"CORRELATION BETWEEN N -TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVEL AND ECHOCARDIOGRAPHY IN ASSESSING LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AMONG HYPERTENSIVE PATIENTS"

By

Dr. MOOSA P.E. MBBS

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Dr. PRABHAKAR K. MD.

Professor

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I hereby declare that this dissertation entitled **"CORRELATION BETWEEN N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVEL AND ECHOCARDIOGRAPHY IN ASSESSING LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AMONG HYPERTENSIVE PATIENTS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. PRABKAKAR K. MD,** Professor, Department of General Medicine, SRI DEVARAJ URS Medical College, KOLAR.

Date: Signature of the Candidate

Place: KOLAR Dr. MOOSA P. E.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR.

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Signature of the Guide

Dr. PRABHAKAR K. MD
Professor of medicine
Department of General Medicine
SDUMC, KOLAR

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR.

ENDORSEMENT BY THE HOD, PRINCIPAL OF THE INSTITUTION

This is to certify that the dissertation entitled **"CORRELATION BETWEEN N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVEL AND ECHOCARDIOGRAPHY IN ASSESSING LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AMONG HYPERTENSIVE PATIENTS"** is a bonafide research work done by **Dr. MOOSA P.E,** under the guidance of **Dr. PRABHAKAR K.** MD, Professor, Department of General Medicine, S.D.U. Medical College, KOLAR.

Seal & Signature of the HOD **Seal & Signature of the Principal**

Date: **Date:**

Place: kolar **Place: kolar**

SRI DEVARAJ URS MEDICAL COLLEGE

TAMAKA, KOLAR.

ETHICAL COMMITTEE

CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved **Dr. MOOSA P.E**, Post-Graduate student in the subject of **GENERAL MEDICINE** at Sri Devaraj Urs Medical College, Kolar to take up the Dissertation work entitled **"CORRELATION BETWEEN N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVEL AND ECHOCARDIOGRAPHY IN ASSESSING LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AMONG HYPERTENSIVE PATIENTS"** to be submitted to the SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, TAMAKA, KOLAR, KARNATAKA.

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Dr. MOOSA P.E

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Place: Kolar **Dr. MOOSA P.E**

LIST OF ABBREVIATIONS USED

LVDD	- Left ventricular diastolic dysfunction
NT-pro BNP	- N-terminal pro brain natriuretic peptide
DD	- Diastolic dysfunction
LVH	- Left ventricular hypertrophy
HF	- Heart failure
ANP	- Atrial natriuretic peptide
FPE	- Flash pulmonary edema
HEPEF	- Heart failure with preserved ejection fraction
DHF	- Diastolic heart failure
SHF	- Systolic heart failure

ABSTRACT

BACKGROUND

Left ventricular diastolic dysfunction is often impaired in association with hypertension. The potential use of assays of N-terminal Pro brain natriuretic peptide for detection of diastolic dysfunction has not been elucidated much. This study was designed to determine whether increased plasma concentration of N-terminal pro brain natriuretic peptide correlate with echocardiographic index of diastolic dysfunction associated with hypertension.

OBJECTIVES

1. To screen for left ventricular diastolic dysfunction in hypertensive patients with echocardiography.
2. To measure the level of plasma NT-pro BNP in hypertensive patients with left ventricular diastolic dysfunction.
3. To determine the correlation of plasma NT-pro BNP levels with echocardiography among hypertensive's for assessing left ventricular diastolic dysfunction.

MATERIALS AND METHODS

A prospective study on 30 Patients aged between 18-65 yrs with newly detected hypertension attending our hospital were considered. Hypertension is defined as Systolic BP >140mmHg and Diastolic BP > 90mmHg (JNC7 CLASSIFICATION). Left ventricular diastolic dysfunction is assessed by using the ratio of transmitral flow

velocities in early diastole (E) and during atrial contraction (E/A ratio), deceleration time and isovolumeteric relaxation time. A simultaneous blood sample is analyzed for the level of NT-pro BNP using Radioimmunoassay. Data were analyzed using SPSS program, student t-test, Spearman's correlation co-efficient.

RESULTS

We studied 30 ambulatory patients with newly detected hypertension, 18 were males and 12 females. Out of 30 screened patients, 50% of patients had grade I diastolic dysfunction and 30% of patients had grade II diastolic dysfunction. The NT-pro BNP level were positively correlated significantly with grades of diastolic dysfunction. Six patients had normal diastolic dysfunction with plasma concentration of 31.3pg/ml. Grade 1 diastolic dysfunction were noticed in 15 patients with NT-pro BNP level of 100pg/ml. 9 patients had grade II diastolic dysfunction with NT-pro BNP level of 218.5 pg/ml which is statistically significant (p= 0.001).

CONCLUSION

In this study, most of the hypertensive patients had diastolic dysfunction. Mean NT-pro BNP levels are significantly elevated with abnormal diastolic dysfunction**.** There is a close correlation between NT-pro BNP levels and echocardiographic index, indicative of diastolic dysfunction in clinically stable hypertensive patients.

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INTRODUCTION

Hypertension is probably the most important public health problem in developed and developing countries. It is commonly asymptomatic, readily detectable, usually easily treatable, and often leads to lethal complications if left untreated. Approximately 7.6 million deaths and 92 million disability adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease, congestive heart failure, renal failure and peripheral vascular disease. It is often associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of the risk factors[1].

Hypertension in Indian Prospective:

There are no well-coordinated national surveys of prevalence of hypertension available from Indian subcontinent. Several regional small surveys with varying protocols have reported a prevalence which varies widely from 3.80% to 15.63% in men and 2% to 15.38% in women in urban areas and 1.57% to 6.93% in men and 2.38% to 8.81 % in women in rural areas[2].

The earliest functional cardiac changes in hypertension are in left ventricular diastolic function, with prolongation and incoordination of isovolumic relaxation, a reduced rate of rapid filling, and an increase in the relative amplitude of the *a* wave, probably caused by increased passive stiffness . Diastolic dysfunction is a treatable precursor of congestive cardiac failure. Echocardiography is the investigation of choice to establish diagnosis of left ventricular diastolic dysfunction (LVDD), but it requires high degree of technical expertise and not always easily accessible.

N – terminal brain natriuretic peptide (NT-pro BNP) – a novel marker, is a 32- amino acid polypeptide cardiac neurohormone secreted by cardiomyocytes in response to ventricular stretch. BNP is to reported to be an equally sensitive indicator of LVDD and its measurement increases the diagnostic value[3].

This study is undertaken to determine the correlation of plasma NT-pro BNP levels with echocardiography among hypertensive's for assessing left ventricular diastolic dysfunction.

OBJECTIVES

1. To screen for left ventricular diastolic dysfunction in hypertensive patients with echocardiography.
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REVIEW OF LITERATURE

HISTORICAL REVIEW

The writings of Sushruta in the 6th century BC has been held by many as being the first mention of symptoms like those of hypertension. Others propose even earlier the descriptions of hypertension dating as back as 2600 BC[4].

Our modern understanding of hypertension began with the work of physician William Harvey (1578–1657), who was the first to describe correctly the systemic circulation of blood being pumped around the body by the heart in his book "*De motu cordis*" [4,5]. The basis for measuring blood pressure were established by Stephen Hales in 1733. Initial descriptions of hypertension as a disease came among others from Thomas Young in 1808 and specially Richard Bright in 1836. The cardiovascular consequences of hypertension have long been appreciated. In 1913, the famous clinician Thomas Janeway described congestive heart failure as the manifestation of hypertensive cardiovascular disease[6]. The relation between blood pressure (BP) and the risk of cardiovascular disease is direct, graded, and continuous over a wide range, apparently beginning at 115 mm Hg systolic and 75 mm Hg diastolic[7].

EPIDEMIOLOGY

Das SK et al[8] reported an epidemiological shift in the prevalence of hypertension in developing countries as compared to developed countries has been observed. Hypertension is a major public health problem in India and in other developing countries. Studies from India and Bangladesh have shown upward trend in the prevalence of hypertension. This is obvious from several Indian urban and rural

studies. The various studies estimated a prevalence rate of hypertension among urban population ranging from 1.24% in 1949 to 36.4 % in 2003 and for rural people from 1.99% in 1958 to 21.2% in 1994. However differential rates are due to different cut off marks in determining hypertension and also differing age groups constituting the study population. Countries with an ageing population in developed countries will be expected to have a higher prevalence of hypertension than a developing country with a younger population such as India, but there are studies, which have documented a high prevalence rate of hypertension in developing countries[9-10].

Mohan V et al[11] reported hypertension was present in one-fifth of the urban south Indian population and isolated systolic hypertension was more common among elderly population. Hypertension in majority of subjects still remain undetected and the control of hypertension is also inadequate. This calls for urgent prevention and control measures for hypertension. In India, there is no composite estimate on prevalence of hypertension among indigenous tribes, but the increasing prevalence of hypertension across the time among tribes has been observed by independent researchers. Isolated studies carried out in these populations like Lepchas of Sikkim Himalayas and tribes of Andhra Pradesh, Gujarat, and Orissa have documented the hypertension prevalence in the range of 15 to 42 per cent[12-13].

CARDIOVASCULAR EFFECTS OF HYPERTENSION

The cardiovascular consequences of hypertension have long been appreciated. Left ventricular hypertrophy is a major cardiac alteration associated with hypertension accounting for a risk that is independent of the elevated arterial pressure. Diastolic dysfunction is an early manifestation of impaired ventricular function associated with hypertrophy later causing systolic dysfunction and cardiac failure. Frolich et al[14]

observed the best means of decreasing the increased mortality and morbidity is to prevent the development of left ventricular hypertrophy, which requires early and continuous antihypertensive therapy even before the hypertrophy, becomes clinically manifest.

Many of the adverse sequelae of hypertension are the direct result of target-organ damage to the vasculature, the kidneys, and the heart. In the heart, long-standing hypertension serves as a stimulus for progressive fibrosis, ventricular hypertrophy[15], and diastolic dysfunction, which may be one of the earliest manifestations of cardiac target-organ damage[16-17.] These changes may be accelerated by age and hypertension-related changes in central aortic stiffness, which may contribute to abnormal pulse wave reflection and enhanced pulsatile arterial load. At Present in 50% of hypertensive patients, diastolic dysfunction likely represents an important intermediate in the development of heart failure, particularly in patients with preserved systolic function[18-19].

Diastolic dysfunction is associated with future occurrence of heart failure, is a predictor of cardiovascular morbidity and mortality in the general population and is associated with a reduced exercise performance in asymptomatic subjects[20]. Several reports have shown that impairment of left ventricular (LV) diastolic function can be present in subjects with diabetes even in the absence of alterations of LV systolic function [21.] However, especially in the elderly, diabetes is often associated with arterial hypertension, which is in turn associated impaired diastolic dysfunction and unfavorable cardiovascular outcome[22].

Cardiac remodeling in essential hypertension is characterized by myocyte hypertrophy and increased interstitial fibrosis which results from increased collagen synthesis and unchanged or decreased collagen degradation. The rise in myocardial collagen content plays a major role in the development of left ventricular (LV) diastolic dysfunction by affecting both LV relaxation and stiffness[23].

Experimental studies have demonstrated the central role of aldosterone in promoting cardiac fibrosis, probably through a direct action on the heart mediated by cardiac mineralocorticoid receptors. This profibrotic action, independent of blood pressure (BP) increase, can be effectively opposed by aldosterone receptor blockade[24]. Diastolic dysfunction may be simply described as a condition in which diastolic filling is impeded. However, diastolic filling of the left ventricle is a complex process determined by the interaction of several factors, including active ventricular relaxation and passive properties influencing left ventricular compliance. Active relaxation is related to calcium reuptake by the sarcoplasmic reticulum, whereas passive ventricular filling properties are determined by ventricular wall thickness, the dimensions of the ventricular cavities, and the structural properties of the cardiac tissue itself [25]. A few studies have attempted to examine the diastolic pressure volume relationship and the data suggested that morbidly obese patients exhibit abnormalities in diastolic filling, with or without the presence of hypertension or cardiac Hypertrophy[26].

The cause and time of occurrence of cardiac impairment in patients with essential hypertension are not precisely known. Age and pressure load are considered possible determinants, where as the role of the autonomic nervous system is still debated[27]. Animal studies have suggested that a high sympathetic tone may favor the

development of hypertrophy, but the role of the autonomic nervous system in the genesis of cardiac abnormalities is unclear. Furthermore, no data are yet available concerning the role of depressed baroreflex sensitivity in determining cardiac impairment in these patients. It is possible that it is too late for any autonomic nervous system abnormalities to be detected once hypertrophy becomes evident, and therefore the early phase of essential hypertension could offer important information on the role of autonomic nervous system activity in determining the presence of cardiac involvement[28].

Epidemiological studies[29] have established that 40% to 50% of patients with heart failure have normal or minimally impaired left ventricular (LV) ejection fraction. These patients typically have cardiac hypertrophy that is induced by long-standing hypertension or by primary hypertrophic cardiomyopathy, as well as increased passive LV stiffness. Among various molecular mechanisms that regulate LV stiffness, abnormalities in the transcriptional or posttranscriptional regulation of the collagen gene can result in the disproportionate accumulation of fibrous tissue and elevation of stiffness in the hypertrophied heart. Recent studies have shown that, in addition to mechanical load, autocrine, paracrine, and endocrine factors, such as angiotensin II, aldosterone (Aldo), endothelin-1 (ET1), natriuretic peptides, osteopontin, and transforming growth factor- 1 (TGF-1), play important roles in the development of myocardial hypertrophy and fibrosis. However, the precise molecular mechanisms that initiate and promote myocardial fibrosis and increases in ventricular stiffness remain largely unknown[30].

ECHOCARDIOGRAPHY IN HYPERTENSION:

Arterial hypertension remains one of the most frequent indications for echocardiography, especially in countries where the direct cost is not perceived as a direct charge for patients. Despite the most common recommendation to perform echocardiographic examinations in hypertensive patients based on indications that might yield modifications of the management strategy and the most recent guidelines that do not list echocardiography in the primary workup for arterial hypertension[31]. Accurately diagnosing diastolic dysfunction (DD) could possibly lead to improved treatments and may have substantial health care implications, both from a clinical and resource utilization perspective. In routine clinical practice, Doppler echocardiography is the method of choice to diagnose DD. Numerous algorithms have been proposed, most based on transmitral Doppler patterns. However, transmitral Doppler derived indices of diastolic function are dependent on loading conditions, and accurate measurements are operator dependent[32].

The substantial reason for echocardiography in arterial hypertension is assessment of left ventricular (LV) mass, based on the broad evidence that LV hypertrophy (LVH) is one of the most important prognostic markers in hypertension, as well as in general populations. However, following the reports on LVH, a large number of studies have indicated other echocardiographic markers of cardiovascular risk to be independent of LVH, including LV geometry and systolic and diastolic function[31-33].

The assessment of left ventricular (LV) diastolic function should be an integral part of a routine examination, particularly in patients presenting with dyspnoea or heart failure. Even in the absence of clinical HF, diastolic dysfunction is associated

with increased rates of future hospitalizations, development of HF, and all cause mortality. Worsening stages of DD on echocardiography are associated with incremental risk of adverse outcomes including the development of clinical HF[34].

Echocardiography and the B-type natriuretic peptides (BNPs) provide powerful incremental assessment of cardiac function, clinical status, and outcome across the spectrum of cardiac disease. There is strong evidence to support their integrated use in the diagnosis and management of cardiovascular disease. NT-pro BNP or BNP may guide more effective use of echocardiography in screening for asymptomatic left ventricular dysfunction[35]. Doppler echocardiography improves the accuracy of heart failure diagnosis in the setting of intermediate BNP or NT-pro BNP levels. Combined assessment of peptides and echocardiography provides more powerful stratification of risk across all stages of heart failure, and integrated use of both tests may identify subjects with valvular disease at greatest risk for progression and guide decision-making for timely intervention[36]. Since their discovery and characterization, B-type natriuretic peptides have become firmly established as biomarkers for heart failure diagnosis and for prognosis across the spectrum of cardiovascular disease. The relationship between the B-type peptides and echocardiographic measures of cardiac structure and function has been widely explored. Peptide measurements provide information complementary or incremental to echocardiography for assessment of cardiac function, clinical status, and outcome[37].

BRAIN NATRIURETIC PEPTIDE:

The natriuretic peptide family includes Atrial, B-type (BNP), C-type natriuretic peptide, and urodilatin (Table 1). BNP is secreted primarily by atrial and

ventricular cardiomyocytes and like atrial natriuretic peptide has vasodilator, lusitropic, and natriuretic actions. It also inhibits cardiac sympathetic traffic, rennin angiotensin- aldosterone activity, and cardiac fibrosis[38].

The BNP gene encodes pre-pro-BNP, a 134-amino acid (aa) molecule from which BNP signal peptide is cleaved to produce pro-BNP (amino acids 1 to 108)[39]. Pro BNP and its two cleavage products, the inactive aminoterminal pro-B-type natriuretic peptide (NT pro BNP) (aa 1 to 76) and the bioactive molecule BNP (aa 77 to 108) are all present in the circulation. Although secretion of BNP and NT pro BNP is equimolar, BNP is actively cleared through natriuretic peptide C-receptors and by neutral endopeptidase, resulting in significantly lower plasma levels and a shorter half-life (21 min) than NT-pro BNP (70 min), for which clearance mechanisms beyond renal filtering are less certain. Further processing of pro-BNP, NT pro-BNP, and BNP within the circulation produces truncated forms presumably variably recognized by immunoassays and possessing variable bioactivity. This appears to have little impact on clinical application of current well-validated immunoassays for BNP and NT-proBNP[40].

BNP is not stored but is synthesized and secreted constitutively in response to cardiomyocyte stretch. Increased ventricular or atrial wall stress, reflecting volume or pressure overload, is the primary driver of myocyte stretch mediated secretion, but ischemia, neurohormones, and cytokines also stimulate or modify BNP gene expression[41].

Table 1: Comparison of different natriuretic peptides

	ANP	BNP	NT-proBNP
Half-life	3-5 minutes	20 minutes	60-120 minutes
Regulation	Granule stores	Transcription	Transcription
Pre-analytic	Exercise, posture	Minimal	Minimal
Stability	EDTA WB unstable	24 hr EDTA at 2-8 ^{0}C	72 hr EDTA at 2-8 ^{0}C

PLASMA LEVELS OF NT-pro BNP

Validated commercial assays are available for BNP and NT-pro BNP. Each assay has different performance characteristics and recognizes different epitopes on the BNP or NT-pro BNP molecule. Although there is generally strong correlation between assays, absolute peptide values may vary considerably, so clinicians should know the reference range and performance characteristics of their local assay[42]. Plasma levels of BNP and NT-pro BNP increase with age and are lower in men than in women. Levels are inversely related to body mass index and lean mass and increase with worsening glomerular filtration rate[43] . Even in stable subjects, peptide levels vary with repeat testing as a consequence of assay characteristics and biological variation. Relative variation is greater in normal subjects, in whom absolute levels are low. In disease states, absolute levels are higher and relative variation is lower. In stable heart failure subjects, changes of more than 23% for NT-pro BNP or 43% for

BNP are likely to indicate a change beyond that due to background biological variation[44].

BNP is secreted soon after its synthesis. Only small amounts of BNP may be stored in atrial secretory granules together with ANP [45].Thus, BNP appears to utilize the constitutive secretory pathway, and increased release of BNP requires a longer stimulus to enhance its rate of synthesis and subsequent secretion. Indeed, the regulation of BNP synthesis appears to occur mainly at the level of transcription and perhaps stabilization of mRNA[46] . Like ANP, BNP gene is induced by pressure and volume overload, but the stimulation is much more rapid. The cardiac BNP mRNA level rises within 30 minutes during constant stretch, whereas the ANP mRNA requires several hours of stretch. Furthermore, the stretch-induced BNP mRNA increase does not depend on protein synthesis, revealing the induction process with available factors. Fast induction of BNP gene resembles the induction of the immediate early genes. Like many other rapidly induced genes, BNP mRNA also contains several AU-rich sequences in the 3' untranslated region[47]. These AU-rich elements are known to destabilize mRNA within the cell, and they may be involved in the translation-dependent degradation of mRNA. In fact, posttranscriptional control has been found to be an important factor in the regulation of left ventricular BNP gene expression *in vivo.*

BNP is a novel natriuretic peptide secreted from the heart that forms a peptide family with A-type or atrial natriuretic peptide (ANP), and its plasma level has been shown to be increased in patients with congestive heart failure. BNP was first isolated from porcine brain and subsequently from the hearts of humans as well as pigs and rats forms a peptide family with ANP and may be involved in the regulation of blood pressure and fluid volume[48]. It has been established a specific radioimmunoassay for

human BNP by developing a monoclonal antibody against it and have shown that BNP is a novel cardiac hormone secreted mainly from the ventricles in patients with congestive heart failure and hypertension[49]. The ratio of BNP released from the left ventricle to that from the heart as a whole had no correlation with the degree of left ventricular dysfunction, indicating that BNP is secreted mainly from the left ventricle regardless of the degree of left ventricular dysfunction, whereas the ratio of ANP released from the left ventricle to that from the heart as a whole increases with the severity of left ventricular dysfunction. Secretion of BNP as well as ANP from the left ventricle increases in proportion to the severity of the left ventricular dysfunction, suggesting that the secretions of ANP and BNP from the left ventricle are regulated mainly by wall tension of the left ventricle and the peripheral plasma level of ANP and BNP reflects the secretion rate of these hormones from the left ventricle and may be used as a marker of the degree of left ventricular dysfunction in patients with left ventricular dysfunction. Elevation of the plasma BNP level is considered to reflect ventricular structural and functional alterations. BNP levels increase with greater severity of overall diastolic dysfunction, independent of LVEF, age, sex, body mass index, and renal function, and the highest levels are seen in subjects with restrictive filling patterns[50].

Yamaguchi et al[51] reported a close relationship between BNP production and myocyte hypertrophy. Of interest is that adaptive hypertrophy did not promote ventricular BNP production in Dahl salt-sensitive rats, and the promotion was provided only in the presence of maladaptive LV hypertrophy with fibrosis that led to symptomatic overt diastolic heart failure [51].

BNP AND ECHOCARDIOGRAPHIC INDEXES OF HEART DISEASE:

Given synthesis primarily by cardiomyocytes, it is not surprising that the greatest secretion of B-type peptides is from the left ventricle (LV).

Iwanaga Y et al[52] reported BNP and NT-pro BNP levels correlate positively with LV dimensions, volume, and mass in a variety of settings and populations and are inversely related to LV ejection fraction (LVEF). Peptide levels are higher with left ventricular hypertrophy (LVH) and are higher still in subjects with LVH and clinical heart failure.

Tschope C et al[53] reported, in diastolic dysfunction the strongest correlations have been reported for BNP with LV diastolic wall stress consistent with stretch-mediated BNP secretion. The peptide levels correlate with indexes of filling pressure including transmitral early filling velocity (E) and its ratio to early diastolic annular velocity (E/Ea) as well as with indexes of compliance and myocardial relaxation. In subjects with normal LVEF, elevated NT pro BNP (>600 pg/ml) or BNP (>100 pg/ml) are the strongest independent predictors of severe diastolic dysfunction. BNP and NT-pro BNP levels also reflect left atrial size, correlating positively with left atrial volume, particularly in the general population and in patients with heart failure with preserved systolic function[54] .

Dahlstrom U[55] observed the right ventricle (RV) also contributes to plasma levels of BNP or NT-pro BNP, with either normal or impaired LVEF. Levels of both peptides correlate with measures of RV size and function, increasing with greater dilatation and systolic dysfunction, and with increasing RV pressure estimates.

Dokainish H et al[56] reported tissue Doppler imaging is a newer technique that can be used in combination with transmitral Doppler to determine the presence and severity of diastolic dysfunction (DD). However, this assessment of DD is more complex and requires expert interpretation.

Studies have shown many parameters associated with DD, including echocardiographic measurements, various clinical characteristics, increased left atrial (LA) volume and elevated levels of B-type natriuretic peptide (BNP) and N-terminal (NT)-pro BNP. Identifying simple clinical and/or biochemical and/or echocardiographic measurements that can reliably identify the presence and severity of DD is particularly important for patients with heart failure with preserved left ventricular ejection fraction (HF-PLEF)[52,55].

Studies have shown that a best set of clinical parameters like left atrial volume and BNP or NT-pro BNP could accurately predict DD, as evaluated by echocardiography[57]. If indeed a simple set of such parameters could be shown to be strongly associated with DD on echocardiography, use of such parameters could help circumvent the need for detailed, difficult, and costly echocardiographic assessments (especially in situations where echo is not readily available) to determine the presence of prognostically important DD[58].

A study conducted by Maisel A et al[59] showed, the transient exacerbation of diastolic, not systolic, dysfunction is thought to cause elevated LV filling pressures. A good predictor of elevated LV filling pressures and therefore a frequently used blood test to aid diagnosis of HF is BNP. The interpretation of BNP levels in Flash pulmonary edema (FPE) is, however, less well established. Normal to low BNP levels

have been observed if blood is assayed very early after dyspnea onset or in patients with preserved LV ejection fraction, a common finding in FPE. Because of its diagnostic value in patients with shortness of breath and its prognostic value in patients with heart failure (HF), BNP has become a widely used biomarker in clinical practice. Generation of mature BNP requires the cleavage of a signal peptide and the biologically inactive NT pro BNP[60]. Although many aspects of the biochemistry of BNP biosynthesis and processing are well known, the physiological regulation of cardiac BNP release is still not well understood.

The most commonly held view is that stretch of ventricular cardiomyocytes is the key stimulus for pre pro-BNP expression. Although measurement of peripheral BNP has clear cross-sectional use, its applicability as a reproducible, reliable serial index of ventricular function appears more limited. This may reflect the fact that BNP concentrations in peripheral blood not only reflect cardiac BNP release but also BNP clearance by the kidneys and other mechanisms[61].

In a sample of hypertensive patients, plasma NT-pro BNP appeared as a strong prognostic marker. This performance, together with the ease of measurement, low cost, and widespread availability of NT-pro BNP test kits, should prompt a wide use of this marker for risk stratification in hypertension. Studies also predicted that NT-pro BNP may be a superior biomarker for mortality because of its prolonged half-life in comparison to BNP and its use in identifying a reduced ejection fraction in the general population[62]. In addition, it is hypothesized that those individuals who have BNP values that predict increased mortality risk would have an increased prevalence of clinical and echocardiographic phenotypes that may predispose these individuals to greater myocardial release of BNP. BNP estimation provides useful insight into

various aspects of CHF which include diagnosis, risk stratification, prognosis, response to treatment and even screening for asymptomatic LV dysfunction in high risk patients. It is being incorporated in most national and international cardiovascular guidelines for heart failure[63].

PATHOPHYSIOLOGY OF DIASTOLIC DYSFUNCTION

Diastolic heart failure refers to the clinical syndrome of heart failure with a preserved left ventricular ejection fraction (0.50 or more) in the absence of major valve disease.

This dysfunction can result either from an impairment in LV compliance (passive mechanism) or from an alteration in LV relaxation (active process). Relaxation is usually the first to alter in LV diastolic dysfunction and relaxation abnormalities can occur abruptly. Since relaxation is an energy-consuming process, it is adversely affected by myocardial ischaemia. Ischaemia precludes optimal calcium exchanges between the cytosol and sarcoplasmic reticulum, and is rapidly associated with impairment in LV relaxation[64]. Sepsis is also likely to alter myocytes energy balance and, thus, to alter LV relaxation[65].

Diastolic heart failure is caused by left ventricular diastolic dysfunction, leading to increased resistance to left ventricular filling and eventually resulting in HF syndrome. Certain conditions such as ischemia, left ventricular hypertrophy, hypertension, and aortic stenosis predispose to Diastolic dysfunction[66].

The pathophysiology of diastolic heart failure is characterised by a low cardiac output that results typically from a ventricle that has thick walls but a small cavity

(increased left ventricular mass/volume ratio). The left ventricle is stiff. It relaxes slowly in early diastole and offers greater resistance to filling in late diastole, so that diastolic pressures are elevated[67]. The low cardiac output manifests as fatigue, while the higher end diastolic pressure is transmitted backwards through the valveless pulmonary veins to the pulmonary capillaries, resulting in exertional dyspnoea. These pathophysiological abnormalities trigger neurohormonal activation as happens in systolic heart failure. Symptoms may be unmasked by exercise because, unlike normal people, patients with diastolic heart failure are unable to augment their stroke volume by increasing their left ventricular end diastolic volume (Frank-Starling mechanism).

These patients often have an exaggerated response of systolic blood pressure to exercise. Mechanisms contributing to abnormal left ventricular diastolic properties include stiff large arteries, hypertension, ischaemia, diabetes, and intrinsic myocardial changes with or without associated hypertrophy[68].

Diastolic function is influenced by passive elastic properties of the left ventricle, by the highly energy-dependent process of active relaxation, and by the atrial contribution to filling. Zile et al[69] demonstrated that patients with heart failure with preserved ejection fraction(HFpEF) had abnormal left ventricular (LV) relaxation and increased resting LV stiffness with a shift in the diastolic pressure-volume relationship upwards and to the left. However, other studies have shown that resting ventricular stiffness is not invariably increased in patients with HFpEF. Increased myocardial mass or changes in the extra-myocardial collagen network (increased collagen content and increased collagen cross-linking) may contribute to increased LV passive diastolic stiffness at rest[70].

A shift toward the stiffer N2B isoform was observed in the diastolic heart failure group and toward the longer N2BA isoform in the systolic heart failure group when compared with previously published results from healthy controls[71]. A shift to expression of the shorter N2B isoform in response to increased arterial stiffness would increase 'contractility' (to compensate for increased aortic impedance) at the price of increased LV systolic and diastolic stiffness. More recently, myocardial biopsies from patients with aortic stenosis and patients with heart failure suggest that, rather than just a shift in titin isoforms, other mechanisms such as relative hypophosphorylation of the stiffer N2B titin isoform were a possible cause of increased LV stiffness in failing myocardium[72].

Ventricular-vascular interaction(VVC) is important in the context of HFpEF because of its important effects on diastolic filling. In patients with HFpEF, the resting VVC is lower than in younger individuals but similar to asymptomatic hypertensive elderly patients and falls within a range in which cardiac work and efficiency are not compromised[73].

Other extra-cardiac factors that may contribute to the pathophysiology of HFpEF include volume overload in conditions such as anaemia, renal dysfunction and obesity [74]. A key coupler of load-dependent LV relaxation is troponin I-protein kinase A (TnI-PKA) phosphorylation. This energy-dependent process of phosphorylation of troponin I by PKA decreases myofibrillar calcium sensitivity and increases the rate at which calcium dissociates from troponin C and this can lead to an increased rate of LV relaxation by increasing the rate of thin filament deactivation. Recently using magnetic resonance spectroscopy, it is demonstrated that HFpEF patients had reduced myocardial energetic reserve at rest (decreased phosphocreatine/adenosine

triphosphate [PCr/ATP] ratio), and this might explain why these HFpEF patients are particularly prone to impaired LV active relaxation during exercise and impaired contractile reserve[75].

The cardiomyocyte cytoskeleton is composed of microtubules, intermediate filaments (desmin), microfilaments (actin), and endosarcomeric proteins (titin, nebulin, actinin, myomesin, and M protein). Changes in some of these cytoskeletal proteins have been shown to alter diastolic Function[76].

In young healthy subjects, exercise is associated with an increase in contractility and in the rate of LV active relaxation, although the latter is attenuated with increasing age . In HFpEF, these physiological changes during exercise are profoundly deranged and this appears to be central to the pathophysiology of diastolic disorder. More recently, a study conducted by Kawaguchi et al. reported a dynamic impairment of LV active relaxation during isometric (handgrip) exercise in a group of HFpEF patients[77].

Using echocardiographic techniques, studies has recently demonstrated that, at rest, LV torsion and strain patterns in HFpEF patients were similar to those in age-related controls but that during exercise HFpEF patients had reduced diastolic function as well as evidence of delayed LV untwisting and LV suction[78].

In a separate study, using radionuclide ventriculography, HFpEF patients during cycle exercise had demonstrated that HFpEF patients had marked disturbances of VVC and of both systolic and diastolic function which appeared to be responsible for exercise limitation. LV stiffness and fibrosis could be addressed by drugs such as

aldosterone antagonists (e.g., eplerenone), which may help to alleviate aldosterone induced cardiac fibrosis, which causes increased stiffness, impaired LV relaxation and impaired LV filling. Diastolic dysfunction is an early manifestation of impaired ventricular function associated with hypertrophy later causing systolic dysfunction and cardiac failure. The best means of decreasing the increased mortality and morbidity is to prevent the development of left ventricular hypertrophy, which requires early and continuous antihypertensive therapy even before the hypertrophy, becomes clinically manifest[79].

DIAGNOSTIC APPROACH TO DIASTOLIC HEART FAILURE

The diagnosis of diastolic heart failure requires three conditions to be simultaneously satisfied (1) Presence of signs and symptoms of heart failure; (2) Presence of normal or only slightly reduced LV ejection fraction (3) Presence of increased diastolic pressure or impaired filling caused by delayed isovolumic relaxation or elevated stiffness[79].

CLINICAL EVALUATION

Asymptomatic diastolic heart failure is more prevalent than symptomatic disease. When present, the symptoms of DHF are indistinguishable from those of SHF. These include: decreased exercise capacity, paroxysmal nocturnal dyspnoea and orthopnoea, S3, rales, hepatomegaly and edema. Because of the increased chamber stiffness, patients with DD cannot increase LVEDV on exertion, preventing the necessary increase in stroke volume. Therefore, exercise intolerance is often an early symptom. The prevalence of DHF relative to that of SHF increases with age and hypertensive disease and is more common in women. The main risk factors for diastolic dysfunction are systolic and diastolic blood pressures and the clinical

severity of hypertension depends on these systolic and diastolic pressures. Recorded blood pressure classified according to JNC7 (Table 2)

Table No: 2 : The classification is according to the JNC 7 category.

Category	Systolic (mmHg) Pressure	Diastolic (mmHg) Pressure
Normal	< 120	< 80
Pre hypertension	< 120-139	85-89
Hypertension	> 140	> 90
Stage I	140-159	90—99
Stage II	≥ 160	≥100

Patients with DD have a particular intolerance of certain kinds of haemodynamic stress like atrial fibrillation, tachycardia, ischemia and hypertension[80].

NON-INVASIVE ASSESSMENT OF DIASTOLIC DYSFUNCTION

Electrocardiography:

Differentiation between DHF and SHF cannot be made on the basis of ECG. But ECG helps to rule out LVH and atrial fibrillation.

X-ray chest can shows evidence of pulmonary congestion, LA enlargement, LVH and pericardial calcifications.

Echocardiography

The assessment of left ventricular (LV) diastolic function should be an integral part of a routine examination, particularly in patients presenting with dyspnea or heart failure and hypertensive patients. About half of patients with new diagnoses of heart failure have normal or near normal global ejection fractions (EFs). These patients are

diagnosed with “diastolic heart failure” or “heart failure with preserved EF”. Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades[81].

In addition to providing fundamental information on the chamber size, systolic function, and valvular integrity, 2D echocardiography can be used to analyse characteristics of diastolic filling. Left atrial enlargement with associated atrial fibrillation provides an easily identifiable indicator of DD and the need for further echocardiographic evaluation[82].

METHODS OF EVALUATION OF DIASTOLIC DYSFUNCTION

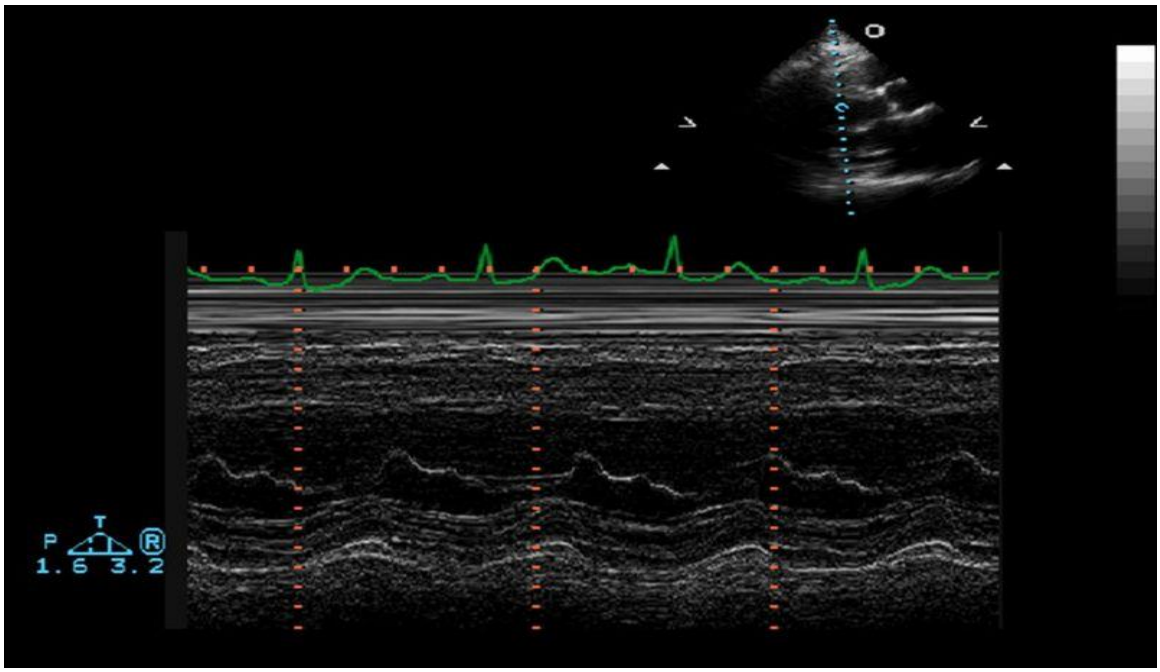
M-MODE ECHOCARDIOGRAPHY

M-mode plays a little role in the evaluation of diastolic dysfunction. One of the findings that has retained clinical relevance is detection of the so called B bump of the mitral valve closure (Figure 1).This closure pattern is seen in patients with elevated left ventricular end diastolic pressure during atrial contraction[83].

COLOR M-MODE FLOW PROPAGATION VELOCITY

The slope of the flow propagation velocity (Vp) during early diastolic filling using color M-mode Doppler demonstrates the pressure gradient between the LV base and apex. A Vp less than 50 cm/sec is consistent with diastolic dysfunction. In patients with dilated cardiomyopathies, an E/Vp ratio greater than 2.5 can predict an elevation in pulmonary capillary wedge pressures; however, this measurement is not reliable in patients with normal-sized ventricles or ejection fraction[84].

Fig 1: showing B bump pattern on M-mode in diastolic dysfunction



TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Twodimensional echocardiography is an excellent surveillance tool for evaluating all forms of anatomical heat disease and assessment of systolic dysfunction. It plays a confirmatory and exclusionary role in that it can identify, characterize and quantify disease that have resulted in diastolic dysfunction. Although accurate for identifying abnormalities of ventricular filling, as manifest by abnormal pattern of volume change in early and late diastole,the technique has a limited clinical use[84].

Doppler evaluation of diastolic dysfunction

There are 3 factors measured by echocardiography that can help in distinguishing abnormal from normal diastolic function: (1) filling patterns (transmitral flow) (2) early deceleration time, and (3) pulmonary venous flow.

(i) Transmitral flow velocity: The transmitral inflow Doppler velocities reflect the relationship between LA and LV pressures during diastole and provide the initial primary assessment of diastolic filling. The measurements are typically obtained using pulsed and continuous wave Doppler at the mitral valve leaf et tips in the apical four-chamber view. The peak velocities of the early rapid filling (E) wave, the late filling atrial contraction (A) wave, the E/A wave ratio, and the E-wave deceleration time (DT) determine the diastolic mitral filling pattern.

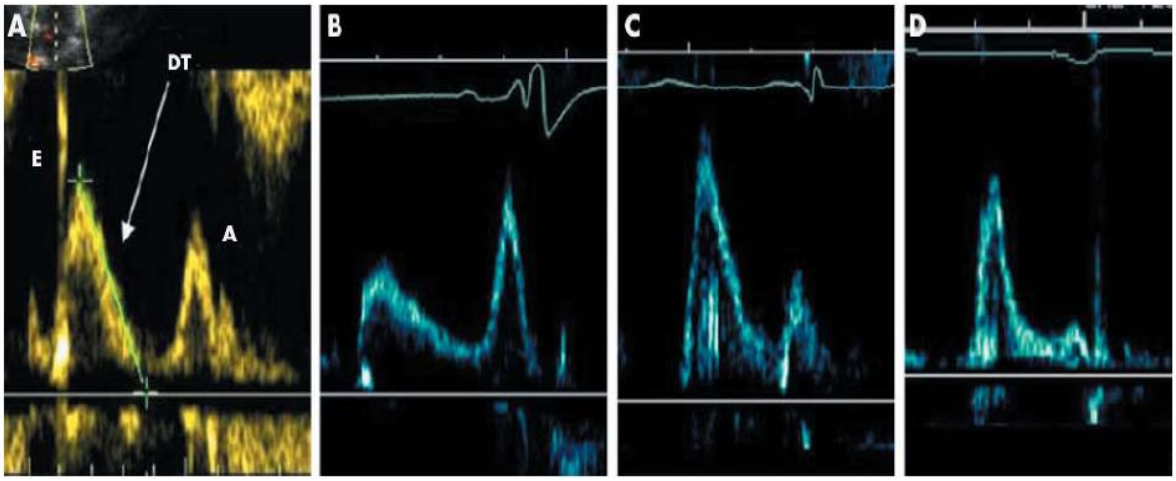
Additional measurements include the A-wave duration and the isovolumic relaxation time, which is obtained by simultaneous display of the end of aortic ejection and the onset of mitral inflow using continuous wave or pulsed wave Doppler interrogation through the LV outflow tract.

Diastolic filling grades:

The diastolic filling patterns are classically categorized into normal and four distinct abnormal grades, each representing a progression to worsening diastolic function and prognosis. The patterns include normal LV filling; impaired LV relaxation (Stage 1); pseudonormal LV filling (Stage 2); reversible restrictive LV filling (Stage 3); and irreversible restrictive LV filling (Stage 4) . Because the normal atrial contribution to total diastolic filling is only 30%, a normal A wave is smaller than the mitral E wave, with an E/A ratio .1. DD initially produces a low E wave and a high A wavevelocity, with reversal of the E:A ratio. As disease progresses and LV compliance is reduced further, LA pressure progressively increases to maintain a transmitral pressure gradient. The E wave increases until E/A ratios are .1.5. During the process of this transition, the E/A ratio will temporarily normalize, despite the presence of moderately severe disease. This is referred to as pseudonormalization and

highlights a limitation to the sole use of E/A ratios for diagnosis (Fig 2). This problem can be overcome by altering the loading conditions on the myocardium, for example, with Valsalva or glycerine trinitrate administration during echocardiography[85-86].

Figure No: 2 showing echo gradings of diastolic dysfunctions. A) Normal B) Impaired pattern C) Pseudonormalistion D) Restrictive pattern



(ii) Isovolumetric relaxation time (IVRT): This is the time between aortic valve closure and mitral valve opening. It reflects the myocardial relaxation time and is normally 70 (12) ms. With DD, poor relaxation prolongs IRT and a value of .110 ms is considered significant. Pseudonormalization of this value also occurs with advancing disease because IRT becomes progressively shortened[87].

(iii) Deceleration time (DT): The rate of dissipation of the transmitral pressure gradient is also a function of LV compliance (Fig. 4). The faster the LV pressure decreases the shorter the DT. Normal DT is 180–240 ms. Again, the prolongation of the DT seen in early DD is reversed in moderate to severe disease, as there is a progressive compensatory increase in LAP[87].

The normal pattern of left ventricular filling is altered in many patients with cardiac disease. Three abnormal patterns (in patients in sinus rhythm without mitral stenosis) have been identified indicating progressively greater impairment of diastolic function.

The first abnormal pattern of filling has been termed *delayed relaxation.* In this pattern there is reduced peak rate and amount of early left ventricular filling and the relative importance of atrial filling is enhanced. This results in a reversed E/A ratio of less than 1.0 (i.e., E<A). The decreased peak rate of early filling is due to a decreased early diastolic left atrial to left ventricle pressure gradient, resulting from a slowed rate of left ventricular relaxation . The E deceleration time may be prolonged, owing to relative underfilling of the ventricle early in diastole. A "delayed relaxation" pattern can be seen in patients with left ventricular hypertrophy, arterial hypertension, and coronary artery disease and in normal elderly subjects. In many of these patients, mean left atrial pressure is within the normal range at rest and the patients are asymptomatic. In this situation, the vigorous atrial contraction compensates for the reduced early filling due to impaired left ventricular relaxation while maintaining a normal mean left atrial pressure.

A second pattern of abnormal filling has been termed *pseudonormalized.* This pattern, in which the E/A ratio is greater than 1.0 (as occurs in normal persons) is seen in patients with a more severe impairment of diastolic performance than the pattern of delayed relaxation. The pseudonormalized pattern is due to a restoration of the normal early diastolic left ventricular pressure gradient due to an increase in left atrial pressure that compensates for the slowed rate of left ventricular relaxation . The pseudonormalized pattern of filling is distinguished from normal by a more rapid rate

of early diastolic flow deceleration, a faster deceleration time (typically<190 msec), and alterations in pulmonary venous flow velocity, mitral annular velocity, and flow propagation . The deceleration time is proportional to the inverse of the square root of the left ventricular chamber stiffness. Thus, the faster deceleration time indicates an elevated left ventricular early diastolic chamber stiffness.

A third abnormal pattern of left ventricular filling indicating a severe diastolic abnormality has been termed the *restrictive pattern.* In this pattern, the early filling is increased above the control level and greatly exceeds the filling that occurs during atrial contraction; thus, the E/A ratio is usually greater than 2.0. In fact, there may be little or no filling during atrial contraction. The deceleration time is less than 150 milliseconds, and the deceleration rate of early flow is rapid. This pattern is seen in patients with severe diastolic dysfunction and pulmonary congestion. The enhanced early filling in the "restrictive pattern" results from a markedly elevated left atrial pressure that more than offsets the slowing of left ventricular relaxation. The "restrictive filling" pattern is seen in patients with severe pulmonary congestion, constrictive pericarditis, and restrictive cardiomyopathies such as cardiac amyloidosis and is associated with a poor prognosis[88-89].

	Doppler Echocardiography Type				
	Standard			M-Mode	Tissue
Stage of Diastolic Dysfunction	E/A Ratio, cm/s	IVRT, ms	DT, ms	V_P, cm/s	E_m, cm/s
Normal*	>1	<100	<220	>45	>8
I. Delayed Relaxation	<1	>100	>220	<45	<8
II. Pseudonormal	1-2	60-100	150-200	<45	<8
III. Restrictive Filling	>2	<60	<150	<45	<8

PULMONARY VENOUS FLOW PATTERNS:

The pattern of blood flow in the pulmonary veins provides additional information on diastolic filling. The velocity of pulmonary venous flow can be measured by transthoracic Doppler evaluation in most patients. The pulmonary venous flow velocity has three waves : (1) the S wave, indicating antegrade flow into the left atrium during ventricular systole; (2) the D wave, indicating antegrade flow early in diastole just following the peak of the E wave mitral valve flow; and (3) the AR wave of retrograde flow out of the left atrium during atrial systole. The S and D waves correspond to the x and y descents in the left atrial pressure, whereas the pulmonary venous AR wave corresponds to the left atrial a wave. When left ventricular end-diastolic stiffness is increased, the AR wave is augmented unless atrial systolic failure or atrial fibrillation is present. Thus, pseudonormalized and restricted mitral flow patterns are associated with large, prolonged AR waves that have a peak flow velocity greater than 35 cm/sec and are prolonged beyond the termination of the "a" wave of the mitral inflow velocity. However, some patients with restricted filling may have atrial systolic failure producing small or absent AR waves[90].

TISSUE DOPPLER MITRAL ANNULUS VELOCITIES:

The pulsed tissue Doppler measurement of longitudinal mitral annular velocities is an important component in interpreting the diastolic filling pattern, estimating LV filling pressures, and differentiating constrictive pericarditis from restrictive cardiomyopathies. For the assessment of diastolic function, measurements are made at the septal and lateral mitral valve leaflet insertion points into the mitral annulus in the apical four-chamber view. The three main waves seen include the early diastolic (e′), the late diastolic (a′), and the systolic (s′) velocities. The e′ velocity is a less preload-dependent measure of myocardial relaxation compared with the

transmitral E wave. The e′ velocity falls as myocardial relaxation worsens with progressive diastolic dysfunction. In comparison, the transmitral E-wave velocity is preload dependent, related to myocardial relaxation and LA pressures. The E-wave velocity falls initially in Stage 1 diastolic dysfunction as myocardial relaxation worsens but increases again as LA pressures rise in Stages 2 and 3 diastolic dysfunction. The E/e′ ratio uses the e′ velocity to adjust for the myocardial relaxation contribution to mitral E velocity, thereby allowing an estimate of LV filling pressures. The septal, lateral, or an average of the two annular velocities can be used to calculate the E/e′ ratio.

Typically, the septal e′ velocity is lower than the lateral e′ velocity . Thus, different cutoff points for estimating filling pressures are suggested depending on which annular velocity is chosen. Using the septal e′, an E/e′ ratio ≤ 8 is associated with normal pulmonary capillary wedge pressures, and an E/e′ ratio ≥ 15 suggests an elevated pulmonary capillary wedge pressure. Other Doppler parameters should be used when intermediate E/e′ ratios fall between 9 and 14. Currently, if the lateral annulus is used, an E/e′ ratio ≥ 12 is a marker of elevated LV filling pressures in patients with preserved systolic function. The lateral annulus may provide a more reliable estimate of elevated filling pressure in patients with preserved ejection fraction . The American Society of Echocardiography guidelines for assessment of diastolic function place emphasis on using an average of the septal and lateral annular velocities, with an average E/e′ ratio ≥ 13 being indicative of elevated LV filling pressures[91-92].

Table 1. Criteria used to define the stages of diastolic dysfunction

Criteria	Normal young	Normal adult	Impaired relaxation (Stage 1)	Pseudonormal (Stage 2)	Restrictive-reversible (Stage 3)	Restrictive-irreversible (Stage 4)
E/A ratio	1–2	1–2	< 1.0	1–1.5 (reverses with Valsalva maneuver)	> 1.5	1.5–2.0 (Doppler values similar to Stage 3 except no change with Valsalva maneuver)
Deceleration time, *ms*	< 240	150–240	≥ 240	150–200	< 150	< 150
IVRT, *ms*	70–90	70–90	> 90	< 90	< 70	< 70
PV S/D ratio	< 1	≥ 1	≥ 1	< 1	< 1	< 1
PV AR – MV A-wave duration, *ms*	≥ 30	≤ 0	≤ 0 or ≥ 30	≥ 30	≥ 30	≥ 30
AR velocity, *cm/sec*	< 35	< 35	< 35	≥ 35	≥ 35	≥ 35
Propagation velocity, *cm/sec*	> 55	> 55	> 45	< 45	< 45	< 45
Mitral e' velocity, *cm/sec*	> 10	> 8	< 8	< 8	< 8	< 8
Left atrium	Normal	Normal	Normal or mildly enlarged LA	Mild to moderate LA enlargement	Severe LA enlargement	Severe LA enlargement

AR—atrial reversal; D—diastolic wave; E/A—ratio of early to late diastolic filling velocities; IVRT—isovolumic relaxation time; LA—left atrial; MV—mitral valve; PV—pulmonary vein; S—systolic wave.
(*From* Garcia et al. [3], Bursi et al. [4], and Yamada et al. [5].)

NEW ECHOCARDIOGRAPHIC MODALITIES

2D speckle tracking assessment of LV longitudinal strain and torsion provide additional potential measures of diastolic function. LV twist and peak untwisting rates are proposed as measures of LV myocardial relaxation. Preliminary studies suggest LV twist is reduced in diastolic dysfunction with impaired LV ejection fraction but not with preserved ejection fraction. These measurements remain investigational at present; however, some limitations already observed include the requirement for good 2D image quality and the significant post processing time[93].

OTHER NON-INVASIVE METHODS:

1. **Magnetic resonance imaging**: This technique has been shown to be of considerable use in the morphological assessment of the heart, but the functional

assessment can be obtained. Techniques such as magnetic resonance myocardial tagging which allows the labeling of specific myocardial regions. The untwisting motion of LV is directly related to relaxation of myocardium which in turn gives inference about diastolic function[94]

2. **Radionuclide angiography**: Used to study the rapid filling phase of diastole, the duration of isovolumetric relaxation phase, the relative contribution of rapid filling to total diastolic filling and the global filling property[95].

INVASIVE METHOD TO EVALUATE DIASTOLIC DYSFUNCTION

Cardiac catheterization

Invasive measurement of diastolic function is often invoked as the gold standard method for assessment of diastolic function. However the cost, complexity, and expertise required, as well as patient risk and lack of tolerability associated with such procedures, mean that cardiac catheterization is rarely performed specifically to evaluate diastolic function[96].

NEW DEVELOPMENTS IN DIASTOLIC FUNCTION ASSESSMENT

The use of resting data alone is an important limitation of the Doppler approach, especially early in the disease, when the heart is compensated at rest and symptoms occur only with activity. The evolving techniques that may help with this diagnosis include assessment of LV filling during exercise, B type natriuretic peptide (BNP), and tissue characterisation. Given the complexity of the echocardiographic evaluation of LV diastolic function, non-invasive diagnosis would be greatly aided by a simpler approach. In particular, a blood test with acceptable accuracy would be a very valuable addition to the diagnostic armamentarium, and recent attention has

turned to BNP for this purpose. BNP is a peptide secreted from the ventricular myocardium in response to dilatation and increased intra-cavity pressure. Elevation of BNP has been associated with a range of cardiac abnormalities which can result in increased filling pressures. In particular, elevation of BNP has been demonstrated in the setting of acute HF, and correlates with the degree of LV systolic dysfunction in this setting. A BNP of 100 pg/ml has been demonstrated to be accurate for the emergency room diagnosis of acute systolic heart failure. In addition, there is increasing evidence that the N-terminal fragment of the pro-BNP molecule that is released during secretion of BNP from cardiac myocytes (so called N-terminal BNP) has similar diagnostic utility.

This relation of BNP to ventricular filling pressure in systolic HF implies that BNP might also have diagnostic potential in patients with diastolic HF, in whom symptoms are also related to elevated LV filling pressures. It also suggests that BNP might be more relevant for the diagnosis of clinical diastolic HF, which is usually associated with pseudonormal or restrictive filling pattern rather than for the detection of exertional dyspnoea attributed to diastolic dysfunction, which is often characterised by an impaired relaxation pattern and may not be associated with high filling pressures at rest. Thus BNP is usually elevated in patients presenting to an emergency room with shortness of breath due to HF regardless of whether the ejection fraction is preserved or impaired and a normal BNP value has high negative predictive value in this setting. Further, high BNP concentrations have been reported in HF patients with normal LVEF, and in those with isolated LV diastolic dysfunction. Even so, BNP is reportedly lower in HF patients with preserved ejection fraction compared to those who have systolic dysfunction.

This is relevant for the diagnosis of diastolic HF because population studies have demonstrated notable increases in BNP with age and female sex, leading to significant overlap in BNP concentrations between dyspnoeic elderly patients with HF and preserved ejection fraction and similar patients without HF. Therefore, a specific BNP cut off may not accurately discriminate diastolic HF from non-HF presentations in the elderly, particularly elderly women (in whom the condition is most prevalent). In addition, since BNP has a short half life (approximately 20 minutes), the timing of sampling in relation to the patient's symptoms may have a profound influence on the utility of BNP for the detection of diastolic HF. In particular, clinically stable or treated patients who are limited by exertional dyspnoea caused by mild diastolic dysfunction often have relatively normal resting LV filling pressures and may therefore have normal BNP concentrations at rest. Therefore, given that reported mean BNP concentrations in diastolic HF have varied from 56 pg/ml in a community setting to 413 pg/ml in acute hospital presentations, it is difficult to apply a simple cut off. However, as a general guide, in symptomatic patients with preserved systolic function, diastolic HF may be considered unlikely if BNP is, 50 pg/ml, and likely if BNP is 100 pg/ml.

Whether BNP has a wider role in the diagnosis of hypertensive heart disease remains unclear. While BNP has been reported to be increased in patients with hypertension and LV hypertrophy , its ability to detect increased LV mass in a community setting was suboptimal. Similarly, a recent study found that BNP was suboptimal for the identification of diastolic (or indeed systolic) dysfunction in more than 2000 subjects randomly selected from the population[91,97-98].

MANAGEMENT OF DIASTOLIC DYSFUNCTION

Unfortunately, there have been no randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic heart failure. Consequently, the guidelines for the management of diastolic heart failure are based on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on pathophysiological mechanisms[74].

Primary prevention of diastolic heart failure includes smoking cessation and aggressive control of hypertension, hypercholesterolemia, and coronary artery disease.

Lifestyle modifications such as weight loss, smoking cessation, dietary changes, limiting alcohol intake, and exercise are equally effective in preventing diastolic and systolic heart failure.

Early diagnosis and treatment is important in preventing irreversible structural alterations and systolic dysfunction. However, no single drug has pure lusitropic properties (i.e., selective enhancement of myocardial relaxation without inhibiting left ventricular contractility or function). Therefore, medical therapies for diastolic dysfunction and diastolic heart failure often are empirical and not as well defined as therapies for systolic heart failure.

Although conclusive data on specific therapies for diastolic heart failure are lacking, the American College of Cardiology and the American Heart Association joint guidelines recommend that physicians address blood pressure control, heart rate control, central blood volume reduction, and alleviation of myocardial ischemia when

treating patients with diastolic heart failure. These guidelines target underlying causes and are likely to improve left ventricular function and optimize hemodynamics[99].

IMPROVING LEFT VENTRICULAR FUNCTION

When treating a patient with diastolic dysfunction, it is important to control the heart rate and prevent tachycardia to maximize the diastolic filling period.

Beta blockers are particularly useful for this purpose; however, they do not directly affect myocardial relaxation. In addition to slowing heart rate, beta blockers have proven benefits in reducing blood pressure and myocardial ischemia, promoting regression of left ventricular hypertrophy, and antagonizing the excessive adrenergic stimulation during heart failure. Beta blockers have been independently associated with improved survival in patients with diastolic heart failure. These medications should be used to treat diastolic heart failure, especially if hypertension, coronary artery disease, or arrhythmia is present[100].

OPTIMIZING HEMODYNAMICS

Optimizing hemodynamics primarily is achieved by reducing cardiac preload and after load. Drugs available are

1. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) directly affect myocardial relaxation and compliance by inhibiting production of or blocking angiotensin II receptors, thereby reducing interstitial collagen deposition and fibrosis. The indirect benefits of optimizing hemodynamics include improving left ventricular filling and reducing blood pressure. More importantly, there is improvement in exercise capacity and quality of life. One retrospective study showed that improved survival was associated

with ACE inhibitor therapy in patients with diastolic heart failure. One arm of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality) trial,which studied the effect of candesartan (Atacand) in patients with normal ejection fraction for 36.6 months, did not show a significant mortality benefit. However, it reduced the incidence of hospitalization for CHF exacerbation[99,101].

2. Diuretics are effective in managing optimal intravascular volume, and they minimize dyspnoea and prevent acute heart failure in patients with diastolic dysfunction. Although diuretics control blood pressure, reverse left ventricular hypertrophy, and reduce left ventricular stiffness, some patients with diastolic heart failure are sensitive to the preload reduction and may develop hypotension or severe pre-renal azotemia. Intravenous diuretics should only be used to relieve acute symptoms.
3. The hormone aldosterone promotes fibrosis in the heart and contributes to diastolic stiffness. The aldosterone antagonist spironolactone (Aldactone) has been studied in a large clinical trial of systolic heart failure, which showed a reduction in mortality related to heart failure. However, the specific effects of spironolactone on diastolic dysfunction are unclear.
4. Calcium channel blockers have been shown to improve diastolic function directly by decreasing cytoplasmic calcium concentration and causing myocardial relaxation or indirectly by reducing blood pressure, reducing or preventing myocardial ischemia, promoting regression of left ventricular hypertrophy, and by slowing the heart rate. However, nondihydropyridine calcium channel blockers (e.g., diltiazem [Cardizem]) and verapamil, should not be used in patients with bradycardia, conduction defects, or severe heart failure caused by left ventricular

systolic dysfunction. Instead, nondihydropyridines, such as diltiazem and verapamil, should be used for rate control and angina when beta blockers are contraindicated or ineffective. Finally, large randomized controlled trials have not proved that calcium channel blockers reduce mortality in patients with isolated diastolic dysfunction.

5. Vasodilators (e.g., nitrates, hydralazine [Apresoline]) may be useful because of their preload-reducing and anti-ischemic effects, particularly when ACE inhibitors cannot be used. The Vasodilator Heart Failure Trial, however, did not show significant survival benefit in patients with diastolic heart failure. Vasodilators should be used cautiously because decreasing preload may worsen cardiac output. Unlike other medications used for diastolic heart failure, vasodilators have no effect on left ventricular regression.
6. The exact role of digoxin for treating patients with diastolic heart failure remains unclear. Digoxin can be deleterious in older patients with left ventricular hypertrophy and hypertrophic obstructive cardiomyopathy; therefore, digoxin is only appropriate for patients with diastolic heart failure and atrial fibrillation[99,102].

Targeting underlying disease

The mainstay of treatment of isolated DD is uncertain. Studies are evaluating the use of ACE inhibitors and ARBs. Inhibition of the renin-angiotensin system reverses interstitial collagen deposition; fibrosis is prevented and distensibility of the ventricle is improved as myocardial stiffness diminishes. In patients with LVH and hypertension, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that losartan reduced cardiovascular complications better than atenolol did.24 Additionally, losartan has been associated with greater regression of myocardial fibrosis and subsequent reduction in ventricular stiffness.

Regression of LVH secondary to hypertension is an important therapeutic goal since it is one of the most common underlying causes of DD. According to AMA guidelines, in patients with DD and LVH secondary to hypertrophic cardiomyopathy, ischemia, or coronary disease, treatment should be aimed at maintaining an appropriate heart rate, relieving pericardial strain, and increasing filling time. Although additional studies are being conducted with ARBs, first-line therapy for DD continues to be CCBs or BBs. Some treatments used for SD are not beneficial in Patients with DD and may prove harmful. Positive inotropic agents should generally be avoided because LVEF is preserved in DD and these agents can therefore worsen symptoms. Digoxin may induce ischemia, tachycardia, and arrhythmias; digitalis may also exacerbate the relative calcium overload during diastole. Arterial vasodilators such as hydralazine and alpha adrenergic receptor blockers such as prazosin are both likely to worsen diastolic function by the sympathetic response of an increased contractile force or heart rate[103].

Prognosis

The prognosis of LV diastolic dysfunction and DHF is slightly less ominous than that of systolic heart failure. The annual mortality rate in patients who have diastolic dysfunction or DHF is 5% to 8% while the rate is 10% to 15% in those who have systolic dysfunction or systolic heart failure. By comparison, the annual mortality rate in the general population without heart failure and of a similar age is 1%. Presence of coronary disease, age, and the LVEF cutoff value are important factors in the prognosis[104]. When patients who have ischemic heart disease are excluded, annual mortality for DHF falls to 2% to 3%.However, in patients older than 70 years who have CHF, mortality is similar in systolic and diastolic heart failure [105].

METHODOLOGY

SOURCE OF DATA

This study was conducted at R.L.JALAPPA Hospital and Research, Centre Tamaka, Kolar, attached to Sri Devaraj Urs Medical College during the years 2009-2010.

The study was done on 30 hypertensive patients attended outpatient clinic and those admitted in the medical wards.

INCLUSION CRITERIA: All patients aged between 18-65 years with newly diagnosed hypertension.

EXCLUSION CRITERIA:

- Elderly patients > 65 years
- Patients on diuretic therapy, beta blockers and ACE inhibitors.
- Patients having - Diabetes, IHD, Chronic kidney disease, Heart failure (EF 50%) , Anaemia.
- Patients with echocardiographically proven LV systolic dysfunction with EF <50%.

Hypertension is defined as Systolic BP >140mmHg and Diastolic BP > 90mmHg (JNC7 CLASSIFICATION).

All newly detected cases of hypertension were recruited for this study. Patients after taking consent were subjected for clinical examination, relevant laboratory investigations and echocardiography to grade for left ventricular dysfunction.

The following investigations were done for all patients to rule out any other cause for elevation of N-terminal pro BNP level.

- Hemoglobin
- ECG
- CK-MB
- RBS\FBS\PPBS
- X-ray chest
- Blood urea and Serum creatinine
- 2D-ECHO
- N-Terminal pro BNP.

All patients who satisfied inclusion and exclusion criteria are then subjected for echocardiography.

Two-dimensional echocardiograms were subjected for careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fraction were derived from biplane apical (2- and 4-chamber) views with a modified Simpson's rule algorithm.

The transmitral pulsed Doppler velocity recordings from 3 consecutive cardiac cycles were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction, respectively, and deceleration time (DT) was the interval from the E-wave peak to the decline of the velocity to baseline. In those cases in which velocity did not return to baseline, extrapolation of the deceleration signal was performed.

Finally, the LV isovolumetric relaxation time (IVRT) was obtained in the apical 5-chamber view with a continuous-wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmitral flow. IVRT was taken as the time in milliseconds from the end of ejection to the onset of LV filling.

All echocardiograms were interpreted by experienced cardiologists who were blinded to the BNP levels.

ECHO CLASSIFICATIONS

Normal Ventricular Function:

Normal ventricular function was defined by normal LV end-diastolic (3.5 to 5.5 cm) and end-systolic (2.5 to 3.6 cm) dimensions, no major wall motion abnormalities, an ejection fraction 50%, and no evidence of impaired or restrictive like relaxation abnormalities as described below.

Systolic Dysfunction:

Systolic dysfunction was defined by an ejection fraction 50% or any wall motion abnormalities. Patients with systolic dysfunction were excluded.

Diastolic Dysfunction:

Diastolic dysfunction was classified in 3 categories.

Stage of Diastolic Dysfunction	E/A Ratio, cm/s	IVRT, ms	DT, ms
Normal*	>1	<100	<220
I. Delayed Relaxation	<1	>100	>220
II. Pseudonormal	1-2	60-100	150-200
III. Restrictive Filling	>2	<60	<150

NT- Pro BNP

Blood samples were drawn from each patient following an overnight fasting and after all had been in supine position for ten minutes. A 10ml of venous blood was drawn into a tube containing EDTA as an anticoagulant and aprotonin to avoid breakdown of natriuretic hormones(provided by Religare labs). The samples were centrifuged at 3000g for 10 minutes and plasma was removed, allocated and frozen at -85^0c. Plasma concentration of NT-pro BNP were measured using radioimmunoassay. A plasma level above 125pg/ml is considered as high.

Statistical Methods

Descriptive statistical anaolysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made: Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$).

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Sensitivity and specificity were computed for NT-pro BNP levels using several possible cutoff points. Receiver operating characteristics (ROC) curve analysis was used to assess ability of NT-pro BNP level to identify diastolic dysfunction. The results were expressed as the area under curve the ROC curve (AUC) and 95% confidence interval for this area. Difference were considered significant at $p< 0.05$.

OBSERVATION AND RESULTS

AGE DISTRIBUTION OF PATIENTS STUDIED (Table No: 3)

Age in years	Number of patients	%
21-30	**2**	**6.7**
31-40	**5**	**16.7**
41-50	**9**	**30.0**
51-60	**9**	**30.0**
61-70	**5**	**16.7**
Total	**30**	**100.0**

Mean ± SD: 49.93±10.94

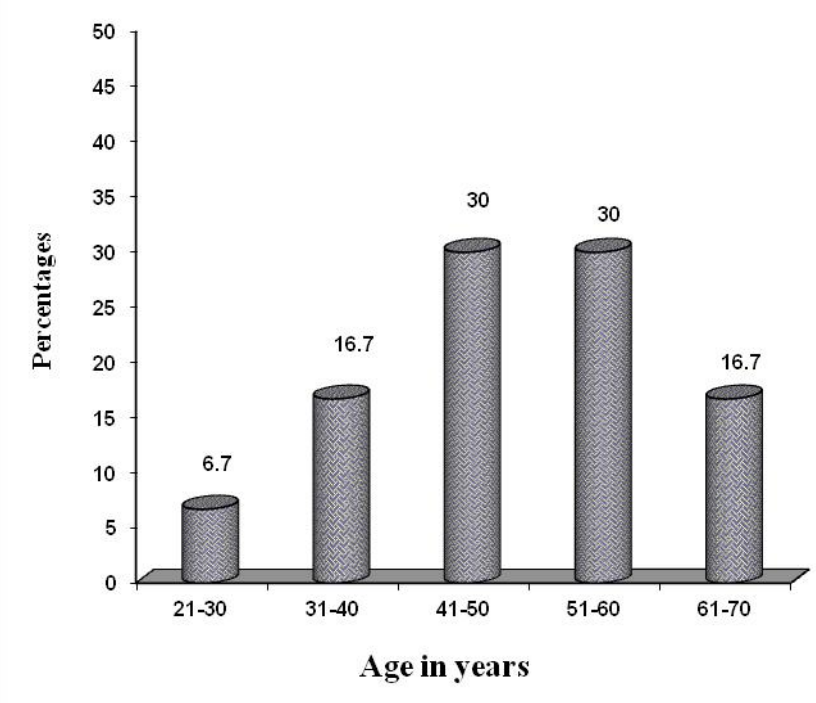


Figure No : 3 Age distribution of patients

Out of 30 patients studied, majority of them were in age group of 40-50 years and 50-60 yrs of age with a mean age of 49.93±10.94years**.**

GENDER DISTRIBUTION (Table No: 4)

Gender	Number of patients	%
Male	18	60.0
Female	12	40.0
Total	30	100.0

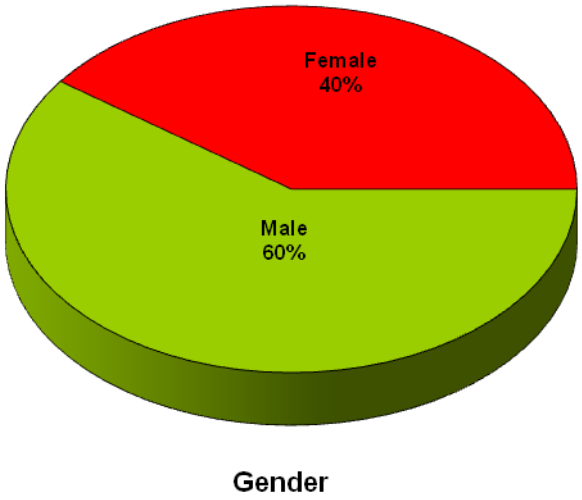


Figure No:4 showing the sex distribution

Out of 30 patients included in this study, 60% of patients were males and 40% of patients were females. The male to female ratio was 1.5:1.

CLINICAL FEATURES OF PATIENTS STUDIED (Table No: 5)

Clinical features	Number of patients	%
DYSPN0EA	4	13.3
PALPITATION	3	10.0
FATIGUABILITY	8	26.7
DIZZINESS	15	50.0
BLURRING OFVISION	7	23.3
HEADACHE	19	63.3
CHEST DISCOMFORT	4	13.3
EPISTAXIS	3	10.0
COUGH	1	3.3
VOMITING	1	3.3
HICCUPS	1	3.3

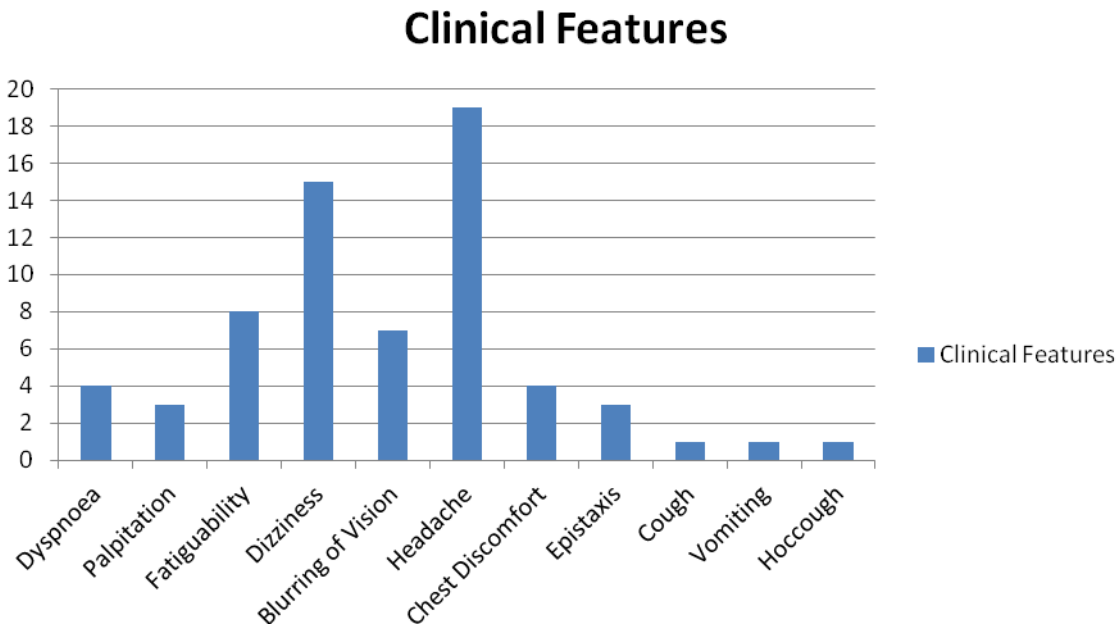


Figure 5: showing the clinical features

The most common complaint among patients studied was headache (63%, n=19) followed by dizziness (50%, n=15). Breathlessness was noticed in only 13% of the patients studied. 23.7% and 23.3% of patients complained of blurring of vision and fatiguability respectively.

BODY MASS INDEX DISTRIBUTION (BMI) (kg/m2) distribution of patients (Table No: 6)

BMI (kg/m2)	Number of patients (n=30)	%
<25.0	14	46.7
25.0-30.0	9	30.0
>30.0	7	23.3

Mean ± SD: 26.32±3.86

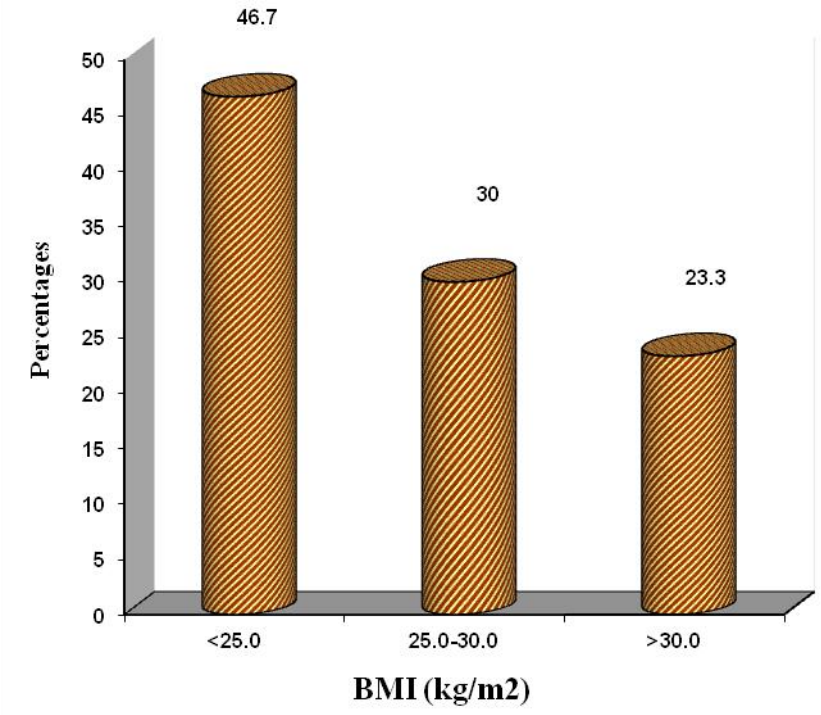


Figure No: 6 showing the BMI of patients studied

In this study the height and weight of the patients was taken and BMI was calculated. 46.7% of patients had normal BMI. Seven out of 30 patients had BMI over 30kg/m^2 .

STAGES OF HYPERTENSION ACOORDING TO JNC 7

JNC class of patients studied (Table No: 7)

JNC class	Number of patients (n=30)	%
Class I	10	33.3
Class II	20	66.7

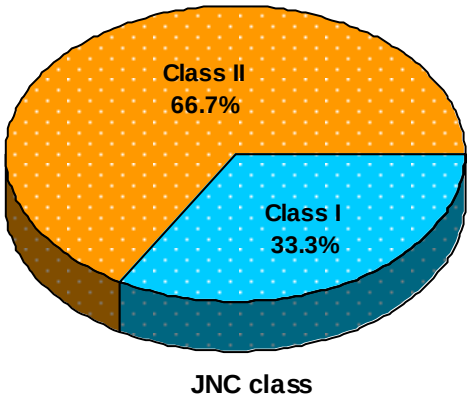


Figure No: 7 showing the stages of hypertension

Out of 30 newly detected hypertensive patients, 66% of patients were in class II and 33.3% of patients were in class I according to JNC 7.

HABITS OF PATIENTS STUDIES (Table no: 8)

Habits

Habits	Number of patients (n=30)	%
Smoking	17	56.7
Alcohol	6	20.0

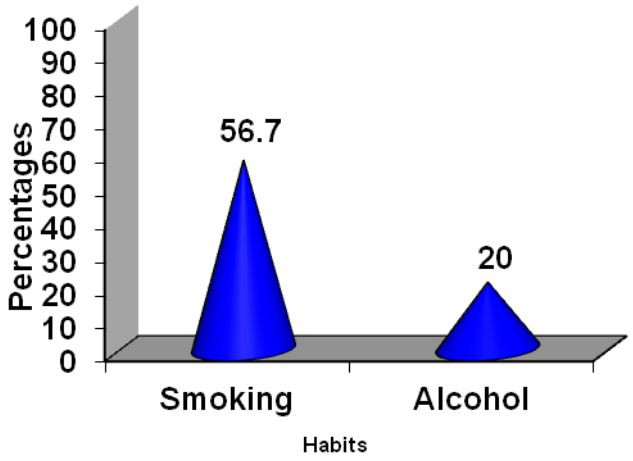


Figure no: 8 shows the habits of patients enrolled

When the habits of patients was considered, majority of the patients were smokers (56.7%) and 20% of the patients used to consume alcohol daily.

LIPID PROFILE OF PATIENTS (Table No: 9)

Lipid parameters

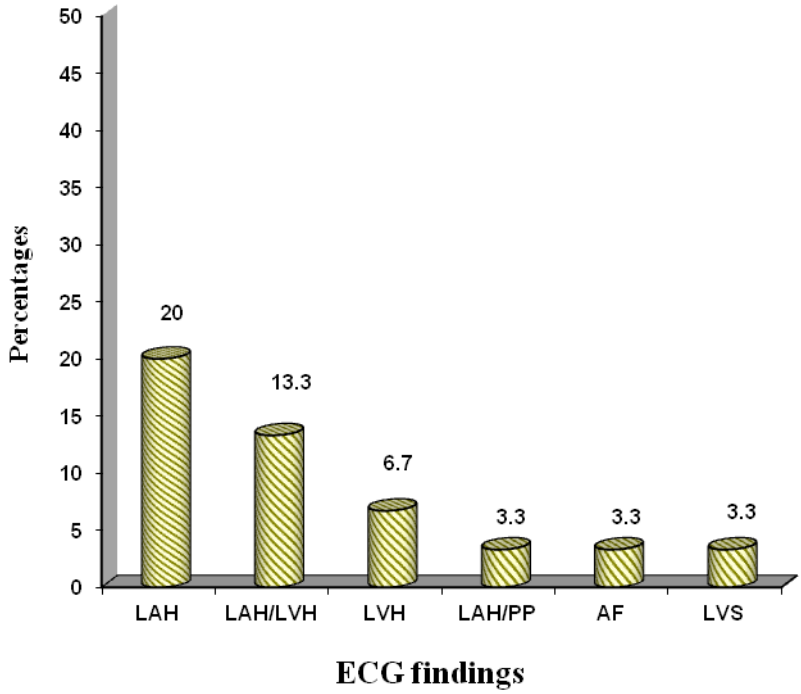
Lipid parameters	Number of patients (n=30)	%	Mean ± SD
Total cholesterol (mg/dl)			
<200	**23**	**76.7**	**176.97±41.44**
>200	**7**	**23.3**	
Triglycerides (mg/dl)			
<165	**16**	**53.3**	**158.33±54.54**
>165	**14**	**46.7**	
HDL (mg/dl)			
<30	**0**	**0.0**	**39.03±3.56**
>30	**30**	**100.0**	
LDL (mg/dl)			
<150	**27**	**90.0**	**100.60±35.47**
>150	**3**	**10.0**	

In this study, we have done lipid profile for patients since dyslipidemia can alter the level of N-terminal pro BNP in the plasma. The mean lipid levels of patients were within normal limits.

ECG CHANGES OF ALL PATIENTS STUDIED (Table No: 10)

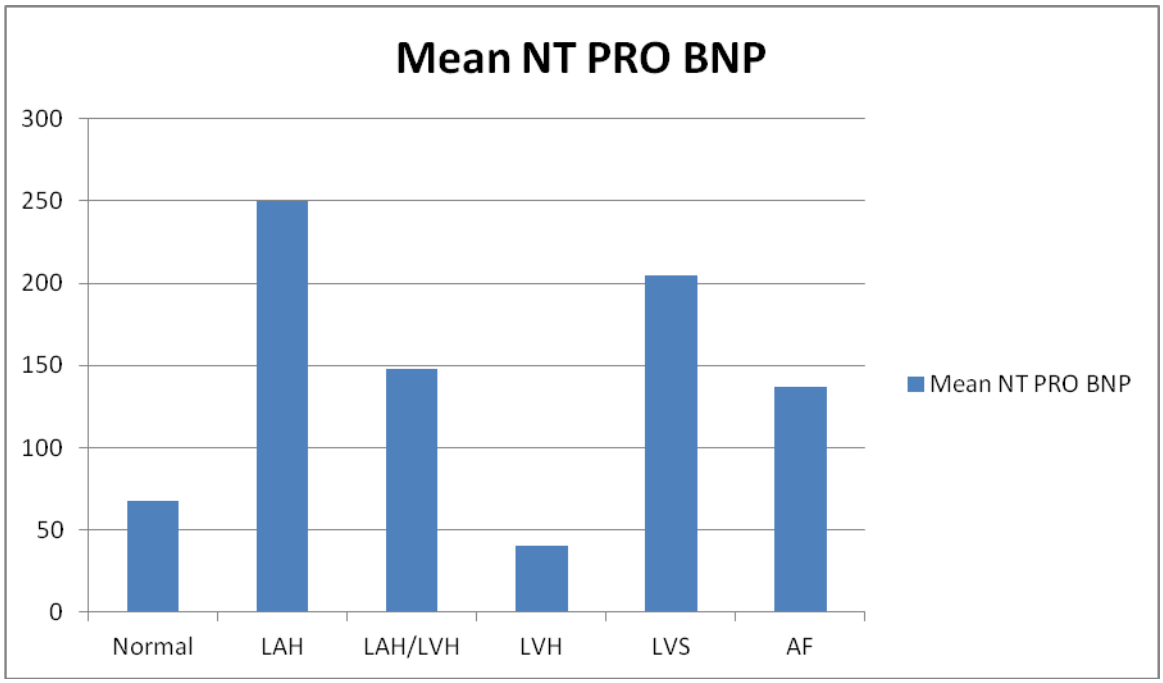
ECG findings	Number of patients (n=30)	%
Normal	15	50.0
Abnormal	15	50.0
LAH	6	20.0
LAH/LVH	4	13.3
LVH	2	6.7
LAH/PP	1	3.3
AF	1	3.3
LVS	1	3.3

Figure No:9 showing the ECG changes



Out of 30 cases, 50% of patients had normal ECG. Left atrial hypertrophy was the most common abnormality noticed (20%). Combination of LAH/LVH was noticed among 13.3% of patients. LVH was present among 6.7% of patients.

Figure 10 : SHOWING THE MEAN LEVEL OF NT- pro BNP LEVELS WITH ECG CHANGES



N-terminal pro BNP level was significantly elevated (250pg/ml) with patients with left atrial hypertrophy (LAH). Patients with LAH/LVH (left atrial hypertrophy/ left ventricular hypertrophy) had a mean level of 148.8pg/ml. Our study also showed high levels of N-terminal pro BNP level (202.2pg/dl) among patients with left ventricular strain pattern.

GRADING OF DIASTOLIC DYSFUNCTION BY ECHO (Table No: 11)

ECHO diastolic dysfunction grade

ECHO-Diastolic dysfunction	Number of patients (n=30)	%
Normal	6	20.0
Grade I	15	50.0
Grade II	9	30.0

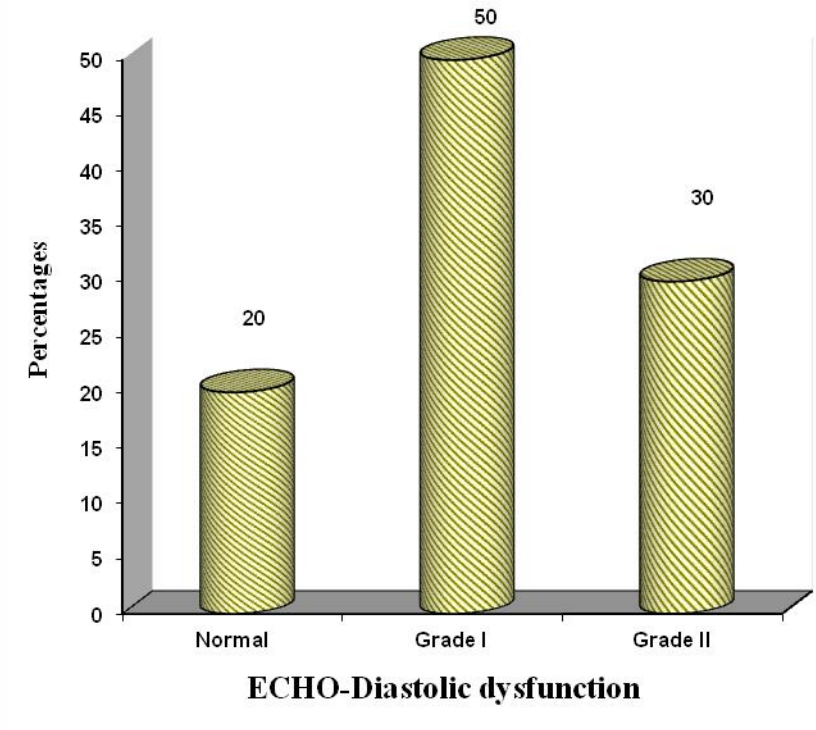
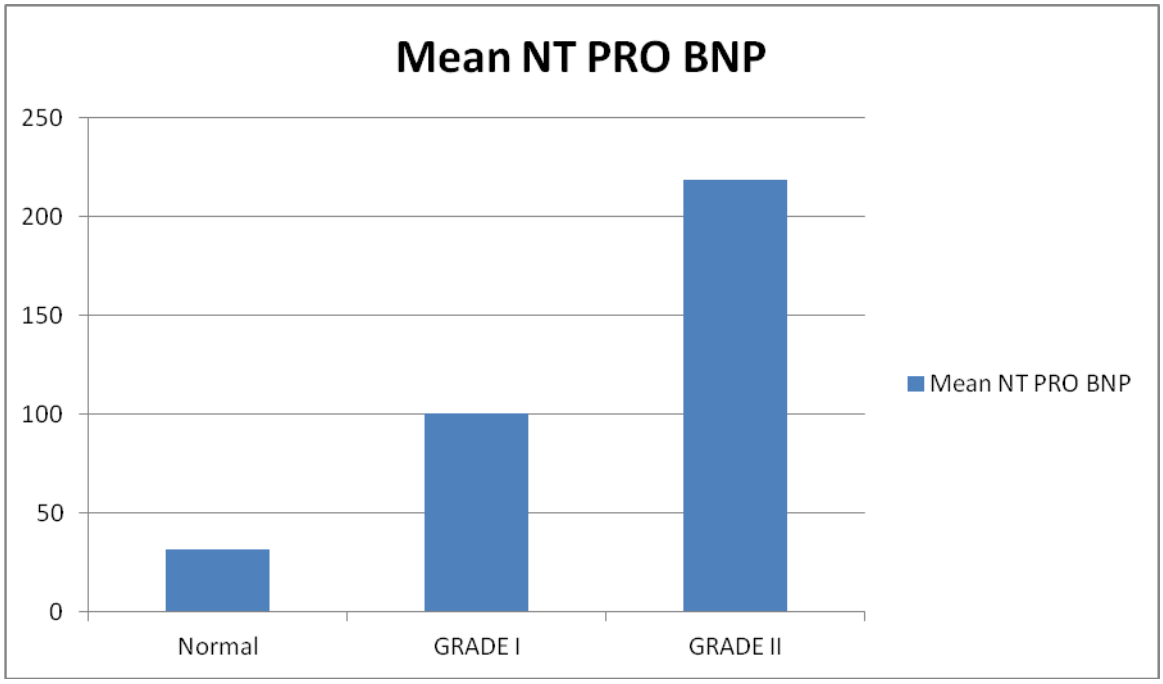


Figure No: 11 showing the grading of diastolic dysfunction

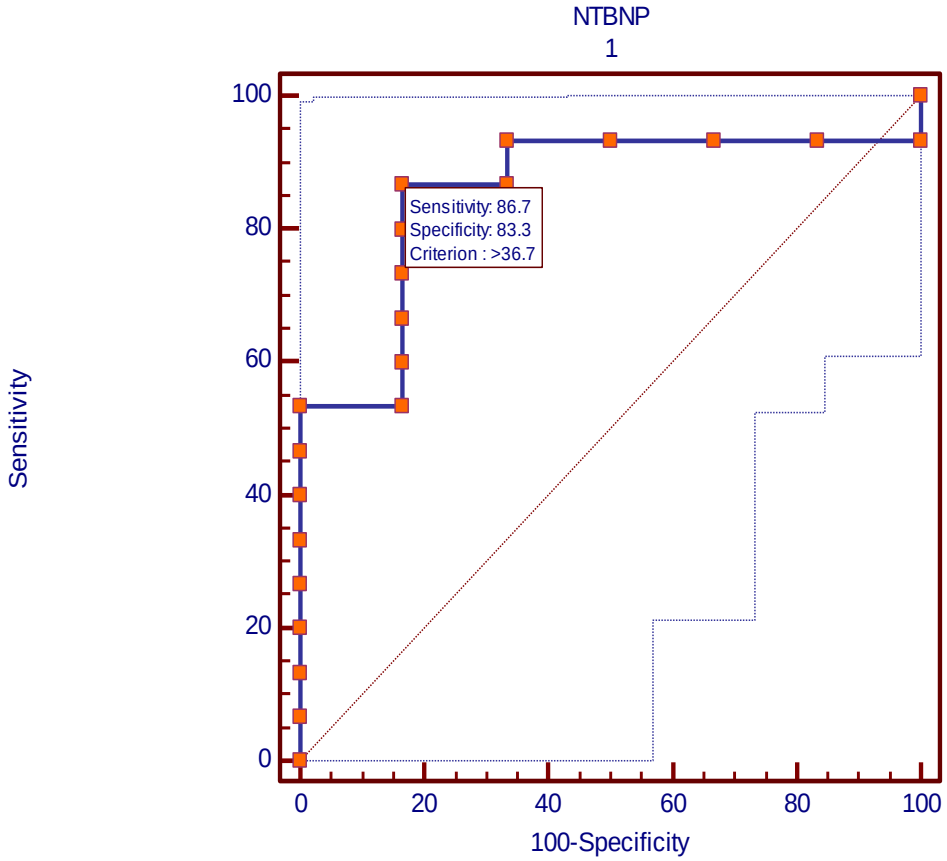
When the patients were categorized according to the grade of diastolic dysfunction, 50% of patients were with grade I diastolic dysfunction. 30% of patients had grade II diastolic dysfunction. Rest of them had normal echocardiographic findings.

Figure 12. SHOWING THE MEAN LEVEL OF NT- pro BNP LEVEL WITH ECHO GRADES OF DIASTOLIC DYSFUNCTION



The mean blood concentration of N-terminal pro BNP of all hypertensive patient without diastolic dysfunction was 31.53± 31.02 pg/ml. Patients with pseudonormal filling pattern (218.50±129.29pg/ml) had significantly higher levels compared with normal and impaired filling groups (100.44±70.61pg/ml)

Figure No: 13. SHOWING THE ROC (Receiver –operating characteristic) CURVE



Receiver –operating characteristic (ROC) curve analysis was used to assess the ability of NT-pro BNP plasma level to identify diastolic dysfunction and elevated LV filling pressures. The optimal cut off point 218.5 pg/dl gave a sensitivity of 86.7% and specificity of 83.3% with 95% CI (Confidence interval) for this area.

CORRELATION OF ALL VARIABLES WITH DIASTOLIC DYSFUNCTION

(Table No:12)

Correlation of study variables according to ECHO- diastolic dysfunction grade

Variables	ECHO- diastolic dysfunction grade			P value
	Normal (n=6)	Grade I (n=15)	Grade II (n=9)	
Age in years	39.67±8.55	50.93±10.06	55.11±9.99	0.018*
Male	4(66.7%)	9(60%)	5(55.6)	1.000
Female	2(33.3%)	6(40%)	4(267%)	1.000
BMI (kg/m2)	26.60±3.72	27.37±4.53	24.37±1.81	0.184
Total cholesterol (mg/dl)	170.00±63.26	177.88±42.19	180.11±23.71	0.899
Triglycerides (mg/dl)	177.33±44.22	148.07±44.72	162.77±74.66	0.533
HDL (mg/dl)	40.33±2.88	39.06±4.28	38.11±2.52	0.511
LDL(mg/dl)	104.33±35.91	102.53±40.99	94.89±27.55	0.851
Blood urea(mg/dl)	24.50±7.29	25.33±7.14	33.88±14.98	0.111
Serum creatinine (mg/dl)	1.15±0.31	1.01±0.26	1.08±0.19	0.462
NT-proBNP pg/l	31.53±31.02	100.44±70.61	218.50±129.29	0.001**

There is a strong positive correlation between NT-pro BNP and grade II diastolic dysfunction for all patients (P = 0.001)

DISCUSSION

Left ventricular diastolic dysfunction is often impaired in association with prolonged or severe hypertension. Diastolic dysfunction is a risk factor for the development of congestive heart failure, and has prognostic value in population settings. As many as 40% to 50% of patients with a diagnosis of heart failure have normal systolic function, which implicates diastolic dysfunction as the most likely potential abnormality responsible for this disorder.

We studied 30 newly detected ambulatory hypertensive patients, of which 18 were males and 12 were females with a mean age of 49.9 years. A study by Luchi RJ et al (1982) and Wong WF et al in 1989 had shown an increase in prevalence of diastolic heart failure with age, with an approximate incidence of 15% to 25% in patients 60 years of age, 35% to 40% in those between 60 and 70 years of age, and 50% in patients with 70 years of age. Our study showed incidence of grade II diastolic dysfunction in 30% of patients with a mean age of 55.1 (p-0.018) and grade I diastolic dysfunction in 50% of patients with mean age of 50.3 years.

Grewal J et al[32] observed a male predominance in patients with diastolic dysfunction. The present study also showed males are more affected than females. Ceyhan C et al[97] however did not report any significant difference in sex, smoking status and BMI of patients with diastolic dysfunction.

Zampaglione et al[106] reported headache (22%) as the most common symptom followed by epistaxis (17%) in hypertensive patients. This study also showed headache (63.3%) as the most common symptom among patients with hypertension.

Left ventricular diastolic dysfunction is one of the major determinants of left ventricular filling pressure. There is no single index that is useful and widely applicable to assess diastolic performance. Indirect non-invasive assessment of filling dynamics has been used to characterize diastolic properties. Appleton et al[85] laid the foundation for applying Doppler transmitral velocity measurements to the evaluation of diastolic function and described 4 distinct patterns (normal, delayed relaxation, pseudonormal and restrictive) which have become the Rosetta stone for the clinician in diagnosing diastolic dysfunction.

Doppler echocardiography demonstrated normal diastolic function in 6 out of 30 patients (20%). Most of the patients with abnormal diastolic dysfunction had an impaired relaxation pattern (n=15) and pseudonormal filling pattern documented in 9 patients. None of our patients had restrictive filling pattern which was a similar observation in the study done by Ceyhan C et al[97].

The mean blood concentration of N-terminal pro BNP of all hypertensive patients without diastolic dysfunction was 31.53± 31.02 pg/ml. Mean NT pro BNP levels were significantly elevated with abnormal diastolic dysfunction when compared with normal diastolic function. Patients with pseudonormal filling pattern (218.50±129.29 pg/ml) had significantly higher levels of NT pro BNP compared with normal and impaired filling groups (100.44±70.61 pg/ml, p=0.001). The close correlation between concentration of NT-pro BNP level and E/A ratio suggests that an increased concentration of NT-pro BNP level is parallel to the increased left atrial pressure.

Ceyhan et al[97], in their study, set an optimal cut-off value for NT-pro BNP (119pg/dl) and noted high sensitivity of 87% and specificity of 100% for the same. This study has also made similar observations, sensitivity of 86.7% and specificity of 83.3% .

Lubien E et al[50] showed relation of BNP to ventricular filling pressure in systolic HF implies that BNP might also have diagnostic potential in patients with diastolic HF, in whom symptoms are also related to elevated LV filling pressures. It also suggests that BNP might be more relevant for the diagnosis of clinical diastolic HF, which is usually associated with pseudonormal or restrictive filling patterns, rather than for the detection of exertional dyspnoea attributed to diastolic dysfunction, which is often characterised by an impaired relaxation pattern and may not be associated with high filling pressures at rest.

Dong et al[49] also reported that clinically stable, ambulatory cohort of patients with cardiovascular disease that exhibited a wide range of systolic and diastolic dysfunction showed that echocardiographic diastolic parameters correlates significantly with plasma level of NT pro BNP.

Furumoto et al[3], Grewal J et al[32] and Ceyhan C et al[97] reported the close correlation between echocardiographic derived index of diastolic dysfunction with the level of N-terminal pro BNP. Our study also showed a parallel increase in plasma levels of N- terminal pro BNP, correlating with the degree of echocardiographic grades of diastolic dysfunction with significant p value of 0.001. The assessment of concentrations of NT- pro BNP in blood can identify the presence of diastolic abnormalities associated with hypertension.

Pitfalls in the echo-Doppler assessment of diastolic dysfunction exist, and the transmitral velocity pattern can be altered by changes in heart rate, preload, afterload, contractility, valvular regurgitation, and position of the sample volume. A simple, rapid blood test that reflects diastolic dysfunction in settings in which systolic function is normal would be of significant clinical benefit. The test should reliably rule out LV diastolic dysfunction with an adequate positive predictive value.

B-natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload in diastolic heart. In diastolic dysfunction patients, high plasma level of NT-pro BNP is attributed to the ventricular volume expansion and pressure overload .

Studies have previously demonstrated that a rapid assay for BNP can accurately rule out the presence of abnormal echocardiographic findings, be they systolic or diastolic. This study extends those findings to patients with normal systolic function. In this group of patients, elevated BNP levels accurately depicted diastolic abnormalities seen on echocardiography regardless of whether the patient had a history or symptoms of heart failure. Although BNP levels alone cannot differentiate between systolic and diastolic dysfunction, a low BNP level in the setting of normal systolic function by echocardiography may be able to rule out clinically significant diastolic abnormalities seen on echocardiography. On the other hand, elevated BNP levels in patients with normal systolic function, especially older patients with a history of CHF, correlate to diastolic abnormalities on Doppler studies.

In the present study, patients with advanced diastolic dysfunction had higher concentration of N-terminal pro BNP levels. Pseudonormal pattern was the most severe abnormality and had highest level of N-terminal pro BNP level compared to

impaired and normal diastolic dysfunction. A restrictive pattern has usually been observed only in patients with severe degrees of systolic dysfunction. However most of our hypertensive patients were symptom free and more than two-third of them had mild to moderate LV diastolic dysfunction. Since the study size was small, we need large scale studies to confirm the utility of N-terminal pro BNP level to pick up asymptomatic diastolic dysfunction in hypertensive patients.

The combination of assessment of concentration of N-terminal pro BNP and echocardiography may facilitate optimal stratification of patients with respect to vulnerability to cardiovascular complications of hypertension and enhances individualization of patient care.

SUMMARY

- Total number of cases was 30.
- Detailed clinical evaluation, laboratory investigations like ECG, renal profile, echocardiography and N-terminal pro BNP level are done.
- Mean age of cases were 49.93±10.94years with a male to female ratio of 1.5:1.
- Most common clinical feature was headache (63.3%), followed by dizziness (50%).
- 66.7% of patients were in JNC 7 class II and 33.3 % patients in JNC 7 class I.
- Out of 30 screened patients, 50% of patients had grade I diastolic dysfunction and 30% of patients had grade II diastolic dysfunction.
- The mean blood concentration of N-terminal pro BNP of all hypertensive patients with normal echocardiography was 31.53± 31.02 pg/ml. .
- Mean N-terminal pro BNP levels were significantly elevated with abnormal diastolic dysfunction when compared with normal diastolic function. Patients with pseudonormal filling pattern (218.50±129.29 pg/ml) had significantly higher levels compared with normal and impaired filling groups (100.44±70.61 pg/ml).
- This study has observed a sensitivity of 86.7% and specificity of 83.3% for NT-pro BNP to identify diastolic dysfunction.
- Study showed a parallel increase in plasma levels of N- terminal pro BNP, correlating with the degree of echocardiographic grades of diastolic dysfunction with significant p value of 0.001.

CONCLUSION

Our study showed that most of the hypertensive patients had diastolic dysfunction. Mean NT- pro BNP levels are significantly elevated with abnormal diastolic dysfunction. This study demonstrates that there is a close relationship between NT-pro BNP blood levels and echocardiographic index, indicative of diastolic dysfunction in clinically stable hypertensive patients. The assessment of the blood concentration of NT-pro BNP is of potential value for identification of those patients with hypertension to detect early cardiovascular changes, especially LV diastolic dysfunction.

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PROFORMA

CASE NO:

NAME OF THE PATIENT:

I.P.NO:

AGE:

SEX:

OCCUPATION:

ADRESS:

DATE OF ADMISSION:

DATE OF DISCHARGE/DEATH:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

1. DYSPNOEA

Duration	_____
Onset	Sudden/insidious
Onset in relation to pain	_____
Aggravating factors	Exertion/stress/heavy meals/others
Precipitating factors	Exertion/stress/heavy meals/others
NYHA Class	I / II / III / IV
PND	Yes/No
Orthopnoea	Yes/No

2. PALPITATION

Onset	Sudden/insidious
Onset in relation to pain	_____
Nature	Continuous/intermittent
Duration	_____
Precipitating factors	Exertion/excitement/fear/drugs/others
Relieving factors	Rest/drugs/other

3. DIZZINESS Yes/No

4. HEADACHE: Duration:

Site:frontal/temporal/occipital

Blurring of vision Yes/No

5. FATIGABILITY Yes/No

6) CHEST PAIN Yes/No

7. OTHER SYMPTOMS

Past history

Anginal pain	Yes/No	Duration-
Diabetes mellitus	Yes/No	Duration-
Hypertension	Yes/No	Duration-
Dyslipidemia	Yes/No	Duration-
Ischemic heart disease	Yes/No	Duration-
SIMILAR COMPLAINTS	Yes/No	
Cerebrovascular accident	Yes/No	
Thyriod disorder	Yes/No	
Renal disease	Yes/No	

Pesronal history

Diet	Vegetarian/non-veg/mixed
Appetite	Good/poor
Bowel habit	Normal/constipation/diarrhea
Bladder	Normal/polyuria/oliguria
Physical activity	Sedentary/Moderate/Heavy
Smoking	Beedis/cigggarettes
	Duration _____yrs
	Number _____/day.
Alchol	Duration _____years.
	Quantity _____
Tobbaco chewing	Yes/no
Marital life	Single/married.
Treatment history:	Any intake of ACE inhibitor –yes/no.
	Beta-blokers-yes/no.
	Diuretics –yes/no

Family history

Ischemic heart disease	Yes/No
Diabetes	Yes/No
Hypertension	Yes/No
Dyslipidemia	Yes/No
Other illnesses	Yes/No

MENSTRUAL HISTORY

1) Age of menarche
2) Married life/no of children
3) Age of menopause

GENERAL PHYSICAL EXAMINATION

1) Appearance normal/ill looking
2) Pallor present/absent

3) Icterus present/absent

4) Cyanosis present/absent

5) Clubbing present/absent

6) Signs of hyperlipidemia xanthoma /xanthalesma / arcus senilis

7) Pedal edema present/absent

8) Significant lymphadenopathy present/absent

9) Height _____cm.

10) Weight _____kg.

11) BMI

12) Thyroid normal/enlarged.

Vitals

Pulse _____/min Peripheral pulses- Felt/Not felt

Locomotar brachii-seen/Not seen

B.P. _____mm Hg:

	Systolic mmHg	Diastolic mmHg
A) stage 1 hypertension	140-159	90-99
B) stage 2 hypertension	>160	>100
C) isolated systolic hypertension	>140	<90

Respiratory rate _____/min

Temperature _____^{0} Celsius

SYSTEMIC EXAMINATION-

CARDIOVASCULAR SYSTEM

INSPECTION

JVP

1) Shape of chest normal/abnormal

2) Precordial pulsations yes/no

3) Apical impulse _____

4) Pulsations (epigastric,parasternal) yes/no.

PALPATION

1) Apical impulse site _____

2) Apical impulse character normal/tapping/hyperdynamic/heaving.

3) Parasternal heave

4) Epigastric pulsations

5) Trill

6) Other palpable sounds

PERCUSION

Cardiac borders

Liver dullness

ASCULTATION

1) Heart sounds normal/faint/accentuated
2) Added sounds S3/S4/S3S4
3) Murmur yes/no
    1. Site
    2. Grade
    3. Position best heard
    4. Radiation

2. Respiratory system examination:

Rate	_____/min
Rhythm	regular/irregular
Depth	normal/deep/shallow
Breath sounds	vescicular/bronchial/others
	Wheeze/crepitations/ronchi/others
Inspection	
Palpation	
Percussion	

3. Abdominal examination

Tenderness	present/absent
Hepatomegaly	present/absent
Splenomegaly	present/absent
Ascites	present/absent
Other findings	Yes/No

4. Central nervous system

Higher mental functions	orientation / memory
Speech	normal/abnormal
Cranial nerves	normal/abnormal
Motor system	normal/abnormal
Sensory system	normal/abnormal
Cerebellar system	normal/abnormal
Autonomic nervous system	normal/abnormal
Optic fundus	normal/abnormal

INVESTIGATIONS

1) Haemogram Hb TC DC-N- L - M-
Platelets- ESR-

2) Urine Albumin-
Sugar-
Microscopy-

3) Blood sugar RBS FBS PPBS

4) Blood urea Sr. creatinine

5) Lipid profile Sr. cholesterol- Triglycerides-
LDL - HDL-

6) CK-MB level

7) Serum N-terminal pro BNP level of the patient-

8) E.C.G

Rate _____/min
Rhythm _____
Voltage _____
Mechanism _____
Axis _____
Position _____
P-wave _____
Q-waves _____
QRS comlpex _____
PR interval _____
Q-T interval _____
ST segment _____
T wave _____
Remarks _____

9) ECHOCARDIOGRAM: A)transmitral flow velocities in early diastole(E) and during atrial contraction(A)

B) E/A ratio, DT, IVRT

C) LV systolic dysfunction

D) Ejection fraction- 1.above 60%

2.45-60%

3.30-45%

4.less than 30%

FINAL DIAGNOSIS

TREATMENT GIVEN

OUTCOME

DISCUSSION

SIGNATURE OF GUIDE **SIGNTURE OF CANDIDATE**

KEY TO MASTER CHART

M	-	Male
F	-	Female
BMI	-	Body mass index
RBS	-	Random blood sugar
BU	-	Blood urea
SC	-	Serum creatinine
LVH	-	Left ventricular hypertrophy
LAH	-	Left atrial hypertrophy
LVS	-	Left ventricular strain
AF	-	Atrial fibrillation
DT	-	Deceleration time
IVRT	-	Isovolumetric relaxation time
NT-pro BNP	-	N-terminal pro brain natiuretric peptide
N	-	Normal
HT	-	Height
WT	-	Weight
BP	-	Blood Pressure
HDL	-	High Density Lipoprotein
TG	-	Triglyceride
LDL	-	Low Density Lipoprotein

MASTER CHART

SL. NO	NAME	IP.NO	AGE	SEX	DYSPN0EA	PALPITATION	FATIGUABILITY	DIZZINESS	BLURRING OF VISION	HEADACHE	OTHERS	SMOKING	ALCOHOLISM
1	RATHNAMMA	642910	50	F	+	-	-	+	-	+	-	-	-
2	MURALI.G	642390	38	M	-	-	+	+	-	-	-	+	+
3	KRITH L MEHTA	642622	52	M	+	-	-	+	-	+	-	+	-
4	SAROJA	646573	60	F	-	+	-	-	-	+	CHEST DISCOMFORT	-	-
5	NEHRU PASHA	635565	46	M	-	-	-	+	-	+	-	+	+
6	SHIRAMAIAH	648287	64	M	-	-	-	+	-	+	VOMITTING	+	-
7	MANJUNATH	648289	29	M							EPISTAXIS	+	+
8	GOPINATH	629675	49	M	-	-	+	+	-	+	EPISTAXIS	+	-
9	SRIRAMAIAH	649254	40	M	-	-	+	+	-	-	-	+	-
10	RAMAPPA	644358	55	M	-	-	-	+	+	+	-	+	+
11	LAKSHMAMMA	659160	40	F	-	-	-	+	-	+	-	-	-
12	JAYAMMA	673722	45	F	-	-	+	-	+	+	-	-	-
13	SAMJITH	601473	34	M	-	-	+	+	-	+	-	+	-
14	CHANDRASHEKAR	569293	64	M	-	-	+	-	-	-	CHEST DISCOMFORT	+	-
15	KANTHAMMA	655453	64	F	-	-	-	+	-	-	EPISTAXIS	-	-
16	KEMPAMMA	644345	55	F	-	-	+	+	+	-	-	-	-
17	NARAYANAPPA	653101	50	M	-	-	-	-	-	-	HICCUPS	+	-
18	RAJESHWARI	604114	60	F	+	-	-	-	-	+	-	-	-
19	NAGARAJ M S	624260	43	M	-	-	-	-	-	+	-	-	-
20	MARIYAPPA	641998	60	M	+	-	-	-	-	+	COUGH	+	-
21	SHANKER	634306	48	M	-	-	-	+	-	+	-	+	+
22	SYED SHABIL	634348	53	M	-	-	-	-	+	+	CHEST DISCOMFORT	+	-
23	RADAMMA	630233	42	F	-	-	-	-	-	+	-	+	-
24	NARAYANAPPA	612806	60	M	-	+	-	-	-	+	-	-	-
25	FEDRICK	635565	26	M	-	-	-	-	-	+	-	+	-
26	RAMAPPA	641494	60	M	-	-	-	+	-	-	-	+	+
27	SHARADAMMA	647689	43	F	-	+	-	-	-	-	-	-	-
28	MUNIYAMMA	662419	65	F	-	-	+	-	+	+	-	-	-
29	VARALAKSHMI	668322	40	F	-	-	-	+	+	-	-	-	-
30	GOVINDAMMA	640437	63	F	-	-	-	-	+	-	CHEST DISCOMFORT	-	-

MASTER CHART CONTINUED

SL. NO	NAME	HEIGHT	WEIGHT	BMI	BP	JNC-CLASS	RBS	BU	SC	S.CHOLESTEROL	TG'S	HDL	LDL	ECG	ECHO-E/A RATIO	ECHO-DT	ECHO-IVRT	ECHO- DIASTOLIC DYSFUNCTION GRADE	NT-BNP
1	RATHNAMMA	150	70	30.9	160/90	1	80	27	1	236	196	40	96	LVH	0.7/1.3	236	108	1	37.9
2	MURALI.G	174	70	25.1	210/130	2	91	69	1.4	168	102	33	114	LVH/LAH	1/0.9	176	96	2	200.8
3	KRITH L MEHTA	168	70	24.8	169/100	2	80	46	1.2	215	309	38	115	N	1.6/1	162	136	2	269.8
4	SAROJA	158	60	25	160/100	2	100	28	0.8	149	135	36	86	2nd HB	1/0.6	160	128	2	175.3
5	NEHRU PASHA	169	80	28.5	150/100	2	90	21	1.3	198	213	42	173	N	1/0.7	230	110	1	64.7
6	SHIRAMAIAH	165	65	24.7	220/130	2	68	26	1.1	215	230	38	115	LVH	0.8/0.6	180	88	2	162.6
7	MANJUNATH	170	68	24.8	230/130	2	86	36	1.2	256	174	35	215	N	0.9/0.6	236	130	1	20.83
8	GOPINATH	176	86	29.4	210/110	2	86	28	1.1	170	143	44	101	N	0.5/0.8	118	126	1	113.6
9	SRIRAMAIAH	156	74	30.8	140/100	2	86	37	0.9	170	143	43	101	N	0.8/0.6	156	80	N	18.4
10	RAMAPPA	175	60	20.8	150/100	2	174	32	1.1	174	110	39	69	N	0.6/1	170	90	2	138.6
11	LAKSHMAMMA	164	76	23.7	160/100	2	118	24	1	173	154	38	91	LVH	0.5/0.9	176	90	2	56.9
12	JAYAMMA	160	60	23.4	160/110	2	76	18	1	230	112	40	90	N	0.9/0.6	160	78	N	91.8
13	SAMJITH	154	68	24.2	140/90	1	76	18	1.2	210	190	40	108	N	1.1/0.6	156	76	N	20.8
14	CHANDRASHEKAR	176	76	27.1	150/100	2	70	20	1	174	110	39	69	N	0.6/0.7	196	84	1	122.4
15	KANTHAMMA	156	58	23.8	180/110	2	136	21	1.1	156	179	42	38	LAH	1.6/1.5	190	140	2	514
16	KEMPAMMA	165	55	21.4	150/90	1	110	31	0.7	140	78	36	88	N	0.5/0.9	206	96	1	265.8
17	NARAYANAPPA	176	88	27.5	160/110	2	97	21	1.7	52	210	35	75	N	0.9/0.9	178	86	N	9.5
18	RAJESHWARI	160	76	30.4	210/110	2	118	37	1.1	157	97	39	98	N	0.9/1.2	228	140	1	84.15
19	NAGARAJ M S	168	91	35.5	160/150	2	96	21	0.7	236	139	30	106	N	0.9/0.8	240	110	1	6.82
20	MARIYAPPA	163	47.5	18.3	140/90	1	110	26	1.1	168	181	36	93	LAH/PP	0.5/0.9	226	110	1	141
21	SHANKER	168	68	24.2	140/90	1	78	22	0.9	168	145	43	78	LAH	0.6/0.8	220	106	1	121.8
22	SYED SHABIL	156	74	30.8	140/90	1	80	37	0.9	170	143	43	101	LVS	0.5/0.8	238	108	1	204.4
23	RADAMMA	147	73	28	170/100	2	96	18	1.7	179	200	46	93	AF	0.8/1.1	217	102	1	137.1
24	NARAYANAPPA	162	62	23.8	150/90	1	102	32	1.2	196	186	40	102	LAH/LVH	0.8/0.8	160	140	2	169.9
25	FEDRICK	169	80	31	140/90	1	82	28	1.3	198	233	42	173	N	1/0.7	202	93	N	36.7
26	RAMAPPA	170	65	22.4	150/90	1	78	20	0.8	190	178	40	96	N	0.1/0.6	236	118	1	103.6
27	SHARADAMMA	155	59	22.7	160/100	2	76	25	0.9	160	176	42	79	N	0.6/1	192	90	N	12
28	MUNIYAMMA	160	68	26.9	150/90	1	70	21	0.8	92	159	39	44	LVH	0.6/0.8	256	142	1	42.1
29	VARALAKSHMI	145	68	32	160/110	2	80	15	0.8	134	65	34	87	N	0.8/0.6	250	130	1	40.5
30	GOVINDAMMA	160	70	27.7	`170/110	2	89	27	0.8	175	60	39	124	2nd HB	0.6/0.6	174	110	2	278.6