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Natriuretic Peptides as Key Regulators and Biomarkers in Cardiovascular Disorders

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***Abstract*— Currently, cardiovascular diseases (CVDs) remain the foremost cause of death and disability across the globe. This is due to the complexity of the underlying biological processes that drive CVDs, including endothelial dysfunction, dysfunction of the heart muscle, and dysregulation of the neurohormones (hormones that affect the nervous system) that affect heart. To maintain cardiovascular homeostasis, natriuretic peptides (NPs), specifically ANP and BNP function to help control blood pressure, fluid status, and vessels. NPs achieve these physiological effects through their regulation of cGMP, which is involved in the modulation of vasodilation, natriuresis, and diuresis. In addition, NPs oppose the RAAS and sympathetic nervous system, thus limiting myocardial remodeling and preventing CVD progression. ANP and BNP and their inactive forms, NT-proBNP, have become reliable clinical biomarkers for diagnosing patients, providing risk stratification, and determining prognosis for CVDs. Elevated levels of NP indicate myocardial stress, ventricular dysfunction, and increased risk of a negative clinical outcome. Furthermore, research suggests that NPs may have therapeutic benefits in modulating the neurohormones to improve CVD outcomes. This article summarizes the key aspects of the structure, physiological functions, and molecular mechanisms of NPs and presents evidence to support their role as both clinically significant biomarkers and physiologically necessary regulators of CVDs.**

***Keywords*— *CVD, ANP, BNP, CAD, natriuretic peptides* .**

I. INTRODUCTION

Cardiovascular diseases (CVDs) comprise many illnesses affecting the heart and blood vessels and are the leading contributors to global morbidity and mortality. As reported in 2022 by the World Health Organization (WHO), there were 19.8 million CVD deaths worldwide that year; this equated to an estimated 32% of all deaths. The leading causes of these CVD deaths were due to myocardial infarction (heart attack) and cerebrovascular accident (stroke). More importantly, 75% or more of these deaths occurred in low- and middle-income countries, illustrating a major global inequity in healthcare access [1]. Beyond the number of people who die, CVDs also create many years of disability worldwide; this can equate to millions of disability-adjusted life years (DALYs) for people who have suffered from CVDs or caused death from them, resulting in a decrease in quality of life for millions of people globally [2] . Also, while CVD • death rates adjusted for age structure have decreased over the last few decades, the total number of cases is continuing to rise, due largely to population growth, increasing life expectances, and ongoing exposure to potential risk determinants (such as hypertension, obesity, diabetes, and an unhealthy lifestyle)[3] . Projections continue to indicate that the global burden of CVDs will continue increasing at an increasing rate over the next several decades, emphasizing the urgent need for improved strategies for preventing, diagnosing, and managing CVDs by early detection of at-risk individuals [4].

Hormonal regulation is critical in regulating the cardiovascular system and maintaining cardiovascular homeostasis via multiple systems of endocrine hormones that regulate elements such as blood pressure, fluid balance, vascular tone, and cardiac function. These key hormonal systems include: the renin-angiotensin-aldosterone system (RAAS), vasopressin, endothelin, and natriuretic peptides, which all work together to create a complex system of regulation and maintain hemodynamic stability. The RAAS represents a major vasoconstrictor and sodium-retaining system; it works to increase blood pressure and blood volume by acting on angiostensin II and aldosterone. Vasopressin also contributes to blood pressure through the kidneys' increased retention of water and causing vasoconstriction [5]. On the contrary, natriuretic peptides have opposing effects by causing vasodilation and promoting natriuresis and diuresis, therefore decreasing the preload and afterload to the heart [6]. Endothelin is also among the most powerful agents causing vasoconstriction produced endogenously and is essential in regulating vascular tone and

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vessel remodeling [7]. The relative balance of these two systems (vasoconstrictor vs. vasodilator) is required to facilitate normal cardiovascular function, and dysregulation of the balance between these two systems is involved in the pathogenesis and progression of cardiovascular disease. Examples of pathology related to the disruption of this balance are hypertension and heart failure [1].

The natriuretic peptides (particularly ANP and BNP) are crucial components of the pathophysiology associated with the cardiovascular disease by providing a mechanism for counterregulation of the neurohormonal system when stimulated. The severity of the disease, such as increased cardiac wall stress, leads to elevated secretion of ANP and BNP, which reflects severity[6]. Functions of the natriuretic peptides include promoting vasodilation, promoting natriuresis, and inhibiting RAAS, which all result in reduced preload and afterload to the heart. In clinical practice, the utility of their respective circulating levels as diagnostic and prognostic biomarkers is well established, particularly for the management of heart failure [8].

Although there are many studies completed to date, it is still unknown how natriuretic peptides interact with other neurohormones and how they contribute to heart disease (cardiovascular pathology). This review will provide a summary of what is known about the normal function of ANP and BNP, how they function abnormally in heart disease, how they can be used as markers for diagnostic and prognostic purposes, and suggestions for their use in patients with heart disease (therapeutic uses). In addition, by summarizing recent literature findings regarding ANP and BNP, we will provide insight into what remains to be learned and will hopefully give direction for future research in cardiovascular medicine.

II. Definition and Classification of Cardiovascular Diseases

Cardiovascular disease is a term used for various disorders that affect the heart and circulatory system. In many cases, it involves pathological changes in the coronary arteries, where the accumulation of atherosclerotic plaques leads to narrowing of the vessel lumen and restriction of blood flow to the myocardium. This reduction in coronary perfusion may result in clinical manifestations such as chest pain and, in severe cases, myocardial infarction [9].

Cardiovascular Disease (CVD) is also defined very broadly as any type of disorder caused by a structural or functional or electrical abnormality affecting normal functioning within the circulatory system. CVD may have an impact on many different parts of the body, such as the heart (myocardium), coronary arteries, peripheral arteries or veins, and cerebrovasculature. As such, CVD can lead to an overall reduction in the amount of blood circulated through the body, or in the amount of oxygen delivered through the blood supply, and ultimately, in the disruption of metabolic processes in tissues [1- 10].

There are four main categories of cardiovascular disease. Coronary heart disease (CAD) causing angina, myocardial infarction, or heart failure) results from decreased blood supply to the heart muscle due to blockage of the coronary arteries; therefore, putting more strain on the heart and resulting in potential angina, myocardial infarction, or heart failure. Cerebrovascular diseases, including stroke and transient ischemic attack (TIA), occur as a result of impaired or interrupted blood flow to the brain. Peripheral arterial disease is caused by reduced circulation to the limbs, often presenting with symptoms such as leg pain, muscle weakness, hair loss, and chronic ulcers. Aortic diseases involve pathological conditions affecting the aorta, the largest artery in the body, which are often asymptomatic but may lead to life-threatening complications such as rupture and severe internal bleeding [11].

III. Types of Cardiovascular Disorders

Cardiovascular disease (CVD) is a broad term encompassing several disorders affecting the heart and vascular system, including coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease [12].

A. CAD

CAD, commonly referred to as ischaemic heart disease, coronary heart disease (CHD), atherosclerotic heart disease, or atherosclerotic cardiovascular disease, is one of the most common forms of CVD [12]. The condition is a chronic inflammatory disease resulting from atherosclerosis, characterised by the formation and proliferation of lipid-laden plaques in the coronary arteries. Myocardial infarction, unstable angina, stable angina, and sudden cardiac death represent various clinical presentations of CAD [13]. The underlying pathological process involves the narrowing or occlusion of coronary vessels due to plaque accumulation, leading to reduced myocardial perfusion. This diminished blood supply compromises oxygen delivery to cardiac tissue and may ultimately result in ischemic symptoms or irreversible myocardial damage [14].

B. Cerebrovascular Diseases

Cerebrovascular diseases comprise a heterogeneous group of disorders that affect the cerebral vasculature, leading to impaired intracranial blood circulation and subsequent brain tissue injury. These conditions primarily include ischemic stroke, intracerebral hemorrhage, transient ischemic attack (TIA), and subarachnoid hemorrhage, among others. The underlying mechanisms involve either vascular occlusion, resulting in reduced cerebral perfusion, or vascular rupture, leading to hemorrhagic damage. Collectively, these events disrupt oxygen and nutrient delivery to brain tissue, contributing to neurological deficits and, in severe cases, permanent disability or death [15].

C. Peripheral Vascular Disease

Peripheral arterial disease (PAD) is a long-term and slowly worsening atherosclerotic disease that is marked by significant narrowing or blockage of the peripheral arteries. PAD is a type of peripheral vascular disease. The most affected anatomical sites are the abdominal aorta, the iliac arteries, and the lower extremities, but the upper extremities may be affected as well. Due to the strong relationship with greater risks of both fatal and non-fatal outcomes from cardiovascular disease such as stroke and myocardial infarction, peripheral artery disease is considered an equivalent to other forms of cardiovascular disease. PAD is a systemic, debilitating condition that severely reduces

functional ability and quality of life, requiring detailed management from various specialties to optimize patient outcomes [16].

IV. PATHOPHYSIOLOGY OF CARDIOVASCULAR DISORDERS

A. Vascular Dysfunction :

Damage to endothelial cells is the primary cause of vascular dysfunction. Vascular dysfunction contributes to the development of cardiovascular diseases. The endothelial cells control the blood vessel's ability to widen (vasodilation), inflammation, thrombosis, and how easily substances pass through the walls of the blood vessels and are responsible for maintaining homeostasis. Endothelial cells also produce a chemical called nitric oxide (NO) which prevents platelet clumping or aggregation, and helps to widen blood vessels. When there is an alteration in the endothelial cells through reduced amounts of NO and increased production of pro-inflammatory cytokines and reactive oxygen species as a result of many major risk factors such as high blood pressure (hypertension), diabetes and oxidative stress, this leads to vasoconstriction, produces inflammation and promotes clotting conditions. This creates an environment that promotes the progression of atherosclerosis and other cardiovascular diseases. When there is chronic injury to the endothelial cells, it greatly increases the risk of experiencing an ischemic episode, which contributes to the remodeling process of the blood vessels and plaque formation [17-18].

The prevalence of sodium imbalance is a major factor in the development of vascular dysfunction and many cardiovascular diseases. The elevation of extracellular volume due to elevated sodium concentrations increases the volume of fluid in that space, consequently increasing the pressure on the circulatory system and providing mechanical stress to the vascular wall. At the endothelial level, the excess sodium concentration in this space decreases the availability of nitric oxide, increases the production of ROS, and contributes to the degradation of endothelial function, ultimately promoting vascular stiffness and the inflammatory process. These pathological mechanisms are key contributors to the initiation and progression of both hypertension and atherosclerosis. The compensatory response to excess sodium in this unit is the release of natriuretic peptides, such as atrial natriuretic peptide and brain natriuretic peptide, which function to promote sodium excretion, induce vasodilation, and decrease resistance within the vascular system. However, if the sodium excess is present for a long period of time or there is extreme sodium excess, this compensatory mechanism may become overwhelmed and thus result in disease progression. Thus, the disruption of sodium homeostasis has a strong association with impairments of the vascular system and demonstrates the importance that natriuretic peptides have in maintaining cardiovascular homeostasis [19- 20].

B. Myocardial Remodeling:

Cardiovascular diseases involve an important pathogenic process, myocardial remodelling, which is characterised by structural changes and functional impairment within the heart resulting from repeated injury or chronic modifications to heart muscle tissue due to long-term stress or injury. Hypertension, myocardial infarction and volume overload are examples of the various insult events involved with myocardial remodelling. Ventricles undergo morphological and functional dimensional remodelling due to myocardial hypertrophy, apoptosis, extracellular matrix remodelling, and fibrosis. Myocardial tissue's ability to undergo cardiomyocyte hypertrophy initially allows for positive remodelling that then becomes maladaptive with prolonged remodelling, resulting in ventricular dilation, decreased contractility, and eventually progression to heart failure. The nephron activation of neurohormonal regulatory pathways (e.g., the renin–angiotensin–aldosterone system), oxidative stress, and persistent inflammation are molecular mechanism based reasons for the development of cardiac fibrosis and disordered myocardial function. These changes represent an important pathophysiological process connecting the progression of heart failure to other cardiac diseases [21-22].

C. Neurohormonal Dysregulation:

Neurohormonal dysregulation significantly promotes the development and progression of cardiovascular diseases. It is marked by the prolonged activation of the sympathetic nervous system and the RAAS, leading to enhanced vasoconstriction, salt retention, and raised blood pressure. This continuous stimulation serves as a compensatory method to sustain cardiac output. Prolonged stimulation, however, becomes maladaptive, leading to endothelial dysfunction, inflammation, and vascular remodelling. Moreover, neurohormonal dysregulation increases oxidative stress and worsens cardiovascular damage, consequently associating various illnesses, such as hypertension and heart failure, with negative clinical outcomes [23].

V. GLOBAL BURDEN AND EPIDEMIOLOGY OF CVDS

Cardiovascular diseases (CVDs) constitute a significant and escalating worldwide health challenge, with both frequency and incidence have markedly risen in recent decades.

A. Prevalence and Incidence

According to Data obtained from the Global Burden of Disease study indicate that the number of individuals diagnosed with cardiovascular disease increased by almost half between 1990 and 2019 (approximately 271 million vs approximately 523 million) due to several factors including population growth, increasing age, and increased rates of modifiable risk factors, including hypertension, obesity, and sedentary lifestyles. Additionally, the prevalence of cardiovascular disease is highly variable across different regions of the world, with some regions reporting prevalence rates of more than 11,000 cases per 100,000 of the population. Worldwide, ischaemic heart disease and stroke are considered the most common types of cardiovascular disease and continue to have very high rates of incidence [3].

B. Mortality and Morbidity Trends

Past research on the Global Burden of Disease have studied temporal trends to find that the total global death rate

from cardiovascular disease was 12.1 million in 1990 and increased to 18.6 million in 2019, based on the fact that the number of deaths from CVD in 2022 corresponds to about 19.8 million people, more than 33% of global deaths [1] and, therefore, making CVD the leading cause of death globally. The increasing global deaths that occur, even though age-standardized death rates have decreased approximately 34.9% since 1990 and improved healthcare systems have produced lower mortality rates, can be attributed primarily to changes in demographic trends, particularly that of a growing and ageing population [1,24]. There is an anticipated increase between 2025 - 2050 of 90.0% in the prevalence of CVDs, a crude death rate increase of 73.4%, and an increase in the number of crude disability adjusted years (DALYs) from CVDs of 54.7% by the year 2050. Therefore, the number of cardiovascular deaths is projected to exceed 35.6 million by 2050 from a total of 20.5 million CVD deaths in 2025 [4].

VI. RISK FACTORS

A. Modifiable Risk Factors

1) Hypertension: Hypertension is frequently disregarded and leads to considerable cardiovascular incidents, making it a silent killer. Hypertension is characterised by a sustained or increased blood pressure of 140/90 mmHg, which is further categorised into distinct stages. Blood pressure is the force exerted by the heart as it drives blood against the arterial walls [25].

2) Diabetes: Diabetes Mellitus and Cardiovascular Disease are significantly related [26]. Arterial stiffness and carotid intimal media thickness (IMT) are greatly impacted by elevated levels of glycaemia. The carotid IMT is also used to assess injury from high blood pressure (BP), so it can independently predict cardiovascular diseases. Endothelial function may also be impacted by the association between hyperglycemia and AGEs (advanced glycation end-products). Chronic high levels of glycaemia have been shown to lead to increased Levels of AGEs which in turn contribute towards Arteriosclerosis [27].

3) Obesity: The cardiovascular system suffers dramatically from obesity, which is classified as being an ongoing metabolic condition. The effect obesity has on the cardiovascular system occurs along several different routes: altered haemodynamics, changes in cardiac morphology and function, ongoing inflammation, neurohumoral changes, and cellular remodelling. All of these effects contribute to reduced cardiac output, increased peripheral resistance, increased mass of the left ventricle, enlargement of the internal dimensions of the left ventricle, hypertrophy of the left ventricular wall and diminished systolic function of the left ventricle. Left ventricular hypertrophy may result from structural remodelling of the heart produced by obesity. The likelihood of left ventricular hypertrophy escalates by 5.1% for each 1 kg/m² increment in BMI, and by 2.6% for each 1 cm increase in waist circumference [28].

4) Lifestyle: To address the correlations between lifestyle practices and cardiovascular disease risk, various research have investigated lifestyle indices. Adherence to various healthy lifestyle behaviours, including maintaining a normal weight, engaging in physical activity, consuming low to moderate alcohol, and abstaining from smoking, resulted in a 66% reduction in the risk of cardiovascular disease. This contrasted with individuals who adopted just a single behaviour or none at all [29].

B. Non-modifiable Risk Factors

1) Age: Cardiovascular function deteriorates more rapidly as people get older, which means that older adults are at a greater risk for developing CVD. Data have shown that CVD rates increase for both genders as people get older — from the formation of atherosclerosis to strokes to heart attacks. According to the American Heart Association (AHA), CVD rates in the United States are approximately 40% for people aged 40 to 59 years, 75% for people aged 60 to 79 years, and 86% for those aged 80 years and older [30].

2) Gender: Older adults often experience gender differences in the frequency and timing of cardiovascular disease. According to the 2019 AHA, Heart Disease and Stroke Statistical Update, the prevalence of CVD by age group for those aged 60 through 79 is 77.2% for men and 78.2% for women; for adults aged 80+, it is 89.3% for males and 91.8% for females. Age and male sex are identified as the most significant risk factors in the development of CAD. Sex hormones, along with their receptors, are believed to play a role in the differences seen between male and female populations for risk factors and outcomes associated with cardiovascular disease [30].

3) Genetics: Cardiovascular disease (CVD) is commonly acknowledged as a highly heritable disorder; thus, it is prudent to address genetic aspects in its therapeutic care. Family history information has long been seen as a method to achieve this goal, and research has shown it to be a highly useful instrument for evaluating the risk of cardiovascular disease [10-12]. Nonetheless, "family history" is a binary characteristic that is difficult to assess in both quantitative and qualitative dimensions [31].

VII. DIAGNOSIS OF CVD:

Assessing the symptoms of the patient along with physically reviewing their risk factors (such as age, family history, lifestyle, etc.) will allow a clinician to make a diagnosis of heart disease according to an evaluation report. Manual analysis takes much longer to compute because of the significant number of considerations used to study each area of interest. In most cases arrhythmias (unevenly timed heartbeats) are present. While transthoracic echocardiography (TTE) is an effective method of non-invasively screening patients with heart disease; TTE is costly, time-consuming, and produces poor quality images [32] .

The Electrocardiogram (ECG) analysis is the predominant approach utilised for diagnosing and monitoring heart problems. Moreover, ECG analysis is a swift and non-invasive technique for identifying primary heart conditions. Six. Nonetheless, the subjective assessment of ECG data is generally intricate, labour-intensive, prone to human error, and difficult due to insufficient experience. Moreover, the phonocardiogram (PCG) signal is utilised to forecast cardiac disease owing to its non-stationary attributes in the integrated time-frequency domain, morphological features in the time

domain, and spectral characteristics in the frequency domain [32].

Artificial Intelligence (AI) represents a broad range of disciplines that include the design and development of intelligent systems to mimic human behaviour in determining disease trends within healthcare data. Machine Learning is one particular area of artificial intelligence that deals with techniques for allowing computers to learn from data and gain experience, through the use of various paradigms of learning (unsupervised, supervised and reinforcement) for the purpose of improving the efficiency of classification calculations [33].

VIII. Economic and Public Health Impact

The two principal causes of global disability are cerebrovascular disease and ischaemic heart disease, with cardiovascular disease (CVD) representing 24% of non-communicable disease (NCD)-related disability-adjusted life years (DALYs). Notwithstanding the global reduction of 14.5% in age-standardized cardiovascular disease (CVD) mortality rates from 2006 to 2016, the burden of CVD continues to be disproportionately significant in low- and middle-income countries (LMICs) relative to high-income countries (HICs), with over 80% of CVD fatalities occurring in LMICs [34- 35].

The total economic burden of cardiovascular disease (CVD) was approximately $3.7 trillion, or about one-half of the estimated economic losses reported in high-income countries, for the period of 2011 to 2015. Compared to high-income countries, CVD has a greater impact on working-age populations in low- and middle-income countries (LMICs). In Sub-Saharan Africa, CVD mortality occurs at earlier ages; or, to put it another way, approximately 50% of deaths from CVD occur among individuals aged 30-69 years, which is approximately 10 years earlier than those in high-income countries [35- 36].

A. Hormonal Regulation in Cardiovascular Homeostasis:

Hormonal regulation is crucial for maintaining cardiovascular homeostasis, achieved through the coordinated activity of neurohormonal systems that control blood pressure, vascular tone, fluid balance, and cardiac performance [37].

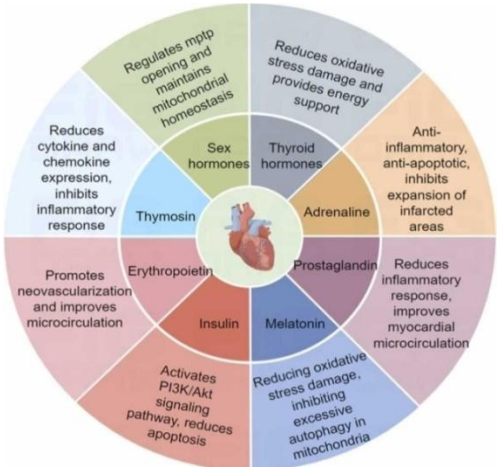

Fig. 1: correlation between different hormone and heart [38].

B. Renin–Angiotensin–Aldosterone System (RAAS):

The main controllers of the RAAS system that help to control vascular resistance and volume of blood in the body are renin, angiotensin II, and aldosterone [39]. Angiotensin II is a very strong vasoconstrictor that increases resistance due to how well blood vessels work together and also cause the release of aldosterone from the adrenal cortex which helps to retain water and salt, which leads to an increase in circulation volume/blood pressure. [40].

Chronic activation of RAAS increases inflammation, myocyte remodelling, endothelial dysfunction and oxidative stress which contributes to damage of the cardiovascular system [41]. More studies have shown that the RAAS has a complex involvement in regulating the cardiovascular system with other systems such as sympathetic system and natriuretic system [42].

C. Sympathetic Nervous System:

SNS has a significant function in controlling hormonal activity and neurohumoral function for cardiovascular homeostasis, particularly in providing quick adaptations to physiological stress [43]. Upon activation of the SNS through catecholamines (norepinephrine and epinephrine) that bind to adrenergic receptors in the heart and circulatory system, the following occurs: vasoconstriction in the periphery; increased myocardial contractility (positive inotropy); increased heart rate (positive chronotropic), and these actions all work together to maintain arterial blood pressure and cardiac output [44]. Additionally, stimulation of the SNS leads to renal secretion of renin, and this mechanism is intimately linked with RAAS to assist in fluid regulation and blood pressure regulation [45]. That said, chronic over-activation of the SNS has significant impact on the pathophysiology of cardiovascular disease.

Hypertension, arrhythmias, heart failure, and vascular dysfunction are all related to long-term sympathetic activation caused by increased oxidative [46-47].

D. Vasopressin and Endothelin:

Vasopressin and endothelin are powerful vasoactive hormones essential for cardiovascular control. Vasopressin increases circulation volume and arterial pressure by facilitating vasoconstriction and water reabsorption, therefore aiding in the control of fluid homeostasis and blood pressure. It exerts direct effects on the heart and vasculature, influencing cardiac function and vascular tone in both normal and pathological states [48-49].

Endothelin-1 (ET-1) is a powerful endogenous vasoconstrictor predominantly synthesized by endothelial cells. It is crucial for the preservation of basal vascular tone. It triggers vasoconstriction, proliferation of vascular smooth muscle, and inflammatory responses via ETA and ETB receptors [50]. Cardiovascular disorders, such as hypertension, heart failure, and coronary artery disease, are significantly linked to the overactivation of the endothelin system [48- 49]. Furthermore, vasopressin and endothelin engage with other neurohormonal systems, thereby augmenting vasoconstrictive and fluid-retaining processes throughout the disease course [49, 51].

IX. Natriuretic Peptides as Key Hormonal Regulators

The system that regulates the heart's endocrine function primarily consists of the natriuretic peptide system (NPS). The NPS is involved in regulating sodium-water balance, blood pressure, and blood volume. The expression of the natriuretic peptide system (NPS) promoter and the functioning of the cardiac myocyte may be influenced by epigenetic modifications (such as DNA methylation), as well as by other factors (like histone modifications and non-coding RNA molecules). The RAAS, as well as the actions of endothelin-1 (ET-1), reproductive hormones, glucocorticoids, and cytokines can all influence the function of the nephron proximal segment (NPS), which has direct consequences on blood pressure and, ultimately, how the heart performs [52].

A. Natriuretic Peptides: Structure and Physiological Function

The natriuretic peptide family (NPs) principally includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), dendroaspis natriuretic peptide (DNP), urodilatin (UNP), and ventricular natriuretic peptide (VNP) [53]. The three principal peptides—ANP, BNP, and CNP—regulate blood pressure via the activation of natriuretic peptide receptors through various processes [54]. A conserved 17-amino acid ring is formed by an intramolecular disulfide bond between two cysteine residues, a structural characteristic common to all. Their biological activity and receptor binding affinity depend on this ring shape [55].

B. Atrial Natriuretic Peptide (ANP)

ANP is predominantly synthesised in the cardiac atria and is primarily expressed and stored in the granules of cardiomyocytes. Nevertheless, the NPPA gene is also expressed in other tissues, including the brain, kidneys, lungs, and ventricles, at reduced concentrations.

The atrial wall elongation that results from an increase in intravascular volume is the primary stimulus for the release of ANP. Hormones and neurotransmitters, including endothelin, arginine vasopressin, and catecholamines, also stimulate the secretion of ANP, which enables its endocrine distribution to its various target organs [56].

ANP's mechanism of action begins with its interaction with NPR-A, which is a guanylyl cyclase receptor on the membrane surface. When ANP binds to NPR-A, it produces cGMP from GTP, which is an important intracellular second messenger. This cGMP levels stimulate PKG to mediate the downstream effects of ANP through vasodilation by causing vascular smooth muscle relaxation (e.g., by inhibiting calcium entry into smooth muscle). ANP also enhances sodium excretion (natriuresis) and fluid excretion (diuresis) by inhibiting sodium reabsorption in renal tubules and increasing the glomerular filtration rate [57]. In addition to these mechanistic effects, ANP decreases renin and aldosterone secretion resulting in decreased sodium retention and lowered BP, which suppresses the RAAS. ANP decreases vascular resistance by inhibiting sympathetic nervous system activity. These synergistic effects create a state of decreased blood volume and reduced preload and afterload on the heart, optimizing cardiovascular function and maximizing cardiovascular health [58].

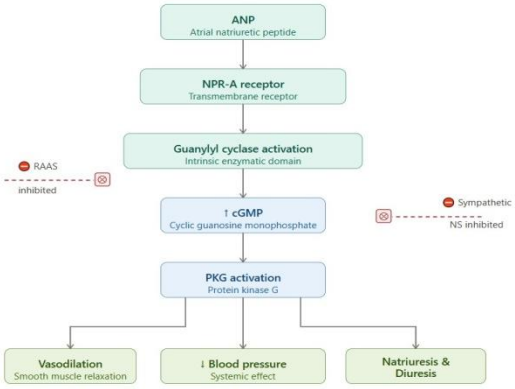

Fig. 2: Molecular Mechanism of Atrial Natriuretic Peptide (ANP) Designed by the authors

C. B- type Natriuretic Peptide (BNP):

Identifying the source of the BNP hormone first occurred in 1988 using preparations of pig brains. It has been identified that the heart contains BNP hormone in the highest concentration, confirming its activity as a hormone in the heart. BNP works to regulate diuresis, natriuresis, and vasodilation, and it is released when the levels of stress in the atrial/ventricular membranes increase. High levels of BNP can be indicative of cardiac dysfunction and ventricular hypertrophy. The N-terminal fragment is released into circulation as the pro-hormone for BNP (pro-BNP) is cleaved from it (N-terminal pro-BNP or NT-proBNP) [59]. Plasma BNP level in a healthy normal person is approximately 0 to 20 pg/mL. In coronary artery disease, pulmonary hypertension, heart failure, myocardial infarction, and left ventricular hypertrophy, plasma BNP levels have been shown to rise as the condition becomes more severe [60].

The BNP gene is activated by mechanical stress, pressure, volume overload, specific hormones (angiotensin II, endothelin), cytokines, and ischaemia by the aforementioned transcription factors, and the resulting transcript is translated into preproBNP at the endoplasmic reticulum. The enzyme signal peptidase converts the preproBNP to proBNP. During transport to the Golgi apparatus for processing, glycosylation occurs on seven residues in the N-terminal of proBNP: Thr36, Ser37, Ser44, Ser48, Ser53, Ser58, and Thr71. The original hypotheses regarding the role of the processing enzyme furin in cleaving glycosylated proBNP into BNP and NT-proBNP were based on the assumption that proBNP would locate to the trans-Golgi network [59].

The BNP and RAAS hormonal systems have received substantial attention in recent decades. These hormones regulate haemodynamic and electrolyte-fluid balance by opposing activities. Furthermore, the complex biological mechanisms of these drugs exert contradictory influences on the cardiac and vascular remodelling processes that contribute to the progression of cardiovascular diseases. The

RAAS, consisting of renin, Ang II, and aldosterone, might act unfavorably when overexpressed. In contrast, the elements of the NPs family serve as hormonal protective factors [61].

X. Natriuretic Peptides in Cardiovascular Diseases

1) Heart Failure: Natriuretic peptides are recognized as cardiac biomarkers in congestive heart failure (HF) and hold prognostic significance for individuals with HF. BNP levels predict cardiovascular outcomes in heart failure and connect with the New York Heart Association (NYHA) symptom classification. Moreover, they are advantageous for differentiating between cardiac and non-cardiac dyspnoea, except in patients with AS [62].

2) Hypertension: Notable studies have elucidated the role of NPs in the development of arterial hypertension. Belluardo et al. compared BNP and NT-proBNP levels in individuals with mild, moderate, and severe hypertension to those in healthy individuals. They demonstrated that BNP levels were unchanged in individuals with mild hypertension, although NT-proBNP levels were markedly lower compared to the control group. The presence of left ventricular hypertrophy did not influence the elevation of BNP and NT-proBNP levels as the severity of mild-to-severe hypertension in people escalated. The BNP system's diminished responsiveness during the initial stage of hypertension may be signified by the decrease of NT-proBNP and the lack of BNP activation in mild hypertension [57].

XI. Myocardial Infarction and Ischemic Heart Disease:

The ventricular release of BNP from the myocardium and NT-proBNP (the inactive form) is caused by pressure on the ventricular wall, hypoxia and myocardial cell injury during an acute or chronic myocardial ischemic event (Coronary artery disease/Coronary event) [63]. These both peptides are primarily used for diagnosing and prognosticating an acute coronary sensitivity; similar to how increased levels of these both peptides occur during acute coronary syndromes, which signify an increased workload on the heart. Increased levels of these natriuretic peptides are correlated with infarct size, left ventricular dysfunction, and potential heart failure/mortality [64].

Natriuretic peptides provide both diagnostic and protective physiologic benefits during ischemic episodes, such as decreasing the workload of cardiomyocytes through vasodilation, thus reducing preload and afterload, along with enhancing natriuresis and diuresis. In addition to decreasing the workload of cardiomyocytes, they also decrease the activation of the sympathetic nervous system and the Renin–Angiotensin–Aldosterone System (RAAS), thus decreasing the amount of damaging cardiac remodelling and Fibrosis that can develop as a result of an acute myocardial infarction. Furthermore, there have been experimental studies that have shown that natriuretic peptides may also reduce ischemia & reperfusion injury through anti-inflammatory and anti-fibrotic mechanisms. Nevertheless, the increased circulating levels are mainly reflective of disease burden and do not provide adequate endogenous cardio protection despite their beneficial effects on heart health [65].

XII. Conclusion

The cardiovascular system uses natriuretic peptides primarily as a mechanism for controlling the body, as well as providing protective benefits by modifying the blood vessels, fluid levels, and the activity of hormones. It is clear from the interaction of natriuretic peptides with other systems within the body, including the Renin–Angiotensin–Aldosterone System, that they play an important role in counteracting cardiovascular disease progression. Both ANP AND BNP can act as reliable biomarkers for assessing diagnosis and prognosis in heart failure or ischemic heart disease.

Despite the positive effects of natriuretic peptides, elevated levels of these peptides are indicative of increased disease severity but not total endogenous protection; hence, this emphasizes the importance of identifying cardiovascular disease early and employing target specific treatment approaches. Future research aimed at developing agents to enhance natriuretic peptide signalling pathways or overcome mechanisms of resistance may provide new treatment options for improving the outcomes of patients with cardiovascular disease. Collectively, natriuretic peptides are two of the most significant regulators of cardiovascular disease and are vital in the management of patients with cardiovascular disorders.

Conflict of Interest

The authors declare that they have no conflict of interest.

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