

Research article

Angiotensin I converting enzyme gene polymorphism and exercise trainability in elderly women: An electrocardiological approach

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Abstract

Angiotensin I converting enzyme (ACE) gene Insertion / Deletion (I/D) polymorphism is associated with exercise trainability and exercise induced left ventricular hypertrophy. However, it is unclear whether this polymorphism influences exercise trainability in the elderly, and the electrocardiological alterations by exercise training is unknown among the genotypes. We herein investigated the association between ACE gene insertion/deletion (I/D) polymorphism, exercise trainability and the electrocardiological alterations by exercise in elderly women. Eighty four elderly women participated in this study. In all subjects the leg extension power (LEP) and lactate threshold (LT) were determined in order to evaluate the muscle strength, aerobic capacity and to also select the appropriate training intensity for each individual. They performed bench step exercise training for 12 weeks. A resting electrocardiogram was recorded for the obtained QTc interval in before and after the program. The baseline of aerobic capacity was higher in I/I than that in I/D, and the QTc interval was shorter in I/I than that in I/D. All other characteristics were similar among the genotypes. The QTc interval tended to be shorten only in the D/D. Furthermore, the value of the QTc interval change showed a significant difference between the I/I and D/D genotype after the program. The LT and LEP demonstrated a similar response among the genotypes. The D allele of ACE gene I/D polymorphism may therefore play a role in the electrocardiological aspect during exercise training, however, it was not found to influence the aerobic capacity.

Key words: Electrophysiology, exercise, genes.

Introduction

It is well known that the effect of exercise training gives inter individual differences, and specific genetic factors are not fully understood to be responsible for this phenomenon. One thoroughly studied genetic factor which influences human physical performance and trainability is angiotensin I converting enzyme (ACE) gene polymorphism (Montgomery et al., 1998; Wolfarth et al., 2005).

ACE is a key enzyme in the renin-angiotensin system (RAS) and the gene polymorphism, based on the presence [insertion (I)] or absence [deletion (D)] within the intron 16 of 287 base pair Alu-repeat segments, accounts for a half of the variation of the enzyme activity. Individuals with the D allele have been shown to have a higher ACE activity in the serum and tissue than in those with the I allele (Rigat et al., 1990).

Pharmacological studies have indicated that the chronically suppressed ACE activity by ACE inhibitor

improves the endurance performance via to increase type I myosin heavy chain gene expression, (Vescovo et al., 1998) and ACE inhibitor treatment showed a slow decline in muscle strength with aging (Onder et al., 2002). On the other hand, a study indicated that D/D individuals with an active life style has fewer limitations in their functional performance than I/I individuals, but no significant difference was observed in their leg strength (Kritchevsky et al., 2005). These results implied us that the interaction between the D allele and the physical activity thus had a favorable influence on the physical function, independent of the muscle strength in active elderly people.

ACE affects not only the skeletal muscle function but also exercise induced left ventricular hypertrophy (LVH) (Hernandez et al., 2003; Montgomery et al., 1997). The LVH due to exercise training (i.e. chronic exercise load on the cardiovascular function), the tissue and cellular electrical features of exercise induced hypertrophy appear to be parallel with those of hypertrophy (Hart et al., 2003). Although, morphological studies have reported an association between ACE gene I/D polymorphism and LVH in relation to exercise training, an electrocardiological analysis of this phenomenon has not yet been performed.

The QT interval corrected by the heart rate (QTc) is a show the electrical cardiac systolic and diastolic duration, and in which the prolongation of QTc interval is associated with arrhythmia and sudden cardiac death (de Bruyne et al., 1999). QTc interval is correlated with the left ventricular wall motion score (Stajer et al., 1993) and inverse correlation was found between the QTc interval and the peak VO₂ in heart failure patients (Boccalandro et al., 2003). Albertine et al reported that QTc as well as aerobic capacity were improved by the results of exercise training in elderly (Schuit et al., 1998). QTc is thus considered to be an important electrocardiological index for assessing the heart function and it may also affect the aerobic capacity.

In the present study, we investigated the association between ACE gene I/D polymorphism and exercise trainability including electrocardiological alterations in the elderly.

Methods

Subjects

In the beginning of the study 767 Japanese people who lived in Ishikawa and Fukuoka prefecture were recruited.

The subjects who fulfilled the criteria were accepted. The criteria were as follows: (1) were considered healthy enough to participate in the program based on a medical check-up (all subjects), (2) took part in the exercise training program for 12 weeks (177 from 767 people were excluded), (3) An age above 65 (77 from 590 persons were excluded), (4) performed exercise test and leg extension power test in 0 week and 12 week completely, (251 from 513 persons were excluded), (5) were recorded electrocardiogram (ECG) by same ECG monitor and automatic analyzer (122 from 262 persons were excluded), (6) recorded the training time at home (2 from 140 persons were excluded), (7) accepted ACE gene polymorphism exclude 2 from 138 persons were excluded). As a result, 136 persons (51 men and 84 women) remained. Since inter sexual differences were observed in QTc, the analysis should be separately conducted for men and women. The male subjects comprised a very small sample, especially in D/D genotype ($n = 7$) and thus was too small to undergo analysis by themselves. Therefore, finally, 84 elderly women participated in this study.

Twenty-two subjects took cardiological medication (13 calcium blocker, 3 beta blocker, 3 ACE inhibitor, 2 alpha blocker, 1 Angiotensin II receptor antagonist, 6 other medications including cardiotonic and vasodilative agent). The frequencies of subjects in medication were 6 (27%), 13 (59%) and 3 (14%) in I/I, I/D and D/D genotype respectively. The ACE gene I/D polymorphism distributions in 84 subjects and in medicated subjects were similar (Chi square test. $P = 0.71$).

Informed consent was obtained from all subjects. This study was approved by the ethics committee of the Hokkaido University School of Medicine.

ACE genotyping

Genomic DNA was obtained from EDTA anticoagulated white blood cells using a blood DNA purification kit (Amersham Biosciences, New Jersey, USA). The insertion and deletion allele fragments of ACE intron 16 Alu were amplified by the method of Lindpaintner et al. (1995). The PCR products were run on 1.5% agarose gel contained ethidium bromide and visualized under ultra violet. The genotypes were confirmed using deletion specific primers as described by Lindpaintner et al. (1995).

Assessment of lactate threshold and leg extension power

All subjects performed a graded bench step exercise test to assess their lactate threshold (LT) intensity, previously described (Ayabe et al., 2003). The evaluation of VO_{2max} or 6 minutes walking tends to be difficult in elderly people. These tests induce a high degree of physical stresses and it is difficult to fulfill the criteria of exhaustion in elderly people. On the other hand, we can measure the LT intensity below the level of maximal exercise test. This is a safe measuring technique and the LT is useful index of aerobic capacity. For these reasons, we use LT intensity for aerobic capacity index.

Initially, they went up and down the 20 cm platform for 4 minutes at 40 steps / min. The cadence is then increased every 4 minutes by 20 steps / min with a 2-

minute rest interval until the LA exceeded 2mmol/l. The LT was calculated by a simple assessment method which has been previously described. The LT is used for the evaluation of aerobic capacity and exercise intensity of the program.

The leg extension power (LEP) was evaluated by an isodynamometer (Anaero press 3000: Combi Co. Ltd. Tokyo, Japan). They sat on the seat and put their legs on the kicking platform. They practiced kicking twice slowly, and the length of their legs was measured. Finally, the subjects push out the plate as fast as possible for 5 times. The average of the maximal and second values was normalized by body weight to determine the LEP. All investigators performed there testing regimen while being blinded to the ACE genotypes.

Electrocardiogram and blood pressure measurement

The standard resting 12 lead ECG was recorded for 5 seconds digitally (CardioStar FCP-7401, Fukuda Denshi, Tokyo, Japan). Thereafter, the QRS, QT interval and $RV5 + SV1$ ($R + S$) were measured automatically (Willems et al., 1985). Briefly, first of all, QRS and QT intervals were measured from all figures of 12 leads ECG. Secondly, the means and mean ± 25 % range of the QRS, QT interval were calculated. Thirdly, values outside of the 25 % range were cut off. Finally, the means of the QRS and QT interval were recalculated and found to be acceptable. The QT interval was corrected by the Bazett formula ($QTc = QT$ interval / \sqrt{RR}). The $R + S$ was sum of the maximum values of R wave of V5 or V6 lead and Q wave or S wave of V1 lead.

The blood pressure was measured 2 times after resting by a digital automatic blood pressure meter (HEM-705IT Fuzzy, OMURON, Tokyo, JAPAN). If the systolic blood pressure (SBP) or diastolic blood pressure (DBP) showed a difference greater than 10 mmHg between the 1st and 2nd test, then a third test was carried out. The mean blood pressure (MBP) was calculated from the SBP and DBP. The mean of 2 of 3 values were used for the blood pressure. These measurements were all carried out between 8:30 and 12:00 am. All investigators performed these tests while being blinded to the ACE genotypes.

Exercise training protocol

The bench step exercise training at LT intensity was carried out for 12 weeks using a 20 cm platform, as previously described (Mori et al., 2006). We instructed the subjects to exercise for 140 min/week or more every week. They performed the exercise at their home and the training time was recorded in a diary. Furthermore, they exercised for 20 minutes under observation once every week. After the group exercise, the exercise leader gave advice and talked with the participants in order to keep the subjects highly motivated. After the 6 weeks, the subjects performed a graded bench step exercise test and their LT was evaluated in order to re-adjust the training intensity. The revised intensity was then applied to their training program for the next 6 weeks.

Statistical analysis

We used a statistical software program (SAS version 9.1, SAS Institute, Cary, NC) for all statistical analyses. To

Table 1. Characteristics of the subjects and phenotypes before and 12 week exercise training among those with angiotensin I converting enzyme gene Insertion / Deletion polymorphism. Values are means (\pm SD).

	0 week			12 week			0 week		12 week	
	I/I (n = 26)	I/D (n = 47)	D/D (n = 11)	I/I (n = 26)	I/D (n = 47)	D/D (n = 11)	I allele (n = 73)	D allele (n = 58)	I allele (n = 73)	D allele (n = 58)
Age (yr)	71.8 (4.7)	71.9 (4.3)	72.3 (5.3)	-	-	-	71.9 (4.4)	72.0 (4.5)	-	-
Tra time (min·w ⁻¹)	134.7 (65.9)	149.8 (55.3)	137.1 (60.5)	-	-	-	144.4 (59.3)	147.4 (56.0)	-	-
Height (M)	1.50 (.06)	1.50 (.05)	1.50 (.04)	-	-	-	1.49 (.06)	1.49 (.05)	-	-
Weight (kg)	53.5 (10.4)	53.1 (8.2)	52.4 (9.1)	53.5 (10.5)	52.6 (8.4)	51.9 (9.5)	53.3 (9.0)	53.0 (8.3)	52.9 (9.1)	52.5 (8.5)
BMI	23.8 (4.2)	24.0 (3.4)	23.3 (3.6)	23.8 (4.1)	23.8 (3.5)	23.2 (3.9)	24.0 (3.7)	23.9 (3.5)	23.8 (3.7)	23.7 (3.6)
SBP (mmHg)	138.6 (27.0)	139.0 (20.6)	135.8 (27.8)	137.7 (28.5)	136.2 (20.2)	134.1 (25.7)	138.8 (22.9)	138.4 (21.9)	136.7 (23.3)	135.8 (21.1)
DBP (mmHg)	77.3 (10.5)	75.9 (9.6)	78.4 (12.0)	77.7 (11.0)	74.7 (11.6)	77.2 (11.9)	76.4 (9.9)	76.4 (10.1)	75.7 (11.4)	75.1 (11.6)
MBP (mmHg)	97.7 (14.2)	96.9 (11.7)	97.5 (16.6)	97.7 (15.5)	95.2 (12.9)	96.1 (15.4)	97.2 (12.6)	97.0 (12.6)	96.1 (13.8)	95.4 (13.2)
LEP (Watt·kg ⁻¹)	8.2 (2.9)	6.6 (3.2)	6.5 (3.6)	8.9 * (2.9)	8.1 * (3.4)	8.0 (3.8)	7.2 (3.2)	6.6 # (3.3)	8.4 * (3.3)	8.1 * (3.5)
LT (METs)	4.6 (.6)	4.0 (.9)	4.2 (.8)	5.0 * (.9)	5.0 * (.8)	5.0 * (1.2)	4.2 (.9)	4.1 # (.9)	5.0 * (.9)	5.0 * (.9)
HR (beat·min ⁻¹)	63 (8)	67 (9)	65 (6)	65 (9)	66 (9)	65 (7)	66 (9)	67 (9)	66 * (9)	66 (9)
QTc (msec)	421.4 (15.6)	433.6 # (22.2)	426.0 (16.0)	431.2 * (16.7)	430.9 (20.8)	418.2 (14.5)	429.3 (20.8)	432.2 # (21.2)	431.0 (19.3)	428.5 (20.3)
R+S (mV)	2.4 (.6)	2.6 (.8)	2.5 (.8)	2.6 (.8)	2.9 * (1.0)	2.5 (.9)	2.5 (.7)	2.6 (.8)	2.8 * (.9)	2.8 * (.9)
QRS (msec)	99.5 (14.4)	99.0 (12.9)	98.5 (7.5)	99.4 (16.3)	94.4 * (8.2)	95.3 (10.0)	99.2 (13.4)	98.9 (12.0)	96.2 * (11.9)	94.6 * (8.5)

Abbreviations: LEP, Leg extension power; LT Lactate threshold.

* p < 0.05 (vs 0 w), # p < 0.05 (vs I/I).

compare the age, training time, height, weight and BMI among genotype, one-way ANOVA was used. The SBP, DBP, MBP, LEP, anaerobic capacity, HR, QRS, QTc and R + S was adjusted by age and then was compared by ANCOVA. The Tukey-Kramer test was used for post hoc test.

The training responses of intra genotype were compared by Student's paired t-test. The training responses for the inter genotype were compared by ANCOVA, after adjusting for age, the mean training time and the baseline values.

Results

Characteristics and baseline phenotypes

The distribution of the ACE genotype in I/I, I/D and DD was 26 (31%), 47 (56%), 11 (13%). The genotype distribution was consistent with the Hardy-Weinberg equilibrium.

Table 1 shows the characteristics and phenotypes before and after 12 weeks of the training. The I/I geno-

type had a higher LEP, LT intensity and shorter QTc than that of the D allele. The I/D genotype have longer QTc than that of I/I. There were no differences in age, height, weight, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), or LEP among the genotypes.

Training response intra and inter genotype

Tables 2 shows amount of changes in the phenotypes. The aerobic capacity improved in all genotypes. The LEP increased in I/I and I/D, but not in D/D. The QRS decreased only I/D genotype. No significantly shortened QTc was observed, and only D/D tended to have a shortened QTc (p = 0.06). Conversely, the QTc in I/I were prolonged. The R + S increased in I/D, but not in D/D. The weight, BMI, SBP, DBP, MBP and HR all remained unchanged by the training program.

The QTc in D/D was greater reduction than in those with I/I, and I/D tended to be shorter than that of I/I (p = 0.06). Furthermore, the QTc in D/D was significantly shorter than that of those with the I allele. As a

Table 2. The exercise training response of the phenotypes among the subjects with angiotensin I converting enzyme gene Insertion / Deletion polymorphism. Values are means (\pm SD).

	I/I (n = 26)	I/D (n = 47)	D/D (n = 11)	I allele (n = 73)	D allele (n = 58)
Weight (kg)	-.78 (1.56)	-.45 (2.56)	-.50 (1.15)	-.32 (2.25)	-.46 (2.35)
BMI	.84 (.07)	.20 (1.20)	.14 (.50)	.16 (1.06)	.19 (1.10)
SBP (mmHg)	-.89 (28.24)	-2.79 (20.17)	-1.67 (19.78)	-2.12 (23.19)	-2.58 (19.93)
DBP (mmHg)	.40 (10.92)	-1.23 (10.70)	-1.21 (11.96)	-.65 (10.73)	-1.22 (10.84)
MBP (mmHg)	-.03 (14.63)	-1.75 (12.26)	-1.36 (13.87)	-1.14 (13.08)	-1.68 (12.45)
LEP (Watt·kg ⁻¹)	.76 (1.42)	1.50 (2.43)	1.52 (4.06)	1.24 (2.14)	1.51 (2.76)
LT (METs)	.43 (.81)	.95 (.79)	.74 (.93)	.76 (0.83)	.91 (.82)
HR (beat·min ⁻¹)	2.14 (8.84)	-.96 (8.17)	-.44 (4.84)	.15 (8.48)	-.86 (7.61)
QTc (msec)	9.81 (17.73)	-2.70 (17.28)	-7.77 (12.28) # *	1.76 (18.34)	-3.66 (16.47) #
R+S (mV)	.18 (.67)	.27 (.71)	.04 (.31)	.24 (.69)	.22 (.66)
QRS (msec)	-.03 (11.20)	-4.54 (11.94)	-3.18 (8.89)	-2.93 (11.81)	-4.28 (11.37)

Abbreviations: LEP, Leg extension power; LT Lactate threshold.

* $p < 0.05$ (vs I/I), # $p < 0.05$ (vs I allele)

result, QTc in D allele showed a greater reduction than that of I/I (Figure 1).

Discussion

This study demonstrates, for the first time, the association between ACE gene I/D polymorphism and QTc alteration during exercise training in elderly women. The D/D tended to shorten the QTc interval by the program. Conversely, the I/I prolonged the QTc interval. Moreover, the magnitude of the response demonstrated significant differences between the genotypes.

Interestingly, when the RAS was blocked, the serum free testosterone concentration, which shortens the QTc interval (Bidoggia et al., 2000), was decreased (Hacihanefioglu., 2002; DeLong et al., 2005) and sex hormone binding globulin (SHBG) which inactivates free testosterone, increased (Koshida et al., 1998). The D/D genotype seems to chronically activate RAS more than I/I, and this phenomenon may contribute higher serum free testosterone concentrations while also shortening the

QTc interval. It remains unclear, whether the D/D genotype has a higher serum free testosterone concentration (i.e. It plays anabolic hormone). According to previous reports, there are greater frequencies of the D/D genotype in elite athletes such as sprinter and short distance swimmer (Myerson et al., 1999; Nazarov et al. 2001), which support our observation.

The QTc in I/I become prolonged after exercise training. Hakkinen et al reported (1994) that strength training reduced the serum free testosterone concentration in elderly women, which may account for the QTc prolongation in I/I by this exercise training. It is known that the serum free testosterone concentration shows great differences between individuals, and perhaps the D/D, which is associated with a higher activity of RAS, may remain unchanged or may increase the serum free testosterone by this exercise training.

Exercise training changes the electrolyte concentration of sodium and the excretion of potassium. Increasing the plasma potassium with amiloride (Farquharson et al., 2002) and a sodium channel blocker,

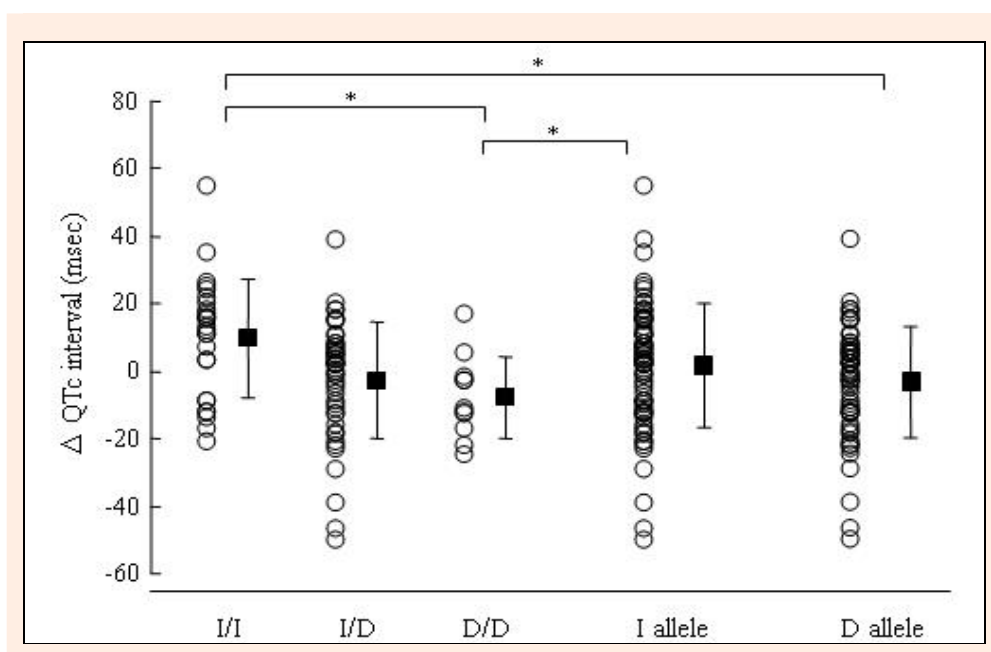


Figure 1. Changes in the QTc interval to exercise training among those with angiotensin I converting enzyme gene Insertion / Deletion polymorphism. Values are shown as the mean (\pm SD). * $p < 0.05$.

lidocaine (Echt et al., 1989) treatments shorten QT interval. Seemingly, the D/D genotype shows a higher aldosterone concentration due to a higher Ang II, and it activates sodium retention and potassium excretion. In fact, previous study reported the ACE gene I/D polymorphism does not influence the plasma aldosterone concentration either at rest, during exercise or after exercise (Tobina et al., 2006). Furthermore, the level of ACE inhibition is not related to the plasma aldosterone concentration (Sato et al., 2000). These results suggest that aldosterone does not account for the difference of QTc alteration among ACE gene I/D polymorphisms by this exercise training.

Previous reports have investigated the association between ACE and human health, but discrepancies in the findings have been observed in several aspects. Although, the D/D of ACE gene I/D polymorphism seems to be a risk factor for myocardial infarction (Cambien et al., 1992), it shows a higher frequency in centenarians (Schachter, et al 1994). Chronic ACE inhibitor treatments (i.e. lower ACE activity as I/I genotype) improved the endurance performance (Vescovo et al., 1998), whereas the D/D is favorable for physical function in active people (Kritchevskiy et al., 2005). In this study, the interaction between D/D and physical activity was suggested to have a favorable effect on the cardiac function. Such an effect is considered to positively contribute to human longevity while also helping elderly individuals maintain their physical function. Future studies could help to clarify some of the paradoxes observed in this study.

The present study has some limitations. Firstly, we did not exclude any subjects who were on medication, but the medication could not be changed during the exercise program. Second, the sample size was small which thus resulted in a low statistical power.

Conclusion

In conclusion, the interaction between D/D of ACE gene I/D polymorphism and the physical activity course was found to have a favorable effect on the electrocardiological aspect in elderly women.

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Key points

- The D allele of ACE gene I/D polymorphism may play a role in the electrocardiological aspects during exercise training
- ACE gene I/D polymorphism was not determined the aerobic capacity and leg strength in elderly people.
- The ACE gene I/D polymorphism did not influence aerobic and strength trainability in elderly people.

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