Effect of Interaction Between Noise and A1166C Site of AT1R Gene Polymorphism on Essential Hypertension in an Iron and Steel Enterprise Workers

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Objective: This study aimed to analyze the interaction of Angiotensin II type 1 receptor (AT1R) gene polymorphism and occupational noise on the occurrence of essential hypertension (EH) in steel and iron enterprise men workers. **Methods:** A case control study of 935 iron and steel enterprise men workers was conducted, which included 312 cases of hypertension and 623 cases without hypertension. The noise at the workplace was assessed. Polymorphism of AT1R of the workers was examined using polymerase chain reaction - restriction fragment length polymorphism. **Results:** Polymorphism of AT1R (AC+CC vs. AA, odds ratio [OR] = 1.760, 95% confidence interval [CI]: 1.061~2.920) and noise (greater than or equal to 85 dB(A), OR = 1.641, 95%CI: 1.225~2.198) were independent determinants of EH using multivariate Logistic regression. Compared with AA carriers without noise, AC+CC interacted with noise (OR = 2.519, 95%CI: 1.254~5.062) based on the multiplied model. **Conclusions:** AC+CC genotype of AT1R and noise were the risky factors of EH. These factors also interacted with each other.

Hypertension essential (EH) is one of the most common cardiovascular diseases. The prevalence rate of hypertension among Chinese people aged 18 and over has raised from 18.8% to 25.2% from 2002 to 2012.[1,2] The etiology of hypertension is complex, and the pathogenesis of hypertension is not clear. The Renin angiotensin aldosterone system (RAAS) is an endocrine system which regulates blood vessel tone, sodium and water metabolism, and plays a key role in the occurrence and development of hypertension. The genes of RAAS are the most likely susceptibility genes in EH. The major components of RAAS include renin, angiotensin, angiotensin II, angiotensin II type 1 receptor (AT1R), aldosterone, and so on. AT1R is mainly distributed in vascular smooth muscle and heart. The vasoconstriction is produced after binding angiotensin II. In 1994, Bonnardeaux et al[3] detected five kinds of genetic polymorphisms, among which T573C, A1166C, and A1062G were the most frequently replaced, and the most frequently studied topics are on the association of A1166C polymorphism and EH. A number of studies have indicated that A1166C polymorphism was associated with EH.[4,5] Noise is one of the major occupational hazards in the workplace of the iron and steel industry.[6] The study on the relationship between occupational noise exposure and hypertension is increasing, but the results are not consistent. A number of studies have confirmed that noise may be a risk factor for hypertension,[7-10] while there are also reports that there was no association between the two.[11] A recent meta-analysis showed that noise was associated with EH.[12] One study has shown that noise can make the body plasma renin, angiotensin II, and aldosterone concentration elevated, and that it activates the RAAS. The excessive activation of RAAS promotes the occurrence and development of EH.[13] Most researches were limited to the effect of simple noise exposure or AT1R gene polymorphism to EH, and the interaction between noise and AT1R gene polymorphism on hypertension has not been reported yet. In our study, men workers from a cold rolling and gas factory were selected and divided into two groups: an EH group with 312 cases of hypertension, and a control group with 623 cases without hypertension. A series of occupational epidemic investigations were carried out and compared between the two groups. The interaction between noise and AT1R gene polymorphism on hypertension was then analyzed.

STUDY POPULATION AND METHODS

Study Population

In 2014, 923 men workers with more than 1 year of experience in an iron and steel enterprise (cold rolling and gas factory) in Tangshan, Hebei Province were selected as observed subjects through an annual physical examination.

The present study had got the approval of Ethics Committee of Hebei United University (No. 13049). All subjects in the study were informed and agreed to this study.

Using the US Preventive seventh report of the Joint National Committee on Detection, Evaluation and Treatment of Hypertension (JNC 7) as a diagnostic criteria,[14] and combining that with the medical history of workers, 312 of them were diagnosed with high blood pressure. The 623 non-hypertensive workers from the diagnosis was categorized as the control group.

Inclusion criteria of the subjects in the EH group: (1) The subjects were the workers in an iron and steel enterprise who participate in occupational physical examination from February 2014 to July 2014. (2) Being diagnosed with hypertension by JNC 7. (3) Men and of Han ethnicity. (4) Younger than or equal to 55 years old. (5) Agreed to participate in the study. Exclusion criteria: (1) with history of liver or kidney disease. (2) Being detected to have high blood sugar in the examination or had history of diabetes. (3) With secondary hypertension or other cardiovascular diseases. (4) Changed his type of work before. (5) Being exposed to high temperature.

The subjects in the control group had the same inclusion and exclusion criteria as the EH group except that the workers were not diagnosed with hypertension by JNC 7.

METHODS

Epidemiological Investigation

Site Survey:

All subjects had a face-to-face interview conducted by a trained staff to complete a questionnaire survey. Topics covered include: demographic data (age, sex, height, weight, marital status, education, income); occupational history (length of service, type of work, work shift), family history of hypertension; medical history; living behavior and habits (smoking, alcohol consumption, tea consumption, salt intake, etc.).

Physical examination including height, weight, heart rate, ECG, etc. were measured by trained professionals in accordance with the standards of the use of instruments. The results of serum total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were measured and observed too.

Determination of Noise and High Temperature

The noise exposure at the workplace was assessed using a sound analyzer (TES-1350A; TES Electronic Corp, Taiwan). Time weighted average (TWA) noise defines a worker's daily exposure to occupational noise (normalized to an 8-hour day), taking into account the average levels of noise and the time spent in each area. This is the parameter that is used by the Occupational Safety and Health Administration Regulations and is essential in assessing a worker's exposure and any actions that would be required. In our study, 40 hours TWA levels were detected according the type of work, detention time, and work shift situation. Noise exposure is greater than or equal to 85 dB(A). According to the reports by Zhao et al,[15] cumulative noise exposure (CNE) were calculated as follows:

$$CNE = 10 \times \log\left(\sum 10^{0.1 \times L(A)eq} \times \text{the years of noise exposure}\right)$$

The temperature at the workplace was detected using a wet bulb globe temperature (WBGT) analyzer (QT-36; Quest technologies Corp, America) in July and August, 2014. After the location and residence time of workers were recorded, WBGT values of the workers were calculated. If the WBGT is greater than or equal to 25 °C, and there were productive heat sources, the workers were exposed to high temperature.

AT1R A1166C Gene Polymorphism Detection

Using whole blood rapid genomic DNA extraction kit made by Beijing Aid lab Biotechnology Co., Ltd., we extracted genomic DNA from the 2 mL of blood sample. Each sample is a fasting blood sample obtained from the vein. The upstream primer was 5′-ATAATG TAAGCTCATCCACC-3′, whereas the downstream primer was 5′-GAGATTGCATTTCTGTCAGT-3′. Polymerase chain reaction (PCR) total reaction volume was 25 μL, which included Taq Master Mix PCR of 12.5 μL, upstream primer of 1.0 μL, downstream primer of 1.0 μL, DNA samples of 1.0 μL, and deionized water of 9.5 μL.

The PCR was performed for 35 cycles using the Biometra Cycled from Germany. The temperature for predenaturation was 94 °C for 5 minutes. The initial denaturation was at 94 °C for 30 seconds, annealing at 55 °C for 40 seconds, extension at 72 °C for 40 seconds. At the end of the last (35th) cycle, there was a final extension at 72 °C for 5 minutes. The PCR product was subjected

to Dde I restricted enzyme digestion for 3 hours at 37 °C and electrophoresed on a 2.0% agarose gel with ethidium bromide staining. The polymorphism of AT1R A1166C was detected by an ultraviolet analyzer. As shown in Fig. 1, the AT1R A1166C polymorphism was visualized as 350 bp fragments for AA genotype, 350, 211, 139 bp fragment for AC genotype and 211, 139 bp fragments for CC genotype.

Statistical Methods

Data were entered into the database using Epidata 3.0, and analyzed using SPSS 17.0 (IBM Corp, Armonk, NY). The distribution of genotype was tested to determine whether it was consistent with Hardy-Weinberg's law of genetic equilibrium. The distribution of polymorphism of AT1R A1166C between the EH group and control group was compared. The relationship between the interaction of gene-noise and EH was analyzed using two models. First one was the additive model using the crossover analysis indicated by Rothman and Greenland.[16] The second was the multiplicative model using Logistic regression.

RESULTS

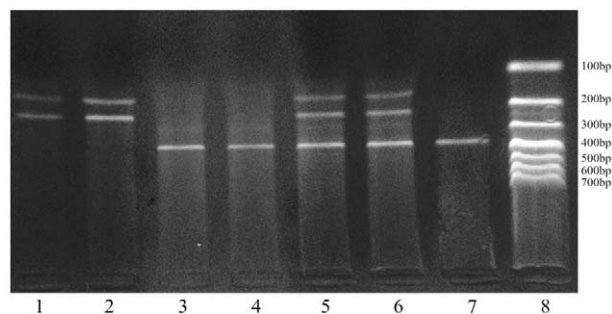### Comparison Between Workers of the EH Group and Control Group

Comparing the two groups, there were no significant difference ($P > 0.05$) in the age, length of service, work shift, smoking, alcohol consumption, tea drinking, and salt intake as shown in Table 1. 93.6% of workers were married in the EH group while 89.4% of the workers in the control group were married. The two groups had significant difference in marital status ($P < 0.01$). The percentage of having university education and above in EH group (19.6%) was lower than that of control group (33.1%) significantly ($P < 0.01$). Body mass index (BMI) of EH group (25.74 ± 3.68) was higher than that of the control group (24.55 ± 3.23) significantly ($P < 0.01$). The percentage of family history of hypertension workers in EH group (42.9%) was higher than that of control group (28.9%) significantly ($P < 0.01$).

Comparison of Noise Exposure Between EH Group and Control Group

As shown in Table 2, the percentage of noise level (greater than or equal to 85 dB[A]) in EH group (58.3%) was higher than that of control group (44.8%) significantly ($P < 0.01$). The risk of EH in the workers exposing to noise increased, OR = 1.726 (95%CI: 1.311~2.272).

Distribution of Genotype and Allele of AT1R A1166C in EH Group and Control Group

The genotype distribution of AT1R A1166C was in accordance with the law of Hardy-Weinberg genetic equilibrium. Due to

FIGURE 1. Agarose gel (2%) electrophoresis of AT1R A1166C. 1, 2: CC(139 bp+211 bp); 3, 4: AA (350 bp); 5, 6: AC(139 bp+ 211 bp+350 bp); 7: PCR product; 8: DNA marker.

TABLE 1. Comparison of the Basic Information Between Workers of EH Group and Control Group

Factors	EH Group ($n = 312$)	Control Group ($n = 623$)	t (χ^2)	P
Age ($\bar{x} \pm$ s, yr)	38.44 ± 8.51	38.11 ± 8.04	0.5803	0.562
Length of service ($\bar{x} \pm$ s, yr)	17.97 ± 9.64	17.54 ± 9.21	0.663	0.508
Marriage (married, %)	292 (93.6)	557 (89.4)	4.357	0.037
Education years (beyond university, %)	61 (19.6)	206 (33.1)	18.611	<0.001
BMI ($\bar{x} \pm$ s, kg/m^2)	25.74 ± 3.68	24.55 ± 3.23	5.063	<0.001
Shift work (%)	229 (73.4)	447 (71.7)	0.282	0.326
Family history of hypertension (%)	134 (42.9)	180 (28.9)	18.415	<0.001
Smoking (%)	187 (59.9)	347 (55.7)	1.524	0.217
Alcohol consumption (%)	76 (24.4)	118 (18.9)	3.712	0.054
Tea consumption (%)	153 (49.0)	274 (44.0)	2.143	0.143
Salt intake (high, %)	102 (32.7)	167 (26.8)	3.515	0.061
TC ($\bar{x} \pm$ s, mmol/L)	4.92 ± 1.77	4.79 ± 1.69	1.092	0.275
TG ($\bar{x} \pm$ s, mmol/L)	1.88 ± 0.73	1.86 ± 0.56	0.4637	0.643
HDL-C ($\bar{x} \pm$ s, mmol/L)	1.41 ± 0.72	1.42 ± 0.64	0.2159	0.8291
LDL-C ($\bar{x} \pm$ s, mmol/L)	2.85 ± 1.05	2.55 ± 0.89	4.571	<0.001

BMI, body mass index; EH, essential hypertension; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

the low mutation rate of AT1R A1166C, the chi-squared test was applied after the AC genotype and CC genotype were combined. The percentage of (AC+CC) genotype and the percentage of C allele of EH group were both higher than that of the control group significantly ($P < 0.05$) as shown in Table 3.

Multivariate Logistic Regression Analysis on the Relationship Among Environmental Factors, Polymorphism of AT1R A1166C and EH

Let EH be the function of environmental factors and AT1R gene polymorphism, multiple-factor logistic regression analysis was conducted. From Table 4, excluding the effects of marriage, education level, BMI, family history of hypertension, noise, LDL-C, the risk of having EH for AT1R A1166C AC+CC genotype carriers was 1.758 times for AA genotype carriers (95%CI: 1.048~2.948), which suggested that C allele may be a susceptibility gene for EH.

The Relationship Between CNE and Hypertension

The difference of CNE between case group and control group was significant ($\chi^2 = 50.638$, $P < 0.01$). As shown in Table 5, compared with the level of CNE less than 85 dB(A), the OR values of the other levels were 1.625, 2.297, 3.068, 4.743. The risk of EH risk gradually increased with CNE increasing. There was a dose–response relationship between CNE and EH (trend $\chi^2 = 50.371$, $P < 0.01$). Adjusted the OR also increased with the increasing of CNE after adjusting of BMI, hypertension family history, LDL-C, and AT1R and A1166C gene polymorphism.

Analysis of Gene–Noise Interaction Based on Additive Model

From the Table 6, no interaction between gene and noise was found based on the additive model ($U = 0.773$, $P = 0.440$).

Analysis of Gene–Noise Interaction Based on Multiplicative Model

Taking EH as the function of environmental factors, polymorphism of A1166C and interactive item with noise, we conducted multiple-factor logistic regression analysis and found how did the interaction between gene and noise impact the EH. Based on the multiplicative model, comparing (AC+CC) genotype on A1166C site of AT1R interacted with noise and AA genotype carriers whose noise exposure is less than 85 dB(A), we had OR = 2.519 (95%CI: 1.254~5.062) as shown in Table 7.

LITERATURE REVIEW AND DISCUSSION

Noise is a common physical exposure factor in the iron and steel enterprises. It has been reported by Afanasova et al[17] that many physical factors such as noise and chemicals were risk factors that cause systolic blood pressure elevation. In addition, the combination of noise and other factors accelerated the onset of hypertension. Fernández-D' Pool[18] conducted a case-control study in the Venezuelan oil company, but determined that there was no association between noise that was greater than 85 dB(A) and hypertension. Vlasova et al[19] observed workers exposed to noise in the nonferrous metallurgy industry in Russia using cross-sectional study. He found that the risk of hypertension of the workers exposed to occupational noise was significantly increased if the noise was greater than 94 dB(A) and the exposure to the noise was for more than 5 years. Skogstad et al[20] collected and reviewed prospective research literatures about workplace noise exposure and hypertension, cardiovascular disease, and conducted a meta-analysis. His results (OR = 1.68, 95%CI: 1.15–1.56.) showed that noise can increase the risk of hypertension. In our study, after making some adjustments in BMI, family history of hypertension, LDL-C, we found that noise increased the risk for men workers to get EH, OR = 1.668 (95%CI: 1.235~2.252).

TABLE 2. Comparison of Noise Level Between Workers of EH Group and Control Group

Noise	EH Group ($n = 312$)	Control Group ($n = 623$)	χ^2	P	OR (95%CI)
<85 dB (A)	130 (41.7)	344 (55.2)	15.271	<0.001	1.726 (1.311~2.272)
≥85 dB (A)	182 (58.3)	279 (44.8)			

CI, confidence interval; EH, essential hypertension; OR, odds ratio.

TABLE 3. The Genotypes and Alleles of AT1R A1166C Distribution in EH Group and Control Group

Gene	EH Group ($n = 312$)	Control Group (623)	χ^2	P
Genotype				
AA	278 (89.1%)	580 (93.1%)		
AC+CC	34 (10.9%)	43 (6.9%)	4.391	0.036
Alleles				
A	589 (94.4%)	1202 (96.5%)	4.436	0.035
C	35 (5.6%)	44 (3.5%)		

EH, essential hypertension.

TABLE 4. Multivariate Logistic Regression Analysis on the Relationship Among Environmental Factors, Polymorphism of AT1R A1166C and EH

Factor	Genotype	β	S.E.	Wald	P	OR (95%CI)
BMI		0.923	0.103	79.545	<0.001	2.517 (2.055~3.083)
Hypertension family history		0.523	0.154	11.568	0.001	1.687 (1.248~2.281)
Noise		0.495	0.149	11.044	0.001	1.641 (1.225~2.198)
LDL-C		0.350	0.152	6.243	0.014	1.353 (1.060~1.942)
A1166C	AA					1.00 (ref.)
	AC+CC	0.565	0.258	4.791	0.029	1.760 (1.061~2.920)

BMI, body mass index; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; S.E., standard error.

TABLE 5. The Relationship Between CNE and Hypertension

CNE (dB[A] × year)	EH Group (n, %)	Control Group (n, %)	OR (95%CI)	OR (95%CI)[*]
<85	64 (20.5)	240 (38.5)	1.00	1.00
85~	65 (20.8)	150 (24.1)	1.625 (1.090, 2.422)	1.321 (1.010, 2.022)
90~	68 (21.8)	111 (17.8)	2.297 (1.534, 3.441)	1.658 (1.104, 2.429)
95~	72 (23.1)	88 (14.1)	3.068 (2.040, 4.614)	1.873 (1.215, 2.976)
100~	43 (13.8)	34 (5.5)	4.743 (2.869, 7.841)	2.291 (1.267, 3.835)

CI, confidence interval; EH, essential hypertension; OR, odds ratio.
[*]OR: BMI, hypertension family history, LDL-C and AT1R and A1166C gene polymorphism were adjusted.

TABLE 6. Analysis of A1166C−Noise Interaction Based on Additive Model

Genetype	Noise	Number of EH	Number of Control	P	OR	95%CI
AA	<85 dB (A)	117	319		1.00 (ref.)	
AA	≥85 dB (A)	161	261	<0.001	1.682	1.260~2.245
AC+CC	<85 dB (A)	13	24	0.280	1.477	0.728~2.996
AC+CC	≥85 dB (A)	20	18	0.001	3.029	1.549~5.927

CI, confidence interval; EH, essential hypertension; OR, odds ratio.

TABLE 7. Analysis of Gene−Noise Interaction Based on Multiplicative Model

Genetype	Noise	OR (95%CI)	OR (95%CI)[*]
AA	<85 dB (A)	1.00 (ref.)	1.00 (ref.)
AC+CC	≥85 dB (A)	2.426 (1.273~4.623)	2.519 (1.254~5.062)

CI, confidence interval; OR, odds ratio.
[*]OR: adjusted noise, BMI, family history of hypertension, LDL-C.

After binding with AT1R, Angiotensin II was activated, causing vascular relaxation and the release of endothelin (ET). It also caused changes in the biological effects of water and salt metabolism, and cardiac and vascular wall fibrosis. It was reported[21] that the levels of ET in carriers of CC genotype were higher than that of AC and AA, while polymorphism of AT1R A1166C participated in the hypertension incidence through increasing ET level. Mehri et al[22] conducted a case-control study of 142 hypertension cases and 191 controls, and found that the risk of hypertension in the carriers of CC genotype was 3.45 times that of the AA genotype. Jinmin et al[23] studied the distribution of AT1R gene A1166C polymorphism in a case-control study, which include 250 cases of hypertension and 250 cases of normal healthy control. He found that the risk of hypertension in the carriers of AC+CC genotype was 2.4 times of AA genotype. However, no association of A1166C polymorphism and hypertension was found in Nigeria and Jordan.[24,25] Our study found that the AC+CC genotype carriers were 1.758 times more prone to suffer from hypertension than the AA genotype carriers.

The etiology of hypertension is very complex. It is caused by genes, environmental factors, and their interactions. The interaction means that when both factors are present, their true impact could be greater than (synergistic) or less than (antagonism) the sum of individual impacts, should only one be present. Thus, understanding the interactions between genes and environmental factors plays a crucial role in the prevention and control of hypertension. This would require the continuing challenge of identification and reasonable explanation of these interactions.

Popular statistical methods that we employed to analyze interaction are cross analysis and multiple-factor logistic regression. Nawaz and Hasnain[8] chose 385 men volunteers in Pakistan and found that the ID and DD carriers of angiotensin-converting enzyme who were exposed to noise (greater than or equal to 85 dB[A]) suffered an increased risk of hypertension. This showed that polymorphism of angiotensin-converting enzyme promoted the development of hypertension caused by noise. The report of Hwang et al[26] obtained similar results. The TT genotype of AGT M235T carriers was more likely to get hypertension. In our study, no interaction of gene−noise was found based on the additive model. While, compared with AA genotype carriers whose noise exposure less than 85 dB(A), (AC+CC) genotype carriers interacted with noise (greater than or equal to 85dB[A]) based on the multiplied model, OR = 2.519 (1.254∼5.062), the interaction of gene−noise may play a role in the occurrence of hypertension.

The effects on hypertension by AT1R gene A1166C polymorphism and noise were discussed in the present study. In our study, AC+CC genotype of AT1R and noise were independent determinants of EH. AC+CC genotype of AT1R interacted with noise based on the multiplied model. But only a single nucleotide mutation (AT1R gene A1166C) was detected in this study, and as a case control study, the ability to verify cause and effect relationship was not strong enough. There are more genes beyond AT1R, whose polymorphism can play important roles in the occurrence of hypertension. In our future work, we would explore further the interactions between RAAS genes and noise by adding more key genes and detecting the expression levels of enzyme or protein or using cohort study.

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