STUDY OF DIASTOLIC FUNCTION IN ASYMPTOMATIC HYPERTENSIVES IN TERTIARY CARE CENTRE
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ABSTRACT: BACKGROUND: Hypertension is the most common underlying cardiovascular disease in patients with isolated diastolic heart failure. Diastolic dysfunction in under detected in most hypertensive patients. MATERIAL AND METHODS: retrospective study carried out in Medicine department, SIMS, Shimoga for one year from June 2012 to June 2013. 50 patients who are hypertensive without any abnormality were studied general and systemic examination done, 2d echocardiography done in which transmitral flow velocity (E/A) is measured. RESULT: Most cases (60%) were between 31-50 yrs of age. Males constituted 58% and females 42% of the study group. 56% of cases had normal diastolic function as defined by E/A ratio (>1), as compared to 44% who had abnormal diastolic function. More than half of the cases with abnormal diastolic function (defined by abnormal E/A ratio <1) had duration of hypertension more than 12 months. Diastolic blood pressures <80 and ≥90 mmHg were significantly associated with abnormal E/A ratio. CONCLUSION: Diastolic function assessment was done on asymptomatic ambulatory hypertensive patients. The abnormal diastolic function as assessed by abnormal E/A ratio was seen in 44% of cases. Both decreased and increased diastolic blood pressure was negatively and positively associated with diastolic dysfunction. The current study demonstrated that the presence of LV diastolic dysfunction in hypertensive patients is actually greater than previously reported by studies that analyzed transmitral flow velocity curves. KEYWORDS: Hypertension, Diastolic dysfunction, Echocardiography, E/A ration, Transmitral flow velocity.

INTRODUCTION: Hypertension is one of the most common diseases afflicting humans throughout the world. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Over the past several decades, extensive research, widespread patient education, and a concerted effort on the part of health care professionals have led to decreased mortality and morbidity rates from the multiple organ damage arising from years of untreated hypertension. Hypertension is the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease.

Several clinical studies have reported that 30% to 50% of patients with congestive heart failure have preserved left ventricular systolic function and isolated diastolic dysfunction, i.e. isolated diastolic heart failure.1-3. Preliminary data from Framingham study indicate that hypertension is the most common underlying cardiovascular disease in patients with isolated diastolic heart failure. Hypertension is postulated to impair diastolic function via multiple mechanisms even without impairment of systolic function.4-5.

Left ventricular filling dynamics can be accurately assessed invasively in the cardiac catheterization laboratory using manometer-tipped catheters placed in the left ventricle with direct...
measurement of filling pressures. However, due to the invasive nature, high cost, and limited availability of laboratories, invasive approach to assess diastolic dysfunction remains impractical for widespread use. Therefore currently only noninvasive methods are being used to assess LV filling dynamics, with pulsed Doppler echocardiography, and by the pulsed Doppler transmitral flow velocity curve which has a biphasic pattern, with early diastolic wave (mitral E wave) and atrial contraction wave (mitral A wave). Hypertensive patients have impaired LV relaxation even in the absence of systolic dysfunction and many previous clinical studies have reported characteristic changes in LV filling dynamics as\textsuperscript{6,7} decreased peak mitral early diastolic filling wave (E) velocity, increased peak mitral atrial contraction wave (A) velocity, and a decreased ratio of peak mitral E to A velocities (E \textbackslash A). This altered flow velocity curve is associated with the presence of impaired LV relaxation\textsuperscript{8-11}, and the decreased E \textbackslash A is called an "abnormal relaxation" pattern and has been used as an indicator of diastolic dysfunction in patients with hypertension. This pattern has been described in 30% to 50% of patients with hypertension with or without preserved systolic function\textsuperscript{12,13}. The current study was designed to assess prospectively diastolic dysfunction in hypertensive patients with preserved left ventricular function by transmitral flow velocity curve.

AIMS AND OBJECTIVES: To assess diastolic dysfunction in hypertensive patients with preserved left ventricular systolic function by combined transmitral flow velocity curve and pulmonary venous Doppler analysis, particularly focusing on the limitation of the transmitral flow velocity curve alone to detect diastolic dysfunction.

TREATMENT: The mainstay of pharmacologic therapy for patients with diastolic heart failure includes diuretics, nitrates, calcium channel blockers (CCBs), beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEI). Diuretics are useful in relieving symptoms of pulmonary congestion. Nitrates may be useful in enhancing relaxation by reducing right ventricular pressure and volume, leading to reduced pericardial restraint and improved LV filling\textsuperscript{14}. As well, animal models have shown an improvement in LV relaxation with endogenous nitric oxide\textsuperscript{15}. The negative inotropic and chronotropic properties of the CCBs make them likely to be effective in treating diastolic dysfunction. Studies have yielded conflicting results with many showing improved relaxation\textsuperscript{16,17}, but others showing no change in the rate of relaxation\textsuperscript{18}. ACEI have not been as well studied, but may hold some promise\textsuperscript{19}, they may be particularly effective in the settings of hypertension with left ventricular hypertrophy and in the situation of concomitant systolic dysfunction\textsuperscript{20}.

Normal Range\textsuperscript{21,22}

| Parameter             | Range          |
|-----------------------|----------------|
| LVIDd                 | 3.6 to 5.4 cms.|
| LVIDs                 | 2.4 to 4.2 cms.|
| EF (ejection fraction)| \geq 50%       |
| DT                    | <220 msec      |
| E/A                   | >1             |

MATERIALS AND METHODS:

STUDY DESIGN: This was a retrospective study where hypertensive patients attending the outpatient department of MC Gann hospital attached to Shimoga institute of medical science, were selected randomly for enrollment into the study, after consideration of inclusion and exclusion criteria. A detailed history was taken, clinical examination and investigations performed in all cases.
STUDY SUBJECTS: A total of 50 patients diagnosed to have hypertension with preserved systolic function (EF > 50%) were studied from June 2012 to June 2013. Informed consent was taken from all the study subjects. In both cases and controls, investigations were done in the clinical biochemistry laboratory of mc gann hospital. Echocardiographic studies were performed by a non-interventional cardiologist.

INCLUSION CRITERIA: Ambulatory asymptomatic patients diagnosed to have hypertension (BP> 140/90 mmHg, average of two recordings taken at two separate occasions).

EXCLUSION CRITERIA:
- Patients with ischemic heart disease with or without symptoms.
- Patients with stroke within previous 6 months.
- Patients with congestive heart failure.
- Patients with atrial fibrillation.
- Patients with severe hypertension BP> 200/140.
- Patients with valvular heart disease.
- Patients with Diabetes mellitus.
- Patients with serum creatinine >1.5 mg/dl.

METHODOLOGY:
A detailed clinical history of subjects was taken. Each subject underwent a detailed physical examination & systemic examination. A standard 12 lead ECG was recorded in all subjects to look for any abnormalities. Routine hematological and biochemical investigations including, hemoglobin concentration, blood sugars, blood urea and serum creatinine were done.

Echocardiography: A qualified cardiologist performed the transthoracic echocardiographic examination on all subjects; Two-dimensional and M-mode Echocardiography was performed on Hewlett Packard SIM 7000 using 3.5 MHz transducer. Blood pressure and heart rate were measured at the time of echocardiography. Ejection fraction was calculated by measuring the internal diameter of left ventricle (LV) at the end diastole (LVIDd) & at the end systole (LVIDs) using the Penn convention method. Two-dimensional and two-dimensional guided M-mode echocardiograms and pulsed Doppler transmitral flow velocity curves were recorded with the sample volume at the mitral tips. The averaged values of all echocardiographic parameters of at least 3 consecutive beats were used for the analysis. Doppler velocity curves were recorded at a horizontal sweep speed of 100mm/s.

Left ventricular diastolic dysfunction was assessed by decreased E/A ratio (transmitral flow velocity curve). Normal E/A ratio was defined as E/A ratio ≥1. Abnormal E/A ratio is defined as E/A ratio < 1.

STATISTICAL METHODS: Chi-square and Fisher Exact test were used to find the significance of proportions of diastolic dysfunction with various study parameters. The Student’t’ test has been used
to find significance of mean pattern of study parameters between cases and controls. Analysis of variance has been used to find the significance of Echo parameters between the categories of diastolic dysfunction.

1. Chi-Square Test
2. Fisher Exact Test
3. Odds ratio = \( \frac{ad}{bc} \)
4. Student t test
5. Analysis of Variance: F test for K Population means

**Statistical software:** The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

**ANALYSIS OF RESULTS:**
**Demographics:** A total of 50 hypertensive patients were included in the study. The number of males was 29 (58%) and that of females was 21 (42%). The patient’s age ranged from 23 to 64 years. Fifty age and sex matched healthy controls were also evaluated to obtain the normal E/A ratio values in different age groups.

| Age in years | Number | %     |
|--------------|--------|-------|
| \( \leq 30 \) | 2      | 4.0   |
| 31-35        | 10     | 20.0  |
| 36-40        | 7      | 14.0  |
| 41-45        | 8      | 16.0  |
| 46-50        | 5      | 10.0  |
| 51-55        | 6      | 12.0  |
| 56-60        | 6      | 12.0  |
| 61-65        | 6      | 12.0  |
| **Total**    | 50     | **100.0** |

Table 1. Age distribution of cases

**Fig. 1:** Distribution age in cases
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Most cases (60%) were between 31-50 yrs. of age (Table 1). Males constituted 58% and females 42% of the study group.

The mean systolic blood pressure and diastolic blood pressure in cases was 156.52±18.36 and 91.40±7.51mmHg respectively.

| Echo parameters | Cases (n=50) | Mean ± SD |
|-----------------|-------------|-----------|
| EF %            | 63.72±4.35  |           |
| LVIDS (cms)     | 2.55±0.51   |           |
| LVIDD (cms)     | 4.19±0.58   |           |

Table 2. Echo parameters of cases

EF: ejection fraction
LVIDS: left ventricular internal diameter systolic.
LVIDD: left ventricular internal diameter diastolic.
Ejection fraction was normal (>50%) in cases (Table 2).

| E/A ratio | Cases (n=50) | Range       | Mean ± SD |
|-----------|--------------|-------------|-----------|
|           |              | 0.40-2.14   | 1.21±0.42 |

Table 3. Comparison of E/A ratio of cases

The E/A ratio ranged from 0.4 to 2.14 in cases with a mean of 1.21±0.42. In E/A ratio was significantly lesser in cases, when compared to normal (>1) (p=0.001) (Table 3).

| Diastolic function defined by E/A ratio | Number (n=50) | %  | E/A Mean ± SD |
|----------------------------------------|---------------|----|----------------|
| Normal E/A ratio                        | 28            | 56.0| 1.52 ± 0.21    |
| Abnormal diastolic function (E/A abnormal) | 22          | 44.0| 0.80 ± 0.22    |

Table 4: Diastolic dysfunction defined by E/A ratio in cases

Fig. 2: Bar chart showing mean E/A ratio in cases

The E/A ratio ranged from 0.4 to 2.14 in cases with a mean of 1.21±0.42. In E/A ratio was significantly lesser in cases, when compared to normal (>1) (p=0.001) (Table 3).
E/A ratio normal- E/A ratio ≥ age and sex adjusted mean value -2SD.
E/A ratio abnormal- E/A ratio < age and sex adjusted mean value -2SD.

Fig. 3: E/A ratio in cases with normal and abnormal diastolic function.

56% of cases had normal diastolic function as defined by E/A ratio, as compared to 44% who had abnormal diastolic function. (Table 4).

Diastolic function defined by E/A ratio | Number (%) | Male | Female
--- | --- | --- | ---
Normal E/A ratio (28) | 18 (64%) | 10 (36%)
Abnormal E/A ratio (22) | 11 (50%) | 11 (50%)

Table 5: Sex distribution of cases with diastolic dysfunction defined by E/A ratio.

Fig. 4: Bar chart showing sex distribution of cases in normal and abnormal E/A ratio diastolic function groups.
 Majority of males had normal diastolic function (62%). In the abnormal diastolic function group sex distribution was equal (Table 5).

| Duration of hypertension | Normal E/A ratio group (n=28) | Abnormal E/A ratio group (n=22) |
|--------------------------|-------------------------------|---------------------------------|
| ≤ 6 months               | 9 (32.1%)                     | 7 (31.8%)                       |
| 6-12 months              | 7 (25.0%)                     | 3 (13.6%)                       |
| >12 months               | 12 (42.8%)                    | 12 (54.5%)                      |

Table 6. Correlation of Diastolic function (defined by E/A ratio) with duration of hypertension

More than half of the cases with abnormal diastolic function (defined by abnormal E/A ratio) had duration of hypertension more than 12 months (Table 6).

| Systolic BP in mm Hg | Normal E/A ratio group (n=28) | Abnormal E/A ratio group (n=22) |
|----------------------|-------------------------------|---------------------------------|
| ≤ 140                | 8 (28.6%)                     | 4 (18.1%)                       |
| 140-159              | 9 (32.1%)                     | 7 (31.8%)                       |
| 160-179              | 7 (25.0%)                     | 8 (36.3%)                       |
| ≥180                 | 4 (14.3%)                     | 3 (13.6%)                       |

Table 7. Correlation of systolic blood pressure with diastolic function (defined by E/A ratio)

The level of SBP was not significantly associated with diastolic dysfunction as defined by abnormal E/A ratio (Table 7).

| Diastolic BP in mm Hg | Normal E/A ratio group (n=28) | Abnormal E/A ratio group (n=22) | p value |
|-----------------------|-------------------------------|---------------------------------|---------|
| <80                   | 11 (39.3%)                    | 1 (4.5%)                        | 0.004   |
| 80-89                 | 2 (7.1%)                      | 3 (13.6%)                       | 0.447   |
| ≥90                   | 15 (53.6%)                    | 18 (81.8%)                      | 0.036   |

Table 8: Correlation of diastolic blood pressure with diastolic function (defined by E/A ratio)
Diastolic blood pressures <80 and ≥90 mmHg were significantly associated with abnormal E/A ratio (Table 8).

| Age in years | E/A Ratio < 1 (DD) | Total no. of cases | No. of DD’s | Percentage of DD’s |
|--------------|--------------------|--------------------|--------------|-------------------|
| ≤30          |                    | 2                  | 2            | 100%              |
| 31-35        |                    | 10                 | 2            | 20%               |
| 36-40        |                    | 7                  | 2            | 28%               |
| 41-45        |                    | 8                  | 6            | 75%               |
| 46-50        |                    | 5                  | 3            | 60%               |
| 51-55        |                    | 6                  | 4            | 66%               |
| 56-60        |                    | 6                  | 2            | 33%               |
| 61-65        |                    | 6                  | 1            | 16%               |
| Total        |                    | 50                 | 22           | 44%               |

Table 8: Diastolic dysfunction in relation to age in hypertensive patients

Incidence of Diastolic dysfunction is more above the age of 40 years.

**DISCUSSION:** Hypertension is one of the most common diseases afflicting humans throughout the world. The prevalence of hypertension in Indian population is 3.80 to 15.63% in men and 2 to 15.38% in women in urban population and 1.57 to 6.93% in men and 2.38 to 8.81% in women in rural population.

Hypertension affects various organs like central nervous system, heart, retina, kidneys and blood vessels. Hypertension affects the heart causing systolic & diastolic dysfunction, left
ventricular hypertrophy\textsuperscript{30}, heart failure\textsuperscript{32} and contributes to atherosclerotic vascular problems, such as coronary artery disease\textsuperscript{29}.

In recent years there is an increased interest in understanding of diastolic function and its importance in common cardiovascular diseases\textsuperscript{1,33-38}.

The aim of our study was to assess the diastolic function in hypertensive patients with preserved left ventricular function by transmitral flow velocity curve to detect diastolic dysfunction. This retrospective cross-sectional study was done on a relatively homogeneous and ambulatory hypertensive population.

Diastolic function is known to be influenced by several interacting factors including age, sex, duration of blood pressure, and LV hypertrophy\textsuperscript{39}, all of which may potentially influence arterial compliance.

Subjects in our study underwent echocardiographic examination where diastolic function was assessed by transmitral flow velocity curves and E/A ratio [ratio of mitral early diastolic filling wave (E) velocity to mitral atrial contraction wave (A) velocity]. In our study, an E/A ratio value of 1.0 was arbitrarily chosen as the lower limit to detect impaired relaxation like in other studies\textsuperscript{40}. The values for the E/A ratio observed in our impaired relaxation group (abnormal E/A ratio; 0.80 ± 0.22) were significantly lower than the normal value.

Majority of cases in our study were males (58%). A similar male preponderance was noted in several earlier studies\textsuperscript{41-44}.

The mean age of cases in our study was 45.70±11.12 years. This was comparable to mean age of cases in the earlier Asian studies. (Masliza et al\textsuperscript{45}. mean age 43.1±5.7 years), whereas other western studies had enrolled older cases (Mottram et al\textsuperscript{41}. 58±8 years, Yamamoto et al\textsuperscript{42}. 69±6 years, Mitra et al\textsuperscript{43}. 54.48 years, Adewole et al\textsuperscript{44}. 59±10.4 years). This may be due to enrollment of follow-up patients with hypertension.

Diastolic dysfunction as defined by E/A ratio was found to be abnormal in 44% of cases in our study. Mottram et al\textsuperscript{41}. had found abnormal E/A ratio in 40% of their patients which is comparable to our finding. Other investigators have found a lower proportion of cases with abnormal E/A ratio in their study group. Yamamoto et al\textsuperscript{42}. found abnormal E/A ratio in 31% of their cases, which may be due to lower mean DBP in their cases as compared to our study (74 v/s 91 mm Hg). Masliza et al\textsuperscript{45}. found abnormal E/A ratio in only 18.6% of their cases. This could be due to lesser duration of hypertension in their cases. In Masliza’s\textsuperscript{45} study all subjects were newly diagnosed hypertensive (duration less than 6 months), whereas only 32% of subjects were newly diagnosed hypertensive in our study.

Although the sex ratio in abnormal E/A ratio group was equal (50% v/s 50%), more males tended to have normal E/A ratio (62% v/s 48%) in our study. Mottram et al\textsuperscript{41}. had found that female sex was an independent predictor of diastolic dysfunction. In our study there was a preponderance of female sex with diastolic dysfunction (52% females v/s 38% of males).

Abnormal E/A ratio correlated with DBP ≥ 90 mm Hg in our study. There was also correlation between normal diastolic function defined by E/A ratio and DBP < 80 mmHg (p=0.004). Mottram et al\textsuperscript{41}. had also found DBP to be significantly associated with diastolic dysfunction a finding similar to our study.
Our study did not find any association between abnormal E/A ratio and duration of hypertension and systolic blood pressure. No other study except Masliza’s study had found an association between systolic BP, duration of hypertension and diastolic dysfunction.

Diastolic BP level ≥ 90 mmHg was significantly associated with diastolic dysfunction. Mottram et al. have also found, elevation in diastolic blood pressure to be significantly associated with diastolic dysfunction. Indeed the study considered the diastolic BP to be an independent risk factor for diastolic dysfunction. Diastolic blood pressure is dependent on peripheral resistance and increases afterload of the heart. Increased afterload may promote myocyte hypertrophy and may also directly slow LV relaxation and contribute to diastolic dysfunction. Our study also found correlation between DBP< 80 mmHg and normal diastolic function (p=0.001). This has not been shown by previous studies.

Although earlier studies had found correlation between left ventricular hypertrophy and diastolic dysfunction, recent studies including our study have not confirmed the association. Masliza et al. also did not find correlation between LVH and diastolic dysfunction and have suggested that a compensatory physiological mechanism in response to pressure load during early hypertension even before onset of demonstrable LVH may be the cause for diastolic dysfunction.

In our study Diastolic dysfunction in relation to age is more in above 40 years of age group; it is comparable to study done by H. Schirmer, P. Lunde et al. lesser incidence in above 55 years of age may be due to pseudonormalization in which E/A ratio will be abnormally high due to severe diastolic dysfunction.

Clinical implications: The current findings have potential relevance in clinical practice for evaluation of hypertensive patients as diastolic dysfunction may be an early manifestation of cardiac involvement in hypertension. Studies have shown that anti-hypertensive such as ACE inhibitors may be more useful in this condition. The presence of diastolic dysfunction also provides an additional evidence of end-organ damage. The frequency of isolated diastolic heart failure in elderly hypertensive patients suggests that asymptomatic hypertensive patients with diastolic dysfunction may be at risk of progression to diastolic heart failure. More longitudinal studies of hypertensive patients with evidence of diastolic dysfunction are needed to determine the predictive value of these noninvasive indicators of diastolic dysfunction.

Study limitations: Our study group consisted of small homogeneous group of hypertensives. As echocardiographic examination could be performed in lesser number of patients than was desirable. Hence, the prevalence of LV diastolic dysfunction obtained in the current study may not be identical when applied to a larger or different population of hypertensives, and a future study with larger population may be required.

The study included patients who were on medications. Diastolic function may be affected by medications as has been shown in several previous studies. This may affect the prevalence of diastolic dysfunction in the current study subjects. The medications were continued by the patients in our study for ethical reasons. In the study diastolic dysfunction was calculated using transmitral flow velocity curve, which fail to detect the diastolic dysfunction in pseudonormal group, which can be detected by studying pulmonary flow velocity curve.
CONCLUSIONS: Diastolic function assessment was done on asymptomatic ambulatory hypertensive patients. Majority were males (58%). The abnormal diastolic function as assessed by abnormal E/A ratio was seen in 44% of cases. There was a preponderance of female sex in this abnormal diastolic function group. Diastolic blood pressure was significantly associated with diastolic dysfunction.

Both decreased and increased diastolic blood pressure was negatively and positively associated with diastolic dysfunction. The diastolic dysfunction was seen in patients with LVH, however this is statistically not significant indicating LVH is not the only cause for diastolic dysfunction in hypertensives.

The current study demonstrated that the presence of LV diastolic dysfunction in hypertensive patients is actually greater than previously reported by studies that analyzed transmitral flow velocity curves.

SUMMARY: Ambulatory hypertensives cases had abnormality in diastolic function (44%) as assessed by transmitral Doppler signals (E/A ratio). The current study demonstrated that the presence of LV diastolic dysfunction in hypertensive patients is actually greater than previously reported by studies that analyzed transmitral flow velocity curves. To avoid overlooking patients with diastolic dysfunction analysis of transmitral flow velocity curves is recommended in all hypertensive patients irrespective of duration of hypertension.

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