■ ORIGINAL ARTICLE

Cardiovascular Adaptation, Functional Capacity, and Angiotensin-Converting Enzyme I/D Polymorphism in Elite Athletes

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Introduction and objectives. Angiotensin-converting enzyme (ACE) is associated with the development of cardiac hypertrophy and improved physical fitness. The objective of this study was to investigate the relationship between the ACE gene insertion/deletion (I/D) polymorphism and adaptation to sports training.

Methods. The study included 299 elite Spanish athletes (193 men and 106 women) from 32 different sports disciplines, which were grouped according to their static and dynamic components. All participants underwent body composition analysis, Doppler echocardiography at rest, and ergospirometry. Their ACE genotype was determined using the polymerase chain reaction.

Results. The most common genotype in both males and females was the deletion-insertion (DI) heterozygote (57.5% and 54.7%, respectively), followed by the DD homozygote (30.6% and 34.9%), and the II homozygote (11.9% and 10.4%). Differences in morphometric and functional cardiac adaptation were observed between the different sports disciplines, but there was no statistically significant relationship with the ACE I/D polymorphism. Moreover, when athletes with different genotypes were compared, the only differences observed were between the DD and DI groups in female athletes, who differed in body mass index and longitudinal right atrial dimension.

Conclusions. The ACE I/D polymorphism did not appear to influence cardiovascular adaptation in response to training. However, the DI genotype was the most common, probably because the sample was biased by being made up of elite athletes.

Key words: *ACE polymorphism. Sport. Cardiovascular adaptation. Body composition.*

Adaptación cardiovascular, capacidad funcional y polimorfismo inserción/deleción de la enzima de conversión de angiotensina en deportistas de élite

Introducción y objetivos. La enzima de conversión de angiotensina (ECA) se relaciona con el desarrollo de hipertrofia cardiaca y mejora de la condición física. El objetivo del estudio es analizar la relación entre el polimorfismo inserción/deleción (I/D) del gen de la ECA y la adaptación al entrenamiento.

Métodos. Se estudió a 299 deportistas españoles de alto nivel (193 varones y 106 mujeres) de 32 disciplinas deportivas, agrupadas según sus componentes estático y dinámico, mediante análisis de la composición corporal, eco-Doppler en reposo y ergoespirometría. El genotipo de la ECA se determinó mediante la técnica de la reacción en cadena de la polimerasa (PCR).

Resultados. El genotipo más frecuente fue el heterocigoto DI (el 57,5 y el 54,7%), seguido de los homocigotos DD (el 30,6 y el 34,9%) e II (el 11,9 y el 10,4%), en varones y mujeres respectivamente. Hay diferencias en las adaptaciones morfológicas y funcionales entre las modalidades deportivas, pero no se obtuvo asociación estadísticamente significativa con relación al polimorfismo I/D de la ECA. En el estudio comparativo entre los distintos genotipos, sólo en la muestra femenina se encontraron diferencias entre los grupos DD y DI en el índice de masa corporal y en la dimensión superoinferior de la aurícula derecha.

Conclusiones. El polimorfismo I/D del gen de la ECA parece que no influye en la adaptación cardiovascular al entrenamiento; sin embargo, el genotipo DI es el más frecuente, probablemente debido a un sesgo de la muestra, compuesta por deportistas de élite.

Palabras clave: *Polimorfismo de la ECA. Deporte. Adaptación cardiovascular. Composición corporal.*

ABBREVIATIONS

RAAS: renin-angiotensin-aldosterone system
$VO_{2máx}$: maximal oxygen uptake
$VO_{2\,kg\,máx}$: relative maximal oxygen uptake

INTRODUCTION

Physiologic cardiac hypertrophy in athletes is known as "athletic heart syndrome."[1] The renin-angiotensin-aldosterone system (RAAS) has an influence on myocardial growth: angiotensin II stimulates synthesis of cardiac proteins, whereas bradykinins have an antiproliferative effect.[2] Physical exercise activates RAAS, and overstimulation during long training periods has been related to the development of left ventricular hypertrophy. In elite athletes and those undergoing aerobic endurance training, physiologic hypertrophy is more evident.[3] Nonetheless, not all athletes who perform similar aerobic training acquire the same degree of hypertrophy, and this suggests that genetic factors may have an influence on heart size.

The genes coding for RAAS components regulate the concentration of angiotensin-converting enzyme (ACE), as well as function and expression of angiotensin II.[4] There seems to be a relationship between the insertion/deletion (I/D) polymorphism of a 287-bp Alu element in intron 16 of the ACE gene and the degree of activity of the enzyme in plasma and tissue. The D allele is associated with higher levels of activity and a greater probability that hypertrophy will occur with exercise; nonetheless, the role of ACE gene I/D polymorphism in the development of athlete heart syndrome remains unclear. Some authors consider that cardiac hypertrophy in response to training is independent of the I/D genotype.[5,6] Others report an association, although with disparate findings: for some authors,[7,8] hypertrophy in athletes who practice predominantly aerobic sports is associated with genotypes DD and DI or with the presence of the D allele, whereas others[9] have found a greater frequency of the I allele.

The aim of this study was to determine the relationship between I/D polymorphism of the ACE gene and adaptation to training in elite Spanish athletes practicing various sports disciplines.

METHOD

Study Population

Among the overall population of elite athletes who came to the Center for Sports Medicine of the National Sports Council of Spain (CSD, Consejo Superior de Deportes) during the 2007 to 2008 season for a medical-sport check-up, 299 signed an informed consent form for participation in the study: 193 men (mean age, 23.8 [5.8] years) and 106 women (23.7 [5.6] years) practicing 32 sports disciplines. Subjects were grouped attending to the dynamic and static components of their activity, determined according to the sports classification of Mitchell.[10] The dynamic component (endurance) is defined as class A (low), B (moderate), or C (high) when the oxygen uptake (VO_2) required during competition is <40%, between 40% and 70%, or >70% of the maximal VO_2 (VO_2max). The static component (power) is categorized as class I (low), II (moderate), or III (high), according to whether the maximal voluntary contraction (MVC) is <20%, 20% to 50%, or >50%. The various sports categorized according to the Mitchell classification[10] are shown in Table 1.

Genetic Study of Angiotensin-Converting Enzyme

Blood samples were drawn into EDTA-K3 tubes. A 185 µL amount of sample was placed on a Whatman FTA Card (VWR International Eurolab, S.L. ref. WHATWB120210). A circle 1-mm in diameter was then cut from the card and incubated in 200 µL of TE buffer (Tris-HCl 10 mmol and EDTA 1 mmol, pH 8) at room temperature for 2 h. DNA extraction consisted of digestion with proteinase K, protein precipitation with ammonium acetate (ACNH4) 4 mol, and posterior DNA precipitation with ethanol. Twenty 20 ng of DNA was used for PCR amplification of a fragment of intron 16 of the ACE gene, which contains the I/D polymorphism (rs 4646994). The primers used were ACE1F, 5'-CT-GGAGACCACTCCCATCCTTTCT-3' and ACE1R, 5'-GATGTGGCCATCACATTCGTCAGAT-3', which generate a 234-bp product and 480-bp product for the D and I alleles, respectively.

In all samples in which only the D allele was amplified, presumably because subjects were homozygous for DD, separate amplification was performed using the primers ACE2F, 5'-TGGGACCACAGCGCCCGCCACTAC-3' and ACE2R, 5'-TCGCCAGCCCTCCCATGCCCA-TAA-3', to confirm the absence of allele I. This

TABLE 1. Distribution of Sports According to Their Static and Dynamic Components

Sport	Static	Dynamic	Men	Women	Total
Running (long distance)	I	C	14	7	21
Racewalking	I	C	3	4	7
Badminton	I	C	1	2	3
Orienteering	I	C	7	0	7
Indoor soccer	I	C	3	0	3
Field hockey	I	C	7	9	16
Sport climbing	I	C	4	0	4
Fencing	I	B	19	3	22
Rhythmic gymnastics	I	B	0	11	11
Golf	I	A	1	1	2
Goal ball	I	A	3	0	3
Riflery	I	A	3	1	4
Running (middle distance)	II	C	18	11	29
Swimming	II	C	10	6	16
Waterpolo	II	C	2	0	2
Field events (jumping)	II	B	12	0	12
Track events (hurdles)	II	B	4	1	5
Running (sprint)	II	B	7	5	12
Figure skating	II	B	0	1	1
Archery	II	A	4	0	4
Athletics, combined events	III	C	4	3	7
Boxing	III	C	7	0	7
Cycling	III	C	1	3	4
Canoeing	III	C	7	4	11
Triathlon	III	C	9	10	19
Wrestling	III	B	4	2	6
Field events (throwing)	III	A	2	1	3
Artistic gymnastics	III	A	9	3	12
Weight lifting	III	A	2	0	2
Judo	III	A	17	13	30
Karate	III	A	8	5	13
Taekwondo	III	A	1	0	1
Total			193	106	299

Mitchell classification[10]: A, low dynamic component; B, moderate dynamic component; C: high dynamic component; I: low static component; II: moderate static component; III: high static component.

amplification yields a 336-bp fragment only when the sample contains allele I.

In addition to this second amplification and to ensure the accuracy of genotyping, 20% of the samples were reanalyzed; confirmation of the genotype obtained in the first analysis was 100%.

Anthropometric Study

The variables included in the anthropometric study were weight, height, 3 perimeters (arm, thigh, and leg), and 8 skinfolds (iliac crest, supraspinal, abdominal, subscapular, biceps, triceps, anterior thigh, and medial leg). Measurements were carried out with a Seca Delta scale, stadiometer, metric tape measure, and Holtain skinfold calipers, using the technique recommended by the International Society for the Advancement of Kinanthropometry

(ISAK).[11] The following parameters were calculated: body surface area (BSA), sum of skinfold results, percentage of body fat,[12,13] muscle mass and percentage of muscle mass,[14] body mass index (BMI), and fat-free mass index (FFMI), which was calculated by subtracting the fat mass from the total body mass and dividing the result by the square of the height in meters.

Cardiologic Study

None of the athletes studied had a history of hypertension, smoking, or kidney disease, or a family history of hypertrophic cardiomyopathy or sudden death. A cardiovascular examination, 12-lead electrocardiography at rest (General Electric MAC 5000 electrocardiograph), and echocardiography (Phillips Sonos 7500, 2-4 MHz

Figure 1. Distribution of angiotensin-converting enzyme I/D polymorphism genotypes according to static and dynamic components of the sports. Mitchell classification[10]: A, low dynamic component; B, moderate dynamic component; C, high dynamic component; I, low static component; II, moderate static component; III, high static component.
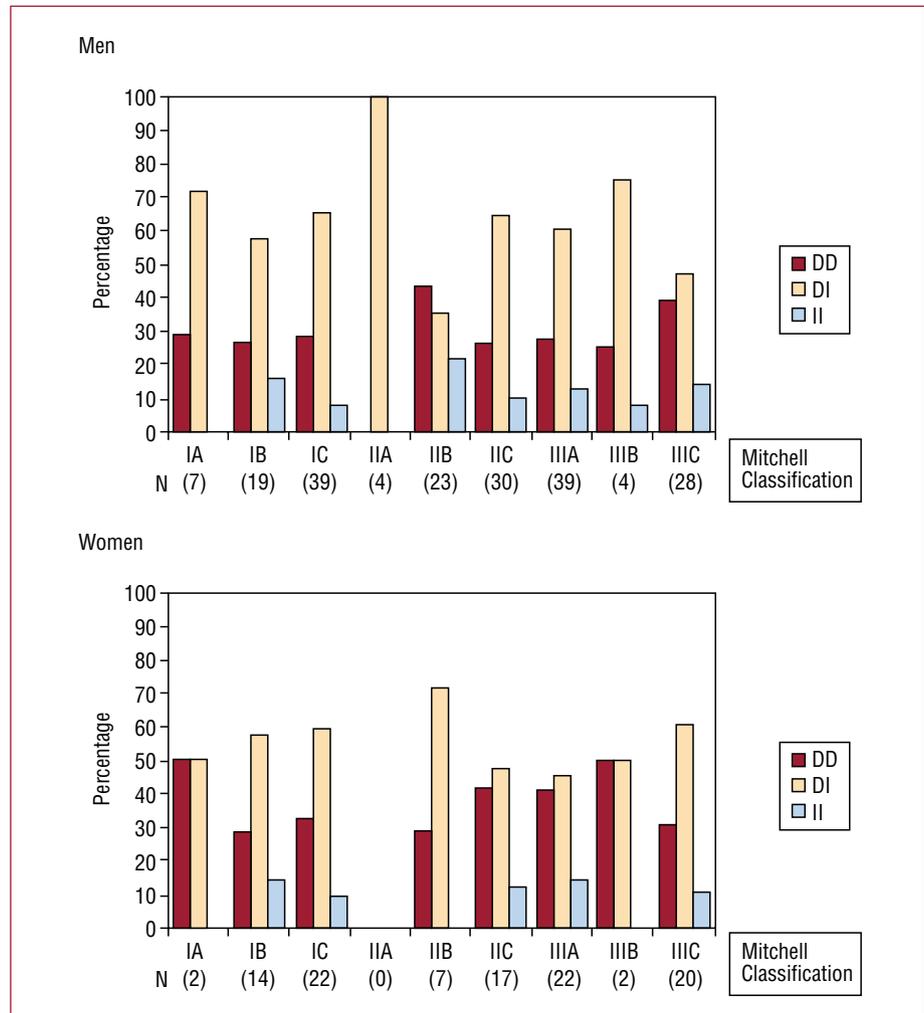
multifrequency transducer) were performed. Two experienced observers analyzed the measurements. Heart chamber diameters and wall thickness were measured in a parasternal, long-axis view (M mode), following the recommendations of the American Society of Echocardiography.[15,16] The left ventricular mass was calculated with the formula of Devereux and Reichek,[17] and the left ventricular mass index was determined by dividing this value by the body surface area.

Ergospirometry

Maximal exercise testing was performed with the use of a treadmill (Jaeger LE 580 C) or cycle ergometer (Jaeger ER 900), applying incremental ramp protocols. The treadmill protocol was as follows: 2-minute warm-up (4 km/h women and 6 km/h men), initial exercise phase to 6 and 8 km/h, respectively, with an increase of 0.25 km/h every

15 s and constant slope of 1% up to minute 13, at which time increases were 0.25% every 15 s. In the cycle ergometry test, warm-up was 1 min at 25 W, with a 5 W load increase every 12 s at a pedal rate of 65 to 90 rpm.[18] In the 12-lead electrocardiographic monitoring (General Electric CASE 8000) and analysis of respiratory gas exchange and pulmonary ventilation (Jaeger Oxycon Pro ergospirometer), the absolute VO_2max and VO_2max relative to body weight (VO_2kg max), pulmonary ventilation, heart rate, oxygen pulse, and blood pressure values were obtained. The criteria used to determine the VO_2max[19] were the presence of a plateau in the VO_2 curve or a respiratory ratio >1.1.

Statistical Study

Statistical analysis were performed with SPSS (version 12.0) for Windows. Descriptive and comparative analyses of the data obtained were
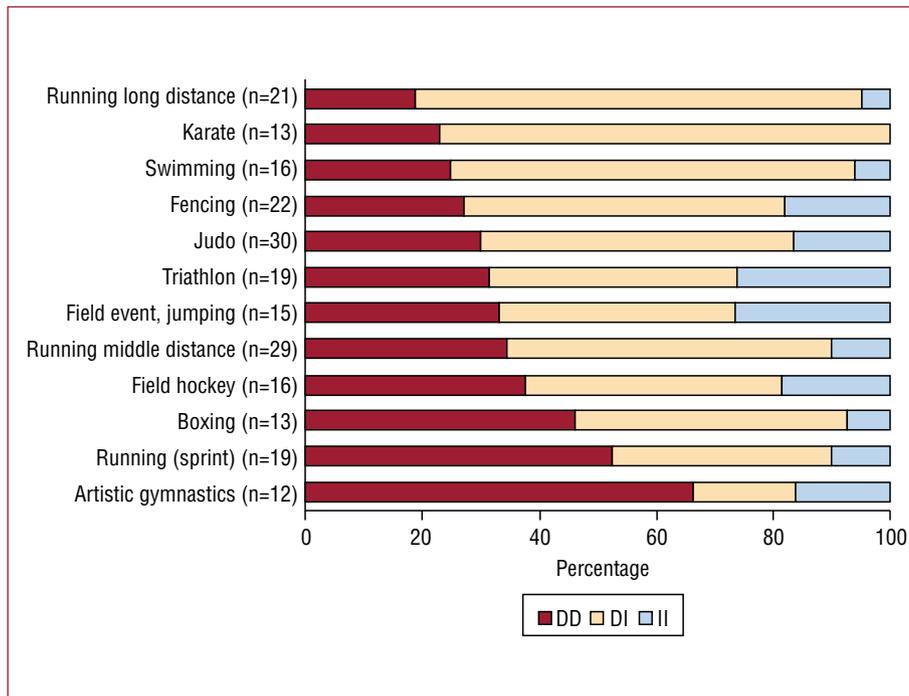
Figure 2. Distribution of angiotensin-converting enzyme I/D polymorphism genotypes in various sports disciplines.

carried out according to sex, sports discipline, and ACE polymorphism, using the Student t test and ANOVA. Data are expressed as the mean (SD). The Levene test was applied to confirm the homogeneity of the variables, and the Bonferroni test or Games-Howell test were used in cases of homogeneity or heterogeneity. The distribution of the various polymorphisms in the sample and their relationship with the sports disciplines were studied with the chi-square test. Differences were considered statistically significant at a P value of ≤.05.

RESULTS

Distribution of Insertion/deletion Polymorphism of Angiotensin-Converting Enzyme

The D allele was found in 60.4% of our sample and the I allele in 39.6%. Genotype distribution of ACE I/D polymorphism by categories according to the Mitchell classification[10] is shown in Figure 1. The most frequent genotype in both men and women was DI (57.55 and 54.7%, respectively) and the least frequent was II (11.9% and 10.4%, respectively). The DD genotype was found in 30.6% of men and 34.9% of women. The genotype frequencies did not conform to Hardy-Weinberg equilibrium because of an excess of DI heterozygotes. There were no differences in genotype distribution between men and women.

There was no association between ACE I/D polymorphism and the sports categories of the Mitchell classification.[10] The genotypes found in the various sports activities having more than 12 participants (running long and middle-distance, field hockey, fencing, field event jumping, running sprint, artistic gymnastics, karate, judo, swimming, triathlon, and boxing) were compared (Figure 2), but there were no significant differences between the groups. Of note, genotype II was not found in any of the athletes practicing karate (DD, 23.1%; DI, 76.9%), and genotype DD was the most prevalent in the group practicing artistic gymnastics (DD, 66.6%; DI and II, 16.6%) and sprinting (DD, 52.6%; DI, 36.8%; II, 10.5%). When power sports (artistic gymnastics, jumping, and sprinting) and aerobic endurance sports (middle/long distance running and triathlon) were analyzed separately, however, there was an association with ACE I/D polymorphism ($\chi^2=6.03$; $P<.049$): genotype DD was more common in power sports (48.8%) and DI in endurance sports (58%), although the D allele predominated in both groups (65.8% in power and 61.2% in endurance).

Adaptation to Training and Insertion/Deletion Polymorphism

Anthropometric Study

The anthropometric characteristics of the sample grouped according to ACE gene polymorphisms

TABLE 2. Anthropometric Characteristics of Athletes According to Angiotensin Converting Enzyme I/D Polymorphism

	Polymorphism							
	DD (n=96)		**DI (n=169)**		**II (n=34)**		**Total (n=299)**	
	Men (n=59)	Women (n=37)	Men (n=111)	Women (n=58)	Men (n=23)	Women (n=11)	Men (n=193)	Women[a] (n=106)
Weight, kg	73.6 (12.3)	59.7 (8.3)	73.8 (13.4)	56.6 (8.2)	71.8 (15.7)	56.8 (3.5)	73.5 (13.3)	57.7 (7.9)
Height, cm	178.9 (8.3)	165.8 (7.9)	178.2 (7.4)	166.3 (7.8)	178.8 (6.4)	164 (6.3)	178.5 (7.6)	165.9 (7.7)
BSA, m^2	1.91 (0.18)	1.66 (0.14)	1.91 (0.19)	1.62 (0.14)	1.89 (0.18)	1.61 (0.07)	1.91 (0.18)	1.64 (0.14)
SUM 8SF, mm	66.7 (32)	96.5 (36.4)	71.8 (34.2)	81.1 (28.2)	60.4 (24.6)	79.7 (22.5)	68.8 (32.6)	86.4 (31.5)
% FATW	10 (4.6)	18 (5.2)	10.8 (5.1)	15.9 (4.5)	9.2 (3.4)	16.1 (3.7)	10.4 (4.8)	16.7 (4.7)
MM, kg	33.3 (4.3)	24.2 (2.7)	33.4 (4.7)	23.2 (2.9)	33 (6.7)	23.6 (1.9)	33.3 (4.8)	23.6 (2.8)
% MM	45.6 (3.1)	40.6 (3.2)	45.8 (3.2)	40.9 (2.8)	46 (2.7)	41.6 (2.6)	45.8 (3.1)	40.9 (2.9)
BMI	22.9 (3)	21.7b (2.3)	23.1 (3.1)	20.4b (2.2)	22.4 (4.1)	21.2 (1.5)	23 (3.2)	20.9 (2.2)
FFMI	20.5 (1.8)	17.7 (1.3)	20.5 (2)	17.2 (1.4)	20.2 (2.8)	17.7 (1.1)	20.5 (2)	17.5 (1.4)

BMI indicates body mass index; BSA, body surface area; FFMI, fat-free mass index according to Withers[12]; MM, muscle mass according to Lee[14]; SUM 8SF, sum of 8 skinfold values; % FATW, percentage of fat according to Withers[13]; % MM, percentage of muscle mass.
[a]Significant differences between men and women for all the variables, $P<.0001$.
[b]Significant differences between DD and DI in the sample of women, $P<.03$.

are shown in Table 2. No statistically significant differences were found between the groups, with the exception of the BMI between genotype DD and genotype DI ($P<.03$) in women. With regard to sex, there were significant differences ($P<.0001$) in all the anthropometric variables, with men showing greater weight, height, muscle mass, BMI, and FFMI than women, whereas women showed a larger fat mass and percentage of body fat.

Cardiologic and Ergospirometric Study

No differences were found between men and women for baseline heart rate (HR) (56.8 [9.7] and 58.1 [10.5] bpm) or maximum HR recorded during the exercise test (189.5 [9.5] and 188.4 [8.9] bpm). There were, however, differences in the baseline systolic pressure (117.5 [10.4] and 108.1 [10.1] mmHg) and diastolic pressure (67.1 [7.6] and 62.3 [7.1] mmHg), which were higher in men. Comparison of these variables between the different ACE I/D polymorphism genotypes in both sexes yielded no significant differences.

TABLE 3. Echocardiographic Parameters in Athletes According to Angiotensin Converting Enzyme I/D Polymorphism

	Polymorphism							
	DD		**DI**		**II**		**Total**	
	Men (n=59)	Women (n=37)	Men (n=111)	Women (n=58)	Men (n=23)	Women (n=11)	Men (n=193)	Women (n=106)[a]
IVS, mm	9.1 (1.3)	8 (1.1)	9.5 (1.2)	7.7 (1)	9.1 (1.1)	7.8 (1)	9.3 (1.2)	7.9 (1)
pW, mm	9 (1.1)	8 (1)	9.4 (1.1)	7.6 (0.9)	9.1 (1)	8.1 (0.9)	9.2 (1.1)	7.8 (1)
EDD, mm	54.3 (3.7)	48.8 (3.6)	53.7 (4.1)	50 (3.2)	53.6 (3.5)	49.4 (2.2)	53.8 (3.9)	49.5 (3.3)
EDD/BSA, mm/m^2	28.5 (2.7)	29.6 (2.8)	28.3 (2.7)	31 (2.9)	28.5 (2)	30.7 (1.9)	28.4 (2.6)	30.4 (2.9)
EDV/BSA, mL/m^2	75.3 (11.3)	68 (11.5)	73.8 (12.1)	73.6 (11.3)	74 (8.8)	71.5 (7.7)	74.3 (11.5)	71.5 (11.3)
LVM/BSA, g/m^2	96.5 (20.7)	79.7 (18)	100.9 (20.3)	80.7 (17.9)	96 (17)	82.4 (14.4)	99 (20.1)	80.5 (17.5)
LA-t, mm	36.2 (4.1)	33.1 (4.8)	37.2 (4.9)	33.6 (4)	35.1 (4.9)	34.6 (4.8)	36.6 (4.7)	33.6 (4.3)
RA-l, mm	53.9 (5.8)	48 (3.7b)	53.5 (5.5)	50.9 (5.2b)	52.2 (5.6)	51 (6.6)	53.5 (5.6)	49.9 (5)
LA-l, mm	52.4 (6.1)	48.1 (4.7)	52.1 (6.2)	49.4 (5.6)	50.7 (5)	50.1 (5)	52 (6.1)	49.0 (5.2)

BSA indicates body surface area; EDD, end-diastolic dimension; EDD/BSA end-diastolic dimension in mm/m^2 of body surface area; EDV/BSA, end-diastolic volume in mL/m^2 of body surface area; IVS, interventricular septum; LA-l, left atrial longitudinal dimension; LA-t, left atrial transverse dimension; LVM/BSA, left ventricular mass in g/m^2 of body surface area; pW: posterior wall; RA-l, right atrial longitudinal dimension
[a]Significant differences between men and women for all variables ($P<.0001$), except in EDV/BSA <0.04.
[b]Significant differences between DD and DI in women, $P<.005$.

TABLE 4. **Maximal Ergospirometric Parameters in Athletes According to Angiotensin Converting Enzyme I/D Polymorphism**

	Polymorphism							
	DD (n=96)		DI (n=169)		II (n=34)		Total (n=299)	
	Men (n=59)	Women (n=37)	Men (n=111)	Women (n=58)	Men (n=23)	Women (n=11)	Men (n=193)	Women (n=106)
VO_{2max}, L/min	4.2 (0.6)	2.9 (0.5)	4.3 (0.5)	2.9 (0.4)	4.3 (0.5)	3 (0.4)	4.2 (0.6)	2.9 (0.4[a])
VO_{2max}, mL/kg/min	57.4 (9.4)	48.3 (6.8)	58.9 (9.1)	51 (7.8)	60.5 (10.6)	51.4 (5)	58.6 (9.4)	50.2 (7.3[a])
HR, bpm	188.1 (10.2)	189.3 (8.2)	190.4 (8.3)	187.2 (9.4)	189.2 (12.6)	191.8 (7.5)	189.5 (9.5)	188.4 (8.9)
O_2 pulse, mL/beat	22.2 (3.2)	15.1 (2.6)	22.5 (3)	15.3 (2.5)	22.7 (3.2)	15.4 (2.1)	22.5 (3.1)	15.3 (2.5[a])
Exp vol, mL	151.1 (21.9)	105.3 (20.5)	156.2 (23.1)	109.7 (16.6)	152.9 (18.9)	108.4 (14.1)	154.2 (22.3)	108.2 (17.6[a])

HR indicates maximal heart rate; O_2 pulse, maximal oxygen uptake/maximal heart rate; $VO_{2kg\ max}$, relative maximal oxygen uptake; VO_{2max}, maximal oxygen uptake, Exp vol, maximal expiratory volume.
[a]Significant differences between men and women ($P<.0001$).

The echocardiographic and ergospirometric values obtained according to ACE I/D polymorphism group are shown in Tables 3 and 4. Significant differences were found for the VO_2max and echocardiographic variables between men and women. There were no differences in any of the echocardiographic or ergospirometric variables in men grouped according to the static component of the Mitchell sports classification.[10] In women, differences were found for interventricular septum (IVS) thickness between sports having a low or high static component (IVS, 7.4 [0.99] and 8.18 [1.08] mm, respectively) and for the BSA adjusted left ventricular mass (LVM/BSA, 74.5 [18.3] and 84.5 [17.8] g/m², respectively); women in group III also presented greater left ventricular hypertrophy.. Considering the dynamic component, athletes belonging to sports group C (both men and women) presented the highest values for wall thickness, end-diastolic volume, and BSA-adjusted left ventricular mass, as well as higher oxygen uptake, as compared to groups A and B.

Separate analysis in men and women of the relationships between the variables studied and ACE polymorphism showed no significant differences except in the longitudinal right atrial dimension between genotypes DD and DI in women ($P=.005$).

DISCUSSION

In this study, there was no association between ACE gene I/D polymorphism and the various sports studied, grouped by their dynamic and static components according to the Mitchell classification.[10] The most frequent genotype found was the DI heterozygote, followed by the DD and II homozygotes. An association was found, however, when power sports and predominantly aerobic sports were separated, with a higher prevalence of the DD genotype in power sports and a higher prevalence of the DI genotype in aerobic sports.

The best cardiovascular adaptation in both sexes was observed in athletes practicing category C sports (oxygen uptake in competition >70% of the VO_2max), with greater wall thickness, diastolic dimension, and oxygen uptake, in agreement with results from previous studies.[20-22] Nonetheless, there were no differences in I/D polymorphism according to the cardiovascular demand (Figure 1): the most common genotype in all the sports categories was DI.

Physical exercise activates the RAAS and stimulates synthesis of various components of this system, such as ACE; hence, increases in angiotensin II concentrations have been related to myocardial growth. Nevertheless, the degree to which left ventricular mass increases in response to exercise is highly variable. It has been shown in a population-based sample that individuals homozygous for the D allele have higher plasma and tissue ACE concentrations and a higher risk of experiencing left ventricular hypertrophy (LVH) than persons with genotypes DI or II.[23] This has led to the idea that athletes homozygous for the D allele with intensive training are more likely to develop LVH. In several studies, the different genotypes of ACE I/D polymorphism have been associated with the sports discipline being practiced. Some authors[24-26] have found an association between genotype DD and the development of LVH in athletes practicing aerobic endurance sports. Other authors[27-28] have reported an association of the I allele with aerobic sports and the D allele with power sports, and a relationship between I allele and good cardiovascular adaptation. However, Karjalainen et al[5] found no association between LVH and I/D polymorphism in

TABLE 5. Distribution of Angiotensin-Converting Enzyme Gene I/D Polymorphism in Various Populations

Country	DD, %	DI, %	II, %	Population
Spain, CSD, Boraita et al	32.1	56.5	11.4	Elite athletes
Spain, Hernández et al (2002)[30]	43.5	41.9	14.6	Canary Is. population
The Netherlands, Danser et al[31]	47	32	21	Dutch population
France, Marre et al[32]	30.6	44	25.4	French population
Germany, Schmidt et al[33]	33	50	17	German population
Lebanon, Sabbagh et al[34]	39.1	45.1	15.8	Lebanese population
United States, Lindpaintner et al[35]	30.9	49.2	19.9	US population
Japan, Mizuiri et al[36]	18.3	48.9	32.8	NID Diabetic individuals
Spain, Álvarez et al[9]	41	44	15	Aerobic sports
Spain, Hernández et al (2003)[24]	44.2	50.8	4.9	Aerobic sports
Israel, Amir et al[25]	52	36	12	Elite athletes
Australia, Gayagay et al[28]	16	55	30	Rowers
	32	51	18	Control group
Italy, Scanavini et al[27]	39.4	39.4	21.1	Aerobic sports
	38.2	56.4	5.5	Anaerobic sports
	44.1	43.4	12.5	General population

athletes practicing aerobic endurance sports. These disparate results may be due to ethic differences and the fact that some of these studies were performed in a small sample or only included sports having a similar cardiovascular demand. The present study included a broad sample of 32 sports disciplines with differing cardiovascular demands, and the participants were all high-level athletes. Our results are consistent with the findings of Karjalainen et al[5] and those of other authors who, like us, studied a variety of sports.[29] The D allele was the most common in our study (60.4%), as in the majority of non-athlete populations in Europe, Lebanon, and the United States,[30-35] in individuals practicing aerobic endurance sports in Spain,[9,24] and in elite athletes in Israel[25] and Italy.[27] This finding differs from the data recorded in an Asian population[36] and in rowers in Australia,[28] a fact possibly related to the different ethnic origins of these groups. The polymorphism distribution in different populations is shown in Table 5.[9,24,25,27,28,30-36]

With regard to the anthropometric profile, no differences were found between athletes grouped according to ACE gene I/D polymorphism, and the results obtained were similar to those reported in other studies involving elite athletes, who show a lower percentage of fat mass and higher percentage of muscle mass than sedentary population.[13,14] Previous studies have associated the I allele with an increase in the BMI and obesity and the D allele with a lower BMI[37] and greater skeletal muscle development.[38,39] In the present study, only 8 male athletes had a BMI within the obese range, with no predominance of any genotype: 3 in DD (5.1%), 4 in DI (3.6%), and 1 in II (4.3%). In addition, the indicators of muscle development (muscle mass, percentage of muscle mass, and FFMI) were similar in the I/D polymorphism groups. This may be because all the individuals studied were elite athletes and therefore, their body composition was already optimal, while being determined by both genetic and environmental factors.

Because multiple factors have an impact on success in sports, it is difficult to evaluate the importance of ACE I/D polymorphism alone in this regard. Although we did not establish a control sedentary population to determine differences, comparison of the results in our series with those of sedentary Spanish controls from previous studies[9,30] seems to indicate a greater prevalence of genotype DI in elite athletes. This may reflect higher aerobic capacity, but we do not have a physiologic explanation for the association between ACE I/D polymorphism and adaptation to training.

Limitations of the Study

The study sample contained almost 300 athletes, but when they were grouped according to the Mitchell classification, the number of individuals in categories IA, IIA, and IIIB was small. This is because these categories contain sports with a scant following in Spain (eg, cricket, curling) and non-olympic sports (eg, motorcycling, auto racing, diving); athletes who consult at our center are mainly those practicing olympic sports. In addition, the overall sample was not in Hardy-Weinberg equilibrium for I/D polymorphism, with an excess of DI heterozygotes (χ^2=9.88; degree of

freedom, 1; P=.0017). It is unlikely that this was due to genotyping errors because 20% of the tests were randomly repeated and the same genotype as in the previous test was identified in all cases. Genotype DI was found in the highest percentage (56.5%) and this differentiates our series from the majority of those shown in Table 5. The percentage of this genotype is, however, similar to that found in samples of athletes practicing endurance sports in the Canary Islands[24] and anaerobic sports in Italy,[27] which leads us to believe that the differences may be due to sample bias: in all cases the populations were individuals practicing competition sports.

CONCLUSIONS

Athletes who practice sports having a high dynamic component show the greatest cardiovascular adaptation. I/D polymorphism of intron 16 of the ACE gene does not seem to have an influence on cardiovascular adaptation to training. Although the DI genotype was the most common in our population, with no differences between sexes, this fact is likely due to bias of the sample, which was entirely comprised of elite athletes. More studies in this line, with a larger number of athletes and different levels of sports (competitive and non-competitive) are needed. Based on our findings, LVH and skeletal muscle development seem to be independent of ACE I/D genotype in elite athletes.

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