Introduction

Cardiac natriuretic peptides are family of hormones that are important in sodium and volume homeostasis. They consist of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-Type natriuretic peptide (CNP) ***(Klapholz, 2003).***

Natriuretic peptides are synthesized and stored as 3 distinct precursor prohormones and each is encoded by separate genes and has distinct sites of synthesis and mechanisms of regulation ***(Vesely, 1995).***

In patients with left ventricular dysfunction and heart failure, natriuretic peptides promote natriuresis, diuresis, peripheral vasodilation, and inhibit the renin-angiotensin system. The serum levels of the natriuretic peptides correlate with the severity of heart failure and appear to have prognostic value ***(Cheng, 2002).***

Burentt et al., 1996 correlated increased circulating concentrations of ANP both with elevated cardiac filling pressures and severity of ventricular systolic dysfunction.

Heart failure in children and infants with rheumatic mitral regurgitation (MR), congenital heart diseases and cardiomyopathy is caused by volume overload and increase in atrial natriuretic peptide (ANP) levels due to atrial stretching ***(Kula et al., 2003).***

Measuring plasma natriuretic peptide levels can aid in identifying patients with impaired left ventricular systolic and diastolic function and in establishing the etiology of dyspnea in patients with compound cardiac and pulmonary pathology ***(MC Donagh et al., 1998).***

Several studies in humans have investigated the efficacy of exogenously administrated ANP in the treatment of chronic heart failure, the response of ANP infusions in heart failure patients generally appears to be attenuated and possibly related to ANP receptors down-regulation, abnormal intrarenal hemodynamics, decreased renal perfusion pressure, phosphodiesterase activity and enhanced renal degradation ***(Cody et al., 2000).***

ANP lowers blood pressure and has potent sodium diuretic and vascular relaxation effects. The renin-angiotensin system, which is involved in raising blood pressure, is antagonized by ANP. Soualemia et al., 2001 reported that administration of angiotensin converting enzyme inhibitor produces a compensatory increase in ANP synthesis and secretion.

Angiotensin converting enzyme inhibitors (ACEIs) are hypotensive agents that have a preventive effect on myocardial remodeling, anti-inflammatory actions and improve function of the vascular endothelial cells ***(Sata et al., 2003).***

Aim of the Work

This study aimed to determine ANP in pediatric cardiac lesions with volume overload with or without heart failure i.e. rheumatic mitral and aortic regurgitation, congenital acyanotic shunt lesions and dilated cardiomyopathy.

The degree of improvement of heart failure clinically, by echocardiographic indices and ANP level will be re-evaluated after the use of ACEIs in the studied groups.

Pathophysiology of Heart Failure

Heart (cardiac) failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only from an elevated filling pressure ***(Hunt et al., 2005).***

The term heart failure denotes the failure of the heart as a pump. The heart has the amazing capacity to adjust its pumping ability to meet the varying needs of the body. During sleep its output declines and during exercise it increases markedly. The ability to increase cardiac output (COP) during increased activity is called the Cardiac reserve, for example competitive swimmers and long-distance runners have large cardiac reserves. During exercise the COP of these athletes rapidly increases to as much as five to six times their resting level. In sharp contrast with healthy athletes persons with heart failure often use their cardiac reserves at rest. For them just climbing a flight of stairs may cause shortness of breath because they have exceeded their cardiac reserves. The pathophysiology of heart failure involves an interaction between several factors: (1) a decrease in COP with a consequent decrease in blood flow to the kidneys and other body organs and tissues; (2) the recruitment of the compensatory mechanisms designed to maintain tissue perfusion ***(Mann et al., 2005).***

Cardiac Contractility

Cardiac contractility refers to the mechanical performance of the heart: the ability of the contractile elements (actin and myosin filaments), of the heart muscle to interact and shorten against a load. Contractility increases cardiac output independent of preload filling and muscle stretch. An inotropic influence is one that increases cardiac contractility. Sympathetic stimulation increases the strength of cardiac contraction (i.e, positive inotropic effect) and hypoxia and ischemia decrease positive contractility (i.e, negative inotropic effect) ***(Hunt et al., 2009).***

Compensatory Mechanisms In Case Of Heart Failure

With a decrease in cardiac performance, tissue and organ perfusion is largely maintained through compensatory mechanisms such as the Frank-Starling mechanism, activation of the sympathetic nervous system and the reninangiotensin-aldosterone mechanism, and myocardial hypertrophy ***(Piran et al., 2002).***

In the failing heart, early decrease in cardiac function often goes unnoticed because these compensatory mechanisms are used to maintain the cardiac output. This state is called compensated heart failure. Unfortunately, these mechanisms were not intended for long-term use. In severe and prolonged heart failure, compensatory mechanisms are no longer effective and may

themselves worsen the failure, causing what is termed decompensated failure ***(Hunt et al., 2005).***

I-Frank-Starling Mechanism

The Frank-Starling mechanism relies on an increase in venous return and a resultant increase in diastolic filling of the ventricles, known as the end-diastolic volume. This volume causes the tension on the wall of the ventricles and the pressure in the ventricles to rise. With increased ventricular end-diastolic volume, there is increased stretching of the myocardial fibers, more optimal approximation of the actin and myosin filaments, and resultant increase in the stroke volume in accord with the Frank-Starling mechanism ***(Katz, 2000).***

In heart failure a decrease in COP and renal blood flow leads to increased salt and water retention, a resultant increase in vascular volume and venous return to the heart, and an increase in ventricular end-diastolic volume. Within limits as preload and ventricular end-diastolic volume increase there is a resultant increase in cardiac output. Thus cardiac output may be normal at rest in persons with heart failure. However as myocardial function deteriorates, the heart becomes overfilled, the muscle fibers become overstretched and the ventricular function curve flattens ***(Tang et al., 2005).***

The maximal increase in COP that can be achieved may severely limit activity while producing an elevation in left ventricular and pulmonary capillary pressure and development of dyspnea and pulmonary congestion. An important determinant of myocardial energy consumption is ventricular wall tension. Overfilling of the ventricle produces a decrease in wall thickness and an increase in wall tension, because increased wall tension increases myocardial oxygen requirements, it can produce ischemia and further impairment of cardiac function ***(Eigel et al., 2004).***

II-Neurohormonal, autocrine and paracrine adjustment

In response to the reduction of cardiac output, the inadequate arterial volume that is characteristic of systolic heart failure, and atrial hypotension a complex series of neurohormonal changes takes place. In the early stages of severe acute systolic failure, these changes heighten adrenergic drive, activation of the renin-angiotensin-aldosterone axis, and augment release of vasopressin and endothelin, compensate and act to maintain perfusion to vital organ, and to expand the inadequate arterial blood volume via renal retention of sodium and water ***(Mann et al., 2005)*** (Figure 1).

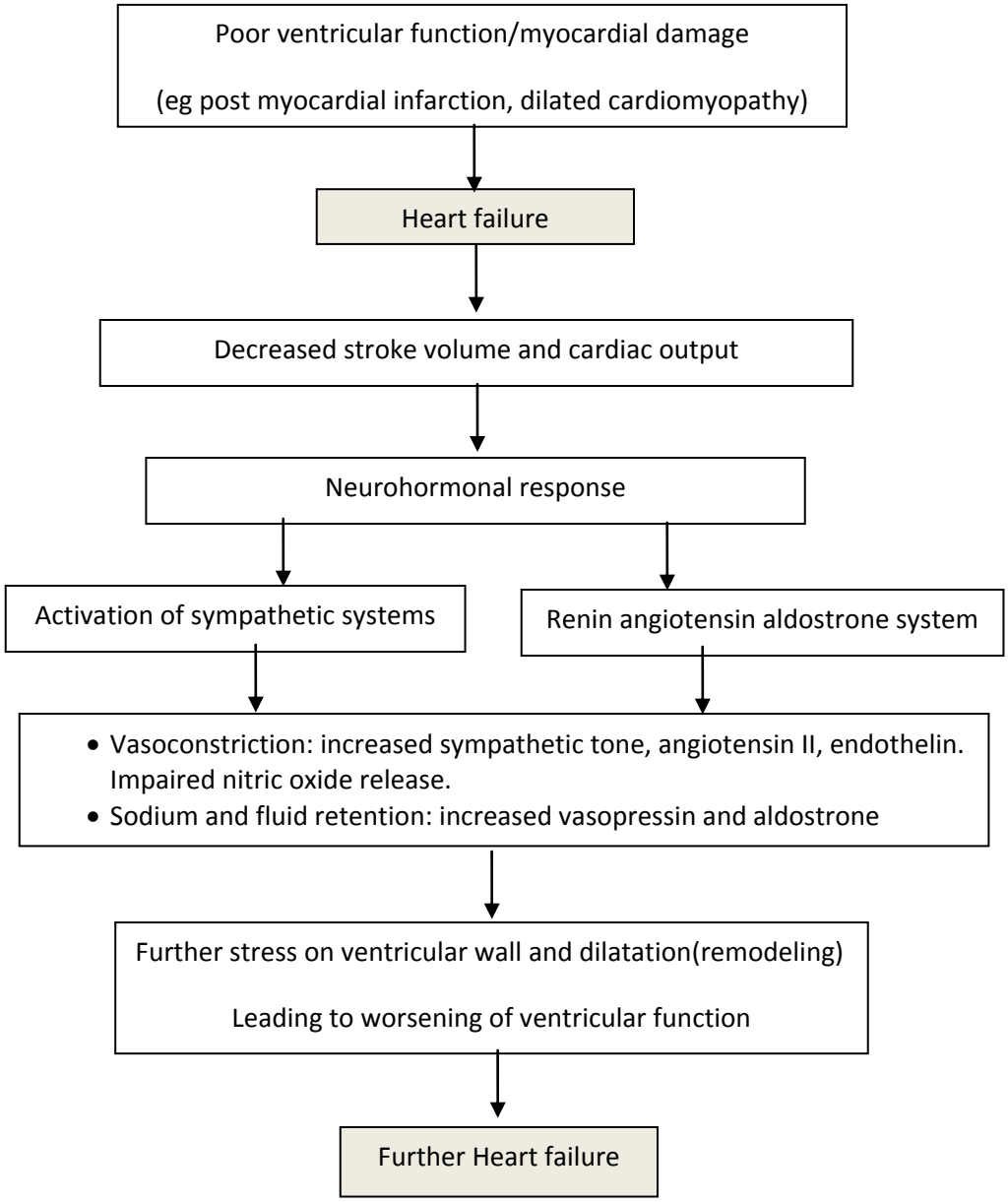

Figure (1): Neurohormonal mechanisms and compensatory mechanisms in heart failure ***(Jackson et al., 2001).***

However each of these mechanisms may be thought of as a (double edged sword) as heart failure becomes chronic, several of these compensatory mechanisms can cause undesirable effects such as, excessive vasoconstriction, increased after load, excessive retention of salt and water, electrolyte abnormalities, arrhythmias and direct effect on cardiac myocytes leading to cell death, or changes in protein expression and functions ***(Eckhart et al., 2002).***

In contrast other responses such as the release of atrial natriuretic peptide (ANP) and Brain Natriuretic Peptide (BNP) in response to distension of the atria and ventricles, may oppose these adverse effects by causing vasodilatation, increased excretion of salt and water, and inhibition of sympathetic activity ***(Silver et al., 2004).***

A-Increase Sympathetic Nervous System Activity: (Figure 2)

Stimulation of the Sympathetic nervous system plays an important role in the compensatory response to decreased cardiac output and the pathogenesis of heart failure ***(Tang et al., 2005).***

At rest, in patients with advanced heart failure, the circulating Norepinephrine (NE) concentration is elevated, generally two to three times the level found in normal subjects, and this elevation is accompanied by elevation of circulating

dopamine and sometimes by epinephrine as well: the latter reflects increased adrenomedullary activity ***(Bristow, 2000).***

Measurement of 24 hours urinary NE excretion also reveals marked elevations in patients with heart failure, plasma NE may be elevated, even in asymptomatic patients with left ventricular dysfunction ***(Eckhart et al., 2002).***

Both cardiac sympathetic tone and circulating catecholamine (epinephrine and norepinephrine) levels are elevated during the late stages of most forms of heart failure. By direct stimulation of heart rate and cardiac contractility and by regulation of vascular tone, the sympathetic nervous systems helps to maintain perfusion of the various organs, particularly the heart and brain ***(Hegar et al., 2002).***

The negative aspect of increased sympathetic activity includes an increase in peripheral vascular resistance and the after load against which the heart must pump. Excessive sympathetic stimulation also may result in decreased blood flow to skin, muscle, kidney and abdominal organs. Catecholamine also contributes to the high rate of sudden death by promoting dysrhythmias ***(Piran et al., 2002).***

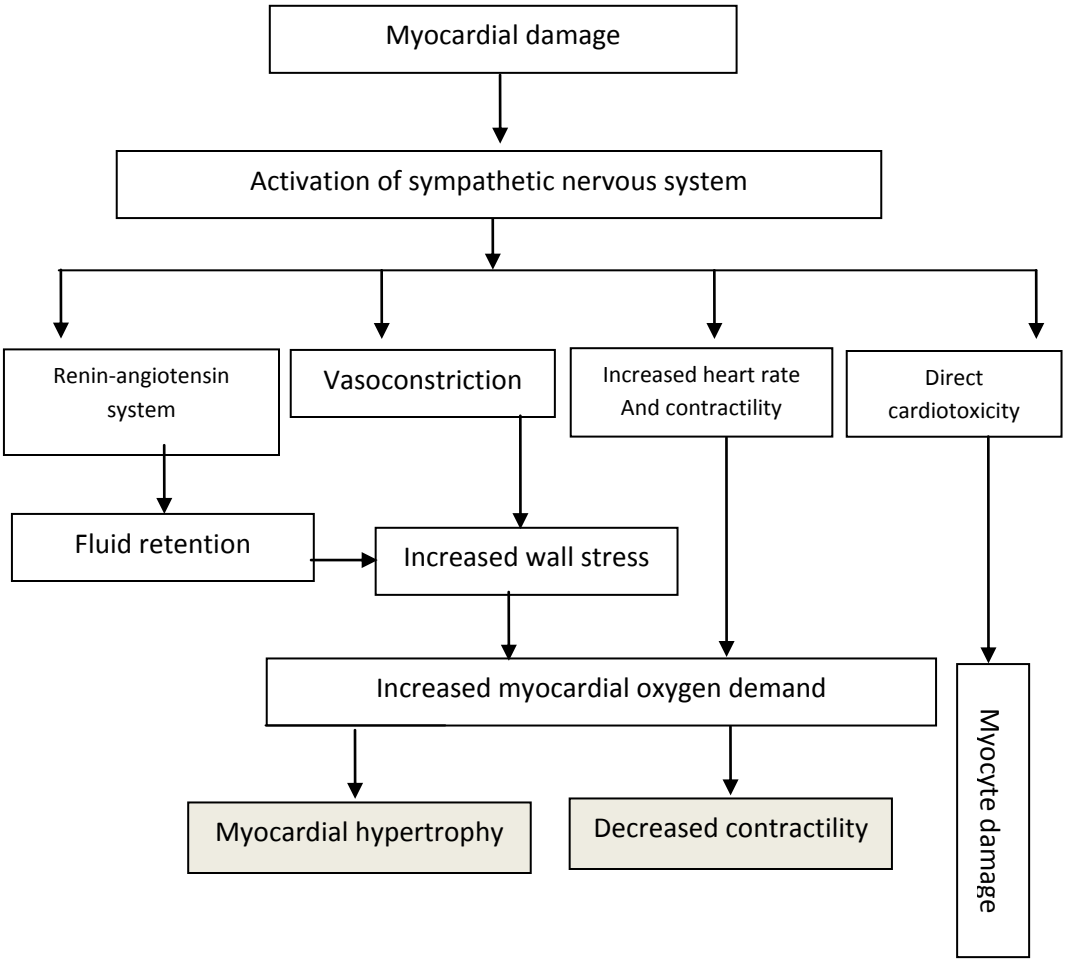

Figure (2): Sympathetic activation in chronic heart failure ***(Kay et al., 2000)***

B- Renin-Angiotensin Mechanism: (Figure 3)

One of the most important effects of the lowered cardiac output in heart failure is a reduction in renal blood flow and

glomeruler filtration rate, which leads to salt and water retention. Normally, the kidneys receive approximately 25% of the cardiac output, but this may be decreased to as low as 8% to 10% in persons with heart failure ***(Jackson et al., 2000).***

With decreased renal blood flow, there is a progressive increase in renin secretion by the kidneys along with parallel increase in circulating levels of angiotensin II. This activation of renin-angiotensin aldosterone system, which operates in concert with the activated adrenergic nervous-adrenal medullary system to maintain arterial pressure and to retain sodium and water. These two systems are clearly coupled. Heightened adrenergic drive stimulates beta, adreno receptors in the juxtaglomeruler apparatus of the kidneys. This process is the principle mechanism responsible for the release of renin in acute heart failure ***(Bisognano et al., 2000).***

Activation of the baroreceptors in the renal vascular bed by a reduction of renal blood is also responsible for the release of renin, and in patients with severe chronic heart failure after salt and water restriction and diuretic treatment; reduction of the sodium presented to the macula densa contributes to the release of renin ***(Yusuf et al., 2003).***

The increased concentration of angiotensin II contributes to a generalized vasoconstriction and serves as a stimulus for

aldosterone produced by the adrenal cortex. Aldosterone, in turn, increases tubular reabsorbtion of sodium, with an accompanying increase in water retention. Because aldosterone is metabolized in the liver, its levels are further increased when heart failure causes liver congestion ***(Bongartz et al., 2005).***

Recent evidence suggest that angiotensin is also a growth factor for cardiac muscle cells and fibroblasts and, as such, may play a central role in modifying the structure and function of the myocardium in persons with heart failure ***(Komajda et al., 2006).***

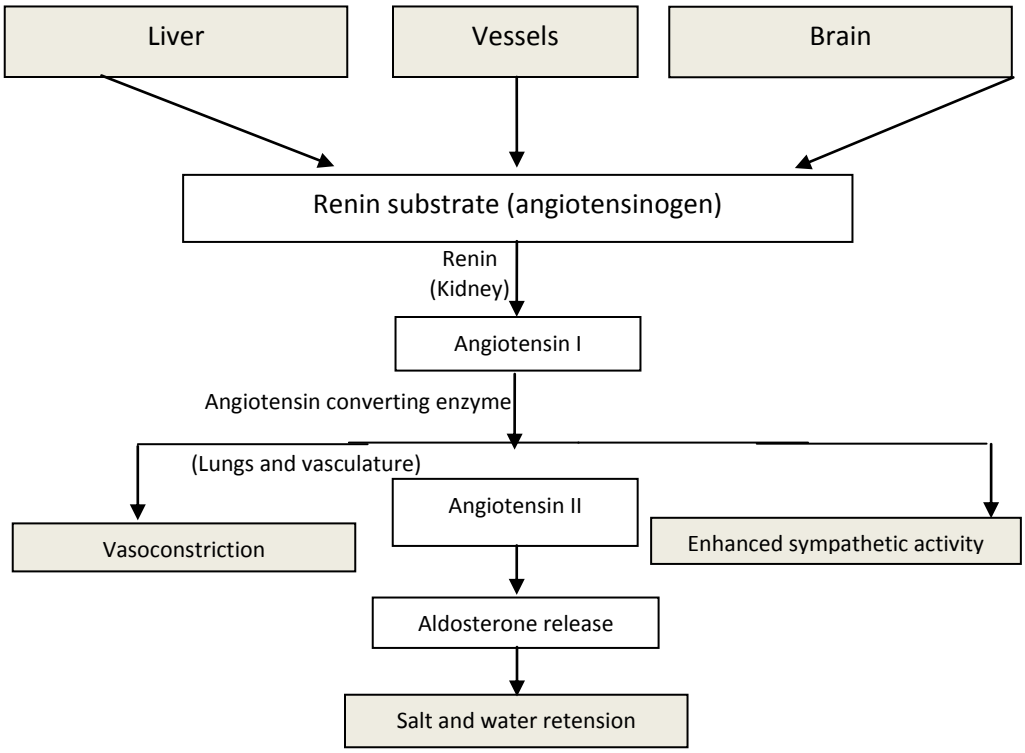

Figure (3): Renin-angiotensin-aldosterone axis in heart failure. (Hegar et al., 2002)

C-Natriuretic peptides: (Figure 4)

There are three natriuretic peptides, of similar structure, and these exert a wide range of effects on the heart, kidneys and central nervous system. Atrial natriuretic peptide (ANP) is released from the atria in response to stretch, leading to natriuresis and vasodilatation. In humans, brain natriuretic peptide (BNP) is also released from the heart, predominantly from the ventricles, and its actions are similar to those of atrial natriuretic peptide. C-type natriuretic peptide is limited to the vascular endothelium and central nervous system and has only limited effects on natriuresis and vasodilation ***(Morrison et al., 2002).***

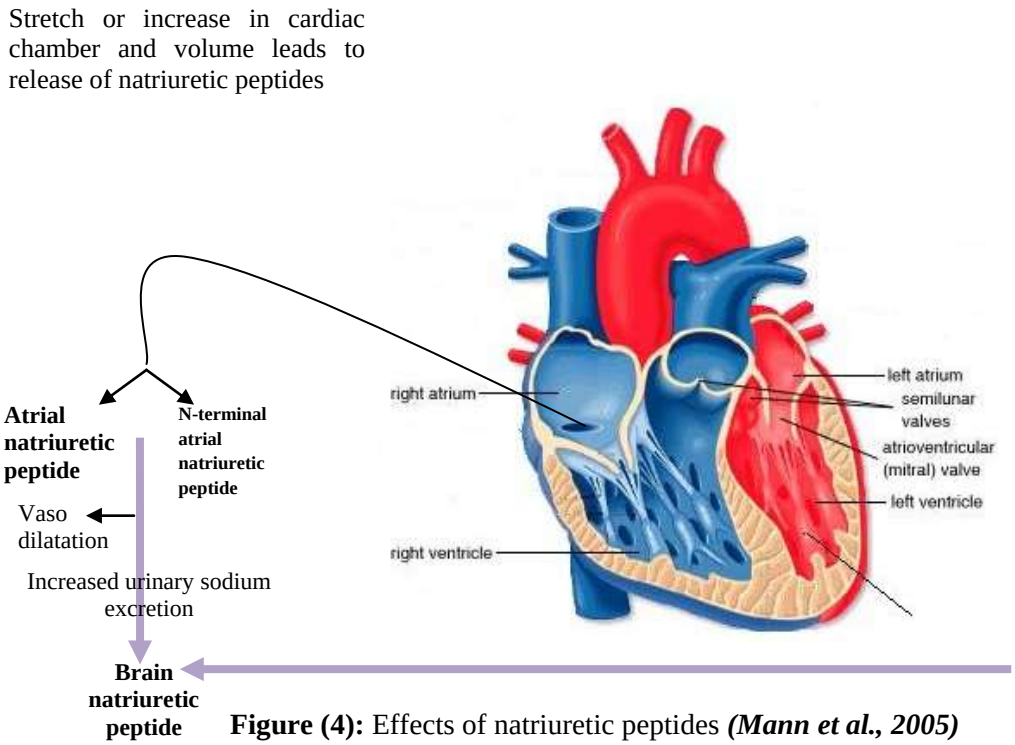

Figure (4): Effects of natriuretic peptides ***(Mann et al., 2005)***

The atrial and brain natriuretic peptides increase in response to volume expansion and pressure overload of the heart and act as physiological antagonists to the effects of angiotensin II on vascular tone, aldosterone secretion, and renal-tubule sodium reabsorption. As the natriuretic peptides are important mediators, with increased circulating concentrations in patients with heart failure, interest has developed in both the diagnostic and prognostic potential of these peptides. Substantial interest has been expressed about the therapeutic potential of natriuretic peptides, particularly with development of agents that inhibit the enzyme that metabolizes atrial natriuretic peptide (neutral endopeptidase), and non-peptide agonists for the A and B receptors ***(Mann et al., 2005).***

D- Other Mediators:

Several mediators are involved in control of the cardiovascular system in heart failure, some are circulating hormones (endocrine effect), some act on neighboring cells of another type (paracrine effect), or on the cell of origin (autocrine effect). These include peptides that act primarily locally in the vicinity of their production, such as endothelin, peptide growth factor (GF-α) and inflammatory cytokines (interleukin-I beta [IL-1β] and TNF-α) ***(Hunt et al., 2009).***