Int J Biometeorol (2003) 48:10–14
DOI 10.1007/s00484-003-0172-4

ORIGINAL ARTICLE

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Association of high-altitude systemic hypertension with the deletion allele-of the angiotensin-converting enzyme (ACE) gene

Received: 27 January 2003 / Revised: 3 March 2003 / Accepted: 5 March 2003 / Published online: 13 May 2003

Abstract People who visit high-altitude areas are exposed to a stressful environment and a good percentage of them suffer from high-altitude-induced diseases, including systemic hypertension. Identification of genetic markers for high-altitude-induced diseases would help to reduce the rate of morbidity/mortality from such diseases. The development of systemic hypertension on exposure to high altitude (3,500 m) for 30 days in otherwise normotensive natives of low-altitudes was investigated. The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotypes and renin-angiotensin-aldosterone system were simultaneously studied. In the hypertensives during their stay at high altitude, the ACE D allele frequency was significantly higher than in the normotensives (0.67 versus 0.32 $\chi^2_1 = 10.6$, $P < 0.05$). In the normotensives during their stay at high altitude, there was no significant increase in plasma aldosterone levels despite increased plasma renin activity. Results of the present study suggest that environmental changes and pre-existing genetic factors, namely the ACE D allele, might be two of the factors predisposing natives of low altitudes to systemic hypertension, a polygenic disease, at high altitude.

Keywords High altitude · Hypertension · ACE · I/D genotypes

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Introduction

High-altitude environments, those at a height of more than 3,000 m, imply stress factors such as hypoxia, cold, humidity, solar radiation, cosmic radiation and isolation. High-altitude exposure causes many physiological and biochemical changes in man. It has been reported that increased sympathetic stimulation and autonomic activity contribute to a rise in systemic blood pressure at high altitude (Malhotra et al. 1976; Wolfel et al. 1994).

Ongoing research on hypertension has established that the renin-angiotensin-aldosterone system, the primary regulator of plasma Na^+ and re-absorption by the kidney, plays an important role in the pathogenesis of hypertension. Molecular studies of hypertension concentrating on the renin-angiotensin-aldosterone system have identified a number of polymorphic proteins in this system with their corresponding genetic loci. Angiotensin I is converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor, regulating blood pressure and, hence, a causative factor for systemic hypertension. There are two alleles in the ACE gene locus, one with a deletion (D) and other with an insertion (I) of 287 base pairs within intron 16. The association of the ACE D allele with systemic hypertension has been shown (Mastana and Nunn 1997; Shen et al. 1998; Nakano et al. 1998).

A large number of people are exposed to the stressful environment of high altitude during visits for a variety of reasons: tourism, mountaineering and in the course of their occupation; the last category includes troops guarding the borders. The aim of the present study was to test whether ACE gene I/D polymorphism can be used as a genetic marker to identify soldiers who are potentially at risk of developing high-altitude-induced systemic hypertension.

Materials and methods

The study population consisted of 46 age-matched healthy normal male volunteers who had never been to high altitude. Informed written consent was obtained from all the volunteers participating in the study. None was taking any medication for blood pressure.

All the volunteers were examined initially at plains. Their age, height and weight were 23.8 ± 0.6 years, 169.6 ± 0.8 cm and 59.3 ± 0.9 kg respectively. The body mass index (BMI) of the volunteers was calculated [body weight/height^2 (kg/m^2)]. Oxygen saturation of the blood (SaO_2) was measured using a Pulse 503 Oximeter, Criticare Systems Inc. USA. Blood pressure and pulse rate of all the subjects were measured in the morning between 0800 and 0900 hours by an automatic blood pressure monitor (model OSIM 0505 from OSIM International, Singapore). SaO_2, pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) values recorded were the means of three readings taken at least 2 min apart. On the basis of blood pressures recorded, potential subjects were classified as normotensive (blood pressure $\leq$ 140/90 mm Hg, 18.6/12 kPa) or hypertensives (blood pressure $\geq$ 140/90 mm Hg, 18.6/12 kPa) according to the International Society of Hypertension Guidelines Subcommittee (1999). All the 46 volunteers were normotensives at plains. Blood samples of the volunteers were collected and heparinised blood was used to analyze the plasma levels of ACE, renin activity and aldosterone. For ACE genotype investigation blood samples with ACD anticoagulant (trisodium citrate 22.0 g/l, citric acid 8.0 g/l, and dextrose 24.5 g/l) were used. Serum was used for electrolyte (Na^+, K^+) analysis; 24 h urine samples were collected for volume measurement and electrolyte (Na^+, K^+) analysis.

After the initial examination at plains, all the volunteers were transported to high altitude (3,500 m) by air. On arrival at high altitude the volunteers were examined on days 1 (HA D01), 10 (HA D10) and 30 (HA D30) of their stay. After 30 days stay at high altitude all the volunteers were returned to the plains by air. On the 7th (DI 07) and 14th (DI 14) days after their return to the plains, the volunteers were re-examined. The parameters studied at high altitude on days 1, 10 and 30 as well as on days 7th and 14th day after their return were similar to those used in the initial examination of the subjects, namely BMI, pulse rate, SaO_2, SBP, DBP, plasma ACE, plasma renin activity (PRA), aldosterone, serum electrolytes, 24-h urine volume, urine electrolyte (Na^+, K^+) levels, and ACE I/D genotypes. On the basis of blood pressures recorded during their high-altitude stay the volunteers were classified as normotensive or hypertensive (International Society of Hypertension Guidelines Subcommittee 1999).

Determination of biochemical parameters

Plasma angiotensin-converting enzyme (ACE) activity was measured by using diagnostic kits obtained from Sigma Diagnostics (P. O. box 14508 St. Louis, USA). Plasma renin activity and aldosterone levels were measured by radio-immunoassay kits obtained from Immunotech (A. Coulter Company, Marseille Cedex, France). Plasma and urinary electrolyte (Na^+, K^+) levels were measured by an AVL 988-3 electrolyte analyzer.

Genotype investigation

Genomic DNA was isolated from the peripheral blood leukocytes by a salting-out procedure (Miller et al. 1988). The polymerase chain reaction (PCR) was used for amplification of the ACE gene. The primer sequence used for the sense strand oligonucleotide was 5′-CTG GAG ACC ACT CCC ATCCTT TCT-3′ and for the antisense oligo nucleotide 5′-GAT GTG GCC ATC ACA TTC GTC AGAT-3′ (Rigat et al. 1992). The PCR conditions and thermocycling procedure, performed with a Gene Amp PCR system, consisted of initial denaturation at 94 °C for 4 min followed by 30 cycles of denaturation at 94 °C for 1 min, annealing at 58 °C for 1 min and extension at 72 °C for 2 min, and a final extension at 74 °C for 7 min (Rigat et al. 1992). The PCR-amplified products were resolved on 2.0% agarose gel and detected by ethidium bromide for identification of ACE I/D polymorphism (a 190-bp fragment in the case of deletion and a 490-bp fragment in the presence of an insertion of the 287-bp *alu* sequence) as suggested by Rigat et al. (1992).

Statistical analysis

Results of BMI, blood pressure, SaO_2, plasma ACE, PRA, aldosterone, serum electrolytes, urine volume and urine electrolytes were expressed as means ± SE. The statistical significance of these parameters between two groups was assessed by one-way analysis of variance. Frequencies of the ACE gene allele were deduced from genotype frequencies and the differences between groups were tested by χ^2-test. A value of P less than 0.05 was considered to be statistically significant.

Results

The results for BMI, blood pressures, pulse rate and SaO_2 changes of all the subjects have been given in Table 1. Out of 46 volunteers 28 were normotensive and 18 hypertensive at high altitude. At high altitude no significant change in BMI of the normotensive volunteers was observed but the BMI of hypertensive volunteers at high altitude showed significant increases in comparison to the responses of normotensives of the respective groups. In volunteers suffering from systemic hypertension there was a significant increase in both SBP and DBP ($\leq$140/90 mm Hg) during their stay at high altitude in comparison to baseline values. In normotensive volunteers a significant increase in pulse rate was observed on the 30th day at high altitude but the pulse rate of hypertensives was significantly high during their whole 30 days at high altitude and on the 7th day after their return to plains. In normotensive and hypertensive subjects, the decrease in SaO_2 during the stay at high altitude was similar but significant in comparison to baseline values (Table 1).

Changes observed in plasma ACE, PRA, aldosterone, sodium and potassium values of volunteers during their stay at high altitude and on return to the plains, in comparison to baseline values, are given in Table 2. On the 1st day the volunteers arrived at high altitude, the plasma ACE values increased significantly in both normotensives and hypertensives. After the peak rise on the 1st day at high altitude, the plasma ACE values gradually declined. On return to the plains, ACE values of all the volunteers returned to baseline values.

The PRA levels showed a continuous rise during the stay at high altitude in both normotensive and hypertensive volunteers in comparison to their respective baseline values. The increase was significant on days 10 and 30 at high altitude and on day 7 after the return in both the groups, but in hypertensive volunteers there was also a significant increase in PRA on the 14th day after returning to the plains (Table 2). There was no increase in plasma aldosterone levels during the high-altitude stay in normotensives volunteers, but in the hypertensive

Table 1 Effect of high altitude on body/mass index (*BMI*), systolic and diastolic blood pressure (SBP, DBP), pulse rate and Oxygen staturation of the blood (SaO_2) Values are means ± SEM; Numbers of subjects are shown in parentheses

Days	Normotensive (28)					Hypertensive (18)				
	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	Pulse rate (min^{-1})	SaO_2 (%)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	Pulse rate (min^{-1})	SaO_2 (%)
Baseline	20.6 ± 0.2	121.4 ± 1.2	74.0 ± 1.3	68.7 ± 1.4	97.8 ± 0.2	20.0 ± 0.5	121.8 ± 1.9	74.6 ± 2.0	71.6 ± 2.3	97.4 ± 0.2
HA D01	20.1 ± 0.2	121.4 ± 1.2	82.8 ± 1.1*	66.2 ± 1.5	90.7 ± 0.4*	21.6 ± 0.6**	141.6 ± 2.6*	92.8 ± 2.0*	74.0 ± 2.6**	90.8 ± 1.0*
HA D10	19.9 ± 0.3	121.1 ± 1.4	80.6 ± 0.9*	68.9 ± 1.8	91.7 ± 0.4*	21.4 ± 0.5**	139.7 ± 2.3	91.0 ± 1.3	79.9 ± 4.8	91.8 ± 0.9
HA D30	20.0 ± 0.2	117.2 ± 1.2	78.2 ± 0.9*	75.0 ± 1.9*	92.1 ± 0.4*	21.5 ± 0.4**	140.1 ± 1.9*	96.3 ± 1.5*	76.1 ± 2.7	92.6 ± 0.7*
DI D07	20.5 ± 0.2	117.8 ± 1.2	74.9 ± 1.1	68.0 ± 1.6	97.0 ± 0.1	22.0 ± 0.6**	128.0 ± 2.7*	83.0 ± 2.0*	80.6 ± 1.8**	97.5 ± 0.3
DI D14	20.5 ± 0.3	120.1 ± 1.1	77.8 ± 0.8*	66.8 ± 1.2	98.0 ± 0.1	22.0 ± 0.6**	121.6 ± 1.4	78.3 ± 1.3	76.9 ± 1.4	98.1 ± 0.2

* Significant in comparison to baseline at $P < 0.05$

Table 2 Effect of high altitude on plasma angiotensin-converting enzyme (*ACE*), plasma renin activity (*PRA*), aldosterone, Na^+ and K^+. Values are mean ± SEM; Numbers of subjects are shown in parentheses

Days	Normotensive (28)					Hypertensive (18)				
	ACE (U/l)	PRA (ng/ml)	Aldost-erone (pg/ml)	Na^+ (mmol/l)	K^+ (mmol/l)	ACE (U/l)	PRA (ng/ml)	Aldost-erone (pg/ml)	Na^+ (mmol/l)	K^+ (mmol/l)
Baseline	36.3 ± 2.1	0.62 ± 0.02	67.8 ± 3.3	143.0 ± 0.3	4.2 ± 0.1	40.0 ± 1.9	0.67 ± 0.07	62.8 ± 3.8	143.5 ± 0.3	4.2 ± 0.1
HA D01	63.0 ± 3.5*	0.68 ± 0.1	66.5 ± 4.5	142.7 ± 0.4	4.3 ± 0.1	66.0 ± 5.6*	0.85 ± 0.1	71.3 ± 3.1	142.5 ± 0.6	4.7 ± 0.1*
HA D10	43.7 ± 3.9	1.14 ± 0.1*	75.9 ± 5.3	136.9 ± 0.6*	4.3 ± 0.1	45.7 ± 2.2	1.20 ± 0.1*	86.6 ± 3.9*	150.1 ± 0.9*	4.5 ± 0.1*
HA D30	44.2 ± 3.6	1.04 ± 0.1*	72.1 ± 4.4	135.9 ± 0.6*	4.5 ± 0.2	40.0 ± 3.3	1.32 ± 0.2*	94.5 ± 5.6*	149.9 ± 1.2*	4.7 ± 0.1*
DI D07	33.1 ± 2.8	1.02 ± 0.1*	56.2 ± 5.2	142.6 ± 0.5	4.1 ± 0.1	36.8 ± 4.2	1.01 ± 0.1*	63.4 ± 8.5	142.7 ± 0.5	4.1 ± 0.1
DI D14	35.5 ± 2.4	0.78 ± 0.1	59.3 ± 4.8	141.4 ± 0.5	4.2 ± 0.1	34.9 ± 4.3	0.99 ± 0.1*	51.7 ± 5.4	140.8 ± 0.6	4.4 ± 0.2

* = Significant in comparison to baseline at $P < 0.05$

Table 3 Effect of high altitude on 24-hour urine volume and urine electrolytes. Values are means ± SEM; Numbers of subjects are shown in parentheses

Days	Normotensive (28)			Hypertensive (18)		
	24-h urine volume (ml/24 h)	Urine electrolytes		24-h urine volume (ml/24 h)	Urine electrolytes	
		Na^+(mmol/l)	K^+ (mmol/l)		Na^+ (mmol/l)	K^+ (mmol/l)
Baseline	1387.6 ± 72.8	130.9 ± 5.2	34.1 ± 2.1	1401.3 ± 109.9	136.9 ± 9.0	35.5 ± 2.8
HA D01	1665.9 ± 88.2*	153.9 ± 6.8*	30.8 ± 1.1	1590.0 ± 82.8	165.1 ± 12.6*	31.7 ± 2.5
HA D10	1610.5 ± 87.1*	165.8 ± 9.2*	30.1 ± 1.7	1539.4 ± 121.1	170.0 ± 16.2*	29.6 ± 2.0
HA D30	1724.4 ± 84.2*	197.7 ± 11.6*	35.2 ± 1.6	1587.5 ± 110.1	192.4 ± 21.1*	33.5 ± 2.8
DI D07	1727.2 ± 86.7*	170.2 ± 7.4*	30.9 ± 1.6	1591.9 ± 94.6	171.2 ± 15.8*	29.2 ± 2.5
DI D14	1491.8 ± 83.5	158.4 ± 5.3*	33.8 ± 1.6	1347.1 ± 95.9	150.1 ± 8.6	28.7 ± 3.2

*=Significant in comparison to baseline at $P < 0.05$

Table 4 ACE insertion (I) and deletion (D) allele frequencies in volunteers normotensive and hypertensive at high altitude. Numbers of subjects are shown in parentheses

Parameters	Normotensive (28)	Hypertensive (18)
I allele frequency	0.68	0.33
D allele frequency	0.32	0.67

$\chi^2_1 = 10.6$, $P < 0.05$

volunteers there was a significant rise in plasma aldosterone levels on days 10 and 30 of the stay at high altitude (Table 2). In normotensive volunteers plasma sodium levels decreased significantly on days 10 and 30 of their stay at high altitude in comparison to their baseline values. By contrast, in hypertensive volunteers, plasma sodium levels increased significantly at high altitude on days 10 and 30 (Table 2). In normotensive volunteers plasma potassium levels remained unaltered at high altitude and on their returns, but in hypertensive volunteers the plasma potassium levels significantly increased during the whole duration of their stay at high altitude in comparison to baseline values (Table 2).

Results on the urine volume excreted in 24 h by both the normotensive and hypertensive volunteers, and urine electrolyte levels at high altitude have been given in Table 3. In normotensive volunteers, during their whole period of stay at high altitude and on the 7th day after returning to the plains, there was a significant increase in the 24-h urine volume excreted in comparison to baseline values. In hypertensive volunteers the 24-h urine volume remained unaltered at high altitude and on their return to the plains (Table 3). Urinary sodium levels increased significantly in both normotensive and hypertensive volunteers, during their stay at high altitude and on returning to the plains (Table 3).

The frequencies of the ACE insertion (I) and deletion (D) allele in normotensive and hypertensive volunteers at high altitude are given in Table 4. The D allele frequency was significantly higher in volunteers who were hypertensive at high altitude.

Discussion

Increase in body weight and obesity have been shown to be positively associated with blood pressure (Gerber et al. 1998). In the present age-matched study also the volunteers who developed systemic hypertension at high altitude showed an increase in BMI, unlike the normotensives. This indicated that people with higher body weight are more likely to develop systemic hypertension at high altitude.

On exposure to high altitude, systemic hypertension results from sympathetic stimulation and it may continue for several weeks in non-acclimatized subjects (Malhotra et al. 1976; Wolfel et al. 1994). In the present study the volunteers who developed systemic hypertension on exposure to high altitude also showed an increase in SBP and DBP during their stay at high altitude. It is reported that on initially exposure to high altitude stroke volume is depressed and an increased heart rate partially compensates for this (Hoon et al. 1977). The observed increase in pulse rate of volunteers exposed to high altitude is in agreement with the previous findings. At high altitude the reduced oxygen pressure limits its diffusion from the alveoli into the blood, resulting in decreased blood oxygen saturation. Similar findings of decreased SaO_2 in volunteers taken to high altitude were observed in the present study.

The involvement of the renin-angiotensin-aldosterone system in the control of the salt and water balance, and thereby blood pressure, is well known during hypoxia and high-altitude exposure (Keynes et al. 1982; Sutton et al. 1977). At high altitude renal renin secretion is stimulated by decreased renal blood flow (Pauli et al. 1968), which in turn activates the renin-angiotensin-aldosterone system. In the present study also the volunteers, on induction to high altitude showed, a significant rise in PRA on the 10th and 30th days of their stay at altitude as well as on the 7th day of after their return to the plains. The level of the rise was similar in both normotensives and hypertensives. We also observed a sharp and significant rise in plasma ACE levels of the volunteers on the first day at high altitude. Afterwards, on the 10th and 30th days of their stay at high altitude, though there were increases in plasma ACE

levels these were not significant because of large inter-individual variations in the values.

In the volunteers normotensive at high altitude there was no change in plasma aldosterone levels despite the observed rises in their plasma ACE and PRA values. This showed a dissociation of the renin-angiotensin-aldosterone system in volunteers normotensive at high altitude. In these volunteers at high altitude an unchanged aldosterone level resulted in a significantly increased 24-h urine volume with an increased urinary sodium excretion. This was reflected in decreased plasma sodium levels during their stay at high altitude. Perhaps the observed diuresis and other biochemical changes resulted in these volunteers acclimatising better and prevented them from developing systemic hypertension.

In the volunteers hypertensive at high altitude there was a significant increase in plasma aldosterone and PRA levels on the 10th and 30th days of their stay at high altitude. The plasma ACE values were significantly high on the first day of their arrival at high altitude. This showed that there was no dissociation of the renin-angiotensin-aldosterone system in volunteers developing systemic hypertension at high altitude. In these hypertensive volunteers increased aldosterone levels, as expected, resulted into no significant increase in 24-h urine volume at high altitude or on their return, with increased plasma sodium levels during their stay at high altitude despite an increased urinary sodium excretion.

A substantial fraction of human blood pressure variation is genetically determined (Lifton 1996). It is hypothesized that hypertension-susceptibility genes operate only in a specific environment (Corvol et al. 1997). In the present study the frequency of the ACE D allele was observed to be significantly higher in volunteers who developed systemic hypertension during their stay at high altitude. This indicated a positive correlation of the ACE D allele with high-altitude-induced systemic hypertension. In our earlier study no significant association of the ACE D allele was observed with systemic hypertension in various Indian populations (Gorkha, Sikh, Assamese, Dogras, Jats, Kumaonis and Yadavas) when studied at plains (Kumar et al. 2001). The results of the present study suggest that interaction between the genes and the environment plays an important role in the development of systemic hypertension at high altitude. It is likely that environmental changes and the exposure of pre-existing genetic factors, namely the ACE D allele (not expressed fully in the previous environment), predispose a population to elevated blood pressure.

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