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Role of angiotensin converting enzyme (ACE) insertion/deletion polymorphism in sudden cardiac arrest.

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Abstract

Objective: To investigate the relationship between Angiotensin Converting Enzyme (ACE) insertion/ deletion polymorphism and sudden cardiac arrest.

Methods: A total of 232 patients who were received in department of cardiology were involved in this study. Genotype frequencies of the first two groups were investigated and compared. After determination of ACE I/D polymorphism, all patients were further divided into new three groups as the II homozygotes, ID heterozygotes, and DD homozygotes to investigate relationship ACE I/D polymorphism and other risk factors of SCA. Statistical analysis was used to analyse the data.

Results: Frequencies of DD genotype in SCA group was higher than the coronary disease group, P<0.05, and the D allele frequencies in SCA group compared with coronary disease group, P<0.05. Results of distribution of patients' characteristics according to the genotypes of the ACE I/D polymorphism showed no significant differences among all characteristics except for percentage of patients survival after SCA in which patients with II genotype had significant higher percentage, P<0.05, and patients died of SCA in which DD genotype had significant higher percentage, P<0.05.

Conclusion: The DD genotype is associated with a higher prevalence of SCA and may be a risk factor of survival rate of sudden cardiac death.

Keywords: Angiotensin converting enzyme, I/D polymorphism, Sudden cardiac arrest.

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Introduction

Sudden Cardiac Death (SCD) remains to be a health threat worldwide leading to almost 4-5 million deaths every year [1-3]. It is thought to be sudden and unexpected for cardiac etiology and an inevitable outcome for most patients with Sudden Cardiac Arrest (SCA) [4]. SCA is a final manifestation of a lethal arrhythmia, for example coronary ischemia, ventricular fibrillation, ventricular tachycardia or a severe bradyarrhythmia [5,6]. Symptoms such as dyspnea, chest pain or palpitations usually appear in very short time when SCA occurs, leading to a very low average survival rate even in developed countries [7,8]. Studies have proved that lots of risk factors are associated with SCA. Despite cardiovascular factors such as Coronary Artery Disease (CAD) or congestive HF [9-13] or other traditional risk factors such as inflammation [14], more and more novel possible factors possibly associated with SCA were studied recently, such as renal dysfunction [15] or epilepsy [16,17]. However, lots of studies showed different results in different regions and there are few researched focusing on risk factors of SCA in China. The human Angiotensin-Converting Enzyme (ACE) is a an extensively glycosylated protein and a membrane-bound monomeric zinc metallopeptidase of 170 kDa which is involved in lots of physiological process such as hypertension, heart failure, diabetes and so on [18]. Lots of studies have shown that the ACE gene locating in chromosome 17q23.3, is one of the risk factors of cardiovascular diseases that genetic epidemiological studies paid attention to, especially for the Insertion/Deletion (I/D) polymorphism which contains a 287 bp Alu repeat sequence in the intron 16 of *ACE* gene [19-21]. Studies showed that the different three genotypes: D/D of whom individuals have the highest levels of *ACE,* I/I of whom individuals have the lowest levels, and I/D of whom individuals have an intermediate levels [22]. The DD genotype have been associated with various of cardiovascular diseases, including myocardial infarction, essential hypertension, left ventricular hypertrophy and so on [23,24]. Though there are lots of studies focusing on effects of Insertion/Deletion (I/D) polymorphism of ACE on different kinds of cardiovascular diseases, to our best knowledge, so far there is no studies about Insertion/ Deletion (I/D) polymorphism of ACE on sudden cardiac arrest, which we tried to discuss in this paper.

Methods and Materials

Patients

A total of 232 patients who were received in department of cardiology in the Shengli Oilfield Central Hospital during 01, 2002~2008, 2016 were involved in this study. All patients were first divided into two groups, the SCA group (mean age 56.15

± 4.38, male: female=49:42) in which all patients had experienced sudden cardiac arrest, and the coronary disease group (mean age 54.32 ± 5.2, male: female=76:65) in which patients were diagnosed to have coronary disease but no SCA occurred during the treatment period. Genotype frequencies of the first two groups were investigated and compared. After determination of ACE I/D polymorphism, all patients were further divided into new three groups as the II homozygotes, ID heterozygotes, and DD homozygotes to investigate relationship ACE I/D polymorphism and other risk factors of SCA. An investigative protocol was used to collect information on age, gender, weight, medicines taken, history of cardiovascular disease and other comorbidities. Data regarding diabetes, strokes, myocardial infarction, and Dyslipidemia (DLP) were used to assess comorbidities. Definition of obesity was BMI>25 kg/m^2, definition of hypertensive was BP>130/85 mmHg. History of strokes and MI was based on clinical history and medical records. Besides above, condition of Left Ventricular Hypertrophy (LVH) was also considered which was defied as Left Ventricular Mass Index (LVMI)>115 g/m^2 in men and >95 g/m^2 in women [25]. This study was approved by the ethics committee of Shengli Oilfield Central Hospital. Written informed consents were obtained from all patients.

The ACE I/D genotype

Peripheral blood was collected and DNA was extracted from leukocytes as described [26]. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to analyse *ACE* I/D gene polymorphisms. Based on the GenBank reference sequence, the following PCR primers were used: Forward-5'-CTGGAGACCACTCCCATCCTTTCT-3' and reverse-5'-GATGT GGCCATCACATTCGTCAGAT-3'. DNA was denatured at 94°C for 10 min, followed by initial denaturation with 30 cycles at 94°C for 1 min, 60°C for 1 min and 72°C for 2 min, and finally ended up with an extension step at 72°C for 5 min [25]. PCR products (D allele of 190 bp and I allele of 490 bp) were separated by 2% agarose gel electrophoresis following by staining with ethidium bromide and viewed with ultraviolet light.

Statistical analysis

The measurement data was expressed by mean ± SD. Independent continuous variables were compared using the t-test or ANOVA and categorical data such as differences in allelic and genotypic frequencies of different groups were compared using the chi square test or Fisher exact test. Cross-products (Odds Ratio (OR)) with a 95% Confidence Interval (95% CI) was also recorded. A P-value was less than 0.05 it was considered to be statistically significant. All analysis were made using SPSS 16.0.

Results

Clinical data of patients in different groups was shown in Table 1. All basic parameters listed in Table 1 between the two groups showed no significant difference. Among all SCA patients, 10 survived after treatment of Cardiopulmonary Resuscitation (CPR) and chest compressions and 81 unfortunately died due to treatment failure or not in time.

Results of genotype frequencies of *ACE* gene Insertion/Deletion (I/D) polymorphisms among two groups showed that frequencies of DD genotype in SCA group was significantly higher than the coronary disease group, P<0.05, as well as the D allele frequencies in SCA group compared with coronary disease group, P<0.05 (Table 2).

At last, when distribution of patients' characteristics were compared according to the genotypes of the ACE I/D polymorphism, no significant differences were shown among all characteristics except for percentage of patients survival after SCA in which patients with II genotype had significant higher percentage and patients died of SCA in which DD genotype had significant higher percentage (Table 3).

Table 1. *Demographic and clinical data of patients in different groups.*

Variables	SCA group (n=91)	Coronary disease group (n=141)	P value
Mean age, years (SD)	56.15 ± 4.38	54.32 ± 5.2	NS
Gender (male: female)	49:42:00	76:65	NS
Body weight (kg)	63.45 ± 5.88	61.27 ± 4.73	NS
BMI (kg/m^2)	27.43 ± 2.35	26.55 ± 3.21	NS
Systolic blood pressure (mmHg)	133.45 ± 12.36	136.21 ± 9.85	NS
Diastolic blood pressure (mmHg)	79.55 ± 6.24	82.13 ± 9.21	NS
Total cholesterol (mg/dL)	189.45 ± 22.22	192.34 ± 31.13	NS
HDL-cholesterol (mg/dL)	55.47 ± 13.25	57.82 ± 11.56	NS
LDL-cholesterol (mg/dL)	105.58 ± 16.42	112.93 ± 20.13	NS
Smoker (%)	50 (55)	72 (51)	NS
Hypertension (%)	35 (39)	59 (42)	NS
History of stroke (%)	15 (17)	21 (15)	NS
History of MI (%)	19 (21)	32 (23)	NS
Diabetes mellitus (%)	17 (19)	28 (20)	NS
LVH (%)	20 (22)	34 (24)	NS

NS: No Significant difference was observed, P>0.05.

Table 2. *Genotype frequencies of ACE gene insertion/deletion (I/D) polymorphisms among two groups.*

Genotype	SCA group (n=91)	Coronary disease group (n=141)	OR (95% CI)
DD	45 (49.45%)*	48 (34.04%)	1.941 (1.098 3.432)
ID	33 (36.26%)	53 (37.59%)	0.933 (0.526 1.655)
II	13 (14.29%)*	40 (28.37%)	0.419 (0.205 0.855)

D	68.09%*	53.03%	1.884 (1.060 3.349)
I	31.91%*	46.97%	

*P<0.05, compared with coronary disease group.

Table 3. *Distribution of patients' characteristics according to the genotypes of the ACE I/D polymorphism*

Variables	DD (n=93)	ID (n=86)	II (n=53)
Mean age, years (SD)	55.32 ± 4.26	54.63 ± 6.77	56.25 ± 5.54
Gender (male: female)	45:38:00	41:36:00	39:33:00
Body weight (kg)	61.25 ± 18.22	63.33 ± 14.91	60.12 ± 15.56
BMI (kg/m^2)	26.35 ± 8.84	28.93 ± 6.85	25.42 ± 3.63
Systolic blood pressure (mmHg)	136.25 ± 23.25	134.51 ± 19.86	131.26 ± 23.13
Diastolic blood pressure (mmHg)	81.37 ± 10.05	80.44 ± 11.37	82.13 ± 14.23
Total cholesterol (mg/dL)	194.36 ± 38.45	191.32 ± 25.96	183.53 ± 28.17
HDL-cholesterol (mg/dL)	56.84 ± 8.45	56.77 ± 9.73	54.62 ± 6.52
LDL-cholesterol (mg/dL)	113.53 ± 12.81	115.26 ± 11.07	110.33 ± 15.32
Smoker (%)	42	42	38
Hypertension (%)	30	33	31
History of stroke (%)	12	11	13
History of MI (%)	17	16	18
Diabetes mellitus (%)	15	16	14
LVH (%)	20	17	17
Patients survival after SCA (%)	3 (30)*	2 (20)	5 (50)
Patients died of SCA (%)	39 (48)*	26 (32)	16 (20)

*P<0.05, compared with II.

Discussion

In the general population, sudden cardiac death is a common manifestation of coronary artery disease, which often presents as cardiac arrest due to fatal heart rhythm disorder triggered often by coronary ischemia [27]. According to lots of data, the incidence of death caused by cardiac arrest remains to be a high level, leading to almost 22% of all deaths, increasing with age [6,28-30]. The incidence of cardiac arrest is even higher among diabetics according to some studies [31].

Generally, timely access to potentially life-saving interventions, such as quality of cardiopulmonary resuscitation, chest compressions or thrombolytic therapy for acute coronary syndromes is the key determinant of survival from cardiac arrest [32]. Furthermore, 40-50% of all SCD cases showed no prior symptoms before occurrence of cardiac arrest [33].

Studies have already demonstrated lots of risk factors on SCD, such as left ventricular dysfunction [34], renal dysfunction which has been considered as a distinct end point in several clinical trials and cohort studies [35], epilepsy which is caused by the same reason of cardiac arrhythmias [36,37] and Coronary Artery Disease (CAD) or congestive HF which was thought to be risks of SCD for long [38].

As well as various studies of sudden cardiac arrest and sudden cardiac dear, ACE insertion/deletion polymorphism was also widely studied recently, especially for its relationship with cardiovascular diseases. But up to now, there was not yet any studies focusing on the possible relationship between sudden cardiac arrest and ACE insertion/deletion polymorphism. In the present study, two groups of patients with cardiovascular diseases were involved to investigate the genotype of ACE in sudden cardiac arrest patients and patients with coronary disease.

First, we compared the clinical characteristics including basic parameters like age, gender, weight, amount of HDL and LDL and history of some related diseases etc. between the two groups. But results showed no significant difference in this section. Then, genotype frequencies of the two groups were investigated and compared and some valuable results were obtained, the frequencies of DD genotype in SCA group was significantly higher than the coronary disease group, $P<0.05$, as well as the D allele frequencies in SCA group compared with coronary disease group, $P<0.05$. It was reported that the DD genotype have been associated with several of cardiovascular diseases. A recent study showed that patients with left ventricular hypertrophy tend to have higher rates of DD genotype [26], and the left ventricular hypertrophy is also a common complication in coronary disease. At last, comparison of distribution of patients' characteristics according to the genotypes of the ACE I/D polymorphism showed no significant differences in all characteristics except for percentage of patient's survival after SCA and patients died of SCA, which is an interesting result. Patients with II genotype had significant higher percentage in the survival SCA patients however patients with DD genotype had higher percentage in the SCD [39,40].

In conclusion, generally, timely treatment was thought to be the most important part to the SCD survival rate, but other factors were rarely noticed but in this study, we found some other possibilities, the ACE I/D polymorphism may be associated with sudden cardiac arrest and may be a risk factor of survival rate of SCD. Though limitations exist in this study, certain results may also give some novel versions to this field.

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Ethics, Consent and Permissions

Ethical approval was given by the medical ethics committee of Shengli Oilfield Central Hospital.

Consent to Publish

All of the authors have consented to publish this research.

Author's Contribution

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.

Interest Conflict

All of the authors have no conflict of interest in this research.

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