

## Ventricular Peptides and Cardiac Function

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### SUMMARY

Seventeen and a half million deaths occur every year due to cardiovascular diseases across the world and one in three deaths in the world are caused by cardiovascular diseases such as, heart attack or heart failure according to WHO. Improved diagnosis and risk stratification of patients with the left ventricular dysfunction can help in preventing the major cause of death. This article review was the results of recent clinical studies relating to various heart diseases with the ventricular cardiac peptides such as B-type natriuretic peptide (BNP) and amino terminal B-type natriuretic peptide (NT-proBNP) levels as potential markers of diastolic and systolic left ventricular dysfunction.

**Sources of Data/Study selection:** Data from survey reports, descriptive, cross-sectional and longitudinal studies published between 1981-2011 on the topic were included. Data searches based on human and animal studies were included.

**Data Extraction:** The data was extracted from online resources of World Heart Failure Society, Heart Failure Society of America, World Heart Federation, The MEDLINE, the internet (e-medicine, medscape resource centre).

**Conclusion:** Analysis of these ventricular peptides appears to be a potential approach for elucidation of the pathophysiology of the heart.

**KEY WORDS:** Ventricular cardiac peptide; BNP; NT-proBNP; Heart failure; Myocardial ischaemia.

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### OVERVIEW

**Cardiac endocrine Function:** Heart is an endocrine organ besides a mechanical pump for circulation. This endocrine function was identified when atrial natriuretic peptide (ANP) was discovered as a first natriuretic peptide.<sup>1</sup> Subsequent studies discovered

two other natriuretic peptides, Brain (or B-type) natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), with the homologous sequence and structure.<sup>2,3</sup> BNP was first detected from brain tissue, but later on was found to be mainly of cardiac origin.<sup>2,4</sup> CNP is mainly produced by endothelial cells.<sup>3</sup> ANP and BNP exert natriuretic, diuretic and vasodilatory effects while CNP causes smooth muscle relaxation in the peripheral vasculature.<sup>3,5</sup>

Cardiac natriuretic peptides are released into the blood in response to stretch or ischaemia of cardiac chambers. BNP is released predominantly by the cardiac ventricles and ANP by atria.<sup>6</sup> After being released into the interstitial space, these cardiac peptides flow either into the coronary sinus through the capillary network or into the pericardial space through the lymphatic channels.<sup>7</sup> After releasing into the circulation, these peptides serve to unload heart through the natriuretic, diuretic and vasodilatory effects.<sup>1,2,5</sup>

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BNP is synthesized as an inactive prohormone (108 amino acids). It is then split into the active hormone BNP (32 amino acids) and the inactive N-terminal pro-BNP (NT-proBNP) (78 amino acids) with an equimolar ratio. Although NT-proBNP is biologically inactive but is more stable due to longer half life of 90-120 minutes as compared to BNP (20-22 minutes). BNP and NT-proBNP appeared to be equivalent diagnostic and prognostic markers.<sup>8</sup>

***Cardiac peptides and left ventricular dysfunction:***

This cardiac peptides can provide information about some pathophysiological mechanisms occurring in myocardial dysfunction, heart failure, and other cardiovascular diseases.<sup>9</sup> It has been reported that plasma levels of ANP and BNP are elevated in patients with various heart diseases including cardiomyopathy and ischemic heart disease.<sup>5,6,10</sup> Since BNP is released predominantly by the cardiac ventricles and ANP by atria, so the increased secretion of BNP from the left ventricle (LV) is the indicator of the severity of left ventricular dysfunction.<sup>6</sup> Hence, LV function may be assessed by the measurement of plasma BNP levels.<sup>10</sup> Several studies have concluded that plasma BNP concentration is a useful indicator of prognosis in patients of cardiovascular disease with LV dysfunction or hypertrophy.<sup>10</sup> NT-proBNP due to more stability, might be a more appropriate marker of milder LV dysfunction than BNP.<sup>8</sup> The high sensitivity of NT-proBNP allows also the detection of mild forms of cardiac dysfunction in asymptomatic patients with structural heart disease.<sup>8,11,12</sup> Elevated plasma levels of NT-pro-BNP have also been reported to predict a greater incidence of asymptomatic left ventricular dysfunction in diabetic patients and by starting appropriate treatment adverse outcomes can be prevented.<sup>13</sup>

***Echocardiography vs. cardiac peptide:*** Initially diagnosis of LV dysfunction was based on clinical signs and symptoms which are supported by ECG, chest X-ray, and echocardiography, but for the last three decades, addition of plasma natriuretic peptides have supplemented the diagnosis.<sup>14</sup> Although echocardiography is considered to be the gold-standard in assessing LV dysfunction, but the cost and limited availability and trained personal might be prohibitive.<sup>15</sup> So in clinical and laboratory practice these two major natriuretic peptides, BNP and NTproBNP, may be used as plasma biochemical markers for the screening, diagnosis and treatment of LV dysfunction.<sup>14</sup> BNP levels in plasma showed significant correlation with left ventricular function

variables i.e. LVEF, LVEDVI and LVESVI measured by echocardiography.<sup>16</sup> William et al compared plasma N-brain natriuretic peptide (N-BNP), with echocardiographic left ventricular ejection fraction (LVEF), with aerobic exercise capacity (peak oxygen consumption [VO(2)]) in patients with chronic heart failure. The results suggested that N-BNP reflects functional cardiac impairment better than LVEF because of significant correlation with peak VO(2).<sup>17</sup>

***Systolic and diastolic dysfunction:***

Earlier studies reported that BNP may be used in the Emergency Department as a marker of acute and chronic LV dysfunction.<sup>18,19</sup> These natriuretic peptide levels are indicators of both LV systolic and diastolic dysfunction.<sup>16</sup> It has been demonstrated that the key mechanical stimulus for cardiac BNP release is the LV end-systolic wall stress.<sup>20</sup> BNP has been used as a prognostic marker of LV systolic dysfunction following acute myocardial infarction.<sup>10</sup> It has been reported that after myocardial infarction, LV systolic function is decreased which may be partly compensated by myocardial hypertrophy. This myocardial hypertrophy provides a stimulus for the synthesis and release of increased amount of BNP.<sup>21</sup> It has been demonstrated that elevated plasma BNP levels are found in post infarction patients when compared to patients with no history of MI. Even these elevated levels would be useful for the detection of asymptomatic LV dysfunction.<sup>22</sup> Watanabe et al concluded that BNP levels are to be sensitive and accurate indicators of LV diastolic dysfunction. In heart failure LV remodelling occurs leading to myocytes hypertrophy and interstitial fibrosis, which in turn causes LV stiffness and diastolic dysfunction. BNP, due to its antifibrotic effect through the inhibition of DNA synthesis in cardiac myocytes and cardiac fibroblasts tends to improve LV diastolic dysfunction.<sup>23</sup>

***Myocardial Ischaemia:*** Plasma levels of BNP may rise during myocardial ischaemia.<sup>24,25</sup> Hypoxia induces the synthesis and secretion of BNP in human ventricular myocytes, likely through hypoxia induced factor -1 (HIF-1)-enhanced transcriptional activity.<sup>26</sup> Bassan et al demonstrated a negative predictive value (NPV) of 94.8% for the diagnosis of acute myocardial infarction. This strong NPV of natriuretic peptide level can be used to rule out the disease.<sup>27</sup> In the acute phase of myocardial infarction, BNP and NT-proBNP release is predominantly stimulated by ischemia, although in stable conditions, permanent wall stretch is the main mechanism.<sup>28,29</sup> It is suggested that measurement of NT-proBNP 3 months after

myocardial infarction is a better indicator of left ventricular function as compared to NT-proBNP in the acute phase.<sup>30</sup> This may be due to the fact that ischemia in the acute phase may cause transient myocardial wall tension and stretch without overload of the left ventricle, whereas myocardial damage may cause permanent wall stretch.<sup>28</sup>

A multicenter evaluation was performed to assess the practicability, and the analytical and clinical performance of a new point-of-care testing (POCT) PATHFAST NT-proBNP assay and the satisfactory results suggested that NT-proBNP would be a reliable tool in clinical practice, in the emergency setting as well as in the central laboratory.<sup>31</sup> Elevated resting BNP levels in the patients with pacemaker implantation, reflected that there should be a limit for daily physical activity.<sup>32</sup>

**Pericardial fluid Vs. serum cardiac peptides:** Previous studies have reported that high cardiac natriuretic peptide concentrations in pericardial fluid (almost 12 fold greater) than does plasma.<sup>16,23</sup> This may be due to the fact that natriuretic peptides are secreted more predominantly into the pericardial space rather than into the blood stream, and have relatively shorter half-life in plasma. In addition to that their plasma levels are rapidly and greatly changed by various factors like exercise, body position, volume overload, and medication.<sup>16</sup> Thus, pericardial fluid BNP levels may have more prognostic and therapeutic values.<sup>16,23</sup> But due to the difficulty in collecting the pericardial fluid by pericardiocentesis except in some pathological conditions like pericardial effusion serum and plasma levels are more suitable.<sup>7</sup> As it is also stated by Wang et al that the most suitable sample type for NT-proBNP and BNP detection was serum and EDTA-anticoagulant plasma.<sup>33</sup>

**Therapeutic implication of cardiac peptides:** For the therapeutic use, the B-type natriuretic peptide may be used by either administration of BNP or inhibition of (enzymatic) clearance of NP. It has been seen that recombinant human BNP (nesiritide) and vasopeptidase inhibitors are used to treat heart failure. Nesiritide, a recombinant human BNP, has been shown to provide symptomatic and haemodynamic improvement in acute decompensated heart failure.<sup>34</sup> Inhibition of the clearance enzyme neutral endopeptidase (NEP) is another promising way for increasing natriuretic peptide level. In addition to this, a new class of drugs, so-called vasopeptidase inhibitors, are also used.<sup>35</sup>

## CONCLUSION

The biomarker of cardiac function, ventricular natriuretic peptides BNP/NT-proBNP being discussed in this review are promising and might lead to improved diagnosis and risk stratification of patients with left ventricular dysfunction, however their clinical application requires further studies.

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