Influence of Angiotensin-Converting Enzyme Gene Polymorphism on Development of Athlete's Heart

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Summary

Background and hypothesis: Genetic influence on development of athlete's heart is uncertain. This study investigated whether angiotensin-converting enzyme (ACE) gene polymorphism influenced development of athlete's heart.

Methods: Forty-three participants in a 100-km ultramarathon were classified on the basis of ACE gene polymorphism into a deletion group ($n = 26$) and an insertion group ($n = 17$). Echocardiograms were recorded to determine left ventricular end-diastolic and end-systolic diameters, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular mass, and ejection fraction.

Results: Left ventricular end-diastolic diameter (65.5 ± 4.0 mm) and left ventricular mass (369.5 ± 73.9 g) were significantly larger in the subjects with deletion than in those with insertion (57.4 ± 4.2 mm, 306.5 ± 93.7 g). However, no significant differences in the other parameters were noted.

Conclusions: In long-distance runners, ACE gene polymorphism of the D/D and D/I genotypes has a stronger influence on left ventricular hypertrophy than polymorphism of the I/I genotype.

Key words: echocardiography, ultramarathon, angiotensin-converting enzyme polymorphism, athlete's heart

Introduction

The athlete's heart in long-distance runners features left ventricular hypertrophy that is related to the intensity of endurance training.¹ However, a difference in the degree of hypertrophy between athletes at the same level of competition or training has been noted, and the reason is unclear. It has recently been reported that genetic factors are involved in various types of heart disease, and that polymorphism of the angiotensin-converting enzyme (ACE) gene influences the morphology of the cardiovascular system.^{2–7} In the present study, we investigated the effects of ACE gene polymorphism on the development of athlete's heart.

Subjects and Methods

Subjects

The subjects were 43 healthy men aged from 23 to 65 years (mean age: 41.5 ± 8.8 years) who participated in a 100-km ultramarathon. Written informed consent to this study was obtained from all. Approval of the study was also obtained from the research ethics committee of our university.

Clinical Parameters

We sent questionnaires to each participant about the running distance per month in order to assess intensity of training. The body surface area was calculated after measuring the weight and height of each subject. The heart rate was determined by limb-lead electrocardiography combined with echocardiography, while systolic and diastolic blood pressures were measured using a mercury sphygmomanometer.

Recording and Analysis of Echocardiograms

Echocardiography was performed the day before the 100-km ultramarathon. For recording echocardiograms, an EUB-565 apparatus (Hitachi Co., Tokyo, Japan) was used. M-mode echocardiograms of the left ventricle, aorta, and left atrium were obtained and recorded on a strip chart recorder at 50 mm/s. Digital measurement of the heart rate was taken five

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times and the mean value was calculated. Using these recordings, left ventricular end-diastolic diameter (Dd), left ventricular end-systolic diameter (Ds), interventricular septal (IVS) thickness, left ventricular posterior wall (PW) thickness, end-diastolic aortic root diameter (Ao), and maximal left atrial (LA) diameter were measured. As an index of left ventricular contractility, ejection fraction (EF %) was calculated from the left ventricular volume by the Teichholz method.⁸ Left ventricular mass (LVM) was estimated by Devereux's equation.⁹

Angiotensin-Converting Enzyme Gene Polymorphism

A venous blood sample was taken from the cubital vein, and analysis of ACE gene polymorphism was done by the polymerase chain reaction.¹⁰

Statistical Analysis

Based on the results of ACE gene polymorphism analysis, the subjects were classified into two groups: (1) a deletion group with the deletion/deletion (D/D) genotype or the deletion/insertion (D/I) genotype, and (2) an insertion group with the insertion/insertion (I/I) genotype. Then the various parameters investigated were compared between the two groups and differences were analyzed using unpaired *t*-tests. Correlations between each parameter were examined by stepwise regression analysis. A probability value <0.05 was considered significant.

Results

Angiotensin-Converting Enzyme Gene Polymorphism

Analysis of ACE gene polymorphism showed that there were 26 subjects in the deletion group (D/D genotype in 3 and

D/I genotype in 23) and 17 subjects in the insertion group (I/I genotype in all 17).

Clinical Parameters

The running distance per month, age, body surface area, heart rate, and systolic and diastolic blood pressures showed no significant differences between the two groups (Table I).

Echocardiographic Findings

There were significantly higher Dd and LVM values in the deletion group ($p < 0.01$ and $p < 0.05$). However, there were no significant differences between the two groups with respect to DS, IVS thickness, PW thickness, Ao, LA, and EF (Table I). Stepwise regression analysis using Dd and LVM as dependent variables versus ACE gene polymorphism (deletion group = 0, insertion group = 1), running distance per month, age, body surface area, heart rate, and systolic and diastolic blood pressures as independent variables showed that ACE gene polymorphism, running distance per month, and heart rate were significant predictors of Dd ($p < 0.0001$, Table II), and only ACE gene polymorphism was a significant predictor of LVM ($p = 0.0184$, Table II).

Discussion

The concept of athlete's heart was first advocated by Henschen in 1899.¹¹ In 1982, Keul *et al.*¹ reported a difference in the pattern of left ventricular hypertrophy depending on the type of athletics, that is, a decrease of EF with centrifugal hypertrophy in athletes participating in endurance sports versus centripetal hypertrophy in athletes participating in static sports. Although hypertrophy is reported to increase in parallel

TABLE I Profile and echocardiographic findings

	All subjects (n = 43)	Deletion group (n = 26)	Insertion group (n = 17)	p Value
Age (years)	41.5 ± 8.8	40.0 ± 9.9	43.8 ± 6.3	NS
Body surface area (m ²)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	NS
Running distance (km)/month	442.1 ± 54.7	439.2 ± 56.6	446.5 ± 53.0	NS
Heart rate (beats/min)	49.9 ± 3.3	49.7 ± 3.6	50.2 ± 2.9	NS
Systolic blood pressure (mmHg)	105.8 ± 7.0	105.3 ± 7.2	106.5 ± 6.9	NS
Diastolic blood pressure (mmHg)	66.4 ± 4.7	65.7 ± 4.7	67.5 ± 4.7	NS
Dd (mm)	62.3 ± 5.7	65.5 ± 4.0	57.4 ± 4.2	<0.01
Ds (mm)	41.2 ± 5.4	42.1 ± 4.5	39.7 ± 6.4	NS
IVS (mm)	10.5 ± 2.2	10.4 ± 1.9	10.6 ± 2.6	NS
PW (mm)	10.0 ± 1.3	10.0 ± 1.3	10.1 ± 1.4	NS
LVM (g)	344.6 ± 87.0	369.5 ± 73.9	306.5 ± 93.7	<0.05
AO (mm)	39.6 ± 3.7	39.5 ± 3.8	39.7 ± 3.6	NS
LA (mm)	44.1 ± 5.8	45.0 ± 5.8	42.8 ± 5.9	NS
EF (%)	60.7 ± 12.2	63.7 ± 7.5	56.3 ± 16.4	NS

Abbreviations: Dd = left ventricular end-diastolic diameter, Ds = left ventricular end-systolic diameter, IVS = interventricular septum, PW = posterior wall, LVM = left ventricular mass, AO = aortic root diameter, LA = left atrial diameter, EF = ejection fraction, NS = not significant.

TABLE II Predictors of echocardiographic findings

	β	p Value
ACE polymorphism vs. Dd	-7.733	<0.0001
Running distance/month vs. Dd	0.020	<0.0001
Heart rate vs. Dd	-0.667	<0.0001
ACE polymorphism vs. LVM	-62.932	0.0184

Abbreviation: ACE = angiotensin-converting enzyme. Other abbreviations as in Table I.

with the intensity of endurance training,¹²⁻¹⁴ a difference in the degree of hypertrophy between athletes at the same level of competition or training has been detected and the reason is unclear. Left ventricular hypertrophy is thought to occur during training as a result of mechanical extension caused by pressure and volume overload, along with increased secretion of catecholamines, growth hormone, thyroid hormone, testosterone, and angiotensin.¹⁵⁻²⁰ Genetic factors are also thought to influence the formation of athlete's heart, although the evidence available is equivocal. In 1984, Bouchard and Lortie²¹ reported on the similarity of cardiac volume in twins shown by chest x-ray films. In 1985, Landry *et al.*²² reported that there was a significant correlation of Dd, IVS thickness, PW thickness, and LVM after 20 weeks of training in monozygotic twin pairs using echocardiography. Also, Bielen *et al.*²³ reported a significant genetic influence on LVM in 1990. Conversely, Adams *et al.*²⁴ reported in 1985 that environmental factors were a stronger influence than genetic factors with respect to the development of athlete's heart in college-age monozygotic twins, dizygotic twins, siblings of the same gender, and unrelated subjects in an echocardiographic study of the effects of exercise (14 weeks of training).

The human ACE gene is localized to the long arm of chromosome 17, and it consists of 26 exons and 25 introns.²⁵ There is an insertion/deletion polymorphism in the Alu-like arrangement at intron 16 of the ACE gene. Various studies concerning ACE gene polymorphism and the development of heart disease have shown that the blood ACE concentration and T-cell ACE activity are significantly higher,²⁶⁻²⁸ and that type 1 angiotensin-II receptor expression is more common²⁹ in patients with deletion polymorphism than in those with insertion polymorphism. It has also been suggested that hypertension and left ventricular hypertrophy develop more readily in patients with deletions because vascular tension is higher and vascular smooth muscle proliferation is greater as a result of the conversion of angiotensin-I to angiotensin-II and accelerated bradykinin inactivation by the local action of ACE on the enlarged myocardium and vessel walls.²⁻⁷ On the other hand, some negative conclusions have been reported.^{30,31} Recently, some reports reached positive results by strict selection of the subjects who contributed to the studies.^{32,33} To our knowledge, there was no other report of the association between the ACE gene polymorphism and cardiac hypertrophy in athletes participating in a 100 km ultramarathon. To avoid the confusing influences of other variables, we adopted running distance

per month, age, body surface area, heart rate, and systolic and diastolic blood pressures as independent variables in a stepwise regression analysis.

In the present study, athletes with similar competitive or training levels showed significantly larger Dd and LVM values in the deletion group than in the insertion group. In addition, ACE gene polymorphism was a significant predictor of Dd and LVM. These findings suggested that ACE gene polymorphism influences the development of athlete's heart, and that the increase of Dd and LVM is more prominent in subjects with deletion polymorphism of this gene. Regarding the mechanism underlying our present findings, a difference in local ACE activity arising from differences in gene polymorphism presumably leads to variation in the extent of development of athlete's heart, because there was no difference in blood pressure between the two groups and blood pressure was not a predictor of cardiac morphology.

Conclusions

In long-distance runners, angiotensin-converting enzyme gene polymorphism of the D/D and D/I genotypes has a stronger influence on left ventricular hypertrophy than polymorphism of the I/I genotype.

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