International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Original Research

Masked hypertension, rather than white-coat hypertension, has a prognostic role in patients with non-dialysis chronic kidney disease

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ARTICLE INFO

Article history:
Received 10 August 2016
Received in revised form 29 November 2016
Accepted 17 December 2016
Available online xxxx

Keywords:
Chronic kidney disease (CKD)
Ambulatory blood pressure (BP)
Clinic blood pressure
Masked hypertension
White-coat hypertension

ABSTRACT

Objective: Masked hypertension (MHT) and white-coat hypertension (WCHT) have been studied among the general population and hypertensive patients. However, little insight is available on the prognosis of MHT and WCHT in patients with chronic kidney disease (CKD). We investigated the role of MHT and WCHT in the prognosis of patients with non-dialysis CKD.

Methods: A prospective cohort study was conducted between July 2010 and December 2014. A total of 588 patients with non-dialysis CKD were enrolled for ambulatory and clinic blood pressure (BP) monitoring. Patients were divided into four groups according to levels of clinic and ambulatory BP: normotension (NT), WCHT, MHT, and sustained hypertension (SHT). We recorded the time to: total mortality, renal events, and cardiovascular events. Multivariate Cox regression analyses were explored to ascertain the prognostic value of MHT and WCHT for these end points.

Results: Fifty-six CKD patients (9.5%) exhibited WCHT and 121 (20.6%) demonstrated MHT. There were no differences in incidence of total mortality or renal and cardiovascular events between patients with WCHT and those with NT, whereas the occurrence of these three events was higher in patients with MHT and SHT than in patients with NT ($P < 0.05$). Moreover, patients with SHT had the highest incidence of renal and cardiovascular events ($P < 0.05$). Multivariate Cox regression analyses showed that MHT (*vs.* NT) and SHT (*vs.* NT) were associated with an increased risk for total mortality (MHT: hazard ratio [HR], 8.88, 95% confidence interval [CI], 1.04–75.59; SHT: 8.15, 1.02–65.24), renal events (MHT: 3.70, 1.23–11.12; SHT: 3.95, 1.42–11.01), major adverse cardiac and cerebrovascular events (MACCE) (MHT: 8.66, 1.09–68.79; SHT: 11.16, 1.48–84.03), whereas WCHT (*vs.* NT) was not associated with these risks.

Conclusions: MHT (rather than WCHT) is associated with a risk of total mortality, MACCE, and renal events in patients with non-dialysis CKD.

Hypertension contributes to 45% of male deaths and 46% of female deaths in patients with chronic kidney disease (CKD) [1]. Hypertension is a modifiable cardiovascular risk factor in CKD, and regulation of blood pressure (BP) can reduce the risk of cardiovascular events substantially and slow the decline of kidney function [2]. Therefore, appropriate evaluation and management of hypertension in CKD are very important to slow CKD progression and reduce the high risk of cardiovascular disease [3].

The diagnosis of hypertension is based on a BP monitor in the physician's office. Recently, more attention has been paid to ambulatory blood pressure monitoring (ABPM) [4–6]. BP can be divided into four types according to levels of clinical BP and ambulatory BP: the concordant categories of "normotension" and "sustained hypertension" (SHT), as well as the discrepant categories of "masked hypertension" (MHT) and "white-coat hypertension" (WCHT). The burden of MHT and WCHT is controversial. WCHT has not been associated with a significant increase in cardiovascular events, whereas prospective studies suggest that the risk for cardiovascular events in MHT approaches that of subjects with "true" hypertension [7,8].

Few studies on MHT and WCHT in CKD patients have been reported: the prevalence of MHT in CKD varies from 5.9% to 42.9%, whereas the prevalence of WCHT in CKD ranges from 2.3% to 31.7% [9,10]. The divergent prevalence of MHT and WCHT in CKD could be related to the diverse definitions of hypertension and the heterogeneity of the diseases pooled under the CKD definition. Prognostic information associated with MHT and WCHT in CKD patients is scarce.

We were the first to report on the prevalence of MHT and WCHT in Chinese CKD patients. Our data suggested that MHT had a close relationship with impaired renal function and left-ventricular hypertrophy, whereas WCHT was associated with abnormal thickness of the carotid

Abbreviations: NT, normotension; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension.

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http://dx.doi.org/10.1016/j.ijcard.2016.12.105
0167-5273/

intima media in CKD patients [11]. The role of MHT and WCHT in the prognosis in CKD patients is not known. We hypothesized that MHT and WCHT might have roles in the prognosis of CKD patients based on that cross-sectional study. To answer this question, we designed a prospective cohort study in Chinese CKD patients not undergoing dialysis.

1. Materials and methods

1.1. Study population

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (Guangdong, China). Written informed consent was obtained from patients before enrollment.

Consecutive patients were recruited from the Third Affiliated Hospital of Sun Yat-sen University from July 2010 to December 2014.

Inclusion criteria were as follows: age ≥ 14 and <75 years; CKD; available follow-up data (duration of follow-up >6 months or end point event was observed in 6 months). Exclusion criteria were as follows: acute changes in the estimated glomerular filtration rate (eGFR) >30% in the previous 3 months; dialysis; recipients of kidney transplantation; atrial fibrillation; cardiovascular events in the previous 3 months; pregnancy; night work or shift-work employment; intolerance to ABPM; invalid ABPM data.

1.2. Measurements

1.2.1. ABPM

Patients underwent 24-h ABPM using a TM-2430 Monitor (A&D, Tokyo, Japan). Cuff size was chosen based on arm circumference and was applied to the non-dominant arm. Three readings were collected in the clinic. BP readings were obtained using a mercury sphygmomanometer by a physician who did not have access to ABP values, then BP was recorded every 15 min in the daytime, and every 30 min at night. Monitoring was done on a working day. Patients were asked to attend to their usual activities but to keep motionless at the time of measurement. Patients had no access to ABP values. Strenuous physical activity was discouraged in all patients during the monitoring period, and their daily activities were comparable. BP series were eliminated from the analyses if any of the following were applicable: >30% of measurements were lacking; they had missing data for >3-h spans; they were collected from subjects who were experiencing an irregular rest–activity schedule or a nighttime sleep span <6 or >12 h during monitoring.

1.3. BP measurement in the clinic

BP was measured for each patient during a visit to the physician. Briefly, measurements were taken from the non-dominant hand in a quiet environment using a mercury sphygmomanometer with the patient in a sitting position after 5 min of rest. BP was not measured if the patient had consumed tobacco, ingested caffeine, or eaten within the previous 30 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values (Korotkoff's phase I and phase V, respectively) at each visit enabled recording of a minimum of 3 BP measurements at intervals of ≥1 min. Reported values of clinic BP were the mean of values recorded during the 2 days in which the ABPM device was installed and removed. For all patients, sphygmomanometric measurements were recorded by the same physician, who was not aware of the results of ABP recordings.

1.4. Collection of other data

We collected urine samples from 7 AM to 7 AM the next day to detect the extent of proteinuria and sodium levels over 24 h. These patients were asked to void their bladders before and after urine collection. Proteinuria was measured by immunoturbidimetry. In addition, medical history, including demographic, laboratory data (hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone, serum fasting glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], homocysteine, uric acid, serum creatinine [SCr], blood urea nitrogen [BUN]), and current therapy were obtained at the initial study visit. All these experimental data were measured using a 7180 Biochemistry Auto-analyzer (Hitachi, Tokyo, Japan).

1.5. Definitions

The patient cohort was divided in four groups according to levels of clinic and ambulatory BP: (i) normotension (NT), patients with clinic and ambulatory normotension; (ii) WCHT, patients with clinic hypertension but ambulatory normotension; (iii) MHT, patients with clinic normotension but ambulatory hypertension; (iv) sustained hypertension, patients with clinic and ambulatory hypertension.

Patients with clinic SBP <140 mmHg and clinic DBP <90 mmHg were regarded as having "clinic normotension", and others were defined as having "clinic hypertension". "Ambulatory normotension" was defined as 24-h SBP <130, 24-h DBP <80 mmHg, daytime SBP <135, daytime DBP <85 mmHg, nighttime SBP <120 and nighttime DBP <70 mmHg, and others were regarded to be "ambulatory hypertension". "Daytime" and "nighttime" were defined as time intervals according to patients' schedules, respectively [10].

CKD was defined according to KDIGO 2012 clinical practice guidelines [12]. That is, abnormalities of kidney structure or function present for >3 months with implications for health, which included (i) one or more markers of kidney damage (albuminuria; urine sediment abnormalities; electrolyte and other abnormalities due to tubular disorders; abnormalities detected by histology; structural abnormalities detected by imaging; history of kidney transplantation) and (ii) reduced GFR (GFR < 60 mL/min/1.73 m^2).

The eGFR was calculated using the 2009 CKD-EPI creatinine equation [13].

Diabetes mellitus (DM) was defined as the need for antidiabetic drugs or meeting the diagnostic criteria based on the American Diabetes Association's *Standards of Medical Care in Diabetes* (Hb_{A1C} ≥ 6.5% or fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L during a 75-g oral glucose tolerance test or in a patient with the classic symptoms of hyperglycemia or hyperglycemic crisis; random plasma glucose ≥11.1 mmol/L) [14].

1.6. Outcomes

Primary end points were time to total mortality. Secondary end points were time to renal events and time to major adverse cardiac and cerebrovascular events (MACCE).

Renal events were a composite of doubling of serum levels of creatinine or end-stage renal disease (ESRD), whichever occurred first. The end point of ESRD was reached on the day of the first dialysis session [15]. MACCE included a fatal or non-fatal major adverse cardiac and cerebrovascular event: myocardial infarction, heart failure, revascularization, stroke, or other events (acute arterial occlusion of lower extremities and thrombotic occlusion of the retinal artery), whichever occurred first. The cause of death was identified according to death certificates and autopsy reports based on the tenth revision of the *International Classification of Disease*. Hospital records were collected to establish the diagnosis based on criteria set by the American College of Cardiology and the European Society of Cardiology [16,17]. Patients were followed up until 31 March 2016 or death, and censored on the date of the last visit to the nephrology clinic.

1.7. Statistical analyses

Data were analyzed using SPSS v20.0 (IBM, Armonk, NY, USA) and STATA v14.0 (STATA, College Station, TX, USA).

Please cite this article as: C. Wang, et al., Masked hypertension, rather than white-coat hypertension, has a prognostic role in patients with non-dialysis chronic kidney disea..., Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.12.105