Electrocardiographic Left Ventricular Hypertrophy, β_3 Adrenergic Receptor Polymorphism and Endpoint of ACEI Treatment of Hypertension

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KEY WORDS: hypertension; electrocardiography; genetic polymorphisms; ACE inhibitors

Abstract

Objectives: Current treatment strategies for essential hypertension are effective only in a portion of patients. Many factors influence the therapeutic effect, including the status of left ventricular hypertrophy (LVH) and genetic variations. LVH influences the intensity of left ventricular depolarization and is a risk factor for many cardiovascular events independent of conventional predictors. The β_3-adrenergic receptor (ADRB3) gene polymorphism is also associated with elevated blood pressure (BP) and cardiovascular disorders. In this study, we examined the impact of LVH (diagnosed by an electrocardiograph) and ADRB3 polymorphism on response to anti-hypertensive therapy.

Methods: We treated a hypertensive cohort with benazepril for a period of 15 days, and evaluated the drug effect by BP drop (ΔBP). We performed standard ECG measurement on each sub-

ject and determined ADRB3 genotypes experimentally. Smoothing plots were first used to visualize the relationship, and additive models were fitted to investigate the role of LVH and ADRB3 polymorphism as well as their interactions with the treatment effect.

Results: Electrocardiographic LVH was positively associated baseline BP, and negatively associated with ΔBP. The relationship was in a linear pattern. The association is greatly modified by ADRB3 genotype. In ADRB3 wild-type patients, the effect size increased, however, among ADRB3 mutant subjects, the association was attenuated and remained statistically non-significant.

Conclusion: Our results suggested the predictive value of electrocardiographically diagnosed LVH to the anti-hypertensive treatment effectiveness, and pointed out the importance of gene-environment interaction. Our finding could have significant clinical implications to optimize the therapeutic dose range based on the ECG indexes.

INTRODUCTION

Primary hypertension affects more than 20% of white adults, significantly increasing the risk of heart attack and stroke.[1,2] Angiotensin converting enzyme inhibitors (ACEI), such as benazepril, are among the most widely prescribed anti-hypertensive medications.[3,4] Despite their popularity, significant inter-individual variations in clinical response to ACEI have been reported,[5] which suggest that environmental or genetic factors influence the drugs' effectiveness.

The Sokolow-Lyon Index (SLI) of an electrocardiogram (ECG), defined as the sum of RV5 and SV1, reflects the intensity of left ventricular depolarization and hypertrophy.[6-8] Subjects with a high SLI value are classified clinically as having electrocardiographic left ventricular hypertrophy (LVH).[6-8] LVH can be considered an adaptive response to the increased afterload in hypertension,[9,10] as well as a result of obesity or stimulation by angiotensin II or insulin.[10] Several studies have suggested that LVH is a surrogate endpoint for many cardiovascular events, independent of all conventional predictors.[10-12] Despite the relation between LVH and hypertension, the predictive value of LVH on the endpoint of anti-hypertensive therapy has not been systematically addressed.

The β_3-adrenergic receptor (ADRB3) is mainly expressed in adipose tissue and contributes to population variations in energy expenditure and body fat distribution.[13] A missense mutation of the gene, resulting in substitution of tryptophan with arginine at codon 64 (W64R), has been reported.[14-16] This single nucleotide polymorphism (SNP) has been associated with insulin resistance, obesity, hyperinsulinemia, and hypertension,[14-19] which could contribute to the development of LVH and cardiac dysfunction.[20-22] It is possible, therefore, that the therapeutic effect of ACEI treatment varies according to ADRB3 genotype and LVH status.

In this study, we treated a hypertensive cohort with benazepril for a period of 15 days and evaluated the drug's effectiveness in lowering blood pressure. The aim of the study was to investigate whether ECG-diagnosed LVH is a significant predictor of blood pressure decrease (ΔBP) after drug therapy and whether the ADRB3 W64R genotype modifies the predictive effects of the initial LVH on the decrease in BP.

METHODS AND MATERIALS

Study Site and Population

The study was conducted in Huoqiu County, Anhui Province, China from July 2000 to May 2001. Huoqiu is located in the western part of Anhui

Table 1. Clinical Characteristics and ADRB3 Genotype of Study Cohort (n = 924)*

	Mean ± SD
Age, y	48.4 ± 8.0
Height, cm	161.5 ± 8.0
Weight, kg	65.8 ± 12.0
Body Mass Index, kg/m²	25.2 ± 3.9
Blood pressure, mmHg	
Systolic at baseline	149.4 ± 14.9
Diastolic at baseline	93.4 ± 8.5
Systolic after treatment	139.5 ± 17.3
Diastolic after treatment	88.2 ± 11.0
Sokolow-Lyon Index (mV × 10)	23.4 ± 7.7
	Percent
Ever anti-hypertensive drug use, %	14.0 %
Female, %	52.0 %
Former cigarette smoker, %	6.4 %
Current cigarette smoker, %	20.3 %
Former alcohol drinker, %	5.8 %
Current alcohol drinker, %	25.9 %
ADRB3 R64 Allele Frequency, %	16.3%

* ADRB3 indicates β_3-adrenergic receptor; and SD, standard deviation.

province, among the plains and foothills of Dabie Mountain. The residents speak a unique dialect, and the population has existed for hundreds of years with limited migration and admixture. Subjects who met the following criteria were enrolled in the study: (1) diagnosed with diastolic blood pressure (BP) of 90 to 120 mmHg or systolic blood pressure of 140 to 200 mmHg on three separate occasions; (2) aged between 21 and 65 years; and (3) lived in Houqiu County for at least 2 years. To avoid misclassification and reduce the risk of severe adverse responses, we excluded patients who (1) were diagnosed with secondary hypertension; (2) were receiving antihypertensive treatment or had taken others drugs within 2 weeks prior to the examination; (3) had a body mass index (BMI) > 33 kg/m2; or (4) had been diagnosed with another severe disease or disorder. Each eligible hypertensive patient who was willing to participate provided written consent. The institutional review board of Anhui Medical University and the Harvard University School of Public Health approved the study procedure. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Blood Pressure and ECG Measurements

Supine blood pressure was measured at 9:00 AM after 60 minutes of resting in a supine position. No alcohol, cigarettes, coffee or tea were taken for one hour prior to the measurements. Systolic blood pressure was defined as Korotkoff phase I (appearance of sound), and diastolic pressure as Korotkoff phase V (disappearance of sound), respectively. Three consecutive readings were taken on the same arm, with 30 seconds between each reading. The average of the 3 readings was used in our analysis. A standard 12-lead ECG examination was then performed on each participant.

Table 2. Association of Electrocardiographic Left Ventricular Hypertrophy with Blood Pressure and Blood Pressure Drop after Benazepril Treatment*

	Systolic, mmHg		Diastolic, mmHg	
	β ± s.e.	*P*	β ± s.e.	*P*
Baseline BP				
Sokolow Lyon Index, mV	4.73 ± 0.66	<0.0001	1.89 ± 0.40	<0.0001
ΔBP after Treatment				
Sokolow Lyon Index, mV	-1.98 ± 0.68	0.004	-1.11 ± 0.47	0.018

*BP indicates blood pressure; ΔBP, blood pressure drop; and s.e, standard error. Regression models were adjusted for age, age^2, weight, weight^2, height, height^2, BMI, smoking status, alcohol drinking, and baseline blood pressure (only in ΔBP).

Questionnaire

After blood pressure was taken, patients were interviewed using a standardized questionnaire. The following information was collected: (1) social-economic characteristics (age, gender, education level, marital status, birthplace, family size, household income, etc.); (2) personal health history, including medication use, allergies, and history of hospitalizations; (3) occupation history, including current and former jobs, work environment, and possible occupational exposures; (4) lifestyle characteristics, including active/passive smoking, alcohol use, and tea consumption; and (5) dietary factors, including intake of meat, fruit, vegetables, rice, and other foods. Body weight and height were also measured to the nearest 0.1kg and 0.1cm, respectively, with light clothing and no shoes.

Benazepril Therapy

All qualified participants were asked to take one 10-mg tablet of benazepril (Ciba-Geigy, Beijing, China) every morning for 15 consecutive days. The first dose was taken at the study center on day 1, and subsequent doses were taken at the patient's home for the next 14 days. The subjects visited the study center every 3 days for follow-up, which included measurement of blood pressure and heart rate and documentation of other medications or therapies received and any adverse reactions. On the 16th day, patients returned to the study center at 8 AM after fasting overnight. They again rested in supine position for one full hour, and supine blood pressure was measured at 9 AM. Patients who reported taking other medicine during the study were excluded from the analysis.

Phlebotomy and DNA Extraction

Blood was drawn via venipuncture from the median cubital vein using a BD Safety-Lok blood collection set (Becton Dickinson, Franklin Lakes, NJ) into a 10 mL vacutainer (Becton Dickinson, Franklin Lakes, NJ) containing EDTA. The blood was kept on ice and subsequently centrifuged for 10 minutes at 4,000 × g at 4˚C. DNA was extracted at the Institute of Biomedicine, Anhui Medical University using the methods previously described. [23]

Genotyping

The ADRB3 polymorphism was genotyped using a PCR restriction fragment length polymorphism (RFLP) method. The genomic sequence flanking the polymorphism was PCR-amplified using primers 5'-CAATACCGCCAA-CACCAGTGGG-3' and 5'-GGTCATG-GTCTGGAGTCTCG-3' in a volume of 10 µL containing 30 ng of genomic DNA, 2.5 mM $MgCl_2$, 200 µM of each deoxynucleotide triphosphate, 200 nM of each primer, 0.5 unit of Taq DNA

Table 3. Interaction of Electrocardiographic Left Ventricular Hypertrophy and ADRB3 W64R Genotype on Blood Pressure and Blood Pressure Drop after Treatment*

	ADRB3	Systolic, mmHg β ± s.e.	Systolic, mmHg *P*	Diastolic, mmHg β ± s.e.	Diastolic, mmHg *P*
W64W (N =737)	**Baseline BP**				
	Sokolow Lyon Index, mV	6.48 ± 0.98	<0.0001	2.28 ± 0.57	<0.0001
	ΔBP after Treatment				
	Sokolow Lyon Index, mV	-2.41 ± 1.03	0.020	-1.42 ± 0.71	0.045
W64R or R64R (N=185)	**Baseline BP**				
	Sokolow Lyon Index, mV	2.06 ± 1.35	0.13	0.07 ± 0.88	0.941
	ΔBP after Treatment				
	Sokolow Lyon Index, mV	-1.26 ± 1.35	0.366	0.32 ± 1.03	0.759

*ADRB3, β_3-adrenergic receptor; s.e, standard error. Regression models were adjusted for age, age^2, weight, weight^2, height, height^2, BMI, smoking status, alcohol drinking, and baseline blood pressure (only in ΔBP).

polymerase (Applied Biosystems, Foster City, Calif), and 1× reaction buffer. The PCR reaction was carried out using a DTC-225 thermocycler (MJ Research, Watertown, Mass) with an initial denaturation at 94˚C for 10 minutes, followed by 14 touchdown cycles of 94˚C for 30 seconds, 61 to 54˚C for 30 seconds (decrease 0.5˚C each cycle), and 72˚C for 30 seconds, then 30 cycles of 94˚C for 30 seconds, 54˚C for 30 seconds, and 72˚C for 30 seconds, and finally 7 minutes of extension at 72˚C. The PCR amplicons were digested with 3 units of MspI (New England Biolabs, Beverly, Mass) at 37˚C for 15 hours. Digested products were separated by electrophoresis on 2.5% agarose gels (FMC Bioproducts, Rockland, ME) and visualized with ethidium bromide staining under ultraviolet illumination.

Statistical Analysis

SAS 6.12 (SAS Institute, Inc.) and Splus 2000 Professional (Mathsoft Inc.) were used in data management and analysis. The Sokolow-Lyon Index was calculated as the sum of |SV1| and |RV5|. First, a residual plot of blood pressure (BP) or blood pressure decrease after treatment (ΔBP) vs. SLI was generated using the lowess smoothing function. Residuals were generated from a linear regression model adjusted for age, age^2, weight, weight^2, height, height^2, body mass index (BMI), gender, smoking status and alcohol use. The plot of ΔBP was also controlled for baseline blood pressure.

Because the plots suggested a linear relation, we performed regression analysis with multivariate linear additive models. In the model, BP or ΔBP was treated as dependent variable, and SLI was the primary independent variable, other covariates also entered the model to adjust for potential bias. Gender is a potential effect modifier in this study, we initially stratified the analysis by gender; however, no evidence of effect modification was detected, so the data were combined and we adjusted for gender in regression models. In examining the potential synergetic effect of SLI and ADRB3 genotype on the outcome (BP or ΔBP), we introduced the interaction term (SLI × ADRB3) into the model. Also, we performed stratified analysis to explore whether the relationship

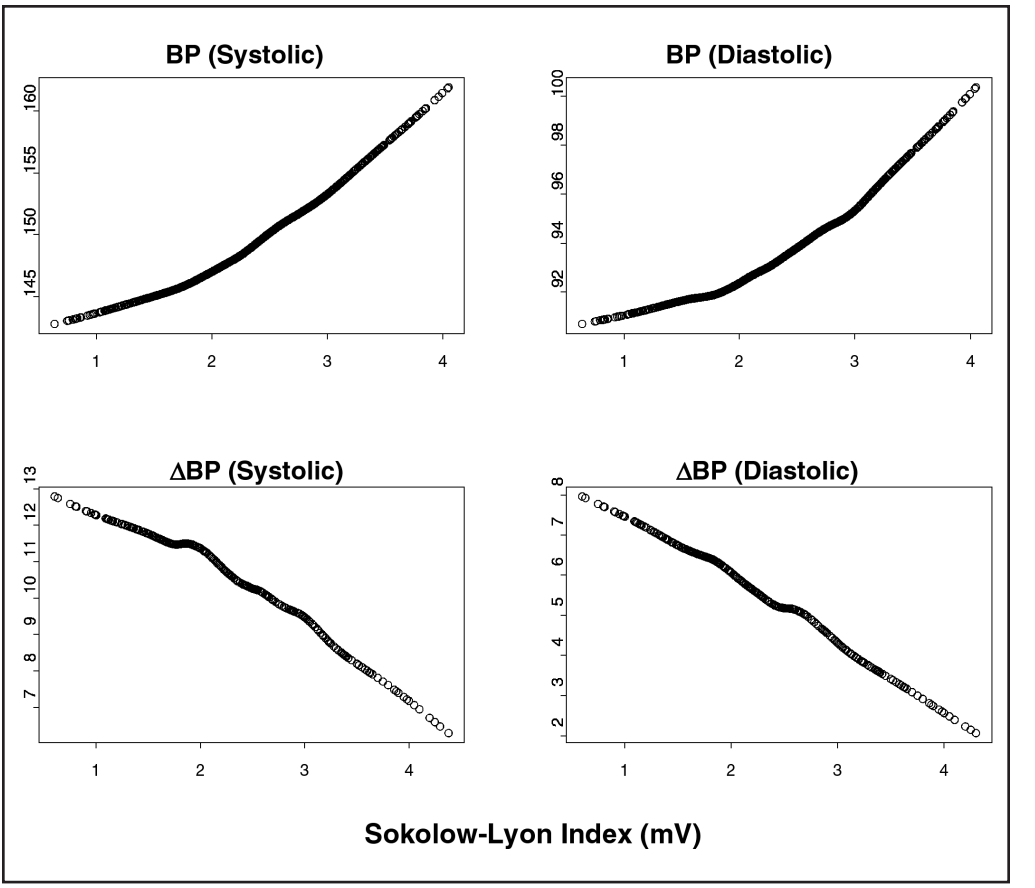

Figure 1. Residual plot of baseline blood pressure (BP) and blood pressure drop after treatment ΔBP) vs Sokolow-Lyon Index with lowess smoothing. Residuals were adjusted for age, age^2, weight, weight^2, height, height^2, BMI, smoking status, alcohol drinking, and baseline blood pressure (only in plotting of ΔBP). Lowess window was set as 2/3. Y-axis for ΔBP plot is the blood pressure drop after treatment ($BP_{baseline}$-$BP_{after\ treatment}$), therefore larger value indicates better therapeutic effect.

between SLI and BP or ΔBP remains consistent in various genetic backgrounds. Because the allele frequency of R64 is relatively low in our sample, we combined the W64R and R64R individuals.

RESULTS

A total of 1,199 hypertensive persons from Huoqiu County were initially recruited for this study. Of these, 129 failed to meet our enrollment criteria, 102 did not complete the follow-up treatment, and 44 were excluded from the study because major phenotypic information was missing. The remaining 924 subjects were included in the analysis of blood pressures. Two more patients were dropped from the ADRB3 analysis because of incomplete genotype information. A clinical summary of the study cohort is presented in Table 1. All participants were diagnosed with essential hypertension and had used no anti-hypertensive therapy for at least 2 weeks prior to the study; most subjects (86.0%) had never received medication for hypertension. Mean blood pressure before treatment was 149.4 mmHg systolic and 93.4 mmHg diastolic. After

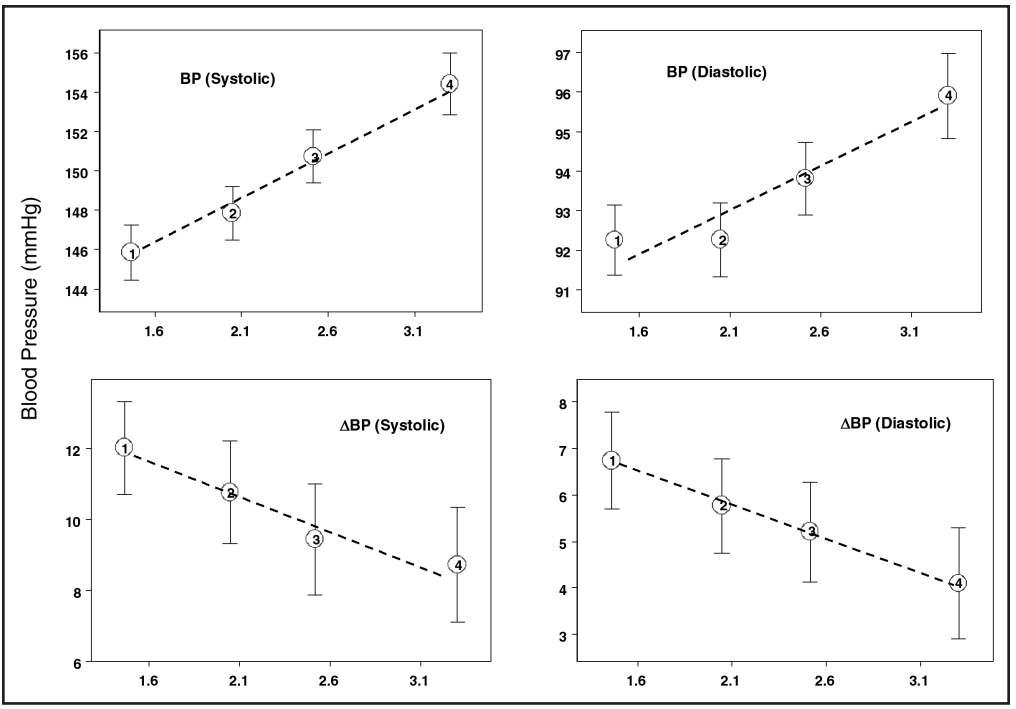

Figure 2. Quartile plot of baseline blood pressure (BP) and blood pressure drop after treatment (ΔBP) vs. Sokolow-Lyon Index (SLI). BP and ΔBP were adjusted for age, age^2, weight, weight^2, height, height^2, BMI, smoking status, alcohol drinking, and baseline blood pressure (only in plotting of ΔBP). Y-axis for ΔBP plot is the blood pressure drop after treatment ($BP_{baseline}$-$BP_{after\ treatment}$). The mean BP or ΔBP of each quartile is represented as a circle, and the number inside the circle stands for the quartile order. The length of the error bar is defined as 1.96×standard error of the quartile. The fitted curves between SLI quartile and BP or ΔBP were shown as dashed lines in each panel.

treatment with benazepril for 15 days, blood pressure decreased to 9.9 mmHg and 5.2 mmHg in systolic and diastolic branches respectively.

To examine the relationship between SLI and blood pressure or its drop, a residual-residual smoothing plot was first constructed (Figure 1, Panels A-D). All four smoothing curves suggested linear patterns. SLI was positively associated with baseline systolic and diastolic BP (Panels A and B), and negatively associated with ΔBP for both systolic and diastolic pressures (Panels C and D). The plots of BP and ΔBP against SLI quartiles also showed similar linear trends (Figure 2).

ECG-diagnosed LVH was significantly associated with both BP and ΔBP (Table 2). Each 1 mV increase in SLI was associated with 4.73 mmHg (P<0.0001) increase in systolic blood pressure (SBP) and 1.89 mmHg (P<0.0001) increase in diastolic blood pressure (DBP). However, SLI was inversely related to the decrease in BP following benazepril treatment; each 1 mV increase in SLI was associated with a ΔSBP of -1.98mmHg (P=0.004) and a ΔDBP of -1.11mmHg (P=0.018). Although ADRB3 genotype was only marginally associated with BP (systolic: β= -0.52mmHg and P=0.61; diastolic: β= -1.16mmHg and P=0.07) or ΔBP (systolic: β = -2.05mmHg and P=0.06; diastolic: β= -0.57mmHg and P=0.45), it strongly modified the effect of SLI on BP (Table 3). In patients with the

ADRB3 wild type, the magnitude of the effect associated with SLI increased, whereas among subjects with the mutant form of ADRB3, the association between SLI and BP was attenuated and did not reach statistical significance. Due to limited sample size and low frequency of ADRB3 R64 allele, the interaction term (SLI × ADRB3) is not significant in the model. In addition, we found the SLI was not associated with ADRB3 genotype.

DISCUSSION

Electrocardiographically diagnosed LVH has long been considered a potent predictor of hypertension and cardiovascular events.[6,10] as well as a consequence of elevated blood pressure and increased afterload.[9] In this study, we observed a strong positive association between SLI and resting BP in hypertensive subjects, and we found that subjects with a lower SLI had a more pronounced response to benazepril treatment. We also found evidence of an interaction between SLI and ADRB3 genotype in the therapeutic response to benazepril treatment: although SLI was significantly associated with both BP and ΔBP in subjects with the wild-type ADRB3, no association between SLI and either BP or ΔBP was observed in persons with the mutant form of ADRB3.

Our findings are biologically meaningful. The inter-individual variation in drug response to antihypertensive medications is partially due to the complex nature of hypertension. For instance, the degree of LVH could reflect a particular subtype of essential hypertension.[9,10,24] such that patients with different SLI showed variant drug response. As a consequence of hypertension, LVH was correlated the blood pressure in our study. Patients with LVH may have more severe or prolonged hypertension, and their response less response to ACEI treatment may due to the geometry change in the cardiovascular system. ADRB3 R64 mutation modified the receptor function and is reported in association with insulin resistance, obesity and LVH, which are closely related with hypertension status and perhaps its subtypes.[14-19]

Our investigation possessed several major advantages in avoiding potential bias and improving power. (1) Before the administration of the benazepril monotherapy, no hypertensive subject was taking any other medication and the potential confounding due to other drug effects or drug-drug interaction was excluded. (2) All hypertensives were free from other cardiovascular conditions such as coronary heart disease or diabetes mellitus at the baseline. (3) The study population has settled for hundreds of years and is thought to be homogeneous genetically. (4) The residential/occupational environmental and dietary habits were similar among our study subjects, by this means, we controlled for potential socio-economic confounders, which is difficult to measure and to quantify.

Managing essential hypertension is a complicated task, because individuals may respond differently to the same type of drug.[25] Our results have extended new horizons in cardiovascular medicine by demonstrating the predictive value of electrocardiographic LVH in anti-hypertensive treatment effectiveness. The underlying mechanisms clearly deserve further studies to resolve. If confirmed independently by another investigation, our results could have significant clinical implications: the choice of medicine and the therapeutic dose range can be predicted based on the ECG indexes, which is widely and inexpensively available. That will allow for optimizing treatment effect at the individual level. Furthermore, there is considerable opportunity for future

investigations to deepen our understanding of hypertension subtypes and their responses to different therapeutic regimens.

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