ORIGINAL RESEARCH

Electrocardiographic left ventricular hypertrophy and mortality in an oldest-old hypertensive Chinese population

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Purpose: Previous studies have identified that electrocardiographic pattern of left ventricular hypertrophy (ECG LVH) is associated with mortality, but studies of its correlation in the oldest-old hypertensive population is extremely limited. We investigated the correlation between ECG LVH and mortality in a hypertensive Chinese population aged 80 years and older.

Patients and methods: In this study, we included 284 Chinese participants older than 80 years. All included participants with hypertension (sitting systolic blood pressure [BP] 160 to 200 mmHg; sitting diastolic BP <110 mmHg) were ascertained at the baseline. ECG LVH was defined as a Sokolow-Lyon voltage calculated as the amplitude of SV1+ (max RV5 or RV6) greater than 3.5 mV. We categorized participants into two groups by the status of baseline ECG LVH. We used Cox regression models to calculate hazard ratio (HRs) for mortality due to ECG LVH, including cardiovascular mortality and all-cause mortality.

Results: In this study, with a 28-month median follow-up, a total of 35 (12.3%) patients died; 21 of those died due to cardiovascular causes. Compared with participants without ECG LVH, there was an increased risk of cardiovascular mortality in participants with ECG LVH (adjusted HR 4.25 [95% confidence interval [CI], 1.50–12.06]) but ECG LVH did not predict all-cause mortality (adjusted HR 2.31 [95% CI, 0.93–5.72]).

Conclusion: Our study shows that ECG LVH predicts the risk of cardiovascular mortality in an oldest-old hypertensive Chinese population.

Keywords: left ventricular hypertrophy, mortality, oldest-old, hypertension, China

Introduction

The aging population is rapidly growing worldwide, but there is little evidence that an extended period of good health accompanies the continuing increases in life expectancy.[1] The number of elderly individuals in China is projected to grow from 212 million in 2013 to 480 million by 2042, while the oldest-old population aged 80 years and older will reach more than 50 million.[2,3] The burden of cardiovascular disease (CVD), as the most common cause of death in the oldest-old Chinese population,[4] is substantial. Thus, further study of CVD in the oldest-old Chinese population is needed.

Accumulating evidence has suggested that electrocardiographic pattern of left ventricular hypertrophy (ECG LVH), which is the most common pathological manifestation of overload in hypertension, strongly predicts the 1.5- to 3-fold increased risk of mortality in individuals with CVD when it is defined by electrocardiogram

(ECG).[5–9] Nevertheless, studies of mortality in the oldest-old is extremely limited.[10] The lack of information on mortality may result in an underestimation of the true impact of ECG LVH in the oldest-old population. Therefore, we prospectively investigated the association between ECG LVH and the risk of mortality in 284 oldest-old hypertensive Chinese participants.

Materials and methods
Participants
In 2004, 284 hypertensive participants aged 80 years and older (confirmed by national documentation; no upper age limit) from Shandong province of the People's Republic of China were recruited to participate in a double-blind placebo-controlled trail designed to establish the benefits and risks of antihypertensive treatment.[11,12] Hypertension was defined as sitting systolic blood pressure (BP) 160–200 mmHg and sitting diastolic BP <110 mmHg. Participants who had accelerated hypertension, secondary hypertension, serum creatinine levels ≥150 µmol/L or clinical diagnosis of dementia at the baseline were excluded. All participants (n=284) signed a written informed consent as required when enrolled into this study. Full details have been previously described elsewhere.[13] Before randomization, all participants underwent a 2-month placebo run-in phase to establish that participants have sustained elevated levels of BP. During the run-in period any active antihypertensive treatment was stopped and 1 placebo tablet was given matching the initial active treatment. Participant randomization was initiated at the coordinating office at the Beijing Hypertension League Institute on receipt of the completed entry form. After randomization, all participants were assigned to receive either matching placebo or the antihypertensive treatment. Participants were followed for up to 3 years after enrollment. This study was approved by the Ethics Committee of the Beijing Hypertension League Institute.

Assessment of left ventricular hypertrophy
ECG LVH was determined according to the Sokolow-Lyon voltage criteria. LVH was considered present when the Sokolow-Lyon voltage, calculated as the amplitude of SV1+ (max RV5 or RV6), was greater than 3.5 mV.

All participants were assessed with 12-lead ECGs by two clinicians at the baseline. All ECGs had an ECG paper speed of 25mm/s. ECGs were recorded at signal heights of 0.5, 1, and 2 cm. With the calibration signal heights of 0.5

and 2 cm, ECGs corresponding to the 1 mV voltage (signal height of 1 cm) were recalculated. QRS duration was measured to the nearest 20 ms and the amplitude heights of the QRS were measured to the nearest 0.1 mV voltage (signal height of 0.1 cm). To ensure a correct interpretation, the recordings were reviewed once by two clinicians.

Assessment of other covariates
Baseline characteristics regarding sex, age, lifestyle behaviors (smoking and alcohol intake), and history of cardiovascular disease (CVD) were obtained using a questionnaire by trained research staff. BP measurement, body weight and body height were collected for all participants. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Blood biochemical items (including total cholesterol, uric acid, fasting glucose and creatinine levels) were measured using an automated biochemical analyzer in the central laboratory. The estimated glomerular filtration rate (eGFR) was calculated to assess the individuals' kidney function by the modified Chinese MDRD equation.[14] All participants were tested with the mini-mental state examination to assess the individuals' cognitive function. Heart rates were also evaluated with an electrocardiogram.

Mortality
The primary study outcome was mortality, including cardiovascular mortality and all-cause mortality. Cardiovascular mortality was defined as death due to stroke, infarction, myocardial ischemia, or cardiac arrest. The causes of death and date were collected through the hospital's electronic medical records.

Statistical analysis
The data are presented as means (standard deviations, SDs) for continuous variables (normal distribution), medians (interquartile ranges, IQRs) for continuous variables (non-normal distribution), or proportions for categorical variables. Differences in continuous and categorical variables between the two groups based on the status of baseline ECG LVH were assessed by using analysis of variance (ANOVA), the Kruskal-Wallis test, the χ^2 test or Fisher's exact test.

Kaplan-Meier curve was used to compare survival rates between participants without and with ECG LVH. The log-rank test was used to assess the differences among the two groups.

Univariate and multivariate Cox proportional hazards regression models were used to explore the associations between ECG LVH and mortality (cardiovascular and all-cause mortality). Adjustments were made for sex (female or male), age (per 1 year increase), current smokers (yes or no), BMI (per 1 kg/m^2 increase), history of CVD (yes or no), antihypertensive treatment (yes or no), total cholesterol level (per 1 mmol/L increase), fasting blood glucose level (per 1 mmol/L increase), eGFR level (per 10 mL/min/1.73 m^2), uric acid level (per mg/dL increase), MMSE scores (per 1-point score increase), systolic BP (per 10 mmHg increase) and heart rate level (per 1 per minute increase).

All *p*-values were two-tailed. The results were considered to be significant at *p*<0.05. All data analyses were performed using SAS version 9.4(SAS Institute Inc., Cary, NC, USA).

Results

The median age of the total study population was 83.0 (81.4–85.2) years, and 26.1% of the participants were male. The median duration of follow-up was 28 months (IQR 14–38 months). There were 35 (12.3%) all-cause death and 21 (7.4%) CVD deaths (including 2 cardiac arrest deaths, 4 myocardial ischemia and infarction deaths, 15 stroke deaths).

Table 1 shows the baseline characteristics of participants grouped by ECG LVH. Participants with ECG LVH (n=37) had higher systolic BP-values and were more likely to die from CVD in comparison with participants without ECG LVH (n=247).

Figure 1 shows the survival curves of the two groups. The participants without ECG LVH tended to have a higher cumulative survival rate (88.7% vs 81.1%), but the result was not statistically significant (*P*=0.12).

The results of the univariate and multivariate Cox analyses are shown in Table 2. Compared with participants without ECG LVH, those with ECG LVH had adjusted hazard ratios (HRs) for cardiovascular mortality and all-cause mortality of 4.25 (95% confidence interval [CI], 1.50–12.06) and 2.31 (95% CI, 0.93–5.72), respectively.

Discussion

We demonstrated that ECG LVH independently predicted cardiovascular mortality in a hypertensive Asian population aged 80 years and older. This finding could assist clinicians in identifying individuals at high risk for cardiovascular mortality.

Table 1 Baseline characteristics of the participants grouped by ECG LVH

Variables	All participants	Participants without ECG LVH	Participants with ECG LVH	p-value
Number of participants, n	284	247	37	
Male, % (n)	26.1(74)	25.9(64)	27.0 (10)	0.90
Age, years	83.0 (81.4–85.2)	82.7 (81.2–85.1)	83.69 (82.7–86.7)	0.58
Current smoking, % (n)	7.7 (22)	7.7 (19)	8.1 (3)	1.00
History of CVD, % (n)	4.9 (14)	4.9 (12)	5.9 (2)	0.70
Antihypertensive treatment, % (n)	48.9 (139)	49.4 (122)	45.9 (17)	0.73
Body mass index, kg/m^2	22.5 (21.2–23.6)	22.6 (21.2–23.7)	22.0 (21.2–23.5)	0.58
Hemoglobin, g/dL	12.1±1.4	12.1±1.5	11.9±1.2	0.23
Fasting blood glucose, mmol/L	5.0 (4.3–5.4)	5.0 (4.3–5.3)	5.1 (4.3–5.7)	0.41
Total cholesterol, mmol/L	4.7 (4.2–5.1)	4.7 (4.2–5.1)	5.0 (4.1–5.3)	0.60
Serum uric acid, mg/dL	4.2 (3.2–5.2)	4.2 (3.2–5.1)	4.0 (3.2–5.3)	0.90
Systolic BP, mmHg	175 (165–186)	173 (165–186)	181 (170–192)	0.05
Diastolic BP, mmHg	85 (78–92)	84 (78–92)	89 (81–93)	0.07
Serum creatinine, μmol/L	102 (84–119)	102 (84–119)	96 (84–118)	0.78
eGFR, median (IQR), mL/min/1.73m^2	55.8 (46.0–72.3)	55.5 (45.6–72.5)	59.6 (48.4–70.1)	0.82
The MMSE score, point	21 (20–23)	21 (20–23)	22 (20–23)	0.38
Heart rate, per minute	71 (68–75)	70 (68–74)	72 (66–76)	0.99
Cardiovascular mortality, % (n)	7.4 (21)	6.1 (15)	16.2 (6)	0.04
All-cause mortality, % (n)	12.3 (35)	11.3 (28)	18.9 (7)	0.19

Notes: The data are presented as percentage (N) for categorical variables, mean ± SD for continuous variables (normal distribution), median (IQR) for continuous variables (non-normal distribution) .
Abbreviations: LVH, left ventricular hypertrophy; CVD, cardiovascular disease; BP, blood pressure; MMSE, mini-mental state examination; eGFR, estimated glomerular filtration rate.
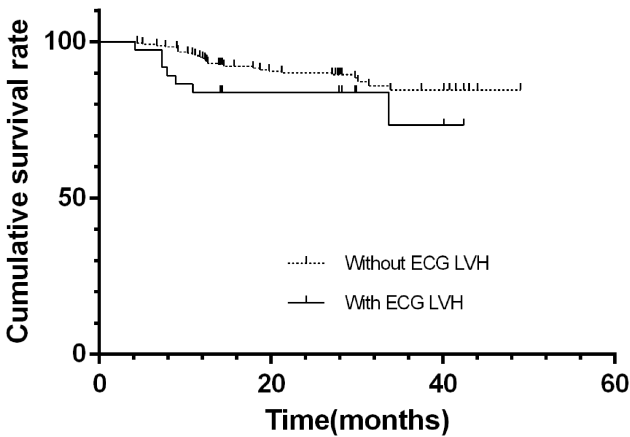
Figure 1 Cumulative survival curves of the two groups (n=284).
Abbreviation: LVH, left ventricular hypertrophy.

Most previous studies have provided adequate strong evidence that LVH is associated with mortality. Data from the Second and the Third National Health and Nutrition Examination Survey (NHANES II/III)[9,15] indicated that LVH is significantly associated with 10-year cardiovascular mortality and all-cause mortality among the general population. However, the risk of mortality in the general population (mean ages of 49.2 and 59.5 years, respectively) cannot be used to estimate the risk in the oldest-old population. Meanwhile, in these two surveys, information regarding the oldest-old, the Asian population and some relevant confounders were not available. As it was based on cross-sectional data, the NHANES III did not include information regarding treatment patterns and BP, which are important predictors of the prognosis of hypertensive patients. Our study built on previous studies and found an association between LVH and cardiovascular mortality in a hypertensive Asian population (median age of 83.0 years in our

study), after adjustment for confounding variables including treatment patterns and BP. Another study of hypertensive patients aged 55 to 80 years[7] suggested that LVH is a time-dependent covariate that predicts increased risk of cardiovascular mortality and all-cause mortality, respectively with adjusted HR of 1.53 (95% CI 1.19–1.98) and 1.57 (95% CI 1.30–1.89). Although the effect of LVH at the baseline is not equivalent to the effect of LVH as a time-dependent covariate, we found that LVH at the baseline contributed to an increased risk of cardiovascular mortality. The Antihypertensive and Lipid-lowering Treatment to prevent Heart Attack Study (ALLHAT)[16] found an association between LVH and all-cause mortality among White, Black, and Hispanic patients (aged ≥55 years) with mild to moderate hypertension. Our study extended the findings regarding this association to the oldest-old Chinese participants with moderate to severe hypertension. These previous studies did not include oldest-old individuals or the Asian population and did not have information pertaining to relevant confounders, such as hemoglobin, serum creatinine and serum uric acid levels. A recent study in a population aged 80 years or older[10] investigated the association of LVH with the risk of mortality. Similar to our results, LVH was not significantly associated with all-cause mortality. Nevertheless, the association between LVH and cardiovascular mortality was not explored in the recent study mentioned above.

There may be several potential mechanisms underlying the association between LVH and the increased risk of cardiovascular mortality. First, LVH is known to increase the prevalence of arrhythmia, such as premature ventricular complexes, couplets, non-sustained ventricular tachycardia, and atrial fibrillation, as reviewed by Shenasa et al.[17] These

Table 2 ECG LVH and mortality

	Without ECG LVH (n=247)	**With ECG LVH (n=37)**
Cardiovascular mortality		
Crude HR	Reference	3.04 (1.18–7.83)
Age, sex adjusted HR	Reference	3.58 (1.35–9.46)
Multivariable adjusted HR[a]	Reference	4.25 (1.50–12.06)
All-cause mortality		
Crude HR	Reference	1.98 (0.86–4.56)
Age, sex adjusted HR	Reference	2.15 (0.92–5.04)
Multivariable adjusted HR[a]	Reference	2.31 (0.93–5.72)

Notes: Data are presented as HR (95% CI). [a]Model was further adjusted for age, sex, body mass index, current smoking, history of CVD, antihypertensive treatment, fasting glucose, total cholesterol, uric acid, systolic BP, eGFR, the MMSE score and heart rate.
Abbreviations: LVH, left ventricular hypertension; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration.; MMSE, mini-mental state examination; HR, hazard ratio.

diseases independently serve to increase the risks of cardiovascular and all-cause death.[18] Second, dilatation of the left ventricle (LV), which slows the intramyocardial conduction velocity, may cause left bundle branch block (LBBB).[19] LBBB may result in heart failure subsequent to LV contractile inefficiency.[20] Third, as the LVH progresses, microvascular changes and subendocardial ischemia occur, which may result in sudden cardiac death.[17] Moreover, further research of the potential biological mechanisms is needed.

There are several strengths and limitations of our study that deserve to be mentioned. The main strength of our study is the capacity to show the elevation of the risks of cardiovascular mortality and all-cause mortality associated with ECG LVH in a previously unreported population by controlling for various potential confounders. Our study has limitations as well. First, our study had a small sample size, and the majority of the participants were women. Second, all participants were recruited from the same province in China. Thus, our results may differ from those in the general population and may not be representative of all people aged at least 80 years. However, the participants' living environments and medical care were likely to be relatively homogeneous, which may strengthen this study's internal validity. Third, the follow-up period may have been too short to observe an increased risk of all-cause mortality. In addition, it is important to note that the prevalence of ECG LVH was relatively low; thus the results of our study thus may not be representative of those in populations with less severe hypertension.

Conclusion

Our analyses show that electrocardiographic LVH independently predicts cardiovascular mortality among the oldest-old hypertensive Chinese population. More attention should be paid to the evaluation and management of hypertension and LVH among the oldest-old.

Acknowledgment

Disclosure

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