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A prospective cohort study of home blood pressure monitoring based on an intelligent cloud platform (the HBPM-iCloud study): rationale and design

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Abstract

Background: Hypertension, as a predominant risk factor for cardiovascular disease, is a severe public health burden in China. Home blood pressure monitoring (HBPM) is an important tool in the detection and management of hypertension. However, there is a lack of HBPM data from prospective cohorts in China. Hence, we designed this study to investigate the impact of HBPM on major health outcomes in Chinese population participating in regular health check-ups.

Methods: Leveraging telemedicine technology, the open prospective, multicenter, HBPM-iCloud (Home Blood Pressure Monitoring Based on an Intelligent Cloud Platform) cohort study will recruit participants from three participating health check-up centers in southern China to participate in cloud-based HBPM for 1 week. The prevalence of sustained hypertension, white coat hypertension (WCH), masked hypertension (MH), white coat uncontrolled hypertension (WUCH), and masked uncontrolled hypertension (MUCH) will be defined by a combination of average readings of home-based and office-based blood pressure (BP). Cardiovascular risk factors and subclinical target organ damage will be recorded. Participants will be followed-up for 5 years to examine the incidence and associated risk factors of composite major adverse cardiovascular and cerebrovascular event.

Conclusion: The study will help to determine the best way to implement telemedicine technology in BP control for better prevention and treatment of hypertension. Results will provide data for a Chinese population to aid in the construction of screening, risk stratification, and intervention strategies for abnormal BP phenotypes, including WCH, MH, WUCH, and MUCH.

Keywords: cardiovascular disease, home blood pressure monitoring, masked hypertension, telemonitoring technology, white coat hypertension

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Introduction

Hypertension is a predominant risk factor for cardiovascular disease (CVD). As a severe public health burden, it occurs in 23.2% of Chinese adults according to the 2018 Chinese guidelines for the prevention and treatment of hypertension,[1] or in up to 46.4% if defined with the thresholds used in the 2017 American College of Cardiology/American Heart Association hypertension guidelines.[2] The prevention and control of hypertension can significantly reduce comorbidities.[3,4] However, the overall awareness, treatment, and control rates of hypertension in China are still very low.[1] Hence, it is imperative to identify optimal ways to diagnose and manage hypertension in China.

Blood pressure (BP) monitoring is a crucial step in the detection and management of hypertension.

The use of office BP monitoring (OBPM) is limited by multiple factors, which may result in misclassification of BP status. Thus, out-of-office BP measurements, including home blood pressure monitoring (HBPM) and ambulatory BP monitoring (ABPM), have been endorsed in clinical practice to detect white coat hypertension (WCH), masked hypertension (MH), and BP variability.[5] However, ABPM is difficult to implement across large populations. Several HBPM cohort studies have been conducted so far in other populations. The Japan Morning Surge-Home blood pressure (J-HOP) study among 4310 participants with at least one risk factor for CVD demonstrated that BP measurements taken at home in the morning are associated with CVD risk.[6,7] The Finn-Home study showed that BP and pulse pressure measured at home were predictive of CVD,[8,9] and people with MH and WCH had a higher risk of progression to sustained hypertension.[10] Recently, the Asia BP@Home study used HBPM to observe the BP distribution and BP variability of hypertensive patients from 11 centers in Asia.[11] However, the study only included 197 Chinese participants, and the cross-sectional study design and enrollment based on hypertensive patients upon treatment limited its value in elucidating the prognostic effect of HBPM in the Chinese population. Thus, there is lack of data on HBPM for prognosis in the Chinese population.

General home BP monitoring suffers from recording bias on account of patients' wrong memory or unreal records. Studies have demonstrated that novel care models leveraging home BP telemonitoring can facilitate better BP control.[12,13] Our group has developed a remote, intelligent HBPM device that can automatically transmit BP readings to a cloud platform using a general packet radio service system. Automatic data transmission can effectively mitigate recording bias and provide timely warning messages in case extreme readings are recorded. Therefore, we propose to conduct the prospective Home Blood Pressure Monitoring Based on an Intelligent Cloud Platform (HBPM-iCloud) study in China. The study aims to (a) determine the prevalence of sustained hypertension, WCH, MH, white coat uncontrolled hypertension (WUCH), and masked uncontrolled hypertension (MUCH), as defined by a combination of home and office BP measurements; (b) identify the risk factors and subclinical target organ damage (TOD) associated with abnormal BP phenotypes, including WCH, MH, WUCH, and MUCH; and (c) evaluate the prognostic effect of HBPM for the long-term incidence of composite major adverse cardiovascular and cerebrovascular event (MACCE) and all-cause mortality. A secondary objective is to establish a serum sample bank from a Chinese HBPM cohort population.

Methods

Study design

The HBPM-iCloud study is an open prospective, multicenter cohort study among participants recruited from three participating health check-up centers in southern China. Broad inclusion criteria will be used to sample the general population attending health check-up examinations: voluntary adults aged 18 years or older who provide written informed consent. There are no restrictions on the use of antihypertensive therapy or other medications. Patients with hypertension will refer to cardiologists for treatment. The strategy of antihypertensive treatment will depend on the patients' clinical characteristics and the communication between the patients and cardiologists. The exclusion criteria are those who are unable to conduct BP by themselves or have a history of malignancy or psychiatric disease.

After enrollment, a unified upper-arm electronic HBPM device (pulse wave BP-88G) will be provided to participants for free use over the following week. A 5-year follow-up will be carried out through annual health check-up examinations; patients who do not return for the follow-up visit will be followed annually by telephone. The study procedure is shown in Figure 1. Data to be collected in follow-up duration is presented in Table 1. Informed consent will be obtained from all participants, and they will have the right to discontinue their participation in the study at any time.

Data collection

Demographic information and medical history will be collected by study staff *via* a questionnaire, including gender, age, smoking history, alcohol consumption history, height, weight, waist circumference, hip circumference, employment in a shift position, and physical activity status. Family history of hypertension, coronary heart disease and stroke, personal history of hypertension, including the highest BP reading

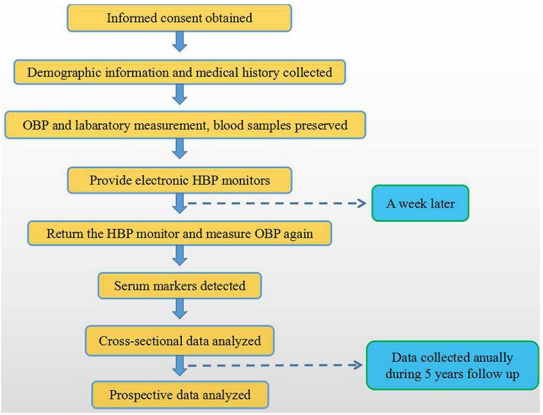

Figure 1. Flow chart of HBPM-iCloud study design.
HBPM, home blood pressure monitoring; HBP: home blood pressure; OBP, office blood pressure.

and age of onset, personal history of cardiovascular diseases, personal history of other diseases, and medications will also be recorded. Office BP, liver function, renal function, blood glucose, glycosylated hemoglobin, uric acid, homocysteine, and blood lipid profile will be measured. Electrocardiography, chest X-ray, and echocardiography will be performed. An additional 5 ml fasting blood sample will be collected, centrifuged to separate the serum and monocytes, and stored in two copies at –80°C for subsequent testing. Detailed data for collection are presented in detail in Table 2.

Office blood pressure monitoring

The OBPM will be conducted based on the 2018 Chinese guidelines for hypertension prevention and treatment.[1] After the participant has been resting in the sitting position for at least 10 min, the BP will be measured by a trained doctor or nurse using a validated automated upper-arm device (OMRON HEM-7118) with the appropriate cuff size. Participants should be in a straight sitting position with measured upper arm exposed, keeping the elbow at the same level with heart. A second measurement will be taken 1–2 min after the first, and the average of the two readings will be recorded as the office BP. If there is a difference of more than 5 mm Hg between the two systolic or diastolic BP readings, the measurement will be repeated, and the average of the three readings will be recorded. Both upper arms will be measured at the first visit, and the higher one will be recorded as a reference. The difference between arms BP is defined as the absolute value of the BP difference between arms.

Home blood pressure monitoring

When home BP monitors are provided to the study participants, the standard measurement technique will be introduced by a trained medical staff.[1] The measurements should be taken in a quiet environment and participants should be in a relaxed and comfortable sitting position for at least 5 min before self-measurement. Two measurements should be taken at a 2 min interval after getting up in the morning and urinating but before taking anti-hypertension medicines and having breakfast. In addition, two measurements should be taken at a 2 min interval in the evening before going to bed. Participants are required to take BP measurements for seven consecutive days, and the average BP of the last 6 days of measurements will be recorded. Considering the fact that some participants may fail to obtain home BP readings for 7 consecutive days, we therefore divide the participants into 3 groups—those with measurements from less than 3 consecutive days, 4–6 consecutive days, and 7 days—to better evaluate the differences among groups with different levels of compliance. HBP variability, which refers to day-to-day variability of mean systolic/diastolic BPs, will be calculated by the coefficient of variation among recorded BP readings. The monitor is for personal use only, and the BP values will be transmitted to the remote platform automatically. When the systolic BP is over 180 mm Hg, or the diastolic BP is over 130 mm Hg, a warning message will be sent to the research center so that appropriate medical action can be taken.

Study outcomes and sample size

The prevalence of sustained hypertension, WCH, MH, WUCH, and MUCH will be observed at baseline. Data for cardiovascular risk factors, subclinical TOD indicators, including carotid intima thickness, pulse wave velocity, left ventricular mass index, and left ventricular hypertrophy, will be observed at baseline and also collected during the annual follow up. The primary outcome of the current study is the composite MACCE, including coronary heart disease (myocardial infarction, angina and coronary revascularization), heart failure, cardiovascular mortality, stroke, transient ischemic attack, and peripheral artery disease. Secondary outcomes will be the risk of all-cause

Table 1. Data collected in follow up duration.

Visits*	Time	Informed consent	Baseline data	Blood sample	Serum biomarker	Physical examination	HBP	OBP	TOD indicators	Outcomes
Visit 0	Week 0	√	√	√	√	√		√	√	
Visit 1	Week 1						√	√		
Visit 2	Year 1			√	√	√		√	√	√
Visit 3	Year 2			√	√	√		√	√	√
Visit 4	Year 3			√	√	√		√	√	√
Visit 5	Year 4			√	√	√		√	√	√
Visit 6	Year 5			√	√	√		√	√	√

HBP, home blood pressure; OBP, office blood pressure; TOD, target organ damage.
*Visit 2–6 refers to visit annually during 5 years follow up.

mortality, fatal and non-fatal coronary heart disease, fatal and non-fatal stroke (including transient ischemic attack), and chronic kidney disease, respectively.

Based on the incidence and relative risk of composite CVD (similar with the definition of primary outcome in the current study) in each abnormal BP phenotypes reported in the International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) study,[14] a sample size of 1915 participants would fulfill the two-tailed hypotheses for 90% study power to detect a type I error at 0.05, with the possibility of 20% drop-out rate.

Data management and analysis

All participants' information will be held confidentially and accessed only by the principal researchers. Continuous data will be expressed as mean ± standard deviation and compared using ANOVA. Categorical data will be expressed as percentages and compared using a Chi-square test. Associations between different BP types and subclinical TOD will be analyzed using multivariable logistic regression analysis. Multivariable Cox regression model will be used to analyze associations between exposures of interest such as HBP variability, WCH, MH, WUCH, MUCH and observed health outcomes. Non-linear dose response between home BP and risk of observed outcomes will be explored non-parametrically using restricted cubic splines,[15] and tests for nonlinear relationship will be done through the likelihood ratio test comparing the model with only the linear term to the model with the linear and cubic spline terms. Adjusted hazard ratio (HR) will also be calculated across strata of key demographic factors (age, sex, diabetes, and body mass index), and χ^2 tests for trend or heterogeneity will be applied to the log HR and their standard errors. p values < 0.05 will be considered statistically significant.

Trial status

The protocol is version 1.1. Recruitment began in January 2019 and will be completed by December 2021. This project has been approved by the ethics committee of Shunde Hospital of Southern Medical University and has been registered in the China Clinical Trial Registration Center (ChiCTR1800018515).

Discussion

Herein, we reported the rationale and design for a HBPM cohort study based on telemonitoring technology. To the best of our knowledge, the HBPM-iCloud study is the first cohort study to investigate the utility of HBPM for prognosis in Chinese population.

HBPM is recommended in multiple academic guidelines for out-of-office BP monitoring to confirm hypertension diagnoses and to titrate BP-lowering medications.[1,2,16] However, it remains unclear based on existing literature whether HBPM has

Table 2. Data collection throughout the trial.

Identifiable patient data	Clinical data	Serum biochemical and TOD indicators
Name	Age	Serum sodium
Identification number	Sex	Serum potassium
Date of birth	Height	Serum Calcium
Telephone number	Weight	Total cholesterol
Centre	Occupation	HDL cholesterol
	HBP	LDL cholesterol
	OBP	Triglycerides
	Smoking history	Albumin
	Alcohol consumption history	Alanine transaminase
	Family history of hypertension	Aspartate aminotransferase
	Family history of CHD	Alkaline phosphatase
	Family history of stroke	Total bilirubin
	Personal history of hypertension and the highest reading of BP and onset age	γ-Glutamyltransferase
	Personal history of cardiovascular diseases	eGFR
	Personal history of other diseases	Serum creatinine
	Medication history	HbA1c
	Shift work status	Homocysteine
	Exercise status	Urinalysis
	Waist circumference	Pulse wave velocity
	Hip circumference	Carotid artery ultrasound
	Heart rate	Electrocardiography
	Variability of HBP	Chest X-ray
		Echocardiography

CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HBP, home blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OBP, office blood pressure; TOD, target organ damage.

a similar utility for predicting CVD in the Chinese population as observed in Western populations.[8] It is worth noting that China has a large hypertensive population with low awareness and control rates. Thus, the prospective HBPM data from a Chinese population which we will collect in this study will be important for public health management.

HBPM is also useful in identifying abnormal BP phenotypes including WCH and MH.[1,2,16–19] MH, which is defined as normal office BP but

elevated out-of-office BP, has been confirmed to be associated with CVD risk.[20] The IDHOCO study showed that classified by HBPM, MH accounted for 5%, 18.4%, and 30.4% of people with optimal BP (<120/80 mm Hg), low-range prehypertension (120–129/80–84 mm Hg), and high-range prehypertension (130–139/85–89 mm Hg), respectively.[21] These results revealed that, without out-of-office measurements, many people with MH may be misdiagnosed and therefore receive inadequate or delayed treatment. In contrast to MH, WCH is defined by normal out-of-office BP and elevated office BP. Whether WCH is associated with increased CVD risk is controversial.[22–25] Our previous study indicated that WCH is associated with an increased risk of all-cause mortality and CVD compared with normotension.[26] Data from the HBPM-iCloud study may provide important information for better risk stratification and intervention for people with abnormal BP phenotypes, including WCH, MH, WUCH, and MUCH.

Compared with the J-HOP study[6] and the Finn-Home study,[8] an important novel feature of the present study is the use of telemonitoring technology, which can avoid record bias and, thus, improve the quality of HBPM. Previous studies have confirmed that telemonitoring technology is useful for BP control.[12,13] However, this study also has some limitations. First, participants will be recruited from health check-up centers, but not a community population, which may result in an underlying bias in the results. Second, the participating centers are all from southern China, so the results cannot be generalized to the national population. Third, due to limited funding, we can only dispatch an electronic HBPM device to every participant for 1 week, for free use, and recycle the device for another participant. It has been reported that both MUCH and WUCH display poor reproducibility over time.[27] Therefore, the short-term use of HBPM in the current study may cause misclassification of BP phenotypes.

Conclusion

In conclusion, the planned HBPM-iCloud study will provide essential information to address several issues in the prevention and treatment of hypertension, including data about HBPM in a Chinese population. These findings will inform the construction of screening, risk stratification, and intervention strategies for abnormal BP phenotypes, including WCH, MH, WUCH, and MUCH. Finally, the study will shed light on how to effectively implement telemedicine technology in BP control.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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