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Name of Journal: *World Journal of Hypertension*

Manuscript NO: 78380

Manuscript Type: MINIREVIEWS

**CARDIAC MARKERS: ROLE IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION**

role of cardiac markers in hypertension

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Abstract
Cardiac biomarkers may have a unique role in the prognostic evaluation of patients with hypertension as many cardiac biomarker levels become abnormal long before the onset of obvious cardiovascular disease. There are numerous cardiac markers, however, this review article reported only Creatinine kinase (CK) and CK-MB, Cardiac troponins, Lipoprotein A, Osteopontin (OPN), Cardiac extracellular matrix, C-reactive protein (CRP), Cardiac matrix metalloproteinases (MMPs), Cardiac natriuretic peptides (NPs), myoglobin, Renin, and Dynorphin role in the pathogenesis of hypertension. This article explained the recent major advances, as well as discoveries, significant gaps, current debates and most importantly, explain the ideas of where research could go next step. Further studies are required to find the association between myoglobin and other cardiac markers in hypertension. Moreover, therapeutic approaches are required to find the early control of these cardiac markers which ultimately reduced the prevalence of cardiovascular diseases.

Key Words: Cardiac Markers; Hypertension; Pathogenesis


Core Tip: The risk for cardiovascular disease is raising, hypertension continues to be a significant global public health concern. It has been demonstrated that effective blood pressure control lowers the risk of stroke, heart attack, and heart failure. For this purpose, this review article explained the role of major cardiac markers (Creatinine kinase (CK) and CK-MB, Cardiac troponins, Lipoprotein A, Osteopontin, Cardiac extracellular matrix, C-reactive protein, Cardiac matrix metalloproteinases, Cardiac natriuretic peptides, myoglobin, Renin, and Dynorphin) in the pathogenesis of hypertension. It could be helpful to the early identification of these cardiac markers and
a therapeutic approach will manage these cardiac markers in hypertensive subjects to reduce the prevalence of cardiovascular diseases.

INTRODUCTION
The prevalence of cardiovascular (CV) disease is rising on a global scale. One of the most significant risk factors for CV disease is hypertension, which is frequently linked to metabolic syndrome, obesity, and both. A growing amount of focus is being paid to the search for the essential processes that connect high blood pressure (BP), glucose and lipid dysmetabolism, increased risk of cardiovascular disease (CVD), and mortality \[1\]. Furthermore, Cardiac markers also called biomarkers are used to evaluate heart function and are measured which are useful in the early prediction as well as diagnosis of disease. Early markers are also identified as enzymes and sometimes also termed cardiac enzymes, but not all of the markers currently used are enzymes as in formal usage, troponin would not be listed as a cardiac enzyme \[2,3\].

In this regard, the study reported higher levels of cardiac markers, inflammation as well as vasoconstrictors in runners with exercise-induced high blood pressure. The scientists also noted that parameters linked to elevated blood pressure in middle-aged marathon runners were related to increases in cardiac troponin I (cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), endothelin-1, and high-sensitivity C-reactive protein caused on by the marathon (hs-CRP). These associations were found without consideration of past running experience, completion rates, or peak oxygen intake \[4\].

Many cardiac biomarker levels become aberrant a long time before the manifestation of evident cardiovascular disease, mounting data shows that cardiac biomarkers may play a special role in the prognostic evaluation of patients with hypertension. The authors provided a summary of cardiac biomarkers that could be utilized to predict the development of cardiovascular disease in people with hypertension \[5\]. Similarly, Pasupathiet et al. reported numerous biochemical markers in clinical cardiology \[6\].

Also, Parsanathan et al. have explained the evidence for the presence of traditional
cardiac biomarkers. Interestingly, Vassiliadis et al. described novel cardiac-specific biomarkers and the cardiovascular continuum including Creatinine kinase (CK) and CK-MB, Myoglobin, Lipoprotein A, Brain natriuretic peptide (BNP), Troponins I and T, Osteopontin, C-reactive protein (CRP), Cardiac extracellular matrix, Cardiac matrix metalloproteinases (MMPs) and so on. However, this review article only reported the Creatinine kinase (CK) and CK-MB, Cardiac troponins, Lipoprotein A, Osteopontin (OPN), Cardiac extracellular matrix, C-reactive protein (CRP), Cardiac matrix metalloproteinases (MMPs), Cardiac natriuretic peptides (NPs), myoglobin, Renin, and Dynorphin role in the pathogenesis of hypertension as explained in figure 1. This article explained the recent major advances as well as discoveries, significant gaps, and current debates and most importantly explains the ideas of where research could go next step.

To review the literature, various databases including Google Scholar, PubMed, and Science Direct were used. The search was completed on May 20, 2022. Cardiac Markers, Hypertension, and Pathogenesis were just a few of the terms that were utilized to search the literature. The relevant articles’ references were examined, and comparable articles were found. Clinical investigations could only be conducted in English. Despite favouring more recent studies, we did not set a time limit.

**Role of major cardiac markers in hypertension**

There are many cardiac markers, but this article only highlighted pathophysiological aspects of major cardiac markers such as Creatinine kinase (CK) and CK-MB, Cardiac troponins, Lipoprotein A, Osteopontin (OPN), Cardiac extracellular matrix, C-reactive protein (CRP), Cardiac matrix metalloproteinases (MMPs), Cardiac natriuretic peptides (NPs), myoglobin, Renin, and Dynorphin in the pathogenesis of hypertension as explained in tables 1,2,3 respectively.

1. **Creatinine kinase (CK) and CK-MB**

Pressure responses are enhanced as well as increased blood pressure by high creatinine kinase activity importantly in resistance arteries. In this context, Brewster et al. (2006) reported that after adjusting for age, sex, body mass index, and ethnicity, the
independent relationship between creatine kinase and blood pressure showed an increase in systolic and diastolic pressure of 8.0 (95% CI, 3.3 to 12.7) and 4.7 (95% CI, 1.9 to 7.5) mm Hg and 4.7 (95% CI, 1.9 to 7.5) mm Hg, respectively \[^{11}\]. In another study, Emokpae \textit{et al} observed the mean CK-MB activity was significantly elevated in female hypertensive subjects as compared with males. On the contrary, the mean CK-MB activity was significantly lower for the female normotensive subjects than for the male counterparts. In hypertensive individuals, serum CK-MB activity was higher in females than in males. Additionally, cardiac indicators should be routinely performed in the assessment of hypertension subjects, and sex-specific considerations may be recognized in the therapy of these patients \[^{12}\].

2. **Cardiac troponins**

The female hypertension participants had a mean cardiac troponin I (cTnl) that was substantially greater than that of the males. Between male and female normotensive patients, there was no difference in the levels of cTnl \[^{12}\]. No history of cardiovascular disease in an ambulatory population and high-sensitivity cardiac troponin-T (hs-cTNT) was linked with incident hypertension as well as the risk of left ventricular hypertrophy (LVH). According to the authors, to see if high-sensitivity cardiac troponin-T (hs-cTNT) can identify people who could benefit from ambulatory blood pressure monitoring or hypertension preventive lifestyle changes \[^{13}\].

Elevated cardiac troponin I during a hypertensive patient crisis may offer helpful prognostic data and allow for the early identification of patients at higher risk of dying. In the groups with high, detectable, and undetectable cTnl, the 3-year all-cause death rates were 41.6\%, 36.5\%, and 12.8\%, respectively. Additionally, a higher risk of death from all causes was substantially linked with cTnl levels that were normal but detectable. Patients with hypertensive crises and increased and detectable cTnl levels need critical treatment and follow-up methods \[^{14}\]. Equally important, Stefanie \textit{et al} concluded that an independent relation was found between High-Sensitivity Cardiac
Troponin I with systolic blood pressure as well as left ventricular hypertrophy \[15\]. Then, Sato et al explained that High-sensitivity cardiac troponin T was 78% of patients presenting with treated essential hypertension and independently correlated with age, renal function as well as ECG voltage of hypertrophy \[16\]. Further, Tehrani et al, reported an elevated range of high-sensitivity cardiac troponin-T (hs-cTnT) over time which is linked with a higher risk of cardiovascular disease even when the blood pressure is stable or decreases over time \[17\]. Moreover, Afonso et al, observed a disturbingly elevated incidence of mortality in individuals representing a hypertensive emergency, although neither the presence nor the extent of cardiac troponin - I releases was linked with greater odds of death \[18\].

Troponin is detectable in about one-third of patients with hypertensive crises. Nevertheless, less than half of these patients have troponin levels that are compatible with myocardial damage, and the majority of them show little change in sequential troponin. Aspirin use, previous CHF, and low body mass index (BMI) are all independently linked to myocardial damage in these patients. Higher initial and serial troponins were strongly correlated with lower body mass index. The significant inverse relationship between body mass index and myocardial damage was more pronounced in-patient populations who were older and female. These findings contribute to the understanding of the pathophysiology, risk factors, and clinical significance of baseline and ongoing troponin levels in hypertensive crisis patients \[19\].

3. Lipoprotein A

Various epidemiological, as well as genetic studies, have identified a higher concentration of lipoprotein (a) as a causal and independent risk factor for CVD. The Lp(a)-induced elevated risk of cardiovascular disease could be mediated by both its prothrombotic as well as proatherogenic mechanisms \[20\]. In the same way, Reaven et al showed the observations which elevated the possibility that abnormalities of lipoprotein, as well as carbohydrate metabolism, could play a role in both the clinical as well as aetiology course of hypertension \[21\].
Additionally, Lui et al analyzed the data by subgroups according to both Lp(a) category and hypertension status, the risk of cardiovascular events (CVEs) was only significantly higher in the high lipoprotein A as well as hypertension group as compared with the reference group with low lipoprotein A concentration and normotensive (hazard ratio: 1.80, 95% confidence interval: 1.11–2.91). The higher Lp (a) was linked with an increased risk of cardiovascular events in stable coronary artery disease patients with hypertension. Additionally, the coexistence of high Lp (a) concentrations and hypertension greatly worsened the clinical prognosis in patients with coronary artery disease, which may recommend a prognostic correlation between Lp (a) and hypertension [22].

Lipoprotein (a) plasma concentrations, as well as apolipoprotein (a) phenotype, did not differ between hypertensive and control groups. Higher Lipoprotein (a) plasma concentrations and apolipoprotein (a) isoforms of low MW were strongly linked with a family history of coronary heart disease in hypertensives. The quantification of Lipoprotein (a) concentration and characterization of apolipoprotein (a) phenotypes could be used for the assessment of familial predisposition to coronary heart disease in hypertensives [23].

The two main risk factors including hypertension and dyslipidemia for vascular diseases on an atherosclerotic basis were linked. However, even though they were within the normal range, higher Lipoprotein (a) plasma concentrations may be a separate risk factor for atherosclerosis and can drive up the prevalence of cardiovascular disease in persons with essential arterial hypertension [24].

Ghorbani et al explained the significant correlation between serum Lipoprotein (a) and age or duration of hypertension (known duration of hypertension period). Also, the possibility that lipoprotein (a) may play a role as a cofactor in essential hypertension has been raised, although the exact mechanism is still unclear [25].

The nighttime systolic and diastolic blood pressures, as well as the mean nighttime decrease in systolic and diastolic blood pressures, were all significantly correlated with Lipoprotein (a) levels. When peroxidative stress data were taken into account, these
associations were further confirmed ($r=0.37$ and $r=0.40$, $P<0.01$ for the nighttime decline in systolic and diastolic blood pressure, respectively; $r=0.34$ and $r=0.38$, $P<0.01$ for the nighttime increase in systolic and diastolic blood pressure). This relationship did not affect the apolipoprotein (a) isoform size. The authors have given a suggestion which explains that lipoprotein A, as well as peroxidative stress, could be involved as cofactors in essential hypertension, with a mechanism that remains to be elucidated [26]. Whereas, Dorgan et al resulted that lipoprotein A was significantly higher in hypertensive patients with atherogenic dyslipidemia group than in hypertensive patients without atherogenic dyslipidemia group as compared to the control group. A significant correlation was found between lipoprotein(a) and intima-media thickness (IMT) between lipoprotein(a) and fibrinogen, and between lipoprotein(a) and brachial flow-mediated vasodilatation (FMD). Total cholesterol, LDL cholesterol, HDL cholesterol, apolipoproteins A or B, or apoA-I/apoB levels did not correlate with lipoprotein(a) levels [27].

Target organ damage has also been linked to lipoprotein (a) levels and apolipoprotein (a) phenotype in patients with essential hypertension, with a higher prevalence of the low molecular weight apo(a) phenotype in individuals with progressive target organ damage. These connections did not seem to be related to blood pressure [28]. Moreover, Ward et al suggested that in ~30% of the patients in this risk, lipoprotein (a) level was elevated in the hypertensive cohort and measurement of lipoprotein A could be useful in risk stratification [29].

Additionally, Chan et al concluded that elevated lipoprotein (a), hypertension and renal insufficiency were independent risk factors beyond elevated pretreatment LDL-cholesterol which predict coronary artery disease in patients with Familial hypercholesterolemia. Despite the cross-sectional design authors proposed the need for identifying and managing these abnormalities to reduce excess coronary artery disease risk in Familial hypercholesterolemia patients. However, this proposal remains to be formally tested in a prospective study [30]. Woo et al revealed that the independent risk
factors for all strokes were a history of hypertension, a high serum lipoprotein(a) concentration, and a low apolipoprotein A-1 concentration \(^{[31]}\).

4. **Osteopontin (OPN)**

Hypertension is a known risk factor for the processes of atherosclerosis and has a direct impact on vascular hypertrophy. The most important protein mediator of inflammation is osteopontin (OPN) which also has a role in remodeling of large arteries. In the same way, according to a study, transgenic mice that specifically overexpress catalase in smooth muscle cells (TgSMC-Cat) prevent the enhanced OPN expression that hypertension causes. Additionally indicating that \( \text{H}_2\text{O}_2 \) is crucial in mediating the rise in OPN expression brought on by hypertension. These findings indicate that osteopontin may play a crucial role in the pathogenesis of hypertension \(^{[32]}\).

In the same context, Matsui et al reported that consequently, Wild-type (WT) mice underwent Ang II therapy, which led to markedly increased blood pressure and heart hypertrophy and fibrosis. The development of cardiac fibrosis and blood pressure increase caused by Ang II could be reduced with eplerenone (Ep) medication and OPN deficiency, whereas the development of cardiac hypertrophy could be prevented with Ep alone. Most convincingly, in OPN-deficient animals treated with Ang II, the reduction of cardiac fibrosis resulted in an impairment of cardiac systolic function and consequent left ventricular dilatation. These findings imply that OPN was essential for the fibrosis and remodelling of the heart caused by Ang II. Additionally, the reduction of OPN expression may have a role in the action of Ep on the prevention of cardiac fibrosis but not ventricular hypertrophy \(^{[33]}\). Yang et al concluded that circulating osteopontin was an independent risk factor for both left ventricular (LV) hypertrophy and left ventricular diastolic dysfunction (LVDD) in essential hypertensive patients. However, osteopontin was not associated with left ventricular dimension and systolic function \(^{[34]}\).

Also, Caesar et al resulted that through hydrogen peroxide, osteopontin is up-regulated with mechanical stress in smooth muscle cells and the aorta with
hypertension. Authors have demonstrated that it is crucial in modulating aortic remodeling and inflammation. Overall, these findings contribute to the understanding of vascular inflammation and have significant implications for the development of future treatments and prevention measures for the side effects of hypertension, such as atherosclerosis. \textsuperscript{35} Moreover, OPN was significantly associated with Pulmonary arterial hypertension among patients with connective tissue diseases, suggesting it may have a role as a non-invasive disease biomarker of PAH \textsuperscript{36}.

5. **Cardiac extracellular matrix**

Through modulating collagen synthesis, degradation, and cross-linking, the T lymphocytes may play a crucial regulatory function in the composition of the cardiac ECM \textsuperscript{37}. Briones \textit{et al} stated that vascular stiffness and fibrosis can be treated with currently available antihypertensive medications. Insights into cutting-edge treatments to lessen arterial stiffness and new applications for currently available antihypertensive medications will come from a deeper knowledge of the molecular mechanisms behind changes in the extracellular matrix in hypertension \textsuperscript{38}.

Also, Cai \textit{et al} explained that Hypertension is the outcome of subsequent structural and functional remodeling of the arterial wall caused by the ECM, which alters the component profiles, mechanical properties, degradation processes, and creation of degraded fragments. According to scientists, more studies involving the application of matridomic and degradomic techniques may offer proof for the identification of various ECM components. Improved comprehension of vascular matrix biology and the complex mechanisms underlying hypertension may offer fresh perspectives on the formation of antihypertensive treatments \textsuperscript{39}.

6. **C-reactive protein (CRP)**

In complex mechanisms that result in endothelial dysfunction, elevated peripheral vascular resistance, and stiffness of the major arteries in hypertension, C-reactive protein plays a role. \textsuperscript{40} Various studies reported that higher concentrations of hs-CRP in healthy subjects were associated with an elevated risk of upcoming stroke, peripheral arterial disease, heart attack, sudden cardiac death and cardiac events in CAD patients.
with obesity, colon cancer and complications of diabetes \[^{41}\]. The levels of hs-CRP could correspond to the extent of risk of a recurrent acute coronary syndrome, heart failure decompensation/development, the size of myocardial necrosis area, ventricular tachycardia, the risk of new-onset atrial fibrillation, and death in patients with AMI \[^{42}\]. Additionally, Smith et al stated that C-reactive protein concentrations were linked with hypertension, and pulse pressure, but adjustment for life course confounding and the Mendelian randomization approach suggested that higher C-reactive protein levels did not lead to higher blood pressure \[^{43}\].

In hypertensive individuals, C-reactive protein has a role in vascular stiffness, atherosclerosis, the onset of end-organ damage, and cardiovascular events. CRP has also higher concerns as a modulator of cardiac and vascular remodeling in response to pressure overload and damage, respectively \[^{44}\]. Also, Sesso et al concluded that C-reactive protein levels were associated with the development of hypertension in the future, indicating that inflammation may play a role in the development of hypertension \[^{45}\]. Lakoski et al reported the presence of a separate link between inflammation and hypertension in both genders. The largest correlation was found in Chinese individuals, whereas there was no variation in CRP levels by hypertension status in Hispanics. Ethnic group differences were clear. \[^{46}\]. Likewise, Pan et al suggested that Yi people frequently have elevated hs-CRP, which did not indicate that it is a risk factor for prehypertension or hypertension. \[^{47}\].

Lack of vitamin D raised levels of the inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) and low-density lipoprotein cholesterol (LDL), and high levels of oxidised LDL were all associated with pulse pressure amplification in people with high blood pressure, respectively. In middle-aged hypertensive and high normal blood pressure patients, vitamin D levels, high-sensitivity C-reactive protein, and LDL provided useful information regarding arterial stiffness and early arterial growing older; however, only hsCRP was a sensitive predictor of early arterial old age and pulse wave velocity \[^{48}\].
Shao et al resulted by tertile of increasing C-reactive protein, the incidence rates of hypertension were 9.3, 19.0, and 33.0 per 1,000 person-years. Baseline C-reactive protein remained strongly predictive of incident hypertension in the multivariate model that was controlled for age, gender, and prehypertension. The concentration of C-reactive protein was connected with systolic blood pressure and pulse pressure (PP), but not with diastolic blood pressure. In conclusion, the authors explained the link between inflammation with future systolic blood pressure in the Taiwanese population[49].

In the same context, Van et al reported the relationship between C-reactive protein levels and Hypertension was varied by sex and geographical location. In age-adjusted models, there was an association between high C-reactive protein levels and Hypertension in urban-Ghanaian women, European-Ghanaian men, and women. Nevertheless, these relationships were attenuated after adjustment for conventional risk factors, especially body mass index. No association was found between rural Ghanaians and urban-Ghanaian men[50].

7. **Cardiac matrix metalloproteinases (MMPs)**

Matrix metalloproteinases (MMPs), which are involved in a variety of physiological and pathological processes, are the most significant extracellular enzymes. Specific MMP’s altered activity and concentration, as well as the imbalance with their inhibitors, such as tissue inhibitors of metalloproteinases (TIMPs), have all been attributed to the pathogenic cascade induced by arterial hypertension. The extracellular matrix contains a variety of protein substrates that matrix metalloproteinases can break down. By doing so, they can affect endothelial cell function, vascular smooth muscle cell migration, proliferation, contraction, and determination of alterations in cardiomyocytes. Chronically high blood pressure values can activate all of these mechanisms. Studies on animals and people demonstrated that, in addition to age and blood pressure readings, MMPs play a critical role in the pathogenesis of hypertension-mediated vascular,
cardiac, and renal damage. As a result, there was growing evidence supporting the use of MMPs as indicators of organ damage caused by hypertension and possible targets for pharmacological treatments to stop future cardiovascular and renal problems in the hypertensive population.\textsuperscript{[51]}

Also, Prado et al stated that unbalanced vascular matrix metalloproteinase activity boosts vascular dysfunction and several structural changes, leading to vascular remodeling in hypertension individuals. Recently, it has become clearer how protective matrix metalloproteinases inhibitors, antioxidants, and medications increase vascular NO activity, and new treatments were emerging that address these crucial mechanisms, which may provide significant benefits to preventing the vascular remodeling of hypertensive patients.\textsuperscript{[52]}

In the same context, Flamant et al explained the cause of the beginning of Ang-II-induced hypertension and increased MMP-9 activity in conductance vessels. Similar to how MMP-9 activation results in vascular stiffness and increased pulse pressure, so does its absence. Similar to MMP-8 activation, MMP-9 activation was associated with an early, beneficial effect in hypertension by maintaining vascular compliance and reducing blood pressure increase.\textsuperscript{[53]}

Human hypertension impairs the production and activity of a few matrix metalloproteinases and tissue inhibitors of metalloproteinases. In response to hemodynamic alterations that may cause cardiac hypertrophy and fibrosis, leading to ventricular remodeling, an altered matrix metalloproteinases/tissue inhibitors of metalloproteinases balance plays a critical role in the rearrangement of the vascular wall. Numerous studies investigated the effects of some antihypertensive molecules on the matrix metalloproteinases/tissue inhibitors of metalloproteinases profile and found positive results. These molecules include ACE inhibitors, angiotensin receptor blockers, calcium-channel blockers, and aldosterone antagonists. A selective antihypertensive therapy focused on the matrix metalloproteinases profile, according to the authors, may also be helpful in clinical settings to lower the risk of cardiovascular problems.\textsuperscript{[54]}. 
When compared to the control groups, the hypertensive crisis groups (urgency and emergency) have considerably greater MMP-9 concentrations. MMP-9 may therefore be a biomarker or a modulator of pathophysiologic pathways in situations involving abrupt increases in blood pressure. In contrast, Kuliczkowski et al. showed that patients with coronary artery disease presented higher TIMP-4 and lower MMP-2 concentrations regardless of Arterial hypertension and DM. Arterial hypertension did not affect MMP-2, MMP-9, and TIMP-4 levels in serum. Higher MMP-2 concentration was independently linked to the onset of diabetes; however, the co-existence of DM and coronary artery disease was linked to a balance in the MMP-2 level. None of the groups under study noted a significant change in MMP-9 concentration.

Moreover, Tayebjee et al. explained the circulating pretreatment was explained with hypertension patients had considerably higher MMP-9 and TIMP-1 levels than normotensive controls. Following therapy, plasma MMP-9 levels lowered but TIMP-1 levels increased. MMP-9 levels did not connect with CVA risk but did with HDL cholesterol and CHD risk. TIMP-1 scores did not significantly correlate with CVA or CHD scores.

The vascular remodeling that occurs in the early stages of hypertension was significantly influenced by matrix metalloproteinases. Still, as people age, MMP-2 and proMMP-1 activity decreased by 40% and 45%, respectively, with a corresponding down-regulation of MMP-2 mRNA. These findings imply that age-related fibrosis was partially caused by depression of the degradative pathway. As a result, MMP plays a variety of roles in the heart remodeling carried on by hypertension or age.

Matrix metalloproteinases are pharmacological targets in hypertension, according to several researchers. It is still unknown if the circulating matrix metalloproteinase concentration in hypertension accurately reflects tissue levels. If this is the case, circulating matrix metalloproteinases could be used to identify people who are more likely to experience cardiovascular problems as a result of their hypertension. Early therapeutic intervention, such as the use of matrix metalloproteinase inhibitors, may be
beneficial for these patients. It is needed to search again. To explain the predictive relevance of matrix metalloproteinases and tissue inhibitors of metalloproteinases in hypertension, well-designed and controlled clinical studies are essential [59].

The myocardium's matrix metalloproteinases are a significant biological system that is responsible for maintaining the extracellular matrix's complex and dynamic milieu. The scientists added that a deeper comprehension of how this system was dysregulated in hypertensive heart disease will likely lead to fresh perspectives on treatment options for heart failure [60].

In patients with hypertension, the tissue inhibitors of metalloproteinases-1, MMP-2, and MMP-9 may serve as indicators of cardiovascular remodeling. If these findings are supported by future clinical research, they may offer a novel method for stratifying cardiovascular risk in hypertensive individuals [61].

8. **Cardiac natriuretic peptides (NPs)**

The three known natriuretic peptides are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), and they all play a part in the control of cardiovascular homeostasis through their diuretic, natriuretic, and vasodilatory activities. The effects of the atrial natriuretic peptide on controlling blood pressure and cardiac function have drawn a lot of interest. No pharmacological strategy directly targeted at modulating atrial natriuretic peptide levels has ever advanced to the point of being incorporated into clinical practice, despite numerous clinical and experimental studies evaluating the potential role of atrial natriuretic peptides in therapeutic application in the treatment of hypertension and heart failure. A potential cardiovascular risk factor for stroke, metabolic syndrome, hypertension, and obesity has been identified as an atrial natriuretic peptide. In the meantime, brain natriuretic peptide has become an important indicator of left ventricular dysfunction and a helpful indicator of future outcomes in heart failure patients [62].
In the porcine brain, Brain natriuretic peptide (BNP) was first investigated and then isolated from porcine, rat as well as human hearts. The increased severity of hypertension, importantly when left ventricular hypertrophy (LVH) is present, plasma Brain natriuretic peptide levels are progressively increased in humans. This is due to increased production and constitutive release of brain natriuretic peptides from ventricular tissue, which results in increases in ventricular mass. Furthermore, according to scientists, plasma levels of brain natriuretic peptide could serve as indicators of hypertensive left ventricular hypertrophy. In hypertensive patients, acute injection of brain natriuretic peptide significantly increases natriuresis while suppressing plasma aldosterone. However, additional research is required to fully understand the pathophysiological role of brain natriuretic peptides in essential hypertension. Then, Nakatsu et al concluded that compared to hypertensive patients with typical circadian blood pressure fluctuation, those with irregular diurnal blood pressure variation patterns (non-dippers, extreme dippers, and risers) displayed greater plasma levels of B-type natriuretic peptide (dippers). Clinically useful for identifying hypertensive individuals who have aberrant circadian blood pressure variability, which raises the risk of cardiovascular events, is the plasma B-type natriuretic peptide level. Furthermore, another study stated that elevated serum concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are associated with prevalent hypertension (PHT) whereas lower concentrations associate with incident hypertension (IHT). In addition, the authors propose that decreased vasodilation and natriuresis brought on by a lower level of circulating B-type natriuretic peptide may contribute to the etiology of early-stage hypertension.

Equally, Freitag et al reported that increased plasma brain natriuretic peptide (BNP) level was related to an increased risk of blood pressure progression in males but not in women in multivariable models controlling for known risk variables. Neither men’s nor women’s brain natriuretic peptide categories showed any apparent trends toward an increase in the prevalence of hypertension. Furthermore, the authors point out that greater plasma levels of brain natriuretic peptides were linked to a higher risk of blood
pressure advancement in males but not in women. To confirm these results and clarify the causes of these gender-related variances, further research is necessary \[66\].

Given their impact not only on blood pressure management but also on glucose and lipid metabolism, cardiac natriuretic peptides (NPs) such as atrial natriuretic peptides and brain natriuretic peptides may be essential in maintaining CV homeostasis and cardiac health. Cardiovascular disease (CV) and salt balance effects, along with all of the metabolic functions of cardiac natriuretic peptides, may play a substantial role in lowering total CV risk. Therefore, one of the key targets to treat these various linked disorders, as well as to lower hypertension and metabolically-related CV risk, may be the cardiac natriuretic peptides system shortly. It has two receptors and a neutralizing enzyme \[67\].

9. Renin

Renin is an important hormone that regulates several physiological processes, including blood pressure. Even though renin was first found over a century ago, a better knowledge of the origin of renin-producing cells and the mechanisms responsible for renin synthesis and secretion has only recently been achieved. The main source of renin is the juxtaglomerular cells (JGCs), which release renin from storage granules. Local RASs are additionally found in several tissues in addition to the renin-angiotensin system (RAS) in the JGCs \[68\].

It has been widely studied how the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) interact to cause CV disease. Renin is the first RAAS limiting step, and there is an ongoing discussion on how it might be used as a biomarker to enhance CV risk stratification. Elevated plasma renin activity has been linked to higher morbidity and mortality in individuals with CV disease, according to several studies \[69\].

The earliest report by Brunner et al. explained in a small study of individuals with essential hypertension would appear to show that over about 10 years of observation, individuals with low plasma renin activity had a significantly lower incidence of myocardial infarction and stroke compared to individuals with normal or high plasma
renin activity [70]. Elevated plasma renin activity levels in a hypertensive population without pre-existing CV disease do not predict the future occurrence of CV events, in contrast to what has been reported in patients with established CHD or heart failure [71].

Furthermore, Haber et al reported that renin is crucial for regulating blood pressure in the salt- or volume-depleted condition and is in charge of the early stages of renovascular hypertension. If salt is allowed to build up or not, renin's role in chronic renovascular hypertension will vary. Renin continues to play a substantial role during the chronic phase if sodium intake is controlled or if sodium excretion is unaffected (such as in two-kidney renovascular hypertension models) [72]. Although the RAAS's participation in the pathophysiology of essential hypertension is unclear, there is an increased number of data to support it, not least because it stimulates the production of reactive oxygen species, which harm target organs [73,74].

To improve BP control and prognosis while lowering medication type consumption and expense, plasma renin activity (PRA) testing can be used to guide the commencement, addition, or subtraction of anti- sodium-volume dependent or anti- renin-angiotensin (R) antihypertensive drug types in the hypertensive patient [75].

10. Dynorphin

The precursor protein prodynorphin gives rise to a group of opioid peptides known as dynorphins (Dyn). Dynorphin A, dynorphin B, and /-neo-endorphin are among the active peptides that are generated when prodynorphin is cleaved by proprotein convertase 2 (PC2) [76]. Dynorphin plays a role as an endogenous hypotensive peptide in healthy rats [77] and those that undergo subsequent bradycardia [78]. Notably, dynorphin modulates sympathetic activity via stimulation of atrial natriuretic factor [79], which can reduce BP in hypertensive subjects.

Another study reported that spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) at ages 4, 8, 12, and 16 had their hippocampus membrane preparations' dynorphin receptor binding sites examined. Compared to WKY controls, spontaneously
hypertensive rats displayed a substantial increase in hippocampus dynorphin receptor binding sites by the time they were 4 weeks old before hypertension became apparent. However, spontaneously hypertensive rats displayed significantly fewer hippocampal binding sites than Wistar-Kyoto rats at 8, 12, and 16 weeks of age, when hypertension is detectable. At any age, there were no differences in the two strains of rats' receptor affinities for dopamine. These findings imply that alterations in the opioid system's hippocampus receptors may be important for the main blood pressure-control mechanism [80].

Furthermore, Wang et al. resulted that dynorphin-A (1-8) (DA1-8) injected into the hippocampal formation (HF) causes a significant drop in blood pressure in conscious hypertensive and normotensive rats, but not heart rate [81]. Another study explained that in hypotensive piglets, indomethacin (5 mg/kg i.v.) potentiated beta-endorphin-induced constriction and the constriction brought on by dynorphin while blocking methionine and leucine enkephalin, dynorphin, and pial arteriolar dilatation [82].

CONCLUSION

This review article concludes that major cardiac markers including creatinine kinase (CK) and CK-MB, cardiac troponins, Lipoprotein A, osteopontin, cardiac extracellular matrix, c-reactive protein, cardiac matrix metalloproteinases, cardiac natriuretic peptides, renin, and dynorphin show a significant part in the pathogenesis of arterial hypertension. Additional studies are required to find the association between myoglobin and other cardiac markers in hypertension. Moreover, therapeutic approaches are required to find the early control of these cardiac markers which ultimately reduced the prevalence of cardiovascular diseases.

ACKNOWLEDGEMENTS

The corresponding author thanks her mother, Mrs Tahira Rafaqat.
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