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ORIGINAL ARTICLE

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Angiotensin-converting enzyme gene polymorphism, left ventricular remodeling, and exercise capacity in strength-trained athletes

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Abstract The mechanisms that regulate the development of human physiological cardiac hypertrophy remain poorly understood. The renin-angiotensin system, which is modulated by genetic polymorphism, plays an important role in the regulation of vascular tone and myocardial hypertrophy. Although a few studies have analyzed the association of angiotensin-converting enzyme (ACE) polymorphism and left ventricular (LV) hypertrophy in isotonic exercise-trained subjects who developed eccentric cardiac hypertrophy, there has been no research done in power athletes who developed concentric cardiac hypertrophy. We have hypothesized that ACE genotypic modulation characteristics may affect LV mass in power athletes. This study included 29 elite Caucasian wrestlers (mean age, 22.6 years) and 51 age-matched sedentary subjects. According to the absence or presence of the insertion segment in the polymerase chain reaction (PCR) product, the subjects were classified as homozygous deletion-deletion (*DD*), insertion-insertion (*II*), or heterozygous insertion-deletion (*ID*). The association of LV hypertrophy with ACE gene insertion/deletion (*I/D*) polymorphism was analyzed. Left ventricular mass and index were determined by echocardiography. Angiotensin-converting enzyme genotyping was performed on peripheral leukocytes using the polymerase chain reaction technique. The study and control group subjects were similar in height and weight. Left ventricular hypertrophy in the athletes was more apparent than in the controls. Angiotensin-converting enzyme genotype *II* frequency was 17.2% (5) in the athletes, 17.6% (9) in the controls; *ID* frequency was 51.7% (15) in the athletes, 56.8% (29) in the controls; and the *DD* frequency was 31% (9) in the athletes and 25.4% (13) in the controls. Left ventricular mass and mass index were found to be higher in genotype *DD* (126.2 ± 2.9 g/m^2) than genotype *II* (85.5 ± 4.0 g/m^2) or genotype *ID* (110.1 ± 2.3 g/m^2) in the athletes ($P < 0.001$). Furthermore, maximal oxygen consumption in genotype *DD* was found to be higher than in *II* and *ID*. An association was found between ACE gene *I/D* polymorphism and LV hypertrophy in strength-trained athletes.

Key words Angiotensin-converting enzyme gene polymorphism · Left ventricular hypertrophy · Exercise · Athlete

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Introduction

In healthy athletes who train regularly, exercise causes cardiac changes resulting in modification of the ventricular chambers. These modifications, called physiological hypertrophy or athlete's hypertrophy, are required to sustain the tremendous increase in cardiac output during exercise.[1] The factors involved in the development of physiological hypertrophy in humans are still unknown and it is felt that once these factors are determined, they might also be relevant for better understanding the mechanisms involved in the cardiac adaptive response to the pathological increase in hemodynamic workload.[1] Although the reasons are unknown, there is some variability in left ventricular mass in athletes who undergo the same type and duration of training.

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, electrolyte balance, and vascular tone. As a key component, angiotensin-converting enzyme (ACE) yields pressor angiotensin II and degrades vasodilator kinins. However, local ACE exists in tissues, including the myocardium, where it may influence cardiac growth responses.[2] A polymorphism ACE gene exists in which the deletion (*D*) variant is associated with higher circulating and tissue ACE activity than the insertion (*I*) variant.[3]

In the presence of a growth stimulus such as exercise, the *D* allele should be associated with cardiac hypertrophy. Although a few studies have analyzed the associations of ACE polymorphism and left ventricular (LV) hypertrophy in isotonic exercise-trained subjects who developed eccentric cardiac hypertrophy, no research has been done in power athletes who have developed concentric cardiac hypertrophy.

On the other hand, skeletal muscle RAS might also influence human physical performance. The ACE *I* allele has been associated with fatigue resistance and elite endurance athletic performance, and the *D* allele in spring capacity in power sports.[4] However, the mechanism underlying this remains uncertain. One explanation might be that the ACE genotype is associated with differences in maximal oxygen uptake. Only a handful of studies have addressed this issue, and offer conflicting data.[4,5]

Hence, the aims of this study were (1) to evaluate the distribution of the ACE gene polymorphism and LV hypertrophy in power athletes, and (2) to assess the relation between ACE *I/D* polymorphism and exercise capacity values in athletes.

Subjects and methods

Subject characteristics

Eighty subjects, consisting of 29 Caucasian male athletes who had won medals at the Olympic Games and in various other international competitions, and 51 age-matched healthy Caucasian male controls were included in the study. The athletes had trained intensively for 15–20 h per week (>70% isometric training) for more than 7 years. Those subjects who served as normal controls (medical school students) did not exercise on a regular basis and when they did, it was mostly walking (or swimming, soccer, or basketball for less than 1 h) for less than 4 h per week. The subjects were excluded if they had coronary artery disease, valvular and congenital heart disease, heart failure, cardiomyopathy, arterial systemic hypertension, diabetes mellitus, or echocardiograms of inadequate quality. All of the subjects were nonsmokers.

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee. Signed informed consent was obtained from all subjects before participation.

DNA analyses

Genomic DNA was isolated from white blood cells following a standard protocol.[6] The ACE *I/D* polymorphism was determined by a polymerase chain reaction (PCR)-based method using the ACE-specific sense primer 5′-CACGAC GTTGTAAAACGACCTGGAGACCACTCCCATCCTTT-3′ and antisense primer 5′-GATGTGGCCATCACATT CGT-3′ with a final reaction mixture of 15 μl containing 100 ng of genomic DNA, 3.0 mM $MgCl_2$, 200 μM each of dNTP, 300 nM primers flanking the insertion sequence 140 nM nested primer, 4.7% dimethyl sulfoxide, and 1.0 U of Taq polymerase. The PCR (Techne thermal cycler; Techne, Princeton, NJ, USA) protocol consisted of one cycle at 94°C for 5 min, 58°C for 1 min, 72°C for 2 min; followed by 30 cycles at 94°C for 1 min, 58°C for 1 min, 72°C for 2 min; and finally one cycle at 94°C for 1 min, 58°C for 1 min, and 72°C for 7 min. Amplification products, the insertion allele (*I*) 490 bp fragment and the deletion allele (*D*) 190 bp fragment, were separated on 3.0% agarose gel and visualized under ultraviolet light after ethidium bromide staining. Because of the preferential amplification of the *D* allele all samples with the *DD* genotype were reamplified with insertion-specific primers. All PCR results were scored by two independent investigators blind to all subject data, and no interobserver variability was found.

Echocardiographic methods

All echocardiographic examinations were performed with a Vingmed System 5 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) by a trained cardiologist blinded to the grouping of the study subjects. Left ventricular internal diameter and wall thickness were measured from M-mode recordings.

Left ventricular mass was calculated by using the method of Devereux and Reichek,[7]

$$1.04 \times [(\text{LVID} + \text{IVSd} + \text{PWd})^3 - \text{LVID}^3] - 13.6$$

where LVID is the left ventricular internal end-diastolic dimension, IVSd is the interventricular septal thickness, and PWd is the posterior wall diastolic thickness.

Left ventricular mass index was calculated by dividing LV mass by body surface area. Individual values for LV mass index are considered normal at $<125\,g/m^2$.[8]

Relative wall thickness (RWT) was calculated according to the following formula:[9]

$$\text{PWT} = (\text{IVSd} + \text{PWd})/\text{LVDd}$$

where LVDd is the left ventricular diastolic diameter.

Left ventricular meridional systolic wall stress was estimated by modifying previously published methods assuming that LV geometry is spherical and wall thickness is uniform as follows.[10]

$$\text{End-systolic wall stress (kdyne/cm}^2) = 0.334 \times \text{SBP} \times \text{LVDs}/[\text{PWs} \times (1 + \text{PWs}/\text{LVIDs})]$$

Table 1. Characteristics of athletes and control subjects

	Athletes (n = 29)	Controls (n = 51)	P value
Age (years)	22 ± 3	21 ± 2	0.06
Height (cm)	170 ± 8	173 ± 7	0.07
Weight (kg)	76 ± 18	67 ± 10	0.02
BSA (m^2)	1.87 ± 0.23	1.79 ± 0.15	0.42
HR (/min)	57 ± 11	75 ± 11	<0.001
$\dot{V}O_{2max}$ (ml/kg/min)	59.9 ± 4.9	44.1 ± 5.2	<0.001

Variables are expressed as mean ± SD
BSA, body surface area; HR, heart rate; $\dot{V}O_{2max}$, maximal oxygen consumption

where LVDs is the systolic left ventricular diameter, PWs is the systolic posterior wall thickness, and SBP is the systolic blood pressure.

Cardiopulmonary exercise testing

The exercise was performed in a quiet, air-conditioned room with an average temperature of 21° ± 2°C and full resuscitation facilities. All participants underwent a standard Bruce multistage maximal treadmill protocol with metabolic measurements. The exercise was discontinued because of fatigue, symptoms, or other criteria.[11] A standard 12-lead electrocardiogram was monitored continuously, and blood pressure was measured simultaneously with a mercury sphygmomanometer at the brachial artery at rest (SBPrs, systolic blood pressure; DBPrs, diastolic blood pressure) during the last 10 s of each exercise stage, at the end of the graded exercise test (SBPex, systolic blood pressure; DBPex, diastolic blood pressure), and at the end of each minute of the subsequent 3-min recovery, by a blinded physician. Oxygen uptake was measured every 10 s using a metabolic chart (2900C B × B, Sensormedics, Yorba Linda, CA, USA). Respiratory gas was analyzed using a zirconium oxygen analyzer and a nondispersive infrared sensor for carbon dioxide. Before each test, the gas analyzers were calibrated with two mixtures of gases of known oxygen and carbon dioxide concentration. Basic gas and flow measurements were also corrected for ambient temperature, barometric pressure, and water vapor. Subjects breathed ambient air through a Rudolph two-way valve during the exercise. To ensure that maximal oxygen consumption ($\dot{V}O_{2max}$; ml/kg per minute) was reached, three criteria had to be met: (1) a leveling off of $\dot{V}O_2$ despite an increase in exercise power over the final stages of the test, (2) attainment of age-predicted maximal HR (210 − 0.65 × age) ± 10 beats/min, and (3) R (respiratory exchange ratio) ≥ 1.10.

Statistical analyses

Allele frequencies were estimated with the gene-counting method. A chi-square test was used to assess the fit of the observed allele frequencies to the agreement of the Hardy-Weinberg equilibrium and the difference in genotype distributions between the control and the study group.

Continuous variables were expressed as mean ± SD or SE according to the genotypes (*II*, *ID*, *DD*). The Mann-Whitney *U*-test was used when comparing the means of two groups. The differences between variables in the different genotype groups were compared with analysis of variance (ANOVA). A one-way ANOVA was used for a potential synergistic effect of the ACE gene on LV mass. The Fisher least significant difference procedure test was used for multiple comparisons between the genotype classes.

Reproducibility of echocardiographic measurements

All measurements were expressed as the mean of three readings made independently by each of the two observers blinded to ACE genotype and training status.

Results

Characteristics of subjects

The study and control groups were similar in age, height, and body surface area. Resting heart rate was lower in the athlete group compared with the control group ($P < 0.001$) (Table 1). Left ventricular mass and LV mass index were higher in the athletes than in the controls (LV mass: 204.3 ± 11.6 vs 150.7 ± 6.1, respectively, $P < 0.001$; LV mass index: 107.2 ± 3.1 vs 83.8 ± 3.1, respectively, $P < 0.001$).

Frequencies of ACE genotypes

The frequency of the *D* allele was 56.8% in the athletes and 53.9% in control subjects. In the whole sample, the ACE gene *D* and *I* allele frequencies were 55% and 45%. The athletes' frequencies did not differ significantly from those of the controls. The genotype distributions in all subjects were in agreement with the Hardy-Weinberg equilibrium.

Association of ACE genotype with LV mass and LV mass index

Interventricular septal thickness, LV mass, and LV mass index were significantly greater in the athletes and controls

Table 2. Comparison of control subjects with different angiotensin-converting enzyme (ACE) genotypes

	II (n = 9)	*ID* (n = 29)	*DD* (n = 13)	*P* value*
HR (/min)	78 ± 5	77 ± 2	72 ± 3	0.42
$\dot{V}O_{2max}$ (ml/kg/min)	48.1 ± 0.6	44.4 ± 0.2	41.6 ± 0.3	<0.001
SBPrs (mmHg)	110 ± 6	108 ± 3	114 ± 4	0.20
DBPrs (mmHg)	74 ± 3	71 ± 1	72 ± 2	0.65
SBPex	171 ± 4	173 ± 2	176 ± 3	0.04
DBPex	70 ± 2	69 ± 1	71 ± 2	0.34
IVSd (cm)	0.79 ± 0.02	0.82 ± 0.01	0.83 ± 0.01	0.22
LVDd (cm)	5.13 ± 0.09	4.92 ± 0.06	4.91 ± 0.14	0.07
PWd (cm)	0.77 ± 0.03	0.79 ± 0.01	0.82 ± 0.02	0.09
RWT	0.30 ± 0.01	0.33 ± 0.01	0.33 ± 0.01	0.11
LVM (g)	143.9 ± 8.5	149.0 ± 4.1	159.9 ± 5.7	<0.001
LVMI (g/m^2)	76.6 ± 3.1	80.9 ± 1.4	94.0 ± 2.1	<0.001
ESWS (kdyne cm^2)	61.1 ± 4.7	59.3 ± 3.7	63.4 ± 5.3	0.36

Variables are expressed as mean ± SE

HR, heart rate; $\dot{V}O_{2max,}$ maximal oxygen consumption; SBP, systolic blood pressure; DBP, diastolic blood pressure; rs, rest stage; ex, peak exercise stage; IVSd, interventricular septum; LVDd, left ventricular end-diastolic diameter; PWd, left ventricular posterior wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index; ESWS, end-systolic wall stress

* *DD* vs *II*

Table 3. Comparison of athletes with different ACE genotypes

	II (n = 5)	*ID* (n = 15)	*DD* (n = 9)	*P* value*
HR (/min)	59 ± 5	58 ± 3	56 ± 4	0.83
$\dot{V}O_{2max}$ (ml/kg/min)	64.5 ± 0.9	60.4 ± 0.6	54.8 ± 0.8	<0.001
SBPrs (mmHg)	108 ± 4	104 ± 3	103 ± 2	0.79
DBPrs (mmHg)	70 ± 2	72 ± 3	74 ± 3	0.27
SBPex	171 ± 4	175 ± 5	179 ± 5	0.03
DBPex	70 ± 3	69 ± 4	68 ± 3	0.16
IVSd (cm)	0.98 ± 0.04	0.97 ± 0.02	1.09 ± 0.03	<0.001
LVDd (cm)	4.63 ± 0.13	4.59 ± 0.07	4.53 ± 0.09	0.45
PWd (cm)	0.96 ± 0.05	0.98 ± 0.03	1.03 ± 0.03	0.02
RWT	0.42 ± 0.04	0.43 ± 0.03	0.46 ± 0.03	0.03
LVM (g)	155.1 ± 15.0	194.8 ± 8.6	264.6 ± 11.2	<0.001
LVMI (g/m^2)	85.5 ± 4.0	110.1 ± 2.3	126.2 ± 2.9	<0.001
ESWS (kdyne cm^2)	53.7 ± 5.1	54.3 ± 4.8	51.4 ± 6.3	0.36

Variables are expressed as mean ± SE

* *DD* vs *II*

with *DD* genotype than in those with *II* genotype (Tables 2 and 3). There were differences in LV mass or LV mass index values between the different genotypes in both the athletes and the control subjects. Tables 3 and 4 show the values of echocardiographic variables in the athletes and control subjects by genotype. There was a significant association between the ACE genotype and LV mass. In the control and study subjects, the *D* allele was also associated with increased LV mass. Four athletes with the *DD* genotype (44.4%) and two athletes with the *ID* genotype (13.3%) had an LV mass index >125 g/m^2. However, no athletes with the *II* genotype and control subjects had an LV mass index >125 g/m^2. Left ventricular mass index in the athletes with the *DD* allele was increased approximately 34%, compared with nonathletic age-matched subjects. In the *II* genotype, this increase was found to be only 11%. According to the LV mass index, differences between the genotypes was at a significant level (P < 0.001) (Fig. 1). Although there were no significant differences in SBP or DBP at rest among the three genotype groups, SBP at peak exercise was higher in the *DD* genotype than in the *ID* and *II* genotypes in both the athlete and control groups (Tables 2 and 3).

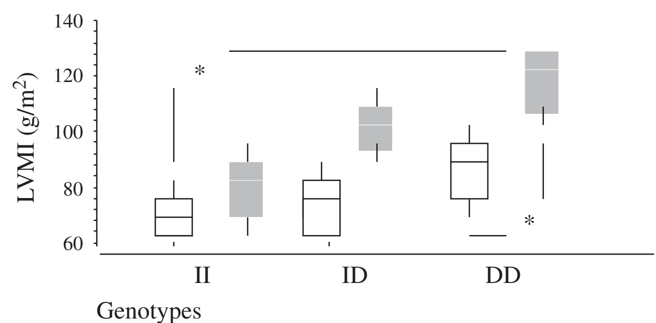

Fig. 1. Left ventricular mass index by genotype in athletes (*shaded boxes*) and controls (*open boxes*). *Asterisk*, Statistically significant. *LVMI*, left ventricular mass index

Cardiopulmonary exercise testing analysis

Although resting heart rate in athletes was lower than in controls, maximal heart rate at peak exercise was similar in both groups (Table 1). There was no difference among genotypes in the athletes and controls. $\dot{V}O_{2max}$ in the athletes was higher than in the controls; however, $\dot{V}O_{2max}$ in both the athlete and control groups with the *DD* genotype was lower than in those with the *II* genotype (Tables 2 and 3).

Reproducibility of the echocardiographic measurements

The intraobserver regression coefficient was >0.87 ($P < 0.001$) and the interobserver regression coefficient was >0.85 ($P < 0.001$) for all echocardiographic measurements.

Discussion

Angiotensin-converting enzyme genotype and LV hypertrophy in athletes

Our present study suggests that the *DD* genotype may be a predictor for the development of athletic LV hypertrophy. The echocardiographic changes in athletes who had the *DD* genotype were characterized by increases in LV wall thickness, LV mass, and LV mass index. It is accepted that cardiac adaptations in power athletes are characterized by an increase in LV mass and wall thickness, with or without a cavity dimension increase.[12] However, these echocardiographic findings are not absolute rules; they may change in each subject and all the affecting factors are not well characterized. While the results of this study suggest that genetic background with exercise overload might contribute to the development and regulation of LV in power athletes, there was also an association of LV mass with genotype seen in control subjects who did not perform intensive or habitual exercise even though the LV mass levels in these subjects did not reach hypertrophic levels in all controls. The reason for this finding may be due to short-term sports activity aside from walking.

Although this study is not the first which has examined the different ACE genotypes and LV hypertrophy in athletes, little information is provided concerning this subject in the literature. Angiotensin-converting enzyme polymorphism is a factor that influences cardiac adaptation in athletes. In the present study, even though the wrestlers were similar in age, training type, and duration, they showed different degrees of cardiac hypertrophy which led us to believe that this difference may be in part due to genetic makeup, more specifically ACE gene polymorphism. Cardiac hypertrophy was a prominent finding in the athletes who carry the *DD* allele and the strong physiological stimulus to myocardial growth in *DD* athletes caused an average increase in the LV mass index of approximately 34%, as compared with nonathletic age-matched subjects. In the *II* genotype, this increase was found to be only 11%. A few other studies show an association between ACE polymorphism and LV hypertrophy due to athletic training. Montgomery et al.[13] found that 10 weeks of training in military recruits increased LV mass more in carriers of the *D* allele than in those with the *II* genotype. In contrast to this finding, Karjalainen et al.[14] found that ACE gene polymorphism was not associated with LV mass in endurance athletes. In that study, their finding may be due to different athletic competition times and types of exercise (isotonic type).

Previous studies done on the general population have reported contradictory results with regard to the association between ACE *I/D* polymorphism and LV hypertrophy or LV mass.[15–19] Schunkert et al.[15] first reported that among subjects homozygous for the deletion allele of the ACE gene, the electrocardiographic criteria for LV hypertrophy was found to be greater than those not homozygous for the gene. Using electrocardiography, Iwai et al.[16] also reported the association of the *DD* genotype with LV mass. Kupari et al.[17] and Lindpaintner et al.[18] observed neither an association nor a genetic linkage between ACE *I/D* polymorphism and LV hypertrophy or LV mass in a study based on the Framingham Heart Study population. In our study, RWT was higher in athletes with the *DD* genotype than in those with the *ID* and *II* genotypes. We believe that cardiac hypertrophy in athletes with the *DD* genotype may be a compensatory response to more increasing SBP during exercise, which leads to abnormally elevated systolic wall stress. Lower wall stress of LV in athletes who had the *DD* genotype, as seen in this study, may be a cardiac adaptation to increased ACE activity during exercise. Ueno et al.[20] also reported that there was a significiant association between *DD* genotypes and RWT in a Japanese population with essential hypertension.

Angiotensin-converting enzyme genotype and blood pressure in athletes

Although we found no significant differences in blood pressure readings at rest among different alleles in each of the two groups, SBP at peak exercise was higher in the subjects with the *DD* genotype than in those with *II* and *ID* genotypes. Some authors have suggested that elevation of blood pressure in itself could potentially account for the increased incidence of LV hypertrophy in subjects homozygous for the ACE *D* allele.[21,22] Schunkert et al.[15] found that 62% of the subjects in their study with electrocardiographic evidence of LV hypertrophy were not hypertensive. In an echocardiographic study of hypertensive subjects, Prasad et al.[21] showed that SBP is significantly correlated with LV mass only in the presence of the *D* allele. In contrast, some studies demonstrated that the ACE polymorphism did not show an association with blood pressure.[3,23] Thus, even if a potential interaction of training cannot be fully excluded, the association of the ACE *DD* genotype and LV hypertrophy seems to involve mechanisms other than just blood pressure levels.

Local renin-angiotensin systems within LV tissue may regulate myocardial growth through the local generation of angiotensin II, although the difficulty in obtaining LV tissue from normal individuals impedes further examination of their importance in human cardiac growth.[24,25] Recently, cardiac tissue ACE activity was demonstrated to be increased in subjects with the *DD* genotype, allowing us to speculate on the possible involvement of the ACE genotype in the regulation of the tissue ACE activity as well as plasma ACE activity. Angiotensin peptides exert trophic influences on cardiomyocytes in culture, and the expression of genes encoding components of the RAS is upregulated in hypertrophy and remodeling.[24,25] The *D* allele could be associated with a greater increase in LV mass in response to training than the *I* allele, and individuals with higher cardiac ACE levels may be expected to exhibit a greater response to a hypertrophic stimulus such as physical training.[13]

The classic paradigm of LV compensation to chronic pressure overload has been that LV wall thickness should increase proportionally to SBP to maintain normal wall stress, leading to concentric hypertrophy.[26] We believe that cardiac hypertrophy in athletes with the *DD* genotype may be a compensatory response to more increasing SBP during exercise, which leads to decreased systolic wall stress. Recently, Hernandez et al.[27] also reported that athletes with the *DD* genotype showed a higher LV mass than athletes with the *II* genotype.

Study limitation

The present study was limited by having a small number of subjects but finding a group of elite athletes with a homogeneous training regime was the limiting factor. Although we did not measure ACE levels in these subjects, several studies have reported a higher plasma level of ACE in subjects with the *DD* allele when compared with other subgroups. We have speculated that exercise may stimulate cardiac hypertrophy in the *DD* allele group. There are several factors that may explain why an association seen in one population may not be replicated in others. In genetic epidemiology, the genetic background of study populations and the selection methods of study subjects are the critical factors.

Conclusions

Left ventricular mass and geometry are determined by hereditary, neurohormonal, and hemodynamic factors in athletes. Although polymorphisms of single genes seem to affect LV mass, the interactions of the gene products within a given biochemical and physiological pathway (RAS) may have a synergistic effect on LV mass. Our results show that habitual and intensive exercise has the effect of inducing LV hypertrophy in athletes. Even though the exact mechanism of the *DD* genotype of the ACE gene causing cardiac hypertrophy is not known, we conclude that increased ACE levels in subjects with the *DD* allele may stimulate cardiac hypertrophy with exercise training.

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