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Advances and applications of biosensors in pulmonary hypertension

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Abstract

Pulmonary hypertension (PH) is a serious disease characterized by elevated pulmonary artery pressure, with its prevalence and incidence continuously increasing, posing a threat to the lives of many patients worldwide. Due to the complex etiology of PH and the lack of specificity in clinical manifestations, there is currently a lack of effective and specific methods for early diagnosis in clinical practice. Biosensors hold significant promise for the early detection, therapeutic monitoring, prognostic evaluation, and personalized treatment of PH, owing to their rapid, sensitive, and highly selective characteristics. The rapid development of various types of biosensors, such as electrochemical biosensors, optical biosensors, microfluidic biosensors, and wireless biosensors, combined with the use of nanomaterials, makes the rapid and accurate detection of PH-related biomarkers possible. Despite the broad application prospects of biosensors in the field of PH, challenges remain in terms of sensitivity, selectivity, stability, and regulation. This article reviews the main pathophysiological mechanisms and commonly used biomarkers of PH, the types and principles of biosensors, and summarizes the progress of biosensors in PH research as well as the current challenges, in order to promote further in-depth research and the development of biosensor technology, thereby improving the diagnosis and treatment effects of PH.

Clinical trial number: Not applicable.

Keywords Pulmonary hypertension, Biosensors, Biomarkers, Nanomaterials

Introduction

PH is a condition characterized by increased pressure in the pulmonary arteries due to various factors, leading to increased strain on the right side of the heart, which can ultimately result in heart failure and death. According to the latest diagnostic criteria, PH is defined by a mean pulmonary artery pressure greater than 20 mmHg measured during a right heart catheterization. In addition, a pulmonary vascular resistance (PVR) greater than 2.0 Wood units is also used for diagnosis and prognosis [1]. Currently, at least 1% of the world's population is affected by PH, and the incidence rate continues to rise annually, with a high mortality rate [2]. Early identification and management are crucial for improving patient prognosis, but early diagnosis is challenging, and many patients are in the advanced stages of the disease at the time of

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diagnosis. Therefore, finding new diagnostic methods has become one of the hot topics in PH research.

Biosensors are analytical tools that combine biological recognition materials with transducers, and their working principle is based on the interaction between the biological recognition elements and target molecules [3–5]. When target molecules bind to the biological recognition elements, certain physical or chemical changes occur, leading to changes in the signal. The transducer then converts this signal into an electrical signal or other measurable signals, and the results are obtained after information processing [6]. According to their structure and working principles, biosensors include electrochemical biosensors, optical biosensors, microfluidic biosensors, and wireless biosensors [7]. In recent years, with the use of nanomaterials, the sensitivity, selectivity, and detection speed of biosensors have been continuously improved, showing great potential in disease diagnosis and monitoring [8, 9].

Early diagnosis and real-time monitoring of PH have always been clinical challenges. Traditional diagnostic methods such as echocardiography, cardiac catheterization, and blood tests have certain limitations [10]. Biosensors offer rapid, convenient, and non-invasive detection methods, making them significant for the early diagnosis and treatment monitoring of PH [6]. In this article, we review the pathophysiological mechanisms of PH and related biomarkers. Additionally, we summarize the applications and recent advancements of biosensors in PH, as well as the existing difficulties and challenges, aiming to provide better insights for clinicians and researchers and to promote the further development of related technologies.

Pathophysiological mechanism of PH

PH exhibits significant heterogeneity and can be categorized into five types based on etiology and prognosis, including PAH, PH due to left heart disease, PH due to lung diseases or hypoxia, chronic thromboembolic PH, and PH due to other factors [2]. The key pathophysiological changes include vascular remodeling, perivascular inflammation, and microthrombus formation [11]. Understanding the classification and pathophysiological mechanisms of PH is crucial for developing targeted biomarkers that facilitate early diagnosis, treatment monitoring, and personalized therapy. It also propels the advancement of related biosensing technologies.

Pulmonary vascular remodeling

Pulmonary vascular remodeling is a key structural change in PH (Fig. 1), involving alterations in the intima, media, and adventitia, often accompanied by the interaction of inflammatory cells [12]. Additionally, PH is a disease with genetic characteristics, where gene mutations activate related signaling pathways, promoting vascular remodeling [13].

The remodeling of the intima is primarily associated with abnormal proliferation and dysfunction of endothelial cells. The abnormal proliferation and migration of endothelial cells are the result of multiple mechanisms, including hypoxia, the action of inflammatory mediators, and the imbalance of growth factors. This can lead to the formation of plexiform lesions, which are associated with increased expression of hypoxia-inducible factors (HIF), pro-inflammatory cytokines, and platelet-derived growth factors (PDGF) [14]. Endothelial dysfunction is mainly related to elevated levels of pro-inflammatory factors, oxidative stress, endothelial-mesenchymal transition (EndoMT), and the impact of the extracellular matrix (ECM) [15]. In the context of PH, the increased production of pro-inflammatory factors and reactive oxygen species (ROS) can directly damage endothelial cells, leading to apoptosis and dysfunction of endothelial cells [16]. Additionally, ROS can impair the synthesis of nitric oxide (NO) in endothelial cells, leading to impaired vasodilatory function [17]. Endothelial cells may undergo EndoMT, transforming into smooth muscle-like cells, which leads to the proliferation of smooth muscle cells and the dysfunction of endothelial cells, promoting vascular remodeling [18]. Abnormal deposition and degradation of ECM components such as collagen, elastin, and fibronectin can lead to increased rigidity of the vascular wall, thereby affecting the function and structure of endothelial cells [19].

The medial layer is primarily composed of smooth muscle cells, whose proliferation and hypertrophy can lead to an increase in the thickness of the media, thereby affecting the compliance and resistance of pulmonary blood vessels. The excessive proliferation of pulmonary artery smooth muscle cells (PASMCs) is associated with various factors, including the increase of HIF, pro-inflammatory cytokines, and growth factors [20]. Under high-pressure conditions, these cells undergo metabolic reprogramming to adapt to hypoxia, inflammation, and other intra- and extra-cellular stresses, providing energy for cell proliferation, which is related to mitochondrial dysfunction [21]. Furthermore, the phenotypic switch of smooth muscle cells, from a contractile to a synthetic phenotype, may lead to an increase in the synthesis of ECM, thereby causing medial fibrosis [22].

The adventitia primarily composed of connective tissue, serves as a signaling center for inflammatory cells. Here, the infiltration of inflammatory cells and the proliferation and migration of fibroblasts jointly drive the process of vascular remodeling [12]. The release of pro-inflammatory factors, adhesion molecules, and chemokines promotes the aggregation of inflammatory cells, which in turn release cytokines that further exacerbate

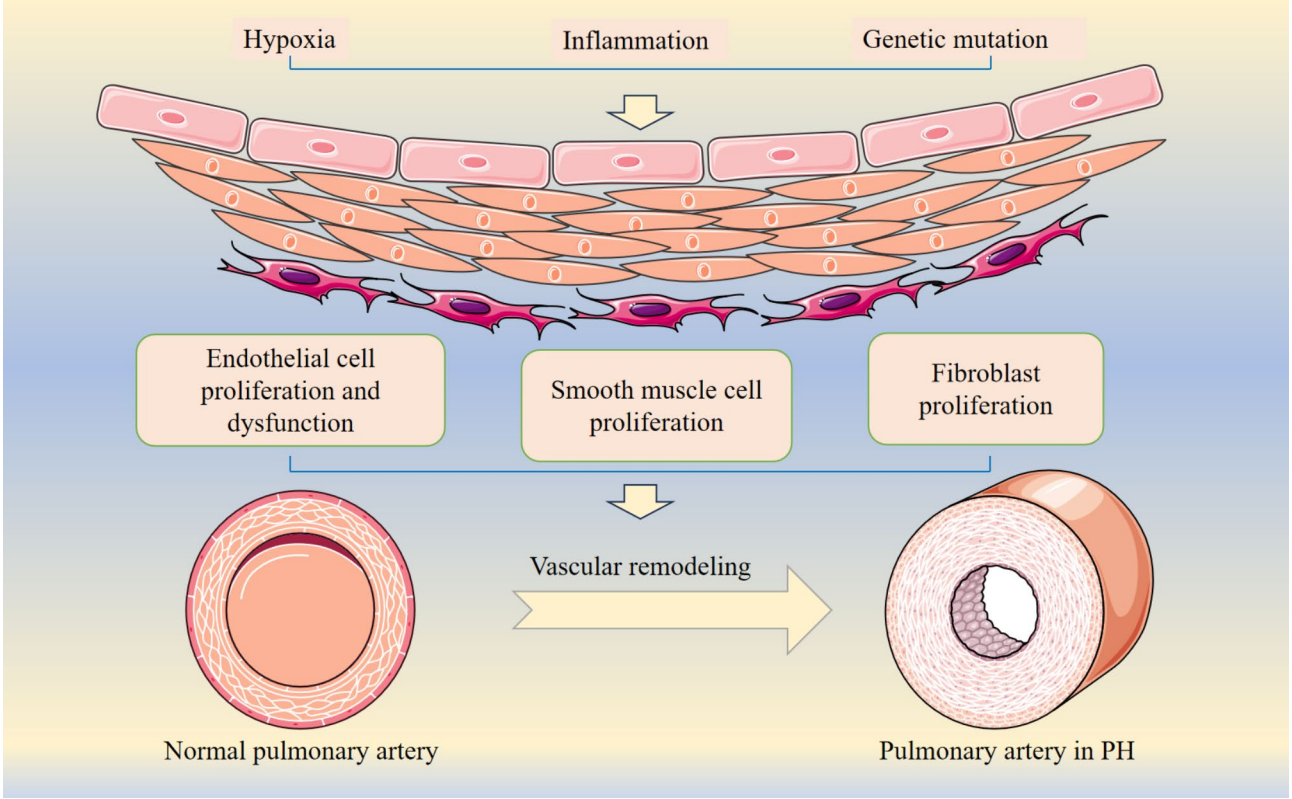

Fig. 1 Pulmonary vascular remodeling in PH. Pulmonary vascular remodeling in PH is primarily stimulated by factors such as hypoxia, inflammation, and genetic mutations. This mainly leads to the proliferation and dysfunction of endothelial cells in the intima, the proliferation of vascular smooth muscle in the media, and the proliferation of fibroblasts in the adventitia. The process is accompanied by the deposition of ECM and infiltration of inflammatory cells

vascular remodeling [23]. The increased expression of growth factors promotes the proliferation of fibroblasts, which secrete various ECM components, ultimately leading to vascular fibrosis [24].

Pulmonary vascular inflammation

PH is often accompanied by perivascular inflammation (Fig. 2), with various immune cells, including neutrophils, macrophages, mast cells, and T lymphocytes, accumulating around the pulmonary vessels [25]. On the one hand, these immune cells produce pro-inflammatory factors to promote the recruitment of inflammatory cells and exacerbate vascular inflammation. On the other hand, they are involved in the process of vascular remodeling and endothelial dysfunction [26].

Neutrophils can exacerbate vascular remodeling by releasing neutrophil elastase (NE) and other proteases that degrade the ECM, or by releasing growth factors that promote the proliferation and migration of smooth muscle cells. In addition, neutrophils can directly damage endothelial cells by forming neutrophil extracellular traps (NETs) or by secreting ROS and pro-inflammatory factors, thereby intensifying vascular inflammation [27]. In PH, the mechanisms of macrophage action involve their polarization state in the local microenvironment, where M1-type macrophages release pro-inflammatory cytokines such as TNF-α and IL-1β, leading to endothelial damage and abnormal proliferation of vascular smooth muscle cells. In contrast, M2-type macrophages promote the proliferation of fibroblasts and the synthesis of ECM by secreting anti-inflammatory factors such as IL-10 and TGF-β, resulting in pulmonary artery fibrosis [28].

The role of mast cells in PH is mainly reflected in the release of various vasoactive substances and proteases, such as histamine, leukotrienes, tryptase, and chymase, which are involved in the inflammatory response and vascular remodeling of the pulmonary vessels [29]. Histamine can directly act on pulmonary vascular smooth muscle cells, causing vasoconstriction and increasing pulmonary arterial pressure. Pro-inflammatory mediators such as leukotrienes can recruit and activate other inflammatory cells [30]. In addition, mast cell-secreted tryptase and chymase are involved in the proliferation of pulmonary vascular smooth muscle and affect the remodeling of pulmonary vessels in PH [31]. In PH, the T cells that primarily play a role are helper T cells (TH) and regulatory T cells (Tregs). TH1 cells can secrete IFN-γ, which promotes endothelial cell apoptosis, leading to endothelial dysfunction and affecting vascular relaxation [32]. TH17 cells can secrete IL-17, inducing

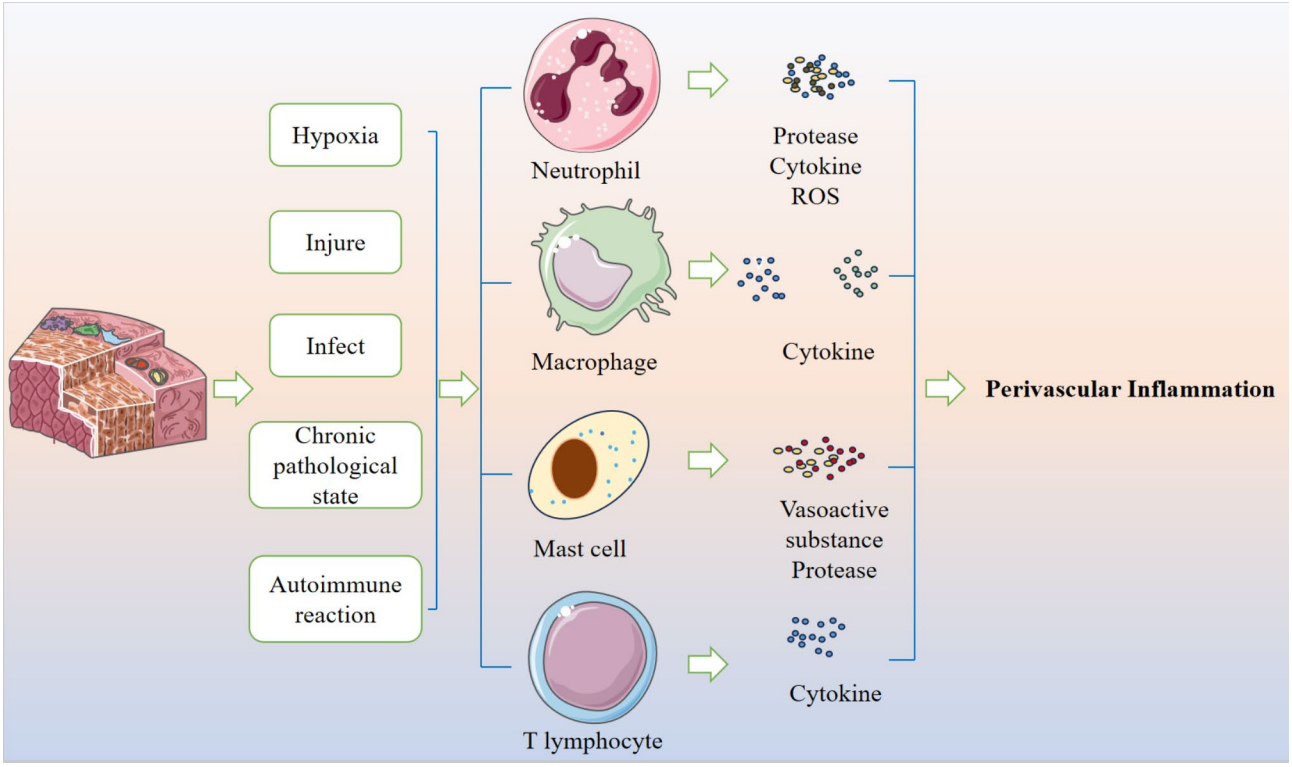

Fig. 2 Perivascular inflammation in PH. In PH, perivascular inflammation is a complex process triggered by various factors, including hypoxia, injury, infection, chronic pathological states, and autoimmune reactions. These factors activate a variety of immune cells, including neutrophils, macrophages, mast cells, and T lymphocytes, which drive inflammatory responses and pulmonary vascular remodeling through the secretion of inflammatory factors. Proteases and ROS released by neutrophils may directly damage the vascular endothelium, leading to endothelial dysfunction. Macrophages release pro-inflammatory factors in the early stages of inflammation and may shift to M2 macrophages that secrete anti-inflammatory factors to suppress inflammation in the later stages. Mast cells exacerbate inflammation by secreting vasoactive substances and release proteases that promote vascular remodeling. T lymphocytes play a key role in regulating immune responses, including Th cells and Treg. Th cells promote inflammation and vascular remodeling, while Treg cells inhibit excessive immune responses and inflammation by secreting anti-inflammatory cytokines such as IL-10 and TGF-β, maintaining immune tolerance

the overexpression and release of pro-inflammatory cytokines by various immune cells, while also acting on endothelial cells, epithelial cells, and fibroblasts, promoting their activation and proliferation, and facilitating vascular remodeling [33, 34]. Additionally, in some PH patients, various autoantibodies can be detected. These autoantibodies may directly damage the pulmonary vascular endothelium, leading to inflammation and vascular dysfunction. The emergence of these antibodies may be related to an increase in autoimmune responses due to a decrease in Tregs [35, 36].

Microthrombus formation

Microthrombosis is a distinctive pathological change in PH, associated with increased inflammation, endothelial cell injury, hemodynamic alterations, and activation of the coagulation system [37]. The release of inflammatory factors can damage the endothelium and activate the coagulation system, leading to microthrombosis [38]. Endothelial cell injury and dysfunction result in reduced production of vasodilators such as NO, while the production of constrictor factors like ET-1 increases, promoting vasoconstriction and thrombosis [14]. In the context of PH, increased PVR and slowed blood flow provide favorable conditions for thrombus formation [39]. The activation of the coagulation system includes platelet activation and increased coagulation factors. Increased platelet activity may be related to chronic hypoxia, endothelial cell injury, and the action of inflammatory factors [40]. Furthermore, the release of granule contents (such as ADP, serotonin, TxA2, and PDGF) from activated platelets can further promote platelet aggregation [41]. Inflammatory responses, endothelial injury, and vascular dynamics changes can all lead to an increase in coagulation factors, especially factor VIII and fibrinogen [42].

The molecular mechanisms of PH involve multiple complex pathways, primarily including the interaction of cytokines, growth factors, and transcription factors, which collectively lead to vascular remodeling and perivascular inflammation, and may even result in microthrombus formation [43]. With the continuous understanding of the molecular mechanisms of

PH, biosensors that specifically target the molecular mechanisms of PH have become an important diagnostic and detection measure, aiding in early diagnosis and treatment.

Biomarkers for PH applicable to biosensor development

In the clinical diagnosis of PH, there is a lack of specific indicators for early diagnosis (Table 1). Genes such as BMPR2, ATP13A3, EIF2AK4, KCNK3, ENG, and KDR are all related to the pathogenesis of PH, and the detection of these genes by RNA biosensors is of great significance for the early diagnosis of PH [13]. Additionally, the detection of biomarkers related to the classification and pathophysiological mechanisms of PH can be used to assist in diagnosis, treatment monitoring, and prognosis prediction. The biosensors currently under research mainly detect biomarkers related to these pathophysiological mechanisms [44]. These biomarkers can be categorized into different types based on their functions, including cardiac stress markers, inflammation markers, vascular dysfunction markers, coagulation and platelet activation markers, and markers of tissue hypoxia and organ injury [45].

Cardiac stress markers including natriuretic peptides and cardiac troponins, which can be used for the early diagnosis of PH [46]. Natriuretic peptides consist of brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and atrial natriuretic peptide (ANP), which play a central role in reflecting cardiac wall stress and injury [47]. Cardiac troponins, including cardiac troponin T (TnT) and cardiac troponin I (TnI), are markers of cardiac injury, and their elevation is related to increased pressure load on the heart [48]. Inflammatory markers, primarily cytokines and C-reactive protein (CRP), are elevated and associated with the progression of PH [49]. Cytokines such as tumor necrosis factor-alpha, interferon-gamma, and various interleukins, together with CRP, play a significant role in the development and progression of PH [50].

Vascular dysfunction markers mainly include ET-1, NO, and its metabolites. ET-1 is directly related to pulmonary hemodynamics and can serve as an ideal marker for disease progression [51]. Metabolites of NO, such as asymmetric dimethylarginine (ADMA), can inhibit NO synthase and are associated with the prognosis of PH [52]. Coagulation and platelet activation markers, including D-dimer and von willebrand factor (vWF), are elevated in PH and are mainly related to the prognosis of the disease [53]. Tissue hypoxia and organ injury markers, such as arterial carbon dioxide partial pressure (PaCO2), serum uric acid (UA), blood urea nitrogen (BUN), and cystatin C (CysC), all have prognostic value in PH patients [54]. According to the classification and pathogenesis of PH, using biosensors to detect appropriate biomarkers can more accurately diagnose PH, monitor treatment, and predict prognosis, achieving personalized treatment. For example, D-dimer is suitable for thromboembolic PH and can be used to exclude pulmonary embolism [55]. Troponins are used to assess the degree of left heart dysfunction caused by PH due to left heart disease [56].

Biomarkers are the targets of biosensor detection, and biosensors are the tools for detecting biomarkers. The combination of the two provides strong support for disease diagnosis, therapeutic monitoring, and prognosis assessment [57]. Currently, biosensors used in PH can be classified based on their working principles and construction. According to different working principles, they are divided into electrochemical biosensors and optical biosensors. In terms of construction, they include microfluidic biosensors and wireless biosensors [58]. Moreover, with the advancement of nanotechnology, nanobiosensors can provide faster, more accurate, and more sensitive methods for detecting PH, which is conducive to achieving early diagnosis and personalized treatment [59].

Table 1 Classification of common biomarkers for PH

Classification	Biomarker	Function
Gene	BMPR2, ATP13A3, EIF2AK4, KCNK3, ENG, KCNK3, KDR	Early diagnosis
Myocardial Stress Markers	BNP, NT-proBNP, ANP, TnT, TnI	Early diagnosis, disease progression, and prognostic prediction
Inflammatory Markers	TNF-α, IFN-γ, IL, CRP	Disease progression, and prognostic prediction
Markers of Vascular Dysfunction	ET-1, NO, Metabolites of NO	Disease progression, and prognostic prediction
Coagulation and Platelet Activation Markers	vWF, D-dimer	Disease progression, and prognostic prediction
Markers of Tissue Hypoxia and Cellular Injury	PaCO2, UA, BUN, CysC	Disease progression, and prognostic prediction

Classification and principles of biosensors

Biosensors are specialized chemical sensors whose core technology lies in utilizing the specific recognition capabilities of biological components to detect target substances. The sensor system primarily consists of two key components: a biorecognition element and a signal transducer. The biorecognition element serves as the chemically sensitive layer responsible for capturing the target analyte, while the signal transducer converts the biochemical response triggered by specific recognition into a quantifiable physical signal (such as an electrical or optical signal) [60]. Based on differences in detection principles, biosensors are mainly categorized into electrochemical biosensors and optical biosensors.

Electrochemical and optical biosensors, when integrated with different sensing technologies, can include microfluidic biosensors, wireless wearable biosensors, and nanobiosensors (Fig. 3). Through the deep integration and synergistic analysis of multimodal sensing technologies, simultaneous detection of multiple biomarkers can be achieved, promoting a shift in medical diagnostics from single-biomarker analysis to a systematic precision medicine paradigm [60, 61].

Electrochemical biosensors

Electrochemical biosensors combine biological recognition elements (such as enzymes, antibodies, nucleic acids) with electrochemical conductive elements to detect and analyze chemical substances. Their working principle can be summarized in the following steps: biological recognition, signal transduction, electrochemical conduction, signal detection, and data analysis (Fig. 4) [62]. The biological recognition elements (biological

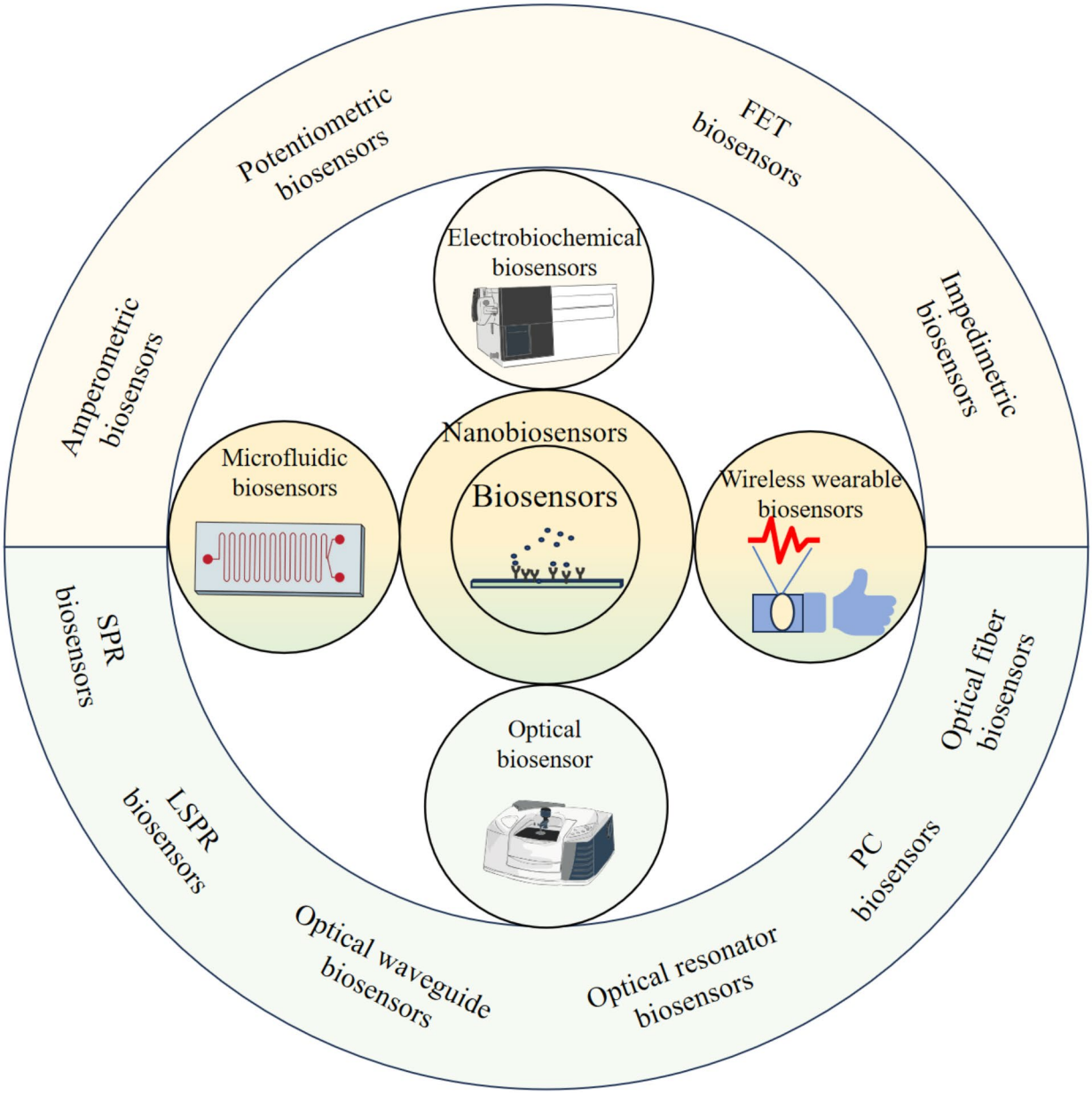

Fig. 3 Classification and principles of Biosensors. Biosensors commonly used in the medical field are primarily categorized into electrochemical biosensors and optical biosensors based on their working principles. By integrating with different sensing technologies, they can include specialized subtypes such as microfluidic biosensors, wireless wearable biosensors, and nanobiosensors. Specifically, electrochemical biosensors can be classified into amperometric, potentiometric, FET-based, and impedimetric. Optical biosensors comprise SPR biosensors, LSPR biosensors, optical waveguide biosensors, optical resonator biosensors, PC biosensors, and optical fiber biosensors.

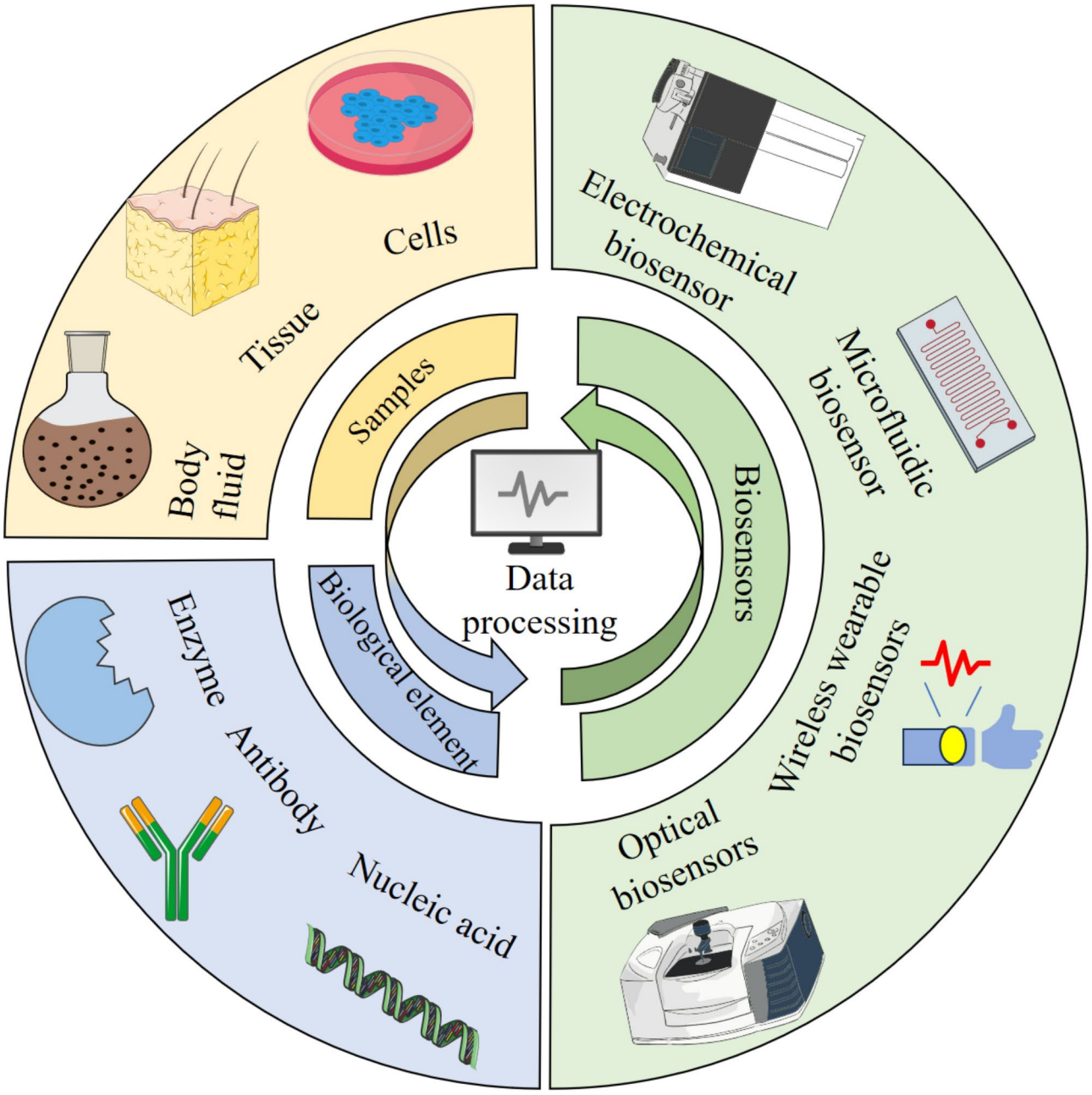

Fig. 4 The basic principle of biosensors. The commonly used detection samples for biosensors mainly include cells, tissues, and body fluids. The target substances in the samples bind with the biorecognition elements of the sensor, such as enzymes, antibodies, and nucleic acids, to produce physical or chemical reactions. Then, the sensor's transducer converts these reactions into measurable signals, such as electrical or optical signals. Finally, after data processing, the detection of the target substances is achieved

receptors) interact specifically with target analytes (molecules or ions), such as the combination of enzymes with substrates, antibodies with antigens, and nucleic acids with complementary strands. This biological recognition event causes changes in the chemical or physical state of the biological receptor, such as enzymatic catalysis reactions, the formation of antibody-antigen complexes [63]. These changes can be converted into measurable electrical signals by electrochemical conductive elements. Electrochemical conductive elements (such as electrodes) detect electrical signal changes related to biological recognition events, which may include changes in current, potential, conductance, or charge. The electrical signals are usually amplified and detected and recorded by electrochemical instruments for quantitative analysis. By analyzing the changes in electrical signals, the presence and concentration of target analytes can be determined [64].

The common electrochemical conduction modes of electrochemical biosensors include amperometry, potentiometry, field-effect transistor (FET), and impedancemetry [64]. Amperometry detects the oxidation or reduction of electroactive analytes by measuring the current flowing through the working electrode at a constant potential, with the current size being proportional to the concentration of the analyte [65]. Potentiometry detects changes in ion concentration by measuring the potential difference between two electrodes, often using ion-selective electrodes (ISEs). The potential change is proportional to the logarithm of ion concentration, following the Nernst equation [66]. FETs detect changes in ion concentration by utilizing changes in the gate voltage of FETs, such as ion-sensitive field-effect transistors (ISFETs) [67]. Impedimetry, also known as conductometric sensors, detects the impact of biorecognition events on charge transfer at the electrode surface by measuring the impedance changes of the alternating current signal between electrodes [68]. The design and application of electrochemical biosensors depend on selecting the appropriate biological recognition elements and electrochemical conduction modes to achieve high sensitivity and high selectivity detection of specific analytes.

Optical biosensors

Optical biosensors are sensors that combine a biological recognition unit with an optical signal transduction unit, capable of detecting various biomolecules such as DNA, RNA, proteins, sugars, and other chemical substances [69]. Optical biosensors can be categorized into different types based on detection methods and principles, including surface plasmon resonance (SPR) based biosensors, localized surface plasmon resonance (LSPR) based biosensors, optical-waveguide-based biosensors, optical-resonator-based biosensors, photonic crystal (PC) based biosensors, optical-fiber-based biosensors [70].

SPR biosensors are based on the interaction between the oscillation of free electron density on metal surfaces (such as gold or silver) and incident light waves, which generates SPR phenomena. Changes in the angle or polarization of the incident light can alter the resonance conditions, thereby changing the intensity or phase of the reflected light. These changes are correlated with changes in the refractive index of the sample, making it possible to detect binding events of biomolecules [71]. LSPR biosensors are based on the localized SPR phenomenon of metal nanoparticles (such as gold or silver nanoparticles). When the frequency of the incident light matches the collective oscillation frequency of free electrons in the metal nanoparticles, strong light absorption occurs, leading to localized SPR. This resonance phenomenon can be used to detect the binding and interactions of biomolecules [72].

Optical waveguide-based biosensors detect changes in the optical waveguide modes, such as variations in light intensity, phase, and wavelength, caused by the interaction of biomolecules with the surface of the optical waveguide, to identify and quantitatively analyze biomolecules [73]. Evanescent waves are electromagnetic fields that exponentially decay near the surface of an optical fiber, and when light propagates through the fiber, evanescent waves are produced that interact with the surrounding medium. By detecting these changes, information about biomolecules can be obtained [74]. Biosensors based on optical resonators utilize the optical resonance phenomenon to highly sensitively detect refractive index changes caused by biomolecular interactions. Fabry–Perot interferometer-based (FPI) biosensors leverage the optical properties of the resonant cavity to highly sensitively detect biomolecular interactions by monitoring changes in the interference pattern caused by biomolecular binding [75].

PC based biosensors utilize the bandgap characteristics of PC for specific wavelengths of light. When biomolecules bind to the surface of the PC, they change its refractive index, thereby altering the bandgap structure of the PC. By monitoring these changes, the binding events of biomolecules can be detected [76]. The principle of fiber optic biosensors is to use optical fibers as a medium for the transmission and modulation of light signals. They achieve biological detection by detecting changes in optical characteristics caused by biomolecular interactions as light propagates through the optical fibers [77].

Additional specialized biosensors utilizing optical and electrical sensing

Microfluidic biosensors

The working principle of microfluidic biosensors is based on microfluidic technology, which involves the manipulation and transport of extremely small volumes of fluids in channels at the micrometer scale. Microfluidic biosensors mainly consist of microfluidic channels, biosensor elements, readout systems, and fluid control systems. These biosensors can be integrated with other technologies such as electrochemistry and optics to achieve more complex detection functions [78]. Compared to other biosensors, microfluidic biosensors are characterized by miniaturization, allowing detection in extremely small volumes, which reduces the consumption of samples and reagents. The short channels and rapid mixing capabilities in microfluidic devices shorten the reaction time, enabling rapid detection [79]. Microfluidic devices allow for precise control of reaction conditions, such as temperature and pH, and precise control of fluid flow, which helps to improve the selectivity for specific analytes. The large surface area-to-volume ratio of microfluidic channels enhances the sensitivity of the biosensors. They can

also integrate multiple functions, such as sample pretreatment, reaction, separation, and detection, achieving automation and integration [80]. Due to the low consumption of samples and reagents, and the integration that reduces the need for additional equipment, microfluidic biosensors are more cost-effective [81]. Furthermore, microfluidic devices can be designed in various shapes and functions according to detection needs, combined with nanomaterials and intelligent systems, such as paper-based devices [82].

Wireless wearable biosensors

Non-invasive wearable chemical sensors analyze the chemical components in human biofluids, such as tears, saliva, sweat, and interstitial fluid, through wireless sensing technology to monitor health status. These biofluids contain various biomarkers that can reflect health conditions and physiological changes [83]. Sensors convert the chemical or biological signals of biomarkers into measurable signals. Optical sensors detect biomarkers using their optical characteristics, such as color, fluorescence, or absorbance, and are known for their good selectivity, making them suitable for detecting target species in complex samples [84]. Electrochemical sensors are based on electrochemical principles, such as changes in potential, current, or conductance, to detect biomarkers. They are suitable for trace analysis of analytes in non-complex matrices and have the advantages of rapid response and ease of operation [85, 86]. Wireless sensors integrate wireless communication modules to enable real-time transmission of monitoring data, allowing the collected information to be synchronized with mobile terminal devices for subsequent processing and analytical operations [87]. They may use technologies such as radio-frequency identification (RFID), Bluetooth, or near field communication (NFC) for data transmission [88]. Many non-invasive wearable chemical sensors utilize energy harvesting techniques, such as piezoelectric, thermoelectric, or triboelectric nanogenerators, converting mechanical, thermal, or light energy into electrical power to power the sensors. These principles of non-invasive wearable chemical sensors work together, enabling real-time and continuous monitoring of physiological and biochemical parameters without invasive procedures, supporting personal health monitoring and disease diagnosis [89, 90].

Nanobiosensors

Nanomaterials, such as nanoparticles and quantum dots, can enhance the signal response of sensors and achieve more effective binding with biomolecules. A nano biosensor is a device that detects biomolecules or chemical substances, combining biological recognition elements with nanoscale signal transduction components. These sensors can convert the recognition events of biomolecules into measurable signals, such as electrical and optical signals [59, 91]. Electrochemical nano biosensors use nanomaterials (such as nanoparticles, nanotubes, nanowires) to enhance electron transfer, improving sensitivity and selectivity [92, 93]. Optical nano biosensors utilize the optical properties of nanomaterials (such as quantum dots, metal nanoparticles), such as fluorescence, SPR, to detect biomolecules [94]. Piezoelectric nano biosensors use piezoelectric materials (such as ZnO nanowires) to convert mechanical pressure into electrical signals for detecting mechanical changes in cells or biomolecules [95]. Field-effect nano biosensors utilize the FET structure of semiconductor nanomaterials to detect charge changes caused by biomolecules [96]. Fluorescent biosensors utilize the excellent optical properties of silicon quantum dots to detect fluorescence changes caused by biomolecules [97]. The application of nanotechnology in biosensors can significantly enhance the sensitivity and selectivity of the sensors, and different nanomaterials and sensing mechanisms enable the design and optimization of nanosensors for various application needs.

Application of biosensors in PH

Currently, research on biosensors in PH remains relatively limited but demonstrates significant potential. Major categories include implantable hemodynamic biosensors, biomarker biosensors, breath biosensors, and wireless wearable biosensors (Fig. 5). These diverse sensors offer complementary advantages in terms of detection dimensions, applicable scenarios, and technical characteristics, collectively establishing a technological foundation for constructing a multimodal PH monitoring system (Table 2).

Implantable hemodynamic biosensors

Biosensors have been less studied in PH but show great potential. Implantable hemodynamic sensors, which integrate electrochemical sensors with wireless sensing technology, hold great promise in the management of PH. By detecting parameters such as blood flow velocity, pressure, and vascular resistance, these sensors can assist physicians in assessing changes in patient conditions, monitoring therapeutic effects, and adjusting treatment plans more precisely. This allows for the optimization of drug dosages to achieve better symptom control and disease management [98]. Implantable monitoring devices have been used in patients with chronic heart failure, post-cardiac surgery, and after implantation of left ventricular assist devices (LVADs), and are being considered for use in patients with PH.

The CardioMEMS™ HF system is an implantable hemodynamic monitor that was previously used only in NYHA Class III heart failure patients and has shown good safety

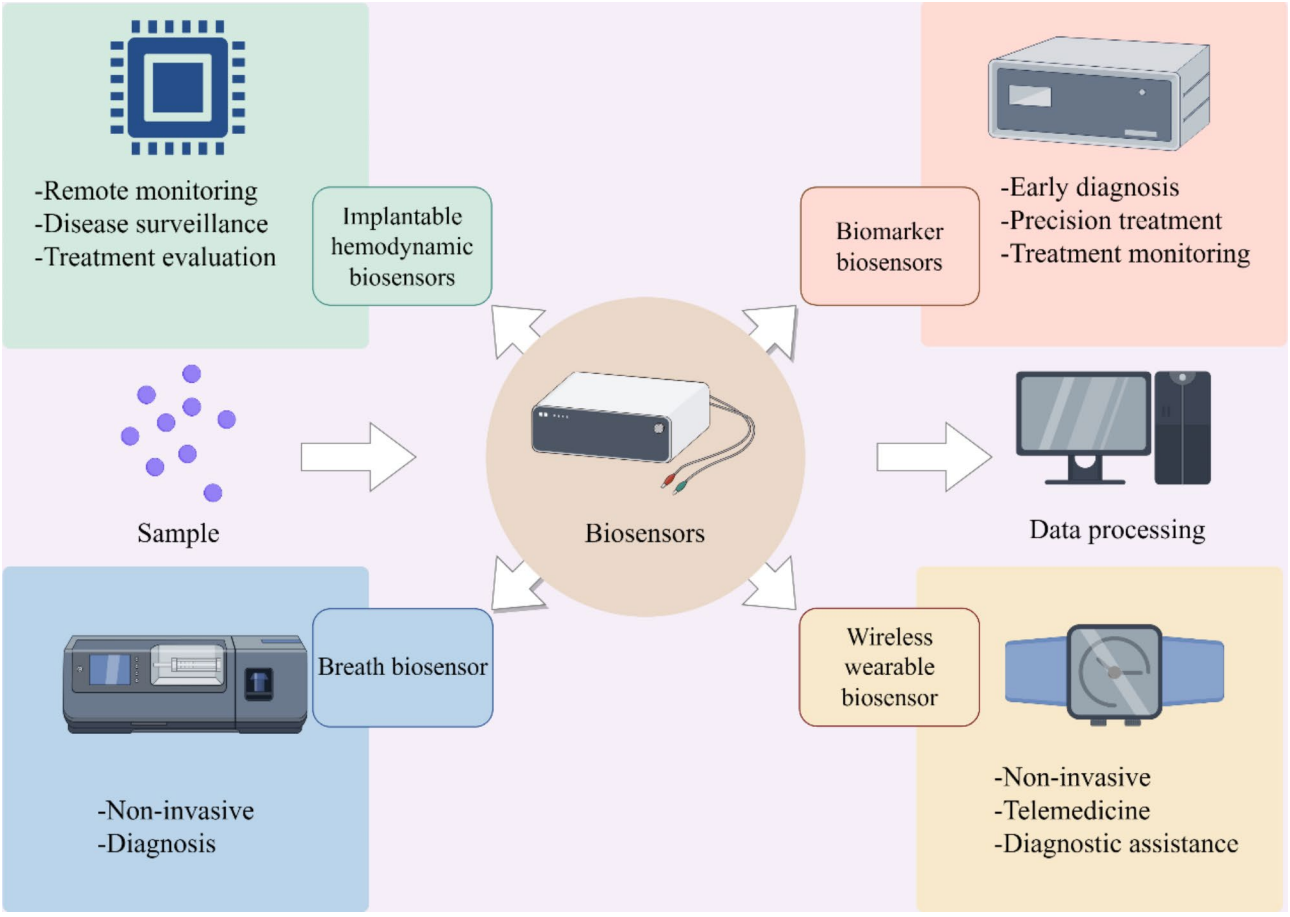

Fig. 5 Applications of biosensors in PH. Biosensors applied in PH primarily include implantable hemodynamic biosensors, biomarker biosensors, breath biosensors, and wireless wearable biosensors. Among these, implantable hemodynamic biosensors play a significant role in remote disease monitoring, early warning of disease progression, and dynamic evaluation of treatment efficacy. Biomarker biosensors provide technical support for early diagnosis, precision therapy, and treatment monitoring by detecting specific biomarkers. Breath biosensors, leveraging their non-invasive detection characteristics, represent a promising new approach for analyzing respiratory metabolites. Wireless wearable biosensors, with their non-invasive advantages, demonstrate innovative applications in auxiliary diagnosis and telemedicine. By Figdraw

Table 2 Characteristics of biosensors applied in PH

Biosensors	Basic principle	Core technologies	Detection parameters
CardioMEMS	A percutaneously implanted pressure biosensor in the pulmonary artery branch monitors hemodynamic parameters	Biocompatible materials, miniaturized circuitry, wireless power transfer	PA waveform、HR、PASP、PADP、mPAP
BNP biosensors	The concentration of BNP in biological samples via biosensor	Electrochemical or optical sensing technology, nanomaterial signal amplification	BNP concentration
miRNA biosensors	Specific disease-associated miRNAs detected via biosensors	CRISPR/Cas-based recognition, SPR, nanopore sequencing	Specific miRNA expression levels
e-Nose	Detection of specific gas biomarkers via biosensors	Sensor array, pattern recognition algorithm	Non-invasive gas biomarkers
Wireless wearable biosensor	A multi-module integrated biosensor system for comprehensive assessment of physical mobility and cardiac function	Wireless communication technology, IMU, biosensing technology	HR、HRV、RR、SpO_2、TFC、BP

[99]. The CardioMEMS device is a percutaneously delivered pressure sensor placed in the branch of the pulmonary artery and continuously monitored remotely via a wireless detection system for pulmonary artery pressure. The sensor collects hemodynamic data, including pulmonary artery pressure waveforms, heart rate, and systolic, diastolic, and mean pulmonary artery pressures, which can be securely transmitted to the doctor's clinic,

hospital, or patient's home [100, 101]. The hemodynamic parameters measured by the CardioMEMS system are correlated with the distance of the 6-minute walk test (6MWT), indicating that these parameters can serve as early indicators of treatment response. By providing daily cardiovascular measurement data through the CardioMEMS system, doctors can remotely monitor disease progression, guide treatment, and detect or prevent early decompensation. Although the CardioMEMS device is not specifically designed for PH, it is valuable for real-time monitoring of pulmonary artery pressure in PH patients, especially when estimating cardiac output [102, 103]. However, before it can be widely used to guide the treatment of patients with severe PH and right heart failure, larger clinical trials are needed.

Traditional implantable devices based on the von Neumann architecture face insurmountable challenges when processing large amounts of biological data due to computational bottlenecks. Memristors integrate memory sensing and computing capabilities, effectively eliminating computational bottlenecks, and with the advantages of low power consumption and miniaturization, they have become one of the most promising products in implantable health monitoring devices [98]. A new type of memristor with an Ag/MnO2/BaTiO3/FTO structure has shown great potential in pulmonary artery pressure monitoring. This study constructed the memristor using magnetron sputtering and encapsulated it with polydimethylsiloxane (PDMS), demonstrating excellent stability and biocompatibility. It is also capable of achieving feedback responses across different pressure ranges and simulating the reduction of noise in pressure signals through the design of logical judgment circuits. The study showcases the potential of implantable memristors in pulmonary artery pressure monitoring and provides new ideas for the design of efficient, real-time, and reliable implantable pressure monitoring devices [104].

Biomarker-driven biosensor

BNP biosensors

The detection of biomarkers by biosensors is of great significance in the diagnosis and therapeutic monitoring of PH. BNP is a marker of ventricular overload in patients with PH, and sensors for detecting BNP are important tools for the diagnosis of PH [105]. Sensors for detecting BNP include both electrochemical and optical sensors, but due to its low concentration in the blood and short half-life, sensitive detection of BNP is a common challenge for both types of sensors [106].

With the updating of sensor materials and technological advancements, especially the use of nanomaterials, the sensitivity of BNP biosensors is increasing. B/N co-doped graphene oxide (GO) hydrogel (BN-GO) is used as the channel material for a FET biosensor targeting BNP. This enables the sensor to detect BNP in just 2 min, with a low limit of detection down to 10 aM, and a wide linear detection range from 10 aM to 1 μM, spanning over 11 orders of magnitude. It also exhibits great selectivity and minimal response to K+, OH- ions, and human epidermal growth factor receptor 2 (HER2) protein [107]. SPR-based biosensors, utilizing functionalized gold nanoparticles (GNPs-Apt) and antibody-modified magnetic plasmonic nanoparticles (MNPs-Ab), can achieve dual screening for BNP. This SPR biosensor has high selectivity, a wide dynamic response range (100 fg/mL to 10 ng/mL), and a low detection limit (28.2 fg/mL) [108].

Nanopore sensors provide an antibody-free method to measure various natriuretic peptides at the single-molecule level and can distinguish between natriuretic peptides, linear analogs, and even minor structural damages caused by a single chemical bond breakage, with an ultra-wide detection range [109]. Amorphous CoSnSx offers more active sites and excellent electrocatalytic activity, and the use of magnetic materials simplifies the sensor preparation process and enhances its stability. Electrochemical immunosensors made with amorphous bimetallic sulfides (x) as signal amplifiers and magnetic materials have high sensitivity, a wide linear response range, and a low detection limit [110]. Quantum dots, with their large surface area and good electronic properties, can enhance electron transfer and signal amplification, improving the sensitivity and selectivity of sensors. Quantum dot-shaped sensors can achieve rapid, sensitive, and specific detection of BNP [111]. The development of new sensor technologies is continuously improving the efficiency and accuracy of BNP detection, which is crucial for the early diagnosis and management of PH.

MicroRNA biosensors

In the context of PH, the expression patterns of specific miRNAs are altered, and these changes can serve as diagnostic markers for the disease. Therefore, sensitive and accurate detection of PH-related miRNAs is of great significance for the early diagnosis of PH [112]. The miRNA biosensor utilizes CRISPR/Cas-based molecular recognition or nanomaterial-enhanced signal amplification technologies, employing complementary nucleic acid probes to specifically capture target miRNA and convert it into fluorescent/electrochemical signals for highly sensitive detection [113]. miRNA electrochemical biosensors utilize specific miRNAs as biomarkers, which means they can target specific genetic signatures, thereby reducing false positives and false negatives, and enhancing the accuracy of diagnosis [114]. Additionally, the stability of miRNAs is an advantage in their use as biomarkers, as stable biomarkers contribute to the reliability of detection results [115]. Although the detection of miRNA is challenging due to their small size, high sequence similarity,

and low abundance in biological fluids, the development of sensing technologies and the use of nanomaterials are expected to enable miRNA sensors to play a greater role in precision medicine and early disease diagnosis [114, 116].

Breath biosensors

Breath sensors, which utilizes various biosensors to detect gaseous biomarkers such as exhaled volatile organic compounds (VOCs), is one of the most promising non-invasive diagnostic methods [117]. The pathological physiological processes and detectable VOCs in exhaled breath have been proposed as non-invasive biomarkers for PH, indicating the potential of breath analysis in the field of PH [118]. Breath analysis utilizes sensors to detect and analyze these gaseous biomarkers. Sensors can recognize specific gas molecules and produce measurable signal changes based on their interactions with gas molecules, such as adsorption and chemical reactions [119]. In breath analysis, it is typically not a single VOC that plays a role but rather a pattern of VOCs (breath print) associated with specific disease states [119, 120]. The collected sensor data usually requires analysis by statistical and machine learning algorithms to identify and differentiate the characteristic gas patterns of different diseases [121]. PH has been shown to be detectable and classifiable through breath analysis and sensor arrays [120]. The use of nanomaterials enhances the sensitivity and selectivity of sensors due to their high surface area-to-volume ratio and tunable physicochemical properties, enabling the sensors to more effectively detect low concentrations of gaseous biomarkers [122].

Electronic nose (e-Nose) technology, which mimics the natural olfactory system, uses sensor arrays and pattern recognition algorithms to identify specific gas patterns, which is of great assistance for disease diagnosis. However, e-Nose technology is generally used as an auxiliary diagnostic tool, and its results often need to be combined with clinical symptoms and other diagnostic tests to ensure accuracy and reliability [123]. Currently, the application scope of e-Nose technology is continuously expanding, and with in-depth research, it may be used for the detection of PH in the future.

Wireless wearable biosensors

Wireless wearable biosensors offer innovative solutions for PH management, with their core value lying in real-time monitoring of physiological parameters. This capability provides objective data for assessing patients' activity capacity and cardiovascular function, aiding clinical judgment in disease severity evaluation, treatment efficacy monitoring, and personalized therapeutic decision-making [124]. These devices can non-invasively monitor multiple physiological indicators including heart rate, heart rate variability, respiratory rate, arterial oxygen saturation, thoracic fluid content, and blood pressure [125]. When integrated with accelerometers and inertial measurement units (IMUs), they can record activity metrics such as step count, exercise intensity, and duration. These devices can be positioned at various body locations (wrist, hip, thigh, chest) to capture diverse mobility data [126]. Research demonstrates that remote 6MWT using chest-worn accelerometers combined with heart rate monitoring are feasible and safe, enabling objective assessment of exercise tolerance in PH patients while providing supplementary approaches for telemedicine and therapeutic research [126]. Although current smart wearables show potential in cardiovascular disease management, technical and clinical integration challenges remain. With advancements in sensor and computational technologies, future development should focus on refining evaluation frameworks and regulatory policies to enhance clinical adoption, promote telemedicine advancement, and reduce healthcare costs [127].

Prospects and challenges

The rapid development of biosensors has been widely applied to various diseases, including PH. The types of biosensors currently used for PH include electrochemical biosensors, optical biosensors, microfluidic biosensors, and wireless biosensors. Despite this, core diagnostic indicators for PH, such as pulmonary artery pressure and PVR, still lack biomarkers that are both highly specific and sensitive. Currently, BNP and NT-proBNP are widely used to evaluate right heart function, risk stratification for PAH, and predict prognosis, but they still have limitations, such as being significantly affected by age and renal function [128]. The development of biosensors for PH faces challenges from both the disease itself, including the lack of specific biomarkers for PH, and from the biosensors themselves, including improving detection sensitivity and specificity, ensuring long-term stability and reliability, reducing costs, simplifying data processing, enhancing patient acceptance, and meeting regulatory approval requirements [129].

Therefore, developing new biomarkers and improving sensing technology are important research directions for the future. miRNAs have great potential in the early diagnosis of PH due to their high specificity and stability [114]. The use of nanomaterials can greatly enhance the sensitivity of biosensors [130]. Multimodal sensors can detect multiple biomarkers or physiological parameters simultaneously, providing more comprehensive diagnostic information for diseases [61, 131]. The application of artificial intelligence technology can improve the accuracy and efficiency of data analysis for biosensors [132, 133]. In future research on sensors for PH, the research direction will focus on utilizing nanomaterials to achieve

miniaturization and integrated design of sensors, developing multimodal sensors, and combining artificial intelligence algorithms for data analysis to detect sensitive and accurate PH-related miRNAs.

Conclusion

PH faces challenges in clinical detection such as difficulty in early diagnosis, large heterogeneity, lack of specific biomarkers, and insufficient monitoring of treatment response, while the development of biosensors offers new possibilities for the early diagnosis, real-time monitoring, and personalized treatment of PH. Although there are still challenges in practical applications, such as insufficient technical stability and reliability, cost-effectiveness, and clinical validation, biosensors show great potential in improving detection sensitivity and specificity, and achieving non-invasive monitoring. The future direction of biosensors in PH should focus on the development of new biomarkers, enhancing the performance and integration of sensors, and promoting interdisciplinary collaboration to achieve more precise PH management and treatment.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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