Introduction

The prevalence of chronic heart failure is significantly increased in dialysis patients and is associated with left ventricular hypertrophy (LVH), which may be secondary to volume overload and hypertension ***(Locatelli et al., 2003)*.**

LVH is present in almost 75% of patients who start dialysis, and left ventricular (LV) systolic dysfunction is present in approximately 16% ***(Foley et al., 2005)*.** LV growth and increase in LV volume is evident over time and pulmonary edema is a frequent clinical event, which is associated with change in LV structure and function ***(Foley et al., 2010)*.**

There is cumulative evidence to support the generally acknowledged idea that volume status is an important predictor of outcome in patients on renal replacement therapy. Good and accurate volume status leads to better control of hypertension and better control of blood pressure results in regression of left ventricular hypertrophy in hemodialysis (HD) patients. A good strategy to avoid volume overload and keep patients euvolemic is thus essential ***(Katzarski et al., 2009)*.**

Although much clinical attention is paid to volume status, 24% of patients still have clinically relevant volume

overload. Implementation of a reliable and clinically applicable tool to assess volume status is therefore necessary ***(Devolder et al., 2010)*.**

Evaluation of "euvolemia" is, however, severely hampered by the lack of a reliable objective tool that can be used to measure volume status in everyday clinical practice. Most physicians rely on clinical evaluation, using absence of edema and good blood pressure control as parameters of interest. However, several liters of water can be retained before edema becomes visible ***(Devolder et al., 2010)*.**

No single method has emerged as a gold standard for evaluation of fluid status, and the combination of clinical, biochemical and other methods such as bioimpedance analysis (BIA) and inferior vena cava (IVC) diameters is generally needed to complement their respective limitations ***(Chih-cheng et al., 2010)*.**

The natriuretic peptides comprise at least three molecules (A, B, and C), which play an important role in blood pressure (BP) and volume homeostasis, with biologic actions on kidney, heart, and blood vessels. ANP is secreted mainly by the right atrium, BNP is produced by the cardiac ventricles, and CNP is produced mainly by endothelial cells. Their biologic effects include increased

glomerular filteration rate (GFR), natriuresis, and diuresis; vasorelaxation with decreased cardiac preload and afterload; suppression of renin-angiotensin-aldosterone axis, sympathetic outflow, antidiuretic hormone (ADH), and endothelin; and inhibition of mitogenesis in vascular smooth muscle cells, growth factor–mediated hypertrophy in cardiac fibroblasts, and cardiac remodeling ***(Skorecki et al., 2008)*.**

B-Type natriuretic peptide (BNP) is synthesized as preproBNP mainly in the ventricular myocardium. On ventricular myocyte stretch, preproBNP is enzymatically cleaved to proBNP and released in the form of the hormonally active BNP and the inactive N-terminal proBNP (NT-proBNP). Both BNP and NT-proBNP have been shown to reflect heart failure severity ***(McCullough and Sandberg, 2003)*.**

Renal function clearly influences the diagnostic performance of NT-proBNP; Goei, et al. had showed that NT-proBNP had more favorable discriminative value in patients with glomerular filtration rate (GFR) more than 90 mL/min/1.73 m^2 and lost its prognostic value in patients with GFR less than 30 mL/min/1.73 m^2 ***(Goei et al., 2008)*.**

Also, Tagore et al. reported that unlike NT-proBNP, BNP levels are relatively independent of GFR. BNP may

therefore be the more appropriate biomarker to screen for volume status in patients with renal failure ***(Tagore et al., 2008)***.

Both BNP and NT-proBNP are eliminated during hemodialysis, but they show different behaviors depending on the chosen dialysis membrane. BNP is cleared by both high- and low-flux membranes. NT-proBNP has clearance and reduction rates similar to BNP when high-flux membranes are used but very low clearance with low-flux membranes, leading to an increase in post-dialysis plasma concentrations ***(Wahl et al., 2004)***.

High plasma BNP concentrations in HD patients were associated with volume overload, left ventricular hypertrophy, cardiovascular disease and DM. Plasma BNP concentration may be a useful parameter for assessing the risk of cardiac death in HD patients by providing prognostic information independently of other variables previously reported ***(Naganuma et al., 2011)***.

Although higher BNP levels may be associated with LVH and with systolic dysfunction, it seems reasonable to conclude that in stable hemodialysis patients with normal LV function on echocardiography, high BNP levels are likely the result of blood volume expansion and require reduction in postdialysis dry weight ***(Parfrey, 2010)***.

BNP predicted mortality in hemodialysis patients ***(Madsen et al., 2007).*** Also, ***Foley et al. (2010)a*** recently reported that in new hemodialysis patients the independent predictors of subsequent cardiovascular events or death were age, diabetes, systolic BP, and BNP.

The fluid overload biomarker, brain-type natriuretic peptide (BNP), previously known as a "cardiac biomarker" in dialysis patients, is an important component of managing patients with kidney disease ***(Booth et al., 2010).***

There is no set cut-point for either BNP or NT-proBNP for predicting death and cardiac hospitalization in renal patients, but abnormally high levels should signal the need to optimize medical management and to monitor more closely ***(Hajjar and Schreiber, 2009).***

Biochemical markers such as BNP are hampered by a lack of standardized cutoff values in HD patients ***(Devolder et al., 2010).***

Aim of the Work

The aim of this work is to find a cut off value for BNP in hemodialysis patients with fair cardiac function which indicates concealed volume overload that need revision of postdialysis dry weight to preserve cardiac function & reduce the risk of cardiovascular mortality on the long term.

Brain Natriuretic Peptide

Historical Perspectives

In 1981, ***de Bold et al (1981)*** provided the definitive demonstration of the endocrine function of the heart by the description of atrial natriureticpeptide (ANP)**.** This was followed by the identification of brain natriuretic peptide, or B-type natriuretic peptide (BNP), in 1988. This natriuretic peptide (NP) was originally discovered in the porcine brain, but it is synthesised, stored and released mainly in the myocardium ***(Cacciaputo et al., 2010)*****.**

Physiology and Pathophysiology

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Physiological Effects of BNP ***(Johannes Mair et al., 2008)*:**

1. Inhibition of drinking and sympathetic activity in the central nervous system.
2. Natriuresis and diuresis.
3. Inhibition of the renin–angiotensin–aldosterone system (RAAS).
4. Vascular smooth-muscle relaxation, vasodilatation.
5. Increase in endothelial permeability.

6. Pulmonary smooth muscle relaxation.
7. Increased lipolysis in adipose tissue.
8. Inhibition of cardiac and vascular remodeling.

Diseases with Increases in BNP and NT-proBNP ***(Johannes Mair et al., 2008)*****:**

- Acute or chronic systolic or diastolic heart failure
- Acute coronary syndrome
- Left ventricular hypertrophy (LVH)
- Inflammatory cardiac diseases
- Atrial fibrillation
- Systemic arterial hypertension with LVH
- Pulmonary hypertension
- Acute or chronic renal failure
- High output states (e.g. liver cirrhosis, sepsis, hyperthyroidism, anaemia
- Endocrine disorders (e.g. hyperaldosteronism Cushing's syndrome)
- Central nervous system diseases (e.g.Subarachnoid haemorrhage, stroke)
- Paraneoplastic syndrome

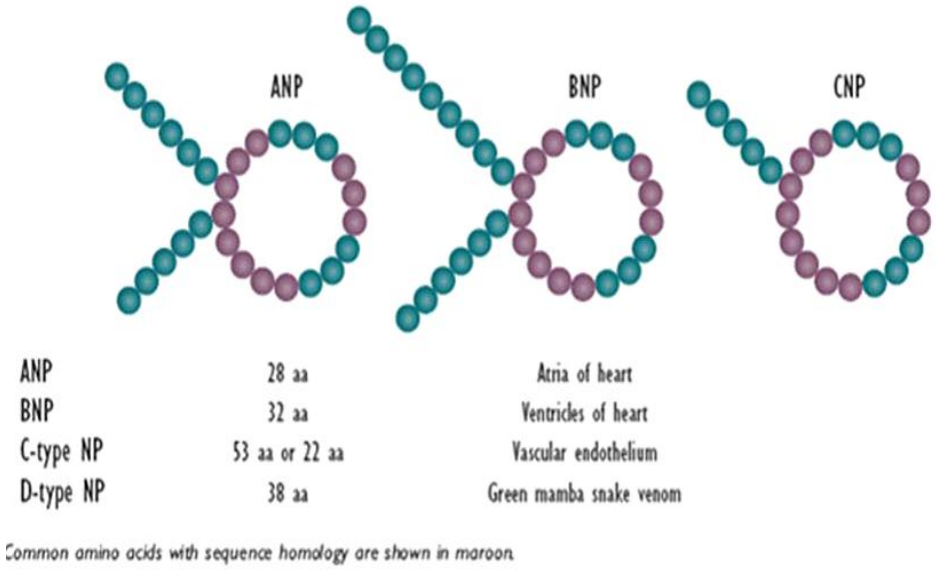

Figure 1: Structure of natriuretic peptides ***(Collinson et al., 2005).***

Biochemistry

Current understanding of the biochemistry of BNP and its circulating forms is far from complete. The human gene for BNP encodes a 134-aminoacid pre-proBNP precursor, which, after removal of a 26-aminoacid signal peptide, gives rise to a 108-amino-acid proBNP polypeptide ***(Yan W et al., 2000)*.**

The regulation of BNP secretion occurs mainly at the level of gene transcription with only minor stores within cardiomyocytes. proBNP is believed to be split into BNP 1–32 and NT-proBNP 1–76, mainly upon secretion although limited amounts of processed BNP have also been

described in the secretory granules of atrial cardiomyocytes. The processing site in proBNP occurs immediately down stream from the Arg73-X-X-Arg76 sequence, at a cleavage site similar to that recognised by the ubiquitous endoprotease furin.

However, other endoproteases such as corin ***(Heublein et al., 2007)*** or prohormone convertases may be involved in the post-translational maturation of ProBNP ***(Hammerer-Lercher et al., 2008).***

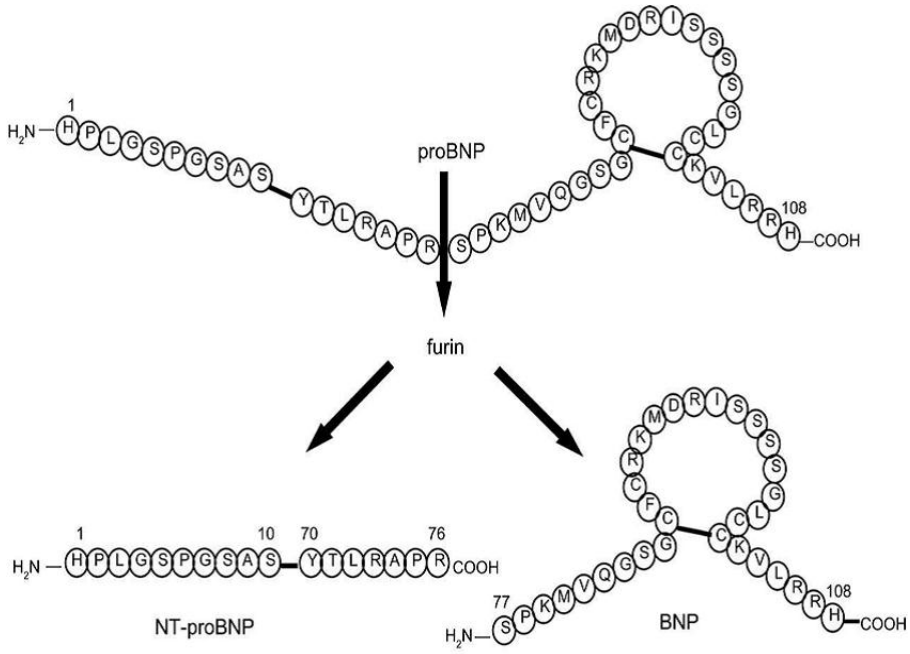

Figure 2: Drawing of pro BNP showing enzymatic cleavage into biologically active BNP and NT –pro BNP ***(Hall et al., 2004).***

BNP exhibits the biological activity, whereas no defined biological function has been found to be associated with NT- ProBNP ***(Ala-Kopsala et al. 2004).*** proBNP can be also detected in the **circulation** ***(Schellenberger et al., 2006).*** It circulates as amonomer and has only weak biological effects compared with BNP ***(Ala-Kopsala et al., 2004).*** There is no evidence for relevant processing of proBNP into BNP 1–32 and NT-proBNP in the circulation. Only small amounts of the intact hormone BNP 1–32 appear to circulate in plasma, and there are no known BNP-binding proteins.

The major circulating BNP forms appear to be split products of BNP 1–32, but are still not sufficiently characterised. Dipeptidylpeptidase IV degrades BNP 1–32 to BNP 3–32 at its Nterminal end. NTproBNP appears to be rapidly truncated at both ends as well ***(Schou et al., 2005).*** proBNP and NT-proBNP are both glycosylated to a variable degree ***(Seferian et al., 2007).*** BNP and NT-proBNP are extracted by the kidneys to a comparable extent of only about 15–20% ***(Seferian et al., 2007).***

Clinical Applications

Heart failure

Chronic heart failure is an illness that is appearing with increasing frequency, especially in elderly patients. Nevertheless, classification is often difficult due to non-specific symptoms and the lack of a 'gold standard' protocol for a correct diagnosis.The European guidelines from 2008 highlight the role of natriuretic peptides as potential markers of heart failure. Measurement of plasma concentrations of BNP has proved to be a very efficient screening technique for the identification of patients with various heart diseases, regardless of aetiology and the degree of systolic dysfunction of the left ventricle, which has the potential to develop into manifested heart failure and has a high risk of producing a cardiovascular event. Recently, the Food and Drug Administration approved NT-pro-BNP for evaluation of the prognosis of patients with congestive heart failure and acute coronary syndromes. Determination of BNP level was also approved for risk segregation in acute coronary syndromes ***(Raizada et al., 2007)*.**

Multiple studies have confirmed the efficiency of the determination of BNP concentrations in the plasma of patients with acute dyspnoea. Together with its role in

acute decompensated heart failure, levels of BNP are also high for diastolic dysfunction. Increased BNP levels can be found with isolated diastolic dysfunction, hypertrophic cardiomyopathy, or associated with systolic dysfunction. Echocardiographic parameters correlated with BNP levels include mass index of the left ventricle, its end-diastolic volume and isometric relaxation time. The further the stage of diastolic dysfunction the higher the levels of BNP ***(Burke et al., 2007)*.**

Other heart diseases

As with congestive heart failure, BNP level has a prognostic value for acute coronary syndromes. BNP is additive with, and independent of, the increases in troponin I for these syndromes ***(Burke et al., 2007)*.**

A sub-study of Breathing Not Properly showed that plasma levels of BNP were high for patients with atrial fibrillation that was not diagnosed with congestive heart failure, but its levels were not different in the presence of heart failure ***(Burke et al., 2007)*.**

In addition, levels of BNP were high with heart valve diseases and aortic stenosis, and were linearly related to the symptoms. Moreover, levels over 190 pg/ml foresaw a negative evolution, suggesting that BNP can be used for identification of subgroups of patients that would benefit

from a replacement of the aortic valve. In addition, BNP level was increased with aortic insufficiency ***(Burke et al., 2007)*.**

For patients with mitral insufficiency, an increased BNP level was correlated with mortality and the onset of congestive heart failure, regardless of the degree of regurgitation present on echocardiography, suggesting that BNP is a reflection of its atrial and ventricular consequences. Finally, it was proven that NT-pro-BNP was correlated with symptoms and echocardiographic severity of mitral stenosis. In addition, the levels of BNP were increased in patients with pulmonary embolism and pulmonary hypertension ***(Burke et al., 2007)*.**

In unstable angina, NT-pro-BNP represents an effective marker of the damage produced by cardiac ischaemia. The severity of the coronary disease is shown by an increase in the levels of NT-pro-BNP. In addition, in the case of acute coronarysyndromes, NT-pro-BNP had an immuno modulating role and offered important information for the prognosis of patients ***(Cacciaputo, 2010)*.**

Castro et al. (2011) divided 87 patients with non-ST-segment elevation acute coronary syndrome into two groups: 37 (42.5%) with unstable angina and 50 (57.5%) with non-ST-segment elevation myocardial infarction. Left