

Effect of Aldehyde Dehydrogenase 2 Gene Polymorphism on Hemodynamics After Nitroglycerin Intervention in Northern Chinese Han Population

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Abstract

Background: Nitroglycerin (NTG) is one of the few immediate treatments for acute angina. Aldehyde dehydrogenase 2 (ALDH2) is a key enzyme in the human body that facilitates the biological metabolism of NTG. The biological mechanism of NTG serves an important function in NTG efficacy. Some reports still contradict the results that the correlation between ALDH2 gene polymorphisms and NTG and its clinical efficacy is different. However, data on NTG measurement by pain relief are subjective. This study aimed to investigate the influence of ALDH2 gene polymorphism on intervention with sublingual NTG using noninvasive hemodynamic parameters of cardiac output (CO) and systemic vascular resistance (SVR) in Northern Chinese Han population.

Methods: This study selected 559 patients from the Affiliated Hospital of Qingdao University. A total of 203 patients presented with coronary heart disease (CHD) and 356 had non-CHD (NCHD) cases. All patient ALDH2 genotypes (G504A) were detected and divided into two types: Wild (GG) and mutant (GA/AA). Among the CHD group, 103 were wild-type cases, and 100 were mutant-type cases. Moreover, 196 cases were wild-type, and 160 cases were mutant type among the NCHD volunteers. A noninvasive hemodynamic detector was used to monitor the CO and the SVR at the 0, 5, and 15 minute time points after medication with 0.5 mg sublingual NTG. Two CO and SVR indicators were used for a comparative analysis of all case genotypes.

Results: Both CO and SVR indicators significantly differed between the wild and mutant genotypes at various time points after intervention with sublingual NTG at 5 and 15 minutes in the NCHD ($F = 16.460, 15.003, P = 0.000, 0.000$) and CHD groups ($F = 194.482, 60.582, P = 0.000, 0.000$). All CO values in the wild-type case of both NCHD and CHD groups increased, whereas those in the mutant type decreased. The CO and Δ CO differences were statistically significant ($P < 0.05; P < 0.05$). The SVR and Δ SVR changed between the wild- and mutant-type cases at all-time points in both NCHD and CHD groups had statistically significant differences ($P < 0.05; P < 0.05$).

Conclusion: ALDH2 (G504A) gene polymorphism is associated with changes in noninvasive hemodynamic parameters (i.e. CO and SVR) after intervention with sublingual NTG. This gene polymorphism may influence the effect of NTG intervention on Northern Chinese Han population.

Key words: Aldehyde Dehydrogenase 2; Coronary Disease; Genetic Polymorphism; Hemodynamic; Nitroglycerin

INTRODUCTION

Increasing evidence suggests that the aldehyde dehydrogenase 2 (ALDH2) (G-504-A) gene polymorphism is associated with nitroglycerin (NTG) inhibition. ALDH2 is a key enzyme in the human body that facilitates the biological metabolism of NTG, which serves an important function in NTG efficacy.^[1] NTG is one of the few immediate treatments for acute angina. ALDH2 is an important mitochondrial aldehyde oxidase, the gene of which is located on chromosome 12q24. The gene has a high degree of genetic polymorphism.^[2] The ALDH2

gene is found outside the 12th exon and exists in 504 point mutations with base substitutions of G to A. The ALDH2 of the GG genotype (i.e., wild-type) has normal activity on the NTG. The GA genotype (i.e., mutant) only has 6% activity, whereas the AA genotype (i.e., mutant) loses all its activities.^[3] The clinical research analysis of Jo *et al.*^[4] revealed that mutant ALDH2 is an independent risk factor for myocardial infarction in elderly men in Korea. Chen *et al.*^[5] used animal experiments to demonstrate that the ALDH2 has a protective effect on myocardial ischemia. However, some reports still contradict the results that the correlation between the ALDH2 gene polymorphisms and NTG or its clinical efficacy is different. However, data on NTG measurement by pain relief are highly subjective.^[6,7]

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.149192

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A thoracic impedance method based on the noninvasive hemodynamic detector (i.e., BioZ.com), which monitors real-time hemodynamic and index parameters of patients, was used in this study. This method was employed to assess hemodynamic status and ventricular function. Cardiac output (CO) is representative of the CO, whereas peripheral vascular resistance (SVR) is representative of the cardiac load. Both parameters have application values in cardiac care.^[8-10] Therefore, this study verified NTG efficacy using noninvasive hemodynamic monitoring results of CO and SVR with objective judgment. Furthermore, this study hinders the effect of subjective factors.

METHODS

Subjects

All patients comprising the noncoronary heart disease (NCHD) and the CHD groups from Jiaodong Peninsula of Northern China were investigated. All procedures conformed to the tenets of the Affiliated Hospital of Qingdao University. Informed consent was obtained from each subject. Furthermore, the study was approved by the Local Institutional Review Board. The exclusion criteria included serious cardiovascular and cerebrovascular diseases, endocrine and digestive disorders, kidney disease in the last 3 years, and NTG contraindications. The clinical diagnosis of obesity was determined from abnormal laboratory experiments before the start of the procedures. Accordingly, 356 patients with non-CHD (i.e., 234 men and 122 women; mean age: 57.01 ± 10.29 years) participated in the study. The inclusion criteria included: (1) Explicit exclusion of coronary artery disease, (2) without NTG contraindications (e.g., hypotension), and (3) without a history of serious alcohol abuse. The CHD group comprises 203 patients (i.e., 147 men and 56 women; mean age: 63.43 ± 9.61 years) diagnosed following the European Society of Cardiology Pocket Guide criteria of 2013. The inclusion criteria included the (1) presence of angina pectoris, (2) other possible causes of similar disease and angina pectoris (e.g., coronary spasm), (3) without NTG contraindications (e.g., hypotension), (4) sublingual NTG was used to cure angina attack, and (5) did not use angina or other antiangina drugs at the same time. The blood pressure of the patients with hypertension was controlled in the 140–120/90–70 mmHg range by taking nonoral nitrates (e.g., angiotensin II type 1 receptor blocker, calcium channel blocker, and diuretics) before the test. All risk factors were determined from routine tests, including blood, urine, and conventional and biochemical blood clotting prior to the study.

Genetic analysis

Genomic DNA was extracted from each subject via blood sample. The genetic variants in the extra ALDH2 (G504A) region were identified using polymerase chain reaction and DNA sequencing in all cases. Genotype determination was measured by the Shanghai Biological Science and Technology Company (China).

The ALDH2 genotypes were divided into wild (GG) and mutant (GA/AA) types. Among 356 patients with NCHD, 196 were GG cases, and 160 were GA/AA. Among 203 patients with CHD, 103 were GG cases and 100 were GA/AA cases.

Clinical and hemodynamic

The history of NTG treatment by objective pain relief was obtained from each participant through interview. This history was then divided into two subgroups of efficacy and nonefficacy. The hemodynamic parameter test included the checking of all patients administered with 0.5 mg sublingual NTG at 0, 5, and 15 minutes. CO and SVR were measured using the noninvasive hemodynamic parameter of BioZ.com (CardioDynamics Company). The patients were placed in a supine position with an empty stomach during the test. Medical professionals then attached the sensor to the patients' necks and to the xiphoid level in the mid-axillary line at the junction on the bilinear sides of the chest according to user instructions. The contact skin was cleaned using alcohol wipes to ensure full conductivity. All personal data related to the test were entered. These data included gender, age, name, height, weight, and body surface area. The systolic and diastolic blood pressure (SBP and DBP), SVR, and CO were then tested and recorded. The SVR showed the state of the body's peripheral vasomotor reactions, whereas the CO depended on the cardiac preload and afterload and myocardial contractility.

Statistical analysis

SPSS software for Windows version 17.0 (SPSS 17.0 Statistical Product and Service Solutions, the software was developed by the company of SPSS in December 2008) was used for statistical analysis. Pearson χ^2 test was employed to assess deviations from the Hardy–Weinberg equilibrium for genotypes. Clinical information was subsequently compared across the genotypes using Pearson χ^2 or Fisher's exact test. Fisher's exact test was used when the expected number in any cell was <5 . The observed number and differences of NTG efficacy among various ALDH2 genotypes were statistically analyzed using χ^2 test. Patient gender and smoking and drinking history were analyzed by *t*-test regression. $P < 0.05$ was considered statistically significant. The changes in CO and SVR at 3 time points were analyzed using repeated measurement data analysis of variance. The relation among the number of multiple impacts of Δ SVR, Δ CO factors, and ALDH2 gene polymorphisms was analyzed using a multivariate linear regression.

RESULTS

The genetic polymorphism balancing test was conducted on the genetic polymorphisms to balance the test allele and the genotype distribution of 510 subjects. The genotype distribution of both groups inherited the Hardy–Weinberg equilibrium ($\chi^2 = 1.59, 0.49, P > 0.05$), which indicated that the sample had a population representative.

Of the 356 cases in the NCHD group, 196 (55.1%) were of the GG genotype and 130 (36.5%) were of the GA genotype. Of

the 130 cases, 30 (8.4%) accounted for the AA genotype with the G and A allele frequencies at 82.8%–17.2%, respectively. Of the 203 cases in the CHD group, 103 (50.7%) were of the GG genotype and 86 (42.4%) were of the GA genotypes. Of the 86, 14 cases (6.9%) accounted for the AA genotype with the G and A allele frequencies of 81.4%–18.6%, respectively. The comparison between the two groups showed that the differences in the genotype distribution were not statistically significant ($P = 0.33$). Moreover, the allele distribution between the two groups was not statistically significant ($P = 0.64$) [Table 1].

GG and GA/AA clinical data comparison

The GG and GA/AA types demonstrated that the GC and GA/AA sample size, gender, age, smoking, and alcohol consumption ratio difference were not statistically significant ($P > 0.05$) [Table 2].

Aldehyde dehydrogenase 2 genotype and nitroglycerin efficacy

Accordingly, 103 cases of GG and 100 cases GA/AA were recorded in the CHD group. The NTG efficacies of the GG and the GA/AA subgroups were 79.4% and 50.6%, respectively. The difference in rapid NTG efficiency was statistically significant ($P < 0.01$) [Table 3].

Changes in cardiac output, SVR, heart rate, systolic and diastolic blood pressure between groups

The repeated measurement data analysis of variance showed that the CO difference of the GG genotype at all three time points was statistically significant ($P < 0.05$) and differed with the significant increase in CO at 0 and 5 minutes ($P = 0.000$). The CO difference in the GA/AA group at 0, 5, and 15 minutes was statistically significant ($P < 0.05$), which indicated an obvious decrease from the CO difference at 0 and 15 minutes in both

groups ($P < 0.001$). The SVR differences in both groups were statistically significant ($P < 0.001$) at all three-time points. A significant decrease was observed at 5 minutes, which suggested a statistically significant difference ($P < 0.01$) [Table 4].

The heart rate (HR), SBP, and DBP differences between the two groups at three-time points were not statistically significant ($P > 0.05$).

Relationship between aldehyde dehydrogenase 2 gene polymorphisms and Δ CO and Δ SVR

Δ CO and Δ SVR included Δ CO1 = CO 0 – CO 5 minutes, Δ SVR1 = SVR 0 – SVR 5 minutes, Δ CO2 = CO 0 – CO 15 minutes, and Δ SVR2 = SVR 0 – SVR 15 minutes. Δ CO1 was used as the dependent variable, whereas ALDH2 polymorphism was employed as the independent variable. The ALDH2 polymorphism significantly influenced the dependent variable ($P = 0.046, 0.000$). Similarly, Δ CO2 was used as the dependent variable. Δ SVR1 and Δ SVR2 were utilized as independent variables. The ALDH2 polymorphism had a significant influence on the dependent variable in both groups ($P < 0.05$).

Noninvasive hemodynamic parameter (i.e., cardiac output and SVR) changes between the GG and GG/AA groups

The comparisons of Δ CO1 and Δ CO2 and Δ SVR1 and Δ SVR2 in the GG and GG/AA types were statistically significant ($P < 0.001$) [Table 5].

DISCUSSION

Nitroglycerin is a classic drug that cures acute angina attack. This drug generates NO or NO-related media in the body. Moreover, NTG directly acts upon guanylate cyclase and increases the amount of second messenger cyclic guanosine

Table 1: ALDH2 of the two groups rs671 gene mutation genotype and allele

Groups	ALDH2 genotype frequencies			χ^2	P	ALDH2 allele frequencies		χ^2	P
	GG	GA	AA			G	A		
Control group	196 (55.1)	130 (36.5)	30 (8.4)	0.969	0.33	82.8	17.2	0.271	0.64
CHD group	103 (50.7)	86 (42.4)	14 (6.9)			81.4	18.6		

CHD: Coronary heart disease; ALDH2: Aldehyde dehydrogenase-2; GG: Wild-type; GA/AA: Mutant.

Table 2: General characteristics of clinical data

Variables	NCHD group ($n = 356$)		t	P	CHD group ($n = 203$)		t	P
	GA + AA	GG			GA + AA	GG		
Number (n)	160	196	-		100	103	-	
Male (%)*	68.8	63.3	1.176	0.313	73	71.8	0.034	0.854
Age (years)	55.281 ± 10.832	58.434 ± 9.619	0.906	0.407	60.090 ± 10.169	66.669 ± 7.782	1.332	0.276
BSA (m ²)	1.819 ± 0.087	1.795 ± 0.077	1.839	0.114	1.946 ± 0.165	1.766 ± 0.149	0.729	0.577
Smoking proportion (%)*	33.3	34.2	0.044	0.910	60	62.4	0.097	0.775
Drinking proportion (%)*	38.5	49.3	4.111	0.054	53	56.1	0.224	0.674
Hypertension proportion (%)*	57.1	57.5	0.022	0.914	55	58.2	0.219	0.673
Diabetes proportion (%)*	26.4	25.5	0.025	0.903	27	27.6	0.001	1.000

*Means χ^2 value, other test statistics value for t value. GG: Wild-type; GA/AA: Mutant; NCHD: Noncoronary heart disease; CHD: Coronary heart disease; BSA: Body surface area.

monophosphate in the vascular smooth muscle, thereby activating downstream target proteins (i.e., protein kinase G and AMP-dependent protein kinase). NTG also reduces the Ca concentration in the smooth muscle cells while reducing myosin sensitivity toward Ca, as well as vascular smooth muscle dilation.^[11]

Aldehyde dehydrogenase 2 is a key enzyme mediating the biotransformation of NTG,^[12] which consequently mediates the biological activation of NTG. Thus, the biological activation of NTG reduces the occurrence of NTG tolerance. ALDH2 prevents NTG conversion into nitrite and 1,2-bis nitroglycerin (1,2-GDN), which reduce NTG-induced vasodilation. Mackenzie *et al.*^[13] used disulfiram-ALDH2 and demonstrated that ALDH2 partially inhibited the effects of NTG on the human body. ALDH2 gene knockout studies in mice have shown the significance and necessity of ALDH2 in vascular activity at therapeutic doses of NTG.^[3,14] The human ALDH2 gene is located in chromosome 12 and contains 13 exons. Exon 12 of its outer 1510 guanine (G) mutated to adenine (A) facilitates the replacement of the protein encoded by this gene (504), glutamate (Glu), with lysine (Lys) (i.e., Glu504 Lys [rs671]). The single nucleotide polymorphism mutation rate in East Asia reaches up to 30%–50%.^[15] The mutations cause a significant decrease in ALDH2 enzyme activity, which diminishes the biological

function of ALDH2.^[16] The results of this study provide clinical evidence that ALDH2 polymorphisms influence the NTG effect.

Recent animal studies abroad have reported that the ALDH2 gene serves an important function in NTG on the pulmonary vascular bed and circulatory system biotransformation.^[17] The ALDH2 gene mutation reduces the vasodilator NTG.^[18,19] Li *et al.*^[19] selected 80 cases of patients diagnosed with coronary artery disease with a history of stable angina in 2006. The ALDH2 gene polymorphism and enzyme activity were detected in patients from each group. The NTG effect on all subjects in the ALDH2 wild-type group was significantly higher than that in the invalid proportion of the wild-type group. Ji *et al.*^[7] enrolled 113 people diagnosed with coronary artery disease in 2010. They found that the ALDH2 gene polymorphisms had no association with NTG effectiveness. Mackenzie *et al.*^[13] also observed that the clinical use of NTG was not found in the ALDH2 gene and had a high mutation rate in the Japanese population. The preceding experiment illustrates that the relationship between the ALDH2 gene polymorphisms and NTG efficacy remains controversial. This experiment also selects subjects with noncoronary and CHD to study sublingual NTG aging and further proves that the ALDH2 gene polymorphisms are related to the NTG clinical effect. The wild-type effect is better than that of the mutant type.

The subjects are divided into the NCHD and CHD groups. The determined ALDH2 genotype is divided into the wild and mutant groups. The ALDH2 genotypes have no significant distribution difference, similar to the findings of previous studies.^[20] The NTG effect rate in the GG-type patients of the CHD group was significantly higher than that of the GA/AA type. This result is similar to that of

Table 3: ALDH2 gene volunteers cases of CHD distribution and efficacy of NTG

Gene	Efficacy number	Valid	Invalid	χ^2	P
GG	103	82	21	41.36	<0.01
GA+AA	100	35	65		

CHD: Coronary heart disease; ALDH2: Aldehyde dehydrogenase-2; GG: Wild-type; GA/AA: Mutant; NTG: Nitroglycerin.

Table 4: Comparison of CO and SVR in different time points

Time points	NCHD		CHD	
	GA + AA	GG	GA + AA	GG
CO ₀	5.944 ± 1.672	5.617 ± 0.817	5.794 ± 0.448	5.566 ± 0.693
CO ₅	5.859 ± 1.396	5.931 ± 0.963	5.162 ± 0.617	5.972 ± 0.620
CO ₁₅	5.483 ± 1.191	5.794 ± 0.777	4.785 ± 0.732	5.855 ± 0.700
SVR ₀	1121.965 ± 170.723	1095.713 ± 248.987	1066.030 ± 241.996	1103.152 ± 93.481
SVR ₅	1047.575 ± 152.840	949.429 ± 218.776	980.897 ± 235.545	933.227 ± 68.699
SVR ₁₅	1059.421 ± 169.084	993.724 ± 165.829	1039.516 ± 221.586	977.628 ± 58.821

CO: Cardiac output; SVR: Peripheral vascular resistance; GG: Wild-type; GA/AA: Mutant; NCHD: Noncoronary heart disease; CHD: Coronary heart disease.

Table 5: Comparison of Δ CO, Δ SVR

Δ CO and Δ SVR	NCHD group		t	P	CHD group		t	P
	GA + AA	GG			GA + AA	GG		
Δ CO ₁	0.089 ± 1.867	-0.313 ± 0.577	2.002	0.046	0.631 ± 0.482	-0.406 ± 0.297	5.732	<0.001
Δ CO ₂	0.461 ± 1.090	-0.176 ± 0.367	6.907	0.000	1.008 ± 0.637	-0.289 ± 0.466	4.997	<0.001
Δ SVR ₁	74.450 ± 56.768	146.283 ± 124.912	-6.453	0.000	85.134 ± 65.712	169.926 ± 84.591	-2.089	0.038
Δ SVR ₂	62.545 ± 107.383	101.988 ± 157.364	-2.272	0.024	26.515 ± 64.011	125.525 ± 69.735	-2.071	0.040

CO: Cardiac output; SVR: Peripheral vascular resistance; GG: Wild-type; GA/AA: Mutant; NCHD: Noncoronary heart disease; CHD: Coronary heart disease.

the previous studies.^[21] The noninvasive hemodynamic detector (i.e., impedance cardiography [ICG]) is employed to evaluate the NTG effect. The CO and SVR changes and other objective indicators are monitored. Furthermore, determining the degree of pain relief as a subjective factor is avoided. This study selects three representative time points (i.e., CO 0, CO 5, and CO 15 minutes) according to the pharmacokinetic characteristics of NTG. The changes in noninvasive dynamic indicators (i.e., CO and SVR) are then combined. Such combination indicates that the CO per minute reveals differences in sublingual NTG efficacy among subjects with different genotypes. Experimental results show that the ALDH2 polymorphisms are relevant to CO and SVR, which confirms the CO NTG effect.

The ICG is an important device for body impedance measurement in the cardiovascular dynamics of blood flow.^[22] The cardiac hemodynamic status is measured on the basis of changes in systolic and diastolic thoracic impedance.^[9] The ICG enables the diagnosis of heart failure and assesses the severity of coronary artery disease^[23] to evaluate the efficacy of drug treatment and prognosis.^[24] This study avoids the influence of subjective factors as much as possible by observing the CO per minute and the noninvasive hemodynamic index changes in SVR. The results of the observation are further employed to determine the differences among volunteers with different gene types after sublingual NTG administration. The obtained results are highly reliable.

The wild-type CO increases, whereas the mutant CO decreases after sublingual NTG administration. The results suggest the following: (1) Wild-type: The sublingual NTG hemorheology (HR) reflex significantly increased, whereas the stroke volume (SV) relatively and insignificantly decreased. (2) The formula $CO = SV \times HR$ demonstrates product increases. Mutant type: SV significantly was reduced, whereas HR was relatively and insignificantly increased after sublingual NTG administration.

Limitations of the study

Only considered ALDH2 polymorphism to the effect of metabolism, and *in vitro* and *in vivo* studies suggest that *in vivo* biotransformation of NTG is also affected by the following process a variety of enzymes, such as: Glutathione-S-transferase, cytochrome P450 reductase, xanthine oxidoreductase enzyme, including a number of species, this study does not exclude the other enzymes in the metabolism of NTG affected.

This research is a clinical experimental study, and the sample size is inadequate. The sample size should be expanded for further investigation. A selection bias in this study as regards the NCHD group and the subject might have affected NTG efficacy.

The researchers of this study plan to expand the sample size and apply invasive monitoring techniques to monitor all indicators. Accordingly, a more in-depth study of the metabolic ALDH2 pathways and processes will be conducted.

CONCLUSION

Aldehyde dehydrogenase 2 (G504A) gene polymorphism is associated with changes in noninvasive hemodynamic parameters (i.e., CO and SVR) after intervention with sublingual NTG. This gene polymorphism may influence the effect of NTG intervention on Northern Chinese Han population.

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Received: 02-09-2014 **Edited by:** Li-shao Guo

How to cite this article: Xia JQ, Song J, Zhang Y, An NN, Ding L, Zhang Z. Effect of Aldehyde Dehydrogenase 2 Gene Polymorphism on Hemodynamics After Nitroglycerin Intervention in Northern Chinese Han Population. *Chin Med J* 2015;128:180-5.

Source of Support: Nil. **Conflict of Interest:** None declared.