Clinical Research

Left ventricular hypertrophy in relation to systolic blood pressure and the angiotensin converting enzyme I/D polymorphism in Chinese

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**Objective** There is little population-based data on the prevalence and the environmental or genetic determinants of left ventricular hypertrophy (LVH) in China. The purpose of this paper is to study LVH in relation to systolic blood pressure and the angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism in Chinese. **Methods** We recorded 12-lead ECG (CardioSoft, v4.2) in 1365 residents in the Jingning County, Zhejiang Province, China. LVH was defined according to the gender-specific Sokolow-Lyon and Cornell product ECG criteria. **Results** Regardless of whether the Sokolow-Lyon or Cornell product ECG criteria was used, the prevalence of LVH (20.7% and 4.8%, respectively) significantly (P<0.0001) increased with male gender (odds ratio [OR] 2.33 and 7.15) and systolic blood pressure (per 10 mm Hg increase, OR 1.46 and 1.33). If the Sokolow-Lyon criteria was used, the prevalence of LVH was also influenced by alcohol intake (OR 1.44, P=0.03) and body mass index (OR 0.83, P=0.0005). The association between the Sokolow-Lyon voltage amplitude and the ACE I/D polymorphism was dependent on antihypertensive therapy (P=0.01). In 1262 untreated subjects, but not 103 patients on antihypertensive medication, the ACE DD compared with II subjects had significantly higher Sokolow-Lyon voltage amplitudes (29.8±0.6 vs. 28.0±0.5 mV, P=0.02) and higher risk of LVH (OR 1.74, 95% CI: 1.12-2.69, P=0.01). **Conclusion** LVH is prevalent in Chinese, and is associated with systolic blood pressure and the ACE D allele. The genetic association might be modulated by antihypertensive therapy (J Geriatr Cardiol 2009; 6:131-136).

**Keywords** left ventricular hypertrophy; blood pressure; angiotensin converting enzyme; genetic polymorphism

Introduction

Left ventricular hypertrophy (LVH) is a well-documented risk factor for stroke, myocardial infarction and heart failure, independent of blood pressure. Antihypertensive therapy can regress LVH, leading to improvement in cardiovascular outcomes. LVH therefore represents a defined clinical entity with serious prognostic implications for the individual and arguably represents a target for therapeutic intervention. The prevalence of LVH varies with the diagnostic method used and the population studied. Several early studies used various electrocardiogram (ECG) criteria to diagnose LVH, reporting a prevalence of 1.5% in women and 2.9% in men in the general adult population, to 9.2% in a community-based cohort in 75-85 years old, and to approximately 30% in hypertensive patients. Proven independent determinants of LVH include age, gender, body mass index, hypertension, amongst others. The angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism is one of the most studied putative genetic

determinants of LVH. A meta-analysis of studies on the ACE I/D polymorphism and LVH showed no relationship on overall analysis. However, in the untreated hypertensive patients subgroup, the DD genotype was associated with a 192% higher risk of LVH.

Most of the previous studies have been performed in Western populations. To date, there is little information on the relationship between LVH, blood pressure and the ACE I/D polymorphism in a Chinese population. In the present cross-sectional analysis of an ongoing population study, we investigated the prevalence of LVH and its relationship with systolic blood pressure and the ACE I/D genotype.

Methods

Study population

The Ethics Committee of Shanghai Jiaotong University School of Medicine approved the protocol of the Jingning Population Study. Fourteen villages were randomly selected from Jingning County, Zhejiang Province, a rural mountainous area approximately 300 miles south of Shanghai. We invited all individuals at least 12 years old within these villages to take part on direct home visit, as previous reports. All study participants gave written in-
formed consent. Totally 1,486 subjects initially participated in our study, and 121 subjects were excluded because of missing information on ECG (n=94), blood pressure (n=2), or the ACE I/D polymorphism (n=25). Thus, the present analysis included 1,365 subjects.

Field work
Trained observers measured each participant’s blood pressure five times consecutively by conventional sphygmomanometry on home visit, according to the guidelines of the British Hypertension Society. These five blood pressure readings were averaged for statistical analysis. A standardized questionnaire was used to collect information on medical history, smoking habits, alcohol consumption and use of medications. Body mass index was calculated as body weight in kilograms divided by the square of body height in meters. Hypertension was defined as a blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic, or as the use of antihypertensive drugs. Venous blood samples, collected after overnight fasting, were analyzed for the plasma glucose and serum total cholesterol by standard automated enzymatic methods.

Resting 12-lead ECG were routinely obtained using an electronic recording system (Cardiosoft, version 4.2, GE Healthcare, Waukesha, Wisconsin). We calculated the Sokolow-Lyon voltage amplitude as SV1 + (RV5 or RV6) and the Cornell product as (RaVL + SV3) × QRS duration. The ECG criteria for the diagnosis of LVH were defined as a Sokolow-Lyon voltage amplitude >38 mV in men and >34 mV in women, or as a Cornell product >2592 mV·ms in men and > 2610 mV·ms in women.

ACE genotyping
Genomic DNA was extracted from peripheral white blood cells. The ACE I/D polymorphism was detected by polymerase chain reaction amplification using three oligonucleotide primers in a single reaction as previously described by Morgan et al.

Statistical analysis
For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC). Means and proportions were compared with the student’s t-test and Fisher’s exact test, respectively. We searched for possible confounders using multiple stepwise regression with the p value for covariates to enter and stay in the model set at 0.15. We used analysis of covariance and multiple linear and logistic regressions to test associations of interest, while controlling for covariates. We defined dummy variables to calculate odds ratios of LVH for each genotype against the overall risk of the study population.

Results
Population characteristics
The 1,365 study participants included 659 men (48.3%), 706 women(29.5) and 316 (23.2%) hypertensive patients, of whom 103 took antihypertensive drugs (Table 1). Age ranged from 12 to 86 years. In all participants, systolic and diastolic blood pressures averaged 123.7±22.8 mm Hg and 75.4±12.0 mm Hg, respectively. Compared to women, men were slightly older, had a smaller body mass index and slower heart rate, and more frequently reported smoking and alcohol intake (Table 1).

Overall, the prevalence of LVH was 20.7% via the Sokolow-Lyon voltage criteria and 4.8% via the Cornell prod-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=659)</th>
<th>Women (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.1±15.5</td>
<td>43.0±14.9*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.0±2.8</td>
<td>22.4±3.0*</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123.9±21.1</td>
<td>123.6±24.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75.7±11.3</td>
<td>75.2±12.6</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>71.8±10.8</td>
<td>74.5±10.3*</td>
</tr>
<tr>
<td>Hypertension (n [%])</td>
<td>141 (21.4)</td>
<td>175 (24.8)</td>
</tr>
<tr>
<td>Taking antihypertensive drugs (n [%])</td>
<td>42 (6.4)</td>
<td>61 (8.6)</td>
</tr>
<tr>
<td>Current smoking (n [%])</td>
<td>418 (63.4)</td>
<td>0*</td>
</tr>
<tr>
<td>Alcohol intake (n [%])</td>
<td>471 (71.5)</td>
<td>184 (26.1)*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>4.43±1.56</td>
<td>4.49±0.78</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>4.86±1.01</td>
<td>4.79±0.98</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage amplitude (mV)</td>
<td>33.0±11.1</td>
<td>25.5±9.3*</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (n [%])</td>
<td>184 (27.9)</td>
<td>99 (14.0)*</td>
</tr>
<tr>
<td>Gender-specific Sokolow-Lyon criteria</td>
<td>56 (8.5)</td>
<td>10 (1.4)*</td>
</tr>
</tbody>
</table>

Values are means±SD, or number of subjects (%). Hypertension was defined as a blood pressure of at least 140 mmHg systolic, or 90 mmHg diastolic, or as the use of antihypertensive drugs. Sokolow-Lyon voltage amplitude equals SV1 + (RV5 or RV6). Cornell product equals (RaVL + SV3) × QRS duration. Left ventricular hypertrophy was defined as a Sokolow-Lyon voltage amplitude >38 mV in men and >34 mV in women, or as a Cornell product >2592 mV·ms in men and >2610 mV·ms in women (21). *P<0.05 versus men.
Dect criteria. Regardless of whether the Sokolow-Lyon voltage criteria or Cornell product criteria was used, the prevalence of LVH was higher in men than women (Table 1).

Dectants of LVH

In stepwise regression, we considered age, sex, body mass index, systolic and diastolic blood pressure, current smoking and alcohol intake, fasting plasma glucose, serum total cholesterol and the use of antihypertensive drugs, as possible determinants of LVH. Of these variables, only sex and systolic blood pressure were identified as significant determinants of LVH diagnosed using the Cornell product criteria (Table 2). In a similar regression analysis, the prevalence of LVH diagnosed by Sokolow-Lyon voltage criteria was higher with male gender, systolic blood pressure and alcohol intake, but was lower with body mass index (Table 2).

In further analyses, we studied the Sokolow-Lyon voltage amplitude and the risk of LVH diagnosed by the Sokolow-Lyon voltage criteria in relation to systolic blood pressure by sex and the use of antihypertensive drugs. In 1262 untreated subjects, men and women alike, the Sokolow-Lyon voltage amplitude and the prevalence of LVH increased with systolic blood pressure (P<0.0001). Treated subjects (n=103), despite being on antihypertensive therapy, had higher systolic blood pressure (157.4 vs 121.0 mmHg in untreated subjects, P<0.0001), and higher Sokolow-Lyon voltage amplitude (35.9 vs 28.6 mV, P<0.0001, Fig.1A), and had higher prevalence of LVH defined by Sokolow-Lyon volt-

Table 2  Dectants of left ventricular hypertrophy diagnosed on electrocardiogram

<table>
<thead>
<tr>
<th>LVH diagnosed by Sokolow-Lyon voltage criteria</th>
<th>Odds ratio (95% confidence intervals)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>2.33 (1.68-3.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (+2 kg/m²)</td>
<td>0.83 (0.75-0.92)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Systolic blood pressure (+10 mmHg)</td>
<td>1.46 (1.36-1.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol intake (0=no; 1=yes)</td>
<td>1.44 (1.05-1.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>LVH diagnosed by Cornell product criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>7.15 (3.55-14.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (+10 mmHg)</td>
<td>1.33 (1.21-1.46)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

In multiple stepwise logistic regression analyses, we considered age, gender, body mass index, systolic and diastolic blood pressure, current smoking and alcohol intake, use of antihypertensive drugs, fasting plasma glucose and serum total cholesterol as potential determinants of left ventricular hypertrophy (LVH), which was defined as a Sokolow-Lyon voltage amplitude >38 mV in men and >34 mV in women, or as a Cornell product > 2592 mV·ms in men and > 2610 mV·ms in women.

![Fig.1  Sokolow-Lyon voltage amplitude and left ventricular hypertrophy in relation to systolic blood pressure. Sokolow-Lyon voltage amplitude (Panel A) and left ventricular hypertrophy prevalence (Panel B) as functions of systolic blood pressure (quintiles) by gender (filled symbols for men and open symbols for women) and the use of antihypertensive drugs (squares for users and circles for non-users). Vertical lines through data points in panel A indicate SE. The analyses for Sokolow-Lyon voltage amplitude were adjusted for sex, age, body mass index, and alcohol intake. Left ventricular hypertrophy (LVH) was defined as a Sokolow-Lyon voltage amplitude >38 mV in men and >34 mV in women.](image-url)
age criteria (40.8% vs 19.1%, \(P<0.0001\), Fig.1B), regardless of gender.

**LVH and ACE I/D polymorphism**

The ACE genotype frequencies (1.423 [0.31], ID 687 [0.50], and DD255 [0.19]) did not significantly deviate from the Hardy-Weinberg Equilibrium (\(P=0.42\), nor differ by the presence of hypertension (\(P=0.17\)) or LVH (\(P=0.46\)). However, both before and after adjustment for covariates, there was significant interaction between the ACE I/D polymorphism and the use of antihypertensive drugs in relation to Sokolow-Lyon voltage amplitude (\(P=0.01\)). In untreated but not treated (\(P=0.12\)) subjects, DD homozygotes, compared with II subjects, had a significantly higher Sokolow-Lyon voltage amplitude (29.8 ± 0.58 vs 28.0 ± 0.45 mV, \(P=0.02\), Fig.2A).

Categorical analyses were confirmatory. Only in untreated subjects was the prevalence of LVH higher in ACE DD than II subjects (23.2% vs 16.0%, \(P=0.03\)). After adjustment for covariates, the relative risk of LVH diagnosed by Sokolow-Lyon voltage criteria in untreated ACE DD vs. II subjects was 1.74 (95% CI: 1.12-2.69; \(P=0.01\), Fig.2B). However, we did not find any significant (\(P>0.25\)) association between ACE genotype and LVH diagnosed by Cornell product criteria.

**Discussion**

Our key finding was the significant positive association between LVH and ACE DD homozygosity in subjects not taking antihypertensive drugs in a Chinese population. In addition, our study demonstrated that ECG diagnosed LVH is highly prevalent in the general population in China, and confirmed that systolic blood pressure was a major determinant of LVH in both male and female Chinese.

A population prevalence of electrocardiographic LVH from 4.8 to 20.6% is substantially higher than that reported in Western populations (1.5%-3.0% in the Framingham Heart Study). This may reflect a high prevalence of risk factors for LVH in Chinese, particularly uncontrolled hypertension. However, it may also be the result of the differences in body habitus and ethnicity, because these factors are known to affect the diagnostic accuracy of current ECG algorithms for the detection of LVH.

In consistent with previous reports worldwide, systolic blood pressure was a strong determinant of ECG diagnosed LVH in our population sample. Subjects on antihypertensive therapy had poorly controlled blood pressure.

![Fig.2 Sokolow-Lyon voltage amplitude and left ventricular hypertrophy in relation to the ACE I/D polymorphism.](image-url)

Sokolow-Lyon voltage amplitudes (panel A) and odds ratios of left ventricular hypertrophy (LVH, panel B) by the angiotensin converting enzyme (ACE) genotype in 1262 subjects not on antihypertensive medication. The analyses were adjusted for sex, age, body mass index, alcohol intake and systolic blood pressure. Odds ratios of LVH were calculated for each genotype against the overall risk of the study population. The number of subjects for each genotype is given at the bottom. For the definition of LVH, see legends to Fig.1.
and higher prevalence of LVH, suggesting inadequate monitoring and treatment of these high risk patients. Hypertension therefore represents a major, prevalent, modifiable risk factor for LVH in China. In fact, hypertension has been attributed with nearly 12% of all deaths in China.34 Despite this, there is minimal awareness and inadequate treatment of this disease.28

To the best of our knowledge, our study was the first that demonstrated a significant association between LVH and the ACE DD allele in a general Chinese population. One previous Chinese study was small and limited to hypertensive patients, and failed to show significant association.29 Our finding was in line with a large population-based European study correlating ACE I/D genotype with ECG diagnosed LVH16 and a meta-analysis of studies analyzing the influence of the ACE I/D polymorphism on the risk of LVH.17 However, probably due to inadequate power in our investigation, we did not find significant genetic association when the Cornell product criterion was used for the diagnosis of LVH. In the Framingham Heart Study which included 331 (13.6%) patients on antihypertensive medication,30 the ACE DD genotype was not significantly associated with LVH diagnosed by echocardiography. This null finding might be attributable to the confounding of antihypertensive treatment.10

The insignificant association between LVH and the ACE polymorphism in treated hypertensive patients is insufficiently understood. Long term antihypertensive treatment may effectively prevent and regress left ventricular hypertrophy. We therefore hypothesize that antihypertensive therapy might to some extent have regressed left ventricular hypertrophy associated with the ACE D allele. How the ACE I/D polymorphism can be involved in the development of cardiac hypertrophy is less clear.31 The ACE I/D polymorphism was originally found to explain up to half of the variance in circulating ACE levels.32 The increased ACE level and enzyme activity associated with ACE D allele33 may modify circulating fluid volume, sodium homeostasis and vascular tone.33-35 The higher degradation rate of bradykinin in carriers of the D allele may also predispose to cardiac hypertrophy.36 However, the possibility that the ACE I/D polymorphism may not be causative and only behaves as a marker for closely linked culprit mutations cannot be excluded.31

Our study should be interpreted within the context of its limitations. First, the applicability of the Sokolow-Lyon voltage and Cornell product criteria in the ECG diagnosis of LVH in a Chinese population is unknown. The high prevalence of LVH in our study, to some extent, can also be a result of idiosyncratically high voltages but not myocardial hypertrophy per se. The fact that body mass index was a negative predictor of LVH in our study, presumably because of attenuation of precordial lead voltages, supports this hypothesis. Obesity is uncommon in rural Chinese, possibly leading to overestimation of ECG diagnosed LVH, especially for those criteria reliant on precordial lead voltage amplitude alone. Second, the ECG has a low specificity for the diagnosis of LVH. Echocardiography and cardiac MRI have higher specificity but their utilization in large epidemiological studies, particularly in rural Chinese, remains very limited. Third, our study was cross-sectional, and hence no conclusions on causation can be inferred.

In summary, our study suggests that LVH is highly prevalent in Chinese, and is associated with systolic blood pressure and the ACE D allele. The genetic association might be modulated by antihypertensive therapy. When confirmed in other Chinese populations and especially in prospective studies, our findings would have clinical implications. LVH is an important, modifiable cardiovascular risk factor and along with its main determinant, systolic blood pressure, represents a major unmet need in the health of the Chinese population.

Acknowledgements

The authors gratefully acknowledge the voluntary collaboration of the study participants and the support of the local public health authorities of Jingning County, Zhejiang Province, China. This study was financially supported by grants from the National Natural Science Foundation of China (grants 30871360 and 30871081), Beijing, China, and the Shanghai Commissions of Science and Technology (grant 07JC14047 and the “Rising Star” program 06QA14043) and Education (grant 07ZZ32 and the “Dawn” program 08SG20), and the European Union (InGenious HyperCare LSHM-CT-2006-037093 and HYPERGENES FP7-HEALTH-2007-201550). Dr Alexander Headley was supported by the AusAID Australian Youth Ambassadors for Development scheme and the George Foundation of the George Institute for International Health, Sydney, Australia.

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