Published in final edited form as:
Hypertension. 2010 December ; 56(6): 1054–1059. doi:10.1161/HYPERTENSIONAHA.110.156380.

Orthostatic hypotension is associated with incident chronic kidney disease: The Atherosclerosis Risk In Communities Study

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Abstract

Background—Orthostatic hypotension (OH) is associated with increased rates of cardiovascular disease and mortality, particularly among middle-aged persons. However, little is known about the association of OH with chronic kidney disease (CKD).

Methods and Results—Postural changes in blood pressure (BP) were estimated using the difference between the average of multiple supine and standing BP measurements. OH was defined as a decrease in systolic BP ≥ 20 mm Hg, or a decrease in diastolic BP ≥ 10 mm Hg upon standing. Incident CKD was defined as an increase in serum creatinine ≥ 0.4 mg/dL at the 3- or 9-year follow-up visits, or a hospitalization (discharge) or death due to CKD. Urinary albumin-to-creatinine ratio (ACR, mg/g) was obtained at visit 4 and used to define albuminuria (ACR≥ 30 mg/g). The association between OH and incident CKD and between OH and categories of albuminuria were modeled using adjusted Cox proportional hazard models and logistic regression, respectively. Among 12,593 individuals, 1,019 developed CKD (3.9 cases/1,000 person-years) over a mean of 16 years. A significantly increased risk of CKD was observed among individuals with OH compared to those without OH after adjustment (hazard ratio 1.67, 95% confidence interval, 1.36, 2.06). OH was associated with increased risk of albuminuria (OR 1.66, 95% CI 1.21, 2.29).

Conclusions—These findings suggest that OH increases the risk of CKD in middle-aged persons.

Multiple physiologic mechanisms are activated in response to gravitational pooling of blood, reduced venous return and reduced cardiac output. The autonomic nervous system, particularly the sympathetic nervous system, has an important role in the short-term regulation of blood pressure (BP).[1] Individuals with autonomic dysfunction are unable to regulate BP in response to postural changes. Orthostatic hypotension (OH), a manifestation of autonomic dysfunction, is associated with incident hypertension [2], coronary heart disease [3] , stroke [4] and all-cause mortality [5] in middle-aged persons.

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Disclosures: None

Orthostatic hypotension is usually associated with supine hypertension [6, 7] but the role of OH on end-organ damage has not been studied. Elevated BP is a strong independent risk factor for end-stage renal disease (ESRD)[8-10], development of CKD [11-14] and albuminuria. [15] Hypertension accounts for one third of the cases of ESRD. [16] However, it is currently unknown if CKD is a cause or consequence of hypertension or if they both arise from a common substrate.

Recent studies have shown an association of increased sympathetic activation in individuals with CKD. [17] There is also some evidence for increased vascular adrenergic vasoconstriction and decreased vasodilation in normotensive black men compared to whites. [18] African Americans have a higher incidence and faster progression of CKD than Caucasians. [19] The hemodynamic response to orthostasis may reflect individual differences in vascular reactivity or sympathetic activity that could contribute to kidney damage. However, the role of autonomic dysfunction on incident CKD is unknown.

The purpose of the current analysis is to examine the association between OH and CKD in the population-based and prospective study of African-American and white participants of the Atherosclerosis Risk in Communities (ARIC) study. We hypothesize that OH is associated with the development of incident CKD and that this association differs by race and baseline hypertension.

Methods

Study population

The ARIC study is a multi-center prospective study of atherosclerosis in a bi-racial population. Individuals aged 45-64 years were recruited from 4 communities: Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); suburban areas of Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals participated in the baseline examination in 1987-1989, with triennial follow-up examinations in 1990-1992, 1993-1995, and 1996-1998. This study was approved by the Institutional Review Board at each participating institution. All subjects provided written informed consent to participate in the main study.

Study variables and outcome definitions

Orthostatic BP measurements were taken during the baseline ARIC visit (1987-1989) using a Dinamap 1846 SX oscillometric device, which has high within-subject reliability and is comparable to Doppler ultrasound BP measurement. [20] Following 20 minutes of supine rest, the participant was instructed on how to change positions. Automated supine BP measurements were taken approximately every 30 seconds for two minutes. As participants stood up, a standing BP measurement was taken. Measurements were repeated during the first two minutes after standing. Because BP restabilization occurs during the first 30 seconds after standing [21], BP change was defined as the difference between the average of the standing and the supine BP measurements, excluding the first standing measurement. OH was defined as a decrease in systolic BP (SBP) ≥ 20 mm Hg or a decrease in diastolic BP (DBP) ≥ 10 mm Hg upon standing. [22] Creatinine in serum (collected at baseline and visit 2) and plasma (collected at visit 4) was measured by a modified kinetic Jaffe reaction. [23] Serum (or plasma) creatinine concentration was corrected for inter-laboratory differences and calibrated with Cleveland Clinic measurement standards by subtraction of 0.24 mg/dl from baseline and year 3 measurements and by addition of 0.18 mg/dl to year 9 measurements as previously described. [24, 25]

An untimed urine sample was collected during the visit 4 (1996-1998) clinical examination. Urinary albumin was measured by a nephelometric method either on the Dade Behring

BN100 (assay sensitivity, 2.0 mg/L) or on the Beckman Immage Nephelometer and urinary creatinine levels were measured using the Jaffe method. The urinary albumin-to-creatinine ratio (ACR, mg/g) was used in the analyses.

Resting, seated BPs and heart rate were measured using a random-zero sphygmomanometer, and the average of the second and third BP measures was used in analyses. Hypertension was defined as a SBP/DBP ≥ 140/90 mmHg or reported use of anti-hypertensive medications during the previous two weeks. Type 2 diabetes was defined by a fasting plasma glucose level of at least 7.0 mmol/L, nonfasting glucose levels of at least 11.1 mmol/L, current use of medications prescribed to treat diabetes, or a positive response to the question “Has a doctor ever told you that you had diabetes?”. Cigarette smoking and alcohol intake were assessed using a questionnaire. Anthropometric measures were obtained during each clinic visit. A list of medications was verified by bottle inspection.

Carotid artery intima media thickness (cIMT), an index of generalized atherosclerosis, was determined by high-resolution B-mode ultrasound as previously described. [26, 27] The reliability coefficient for mean carotid IMT was 0.67, estimated from repeat measurements at three visits, 7–14 days apart in 36 volunteers from each of the four ARIC field centers. [28]

Incident CKD cases were defined as an increase in serum creatinine levels of at least 0.4 mg/dl above baseline (twice the minimum within-person detectable difference in serum creatinine [29] or a hospitalization discharge or death coded for CKD (including cases of ESRD, defined as dialysis or transplant, and death due to kidney failure). [24, 2530] ESRD was defined by renal replacement by dialysis or a kidney transplant. Non-cases were censored at the earlier of the date of last contact (or date of non-CKD death) or 12/31/04. eGFR was calculated using the simplified Modification of Diet in Renal Disease equation (MDRD). [31]

$$GFR = 186.3 \times (\text{serum creatinine level})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

Microalbuminuria was defined as an ACR 30-299 mg/g and macroalbuminuria was defined as an ACR≥ 300 mg/g.

We excluded individuals with ethnicity other than African American or white, African American individuals from Minneapolis (n=12) and Washington County (n=26) and individuals without creatinine measures at baseline (n=149), those with CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) at baseline (n = 459). In addition, we excluded individuals with missing data on orthostatic measures and covariates including hypertension and diabetes status. Therefore, a total of 12,593 individuals contributed to this analysis.

Statistical analysis

For descriptive analyses, means, standard deviation and frequencies were measured, as appropriate. We used t-tests or Pearson's chi-square to compare individuals with and without OH. Overall and race-specific incidence rates of CKD and ESRD per 1,000 person-years were estimated relying on the Poisson distribution by dividing the number of events by person-time at risk. The association between OH and incident CKD was modeled using Cox proportional hazards (PH) models. The PH assumptions were tested by comparing estimated −ln(−ln) survivor curves of those with and without OH. We report hazard ratios (HR) and 95% confidence intervals (CI). Multivariate models adjusted for age (centered at 54 years), sex, race, type 2 diabetes, resting systolic SBP, current smoking and alcohol intake, body mass index (BMI), resting heart rate, and use of hypertensive medications (Model 1). We also performed sensitivity analyses excluding individuals using medications known to be

associated with OH (tricyclic antidepressants, benzodiazepines, phenothiazines, n=965) (Model 2).

We tested the a priori hypothesis of effect measure modification by race/ethnicity and baseline hypertension using interaction terms and the likelihood ratio test (LRT). The likelihood estimate from the model with interaction terms was compared to the model without interaction terms using an alpha=0.10. In addition, we performed analyses excluding individuals with baseline hypertension (n=4227) while adjusting for age, sex, race, resting systolic blood pressure, resting heart rate, type 2 diabetes, BMI, and current smoking (Model 3). Lastly, we performed analysis adjusting for measures of generalized atherosclerosis (cIMT) (Model 4).

Using available urine data from visit 4, we studied the association of OH with micro- and macroalbuminuria using logistic regression, while adjusting for age, sex, center, race, type 2 diabetes, resting systolic BP, current smoking and alcohol intake, BMI, resting heart rate and use of hypertensive medications. We also tested for interactions with hypertension and race as described above.

Results

The participant characteristics, overall and by OH status, are displayed in Table 1. The mean age of individuals was 54 years, 45% were male and 26% were African Americans. Thirty-four percent had hypertension, 29% used medication to control BP, 11% had type 2 diabetes, and 9% reported using other medications associated with OH. OH was present in 604 (5%) of participants. As previously reported, individuals with OH were more likely to be older, African-American, smokers and have co-morbidities (hypertension and type 2 diabetes) than those without OH but less likely to report drinking alcohol (Table 1).

Over a mean follow up of 16 years, 1,019 (8.1%) individuals developed CKD (3.9 cases/ 1,000 person-years) (Table 2), of which 116 (0.9%) developed ESRD. The incidence of CKD was markedly higher among those with OH (10.4 per 1000 person-years) than among those without OH (3.7 per 1000 person-years) (Table 2). The overall rates of ESRD were considerably low in the ARIC study (0.27 per 1000 person-year, 95% CI 0.19, 0.39).

The overall and OH-stratified incident rates of CKD were higher in African-Americans compared to whites (Table 2). In multivariable analysis, we did not identify significant interactions by race (p=0.48) or hypertension (p=0.50). Thus, overall models are presented. Individuals with OH had a 67% increased hazard of CKD compared to those without OH (Model 1, Table 3). OH was not associated with ESRD (HR 1.00, 95% CI 0.997, 1.003), but the number of events was small.

After excluding 965 individuals using drugs that could affect OH other than anti-hypertensive agents (Model 2, Table 3), the risk of CKD among those with OH was similar and still elevated (HR 1.81). A stronger association was noted when we repeated analyses in the subset of participants without hypertension at baseline (Model 3, Table 3), with a 2.2-fold increased hazard of CKD for individuals with OH compared to those without it. Adjusting for baseline cIMT measures did not change the association between OH and CKD (Model 4, Table 3).

Among 9,249 individuals with available urine ACR at Visit 4 and complete data on risk factors, 580 had microalbuminuria and 148 had macroalbuminuria. OH was associated with increased risk of albuminuria (micro and macro) (OR 1.66, 95% CI 1.21, 2.29, n=9,249) after adjustments for age, sex, race, systolic BP, hypertension treatment, BMI, smoking, drinking, HDL, LDL and baseline heart rate. In adjusted analyses, the interactions of race

and baseline hypertension with OH on increased CKD risk were not significant (p=0.99 for both interactions). After exclusion of individuals with hypertension at visit 1, OH was associated with 76% increased risk of albuminuria (95% CI, 1.05, 2.96, n=6,472).

Discussion

OH is associated with incident hypertension [2], one of the most common causes of CKD, and CVD events [3, 32] in population studies of middle age persons. In our study, OH was independently associated with an increased risk of incident CKD and presence of increased albuminuria at follow up. Individuals with OH more often had baseline hypertension but the associations of OH with CKD were independent of BP and remained strong after excluding individuals with baseline hypertension. Hypertension is a risk factor for CKD but BP also increases as a consequence of developing CKD. Because OH precedes both development of CKD and hypertension in the ARIC study [2], our findings suggest that both outcomes may be secondary to the same disease process. Therefore, autonomic dysfunction may be causally related to development of hypertension and to target organ damage to the kidneys.

Conditions affecting autonomic nervous system response to hemodynamic changes may contribute to CKD in susceptible individuals. These conditions may affect the autonomic innervation in large vessels and in renal microcirculation and consequently may affect kidney perfusion or the compensatory pathways triggered by changes in kidney perfusion during orthostasis. Decreased kidney perfusion and intraglomerular pressure due to impaired glomerular autoregulation may be causally linked to the development of CKD. In familial dysautonomia, a condition associated with severe dysfunctional autonomic nervous system, a large proportion of affected individuals develop CKD and kidney disease occurs at early ages. [33] These individuals lack proteinuria. Renal biopsy usually shows glomerulosclerosis and tubular atrophy suggesting a hemodynamic cause for CKD. The association with microalbuminuria (which constitute most of the cases of increased albuminuria in our study) has not been investigated in individuals with familial dysautonomia.

Although the incidence of CKD was higher in African Americans than whites, the increased risk of CKD related to OH due to a decline in renal function or presence of increased albuminuria did not vary by race, suggesting that similar mechanisms are involved in promoting kidney damage in both whites and African-Americans presenting with OH. Therefore, OH does not appear to explain the racial disparities in CKD.

Atherosclerosis and CVD risk factors could play a role in the increased risk of CKD due to OH in middle aged individuals through, for example, stiff arterial vasculature leading to impaired renal perfusion and auto-regulation. However, the analysis adjusting for CVD risk factors including diabetes, hyperlipidemia, blood pressure, smoking, and measures of atherosclerosis, i.e., baseline cIMT, did not change the strength of the association of OH and incident CKD.

To our knowledge, the association among OH and increased albuminuria has not been previously reported. Similar to findings of analysis of eGFR decline, increased albuminuria associated with OH was independent of baseline hypertension and CVD risk factors. These findings in middle age adults of the ARIC study (mostly asymptomatic for OH) support the hypothesis of causal mechanisms related to postural hemostasis contributing to kidney damage.

Our study has several strengths including the availability of a large population-based cohort of middle age individuals with standardized measures of orthostasis at baseline and incident data on kidney function and albuminuria at follow up. Some limitations are related to the definition of CKD events which relies only on measures of kidney function and not kidney

damage/albuminuria (since ACR was only measured at visit 4) which could have underestimated the strength of the associations. Most of the CKD events occurred due to increased serum creatinine over 3 clinic visits but some cases were obtained from hospitalization discharge or death coded for CKD and therefore misclassification of some events due to acute instead CKD may have occurred. In addition, slow progressing kidney disease may not have been identified in individuals with low muscle mass such as the elderly and women in whom serum creatinine may not raise to levels above 0.4 mg/dl with reductions of GFR.

Conclusions

OH is associated with reduced kidney function and albuminuria among middle age individuals. Because OH also precedes hypertension in this population, autonomic dysfunction may be causally related to development of both hypertension and damage in kidneys.

Acknowledgments

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. Dr. Astor was supported in part by R01-DK-076770 from the National Institutes of Diabetes and Digestive and Kidney Diseases. Dr Franceschini is supported in part by a grant from the American Heart Association (AHA #0675001N). The authors thank the staff and participants of the ARIC study for their important contributions.

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Table 1
Descriptive characteristics of individuals by presence or absence of OH

	Overall (N=12,593)	OH present (N=604)	OH absent (N=11,989)	P-value
Mean age, years	54.0 (5.7)	57.0 (5.2)	53.8 (5.6)	<0.0001
Male sex, %	5,609 (45)	280 (46)	5,329 (44)	0.36
African-American race, %	3,311 (26)	195 (32)	3,116 (26)	<0.0001
Current drinking, %	7,143 (57)	278 (46)	6,865 (57)	<0.0001
Current smoking, %	3,307 (26)	201 (33)	3,106 (26)	<0.0001
Mean body mass index, kg/m^2	27.6 (5.3)	27.7 (6.0)	27.6 (5.3)	0.59
LDL, mg/dL	136.9 (38.9)	145.9 (39.9)	136.8 (38.8)	<0.0001
HDL, mg/dL	51.7 (17.3)	50.5 (16.6)	51.7 (17.3)	0.10
Type 2 diabetes, %	1,427 (11)	120 (20)	1,307 (11)	<0.0001
Hypertension, %	4,227 (34)	344 (57)	3,883 (32)	<0.0001
Anti-hypertension medication use, %	3,669 (29)	303 (50)	3,366 (28)	<0.0001
Mean resting SBP, mm Hg	121.0 (18.7)	130.1 (22.0)	120.5 (18.4)	<0.0001
Mean resting heart rate, beats/minute	66.6 (10.2)	68.7 (12.6)	66.5 (10.0)	<0.0001
Tricyclic antidepressant medication use, %	281 (2)	26 (<1)	255 (2)	
Benzodiazepines medication use, %	712 (6)	60 (<1)	625 (5)	
Phenothiazine medication use, %	54 (<1)	4 (<1)	50 (<1)	
Other medication use, %*	52 (<1)	47 (<1)	5 (<1)	
Carotid IMT, mm	0.72 (0.18)	0.82 (0.23)	0.72 (0.18)	<0.0001

*Includes thioxanthenes, butyrophenones, antiparkisonian anticholinergic drugs, antiparkinsonian dopaminergic drugs, MAO monoamino-oxidase inhibitors. Some individuals were taking for than one medication.

SBP= systolic blood pressure; OH= orthostatic hypotension; IMT= intima media thickness

Table 2

Incidence rates and age and sex cumulative incidences of chronic kidney disease overall and by race

	Overall		African American		White	
	Events/Total	**Incident CKD* (1,000 py)**	**Events/Total**	**Incident CKD† (1,000 py)**	**Events/Total**	**Incident CKD† (1,000 py)**
Overall	1,019/12,593	3.87 (3.50, 4.29)	416/3,311	8.8 (7.2, 10.0)	603/9,282	3.8 (3.4, 4.2)
OH present	104/604	10.41 (7.37, 14.70)	46/195	27.8 (19.5, 39.7)	58/409	8.1 (5.2, 12.8)
OH absent	915/11,989	3.65 (3.28, 4.06)	370/3,116	8.0 (7.0, 9.2)	545/8,873	3.6 (3.2, 4.1)

*adjusted for a mean age of 54 years, age and race

†adjusted for a mean age 54 years and sex.

OH=orthostatic hypotension; CKD= chronic kidney disease; ESRD= end-stage renal disease; py= person-year

Table 3

Hazard ratios (95% CI) for chronic kidney disease associated with orthostatic hypotension among participants of the Atherosclerosis Risk in Communities study

	Model 1† HR (95% CI)	Model 2* HR (95% CI)	Model 3† HR (95% CI)	Model 4‡
Number	12,507	11,542	8,325	11,662
OH present	1.67 (1.36, 2.06)	1.81(1.44, 2.27)	2.27 (1.57, 3.26)	1.67 (1.33, 2.09)
OH absent	1.00	1.00	1.00	1.00

P for interaction by race = 0.48

†Adjusted for age, sex, race, resting systolic blood pressure, resting heart rate, type 2 diabetes, body mass index, current smoking and use of anti-hypertensive medications.

*Excluding individuals taking other medications that can lower blood pressure (tricyclic antidepressant, benzodiazepines, phenothiazine and others, see Table 1) and adjusted for age, sex, race, resting systolic blood pressure, resting heart rate, type 2 diabetes, body mass index, current smoking, and use of anti-hypertensive medications

†Excluding prevalent hypertensive individuals and adjusted for age, sex, race, resting systolic blood pressure, resting heart rate, type 2 diabetes, body mass index, and current smoking.

‡Adjusting for age, sex, race, resting systolic blood pressure, resting heart rate, type 2 diabetes, body mass index, current smoking and use of anti-hypertensive medications and cIMT measures taken at visit 1.

OH=orthostatic hypotension; HR=hazard ratios; CI=confidence interval

Hypertension. Author manuscript; available in PMC 2011 December 1.