INTRODUCTION

B-type natriuretic peptide (BNP) is released from the ventricles in response to cardiac overload from CHF or some other forms of left ventricular systolic dysfunction. Therefore, the detection and measurement of BNP is a fast and accurate method of determining if CHF is the cause of a patient's breathing difficulties ***(Gray et al., 2006).***

In the normal heart, the endocrine capacity resides in the atria. Atrial myocytes express and secrete natriuretic hormones that regulate fluid homeostasis and blood pressure. But in ventricular disease, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) gene expression is also activated in ventricular myocytes. Plasma concentrations of natriuretic peptides and their biosynthetic precursors are accordingly increased in patients with marked ventricular dysfunction ***(Goetze et al., 2006).***

Left atrium (LA) enlargement has been recognized as a marker of the duration of left ventricular diastolic dysfunction. LA volume index (LAVI) may be useful to differentiate normal from pseudonormal left ventricular filling pattern ***(Barberato et al., 2007).***

Left atrial size could provide prognosis on congestive heart failure (CHF). N-terminal Pro B-type natriuretic peptide (NT-ProBNP) has also been useful for predicting adverse cardiac events. Both NT-ProBNP and LAVI might

have the most predictable power, particularly in non-ischemic advanced DCM ***(Kim et al., 2008).***

There is close association between natriuretic peptide concentrations and parameters of LA size derived from planimetry and volumetry. This suggests a superiority of these parameters over LA diameter ***(Buchner et al., 2008).***

Left atrial (LA) volume and B-type natriuretic peptide (BNP) represent powerful outcome predictors in patients with heart failure (HF). Although directly related to Left ventricular diastolic diameter and to BNP levels, only Left atrium volume index emerged as an independent outcome predictor in elderly patients with symptomatic stable chronic HF ***(Popescu et al., 2007).***

In another study, there is relation between left atrial volume and B-type natriuretic peptide levels in patients with stable chronic heart failure ***(Barclay et al., 2006).***

In patients with heart failure with a preserved ejection fraction evidenced by high NT-pro-BNP level, Left atrium volume index correlates with NT-pro-BNP level ***(Kim et al., 2008).***

Left atrial dilation and systolic dysfunction (left atrial remodelling) contributes to the progression of asymptomatic LV dysfunction to chronic symptomatic systolic HF as it is a prerequisite for the development of the pulmonary congestion and marked neurohormoral activity that characterize the symptomatic state ***(Karayannis et al., 2008).***

AIM OF THE WORK

The aim of the study is to identify the relation between left atrial volume index and NT-ProBNP level as prognostic factors in patients with left ventricular systolic dysfunction.

Chapter I

HISTOLOGICAL AND PHYSIOLOGICAL ASPECTS

Cardiac myocytes are large cells. They are joined together in a syncytium. The sarcolemma surrounding the myocyte through the intercalateddisk joins to adjacent cells and invaginates into the myofibril through the T-tubules ***(Robert, 2008).***

The sarcomeres are joined in series with each other via the Z-lines. The sarcomere is composed of many proteins, with myosin and actin being the predominant proteins comprising the thick and thin filaments. ***(Robert, 2008).***

The sarcoplasmic reticulum (SR) is the most important organelle (Fig.1). Anatomically, the SR is a fine network spreading throughout the myocytes ***(Opie, 2008).***

Mitochondria are interspersed between the myofibrils and immediately beneath the sarcolemma.The cytoplasm is the intracellular fluid and proteins, contained within the sarcolemma but excluding the contents of organelles such as mitochondria and the SR ***(Opie, 2008).***

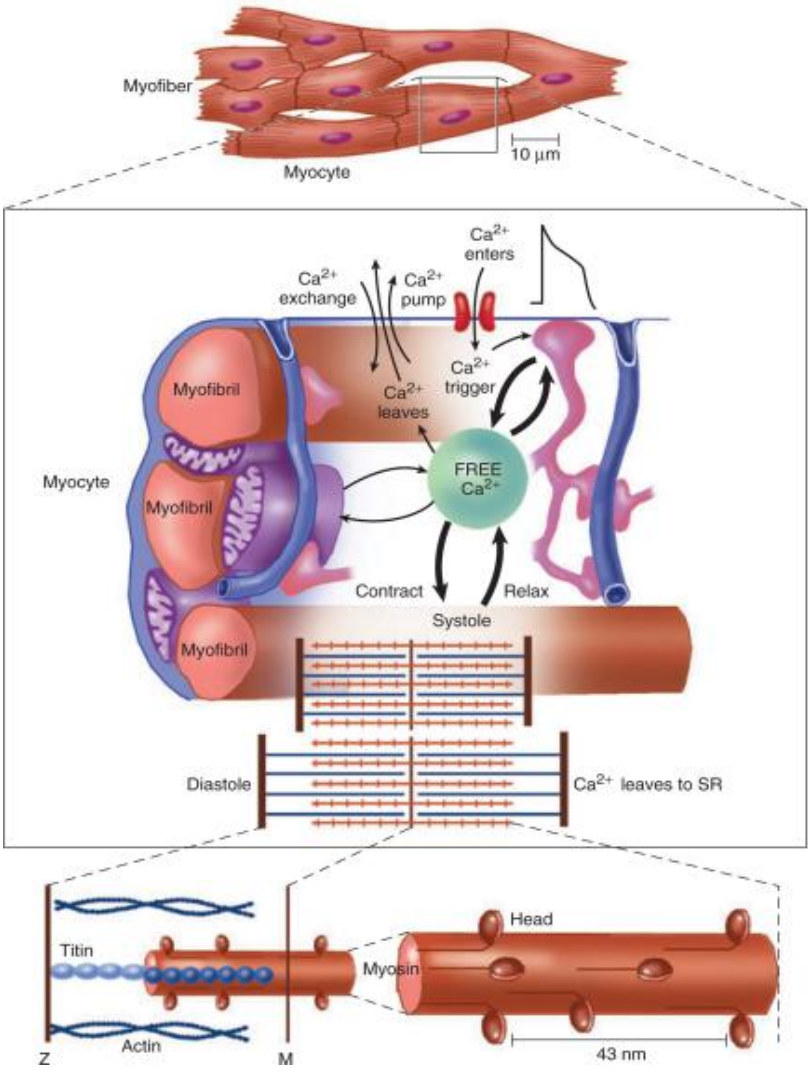

Figure (1): Myocytes and the role of Ca^{2+} ions. Upper panel: Difference between the myocardial cell or myocyte, and the myofiber, composed of many myocytes. Middle and lower panels: Ca^{2+} ions are schematically shown as entering via the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma ***(Opie, 2008).***

Calcium ion flux within myocytes plays a pivotal role in the regulation of contractile function. Excitation of the myocyte cell membrane causes the rapid entry of calcium into myocytes from the extracellular space via calcium channels. This triggers the release of intracellular calcium from the sarcoplasmic reticulum and initiates actin myosin filaments interaction and therefore contraction results ***(John Camm, 1997).***

Relaxation results from the uptake and storage of calcium by the sarcoplasmic reticulum. In heart failure, there is a prolongation of the calcium current in association with prolongation of contraction and relaxation ***(John Camm, 1997).***

The left atrial function:

1. It is a blood-receiving reservoir chamber .
2. It is a contractile chamber, which, by presystolic contraction helps complete LV filling .
3. It functions as a conduit that empties its contents into the LV down a pressure gradient.
4. It is the volume sensor of the heart, releasing atrial natriuretic peptide (ANP) in response to intermittent stretch, so that an ANP-induced diuresis can help restore blood volume to normal.

5. The atrium contains receptors for the afferent arms of various reflexes, including mechanoreceptors that increase sinus discharge rate, thereby contributing to the tachycardia of exercise as the venous return increases (Bainbridge reflex) ***(Pagel et al., 2003).***

Chapter II
PATHOGENESIS OF HEART FAILURE

Chronic heart failure is a syndrome in which structural or functional alterations of the heart lead to secondary phenomena such as exertional dyspnea and circulatory congestion. The diseased heart is the centerpiece of the syndrome ***(Gray et al., 2008).***

Heart failure may be viewed as a progressive disorder that is initiated after an "index event" damages the heart muscle. This index event may have an abrupt onset, as in (MI); it may have a gradual or insidious onset ***(Mann, 1999)***.

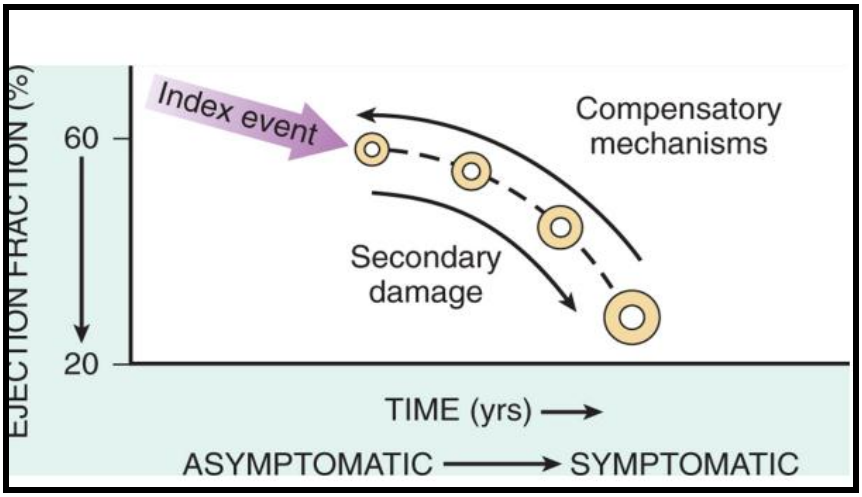

Figure (2): Pathogenesis of (HF) ***(Mann, 1999).***

Cardiogenic pulmonary edema is the result of an imbalance in fluid resorption and accumulation in the pulmonary interstitium and alveolar space that can be described by a sequence of three stages, progressing from pulmonary venous engorgement to interstitial edema to alveolar edema ***(Ware and Matthay, 2005).***

Myocardial ischemia potentiates this cycle by further increasing diastolic dysfunction and possibly reducing systolic function, as well as by inducing acute ischemic mitral regurgitation ***(Pierard and Lancellotti, 2004).***

Increases in plasma concentrations of surfactant protein-B (SP-B), a small protein normally confined to the alveolar space with a short half-life, have been demonstrated in patients with pulmonary edema, and these levels remain elevated for at least 3 days after resolution of the inciting increase in blood pressure and volume overload, suggestive of significant alveolar capillary structural damage ***(De Pasquale et al., 2004).***

Heart failure is a known complication of ACS and portends a poor clinical outcome, suggesting that an aggressive evaluation of ischemic etiologies should be performed with the potential goal of earlier revascularization ***(Steg et al., 2004).***

Several studies with serial measurements of troponins have demonstrated significant and sustained increases,

confirming that ongoing myocardial necrosis in the absence of acute coronary syndrome occurs in HF ***(Burger et al., 2003; Milo et al., 2003).***

Neurohormonal Mechanisms:

Some experts have suggested that HF should be viewed as a neurohormonal model, in which HF progresses as a result of the over expression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation ***(Mann and Bristow, 2005).***

The compensatory mechanisms that have been described include activation of the adrenergic nervous system including norepinephrine (NE) and renin angiotensin system (RAS) including angiotensin II, which are responsible for maintaining cardiac output through increased retention of salt and water, peripheral arterial vasoconstriction and increased contractility ***(Mann and Bristow, 2005).***

Among the most important counterregulatory neurohormonal systems that become activated in HF are the natriuretic peptides which consist of five structurally similar peptides, termed ANP, urodilantin (an isoform of ANP), BNP, C-type natriuretic peptide (CNP), and Dendroaspis natriuretic peptide (DNP**)** ***(Cea, 2005).***

Natriuretic Peptides and Heart Failure

ANP: A 28–amino acid peptide hormone is produced principally in the cardiac atria with short half-life of 3 minutes.

BNP: A 32–amino acid peptide originally isolated from porcine brain, was later identified as a hormone produced in the cardiac ventricles with half-life of 20 minutes ***(Rademaker and Richards, 2005)***.

Both ANP and BNP are secreted in response to increasing cardiac wall tension. ANP and BNP are initially synthesized as prohormones that are subsequently proteolytically cleaved, respectively, by corin and furin, to yield large biologically inactive N-terminal fragments and smaller biologically active peptides (ANP or BNP) ***(Munzel et al., 1992).***

These peptides stimulate the production of the intracellular second messenger cGMP via binding to the natriuretic peptide A receptor (NPR-A), which preferentially binds ANP and BNP, and the natriuretic peptide B receptor (NPR-B), which preferentially binds CNP) (Figure 3) ***(Munzel et al., 1992).***

Natriuretic peptides are degraded by neutral endopeptidase (NEP), which is expressed in multiple tissues, where it is localized with ACE. The infusion of the

endopeptidase inhibitor candoxatrilat into patients with HF resulted in a reduction in left -and right-sided filling pressures that was associated with suppression of plasma NE levels and a transient reduction in plasma vasopressin ***(Munzel et al., 1992).***

Although some early trials suggested that neutral endopeptidase inhibition would have a greater benefit than ACE inhibition, more recent trials have found the two classes of drug to exert similar effects on survival ***(Packer et al., 2002)***.

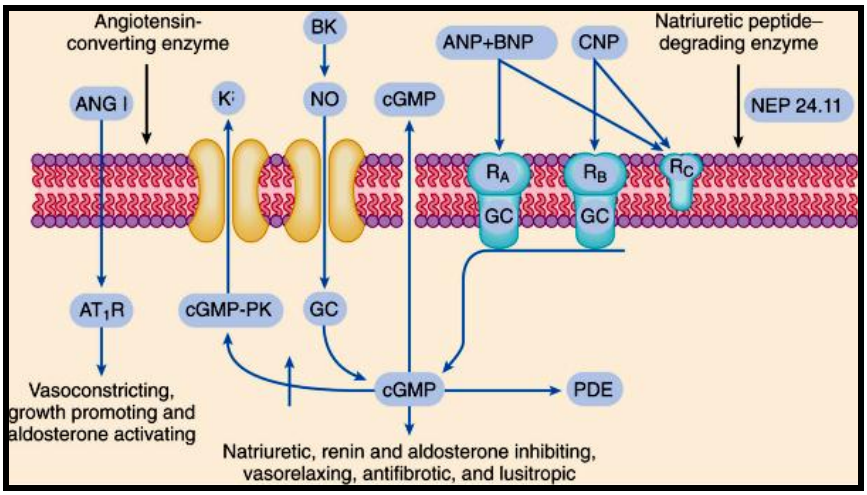

Figure (3): Cellular actions in signaling of the natriuretic peptide system ***(Burnett* et al., *2004).***

Classifications and causes of Heart Failure

- One system classifies patients based on the presence of a history of cardiac dysfunction.

Acute de novo heart failure: Patients without a history of heart failure are considered in this class of HF, sympathetic activation is more pronounced and the clinical picture is complicated by redistribution of intravascular fluid and marked systemic vasoconstriction ***(Nieminen et al., 2005).***

Chronic heart failure: those with known disease or history of chronic heart failure usually have a less dramatic clinical presentation because the chronic nature of the disorder has allowed for recruitment of compensatory mechanisms and remodelling, such as increased pulmonary lymphatic drainage ***(Nieminen et al., 2005).***

- Stevenson and colleagues developed another clinically relevant and widely used classification system. This system evaluates patients based on the clinical presence or absence of hypoperfusion (cold versus warm) and congestion at rest (wet versus dry) (Fig. 4) ***(Nohria et al., 2005).***

These clinical profiles can have prognostic significance. In addition, these profiles have been used to guide therapy ***(Thom et al., 2006; Swedberg et al., 2005).***

- Another very important classification is (NYHA) Classification of Cardiac Disease (Table 1).

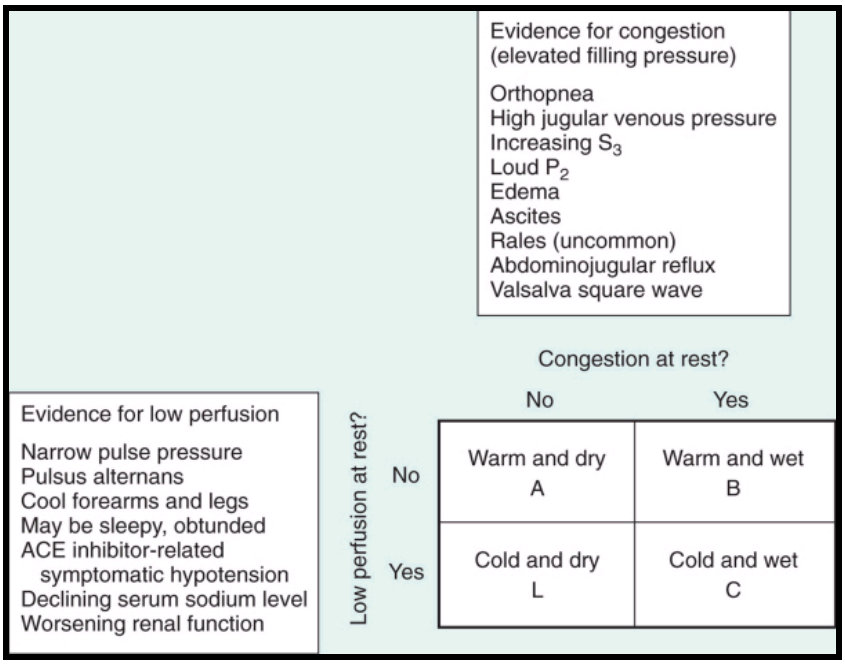

Figure (4): Hemodynamic profiles of patients presenting with advanced heart failure as described by a 2 × 2 table ***(Nohria et al., 2005).***