HYPERTENSIVES AND MEDICAL MANAGEMENT: ARE THEY SILENT CONTRIBUTORS TO THE BURDEN OF LUNG DISEASE IN OUR SOCIETY

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Background and objectives: Hypertension is increasing globally with another 60% expected increase by 2025. In spite of advancing research and different classes of anti- hypertensive medications (anti-HT), not all of them can be branded safe. Pulmonary complications of different classes of anti-HT were unexplored in South India. Our aim is to compare PFT among hypertensive (HT) &healthy controls and also among HT taking various classes of anti-HT. **Methods**: Case control study. Age- matched healthy controls (n=91) HT cases (n=93) randomly selected. Group I Beta blockers (n= 14), Group II Calcium Channel blockers (n= 18), Group III Angiotensin receptor blockers (n=23), Group IV drug combinations (n= 38).Anthropometry taken, BP recorded, PFT assessed using Easyone Spirometer and data analysed using ANOVA and Student "t" test. **Results:** Study results show statistically significant reduction in PFT values in all groups of cases and also in females. Out of 93 cases, 49 normal PFT, 7 obstructions, 5 restrictions, 32 mixed airway disease. PFT statistically significantly reduced among various classes of anti –HT, FVC (p=0.026), FEV1 (p=0.000), PEFR (p=0.038). **Interpretation & Conclusion**: We conclude reduction in PFT among HT taking various common classes of anti-HT and hence recommend periodic evaluation of PFT in all HT patients.

Key words: Hypertension, anti-hypertensive medications, pulmonary function tests

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Introduction:

Hypertension is increasing globally with a 60% expected increase by 2025 totalling to 1.56 billion[1] and needless to say it is very rampant in India also. Hypertension is a disease that affects the body as a whole. Various complications of hypertension that are well documented are congestive cardiac failure, stroke, retinopathy and nephropathy[2-6]. Today, in India, treatment of hypertension includes anti-hypertensive medications, life style modification, salt –restricted diet, and treatment of complications, if any. Voluminous research in pharmacology has helped in the introduction of newer drugs in addition to the existing classes of anti- hypertensive medications. In addition to sudden drastic fall in BP, anti- hypertensive medications produces many undesirable sides –effects. To mention some, headache (caused by ACE inhibitors, Calcium Channel Blockers, Alpha blockers), frequent urination (beta blockers and diuretics) increased cold sensitivity (alpha blockers, beta-blockers, vasodilators) bleeding gums (Calcium Channel Blockers) and obesity[7, 8]. Such side effects could be so severe that they might even force the patient to stop medicines.

Very few studies have been done in the past relating hypertension and lung insult. Some of them have shown decreased pulmonary parameters[9,10] attributable to hypertension. Chronic obstructive pulmonary disease is the forerunner of various systemic complications and is one of the leading causes of preventable death in developing countries[11]. The Framingham study is one such international study that has concluded an inverse relationship between forced vital capacity (FVC) and cardiovascular diseases and mortality, particular in women[12]. Other American studies have shown that FVC is a strong, inverse predictor for the development of hypertension[13,14]. The sustained negative impact of hypertension with added use of anti- hypertensive medications, on the respiratory system probably needs to be explored better.

In India, there are many silent contributors to lung diseases especially usage of bio- mass fuel for cooking, poor socio-economic conditions, overcrowding & poor sanitation[15, 16, 17] and vehicle exhaust. The lungs are vulnerable to assault very easily leading to reduction in the PFT values which can be picked up early if screened regularly. Are hypertension and anti- hypertensive medications silently contributing to pulmonary disease morbidity? Reduction of PFT is only an early indicator of pulmonary morbidity. The combined effects of hypertension and anti- hypertensive medications on the lungs are not well documented in Southern parts of India. The aim of our study was to compare PFT values of hypertensives with controls and also compare PFT among cases on treatment with various classes of anti-hypertensive medications. The role of gender differences and impact of waist hip ratio (WHR) on the lung functions also were taken into due consideration.

Study Design:

This case –control study was carried out over a period of 7 months spanning from February to August 2015. Hypertensive cases (n=111) and age and sex matched healthy controls (n=91) attending the Medicine outpatient department of Sree Balaji Medical College and Hospital, Chennai, India were randomly selected for our study. They were explained the benefit of enrolling in our study and written consent was obtained from the volunteers.

Hypertensives with history of hypertension more than 2 years and on regular anti-hypertensive medications were taken as cases and apparently healthy, age- matched controls with BP$\leq$ 140/90 mmHg were the control population. Patients with positive history of active tuberculosis, bronchial asthma, respiratory infection less than 3 weeks, hemoptysis less than 3 months, ocular or abdominal surgery less than 6months, stroke / heart attack <less than 3 months, smokers, pregnancy and lactation were excluded from our study.

Materials and Methods:

The study was commenced after obtaining the Institutional ethical committee clearance. Validated questionnaire with details on anthropometry, personal habits, and particulars of drug treatment received so far was administered. Respiratory history was taken in detail. Socio-economic status was assessed by Modified Kuppuswamy's classification[18].

Blood pressure (BP) was measured thrice after a gap of 5 minutes every time in the dominant arm and the average was recorded with the usual precautions using OMRON apparatus[19,20]. Grading of hypertension was done as per the Seventh Report of the JNC on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[21]. PFT was assessed using EasyOne Spirometer from Pulmonary Research Laboratory of our hospital and other hospitals as per ATS guidelines[22] after proper demonstration of the procedure. Best of three attempts taken. Forced Vital capacity(FVC), Forced expiratory volume at the end of the first second(FEV_1), Peak expiratory flow rate(PEFR), Predicted Forced Vital Capacity(Pred FVC), Predicted Forced expiratory volume at the end of 1st second (Pred FEV_1) were the pulmonary parameters that were measured and recorded. The cases were sub-divided into 4 groups depending on the anti- hypertensives they were using: Group I Beta blockers (BBL) (n= 14), Group II Calcium Channel blockers (CCB) (n= 18), Group III Angiotensin receptor blockers (ARB) (n=23), Group IV combination of 2 or more of these drugs (ACE inhibitors, centrally acting drugs and diuretics) (n= 38).

Statistical analysis

Data entry done manually and analysed using SPSS software 11. ANOVA done and p values <0.05 was taken as statistically significant. Pearson's correlation and students "t" test were the additional methods that helped in our statistical analysis.

Results

Our study included 93 cases and 91 apparently healthy controls both age and sex matched (between 55 to 68 years) who were on regular anti- hypertensive medications. We excluded 18 cases due to very high BP and poor and inconsistent efforts while performing PFT. The anthropometric parameters of the cases and controls of our study population are given in Table 1.

Table 1: Description of the study population

	CONTROLS (n=91)	CASES(HYPERTENSIVES)			
		Group I (n=14)	Group II (n=18)	Group III (n=23)	Group IV (n=38)
Age (yrs)	57.41 ±7.93	57.21 ±11.59	57.72 ± 8.14	54± 8.20	57 ± 9.94
Height(m)	1.63± 0.09	1.59± 0.12	1.58 ± 0.97	1.61 ± 0.08	1.63 ± 0.11
Weight(Kg)	71.93 ±15.54	70.6 ± 12.16	64. 47 ±10.40	75.85 ± 14.84	76.07 ± 16.58

Values expressed as mean± S.D
Group I Beta blockers (BBL), Group II Calcium Channel blockers (CCB), Group III Angiotensin receptor blockers (ARB), Group IV combination of 2 or more drugs.

The highest r values for height and FVC, FEV_1 being 0.52, 0.58 among cases, 0.59, 0.49 respectively among controls. The highest r values for weight and FVC, FEV1 being 0.75, 0.16 among cases, 0.25, 0.30 respectively among controls.

Average systolic and diastolic BP of the controls was 136 ± 8.25, 84±7.14 mm Hg and that of cases was 146±9.25, 86± 6.87 mmHg. There were 55 males and 38 female cases and 66 males and 25 female controls in our study population. PFT values of the males and females were compared using students 't" test and found to be reduced among the females as shown in Table 2.

Table 2: Pulmonary function tests and BP among males and females of our study population

	Males			Females		
	FVC(L)	FEV_1(L/sec)	FEV_1/FVC	FVC(L)	FEV_1(L/sec)	FEV_1/FVC
Cases	2.77 ±0.80	2.21 ±0.66	0.79 ±0.09	1.95 ±2.44	1.43 ±0.67	0.79 ±0.08
Controls	2.96 ±0.73	2.57 ±0.13	0.65 ±0.04	2.23 ±1.16	2.01 ±0.31	0.61 ±0.03

Our results showed that among 93 cases, 49 had normal PFT values, 7 had obstruction, 5 had restriction and 32 had mixed airway disease. FVC was reduced by 300 ml or more in each group and FEV_1 reduced by 0.5 L/sec or greater in each group when compared with the controls as clearly shown in Table 3. The predicted pulmonary values were also reduced in cases when compared to controls though not significant statistically.

Table 3: Pulmonary function parameters of our study population

PFT	CONTROLS (n=91)	CASES				
		Group I (n=14)	Group II (n=18)	Group III (n=23)	Group IV (n=38)	p value
FVC(L)	2.9±0.62	2.6 ± 0.97	2.38 ±0.79	2.52 ± 0.7	2.38 ± 0.88	0.026 **
FEV_1(L/sec)	2.57±0.49	2.03 ± 0.69	1.74 ± 0.55	2.04 ± 0.64	1.91 ± 0.75	0.000 **
FEV_1/FVC	0.73±0.32	0.78 ± 0.78	0.74 ± 0.16	0.8 ±0.05	0.79 ± 0.08	0.000 **
PEFR(L/min)	6.07±2.1	5 ± 2.18	4.25 ± 1.90	6.33 ± 2.27	5.26 ± 2.57	0.038 **
Pred FVC(L)	90.07±15.58	86.07 ± 36.39	83.56 ± 22.71	77 ± 18.35	72.55 ± 25.09	0.005 **
Pred FEV_1(L/sec)	97.63±19.86	80.71 ± 27.85	73.67± 16.38	77.35 ± 20.07	70.89 ± 22.67	0.000 **
Pred FEV_1/FVC	104.07±35.67	97.43 ± 9.86	93 ± 20.37	100.26±6.07	99.55 ± 9.91	0.026 **

Values expressed as mean± S.D
**p value<0.05 is statistically significant.
FVC- Forced Vital Capacity
FEV_1 - Forced expiratory volume at the end of 1st second
PEFR- Peak expiratory flow rate
Pred FVC- Predicted Forced Vital Capacity
Pred FEV_1- Predicted Forced expiratory volume at the end of 1st second

PFT values were significantly higher in non-obese subjects than the obese subjects (p<0.000).The subjects were categorised into four classes based on Modified Kuppuswamy's scale. There were 22 cases in Class I, 25 in Class II, 29 in Class III, 17 in Class IV and 19 controls in Class I, 22 in Class II, 34 in Class III, 16 in Class IV. There was no significant correlation between SES and PFT values of our subjects.

Discussion

Global Burden of Disease study has estimated that hypertension led to 1.6 million deaths and 33.9 million disability-adjusted life years in 2015 and is most important cause of disease burden in India[23]. The magnitude of the disease is increasing on yearly basis in India. The indication for treatment of hypertension today is systolic ≥ 140 mmHg and

diastolic ≥ 90 mmHg. The WHO/ISH 2003[24]statement on the management of hypertension reflects in detail about the risk factors for developing hypertension, target-organ damage and associated clinical conditions, but pulmonary complications has been overlooked. Our studies not only aimed to estimate the extent of lung damage in hypertensives but also to measure the PFT in subjects taking various classes of anti – hypertensives and compare it with healthy controls.

The description of our study population is given in Table1. Males were taller by 13 cms and heavier by 5 kgs than their female counterparts. The mean age, height and weight of the controls and cases are comparable without any significant differences. Age had negative correlation trend while height and weight showed positive trend with most of the pulmonary parameters, correlation being greatest with FEV_1, FVC, FEV_1/FVC followed by PEFR. Earlier studies from our country and other Asian countries have proven the same [25,26,27].

There is a statistically significant decrease in FVC, FEV_1, FEV_1 / FVC (p=0.000) among females (both cases and controls) in our study as shown in Table 2. Studies comparing the PFT values of hypertensive cases with controls showing such gender variations are very few in South India. Amongst cases, 49 out of 55 males, were obese with WHR>0.9 and 28 out of 38 females, were obese with WHR>0.85. Amongst controls, 50 out of 66 males were obese and 21 out of 25 females were obese. FVC, FEV_1 and FEV_1/FVC values were significantly higher in non-obese subjects than the obese subjects (p<0.000). Similar results have been shown by Collins et al[28] in normotensive subjects where they have proved that increase in upper body fat distribution (WHR>0.9) is associated with lower FVC, FEV_1 and total lung capacity.

Average systolic and diastolic BP of the controls was 136 ± 8.25, 84±7.14 mm Hg and that of cases was 146±9.25, 86± 6.87 mmHg. Almost 96% of the cases were taking anti-hypertensives regularly attributing to very good control of their BP. Both systolic and diastolic BP values showed negative correlation trend with FVC, FEV_1, PEFR values. FVC was reduced by 300 ml or more in each group and FEV_1 reduced by 0.5 L/sec or greater in each group when compared with the controls. Though there was a reduction in PFT with increasing duration of hypertension, it was not statistically significant in our study. The reasons could be greater awareness among subjects in taking medications regularly, reduction of stress and adopting life style modification measures. Reduced FEV_1 and FVC in hypertensives increases the risk of cardiovascular mortality and ultimately can lead to death[2,3]. The pathophysiology of respiratory complications in hypertension has been postulated as increased pulmonary arterial pressure and subsequent development of interstitial pulmonary edema[29].

Our study population were categorised into 4 classes based on Modified Kuppuswamy's scale taking into account their education, occupation, total family income and present living conditions. There were 22 cases in Class I, 25 in Class II, 29 in Class III, 17 in Class IV and 19 controls in Class I, 22 in Class II, 34 in Class III, 16 in Class IV. There was no significant correlation between socio economic status and PFT values of our subjects. Literature has shown reduction in PFT values with lower classes of socio economic status in contradiction to our study. Small sample size, high BMI, advance age group and inclusion of more female subjects could be some possible reasons for our study results. Many international studies[30,31,32] have also demonstrated progressive decline in pulmonary parameters especially FEV_1 with decline in socio-economic status. In 2005, an Indian study by Raju et al[33] has shown 14 to 16.7% reduction in PFT values in children of parents who belonged to lower socio-economic status. Socio-economic status is one of the important determinants of health status reflecting health care affordability of an individual. Future studies warranting adjustments for these parameters are neede

The PFT values in our present study are- among 93 healthy cases, 49 had normal PFT values, 7 had obstruction, 5 had restriction and 32 had mixed airway disease. Swati Shah[10] had shown 74% with obstruction, 13% with restriction, 13% with normal PFT values. More number of cases had mixed airway disease in the present study that can be explained because of higher female cases and also inclusion of chronic hypertensives (>15 years) in our study. The disadvantages of Swati et al study was they have not mentioned the gender difference and their study subjects gave H/O

hypertensives on an average of only 6.5 years and not greater than that.

Anti-hypertensive drugs and pulmonary function tests Pulmonary complications of BBL are well established and needless to say, they are contra-indicated in COPD patients. Earlier study by[34] McNeil et al had proven that BBL were safe for young, uncomplicated hypertensives but recently Eva Schanbel et al[9] have shown that BBL are well known for their adverse effects on lipid metabolism causing increase in body weight and also development of insulin resistance. But their safety in elderly hypertensives is still under debate. ACE inhibitors are commonly used in elderly subjects because of its easy tolerability, beneficial effects post myocardial infarction and relative safety in diabetic and non –diabetic nephropathy cases too. But again, the most common side effect of ACE inhibitors is dry, irritating and persistent cough, which develops in 5%–20% of patients[35] necessitating drug withdrawal. Thiazide diuretics causes metabolic alkalosis which can suppress the ventilatory drive, potentially worsening the degree of hypoxemia and hypercapnia as shown by Bear R et al[36]. Literature[37,38,39] shows CCB do not cause much pulmonary complications in hypertensive patients and hence safe to be used in elderly hypertensives. Diuretics and CCB[40] are more effective in elderly patients with isolated systolic hypertension. A German study[41] showed Angiotensin II antagonists were well tolerated in patients with stage III and IV COPD, although they did not improve respiratory muscle strength or exercise capacity.

In 2001, Ross et al[42] in a meta-analysis of 190 drug trials showed that anti-hypertensives were discontinued due to various side-effects , the order being highest with CCB (6.7%) followed by thiazide diuretics or ARB (3.1%). But, in 2011, Salpeter S et al[43] have concluded in their Cochrane review that cardio-selective BBL are safe in patients with reversible airway diseases and those who have compromised lung functions even before the development of hypertension. But monotherapy is not effective especially in elderly subjects as they are prone to develop side effects like obesity [8,44] metabolic syndrome and left heart failure. There are other contradicting studies and a the lung functions of all hypertensive patients irrespective of the class of anti- hypertensive medications they prescribe. It is difficult to assess whether hypertension alone or its medications or a combination of both are the cause for the reduced lung functions. Large scale multivariate regression analysis studies are needed to throw more light on this issue.

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