Albuminuria and masked uncontrolled hypertension in chronic kidney disease

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ABSTRACT

Background. Masked uncontrolled hypertension (MUCH) is associated with greater target organ damage such as left ventricular hypertrophy, increased arterial stiffness and albuminuria. Whether MUCH independently associates with greater cardiovascular end-organ damage or kidney damage is unclear. The objective of this study was to assess the strength of the relationship of MUCH (awake ambulatory blood pressure ≥135/85 mmHg and clinic blood pressure <140/90 mmHg) with target organ damage.

Methods. In a cross-sectional study at a veterans’ administration medical center, clinically normotensive veterans without chronic kidney disease (CKD) (n = 29) and 287 patients with...
INTRODUCTION

Cardiovascular disease frequently coexists with chronic kidney disease (CKD) [1]. In the general population, it has long been recognized that elevated blood pressure (BP) at home but normal BP in the clinic—masked hypertension—is associated with arterial and ventricular damage [2]. It is now becoming increasingly apparent that among treated hypertensives, elevated BP at home but normal BP in the clinic—masked uncontrolled hypertension (MUCH)—is associated with arterial and ventricular damage [3–6]. Furthermore, MUCH is also associated with lower estimated glomerular filtration rate (eGFR) and greater proteinuria [3, 4, 6, 7]. What is less clear is whether MUCH is associated with greater arterial, ventricular or renal damage. In other words, whether MUCH is associated with greater end-organ damage on the cardiovascular system or the kidney is unclear.

The importance of this question lies in the fact that elevated hypertension outside the office may be due to cardiovascular damage which would be reflected by increased left ventricular mass or increased arterial stiffness. On the other hand, it could be related more strongly to renal damage as assessed by albuminuria. If MUCH is associated more strongly with renal damage, it would suggest that renal mechanisms may be operative in the genesis of MUCH. This would provide clues to the understanding of MUCH and where efforts should be directed to understand its pathogenesis; the pathogenesis of MUCH is largely unknown.

This study explores the strength of the relationship of MUCH with target organ damage. Target organ damage was evaluated by measuring echocardiographic left ventricular mass index (LVMI), aortic pulse wave velocity (PWV) and 24-h urine for albuminuria.

MATERIALS AND METHODS

Details regarding the clinical characteristics of this cohort have been previously published [8]. Briefly, this was a prospective study of CKD patients stages 2 through 4 (eGFR defined using the modification of diet in renal disease equation <90 mL/min/1.73 m² but >15 mL/min/1.73 m²). For those with stage 2 CKD, albuminuria (A2 or >300 mg/g creatinine) was required for inclusion in the cohort. Those with an initial clinic BP of 140/90 mmHg or less were considered eligible and studied further. However, about 10% of people with a single clinic BP of ≤140/90 mmHg were found to be hypertensive on further evaluation and were not excluded.

Healthy control veterans were selected to participate if they did not have hypertension, diabetes, prior history of cardiovascular disease, CKD and were not current smokers.

After obtaining a clinical history, performing a physical examination and obtaining basic laboratory tests, measurements of BP in the clinic (average of three visits) and by 24-h ambulatory monitoring were performed as reported earlier.

Classification of hypertension

Masked uncontrolled hypertension (MUCH) was defined as controlled clinic BP (<140/90 mmHg on average of three clinic visits by oscillometric BP measurement) but elevated ambulatory BP [9–11]. Elevated ambulatory BP was defined as elevated daytime (≥135/85 mmHg) BP. Those with clinic and daytime ambulatory BP below thresholds were classified as controlled hypertension (CH) and those with both above threshold were defined as uncontrolled hypertension (UCH). To define daytime and night-time, we used patient diaries.

The assessment of target organ damage was as follows.

Assessment of albuminuria

During the time of 24-h ambulatory BP monitoring, participants were asked to collect urine over the 24-h period that was assayed for urine albumin by an immunoassay and urine creatinine using standard methods in the hospital laboratory. Results are expressed as the ratio of albumin to creatinine (mg/mg) and to approximate normal distribution and facilitate interpretation of the ratio was log2-transformed prior to analysis.

Left ventricular mass measurements

Two-dimensional guided M-mode echocardiograms were performed by an accredited technician during one of the study visits by oscillometric BP measurement. Comparisons were performed by one of the authors (RAF) to ensure quality and accuracy of measurements. LVMI was calculated in milligrams per square meter (mg/m²) as follows:

\[ \text{LVMI} = \frac{4}{3} \pi \left( \frac{LVT^2 - LVP^2}{LVT} \right) \]

Where LVT is left ventricular thickness and LVP is left ventricular posterior wall thickness. PWV was measured in meters per second (m/s) and was calculated as follows:

\[ \text{PWV} = \frac{d}{t} \]

Where d is the distance between the two ends of the aorta and t is the time delay between the two waves as measured by pulse wave transmission through the aorta.

Results

Compared to that of controls, LVMI was higher by 21.8 g/m² (CI, 4.0–39.7 g/m²) in CH, 27.9 (CI, 8–47.8) in MUCH and 39.5 (CI, 15.7–63.2) in UCH (P < 0.01 for group differences, P < 0.01 for linear trend). Although differences persisted after adjustment for age, sex and race, they lost significance after adjustments for cardiovascular risk factors and their treatment. Compared to that of controls, PWV was different among CH, MUCH and UCH (P = 0.04 for group differences, P = 0.02 for linear trend). However, differences lost significance after adjustments for age, sex and race. Compared to that of controls, log2 UACR was higher by 2.40 mg/mg (CI, 1.28–3.52) in CH, 4.94 (CI, 3.70–6.18) in MUCH and 6.01 (CI, 4.49–7.53) in UCH (P < 0.0001 for group difference, P < 0.0001 for linear trend). Differences persisted after adjustment for age, sex and race, cardiovascular risk factors and their treatment and cardiovascular disease (P < 0.0001 for group difference, P < 0.0001 for linear trend).

Conclusions.

MUCH is more strongly related to albuminuria compared with cardiovascular damage as assessed by left ventricular mass and PWV. A graded and an independent relationship of blood pressure classification status with albuminuria is consistent with the hypothesis that renal mechanisms may be more important than cardiovascular disease in mediating the pathogenesis of MUCH.

Keywords: albuminuria, chronic kidney disease, left ventricular mass, masked hypertension, pulse wave velocity
visits (on the same day or at most within 30 days of ambulatory BP measurement) with a digital cardiac ultrasound machine (Cypress Acuson, Siemens Medical). The protocol specified recording of at least 12 cycles of two-dimensional parasternal long- and short-axis left ventricular (LV) views with optimal orientation of the cursor beam used to derive additional M-mode recordings. Each patient underwent six M-mode measurements of interventricular septal thickness in diastole (IVSTd), LV internal diameter in diastole (LVIDd) and systole (LVIDs), LV posterior wall thickness in diastole (LVPWd) and systole (LVPWs) and left atrial (LA) diameter using standards of the American Society of Echocardiography [12]. LV mass was calculated with a previously validated formula [13]:

$$\text{LVmass (g)} = 0.832 \times \left( \frac{(\text{IVSTd} + \text{LVIDd} + \text{LVPWd})^3}{\text{LVIDd}^3} \right) + 0.60$$

**PWV measurements**

Arterial stiffness is best measured using the aortic PWV [14]. Accordingly, arterial stiffness was assessed by measuring aortic PWV through direct visualization of the descending aorta with the use of an echo-Doppler technique (Acuson Cypress, Siemens Medical). Flow pulse was recorded by continuous Doppler from the root of the left subclavian artery and just proximal to the bifurcation of the abdominal aorta with simultaneous electrocardiographic recording [15]. The length of the descending aorta was estimated by measuring the body surface distance from the suprasternal notch to the recording site of the aortic signal (near the umbilicus). Time elapsed from the peak of the R wave to the foot of the systolic impulse was recorded over six beats. The length of the descending aorta divided by the difference between transit times was calculated to yield the aortic PWV [15].

**Statistical analysis**

Baseline characteristics among groups were compared by ANOVA for continuous variables and χ² tests for discrete variables such as sex, race, tobacco use and comorbidities.

To detect the association of BP classification status with target organ damage, unadjusted analyses were performed using linear regression using BP classification as indicator variables. The reference group was healthy controls. The P-value reported is the test of the hypothesis that there is no association of BP classification status with target organ damage. Adjustments were performed in model 1 for age, sex and race and in model 2 for all variables in model 1 and cardiovascular risk factors and their treatment including tobacco use, body mass index, diabetes mellitus, serum cholesterol, number of antihypertensive drugs used, angiotensin–converting enzyme (ACE) or angiotensin receptor blocker (ARB) use, calcium channel blocker (CCB) use, beta blocker use, diuretic use, statin use and aspirin use and model 3 was further adjusted for cardiovascular disease such as myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, peripheral vascular disease and congestive heart failure. An analysis for the presence of a linear trend in coefficients from controls to CH, MUCH and UCH was performed using orthogonal polynomials and reported as P trend in Figures 2 and 3.

All statistical analyses were done with Stata 14.0 (Stata Corp, College Station, TX, USA). Nominal level of statistical significance was taken as two-sided P of 0.05.

**RESULTS**

Baseline characteristics of participants are given in Table 1. The control group of 29 veterans did not have CKD, hypertension, diabetes or cardiovascular disease. The CKD group of 287 veterans predominantly had CH, 23% had MUCH and 9% had UCH. As expected of a veteran population, participants were older, mostly white men, and two-thirds were past smokers. Notable was a high prevalence of diabetes mellitus and cardiovascular disease ascertained by a review of medical records. The average eGFR was 44 ml/min/1.73 m² and was similar among CKD groups. All but four participants were receiving antihypertensive drugs for BP control and the average number of antihypertensive drugs used was 3.1. As expected, BP both in the clinic and by ambulatory recordings was progressively higher with progressive increases in hypertension severity.

The distribution of markers of target organ damage is shown as box plots in Figure 1. Slight differences in medians are seen for PWV, greater for LVMI, and the greatest for log of the 24-h urine albumin/creatinine ratios. The distribution of severity of albuminuria is shown as an inset in panel C. Very high albuminuria (>300 mg/g creatinine, A2) was present in none of the controls, 11% of CH, 44% of MUCH and 48% of UCH. In contrast, normoalbuminuria (<30 mg/g creatinine, A0) was present in 96% of controls, 61% of CH, 33% of MUCH and 9% of UCH. The relationship between BP classification status and albuminuria was highly significant ($\chi^2 = 70.9, P < 0.0001$).

Figure 2 shows the results of progressively adjusted models for log2 urine albumin to creatinine ratio (UACR). The unadjusted model is shown first. Given that the coefficients are in log2 scale, compared with those of controls, the CH, MUCH and UCH groups are approximately 5.3-, 30.7- and 64.4-fold higher. The P-value for both among-group differences (P-value) and a linear trend (P trend) is highly significant. Model 1 is age-, sex- and race-adjusted; model 2 is further adjusted for cardiovascular risk factors and its treatment and model 3 is further adjusted for cardiovascular disease as noted in Methods. Progressive adjustment did not remove the statistical differences among groups and the linear trend remained highly significant. Further adjustment for eGFR did not remove the statistical significance among group differences ($P < 0.0001$) or the linear trend ($P < 0.0001$).

Figure 3 shows the progressive adjusted models for LVMI and PWV. In the case of LVMI, clear differences were seen in the unadjusted model and model 1, and further adjustment removed the statistical significance of the observations. In the case of PWV, only the unadjusted model was significant. Any adjustment increased the P-value to above the nominal level of significance.
That albuminuria is associated with greater ambulatory BP is now well established. We first reported this observation in a cross-sectional survey in which it was noted that the strength of the relationship between proteinuria and systolic BP followed the order: ambulatory > home > clinic [16]. Next, it was noted that even slight degrees of albuminuria were associated with an elevated ambulatory BP, independent of eGFR [17]. Large epidemiological surveys note that the odds of poorly controlled hypertension are greater in the presence of albuminuria [18]. In these surveys, eGFR does not emerge as an independent predictor of poorly controlled hypertension. Among those with CKD, after adjusting for baseline clinic BP, Minutolo et al. reported that the odds of sustained hypertension diagnosed by 24-h ambulatory BP monitoring, compared with white coat hypertension, are greater in the presence of albuminuria [19].

More recently, the Chronic Renal Insufficiency Cohort reported that those with masked hypertension have nearly 2-fold higher proteinuria compared with those with well-controlled hypertension [3].

Our study provides a strong association between MUCH and albuminuria. Furthermore, it extends the findings of the above investigations by having an age- and sex-matched group of normotensive veterans without CKD. By performing a trend analysis, it demonstrates a graded relationship among CH, MUCH and UCH and increasing severity of albuminuria even after multiple adjustments. Thus, MUCH—the prevalence of which was nearly one in four in this cohort—appears to be an intermediate phenotype that lies between those with CH and those with UCH. Our study also provided novel information regarding the type of antihypertensive agent used and the propensity for MUCH. We found that CCB use was more common in those with MUCH and diuretic use was less. This is not
widely appreciated, but it may be causally related [20]. We have previously reported that CCB use is associated with a lower clinic BP and a higher ambulatory recording [21]. This would lead to a greater propensity for masked hypertension. The reverse is the case for diuretics. We included diuretic use and CCB use in our adjusted models, but excess albuminuria with increasingly severe hypertension classification persisted. This suggests that these antihypertensive agents per se are not sufficient to account for excess albuminuria with increasingly severe hypertension.

Whether a causal link exists between albuminuria and MUCH cannot be answered by a cross-sectional investigation, but if one exists then what could be the mechanisms? It is now generally accepted that albuminuria is a marker of endothelial dysfunction [22]. Albuminuria in the nephrotic range is associated with leakage of plasmin in the urine; this serine protease can activate the epithelial sodium channel in the cortical collecting duct and aggregate hypertension [23]. On the other hand, albuminuria may simply be a marker of renal damage. If so, the increasing severity of renal damage may lead to volume expansion and impaired natriuresis that may provoke hypertension, especially outside the clinic. Damage to the renal parenchyma may lead to the accumulation of asymmetric dimethylarginine, a potent inhibitor of nitric oxide synthase. This in turn would reduce the production of the potent vasodilator nitric oxide that may further provoke hypertension [24–27] and target organ damage [28]. Accumulation of the potent vasoconstrictor endothelin [29] and lack of production of the enzyme renalase [30, 31] that breaks down catecholamines, and adrenergic activation seen even in earlier stages of CKD [32] may further provoke hypertension. Whether any of the above mechanisms are of pathophysiological importance for MUCH will require future investigations.

Whereas a direct and strong link was seen between albuminuria and MUCH, a weaker cross-sectional relationship emerged between LVMI and MUCH. Even a weaker relationship was seen between PWV and MUCH. Whereas it is now well established that MUCH is associated with LVMI in the general population [2, 33] and those with CKD [3, 4] and that MUCH is associated with arterial damage in the general population [2] and CKD [3, 34, 35], the recognition that the albuminuria–MUCH relationship is much stronger further suggests that MUCH may have a renal basis as discussed above. The fact that the relationship between BP categories and LVMI or PWV disappears after multiple adjustments suggests that other factors besides elevated BP outside the clinic may account for the target organ damage.

Limitations of the study include the following: participation in the study was restricted to veterans who are older and are predominantly men. Whether our findings apply to younger
people and women will need future studies. The study is cross-sectional in nature and can only detect associations. Whether the relationships are causal is unclear. There are several strengths to our study: our study used 24-h ambulatory blood pressure monitoring, the gold-standard method to diagnose out-of-office hypertension. Our study was prospective, and it carefully collected information on Doppler-assessed PWV, echocardiographic left ventricular mass and 24-h urine albumin collections solely for the purposes of the study. All measurements were concurrent, unlike some of the earlier reports where median time elapsed between target organ damage assessment and 24-h ambulatory BP measurement exceeded 300 days [3].
Furthermore, having a group of control age- and sex-matched veterans without CKD increased the validity of the findings. A large number of clinical characteristics were collected prospectively to facilitate adjustments in statistical models and interpretation.

In conclusion, among patients with CKD, nearly all of whom were taking antihypertensive medications, a graded relationship was found between BP categories and severity of target organ damage in general. MUCH was most strongly related to renal damage—not when assessed by eGFR—but when assessed by albuminuria. MUCH was less strongly related to LVMI and PWV. These results are consistent with the notion that kidney damage may have a central role in the pathogenesis of MUCH. Further investigations into the mechanisms centered on the renal pathogenesis of MUCH are warranted. Finally, the strong association of MUCH with albuminuria may in part explain the mechanism of the ability of albuminuria to predict adverse outcomes [36].

ACKNOWLEDGMENTS

The author thanks Maria K. Pappas for technical assistance and the participants for their time and effort. The study is supported by a grant from VA Merit Review 5I01CX000829-04.

CONFLICT OF INTEREST STATEMENT

R.A. has consulted for several pharmaceutical companies that make antihypertensive drugs, including Merck, Takeda, Novartis, Daichi Sankyo, Abbvie, Bayer and Johnson and Johnson.

REFERENCES

Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure

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ABSTRACT

Background. Chronic hepatitis C virus (HCV) infection is the most common chronic liver disease in patients with end-stage renal disease (ESRD). Over the last few years, second-generation direct-acting antivirals have been revolutionary in the treatment of hepatitis C, and sofosbuvir (SOF) is the backbone of most modern treatment strategies. Since SOF is eliminated through the kidney, the aim of this multicentre retrospective study was to assess its antiviral efficacy and safety in HCV-infected patients with severe renal failure [including haemodialysis (HD) patients].

Methods. Fifty patients (36 males, mean age ± standard deviation 60.5 ± 7.5 years) with chronic HCV infection (G1: 28/56%, cirrhosis: 27/54%) and severe renal failure [i.e. MDRD estimated glomerular filtration rate (eGFR) <35 mL/min], including 35 on HD, were enrolled. Antiviral treatment consisted of SOF/ribavirin (RBV) (n = 7), SOF/RBV/pegylated interferon (n = 2), SOF/daclatasvir ± RBV (n = 30) or SOF/simeprevir ± RBV (n = 11) for 12 or 24 weeks. A reduced dose of SOF (400 mg three times a week or 400 mg every other day) was given to all HD patients. Initial dose of RBV (n = 12) ranged from 400 to 4200 mg/week.

Results. On an intent-to-treat-based analysis, sustained virological response rate was 86% at 12 weeks. During therapy, haemoglobin levels were not significantly modified, but recombinant erythropoietin (rEPO) dose significantly increased in patients treated with RBV. Two patients (4%) required blood transfusion. No patient had treatment discontinuation due to side effects. Dose of RBV was reduced in two patients (16.7%) during antiviral therapy. Dose of SOF was reduced in two non-HD patients because of side effects. In non-HD patients, median eGFR was not significantly modified during treatment.

Conclusions. Our results strongly suggest that SOF-based antiviral therapy, with a reduced dose of SOF, is safe and effective for the treatment of HCV patients with ESRD, including HD patients.