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Research Article

Endurance Work Capacity of Children is Related to Cardiac Function, But the Trainability is Associated with Angiotensin-Converting Enzyme Genotype

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Abstract

It has been reported that physical work capacity in elite athletes may be influenced by the genotype of angiotensin-converting enzyme (ACE) with insertion (I) and/or deletion (D) of 287 base pairs. However, it is not known what is the major cause for the clear individual differences seen in the endurance running capacity among the non-trained children. The relationships between the physical work capacity, genotype of ACE, and morphological and/or functional profiles of heart were investigated in Japanese elementary school children, male soccer players with various ages, university and national-ranking elite long distance runners, and mountaineers. The ACE gene expressions were analyzed in saliva samples. Cardiac function and morphology were measured by echocardiography at rest. Percent distributions of II, ID, and DD genotypes were 54, 37, and 9% among the elementary school children. No effects of ACE genotype, training status, or even sex on the running times were observed. Negative correlation was seen between the running time and cardiac output, left atrial diameter, and also interventricular septal thickness. The mean percent distributions of II, ID, and DD genotype in elite runners and mountaineers were 66, 34, and 0%, respectively. No significant relationships among the cardiac function and morphology, endurance capacity, and ACE gene expression were observed in children, junior and senior high school and university runners. However, it is suggested that endurance work capacity is influenced by cardiac output function, regardless of the specificity of physical training in children. The data also suggested that I allele may have an important role for trainability for endurance-type performance.

Introduction

An insertion (I) / deletion (D) polymorphism due to the presence/absence of a 287-base pair fragment in the 16th intron of the angiotensin-converting enzyme (ACE) gene has been identified [28]. Although some studies indicated no direct relationship between ACE genotype and athletic performance [27, 32], it has been reported that physical performance in human may be influenced by the genotype of ACE [1, 5-8, 13, 16, 17, 21, 23, 26, 34, 36]. The I allele of ACE gene is associated with an improved endurance running [1, 7, 13, 16, 21] or high-altitude mountain climbing performance [3, 20, 25, 33, 37]. On the other hand, it is reported that the D allele has a close association with sprint type or short-duration aerobic performance [5, 8, 17, 23, 34, 36].

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Further, genotype-specific training effects are also reported [4, 9, 18, 20, 35]. For example, enhanced improvement of mechanical [35], metabolic efficiency or endurance capacity [4, 9, 18, 20] was noted in subjects with II genotype. It is also reported that the exercise-induced increase of the left ventricular mass is strongly associated with ACE D genotype [19, 22].

Maximal oxygen consumption (VO_2 max), which is the good indicator for the endurance work capacity, is well related to the level of cardiac output [2, 11]. Therefore, these results, shown above, strongly suggest that the ACE genotype could be one of the main factors, which influence the maximal work capacity and trainability. However, it is not known what is the major cause for the clear individual differences seen in the endurance running capacity among the non-trained children. Therefore, the relationships between the ACE genotype, cardiac function and/or morphology, and endurance performance in children were investigated in the current study. The ACE genotype in elite distance runners and mountaineers were also investigated to estimate the effects of ACE genotype on the trainability.

Methods

All experimental procedures were conducted in accordance with the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). The study was also approved by the Committee on the Human Study at the National Institute of Fitness and Sports. All subjects were informed about the possible risks and ethical concerns in this study, and a signed informed consent was obtained from each subject and their parents.

Subjects

All of the subjects (n=309) in this study were physically healthy Japanese, selected randomly from various age groups. Second (9 boys and 10 girls), 4th (11 boys and 10 girls), and 6th graders (13 boys and 10 girls) in an elementary school volunteered as the subjects (Table 1). Some of them had been physically training by attending either swimming, soccer, or softball clubs a couple days per week. But, approximately half of them were not attending any sport clubs. Male soccer players (n=114), training daily as a regular sport activity, in elementary school (n=13), junior (n=20) or senior high school (n=27), and university (n=54) were also volunteered. Further, male middle and/or long-distance university (n=13) and/or elite runners (25 for 5,000 m, 23 for 10,000 m, and 13 for marathon), and mountaineers (n=13) were also the subjects. Finally, some parents (n=45) of the elementary school children, stated above, were also helpful to be the volunteers for the examination of the genotype of ACE.

Analyses of the Genotype of Angiotensin-converting Enzyme:

Table 1: The percent distribution of subjects with various genotypes of angiotensin-converting enzyme

	n	II	ID	DD
E.S. children	63	54.4	36.8	8.8
(Parents)	45	60.0	35.6	4.4
Soccer players	114	40.0	50.9	9.1
Univ. runners	13	69.2	23.1	7.7
Elite runners	61	70.8	29.2	0
Mountaineers	13	61.5	38.5	0
Total	309	59.3	35.7	5.0

n= Number of Subjects; **E.S.**= Elementary School; **Univ.**= University

The subjects brushed their teeth before the sampling of saliva (~2 ml). DNA was extracted from oral mucosa cells in saliva. The structure of cells, nuclei and chromatin was dissected during incubation with proteinase K solution containing 0.02 % proteinase K, 0.1 % SDS, 150 mM NaCl, 10 mM tris-HCl pH 8.0 and 10 mM EDTA at 37 °C for 2 hours. Subsequently, a part of soluble phase containing DNA in proteinase K-treated mixture was separated by addition of phenol-chloroform-isoamyl alcohol solution mixed by 25: 24: 1 ratio and centrifuged at 15,000 g. 3-M NaOAc and 100 % ethanol were, then, added to the supernatant, as sample: NaOAc: ethanol = 10: 1: 20 ratios, to precipitate total DNA from the mixture.

Polymerase chain reaction (PCR) was used to clone and amplify the nucleotide of the intron 16 of the original DNA cording the ACE gene with three primers, ACE1 (D-specific oligonucleotide sense primer: 5'-CATCCTTTCTCCCATTTCTC-3'), ACE2 (I-specific oligonucleotide sense primer: 5'-TGGGATTACAGGCGTGATACAG-3') and ACE3 (common oligonucleotide antisense primer: 5'-ATTTCAGAGCTGGAATAAAATT-3'). DNA was denatured at 95 °C for 1 min and annealed at 58 °C for 1 min, and a primer-binding site was extended at 72 °C for 30 sec in a reaction buffer (Expand TM High Fidelity PCR System, Roche Diagnostics, Mannheim, Germany) containing 0.2 mM dNTP. This cycle was repeated 30 times using a temperature controller (PC801, ASTEC, Fukuoka, Japan). The yielded amplification products were separated using 8 % polyacrylamide gel electrophoresis (PAGE). The constant 200 volts was maintained during PAGE. After PAGE, the amplified products of 84 bp for D allele and 65 bp for I allele were visualized by the ethidium bromide staining on gels.

Doppler measurement

The M-mode and two-dimensional echocardiographic study with pulse Doppler analysis was performed for investigation of resting cardiac function and morphology using Toshiba sonolayer SSH140A with a 2.5 MHz transducer (Toshiba, PSF-25LT, Tokyo, Japan), as was reported previously [30, 31]. The echocardiograms were derived from the two-dimensional images under direct anatomical visualization and recorded on a chart recorder. The thickness of the left ventricular wall and the dimensions of the left ventricular and left atrial cavities were measured on the M-mode echocardiograms according to the recommendations of the American Society of Echocardiography [29]. Simultaneous visualization during the whole cardiac cycle of the interventricular septal thickness, left ventricular internal diameter, and posterior wall thickness was sought at or just below the tips of the mitral valve leaflets.

The left ventricular volume was calculated based on Pombo's rule [24], and the left ventricular systolic function was determined from the measurements of ejection fraction. The left ventricular mass was calculated from end diastolic wall thickness and cavity dimension using the formula proposed by Devereux and Reicheck [10]. The probe was placed at the tips of the mitral valve leaflets as they open during diastole, in the four-chamber view using the pulsed-wave Doppler. From the Doppler spectral tracing, following data were obtained; peak velocity of early diastolic rapid filling flow (Ep), peak velocity of atrial filling flow (Ap), deceleration time, and the Ep/Ap ratio. The left ventricular isovolumetric relaxation time was measured from the aortic valve closure on the phonocardiogram to the start of mitral flow [14]. The relative contribution of the atrial systole to stroke volume was calculated as the area under the flow velocity profile during atrial systole divided by the total area of the flow velocity profile and expressed as a percentage [12].

All parameters of the echocardiogram and Doppler spectral tracing in each of 3 successive cardiac cycles were measured blindly and

independently by 2 investigators. Investigator variability was minimal; correlations for the parameters, measured, ranged from 0.96 to 0.99 for variability. All echocardiographic values, used in this study, represent the mean of 3 measurements. It was possible to obtain good-quality images in all subjects.

Work performance

The relationships between endurance work capacity and ACE genotype and/or morphological and functional properties of heart were investigated in elementary school children and soccer players. The 1,200 m, 2,000 m, and 2,400 m running times were utilized as an index for the endurance work performance in the 2nd, 4th and 6th graders, respectively.

The VO_2 max levels in the 2nd, 4th and 6th graders were indirectly estimated from the results (number of turns during gradual increase of speed) of shuttle running with 20-m interval. The 1,500 m running was performed to estimate the work capacity in the soccer players from elementary school and junior and senior high school. In university soccer players, 3,200 m running time and VO_2 max level were determined. The VO_2 max was determined during a treadmill running to exhaustion, by collecting and analyzing the expired gas. And the best record of each athlete in 5,000 m, 10,000 m, or marathon was used for the university and elite runners.

Statistical Analyses

All values were expressed as means ± SEM. Significant differences were examined by repeated measures of ANOVA followed by Scheffé's post hoc test. Coefficient of correlation between each parameter was also analyzed. Differences were considered significant at the 0.05 level of confidence.

Results

The mean percent distributions of ACE II, ID, and DD genotypes were 59.3, 35.7, and 5.0% among the whole 309 subjects (Table 1). More distribution of II than ID genotype was noted in most of the groups, although that in soccer players was opposite. Further, no subjects with DD genotype were observed in the elite runners and mountaineers. As is shown in Figure 1, no effects of ACE genotype on the running times were observed in the elementary school children.

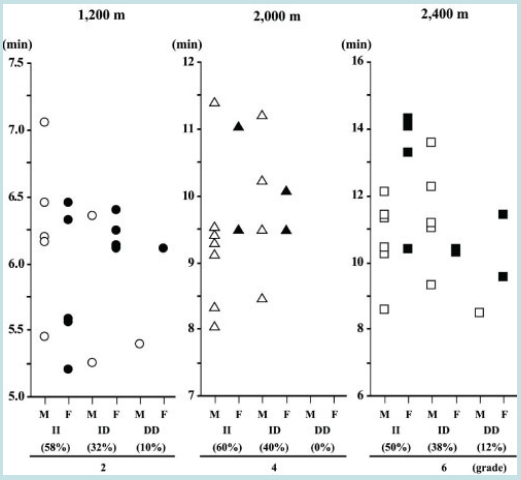

Figure 1: The relationship between the genotype of angiotensin-converting enzyme (ACE) and running performance in non-trained elementary school boys (M, open symbols) and girls (F, closed symbols). The work performances among each genotype, analyzed by analysis of variance, were not significantly different in any graders. The percent distributions of ACE genotypes are shown in the parenthesis.

However, the endurance work performance was closely related to the heart size and/or cardiac output levels. The coefficient of correlation between the running time and cardiac output level, normalized with body weight, in the 2nd, 4th and 6th graders was –0.51 (p=0.06), –0.64 (p<0.05), and –0.54 (p<0.05) for grade 2, 4, and 6, respectively (Figure 2). The mean VO^2 max levels in the 2nd and 6th graders were 34.4 ± 0.6 and 38.9 ± 1.4 ml/kg/min (p<0.05), respectively. But genotype-specific effects on these levels were not observed. The running time in 1,500 m was improved with increasing age in soccer players (Figure 3). However, the work performance levels in these subjects were not influenced by ACE genotype. No effects of ACE genotype on the running time of 3,200 m and VO_2 max in university soccer players were observed, either. The mean running time and VO_2 max in subjects with II, ID, and DD genotype were 11.8 ± 0.1, 11.9 ± 0.2, and 12.2 ± 0.3 min and 56.0 ± 1.3, 57.5 ± 1.4, and 59.7 ± 1.2 ml/kg/min, respectively (p>0.05).

Significant negative correlations were seen between the 1,500 m running time and left atrial diameter in soccer players (r = – 0.39, p<0.05, Figure 4). The 1,500 m running time was also significantly correlated with interventricular septal thickness (r = –0.51, p<0.05, Figure 5). Similar, but insignificant, negative correlations were also observed against other parameters, such as ejection fraction, left ventricular internal systolic dimension, left ventricular mass, and/or posterior wall thickness.

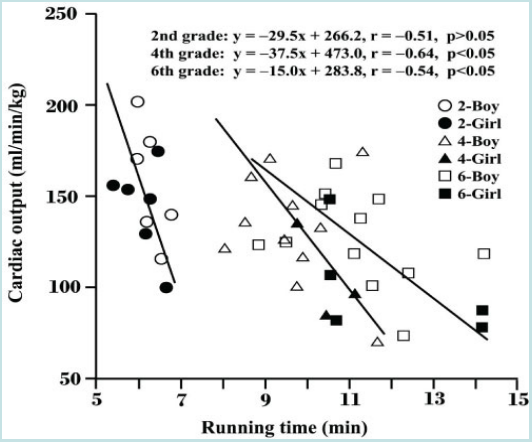

Figure 2: The relationship between running time and cardiac output level, normalized with body weight, in elementary school children. The 1,200 m, 2,000 m, and 2,400 m running time was utilized as an index for the endurance work performance in the 2nd, 4th and 6th graders, respectively.

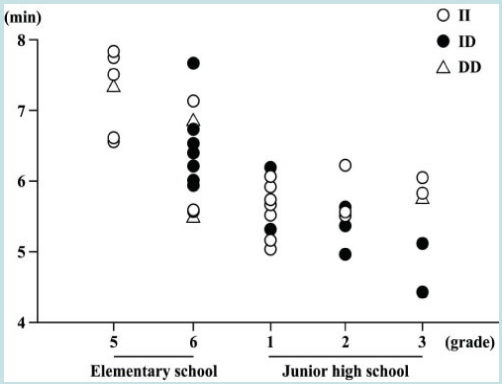

Figure 3: Effects of the genotype of angiotensin-converting enzyme on 1,500 m running time in male soccer players (10-15 years old) from elementary school and junior high school.

The ACE genotypes in all of the elite runners, as well as mountaineers, were either II or ID (Table 1, Figure 6). The work performance levels in 5,000 m, 10,000 m, and marathon were identical in runners with II or ID genotype. Genotype-specific differences in the work performance were not observed in university runners, either.

Discussion

The relationships between the ACE genotype, cardiac function and/or morphology, and endurance performance in children were investigated in the current study. The ACE genotype in elite distance runners and mountaineers were also investigated to estimate the effects of ACE genotype on the trainability. Here we report no significant relationships among the work capacity and ACE gene expression in children. However, endurance work capacity was closely related to cardiac output function, regardless of the specificity of physical training.

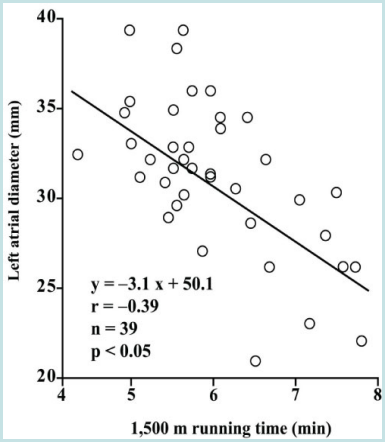

Figure 4: The relationship between 1,500 m running time and left atrial diameter in male soccer players (10-15 years old) from elementary school and junior high school.

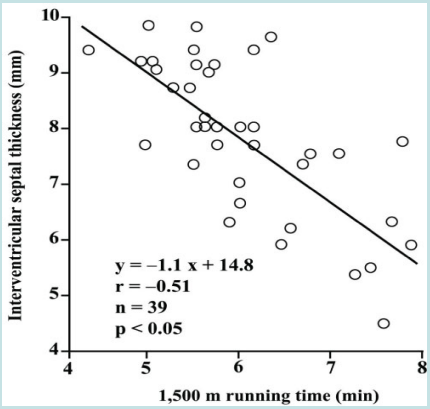

Figure 5: The relationship between 1,500 m running time and interventricular septal thickness in male soccer players (10-15 years old) from elementary school and junior high school.

The mean percent distributions of ACE genotypes were in the order of II > ID > DD among the whole subjects. These results generally agree with other report on Japanese population [15]. None of the elite runners and mountaineers had DD genotype in the present study. The percent distributions of II and ID genotype were 66 and 34%, respectively. The data may suggest that I allele have an important role for the trainability in endurance-type performance, as was also suggested elsewhere [4, 9, 18, 20, 35].

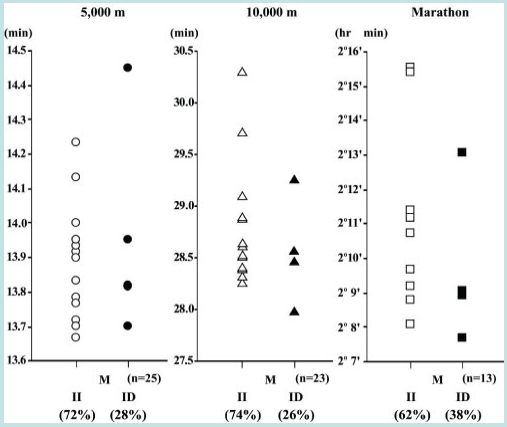

Figure 6: The relationship between the genotype of angiotensin-converting enzyme (ACE) and physical work performance in male elite runners. The work performances among each genotype, analyzed by analysis of variance, were not significantly different in any runners. The percent distributions of ACE genotypes are shown in the parenthesis. The percentage of DD was 0%.

It has been reported that improvement of endurance performance was closely related with cardiac output and oxygen utilization capacity [2, 11]. Saito *et al.* [31] also reported a significant positive correlation between the left ventricular mass per body weight and VO_2 max in elite runners. Such phenomena were also seen in young Japanese, who were the subjects in the present study. Data indicated that the greater the cardiac output level, the better the running performance. The running time was also negatively correlated with VO_2 max level (data not shown). The 1,500 m running time was improved and left ventricular mass per kg body weight was increased with increasing age generally in soccer players. The mean level of VO_2 max in university soccer players was 56.9 ±1.0 ml/kg/min, indicating a greater aerobic work capacity.

Further, there was a significant negative correlation between the 1,500 m running time and left atrial diameter and interventricular septal thickness in soccer players. It is suggested that endurance running performance and cardiac function in young children are not associated with ACE genotype. But the data indicated that their endurance work capacity is influenced by cardiac output function.

A significant correlation between ACE genotype and endurance performance has been observed previously [1, 7, 13, 16, 21]. However, no significant effects of ACE genotype on work performance, VO_2 max level, and the characteristics of heart were observed in young children and university students in the current study. The work performance levels in elementary school children were not influenced by the training status, or even sex, either.

Conclusion

No significant relationships among the cardiac function and morphology, and ACE gene expression were observed in young Japanese. However, it is suggested that endurance work capacity is influenced by cardiac output function, regardless of the specificity of physical training in children. The data also suggested that I allele may have an important role for trainability for endurance-type performance.

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