

A Prospective Study Determining the Efficacy of Anti-Hypertensive Combination Medication by the Application of Applanation Tonometry

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ABSTRACT

BACKGROUND : Hypertension is a condition of elevated arterial blood pressure (BP), the excessive pressure on the artery walls may cause complications such as arterial stiffness, stroke, heart failure, metabolic syndrome. The aim of the study is to assess the relative efficacy of anti-hypertensive medications in lowering the blood pressure by the use of an applanation tonometry device.

METHODS : A total of 88 patients were enrolled in the study who were on anti-hypertensive combination therapy. Each group consists of 44 patients each, who are receiving Angiotensin Receptor Blockers + Calcium Channel Blockers (ARBs + CCBs) and Angiotensin Receptor Blockers + Diuretics (ARBs+ diuretics). A baseline brachial blood pressure and central aortic blood pressure (non-invasively) using applanation tonometry were noted in the first outpatient visits who are taking the drugs for at least a month. In the next follow up, end point brachial blood pressure and central aortic blood pressure were noted. Along with this cardiovascular risk were also noted and categorized into three. There were effective counseling held to observe the medication adherence in patients.

RESULTS : A total of 88 patients were enrolled in the study who were on anti-hypertensive combination therapy. Each group consists of 44 patients each, who are receiving Angiotensin Receptor Blockers + Calcium Channel Blockers (ARBs + CCBs) and Angiotensin Receptor Blockers + Diuretics (ARBs+ diuretics) and showed that ARBs + CCBs brings about a significant decrease in central aortic blood pressure, and the risk was assessed along with medication

adherence before and after counseling.

CONCLUSION: The CABP is effectively reduced when the ARBs + CCBs are administered and specifically the systolic BP is significantly reduced.

KEYWORD: CABP, Brachial pressure, medication adherence

I. INTRODUCTION:

Central aortic blood pressure is the pressure in the ascending aorta, just outside the left ventricle. It is the pressure that the target organs are exposed to and, due to arterial pressure amplification, is lower than brachial cuff pressures^[1].

Blood pressure is not constant throughout the body. Many factors such as arterial stiffness affect the pressure wave as it travels from the aorta to the arm, making cuff pressure an unreliable indication of central pressure. As age increases arteries stiffen and amplification is reduced^[1,2].

Central aortic pressure (CAP) is an important surrogate of brachial blood pressure in both clinical practice and routine health screening. It directly reflects the condition of the central aorta. Non-invasive measurement of CAP becomes a crucial technique of great interest. Earlier central aortic pressure (CAP) and brachial artery pressure were considered the same by clinicians. But blood pressures in the proximal aorta and brachial artery are different due to wave reflection, the systolic blood pressure (SBP), and pulse pressure (BP) increase from the aorta to periphery, while diastolic blood pressure (DBP) and mean arterial pressure (MAP) just decrease 1–2 mmHg toward the peripheral arteries.

CAP is a better indicator of central hemodynamic stress that is propagated to the peripheral vasculature and target organs, such as the brain and kidneys. Peripheral vasculature and target organs are directly exposed to CAP instead of brachial blood pressure. Measurement of CAP can provide more clinically useful information about cardiovascular system beyond brachial blood pressure. First, recent evidence suggested that CAP may be more strongly related to cardiovascular outcomes. For example, central pressure has been shown to have a closer correlation with surrogate measures of cardiovascular disease. Second, CAP responds differently to certain drugs from brachial blood pressure. For example, Conduit Artery Function Evaluation (CAFE) which is frequently cited as an example of differential effects of interventions on central and peripheral pressure demonstrated that CAP provides a superior measure of hemodynamic load on the heart and central organs. Besides hypertension, CAP also provides insights into the prevention, diagnosis, and treatment of cardiovascular diseases including coronary artery disease, stroke, myocardial infarction, and heart failure. Therefore central aortic blood pressure is more accurate in the measurement of future cardiovascular diseases.^[3,4,5] In this study we are using a non-invasive technique (applanation tonometry) for measuring central aortic pressure.

II. METHODS

A prospective observational study was conducted in patients from the department of Cardiology in Cosmopolitan Hospital, Trivandrum who were diagnosed with both Peripheral blood pressure and Central aortic blood pressure. The data collection forms were obtained after the approval from the Institutional Ethical Committee. The study period was for a period of 6 months from December 2019 to May 2020. The study participants were recruited from the outpatient and inpatient department of cardiology of Cosmopolitan Hospital, Trivandrum. A written Informed Consent was obtained from the patient diagnosed with both PBP and CABP satisfying the inclusion and exclusion criteria. A total of 88 patients were enrolled for the study.

Inclusion Criteria

- Age 30-80 years.
- Patients diagnosed with PBP and CABP

- Patients who are taking any one of the combination drugs (ARBs + Diuretics or ARBs + CCBs)
- Patient who are willing to participate in the study.

Exclusion Criteria

- Age <30 years.
- CKD patients.
- Pregnant women.
- Psychiatric Patients.
- Patients who are not willing to participate in the study.

All information relevant to the study was collected from case records by using a suitably designed proforma. In this study we recorded a baseline BBP and CAP on the first visit who are taking drugs for atleast a month. During the second OPD visit, again BBP and CAP were recorded to note the decrease in the BBP and CAP after taken the medication. The PBP was measured using the standard sphygmomanometer and CABP was measured using applanation tonometry.

Applanation tonometry was applied for the measurement of arterial pressure waveforms. The device records all the pressure waveforms detected by the sensors and automatically selects the one with the highest quality. This automatic method makes the ubiquitous measurement of radial blood pressure waveform and estimation of CAP possible.^[6] GRACE ACS risk scores were used to detect the risk of developing cardiovascular death after hospital discharge within 6 months.^[7] The impact of patient counselling on medication adherence was assessed using Hill bone medication adherence scale which consists of 14 item questionnaire to check the compliance.^[8]

Patients were requested to answer the questionnaire and were counselled regarding the disease, drugs and lifestyle modification using patient information leaflet (PIL), which was provided in both English and local language (Malayalam). Patients were asked for review after first and second month of taking the medication. At the end of the study, all the parameters and scores were compared from baseline to end of study.

For data entry we had used the software Microsoft excel and all the analysis were carried out with the help of statistical software SPSS V.2.2 for windows. Paired t test were used for goodness of fit for testing significance.

III. RESULTS

In our study we analysed the data collected from hypertensive patients from cardiology department. A total of 88 patients were selected according to the inclusion criteria and 44 persons were enrolled in each group. This study aimed to identify the relative efficacy of two antihypertensive medication combination and it also identifies the risk factors for developing cardiovascular diseases. Pre and post medication counselling was done to assess medication

adherence. The comparison of improvement before and after counselling was assessed by paired ‘t’ test. A calculated p-value less than 0.05 was considered to be statistically significant.

Demographic details of the patients

In this section, the data related to the patients were collected and the calculated frequencies and percentage were reported. The distribution of total patients based on age from both groups have been shown in (table 1). The age distribution of the patients is shown in table 2)

DISTRIBUTION OF PATIENTS BASED ON AGE AND GENDER:

TABLE 1: Frequency and percentage distribution of patients based on Gender

GENDER	FREQUENCY	PERCENTAGE
Male	48	54.5
Female	40	45.5

TABLE 2: Frequency and percentage distribution of patients based on age.

AGE	FREQUENCY	PERCENTAGE
35-45	21	23.85%
46-55	34	38.6%
56-65	12	13.6%
66-75	15	17%
76-85	5	5.6%
86-95	1	1%

It was calculated using the paired t test as the data was collected from a normal population. From the demographic data, it was observed that 48(54.5%) of the population were males and 40(45.5%) of the population were females. Thus the majority of the patients were male and based on

age distribution, it is observed that the highest number of patients were between the age group of 46-55(34 patients, 38.6%) followed by the age group of 35-45, 66-75, 56-65, 76-85 and 86-95 (1 patient, 1.1%)

IMPACT OF SYSTOLIC PERIPHERAL BLOOD PRESSURE AFTER MEDICATION

TABLE 3: Based on change in systolic peripheral blood pressure after medications.

Medication	N	Change in Sys. PBP		t	P
		Mean	Sd		
ARBs+Diuretics	44	19.1	11.0	3.779	<0.001
ARBs+CCBs	44	28.8	13.1		

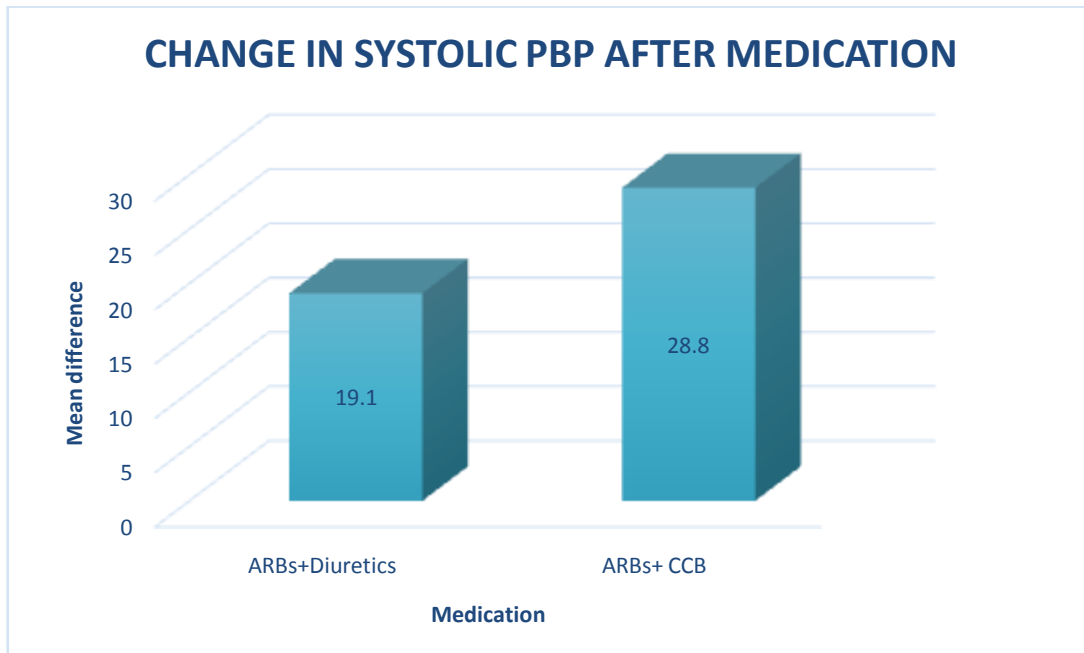


FIGURE 1:Diagrammatic representation of change in systolic PBP after medication

The impact of systolic peripheral blood pressure after medication was analysed by the paired t test, a p value of (<0.001) ARBs+CCBs shows significant effect in reducing systolic PBP

than ARBs+Diuretics as the mean difference value is higher in ARBs+CCBs that is 28.8. This suggests that the ARBs + CCBs is more significant in reducing the Sys. PBP. This is shown in (table 3)

IMPACT OF DIASTOLIC PERIPHERAL BLOOD PRESSURE AFTER MEDICATION

TABLE 4 :Based on change in diastolic peripheral blood pressure after medications.

Medication	N	Change in Dia PBP		t	P
		Mean	Sd		
ARBs+Diuretics	44	9.8	8.2	1.961	0.05
ARBs+CCBs	44	13.2	8.2		

Impact of diastolic peripheral blood pressure after medication was analysed by paired t test. Here p value is 0.053 which is not significant, implies that both the medication reduces diastolic PBP, but it doesn't show that which combination drugs had effectively reduced Diastolic PBP. This

is shown in (table 4). there is a significant reduction is seen in diastolic PBP when both ARBs+CCB was administered since the p value is 0.05 using the paired t-test.

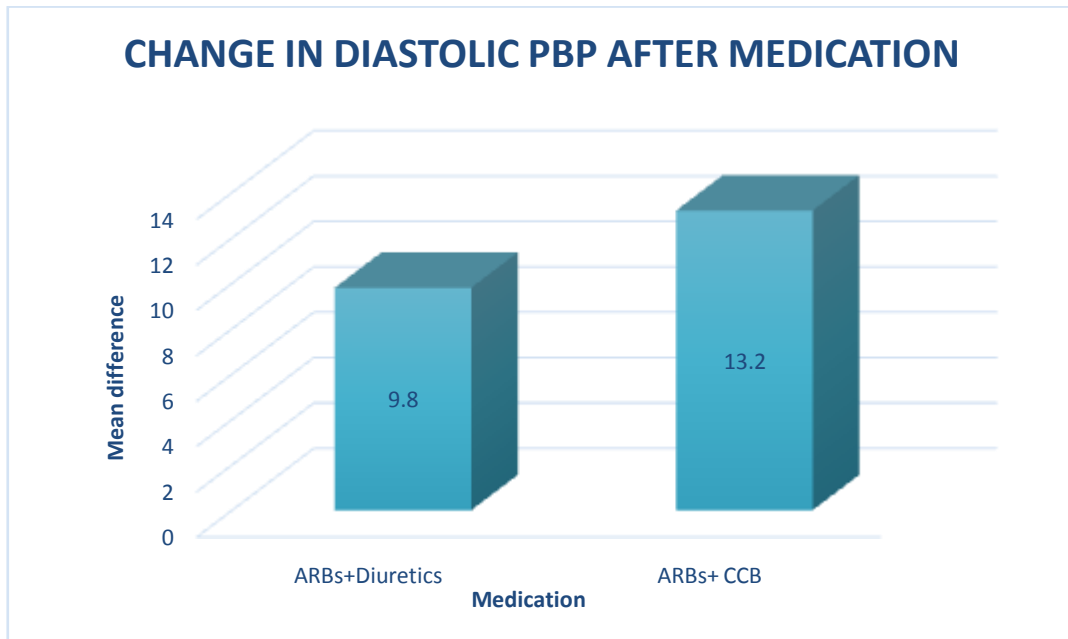


FIGURE 2:Diagrammatic representation of change in diastolic PBP after medication

The graph shows mean difference on the x axis and medications on the y axis. This graph depicts that ARBs+CCB is far more effective than ARBs+Diuretics. Hence there is a significant

reduction is seen in diastolic PBP when both ARBs+CCB was administered since the p value is 0.05 using the paired t-test.

BASED ON THE CHANGE IN SYSTOLIC CABP

TABLE 5: Based on change in systolic CABP by both medications.

Medication	N	Change in Sys. CABP		t	p
		Mean	Sd		
ARBs+Diuretics	44	18.8	15.2	5.042	<0.001
ARBs+CCBs	44	35.5	15.9		

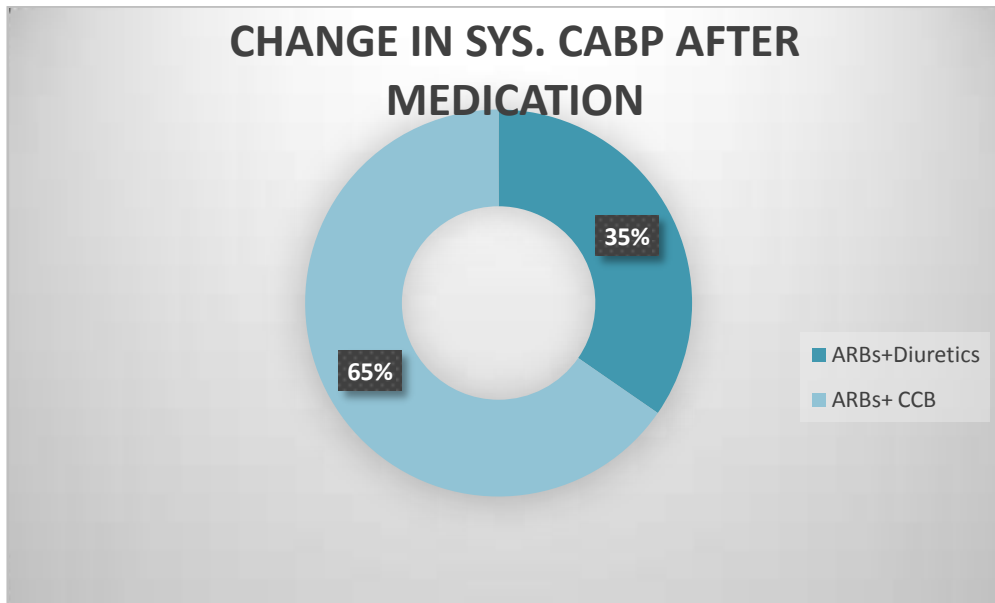


FIGURE 3: Diagrammatic representation of change in systolic CABP after medication

Here the p value (<0.001) ARBs+CCBs shows significant effect in reducing systolic PBP than ARBs + Diuretics as the mean difference value is higher in ARBs + CCBs that is 35.5. this data is seen in (table 5). from the graph itself that

the mean difference values of ARBs+CCBs is greater than the mean difference of ARBs+Diuretics. This suggests that the ARBs+CCBs is more significant in reducing the Sys.CABP (figure3)

BASED ON THE CHANGE IN DIASTOLIC CABP

TABLE 6: Based on change in diastolic CABP after medications.

Medication	N	Change in Dia. CABP		t	P
		Mean	Sd		
ARBs+Diuretics	44	10.5	8.2	2.296	0.024
ARBs+CCBs	44	14.5	8.2		

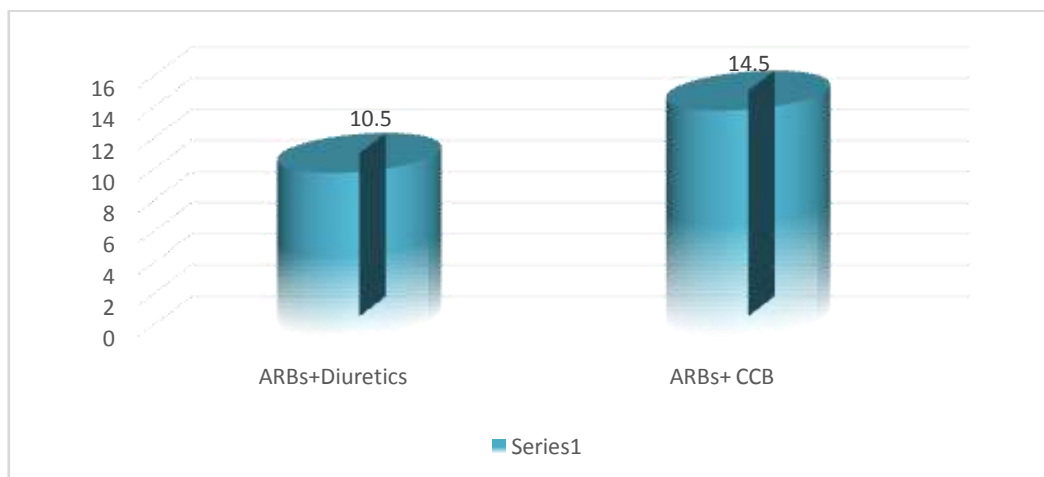
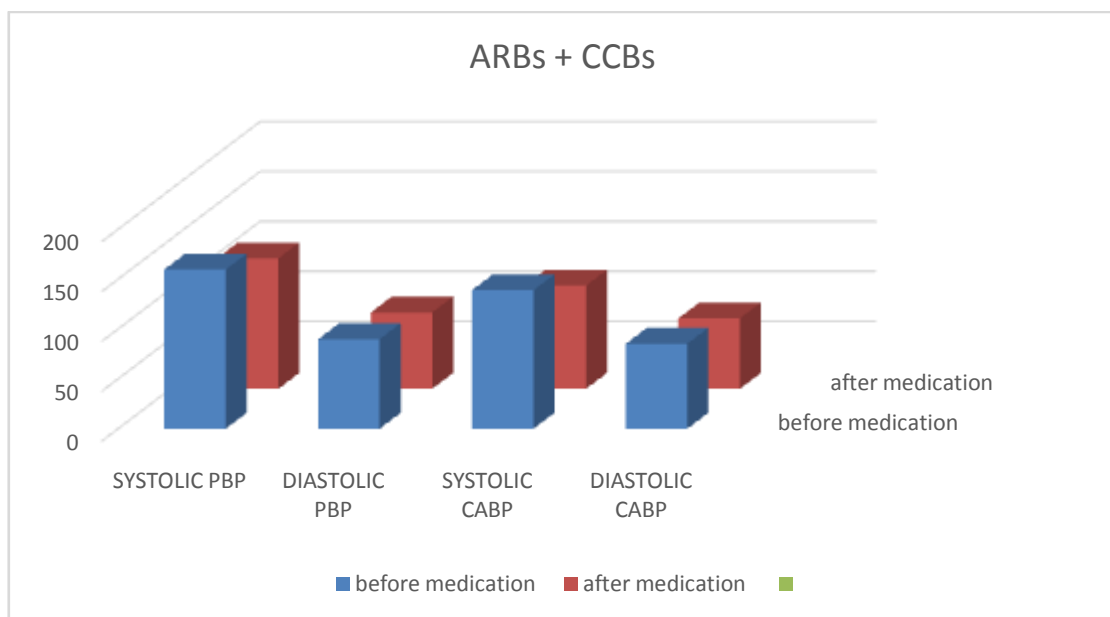
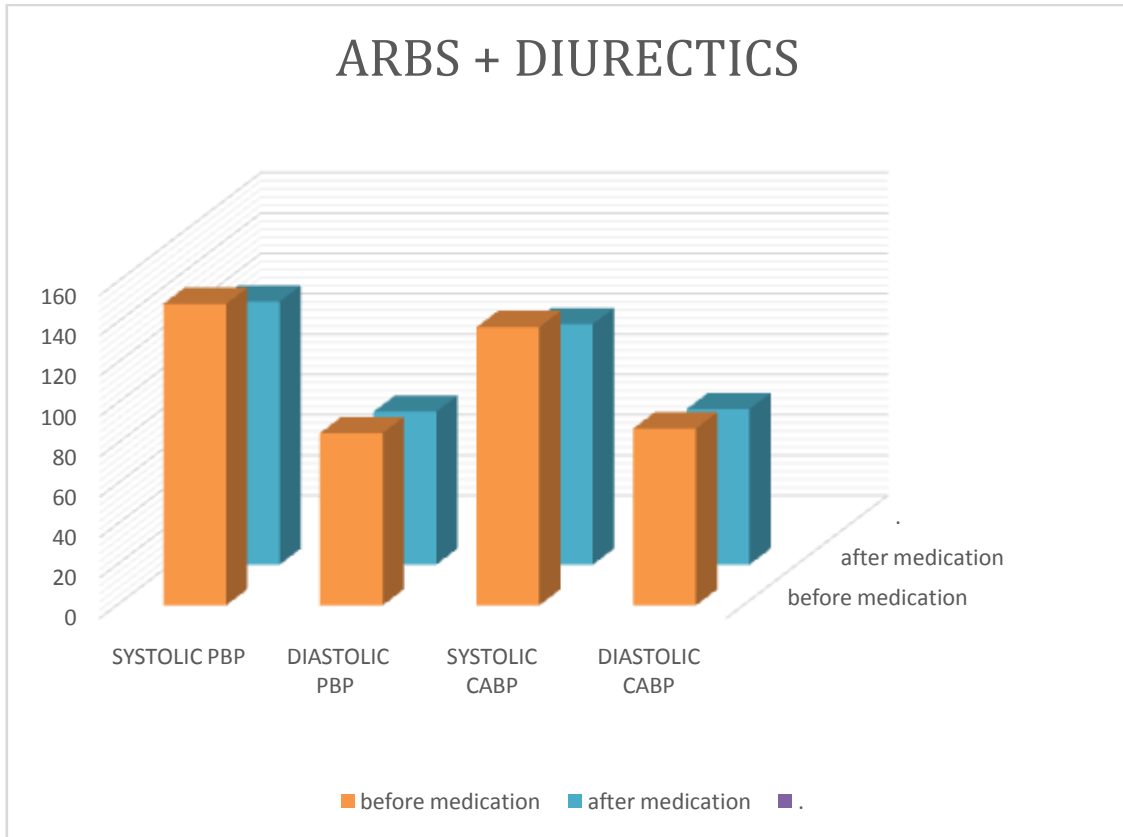


FIGURE 4:Diagrammatic representation of change in diastolic CABP after medication

From the (table 6) , it is clear that p value is 0.024 which is significant , implies that ARB+CCB medication reduces diastolic CABP using the paired T test gives a p value of

0.024.from the graph(figure 4) the mean difference of ARBs + CCB is greater than the mean difference of ARBs+ Diuretics. Hence a significant reduction is seen in diastolic PBP



IV. DISCUSSION:

In our study, which compared the therapeutic efficacy of anti-hypertensive medications i.e; ARBs+Diuretics and ARBs+Calcium channel blockers. We divided our subject population into two groups where group A was ARBs+CCBs and Group B was ARBs+Diuretics which was postulated by **Williams B et al**^[9]With a total of 88 patients, after 24 weeks treatment, it was observed that ARBs+CCBs showed a significant impact in reduction of blood pressure in both peripheral and central aortic blood pressure. A baseline measurement for both peripheral and central aortic blood pressure was taken and then they were observed during this period along with their medication adherence before and after patient counselling done by **Boutouyrie et al**^[10]Apart from this, a complete risk assessment for cardiovascular diseases were also done and categorized patients into 3 categories namely High risk, Intermediate risk and Low risk Patients using the GRACE score as postulated by **A.R. Prabhudesai et al**^[11]. Here, we would like to highlight the importance and accuracy of measuring central aortic pressure in producing desirable effects in hypertension treatment.

Calcium channel blockers and ARBs are expected to reduce both central and peripheral BP and our results have confirmed the findings as well. Whereas, diuretics are considered to have little or no effect on the blood pressure as compared to CCBs.

Even if limited by a small sample size and lack of further follow up, it was shown that both anti-hypertensive combinations does not effect the normal renal function. Hence the side effect profile is considered to be safe.

A reduction of central aortic pressure maybe due to decrease in arterial stiffness of the blood vessels, a modification of wave reflections or both. The agents used in this study are known to modify the pulse wave velocity (PWV), depending on the dose and treatment duration of each combination.

In this study, no patients dropped out during the course of treatment but the increase in medication adherence after patient counselling proved the importance and the need for providing education to patients about their disease and use of the medications. We used the Hill-bone scale for assessing medication adherence which confirmed that there was a significant increase in medication adherence and improved results. **Kim M T et al**^[12]

The limitation of the study was the, relatively small sample size and the follow-up period which could have masked the therapeutic effects on the BP parameters which could have been studied in depth.

The major finding in this study is that measurement of central aortic pressure is more accurate and that agents that could be used to produce significant effects can also be short-listed in order to provide a better and healthy life as implied by **Roman M J et al**^[13]

V. CONCLUSION:

The present study was conducted to assess the relative efficacy of anti-hypertensive medications on central aortic pressure in hypertensive patients. The study also aims to find out the risk factors for developing cardiovascular diseases and patient counseling was done to improve the medication adherence of the patients. The study was conducted in 88 patients with hypertension taking either one of the combination drugs (ARBs + Diuretics or ARBs + CCBs) came to the cardiology department. All details about the patient including informed consent form, patient information sheet, blood pressure measure, serum Creatinine values, heart rate, age and other cardiovascular measure related to the study was collected.

Out of the 88 patients included for the study, 48 patients were male and 40 patients were females. In this 19 males and 25 females were taking ARBs + diuretics and 29 males and 15 females were taking ARBs+ CCBs. All inclusion and exclusion criteria were followed. A total of two visits was done, where the second visit was taken as the follow up where the data was compared to the baseline.

Here we introduced an innovative tool for measuring central aortic pressure which is the applanation tonometry. It has various indices like pulse wave velocity, Augmentation index @75, pulse pressure amplification, peripheral resistance, cardiac output, stroke volume, cardiac index, augmentation pressure, reflection coefficient. The main advantage of this measurement is, it is a non invasive measurement that does not involve incision and is recorded by the pulse waves sensors produced in the central artery which is then converted numerically. Central aortic pressure is a predictor of cardiovascular risk assessment and increased CABP can predict the chance of developing cardiovascular disease. Moreover it has greater advantages of predicting the risk of

acquiring various metabolic diseases like hyperglycemia and hypercholesterolemia.

The pharmacist has a major role in educating the patient about the various aspects of disease and improving the medication taking behavior of patients. The patients with hypertension were counseled with emphasis on various aspects like lifestyle modification, diet control, the necessity for regular exercise, sugar control, cholesterol management etc and the medication adherence were assessed before and after counseling using Hill Bone medication adherence scale which is a 14 item questionnaire divided into three subset of behavioral domains. The questionnaire includes appointment keeping (3 items), Diet (2 items), Medication adherence (9 items), it is useful for in planning and implementing effective and individualized care. The results implicated that the medication adherence was improved after counseling as control of hypertension can only be done if proper compliance to treatment regimen guidelines and recommendations by providers and organizations.

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DECLARATION :

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Conflict of Interest: None declared

Ethical Approval : Not required

REFERENCE

- [1]. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest*. 1992;102(4):1193-1198.
- [2]. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *Journal of Applied Physiology*. 2008;105(5):1652-1660.
- [3]. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, et al. Role of pulse pressure amplification in arterial hypertension. *Hypertension (Dallas, Tex : 1979)*. 2009;54(2):375-383.
- [4]. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, et al. Central blood pressure measurements and antihypertensive therapy. *Hypertension (Dallas, Tex : 1979)*. 2007;50(1):154-160.
- [5]. Theilade S, Hansen TW, Rossing P. Central hemodynamics are associated with cardiovascular disease and albuminuria in type 1 diabetes. *American Journal of Hypertension*. 2014;27(9):1152-1159.
- [6]. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation*. 1989;80(6):1652-1659
- [7]. A.R. Prabhudesai , M.A. Srilakshmi, M.J. Santosh, Gurappa G. Shetty, Kiron Varghese, Chandrakant B. Patil, Shamanna S. Iyengar. Validation of the GRACE score for prognosis in Indian patients with acute coronary syndromes / *Indian Heart Journal* 64(3) (2012): 263–269
- [8]. Youngshin song R N , Miyong T. Kim. Psychometric Evaluation of Hill bone Medication Adherence Subscale. *Asian Nursing Research*. Vol 5, Issue 3, Sep 2011, pages 183-188
- [9]. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. *Circulation*. 2006;113(9):1213-1225.
- [10]. Boutouyrie P, Achouba A, Trunet P, Laurent S; EXPLOR Trialist Group. Amlodipine – valsartan combination decreases central systolic blood pressure more effectively than the Amlodipine-atenolol combination: the EXPLOR study. *Hypertension*. 2010 Jun;55(6):1314-22. Doi:10.1161/Hypertensionaha.
- [11]. Prabhudesai AR, Srilakshmi MA, Santosh MJ, et al. Validation of the GRACE score for prognosis in Indian patients with acute coronary syndromes. *Indian Heart J*. 2012; 64(3):263-269. Doi: 10.1016/S0019-4832(12)60084-4.
- [12]. Kim MT, Hill MN, Bone LR, Levine DM. Development and testing of the Hill-Bone Compliance to High Blood Pressure Therapy Scale. *Prog Cardiovasc Nurs*. 2000 Summer;15(3):90-6. doi: 10.1111/j.1751-7117.2000.tb00211.x. PMID: 10951950.
- [13]. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure. *Hypertension (Dallas, Tex: 1979)*. 2007;50(1):197-203.