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EDITORIAL

Exploring the Utility of Pulse Wave Analysis in Patients with Uncontrolled Brachial Blood Pressures in the Routine Outpatient Setting

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ABSTRACT

BACKGROUND: Hypertension if left untreated can lead to arteriosclerosis, heart attacks, strokes and kidney disease. Studies suggest that central pressure may be more strongly related to future cardiovascular events than brachial pressure. Proportion of patients not at goal blood pressure is astounding. The aim of this study was to identify patients with hypertension not achieving goal brachial blood pressure and to investigate the co-relation between brachial blood pressure and central systolic blood pressure by using Pulse Wave Analysis (PWA).

METHODS: We conducted a single center, prospective, cohort study at the Outpatient Nephrology clinic operated by West Virginia University Hospitals between January 2017 and February 2018.

RESULTS: 22 patients met the inclusion criteria for the study, however only 14 (63.6%) followed through with getting at least one follow up PWA testing. 7/14 (50%) were males. 12/14 (85.7%) were older than 60 yrs. 10/14 (71.4%) had elevated central systolic pressures and pulse pressures at the initial visit and 2/14 (14.3%) an elevated augmented index. At the end of the study 9/14 (64.2%) were at goal central systolic blood pressure, 6/14 (42.9%) at goal Pulse pressure, with 8/14 (57.1%) at goal augmented index. At study end there was on average a 8.2 mmHg decrease in the central systolic pressure and 9.8 mmHg reduction in the pulse pressure after the lifestyle and anti-hypertensive regimen modification.

CONCLUSION: Our results showed a predominantly elderly and obese population. Discrepancies between brachial and central systolic blood pressure may exist. Patients may benefit from the management of their blood pressure with the use of central blood pressure, pulse pressure and augmented index measurements as obtained by the Atcor Medical XCEL Pulse wave analysis machine. Further studies are needed to reinforce the importance of the utility of Pulse wave analysis and central blood pressure monitoring in the treatment of hypertension.

Keywords: Pulse wave analysis, hypertension, central blood pressures, pulse pressure, augmented index, arterial stiffness

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BACKGROUND

Blood pressure is the force of blood pushing against the walls of arteries as it flows through them. The more pressure the blood exerts on the arterial walls, the higher the blood pressure will be. The understanding about hypertension (HTN) began with the work of William Henry describing the circulation of blood in his book. The English clergyman Stephen Hales made the first published measurement of blood pressure in 1733. It was not until 1896 when Scipione Rivi Rocci invented the sphygmomanometer that HTN as a clinical entity came into being. Subsequently, Eberhard Frank in 1911 coined the term essential hypertension that described elevated BP for which no cause could be found. HTN remains one of the most important preventable contributors to disease and death. If left untreated it can lead to arteriosclerosis, heart attacks, strokes and kidney disease. A 10% increase in HTN treatment would prevent approximately 14,000 deaths each year[1]. The global prevalence of HTN is high. For decades the definition of HTN was a systolic pressure > 140 mmHg and/or a diastolic pressure > 90 mmHg and thus about 85 million people aged six and older were known to have HTN. In the last few months the American College of Cardiology/ American Heart Association (ACC/AHA) reported in the 2017 guidelines a new definition of HTN in adults which states HTN as any systolic pressure > 130 mmHg and/or diastolic pressure > 80 mmHg. This has led to an increase in the prevalence of HTN amongst adults in US. According to NHANES data from 2011 to 2014, 46% of adults 18 years and older had HTN[1], which is about 103 million adults in the United States. Long-term projection suggests that 1.56 billion people worldwide will have HTN by 2025 based on the old HTN definition[2].

Hypertension is not adequately controlled worldwide; using the prior definition of HTN, 69 to 70% of adults treated for hypertension were controlled to < 140/90 mmHg[3,4]. However, under the new definition only 47% of patients taking antihypertension drug therapy have controlled blood pressure[1]. As blood pressure increases the likelihood of having a cardiovascular event increases. In the meta-analysis by *Lewington et al*[5] the risk of death from heart disease and strokes doubles with every increment of 20 mmHg in systolic and 10 mmHg in diastolic blood pressure above 115/75. As per *Franklin et al*[6], systolic pressures and pulse pressures are greater predictors of risk in patients over the age of 50 to 60 years. HTN is associated with a significant increase in risk for adverse cardiovascular and renal outcomes such as left ventricular hypertrophy (LVH), heart failure (both systolic and diastolic) ischemic stroke, intracerebral hemorrhage, ischemic heart disease, chronic kidney disease and end stage renal disease (ESRD). Pulse pressure is the difference between the systolic and diastolic blood pressures and is determined primarily by the stiffness of the large arteries.

Diagnosing and treating hypertension appropriately plays an important role in minimizing the risk for cardiovascular disease and stroke. The diagnosis of HTN is most often made by using the measurement from brachial blood pressure monitors/ sphygmomanometer readings done in the office setting, however, lately there is an increase in the use of ambulatory blood pressure monitoring (ABPM) to help come to that diagnosis. ABPM is regarded as the "gold standard" for BP measurements based on the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO) database. The systolic and diastolic ABPM measurements significantly and independently predict cardiovascular outcomes over and above clinic blood pressure[7]. Technically direct intra-arterial blood pressure measurement is considered the gold standard for blood pressure measurement but that is not something commonly performed due to its invasive nature. Hence, the next best way to get accurate blood pressure readings is via pulse wave analysis (PWA) through brachial blood pressure cuff measurements that give accurate central BP readings. Pulse wave analysis measures pressure wave forms from peripheral arteries such as the brachial or radial artery and subsequently corresponding central aortic pressures are derived either using a generalized transfer function, a proprietary algorithm or identification of the late systolic shoulder of the peripheral pressure waveform. The aim of this study was to identify patients with hypertension who were not achieving their target blood pressure goal based on brachial blood pressure monitor readings in the clinic. Furthermore to investigate the co-relation between brachial blood pressure and central systolic blood pressure in these patients and for those not at goal to treat them to help reach goal central blood pressure.

MATERIALS

We conducted a single center, prospective, cohort study at the Outpatient Nephrology clinic operated by West Virginia University Hospitals between January 2017 and February 2018. The study initially planned to enroll 200 patients in 2 years. We decided to end the study early and report on the data that we have thus far in order to enable us to make changes to our protocol and data collection methods as required and to help guide us to create a standard treatment algorithm so as to effectively meet our primary and secondary objectives in the long term. Before commencement of the study, the protocol was reviewed and approved by the Institutional Review Board at our institution. Patients 18 years of age and older presenting to the WVU Medicine Nephrology clinic with uncontrolled hypertension were enrolled after informed consent. Uncontrolled hypertension was defined as a blood pressure > 140/90 in patients 18-60 years of age, and 150/90 in patients > 60 years of age. Patients were enrolled if their blood pressure was not at goal per JNC 7 guidelines. Pregnant patients were excluded.

METHODS

The purpose of the study was to identify patients with hypertension who were not achieving their target blood pressure goal based on brachial blood pressure monitor readings in the clinic. For those not at goal, their central pressures, pulse pressure and augmented index were measured using the Pulse wave analysis technology. Subsequently for those not at goal the physician would then place together a therapeutic plan specific to the patient to reach goal blood pressure. The primary end point was to identify the subgroup of patients that would benefit most from the application of this technology. The secondary end points included assessing the ease of incorporating SphygmaCor apparatus into clinical practice and designing a possible treatment algorithm in order to aid physicians in the management of hypertension so as to meet blood pressure goals. Lastly, also to see how many patients at the end of the study were at central systolic goal blood pressure as a result of our implemented medication and life style changes.

We conducted PWA testing with the SphygmaCor machine, which uses an inflatable brachial cuff to measure blood pressure, analyze aortic waveforms and estimate central aortic systolic and diastolic pressures. It also provides information on central pulse pressure, augmentation pressure, and arterial stiffness after digitalization of measured data and application of non-linear mathematical

transformations. This apparatus has previously been validated by comparisons to invasive measurements of central pressures[8-10]. Brachial blood pressure manual readings were obtained by standard technique by trained nursing staff. The patients underwent manual blood pressure recordings at presentation to the clinic and then had central pressures measured with the above apparatus at the end of a 30 minute clinic visit. If the central pressure was not at goal per the SphygmaCor apparatus, lifestyle modifications and medication adjustments were recommended, and patients were followed at 8-12 weeks for reassessment of hypertension until target central blood pressure was achieved. Standardized lifestyle modification information was provided to each patient at each visit. This included information on a low salt diet, recommendations on exercise, weight loss, smoking cessation if they were smokers, alcohol consumption, getting evaluated for obstructive sleep apnea if it was warranted and increasing compliance with obstructive sleep apnea therapy.

Data was collected at each visit by study personnel and documented in electronic health records. Variables included demographic characteristics, co-morbids, BMI, initial weight, CKD stage, HbA1C readings, Left ventricular hypertrophy documented on TTE or EKG, urine protein to creatinine ratios, antihypertensive medications at presentation and adjustments during study period, and smoking status. All PWA readings, mean follow up and number of visits needed to achieve goal were documented. At the end of the study period, the data was compiled and analyzed. Patients who had only one PWA reading were excluded from analysis. Descriptive data were obtained and tabulated. The proportion of patients achieving blood pressure control was calculated. Patient demographics and data that was obtained as part of the study was carefully analyzed. Changes in the anti-hypertensive medication regimen was analyzed as was the proportion of patients at goal pulse pressure.

RESULTS

In our study, 22 patients met the inclusion criteria for the study, however only 14 (63.6%) followed through with getting at least one follow up PWA testing to assess for changes in blood pressure post treatment modifications. Of the 14 patients that we reported on, 7/14 (50%) were males. 12/14 (85.7%) were older than 60 years of age at the time of enrollment (Table 1).

10/14 (71.4%) were obese with a BMI greater than 30 (Figure 1). None of the patients had a history of prior CVA. 10/14 (71.4%) were diabetic. 3/14 (21.4%) were ex-smokers and 9/14 (64.3%) had never smoked. 9/14 (64.4%) had CKD stage III at the time of enrollment (Table 1).

Of the 14 patients with elevated blood pressure readings manually all had an elevated brachial reading by the PWA machine and of these 11 (78.6%) had elevated central systolic pressures at the initial visit. Despite having significantly elevated brachial systolic pressures only 3 (21.4%) had central systolic pressures that were at goal at the initial visit. 10/14 (71.4%) had elevated central systolic pressures and pulse pressures at the initial visit only 2/14 (14.3%) had an elevated augmented index initially (Figure 2). Only 5/14 (35.7%) had an elevated central systolic pressure at the end of the study. After adjustments of medications upon the initial visit and PWA, 7/14 (50%) patients were at goal central systolic blood pressure. At the end of the study 9/14 (64.2%) patients were at goal central systolic blood pressure and 6/14 (42.9%) patients at goal Pulse pressure, with 8/14 (57.1%) at goal augmented index and only 3/14 (21.4%) with high augmented index (Figure 2). At the end of the study 12/14 (85.7%) had a > 5 mmHg drop in their systolic brachial blood pressure

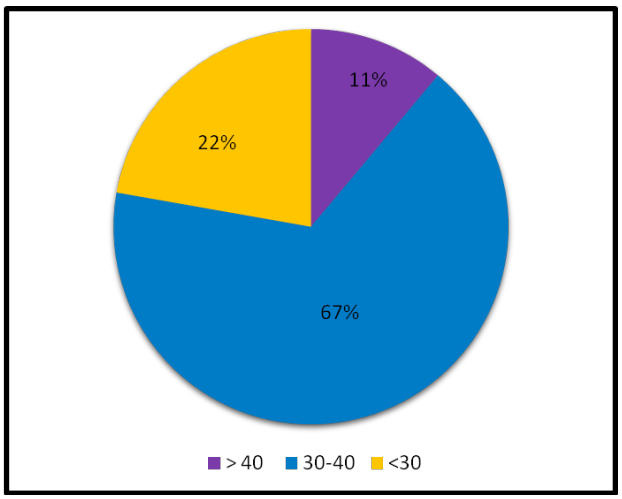

Figure 1 Distribution of Body Mass Index (BMI).

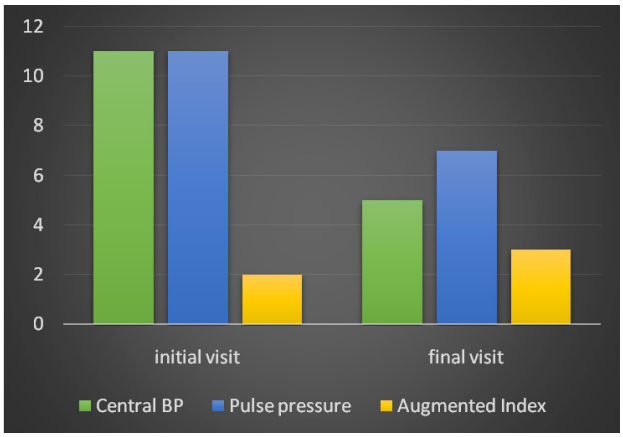

Figure 2 Patients with elevated central pressures, pulse pressures and augmented index at the initial and final visit respectively.

Table 1 Demographics of enrolled subjects.

Demographics	n/percentages
Age (average)	65.9
Sex	
Males	7/50%
Females	7/50%
Race	
Non-hispanic Caucasians	14/100%
History of	
DM	10/71%
CAD	3/21%
OSA	6/43%
CKD Stage 3 or greater	9/64%
Smoking status	
Never smoker	9/64%
Ex-smoker	3/21%
Current smoker	2/14%
Weight (BMI)	
Normal (18.5-24.9)	2/14%
Overweight (25-29.9)	2/14%
Obese (30-34.9)	5/36%
Severely Obese (35-39.9)	3/21%
Morbidly obese (40+)	2/14%

readings. On average by the end of the study there was a 8.2 mmHg decrease in the central systolic pressure and 9.8 mmHg reduction in the pulse pressure after all the lifestyle and anti-hypertensive regimen modifications (Figure 3).

At the initial visit 9/14 (64.3%) were on Angiotensin Converting Enzyme Inhibitors (ACEI) / Angiotensin II Receptor Blockers (ARBs). At the initial visit 8/14 (57.1%) were on diuretics (furosemide, hydrochlorothiazide, triamterene, aldactone). At the initial visit 9/14 (64.3%) were on Beta-blockers (BB). At the initial visit 9/14 (64.3%) were on calcium channel blockers or vasodilators (nitrates, hydralazine). Overall at the end of the study 8/14 (57.1%) were on ACEI/ARBs, 10/14 (71.4%) were on diuretics, 11/14 (78.6%) were on BB and 9/14 (64.3%) were on a CCB/vasodilator (Figure 4).

DISCUSSION

HTN remains one of the most important preventable contributors to premature cardiovascular disease and death. If left untreated it can lead to arteriosclerosis, heart attacks, strokes and kidney disease. As per the Center of Disease Control and Prevention, a 10% increase in HTN treatment would prevent approximately 14,000 deaths each year[1]. In a large cohort study by *Kannel et al*[11] hypertension (defined as ⩾ 140/90 mmHg) increased the relative risk of stroke (by 3.8 and 2.6 in men and women, respectively) and heart failure (by 4.0 and 3.0, respectively). Thus we wanted to see how well blood pressure is controlled in our outpatient setting and to identify the patients that would benefit most from measures to help get them to goal blood pressure. Consequently in the long term reducing morbidity and mortality secondary to it such as stroke and heart failure. Of the 14 patients in our study, all were Caucasian and 50% were males. 85.7% of the subjects were aged 60 years or greater at the time of enrollment. This coincides with the overall high prevalence of HTN worldwide in this age group. We also found that 71.4% were obese with a BMI greater than 30, and this corresponded with a similar percentage of patients having diabetes. West Virginia now has the second highest adult obesity rate in the United States according to The State of Obesity: Better Policies for a Healthier America. West Virginia's adult obesity rate is 35.7% up from 23.9% in 2000 and from 13.7% in 1990. There was not an increased prevalence of a history of CVA or CAD noted in our patient population. Of the 12 patients that had data on proteinuria, all had non-nephrotic range proteinuria. Although 22 patients met the inclusion criteria for the study, however only 14 (63.6%) followed through with getting at least one follow up PWA testing to assess for changes in blood pressure post treatment modifications. From our results it can be inferred that the population most likely to benefit from close evaluation would be those that are obese and elderly. The compliance rate for follow up through PWA testing was low but likely due to the increased travel distance that patients had to cover to get to the PWA testing site.

A number of methods are available to measure central pressure ranging from cardiac catheterization and recording the blood pressure in the ascending aorta to non-invasive means where pressure waveforms are recorded from sites distal to the aorta, such as the carotid, radial or brachial arteries and calibrated to blood pressure recorded by cuff sphygmomanometry. We used the At Cor medical XCEL device for our study. The major criticism of this and other similar devices is that they tend to under estimate the "true" (invasive) brachial artery pressure, leading to falsely low estimates of central pressure[12]. There is growing evidence that central pressures

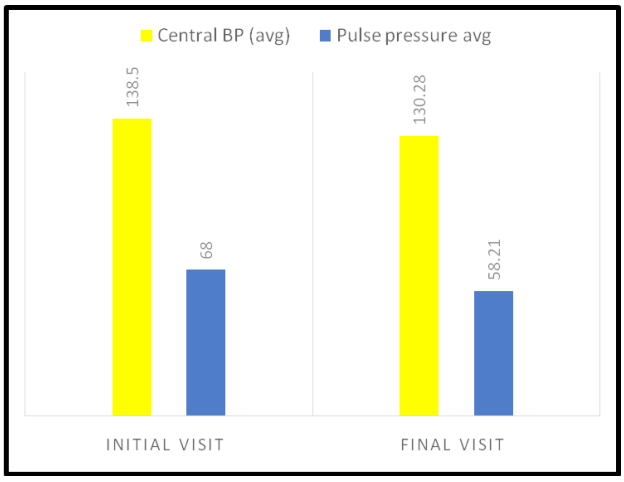

Figure 3 Changes in average Central systolic blood pressure and average Pulse Pressure between the initial and final visit.

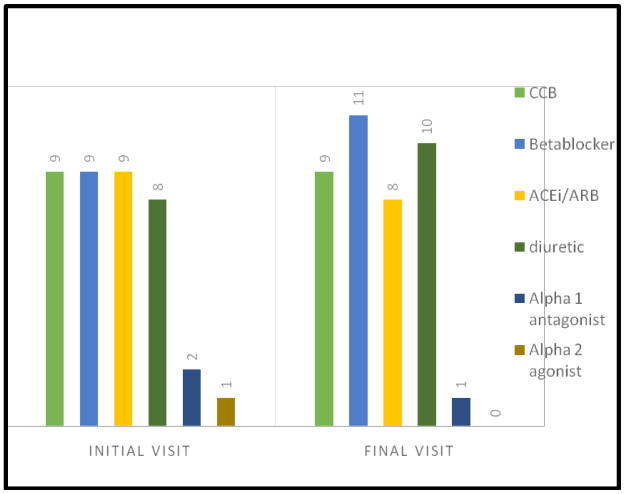

Figure 4 Number of patients on the various classes of anti-hypertensives at the initial and final visit.

correlate better with morbidity and mortality relative to brachial pressures. Patients' may have a discrepancy when comparing if they have high vs at goal readings for central vs brachial pressures. Of the 14 patients with elevated brachial blood pressure when checked manually and by the PWA machine, 11 (78.6%) also had an elevated central systolic pressure at the initial visit. 71.4% had both an elevated central systolic pressure and pulse pressure at the initial visit. By the end of the study only 5 of 14 (35.7%) had an elevated central systolic pressure. This shows that the changes that we made in the therapy plan did indeed help patients reach to goal central pressures in the long term. In the REASON study, regression of left ventricular mass was more strongly related to change in central compared with brachial pressure and after adjustment, only central pressure remained predictive[13]. Similar observations were made in the sub study of the Ascot trial[14]. *Safar et al*[15] found that after adjustment for cofounders, only central pressure remained predictive in patients with renal failure. The Dicomano Study in Italy and a community based Taiwanese study also observed a stronger association between cardiovascular events and central, rather than brachial pressure[16,17]. Unfortunately with our study we did not have sufficient long term follow up to assess if elevated central blood pressure were indeed more predictive of adverse cardiovascular outcomes as compared to brachial blood pressure readings.

Central blood pressure can differ significantly in people with the same brachial pressure. Central blood pressure cannot be reliably predicted by brachial blood pressure. *McEniery et al*[18] reported on a cohort of 10,000 healthy volunteers that they observed a greater than 70% overlap in aortic systolic pressure between people with "high normal" brachial systolic pressure (130-139 mmHg) based on Joint European Cardiology and Hypertension Society guidelines and those with stage I hypertension (140-159 mmHg). In our cohort, we found that 3/14 (21.4%) patients did not have an elevated brachial blood pressure corresponding with an elevated central systolic pressure. *Ohte et al*[19] have shown how diastolic and mean arterial pressures are relatively constant, systolic pressure may be up to 40 mmHg higher in the brachial artery than in the aorta. This phenomenon of systolic pressure amplification arises principally because of an increase in arterial stiffness moving away from the heart[12,18]. *McEniery et al*[18] evaluated a cohort of 10,000 volunteers deemed to be healthy and found that there was a significant, and highly variable, difference between aortic and brachial systolic pressure at all ages. It is important to recognize that because of the phenomenon of pressure amplification, the current brachial threshold for diagnosing and treating hypertension may need modification to central pressure. Central pressure is the most clinically relevant measure of load on the heart and vital organ perfusion. Elevated aortic pressure augmentation indicates significant contribution of arterial stiffness and early wave reflections to central pressure waveform profile. In our study only 2 (14.3%) had an elevated augmented index initially. Overall in the study cohort we noted that the addition of or optimization of the dosage of Angiotensin Converting Enzyme Inhibitors (ACEI)/Angiotensin II Receptor Blockers (ARB), Calcium Channel Blockers (CCB), Beta- Blockers (BB) in 8 patients led to 5/8 (62.5%) being at goal central systolic pressure and 4/8 (50%) being at goal augmented index. Vasodilating medications such as ACEI/ARB, CCB, Vasoactive BB help reduce effects of early wave reflection. Low aortic pressure augmentation indicates that elevated central systolic pressure and pulse pressure are likely due to other causes such as fluid volume imbalance, high cardiac output or sympathetic over activity. In these scenarios diuretics may be more effective in lowering blood pressure than vasodilating medications which reduce wave reflections.

With increasing age the pulse pressure tends to more closely correlate with the systolic pressure rather than the diastolic pressure and is therefore also a good predictor of cardiovascular disease among older adults. An increased pulse pressure places greater stress on the arteries resulting in increased breakdown of the elastic component of the vessel wall leading to intimal damage and subsequent increased risk of thrombosis and atherosclerosis. Reviewing data from *Winston et al*[20], brachial pulse pressure was associated with increased stress on the left ventricle resulting in ventricular hypertrophy and failure. The Framingham Heart Study reported that each 10 mmHg increment in pulse pressure was associated with a 23 percent higher risk of developing coronary heart disease[21]. Pulse pressure is believed to be an independent risk factor for progression of chronic kidney disease (CKD). *Bakris et al*[22] in a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Trial reported that a 10 mmHg higher pulse pressure was significantly associated with a 17% high relative risk of developing ESRD. Not only that *Weir et al*[23] found that increased pulse pressure is also associated with urine protein excretion. On further analysis on the Strong Heart Study *Roman et al*[24] showed that individuals with centrals pulse pressure $\geqslant$ 50 mmHg are at greatest risk for future cardiovascular events. At the end of the study 9/14 (64.2%) patients were at goal central systolic blood pressure and 6/14 (42.9%) at goal pulse pressure and 8/14 (57.1%) at goal augmented index. Of the 9 patients at goal central systolic pressure by the end of the study 6/9 (66.7%) were at goal pulse pressure too. Although certain studies have shown reduced cardiovascular morbidity and mortality when using pulse pressure to titrate hypertension treatment, based on the Clinical Advisory Statement by *Izzo et al*[25] it's too premature to use pulse pressure as a factor in deciding which anti-hypertensives to use or if to use the measurement as a treatment endpoint. Thus further prospected studies are required to define pulse pressure as a predictor of cardiovascular outcomes and to determine if it is a better index of response to therapy. In our study we found that 11/14 (78.6%) had elevated pulse pressure at the initial visit.

Numerous cross sectional studies have shown that central pressure is more closely correlated with cardiovascular risk such as carotid intima medial thickness (CIMT)[26,27] and left ventricular mass[28]. In the Strong Heart Study, central pressure was more strongly related to future cardiovascular events than brachial pressure, in disease free individuals[26]. Numerous studies have examined the influence of different anti-hypertensive drugs on brachial vs. central pressure. Nitrate[29] and ACEi[30,31] have shown to reduce central systolic pressure while BB[32] have shown to increase central systolic pressure relative to other classes of drugs. The CAFÉ sub study[33] of the ASCOT trial[34] subsequently reported that individuals randomized to atenolol had a 4.3 mmHg higher central systolic pressure than those given amlodipine despite identical brachial pressures. In our cohort we had 7/14 (50%) of the patients had resistant HTN at the beginning of the study. Of note is that at the initial visit 9/14 (64.3%), 8/14 (57.1%), 9/14 (64.3%) were on ACEI/ARB, diuretics and BBs while at the end of the study there were a higher proportion of patients on diuretics (71.4%) and BBs (78.6%). At the end of the study 85.7% had a > 5 mmHg drop in their systolic brachial blood pressure reading as per the PWA machine. Also to note at the end of the study 64.2% patients were at goal central systolic blood pressure and 42.9% patients at goal pulse pressure with 8/14 (57.1%) at goal augmented index and only 3/14 (21.4%) with high augmented index. Overall by implementing lifestyle modifications and changes in the anti-hypertensive regimen we were successfully able to get patients to goal blood pressure.

CONCLUSION

At this time it is soon to say with full confidence as to which class of anti-hypertensive drugs should be used when, but there is increasing evidence for the use of vasodilating agents such as CCB, ACEI/ARB, vasoactive BB in situations with elevated augmented index. Furthermore solidifying the need to have the ability to measure central pressures and waveforms in the outpatient setting. Further data gathering will help to achieve conclusive results to promote use of central pressure measurements and possibly even use them as target guidelines for the effective treatment of HTN in the future. There should be increased awareness of the concept of arterial stiffness especially since that can account for significant differences between brachial and central pressures. Excessive treatment measures to lower brachial blood pressure can lead to increased morbidity and mortality via hypotensive episodes and ischemic hypo-perfusion leading to CVA or Acute Kidney Injury (AKI). It is also important to note that it is this failure to auto-regulate due to the presence of atherosclerosis leading to arterial stiffness that contributes highly to the increasing incidence of AKI in the elderly population and those with hypertension. It would be beneficial in the outpatient setting to

take advantage of parameters such as the augmented index via non-invasive apparatus such as the AtCor XCEL to help guide therapy towards the management of HTN and getting patients to goal blood pressure. Further studies are required to reinforce the importance of the utility of pulse wave analysis to determine central systolic pressures, pulse pressures and augmented index on a routine basis to help in the management of blood pressure and subsequently reducing cardiovascular events.

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