connected layer receives the extracted features from the last convolutional layer and assigns them to their specific class by generating classification scores, which represent the probability for each specific class [36].

In addition to CNN, other ML algorithms are being utilized as well to collect and categorize cardiovascular data. Hidden Markov Model (HMM) is a statistical model that is widely used in areas such as speech recognition, named entity finding, optical character recognition, and topic identification for sequence classification problems [35,128,129]. The Markov model consists of “hidden states” and observed variables, which are influenced by the outcomes of the “hidden states” in a known manner. Essentially, HMM allows for the prediction of unknown variables from a series of observed variables. In Fig. 10C, each hidden state (four in total) has a transitional probability (circular and right arrows) that displays the probability of moving from one state to another and an emission probability (down arrows) that displays the probability corresponding to the observed variables. The HMM algorithm then computes the highest probability of the observation sequence to deduce the hidden state path.

Another type of machine learning model used to process and categorize cardiovascular signals is the Random Forest algorithm (Fig. 10D). This classifier randomly selects subsets of training data and creates numerous randomized “decision trees” [130,131]. Each individual tree provides a class prediction, and the model predicts the class based on the majority votes. Furthermore, a binarized neural network (BNN) algorithm has also been implemented in cardiac sensing processing. Essentially, BNN binarizes deep neural networks to significantly reduce computational power and increase power efficiency by reducing memory size and substituting mathematical operations with bit-wise operations [132,133]. It uses binary values ($+1$ or -1) for network weights and hidden layer activations in place of full precision values. Deep neural networks are used for large datasets that require a lot of computational power and storage; however, BNN can be utilized as an alternative to save on computational power and time while still providing similar working capabilities.

4.2. ML Algorithms for cardiac monitoring

Researchers have utilized various ML algorithms to process raw cardiac sensing data and categorize the data in real-time. Several researchers have implemented CNN for signal processing to detect cardiac abnormalities. Kim *et al.* created a thin-film, stretchable, flexible electronic system that monitored, detected, and notified physicians of real-time cardiac conditions through continuous assessment of recorded ECG signals [26]. Researchers utilized two CNN units to process raw ECG data, acceleration, and angular velocity data and categorize them into respiratory rate (RR), heart rate (HR), different types of cardiac conditions, and motion activity data for real-time monitoring. The first CNN unit incorporated inception-type convolutional units with residual connections to classify user activity (idle, walk, stairs, run, and fall) from acceleration and angular velocity data. The second CNN unit implemented semantic segmentation of raw ECG data to provide ECG annotation and categorize them into cardiac conditions (normal sinus rhythm, myocardial infarction, heart failure and miscellaneous arrhythmia, fusion beat, supraventricular ectopic beats, and ventricular ectopic beats). Through convolutional operations and max pooling, dimensionality reduction was conducted to decrease the number of features. Deconvolutional layers were also included to up-sample the signals. Then, residual connections were created between the convolutional and deconvolutional layers to optimize accuracy during training. The HR and RR were derived from the raw ECG data using R-peak detection and interpolation algorithms. To determine the accuracy of the ML model, researchers used two publicly available ECG datasets (PTB Diagnostic ECG Database and St. Petersburg Institute of Cardiological Technics 12-lead Arrhythmia Database) through fivefold cross-validation that evaluated their ML model. The development of the CNN algorithm for their flexible cardiac sensor achieved an accuracy of $98.7 \pm 1.4\%$ [26]. In addition, Ha *et al.* created a RF-SCG system that captured SCG signals without any bodily contact through sensing RF signals [28]. The RF-SCG sensor used a hybrid mixture of signal processing and deep learning, which consisted of a series of learnable spatio-temporal filter functions that incorporated domain knowledge from both RF and physiological models. They also implemented the 4D Cardiac Beamformer, which discovered the 3D location of the heart and estimated the heart rate by using a CNN-assisted template matching and 1D CNN architecture. Another type of CNN model researchers utilized was Unet architecture, which is primarily utilized for biomedical image segmentation [134]. The model automatically labeled the five fiducial points of interest on SCG waveforms: mitral valve closing, isovolumetric contraction, aortic valve opening, aortic valve closing, and mitral valve opening. Moreover, Ullah *et al.* created a CNN algorithm as a stage-based model that annotated and classified ECG signals [29]. For the first stage, researchers incorporated 1D CNN that extracted useful features from the given data and transformed them into 2D ECG images. With these 2D images, healthcare professionals would be able to diagnose arrhythmias through eye vision inspection. For the second stage, researchers incorporated 2D CNN that took the 2D ECG images as input to classify them into different types of arrhythmias. To determine the accuracy of their stage-based model, researchers used the arrhythmia database from Massachusetts Institute of Technology - Beth Israel Hospital (MIT-BIH). Their 1D CNN stage provided an accuracy of 97.38% while the 2D CNN stage provided an accuracy of 99.02%. Kamaleswaran *et al.* designed a deep learning model with the goal of reducing test run time that identified normal sinus rhythm, atrial fibrillation, other abnormal rhythms, and noise from 8528 short single-lead ECG recordings [30]. From the 8528 recordings collected from AliveCor’s single channel (lead I) ECG device, researchers identified 5050 normal rhythm, 738 atrial fibrillation, 2456 other abnormal rhythms, and 284 noise. For the CNN model, researchers tested two design models. The first model utilized MatLab to extract a total of 62 features that could be fed into the CNN architecture for classification of the recordings. Researchers down sampled the recordings at 200 Hz and low-pass filtered the data between 1 and 35 Hz to filter out motion artifacts and environmental noise. The second model utilized Python to analyze raw data input of the ECG recordings. For the second model, researchers implemented a 13-layer 1D CNN architecture to limit the signal bandwidth between 3 and 45 Hz and detect the QRS complex. Their two-model approach allowed researchers to optimize parameters and finalize their model for identifying and categorizing abnormal cardiac rhythms. Increasing the number of layers increased validation loss while also improving model performance up to a certain threshold. Furthermore, certain activation functions provided the highest validation accuracy while also providing the highest average epoch runtime. Ultimately, they settled with the 13-layer 1D CNN model approach with ReLU as their activation function since their goal was to reduce test run time [30].

Other ML techniques, such as HMM, Random Forest and BNN, have also been implemented to analyze cardiovascular signals. Lee *et al.* designed a mechano-acoustic sensor and utilized HMM for data processing [10]. The sensor was mounted on the suprasternal notch, the throat, that collected multimodal data related to various physiological processes, such as HR, RR, talking time, swallow counts, and energy expenditure, by analyzing the acceleration data measured normal to the skin surface. Researchers transferred raw physiological data to a phone via Bluetooth and used the statistical model for their ML algorithm that exploited time- and frequency-domain representations to analyze the data and categorize them. They used multi-band z-axis signal power on logarithmic scales as the observable clustering features, with a multi-band choice featuring a variety of frequency ranges for different types of signals. The three-axes time series data recorded real-time data over a time interval as the patient engaged in various activities that included sitting at rest, talking, drinking water, changing body orientation, walking, and jumping. Additionally, Kung *et al.* used the Random Forest algorithm to create a resource-saving system that extracted important features of ECG signals to classify them into different types of arrhythmias with the extracted features [27]. The feature extraction system consisted of two delta-sigma modulators (DSMs): the first DSM converted the collected ECG signals into binary or ternary digit streams, and the second DSM developed algorithms that extracted the required features from the streams. The DSMs utilized low-complexity algorithms, adopted a low sampling rate of 250 Hz, and compressed the extracted ECG features to save power and lower memory usage. For the classifier, researchers used Random Forest to utilize binary classification and regression trees to categorize the ECG signals into two major arrhythmia types: supraventricular ectopic beats (SVEB) and ventricular ectopic beats (VEB). To aid with the classification, the researchers used the MIT-BIH arrhythmia database for their algorithm to derive patterns and observations. Furthermore, Wu *et al.* employed a binarized 1D CNN model to analyze ECG signals for real-time arrhythmia detection [31]. Researchers initially designed a 1D CNN model that utilized bucketing data padding, layer normalization, and global pooling layer with the dataset from *PhysioNet/CinC* Atrial Fibrillation Classification Challenge 2017. To reduce model complexity and computing resources, researchers further implemented a binarized CNN model. Since the BNN model presented some model performance loss due to the simplification of the model, researchers utilized knowledge distillation to transfer knowledge from their full-precision CNN model to the BNN model, which regularized the binarized model.

Machine learning, more specifically supervised learning, is utilized in the cardiac sensing field such that the machine can learn from previously labeled data to properly classify new cardiovascular data into its appropriate category. A summary of the various ML algorithms discussed in this review for the cardiac sensing field is provided in Table 3. By integrating ML techniques to cardiac sensors, a patient's cardiovascular health can by analyzed by computers or smartphone applications for a real-time cardiac analysis with automatic cardiac abnormality detection. Of the various ML algorithms used in this field, CNN is the most commonly used for image classification due to its high accuracy output and its ability to reduce the number of parameters or features (dimensionality reduction) without losing the quality of the image. Thus, the integration of ML opens new horizons for identifying and classifying cardiovascular signals with ease of access.

5. Conclusions

With CVDs causing an estimated 32% of deaths globally, flexible cardiac sensing devices are some of the most effective methods for diagnosing cardiovascular conditions and diseases and providing early warnings to patients in and outside the hospital setting, especially considering the unpredictability of CVDs [1]. Flexible cardiac sensors can facilitate long-term, continuous monitoring of the heart by removing wiring and providing solutions to rigid interfaces, thus increasing patient's comfort and quality of life. Cardiovascular signals include two major heart mechanisms, ECG and SCG, and other heart mechanisms such as heart rate, blood pressure, pulse waves, respiration rates, and systolic time intervals. ECG pertains to the heart's electrical activity, while SCG captures the heart's mechanical activity. Both require the sensors to be sensitive and filter out any motion artifacts in order to accurately capture the signals that register on a microscale level.

Traditional cardiovascular monitoring systems, such as Holter monitors for ECG monitoring and accelerometers for SCG monitoring, have various key challenges that can be addressed by engineered solutions. Essentially, due to the rigid interfaces and multiple wiring components, long-term monitoring is difficult and vigorous movement and exposure to water from the patient would affect the quality of the cardiovascular signals. Thus, to address those issues, the ideal flexible cardiac sensor should be flexible, conformable, biocompatible, and have an extended or unlimited battery life that can facilitate continuous cardiac monitoring in order to observe irregular heartbeats. Flexible and conformable cardiac sensing devices can also better match the dynamic mechanical properties of the epidermis to collect accurate cardiac signals. To do so, the device's structural layout, material development, and fabrication method should complement each other during the design process. In this review, flexible cardiac sensors are discussed, especially on the structural layout, material design, and fabrication methods. For the structural layout, non-conventional smart structures such as serpentine, wavy, Kirigami, and more are employed to improve the

Table 3
Summary of ML for cardiac monitoring.

Refs	ML Algorithms	Goals	Heart Signals	Dataset	Sample Size	Performance Metric
[26]	CNN	Classification of cardiac conditions using ECG annotation	ECG	PTB Diagnostic ECG Database	–	$98.7 \pm 1.4\%_{acc}$
				INCART Arrythmia Database	75 recordings	
[28]	CNN Unet architecture	Extraction of heart rate Automatic labeling of fiducial points of SCG waveforms	SCG	21 healthy subjects	40,000 heartbeats	$< 2.5\%_{err}$
[29]	CNN	Transformation of 1D ECG signals into 2D ECG images	ECG	MIT-BIH	4000 recordings	$97.38\%_{acc}$
	2D CNN	Classification of 2D ECG images into different arrhythmia types				$99.02\%_{acc}$
[30]	CNN	Classification of ECG recordings into normal sinus rhythm, atrial fibrillation, other abnormal rhythms, and noise	ECG	PhysioNet/Comuting in Cardiology Challenge 2017	8528 recordings	$85.99\%_{acc}$, $0.83_{F1\text{-}score}$
[10]	HMM	Determination of sleep stages	Acceleration data measured normal to the skin surface	One participant	–	–
[27]	Random Forest	Classification of different types of arrythmias	ECG	MIT_BIH	44 records	$81.05\%_{F1\text{-}score}$ (SVEB), $97.07\%_{F1\text{-}score}$ (VEB)
[31]	BNN	Real-time arrythmia detection using ECG signals	ECG	PhysioNet/CinC AF Classification Challenge 2017	8528 recordings	$0.87_{F1\text{-}score}$

flexibility and stretchability of non-flexible materials. In order to design a flexible, conformable cardiac sensor, conventional structures such as planar, cantilevers, and disks can still be implemented with soft materials such as PDMS, PU, and ecoflex due to their inherent flexibility. Encapsulation methods by biocompatible materials are also discussed if the design of the cardiac sensor has rigid components or uses non-biocompatible functional materials. For the choice in materials, various flexible functional materials such as polymers, nanofibers and conductive materials are considered, along with flexible substrate materials such as PDMS, PI, and PU. Lastly, various fabrication methods include the cut-and-paste, electrospinning, spin-coating, and more to either provide a cost-effective fabrication process or to enhance the properties of the materials. Other fabrication processes, such as chemical layering, 3D printing, inkjet printing and other printing techniques, could also be integrated with these flexible functional and substrate materials; however, they are not widely used and preferable for cardiac sensing applications in the field [135–141]. Specifically for additive manufacturing in the biomedical field, the fabrication method limits the selection of materials, especially polymer and composite-based materials [140,141]. Moreover, many materials with excellent performance in 3D printing are not biocompatible, which is a significant consideration in the cardiac sensing field. In terms of printed electronics, the issue of device-to-device variability arises due to the instability of the materials [140,141].

Strategies of cardiovascular monitoring have been intensively investigated in the field. However, there are still certain challenges for the design and optimization of flexible cardiac sensing devices. Regarding the battery life of the sensing devices, longevity is a critical consideration for future work. Self-sustainable energy generation such as the piezoelectric or triboelectric effect has been mentioned in this paper. Nevertheless, tests for measuring battery capacity should also be conducted to observe how long the self-sustainable methods can sustain cardiac sensors outside the test time frame that researchers have experimented for their research. Improving energy usage for future work can increase patient comfortability by decreasing the number of battery replacements or replacing the need for batteries. Additionally, biocompatibility is a critical factor when considering the longevity of the device. To become a biosafe cardiac sensor that comes into contact with the human skin, biocompatible and biosafe materials are essential during the design process. Biocompatibility tests such as cell viability and cytotoxicity tests can be conducted to prove biocompatibility status of the device. However, for continuous cardiovascular monitoring, long-term tests should be conducted within a reasonable timeframe to validate biocompatibility status for lasting devices since it would be unfeasible to test for the entire lifetime of the device. Longevity of the device is also critical when considering the durability of the sensor. For continuous cardiovascular monitoring, the patients go through their regular physical activity and as such, the device would encounter constant deformation through various types of motion such as tensile, compressive, and bending. Thus, long-term studies for device durability should also be conducted as future work.

Recent advances in ML have also been significant in facilitating a new, real-time sensing approach for healthcare professionals. To easily provide early warnings to patients, cardiac monitoring sensors can utilize ML algorithms to provide an automated detection system for cardiovascular abnormalities. Moreover, application of real-time ML processing can improve the achievability of device-based diagnoses, and human dependency on detecting cardiac conditions can be significantly reduced depending on the level of ML implementation [142]. Due to the infrequency of irregular or abnormal heartbeats, continuous and long-term cardiac monitoring is necessary to detect those diseases as soon as they occur in patients who are at risk, so healthcare professionals can take immediate action to prevent premature death. Essentially, flexible cardiac sensors that utilize real-time ML processing would be able to send out alerts the moment a cardiac abnormality occurs, allowing for doctors, Emergency Medical Technicians (EMTs), and other healthcare professionals to provide immediate aid. ML can still be used in post-processing applications during the experimental process of designing flexible cardiac sensors [10,28]. The researchers can analyze the obtained cardiovascular signals and build a more accurate model if needed. This review discusses different ML algorithms for cardiac monitoring such as CNN, HMM, Random Forest, and BNN that have been employed to detect and classify various physiological processes within the human body. In recently published work, applications of ML have shown more effective and faster detection of cardiac abnormalities [10, 26–31]. However, there are certain challenges that should be addressed for future work to optimize the application of ML in the field of cardiac sensing. Especially for ML algorithms like CNN, a considerable amount of computational power is required to work with large amounts of data such as cardiovascular signals [147]. The more complex the algorithm is, the greater the need for higher computational processors. As can be seen in Table 3, most works that utilize CNN typically include large sample sizes, with Ha *et al.* working with 40,000 recordings from 21 subjects [28]. Additionally, HMM is a statistical model consisting of "hidden states" and observed variables. However, the model is dependent on the last known state and cannot correlate between them [129]. For the Random Forest algorithm, each randomized "decision tree" provides a class prediction for the model to predict the class [131]. The greater the number of "decision trees", the higher the accuracy of the prediction. However, an increase of the number of trees can slow down the model. This could effectively make it difficult for real-time processing of cardiovascular signals, in which time is of the essence. For BNN, this model binarizes deep neural networks to reduce computational power and memory size, which ultimately increases power efficiency [133]. Binarizing neural networks replaces full precision values with binary values to reduce computational power at the expense of decreasing the accuracy of detecting cardiac abnormalities. Moreover, besides the major heart mechanisms ECG and SCG, there are various other cardiovascular signals that can be considered as input data for signal processing. Various medical devices also exist to capture each type of cardiovascular signal differently. Thus, the classification of the cardiovascular signals would vary significantly, making one ML algorithm for a specific cardiovascular signal incompatible with analyzing other signals. Consideration of various types of cardiovascular data for the implementation of ML would be conducted as future work.

Development in the cardiac sensing field has also introduced implantable flexible cardiac sensors for long-term, continuous monitoring. Despite the inclusion of surgical elements for implantable cardiac sensors, certain heart mechanisms such as blood pressure need in vivo measurements for localized and accurate diagnosis of cardiovascular signals [11]. For example, Cong *et al.* designed an implantable silicone cuff for real-time blood pressure monitoring, which was tested on laboratory mice [143]. The blood pressure cuff wrapped around the blood vessel with an approximate diameter of 200 μm. The implantable cardiac sensor is wireless and requires no battery due to an external radio frequency (RF) powering station and RF powering coil located outside the animal cage. The flexible silicone material prevents restriction of the blood vessel and also allows for the incorporation of a MEMS pressure sensor positioned over an IC base. Liu *et al.* also used hydrogels to design a liquid-metal-based implantable cardiac patch to test on healthy rabbit hearts [81]. The patch conformed to the movement of the rabbit's heart tissues to provide signals resembling cardiac electrophysiological signals, such as breathing and the heart beating. Moreover, Zheng *et al.* designed an implantable triboelectric nanogenerator (iTENG) mainly for in vivo biomechanical energy harvesting but later realized its application as a self-powered, wireless cardiac sensor [97]. The sensor used nanostructured polytetrafluoroethylene (n-PTFE) as the functional triboelectric layer, which was encapsulated in PDMS and parylene in order to harvest energy from the heart of an adult swine by utilizing the triboelectric effect. Its energy harvesting performance over 72 h showed that it continuously generated electricity, thus demonstrating its great potential as a power source for other implantable medical devices. As a cardiac sensor, iTENG was able to monitor three different heart rates (60, 80, and 120 beats per minute) and also wirelessly transmit real-time cardiac data due to its self-powered capability. Ultimately, implantable flexible cardiac sensors could provide another promising direction to long-term continuous cardiovascular monitoring. For biodegradable cardiac sensors that are soft and flexible, material degradation within the human body generally decreases the electrical output. As future work, this topic can be further explored in designing biodegradable cardiac sensors but note that biodegradable sensors are not applicable for long-term, continuous cardiovascular monitoring. Patients at risk of CVDs cannot easily lower the risk as there is no sole solution. Thus, soft and flexible cardiac sensors that can monitor the patient long-term and continuously are preferred within the cardiac sensing field.

This work mainly focuses on the piezoelectric effect as the sensing mechanism of soft and flexible cardiac sensors, since this transduction mechanism allows for energy conversion to self-power for long-term, continuous cardiac monitoring. However, it should be noted that there are other sensing mechanisms utilized in the sensing field [144–149]. One main mechanism is the capacitance measurement. This sensing mechanism essentially harnesses the ability to store an electrical charge, as a capacitor would do [145,146]. The most common form of capacitors is the parallel plate capacitor, which consist of two parallel plates that carry equal but opposite charges. The electric field lines begin at the charged plate with the higher voltage potential and stop at the charged plate with the lower voltage potential. As a capacitor sensor, it would sense the capacitance, or displacement currents, produced by the human body [147]. In terms of cardiac sensing, a dielectric material, such as an electrically insulated layer or air, can be used instead of relying on electrode-skin interface; thus, non-contact sensing can be realized. However, localized measurement of cardiovascular signals would be challenging. Another sensing mechanism is the resistive mechanism, which measures the material's change in electrical resistance when bent or stretched [148]. As a resistive sensor, it is commonly used as a pressure or strain sensor. Due to its ability to convert mechanical energy to electrical energy, piezoelectric materials can be incorporated to create piezoresistive sensors that detect small resistance variations [149]. As future work, those sensing mechanisms could be further explored due to their expanding possibilities in the field of cardiac sensing.

A cardiac sensor that facilitates continuous monitoring outside the hospital setting and increases patient comfortability without negatively impacting the patient's quality of life is an emerging prospect for diagnosing CVDs early and potentially reducing the number of fatalities. Moving forward, long-term studies on humans will be required to validate the biocompatibility, durability, and battery life of flexible, conformable cardiac sensors. Long-term studies should span months and years and consist of volunteers or patients who undergo regular physical activity. It is a promising direction within the cardiac sensing field for these devices to be clinically operated in the future in order to provide patients a multifaced diagnosis of their cardiovascular status.

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.

Data Availability

No data was used for the research described in the article.

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