Aortic stiffness and central systolic pressure are associated with ambulatory orthostatic BP fall in chronic kidney disease

Article (Accepted Version)

Title page

Title

Aortic stiffness and central systolic pressure are associated with ambulatory orthostatic BP fall in chronic kidney disease

Running title

Aortic stiffness and orthostatic hypotension in CKD

Frances A Kirkham[1], Philip Rankin[1], Nikesh Parekh[1,2], Stephen G Holt[3], Chakravarthi Rajkumar[1,2]

1 Department of Elderly Care and Stroke Medicine, Brighton and Sussex University Hospitals Trust, Brighton, UK

2 Department of Medicine, Brighton and Sussex Medical School, University of Sussex, UK

3 Dept Nephrology, Brighton and Sussex University Hospitals Trust, Brighton, UK

Corresponding author: Dr Frances A Kirkham franceskirkham@btinternet.com

Address: C/o Professor Rajkumar, Audrey Emerton Building, Royal Sussex County Hospital, Brighton, BN2 5BE

Phone: +44 7894315034

Word count: Text (exc. tables and references) – 3041, Abstract – 294

Acknowledgements: none

Funding sources: none

Conflicts of interest: none

Impact statement: We certify that this work is **A) novel** clinical research

Novelty

This study found increased aortic stiffness and central systolic blood pressure are independently associated with orthostatic systolic BP fall in CKD patients**.** This study found increased carotid-femoral PWV, but not carotid-radial PWV or aortic augmentation index, suggesting that aortic stiffening may have a larger role in baroreceptor insensitivity in CKD than small arterial segment changes. Aortic stiffness may represent a potential therapeutic target for reducing the cardiovascular risk associated with CKD. Measures of central arterial pressures may be a more useful tool than peripheral measures in CKD patients

Structured Abstract

Objective:

Orthostatic hypotension (OH) has a significant association with cardiovascular disease. OH becomes more common in older age, as does arterial stiffness, shown to be independently associated with impaired baroreflex sensitivity and OH. Measurement of arterial compliance and central blood pressures are increasingly important, with evidence that central BP more closely correlates to end-organ damage and mortality than peripheral measurements.

Patients with chronic kidney disease (CKD) are high risk for cardiovascular events, which can be predicted through measures of arterial compliance. We hypothesised that OH is associated with arterial stiffness and central blood pressure in CKD patients.

Design/Setting:

We tested this hypothesis within the Arterial Compliance And oxiDant strEss as predictors of loss of renal function, morbidity and Mortality In Chronic kidney disease (ACADEMIC) study, a single-centre prospective observational study of the progression of arterial stiffness and renal function.

Participants:

146 patients with CKD 3 or 4.

Measurements:

24-hour ambulatory BP monitoring with postural sensing (DIASYS Integra 2, Novacor France); Central Systolic and Diastolic BP (cSBP and cDBP) and aortic Augmentation Index using Sphygmocor® (Atcor, Australia); Carotid-femoral pulse wave velocity (cfPWV) using Complior® (ALAM Medical, France).

Results:

23 patients had a postural SBP fall (prevalence 15.8%), with mean drop 7mmHg. Patients with OH had higher cfPWV (15.2m/s vs 12.7m/s in patients without OH ($p<0.001$)) and central SBP (147.5 vs 135.7, $p=0.012$). Regression analysis gave an odds ratio (OR) of orthostatic SBP fall for cfPWV of 1.46 (95% CI 1.16-1.84, $p=0.001$) and 1.03 for cSBP (95% CI 1.004-1.06, $p=0.024$) after adjustment for cardiovascular risk factors.

Conclusion:

Aortic stiffness and central SBP are independently associated with orthostatic SBP fall in CKD patients. This suggests that enhanced arterial stiffness may be an underlying mechanism in baroreflex dysfunction, and may partly explain the vascular risk in CKD patients.

Key words: Aortic stiffness, Chronic Kidney Disease, Orthostatic hypotension, Pulse wave velocity, Central Blood Pressure

Text

Introduction

Orthostatic hypotension (OH) is a descriptive term for a reduction in blood pressure on standing, due to impairment of compensatory autonomic reflexes necessary to maintain venous return and cardiac output as blood pools in the lower limbs [1]. The relationship between orthostatic hypotension (OH) and cardiovascular disease has been compellingly demonstrated [2, 3], with multiple meta-analyses finding a significant association of OH with all-cause mortality [4, 5].Orthostatic hypotension becomes increasingly common in older age, with prevalence estimates ranging from 5-50% depending on the population and threshold criteria used [6-8]. Aortic stiffness is also closely related to ageing [9-11] and has been shown to be independently associated with impaired baroreflex sensitivity and clinic-based OH [12-14]. Measurement of central arterial pressures has become progressively more important in cardiovascular assessment, with growing evidence that central BP more closely correlates to end organ damage, cardiovascular events and all-cause mortality when compared with peripheral measurements [15]. Non-invasive measurement of central blood pressure is now being increasingly used in a research and clinical setting to evaluate this risk for patients.

Patients with chronic kidney disease (CKD) are known to be at high risk for cardiovascular events and mortality [16], which can be independently predicted through measures of arterial compliance such as aortic pulse wave velocity (PWV) [17, 18].With daytime fatigue documented as one of the most common symptoms of CKD, this patient group have been shown to change posture between lying and

standing more frequently than healthy individuals [19], increasing the potential negative consequences of OH, such as falls. Thus far, there have been few studies of the epidemiology of OH in CKD and its relationship to arterial stiffness. A 2013 study showed the prevalence of OH in a stable outpatient CKD population to be 12.6% [20], while a prospective Japanese study found a prevalence of 42% in end-stage renal failure prior to haemodialysis, with the presence of OH indicating a doubling in risk for all-cause mortality [21]. A 2016 Chinese study suggested that OH was associated with increased aortic stiffness but had a less clear relationship with central systolic pressures [22].

Twenty-four hour ambulatory BP monitoring (ABPM) has been endorsed by the European Society of Hypertension as superior to clinic BP measurements and is particularly important in identifying BP-related risk in CKD patients [23]. The high variability of brachial BP in orthostatic hypotension, due to impaired BP regulatory mechanisms [24], is an important consideration in the evaluation of OH. ABPM with position sensing within a patient's natural environment and activity removes the confounding effects of 'white-coat hypertension' and an artificial clinic environment [25, 26]. ABPM therefore has an important role in evaluating and managing cardiovascular disease in patients with CKD [27].

We hypothesized that the presence of ambulatory orthostatic BP fall in CKD stage 3 and 4 patients would be associated with increased aortic stiffness, independent of known cardiovascular risk factors. We further hypothesized that measures of central systolic blood pressure would be more strongly correlated with OH in this patient group than peripheral blood pressure.

We tested this hypothesis within the Arterial Compliance And oxiDant strEss as predictors of loss of renal function, morbidity and Mortality In Chronic kidney disease (ACADEMIC) study, a single-centre prospective observational study of the progression of arterial stiffness and renal function in a cohort of 200 patients with CKD stage 3 or 4 [28].

Methods

Population

Patients with CKD stage 3 and 4 were recruited from outpatient nephrology clinics at Brighton and Sussex University Hospitals National Health Service Trust, United Kingdom. Exclusion criteria were: previous diagnosis of left ventricular failure, aortic stenosis with gradient >30mmHg and atrial fibrillation with uncontrolled ventricular response. All patients were treated with the aim of achieving UK Renal Association targets for the management of BP in CKD [29]: a target BP of 130/80 mmHg for patients with a urine protein:creatinine ratio (uPCR) <100 mg/mmol and a target of 125/70 mmHg if uPCR >100 mg/mmol. The choice of antihypertensive medication was at the discretion of the clinician but generally followed British Hypertension Society guidelines [30]. Data on the specific antihypertensive regimen or length of antihypertensive treatment for each patient were not collected during this study. At the time of the study all participants were outpatients and stable on their antihypertensive regime. A history of cardiovascular disease and associated risk factors was obtained.

This study was approved by the West Sussex Research Ethics Committee, and patients gave written informed consent. The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Clinic Measurements

Measurements were conducted in a quiet, temperature-controlled room by the same two trained research staff throughout the study. BP was measured twice using an appropriate cuff size with the patient supine at 5 and 10 minutes after rest (Omron 705 CP, Tokyo, Japan), and the mean of the two readings recorded. The mean blood pressure (MBP) was calculated as: MBP=(SBP-DBP)/3 +DBP.

Aortic stiffness was measured using Complior (®ALAM Medical) following best practice guidelines [31]. Pulse waves were assessed transcutaneously at the right femoral, radial and common carotid arteries, and the distance between the two recording sites was measured. The time interval between the recorded pulse waves was calculated by Complior software, and the PWV obtained using the equation PWV(m/s)=Distance(m)/Time(s).

Central Systolic and Diastolic BP (cSBP and cDBP) and aortic Augmentation Index (AIx) were recorded using Sphygmocor® (Atcor, Australia) through applanation tonometry at the radial artery.

24-Hour ABPM measurements

Twenty-four hour ABPM with postural sensing was measured using a Diasys Integra II recorder (Novocor, Cedex, France) on the non-dominant arm. This machine measures posture as horizontal (lying) or vertical (standing or sitting). Daytime BP

measurements were taken at 30 minute intervals (0700-2200) and night-time readings at 60 minute intervals (2200-0700). Following European Society of Hypertension guidelines [23], we included patients in statistical analysis if they had at least 5 valid lying and 5 valid standing measurements with 2/3 of overall measurements being assessed as valid (26 of the 39 readings taken).

Although definitions of OH vary, a consensus statement by Freeman et al. has been broadly accepted as a sustained reduction of systolic blood pressure (SBP) of at least 20mmHg or diastolic blood pressure (DBP) of 10mmHg within 3 minutes of standing or head-up tilt to at least 60˚ on a tilt table [1]. However, it has been argued that criteria defining OH are arbitrary and the degree of OH does not correlate well with morbidity and mortality in all patient groups and contexts [32, 33]. For the purposes of this study, we have included all degrees of orthostatic blood pressure fall calculated as: Ambulatory orthostatic BP fall = mean lying BP – mean upright BP.

Statistical Analysis

Statistical analysis was carried out using SPSS version 23 (SPSS). Data were analysed using appropriate statistical tests following examination of distribution and skew. Differences in means between patients with and without ambulatory orthostatic BP fall were compared using the Independent samples *t* test. Binary logistic regression analysis was performed to assess whether carotid-femoral PWV or central SBP (continuous determinant) are independently associated with ambulatory orthostatic BP fall (binary outcome). This calculated odds ratios (ORs) and corresponding 95% confidence intervals (95% CI). Analysis was adjusted for age, gender, estimated Glomerular Filtration Rate (eGFR), smoking history, Body Mass

Index (BMI), Total Cholesterol, Diabetes Mellitus, use of anti-hypertensives. Univariate analysis of variance was used to compare mean carotid-femoral PWV between groups with and without OH fall, adjusting for baseline clinic SBP.

Results

The total study population included 200 patients, of which 158 underwent ambulatory BP recording. 146 patients had adequate numbers of valid lying, standing and overall readings according to ESH guidelines and constituted the population for analysis. Baseline characteristics of the population are shown in Table 1 with prevalence of diabetes 21.2%. Of the 146 patients included in analysis, 23 had a fall in systolic blood pressure on standing, giving a prevalence of OH (defined in Methods section as ambulatory orthostatic BP fall) of 15.8%. The mean change in blood pressure with posture for each group is shown in Table 2, demonstrating an average drop in systolic BP of 7mmHg in the OH group compared to a rise of 13mmHg in the group without OH.

There was a significant difference in carotid-femoral PWV for patients with and without ambulatory orthostatic BP fall (15.2m/s vs 12.7m/s, p=0.00016, 95% confidence interval of the difference 1.23-3.78) (see Table 1). After adjustment for baseline clinic systolic BP, carotid-femoral PWV remained significantly different between groups (15.00m/s vs 12.7m/s, p=0.001). The Pearson correlation between cfPWV and mean postural SBP drop in the whole patient population was 0.17 (p=0.04). Patients with an ambulatory orthostatic BP fall had a significantly higher central systolic BP measured at the carotid artery (147.5 vs 135.7, p=0.012, 95% CI

2.7-21.1), and a higher systolic BP on both clinic measurement (159 vs 149 p=0.03, 95% CI 1.2-18.9) and lying systolic BP on 24-hour ABPM (133.4 vs 111.3, p<0.0001, 95% CI 15.9-28.3). In terms of measures of peripheral arterial compliance, there was no statistically significant difference between the groups in carotid-radial PWV or aortic augmentation index, suggesting that the central arteries may play a larger role in mediating this variation. Diastolic blood pressure measurements did not differ significantly between the groups when measured either peripherally or centrally.

The associations between carotid-femoral PWV, central SBP and 24 hour ambulatory orthostatic BP fall remained statistically significant following adjustment for potential confounders (Table 3). Regression analysis gave an adjusted odds ratio (OR) of ambulatory orthostatic systolic BP fall for carotid-femoral PWV of 1.46 (P = 0.001, 95% CI 1.16-1.84) and an adjusted OR of ambulatory orthostatic BP fall for central SBP of 1.03 (P = 0.024, 95% CI 1.004-1.06). Neither clinic systolic BP or MAP were significant predictors of ambulatory orthostatic systolic BP fall and carotid-femoral PWV remained significant after adjustment for these potential confounders (Table 4) with OR 1.51 (P=0.001, 95% CI 1.19-1.91). Central SBP remained significant after adjustment for clinic SBP with OR 1.13 (P=0.036, 95% CI 1.008-1.269).

Discussion

The prevalence of ambulatory orthostatic SBP fall in our population was 15.8%, congruent with that found by Bhat (12.6%) et al in a statistically similar CKD population [20]. Information on duration of CKD or hypertension was not collected during this study but there was no significant difference in eGFR or use of antihypertensives between groups.

The patient group with ambulatory orthostatic SBP fall had significantly higher clinic and 24 hour ABPM lying SBP, which is consistent with previous studies [34-36]. It has been proposed that isolated systolic hypertension, particularly in older patient groups, is related to impaired arterial compliance [37], which in turn is linked to orthostatic hypotension [38].

The few studies that have been published on the relationship between aortic stiffness and OH have shown mixed results. A large cross-sectional study of older adults in Rotterdam showed an independent association between arterial stiffness and clinic orthostatic hypotension, with subjects in the last quartile of carotid-femoral PWV measurements having an OR of 1.45 (95% CI 1.09-1.93) for orthostatic hypotension compared with the first quartile [12]. A limitation identified by the authors was that the findings were based on BP levels from a single occasion, and it was suggested that the use of ABPM monitoring had the potential to improve accuracy and precision. A study of 57 elderly subjects with a recent fall showed upper-limb arterial wall stiffness was significantly greater in patients with OH than in patients without OH [39]. A small Greek study of hypertensive subjects found that there was a significant relationship between orthostatic change in systolic BP and aortic stiffness in untreated

hypertensive patients. In treated hypertensive patients, no significant relationship was found between orthostatic systolic or diastolic BP change and carotid-femoral PWV [40], with the caveat that the results were based on only nine OH subjects. The majority of the population in our study were treated hypertensive patients and therefore our results draw contrary conclusions, suggesting that there is an association between orthostatic BP change and arterial stiffness in treated hypertensives.

The loss of compensatory autonomic reactions to a change in posture, attributed to an impairment in baroreflex sensitivity, has also been linked to increased arterial stiffness [13]. This reflex is in part dependent upon changes in transmural pressure stimulating stretch-sensitive baroreceptors in the carotid sinus and aortic arch. With reduced elasticity of the arterial wall, this stretch response may be diminished, leading to impaired triggering of neurally mediated pathways. Studies in healthy patients and haemodialysis patients have demonstrated an association between increased arterial stiffness and reduced cardiovagal baroreflex sensitivity [41, 42].

Further related mechanisms include changes in the reflection wave arriving back from the peripheral resistance vessels, with this wave arriving sooner in stiffer vessels, elevating the baseline systolic BP. Previous studies have suggested that augmentation index was positively associated with OH [43]. We found that aortic augmentation index, although high in the OH group, did not reach statistical significance. This may be due to the low number in this group or lack of sensitivity of this index in older patient groups, or may be influenced by other variables such as height or drugs. For example, drugs acting to relax arterioles may dampen the reflected wave and reduce neurogenic vasoresponses associated with orthostatic changes [44]. Other influences

over OH may be sympathetic activity which may also be modulated by drugs [45]. Whilst there was no significant difference in antihypertensive use between groups, we were unable to compare doses or types of antihypertensive medication, which may have had an influence over SBP and OH. However, as antihypertensive use was in accordance with British Hypertension Society guidelines, it is likely that regimens were similar between patients with similar eGFR. There is no clear evidence suggesting certain antihypertensives are more likely to cause OH in this patient group, with some weak evidence linking beta blockers to OH in some combinations and at some eGFR levels [46]. Chan et al found no significant difference in OH risk between patients on ACE I or ARB medications in a variety of combinations [47], while Sasaki et al found no significant difference in the presence or absence of OH in patients taking calcium antagonists, beta blockers, ACE I or diuretics either before or after initiation of haemodialysis [21]. Future studies in this area would benefit from comparison of different types of antihypertensive regimens on SBP and OH.

Nevertheless, our results suggest that aortic stiffness and central (aortic) SBP are significantly associated with ambulatory orthostatic systolic BP fall, which remains significant following adjustment for other cardiovascular variables that could represent potential confounders. These results suggest that aortic stiffness may be an important determinant of orthostatic hypotension in CKD patients, and may be linked to the increased cardiovascular risk in this patient group.

The high risk of cardiovascular events and mortality in this group is well documented, for example a 2013 meta-analysis found a 30% increase in the risk of congestive heart failure in this group [4]. There are few studies exploring the impact of OH on

cardiovascular outcomes in CKD patients, but Sasaki et al found a significant increase in all-cause mortality for ESRD patients with OH [21]. Baroreflex dysfunction has been found to be common in both OH and poor prognostic groups with CHF [14, 48], and it has been suggested that this may be an important intermediate in the relationship between OH and CHF. Similarly, since we have shown that aortic stiffness is independently associated with the presence of orthostatic SBP fall in CKD patients, we propose that enhanced arterial stiffness may also be an important underlying mechanism which may be mediated by baroreflex dysfunction, and may explain some of the vascular mortality risk in CKD patients.

Central vs peripheral measures in CKD patients

Measurement of central blood pressure has been shown to be a better predictor of cardiovascular outcomes than peripheral measures [49, 50]. This may be particularly relevant in CKD, where aortic stiffening has been proposed both as a cause, and consequence, of renal dysfunction [51].

This study found a significant increase in aortic stiffness as measured by carotid-femoral PWV, but not carotid-radial PWV or aortic augmentation index, suggesting that aortic stiffening may have a larger role in baroreceptor insensitivity in CKD than small arterial segment changes.

There was also a significant difference in central SBP between patients with and without ambulatory orthostatic SBP fall. The ratio of peripheral to central blood pressure is different between those with and without ambulatory orthostatic BP fall despite similar heart rates in both groups, suggesting this is a real difference and not heart-rate dependent. This reinforces the concept that orthostatic hypotension in this patient group is related to aortic dysfunction, measurable as aortic stiffness.

This may be important because it represents a potential therapeutic target as well as a means by which to stratify risk in patients with CKD and OH, and may be more accurate than relying on peripheral measures alone. Further studies are warranted to investigate the impact of OH and arterial stiffness on cardiovascular outcomes in this patient group.

Limitations

This was a cross-sectional analysis and thus cannot infer causality or prognosis of OH in this group, but our findings offer an important starting point for a prospective study on this subject.

A potential limitation of ABPM monitoring is that the time interval between change in posture and BP measurement is not recorded or the length of time in the vertical or lying position, potentially underestimating the level of OH measured. Therefore we cannot draw conclusions on the importance of time intervals in measuring orthostatic BP change, and the prognostic implications of the time interval of orthostatic measurement is an area that warrants further research. Similarly, the ABPM machine used does not take into account sitting vs standing, considering both as 'vertical' on measurement – if anything, this may underestimate the true level of OH.

We chose to investigate the association between all degrees of ambulatory orthostatic BP fall and aortic stiffness, rather than using consensus criteria for defining OH, as no guidelines for measurement of OH on ABPM exist. The validity of consensus criteria

has been questioned [52].A large study of elderly Japanese American males found that smaller systolic and diastolic drops were associated with significant differences in mortality, recommending lower diagnostic thresholds [32]. The low degree of accuracy and precision of measuring BP in a clinic setting makes it more appropriate to have criteria for the diagnosis of OH on clinic readings. However, ABPM is not subject to the level of unreliability recognised with clinic BP measurement and the value of such criteria is yet to be established for ABPM [53]. For the purposes of space, we chose not to investigate the difference between SBP and DBP orthostatic falls.

Although there was no significant difference in the use of antihypertensives between those with and without OH, data was not collected on the number and type of antihypertensives being taken by each patient. Controlling for the use of vasodilator medications, which may antagonise the vasoconstrictor stimuli activated by baroreceptors, would be useful in future studies.

Although carotid-femoral PWV measures the intrinsic stiffness of the aorta, there is a component of muscular artery in the arterial tree which may be subject to neurogenic influences, representing a potential confounder.

Conclusions

Aortic stiffness and central systolic BP are independently associated with ambulatory orthostatic SBP fall in patients with CKD 3 and 4. Our results build on previous research in this area and together appear to suggest that aortic stiffness may be an independent risk factor for ambulatory orthostatic SBP fall in CKD patients, with measures of central arterial pressures offering a more useful tool than peripheral measures in assessing risk in this patient group. This has important implications for

the high cardiovascular morbidity and mortality in CKD patients. The next step would be a prospective study to explore the relationship between arterial stiffness and incident orthostatic hypotension, as well as further research into the clinical correlations of orthostatic hypotension in CKD patients.

Acknowledgements: none

Conflicts of interest: none

Author Contributions: F Kirkham – study design and conception, acquisition of data, analysis, interpretation, manuscript preparation

P Rankin – study design and conception, acquisition of data, analysis, interpretation, manuscript preparation

N Parekh – study design and conception, acquisition of data, analysis, interpretation, manuscript preparation

S Holt – study design and conception, acquisition of data, manuscript preparation

C Rajkumar – study design and conception, acquisition of data, analysis, interpretation, manuscript preparation

Sponsor's Role: none

References

1. Freeman R. Neurogenic orthostatic hypotension. N Engl J Med 2008; 358:615-24
2. Xin W, Lin Z, Li X. Orthostatic hypotension and the risk of congestive heart failure: A meta-analysis of prospective cohort studies. PLoS ONE 2013;8(5):e63169
3. Franceschini N, Rose KM, Astor BC, et al. Orthostatic hypotension and incident chronic kidney disease: the atherosclerosis risk in communities study. Hypertension. 2010;56(6):1054-9
4. Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. Heart (published online first 22 July 2013) doi:10.1136/heartjnl-2013-304121
5. Angelousi A, Girerd N, Benetos A, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J Hypertens. 2014;32(8):1562-71; discussion 71.
6. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res. 2008;18 Suppl 1:8-13.
7. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.
8. Valbusa F, Labat C, Salvi P, et al. Orthostatic hypotension in very old subject living in nursing homes: the PARTAGE study. *J Hypertens* 2012; **30**:53–60.

9. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005;111(25):3384-90.
10. Bulpitt CJ, Cameron JD, Rajkumar C, et al. The effect of age on vascular compliance in man: which are the appropriate measures? J Hum Hypertens. 1999;13(11):753-8.
11. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2013; S0735–1097(13) 0597–3
12. Mattace-Raso FU, van den Meiracker AH, Bos WJ, et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. J Hypertens. 2007;25(7):1421-6.
13. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, et al. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. J Hypertens. 2006;24(2):339-44.
14. Protogerou AD, Stergiou GS, Lourida P, et al. Arterial stiffness and orthostatic blood pressure changes in untreated and treated hypertensive subjects. J Am Soc Hypertens. 2008;2(5):372-7.
15. Sharman JE, Marwick TH, Gilroy D, et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. Hypertension. 2013;62(6):1138-45.

16. Almutary H, Bonner A, Douglas C. Symptom burden in chronic kidney disease: a review of recent literature. Journal of Renal Care 2013;39(3):140-150
17. Temmar M, Liabeuf S, Renard C, et al. Pulse wave velocity and vascular calcification at different stages of chronic kidney disease. J Hypertens. 2010;28(1):163-9.
18. Chue CD, Townend JN, Steeds RP, et al. Arterial stiffness in chronic kidney disease: causes and consequences. Heart. 2010;96(11):817-23.
19. Roumelioti ME, Buysse DJ, Sanders MH, et al. Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis. Clin J Am Soc Nephrol. 2011;6(5):986-94.
20. Bhat S, Hegde S, Szpunar S. Orthostatic Blood Pressure (BP) Variance in a Chronic Kidney Disease (CKD) Clinic [abstract]. Journal of Clinical Hypertension 2013;15 Suppl 1 :72
21. Sasaki O, Nakahama H, Nakamura S, et al. Orthostatic hypotension at the introductory phase of haemodialysis predicts all-cause mortality. Nephrol Dial Transplant. 2005;20(2):377-81.
22. Liu K, Wang S, Wan S, et al. Arterial Stiffness, Central Pulsatile Hemodynamic Load, and Orthostatic Hypotension. J Clin Hypertens (Greenwich). 2016;18(7):655-62.
23. O'Brien E, Asmar R, Beilin L, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertens. 2005;23(4):697-701.

24. Ejaz AA, Kazory A, Heinig ME. 24-Hour blood pressure monitoring in the evaluation of supine hypertension and orthostatic hypotension. J Clin Hypertens 2007;9:952-955
25. Minutolo R, Borrelli S, Scigliano R, et al. Prevalence and clinical correlates of white coat hypertension in chronic kidney disease. Nephrol Dial Transplant. 2007;22(8):2217-23.
26. Stuebner E, Vichayanrat E, Low DA, et al. Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. Front Neurol. 2013;4:49
27. Mojón A, Ayala DE, Piñeiro L, et al. Comparison of ambulatory blood pressure parameters of hypertensive patients with and without chronic kidney disease. Chronobiol Int. 2013;30(1-2):145-58.
28. Ford ML, Tomlinson LA, Chapman TP, et al. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension. 2010;55(5):1110-5.
29. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med 2005;5:635-642
30. Sever P. New hypertension guidelines from the National Institute for Health and Clinical Excellence and the British Hypertension Society. J Renin Angiotensin Aldosterone Syst 2006;7:61-63.
31. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27(21):2588-605.

32. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation. 1998;98(21):2290-5.
33. Naschitz JE, Rosner Itzhak. Orthostatic hypotension: framework of the syndrome. Postgrad Med J 2007;83:568-574
34. Rose KM, Tyroler HA, Nardo CJ, et al. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. Am J Hypertens. 2000;13(6 Pt 1):571-8.
35. Boddaert J, Tamim H, Verny M, et al. Arterial stiffness is associated with orthostatic hypotension in elderly subjects with history of falls. J Am Geriatr Soc. 2004;52(4):568-72.
36. Luukinen H, Koski K, Laippala P, et al. Prognosis of diastolic and systolic orthostatic hypotension in older persons. Arch Intern Med. 1999;159(3):273-80.
37. Applegate WB, Davis BR, Black HR, et al. Prevalence of postural hypotension at baseline in the Systolic Hypertension in the Elderly Program (SHEP) cohort. J Am Geriatr Soc. 1991;39(11):1057-64
38. Pasierski T, Pearson AC, Labovitz AJ. Pathophysiology of isolated systolic hypertension in elderly patients: Doppler echocardiographic insights. Am Heart J. 1991;122(2):528-34.
39. Boddaert J, Tamim H, Verny M, et al. Arterial stiffness is associated with orthostatic hypotension in elderly subjects with history of falls. J Am Geriatr Soc. 2004;52(4):568-72.

40. Chesterton LJ, Sigrist MK, Bennett T, et al. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. Nephrol Dial Transplant. 2005;20(6):1140-7
41. Monahan KD, Dinenno FA, Seals DR, et al. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. Am J Physiol Heart Circ Physiol. 2001;281(1):H284-9.
42. Sabbah HN. Baroreflex activation for the treatment of heart failure. Curr cardiol Rep 2012;14(3):326-333
43. Hoshide, S, Kario, K, Eguchi, K, et al. 2005. Altered aortic properties in elderly orthostatic hypertension. Hypertens. Res. 28, 15–19
44. Metzler, M, Duerr, S, Granata, R et al. 2013. Neurogenic orthostatic hypotension: Pathophysiology, evaluation, and management. J. Neurol. 260, 2212–2219
45. Joyner, M.J., Charkoudian, N., Wallin, B.G., 2010. Sympathetic Nervous System and Blood Pressure in Humans Individualized Patterns of Regulation and Their Implications 10–16
46. Januszko-Giergielewicz, B., Gromadziński, L., Dudziak, M., Dębska-Ślizień, A. Orthostatic Hypotension in Asymptomatic Patients with Chronic Kidney Disease. Medicina 2019, 55(4), 113
47. Chan, K.E., Ikizler, T.A., Gamboa, J.L, et al. Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients. Kidney Int. 2011 Nov; 80(9): 978–985.
48. Freeman R. Neurogenic orthostatic hypotension. N Engl J Med 2008; 358:615-24

49. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation. 2006;113(9):1213-25

50. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension. 2007;50(1):197-203.

51. Ohno Y, Kanno Y, Takenaka T. Central blood pressure and chronic kidney disease. World J Nephrol. 2016;5(1):90-100

52. Naschitz JE, Rosner Itzhak. Orthostatic hypotension: framework of the syndrome. Postgrad Med J 2007;83:568-574

53. Tomlinson LA, Holt SG, Leslie AR, et al. Prevalence of ambulatory hypotension in elderly patients with CKD stages 3 and 4. Nephrol Dial Transplant. 2009;24(12):3751-5.

Tables and Figures

Table 1: Characteristics of the study population

	All patients (n=146)	**No ambulatory orthostatic BP fall^{+} (n=123)**	**Ambulatory orthostatic BP fall^{+} (n=23)**	**Significance level**
Age (Years)	68.6±11.4	68.0 ± 11.5	72.2 ± 10.3	.103
Men (%)	75	76	74	.864
BMI (Kg/m^2)	29.2±5.2	29.2 ± 5.2	28.9 ± 5.2	.759
eGFR (mL/min/1.73 m^2)	32±11	31.7 ± 10.8	33.5 ± 12.2	.472
Systolic BP Clinic (mmHg)	**150±20**	**149.0* ± 19.4**	**159.0* ± 21.7**	**.027**
Diastolic BP Clinic (mmHg)	81.6±12	81.2 ± 12.0	83.7 ± 10.6	.364
Mean Arterial pressure (mmHg)	104.8 ± 13	104.0 ± 13.3	109.0 ± 11.1	.093
24hr SBP lying (mmHg)	**114.8±16.0**	**111.3*± 13.8**	**133.4*± 14.1**	**<0.0001**
24 hr SBP standing (mmHg)	125.0±13.9	124.8 ± 14.3	126.1 ± 12.4	.682
Heart Rate (beats/minute)	70.3±12.1	71.1 ± 12.2	66.0 ± 10.9	.065
Smoking History (%)	59	59	61	.836
Total Cholesterol (mmol/l)	4.4 ± 1.0	4.4 ± 1.0	4.3 ± 0.9	.735
Diabetes Mellitus (%)	21	20	26	.538

Use of antihypertensives (%)	93	94	87	.203
Cf-PWV (m/s)	**13.1±3.0**	**12.7* ± 2.6**	**15.2* ± 3.8**	**.00016**
Cr-PWV (m/s)	11.14	11.2 ± 1.8	11.0 ± 1.7	.629
Central Systolic BP (mmHg)	**137.6±20.8**	**135.7*± 20.2**	**147.5*± 21.3**	**.012**
Central Diastolic BP (mmHg)	82.7±12.0	82.5 ± 12.4	83.5 ± 10.5	.708
Aortic Augmentation Index (%)	28.6±11.0	27.9 ± 11.4	32.1 ± 7.9	.093

Values expressed as the mean ± SD, or percentage

[+] **24 hour systolic blood pressure readings**

*** Statistical significance** *P-value <0.05*

Table 2: Changes in blood pressure with posture

	Patient group	N	Mean	Std. Deviation
Mean 24h SBP postural drop	no drop	123	+ 13.5	7.0
	postural drop	23	- 7.3	6.6
Mean 24h DBP postural drop	no drop	123	+ 8.7	5.8
	postural drop	23	-0.1	5.4

Table 3: Binary logistic regression analysis

	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age	.620	.985	.929	1.045
Smoking history	.745	1.003	.984	1.023
Cholesterol	.897	.963	.543	1.707
BMI	.712	1.021	.916	1.137
eGFR	.261	1.029	.979	1.081
Anti-hypertensives	.161	.309	.060	1.598
Mean cfPWV	**.001**	**1.459**	**1.159**	**1.835**
Diabetes	.970	1.028	.248	4.255
Central SBP	**.024**	**1.032**	**1.004**	**1.060**
Gender	.697	.781	.225	2.709
Constant	.016	.000		

Table 4: Binary logistic regression analysis including baseline clinic SBP

	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age	0.758	0.991	0.933	1.051
Smoking history	0.700	1.004	0.984	1.024
Cholesterol	0.839	1.063	0.589	1.918
BMI	0.461	1.044	0.931	1.171
eGFR	0.219	1.033	0.981	1.087
Anti-hypertensives	0.129	3.773	0.680	20.942
Mean cfPWV	**0.001**	**1.508**	**1.189**	**1.911**
Diabetes	0.707	0.756	0.176	3.248
Central SBP	**0.036**	**1.131**	**1.008**	**1.269**
Gender	0.838	1.141	0.323	4.035
Baseline clinic SBP	0.101	0.909	0.811	1.019
Constant	0.005	0.000		

Figure 1: Box and Whisker Plots of cf-PWV and Central SBP in patients with and without ambulatory orthostatic BP fall