ROLE OF GATA-4 TRANSCRIPTION FACTOR ASSOCIATED WITH B-TYPE NATRIURETIC PEPTIDES IN HEART FAILURE

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ABSTRACT
Congestive heart failure is a condition in which heart loses its ability to fill with or pump sufficient amount of blood through the body. Two cardiac natriuretic peptides atrial natriuretic peptide and brain natriuretic peptide are secreted by the heart with a homologous structure. The level of brain natriuretic peptide surges in Heart Failure so brain natriuretic peptide level is used to diagnose Heart failure. Brain natriuretic peptide physiology is exaggerated by NPPB sequence variants, possibly via transcriptional regulation. The GATA cofactors are involved in the regulation of ANP and BNP promoters and a single mutation in the GATA-4 leads towards the diseases linked with heart. Mutations of GATA 4 transcription factor in promoter region of brain natriuretic peptide may cause increase level of brain natriuretic peptide.

Keywords: CCF (Congestive cardiac failure), CHF (Congestive heart failure), BNP (brain natriuretic peptide), ANP (Atrial natriuretic peptide), NPPB (Natriuretic peptide precursor B), ISO (Isoproterenol), NYHA (New York Heart Association).

INTRODUCTION
Congestive heart failure also referred to as congestive cardiac failure (CCF) or just heart failure is a condition that is characterized by the impairment of cardiac structure or function and an increase in neurohormonal activity which prejudices the ability of the heart to fill with or pump a sufficient amount of blood through the body (Quyen et al., 2001; Dhingra and Vasan, 2012). The symptoms depend largely on the side of the heart which is failing predominantly. In human circulatory system, blood from the lungs to the organs is pumped by the left side of the heart and the failure leads to the congestion of the lung veins and symptoms results in the reduced supply of blood to the
tissues (Auble et al., 2007). Hypertension, ischemic heart disease, valvular insufficiency and cardiomyopathy such increased mechanical and neurohumoral load, increases wall thickness which may cause hypertension (Lorell and Carabello, 2000). The American Heart Association has reported the following causes of CCF such as hypertension, aortic and mitral valve disease, aortic coarctation in left-sided CCF, pulmonary hypertension (e.g. due to chronic lung disease), pulmonary valve disease, tricuspid valve disease in right-sided CCF (Hunt et al., 2005), ischemic heart disease (due to insufficient vascular supply, usually as a result of coronary artery disease); this may be chronic or secondary to acute myocardial infarction (a heart attack), chronic arrhythmias (e.g. atrial fibrillation), cardiomyopathy of any cause, cardiac fibrosis, chronic severe anemia, and thyroid diseases may affect both sides (Hamzullah and Saadullah, 2008). The most common cause is ventricular tachycardia (VT) or ventricular fibrillation (VF) due to either the acute ischemia or entry into the new scar infarction (Golldstein et al., 1981). Cardiac dilation with left ventricular systolic dysfunction, which we called dilated cardiomyopathy, is the most common cause of congestive heart failure. Hypertension and coronary heart disease are the predominant causes of heart failure and accounted for more than 80% of all clinical events (Kalon et al., 1993). Molecular genetics causes of myocardial diseases have highlighted the importance of single gene defects in the pathogenesis of heart failure. The molecular control of cardiac gene transcription led to the identification of several key molecules that orchestrate the physiological expression of proteins involved in force production and transmission, metabolism and cycling of calcium. Since the mutation in the structural proteins involved in these complex processes is sufficient to induce cardiac remodeling, it is surprising that defects in transcriptional regulation of these proteins have been identified as major causes of heart failure (Morita et al., 2005). Environmental factors are considered key determinants of cardiovascular disease. Although some lifestyle choices such as smoking, diet and exercise are seen as major effects of the environment, the contribution of pollutants and chemicals in the environment is less clear. Exposures to arsenic, lead, cadmium, pollutant gases, solvents and pesticides have also been associated with an increased incidence of cardiovascular disease cardiology (Bhatnagar, 2006). Cardiac peptides play an important clinical role in the diagnosis and risk classification of patients with HF (Clerico et al., 2007). The most important cardiac peptide is B-type natriuretic peptide (BNP) which levels associate with the severity of heart failure (Fisher et al., 2003). The aim of this review is to reveal the potent role of GATA-4 transcription factors associated with the increase level of B-type natriuretic peptides which may be one of the causes in Heart Failure.

**B-type Natriuretic peptide**

BNP peptides are derived from precursor molecules that are encoded by two different genes, the atrial natriuretic peptide precursor A (NPPA) and the B-type natriuretic peptide or natriuretic peptide precursor B (NPPB) (Jochem et al., 2005). The Human BNP gene is located on chromosome 1 and encodes 108 amino acid prohormonepro BNP (Chiu et al., 2006). Biologically inactive peptide NT-proBNP causes natriuresis, diuresis, vasodilatation and smooth muscle relaxation. ANP is produced by atria, but has similar properties to BNP. Two cardiac natriuretic
peptides with a homologous structure are secreted by heart namely ANP and BNP as shown in (Fig. 1). A third homologous natriuretic peptide, termed CNP, is produced in brain and endothelium, but apparently not in cardiac myocytes (Christian, 2004). There were no mutations identified in the NPPB gene that can cause Heart disease, indicating that mutations in this gene are unlikely to be responsible for HF (Chiu et al., 2006). BNP physiology is affected by NPPB sequence variants, possibly via transcriptional regulation (David et al., 2007). In human the distribution of BNP are higher in the spinal cord, while only small amounts are detected in the brain (Aburaya et al., 1991). ANP and BNP have a significant role in the regulation of blood pressure and fluid homeostasis (Neubauer, 2007). In heart failure ventricular BNP production is higher than ANP (Sumida et al., 1995).

**Diagnosis of BNP**

B-type natriuretic peptide (BNP) blood concentration measurement appears to be a subtle and precise test to diagnose CHF. The significance of B-type natriuretic peptide as a diagnostic and therapeutic modality in cardiovascular disease is well known (David et al., 2007). Several different tests are accessible to measure serum BNP levels such as the Biosite Triage Test, Abbott Axsym Test, and the Bayer ADVIA Centaur Test measures BNP itself. BNP level related to different heart failure classes is shown in table I (Carolyn and Strimike, 2006). BNP measurement is cheaper and is potentially more approachable than the echocardiography because within 20 minutes the results of BNP testing can be obtained after blood collection (Jochem et al., 2005). Additional information is provided by the echocardiography that may be important in the clinical treatment of patients with heart failure; the most likely use of BNP will be in the ambulatory care setting to determine which patients require further testing with echocardiogram (McCullough et al., 2002). BNP level less than 100 pg/ml and NT pro BNP less than 400 pg/ml results in normal wall stress causing chronic HF unlikely whereas BNP greater than 400pg/ml and NT pro BNP greater than 2000pg/ml results in increased ventricular wall stress cause chronic HF likely (Kenneth et al., 2008). Patients with higher BNP levels should undergo further investigations, in order to estimate the etiology and pathophysiology of the underlying cause (McCullough et al., 2002).

**Risk Factors Associated With BNP**

Age and gender may influence circulating natriuretic peptide levels (Sayama et al., 1999). With the increase of age, the level of BNP also increases. Age and ethnic groups are responsible in finding significant differences in CHF excluding the other factors like sex (Alan et al., 2004). BNP / NT-proBNP level are influenced by age to a greater extent than ANP / NT-ANP level (Jochem et al., 2005). BNP levels increase with increasing age and are significantly higher in women than in men. The plasma levels of BNP being approximately 25% higher in females (Redfield et al., 2002). Mean normal BNP levels with the Biosite Triage Test are 26 pg/ml for persons aged (55-64), 31 pg/ml for those aged (65-74), and 63 pg per ml for those aged 75 years or older (Carolyn and Strimike, 2006). Only indication of age, sex, and left atrial volume are independently associated with BNP, BNP increased according to the volume index of the left atrium for each sex (Fig.2).
Tension or pressure increase inside the atria are followed by increase BNP’s level within 60 min, while in the ventricles, BNP’s levels increase in a few hours (Kruger et al., 2002). Response to ventricular volume expansion and pressure overload results in brain natriuretic peptide (BNP) secretion from membrane granules in the cardiac ventricles (Nakao et al., 1992). Increase cardiac wall stress is a common denominator of many cardiac diseases; it follows that circulating natriuretic peptides may serve as clinical biochemical markers of these states (Chiu et al., 2006). BNP plasma concentration also rises in pulmonary hypertension, but in this case the right ventricle is responsible for increased secretion (Cowie and Mendez, 2002).

Fluctuation in BNP is reported in the presence or absence of hormone replacement therapy (HRT). Margaret et al. (2002) reported that BNP appears to be partly related to estrogen status, as BNP levels are higher in women using HRT as shown in Figure (3). Diabetes mellitus (DM) is a fostering factor for increased plasma BNP levels in CHF patients. BNP level in CHF patients with diabetes mellitus (DM) is greater than in patients without DM as shown in Figure (4). Research depicted that BNP levels of coronary heart disease patients with DM significantly elevated compared to those of coronary heart disease patients without DM. The underlying mechanism of the highest concentration of BNP in CHF patients with DM is not clear, however, this can lead to an increase in the formation of BNP (Qiang et al., 2013). BNP plasma concentration is also influenced by non-cardiac disorders such as renal failure, Inappropriate BNP production from tumors, Thyroid disorders, Increase of circulating glucocorticoids and Hypoxia (Dorothea et al., 2003).

GATA-4
Inside the cell several proteins serve as regulatory transcription factors, which recognize and bind specific DNA sequences in promoters and regulates gene transcription. The expression of cardiac genes is regulated by several transcription factors, many of those induced during cardiogenesis and hypertrophic cardiomyocyte growth (Srivastava, 2001). The initially identified GATA family of transcription factors has an indispensable role in regulation of the two natriuretic peptide genes and appears to be at the heart of the molecular circuits controlling cardiac growth and the process. Particularly, GATA-4 act as the nuclear effect of several signaling pathways and its function is modulated by post-translational modifications and protein–protein interactions (Rana and Mona, 2005). The promoters of cardiac genes of BNP and ANP have been identified with numerous transcription factors that are up regulated in response to increased hemodynamic load. Mechanisms of controlling the expression of natriuretic peptide genes, ANP and BNP, have been analyzed which revealed many key regulatory elements, along with binding sites for transcription factors GATA4, NFATc4 and Elk-1 (Karen et al., 1995). Identification of binding motifs for GATA-factors within the promoters of a number of cardiac-expressed genes, and BNP is one of them. GATA-4 is also regulated by interactions with other transcriptional cofactors in addition to phosphorylation and increased gene expression. A number of transcription factors and nuclear cofactors have been found to interact with GATA-4 to activate or repress cardiac gene expression.
GATA-4 is the member of the zinc finger GATA transcription factor family and is involved in cardiac development and regulation of the hBNP promoter. The hBNP gene, proximal promoter region is located from −127 to −40 relative to the transcription start site, and is important for tissue-specific expression (LaPointe et al., 1996). The hBNP gene expression indicated that the hBNP promoter is more active in myocytes than in fibroblasts. The site at −85 is required for basal hBNP promoter activity and transactivation of the hBNP promoter by GATA-4 (Thuerauf et al., 1994). Isoproterenol and cAMP activation of the hBNP promoter is reduced by 60% and 75% respectively by the mutation of the GATA element. GATA proteins play a role in inducible gene expression and cardiac hypertrophy. During hypertrophy the BNP gene is induced and hypertrophic factors target the GATA site in the proximal hBNP promoter. The GATA element is in part a target for signaling pathways activated by ISO and cAMP. The isoproterenol and its second messenger cAMP have effect on the proximal hBNP promoter and it is found that ISO stimulated it 4-fold and cAMP stimulated it 3-fold. GATA co-factors are involved in the regulation of the ANP and BNP promoters and mutation in GATA-4 gene results in congenital heart defects. GATA-4 has a stimulatory effect on ANP and BNP, and both genes are direct GATA targets (Quan et al., 2002). The structure of the proximal BNP promoter is evolutionarily conserved and contains two GATA motifs, one YY1, one CACC box-binding protein and an MCAT motif at _100 bp (Fig.5). The MCAT element has been linked to BNP promoter activation in response to interleukin-1h, an inflammatory cytokine, through a p38 kinase-dependent pathway. GATA-4 recruits YY1 protein to enhance BNP transcription by forming a transcriptional complex with the c-AMP response element-binding protein. In a recent study both BNP and ANP promoters were synergistically activated by GATA-4 (Rana and Mona, 2005). In human hearts, GATA4 has also been shown to be a critical regulator of cardiac development, as shown by the association between GATA4 mutations and the presence of congenital cardiac malformations (Garg et al., 2003). Adult cardiomyocytes reactivate the fetal gene regulatory program and down regulate different isoforms of the adult in response to hypertrophic stimuli. Re-expression of the GATA4-regulated genes ANP and BNP is considered a hallmark of pathological hypertrophy and heart failure (Olson and Molkentin, 1999; Miyata et al., 2000).

CONCLUSION

This review summarizes that heart secrets two cardiac peptides BNP and ANP. The production of BNP level is higher than the ANP in HF. BNP level surges in the patients with CHF and shortness of breath. BNP improves the diagnostic accuracy of dyspneic patients along with the clinical judgments. The level of BNP increases with the increase of age and has been seen significantly higher in elderly women than men. The promoters of the cardiac genes have certain transcription factors that regulate the natriuretic peptide genes and GATA-4 is one of the major members of transcription factor family. The mutation in the human GATA-4 may be the cause of heart defects and elevated level of BNP in HF patients because the GATA-4 is involved in the regulation of BNP promoters and cardiac development.
**Fig.1:** Cardiac natriuretic peptides ANP (28 amino acids) and BNP (32 amino acids) are homologous in structure, forming a ring with a disulfide bridge. Black color shows similar amino acids (Christian, 2004).

**Fig.2:** Relation of BNP level with males and females (Margaret et al., 2002)

**Fig.3:** Relation between BNP level and female Hormone Replacement Therapy (Margaret et al., 2002).
Fig. 4: B-type natriuretic peptide (BNP)-score curves of the CHF patients with Diabetes mellitus and without Diabetes Mellitus (Qiang et al., 2013).

![Graph showing BNP-score curves for CHF patients with and without Diabetes Mellitus.](image)

Fig. 5: GATA motifs in BNP promoter region (Rana and Mona, 2005).

![Diagram showing GATA motifs in BNP promoter region.](image)

Table I. Levels of BNP with Different Heart Failure Classes

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<thead>
<tr>
<th>New York Heart Association Classes</th>
<th>BNP level (pg/ml)</th>
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<tbody>
<tr>
<td>Mild (NYHA Class I)</td>
<td>83-152</td>
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<tr>
<td>Mild to moderate (NYHA Class II)</td>
<td>235-322</td>
</tr>
<tr>
<td>Moderate to severe (NYHA Class III)</td>
<td>459-590</td>
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<tr>
<td>Severe (NYHA Class IV)</td>
<td>960-1119</td>
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