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Geriatric Men at Altitude: Hypoxic Ventilatory Sensitivity and Blood Dopamine Changes

T.V. Serebrovskaya[a] I.N. Karaban[b] E.E. Kolesnikova[a] T.M. Mishunina[c]
R.J. Swanson[d] P.V. Beloshitsky[a] V.N. Ilyin[a] A.N. Krasuk[a] O.S. Safronova[a]
L.A. Kuzminskaya[c]

[a]Bogomoletz Institute of Physiology NASU, [b]Institute of Gerontology AMSU, and
[c]Institute of Endocrinology AMSU, Kiev, Ukraine; [d]Old Dominion University, Norfolk, Va., USA

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Key Words
High altitude · Hypoxic ventilatory response · Dopamine · Aging

Abstract
Background: Short-term exposure to high-altitude hypoxia increases hypoxic ventilatory sensitivity (HVS) in healthy humans. Dopamine (DA) is the implicated neurotransmitter in carotid body (CB) chemoreceptor response, and the microenvironmental conditions in CB tissue are comparable to blood. Continuous DA infusion affected ventilation in animals and humans. Age-related oscillations in blood DA levels may influence peripheral chemoreflexes. ***Objective:*** Hypoxic ventilatory responses (HVR) relative to blood DA concentration and its precursor, dihydroxyphenylalanine (DOPA) was measured in young and elderly men during short-term altitude adaptation. ***Methods:*** Nine elderly climbers (group 1: 61 ± 1.4 years) and 7 young healthy subjects (group 2: 23 ± 2 years) were tested at sea level on day 0, on day 3 after passive transport to 2,200 m, and on day 14 after climbing to 4,200 and 5,642 m. ***Results:*** Sea level HVR in group 1 was 47% lower than in group 2, accompanied by higher blood DOPA (300%) and DA (37%) content. Initial DA and DOPA concentrations showed a negative correlation with initial HVR but a positive correlation with age. Passive transport to middle altitude (2,200 m) increased HVS, doubling HVR slopes in groups 1 and 2 and producing increased maximum expired minute ventilation during isocapnic rebreathing (29 and 28%, respectively). Day 3 2,200-meter blood DOPA content decreased by 22% in group 1 and increased by 300% in group 2. DA increased in both groups. ***Conclusion:*** The relationship between HVR and the reciprocal DA and DOPA values seen in both groups is associated with age, producing decreased DA receptor sensitivity and enhanced DA reuptake during adaptation to high altitude.

Introduction

Human life can be viewed as a time line spanning birth, infancy, childhood, adolescence, adulthood, senescence and death. Conforming to the laws of nature, the

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Tatiana V. Serebrovskaya, PhD
Bogomoletz Institute of Physiology
Ukrainian Academy of Sciences
4 Bogomoletz Street, 252024 Kiev (Ukraine)
Tel. +380 44 256 2492, Fax +380 44 293 3431, E-Mail sereb@mail.kar.net

vigor of adult maturity is replaced by the increasing fragility of old age. Elderly individuals desire the same full and active life as younger adults in spite of biologically inescapable decreases in physiological processes and reserves. Humans past middle age find new ways peculiar to old age for accommodation, allowing them to 'stay in the saddle'. Investigators must comprehend these adaptive mechanisms and help old people to enjoy implementing these mechanisms without detriment.

In recent years, many older men and women, especially former alpinists, have gone to high altitudes for recreation and sport, but little attention has been given to the effect of age on their tolerance to altitude. Honigman et al. [1] reported that 25% of the visitors from 16 to 87 years of age traveling to moderate elevations developed acute mountain sickness, but this phenomenon occurred mostly in the younger age group. Increased susceptibility to acute mountain sickness among younger persons was also noted by Hackett and Rennie [2]. Levine et al. [3] and Roach et al. [4] both noted that the elderly appear to acclimatize well to 2,500 m. These findings are surprising because some physiological components of gas exchange that maintain oxygenation, such as vital capacity and hypoxic ventilatory drive, decrease with age [1, 5, 6]. Levine et al. [3] noted that moderate altitude exposure in the elderly is associated with hypoxemia, sympathetic activation, and pulmonary hypertension resulting in a reduced exercise capacity. However, the hypoxic ventilatory response (HVR) is an essential defense mechanism against high-altitude hypoxia. There are data that the elderly have a reduced hypoxic ventilatory drive that may impair the normal adaptive response to altitude [7–9].

The mechanisms mediating changes in the ventilatory response during adaptation to hypoxia are not well understood, though there is evidence that dopamine (DA) is involved as a neurotransmitter in the carotid body (CB) chemoreceptor cells [10–12]. The catecholamines, DA and norepinephrine (NE), are synthesized and stored in CB chemosensory type I cells, and hypoxia mobilizes DA and NE in proportion to their stores in the tissues [13]. Studies have indicated age-related declines in the activity of several neurotransmitters in the central nervous system [14]. Additionally, DA has widespread effects in nonneural tissues as an endocrine and paracrine agent [15, 16]. Neurochemical data support the hypothesis that DA is an excitatory neurotransmitter in the CB [11, 17, 18], although DA, administered intravenously, results in ventilatory inhibition [19, 20].

The main sources of circulating DA and its precursor dihydroxyphenylalanine (DOPA) are sympathetic terminal endings, adrenal medulla chromaffin cells and paravertebral ganglia which are derived from common embryonic neuronal crest tissue together with chemoreceptor cells in the CB [21, 22]. The carotid bodies are rich in DA, but it is unlikely that they contribute materially to the plasma DA pool. On the contrary, blood DA concentration could reflexively influence the CB chemosensory function. The CBs are known as glomera because of their extensive capillary network. This unusually large flow is likely to establish a microenvironmental condition in the CB tissue comparable to blood alone [23]. Continuous infusion of DA, a common clinical treatment, affected ventilation in animals [24] and humans [25]. Thus, naturally occurring oscillations in blood DA levels may modulate peripheral chemoreflexes. Therefore we have measured a change in HVS relative to blood DA and DOPA concentration during short-term adaptation to altitude.

Materials and Methods

Two groups of old and young volunteers, sea level residents, participated in this study after having given informed consent. Group 1 consisted of 9 elderly climbers (5 men; 4 women) age 61.0 ± 1.47 years, weight 69 ± 2.9 kg; height 169 ± 1.9 cm. All subjects were in good physical condition. Less chronic disease was present in veteran climbers than is typical for elderly persons. Four climbers (44%) had moderate heart disorders (sinus arrhythmia, incomplete AV bundle block, and other factors indicative of coronary disease); 3 (33%) had hypertension; 3 (33%) had gastric, liver or intestinal disorders. No pulmonary disorder was registered in the old alpinist group. No one smoked. Most consumed one or more alcoholic beverages per day. Mean length of active climbing covered a 35-year span. However, no member of this group had climbed during the past 10 years due to the harsh political and economic situation in Ukraine.

Group 2 consisted of 7 young healthy climbers (3 men, 4 women) age 23.4 ± 2.0 years, weight 54.5 ± 3.1 kg; height 171 ± 1.9 cm. No one smoked or consumed alcohol in this group.

Both groups were tested at sea level, and twice at the Elbrus Medical Scientific Center in the Terskol settlement of the Caucasus mountains on the 3rd day and again on the 14th day after arrival at 2,200 m. During their stay at this altitude, all subjects participated in daily walking tours, initially at 3,000–3,500 m, then at 4,000–4,200 m. Four old alpinists and 2 young subjects successfully traversed the top of Mt. Elbrus (5,642 m) on the 13th day of sojourn at base-camp altitude. No headache, fatigue, shortness of breath or any other symptoms accompanying acute mountain sickness were observed in either young or veteran climbers after arriving at the final altitude. All alpinists maintained their prescribed activity and tolerated their sojourn at moderate altitude without incident. Furthermore, no serious disturbances were observed in the 4 elderly climbers while they climbed Mt. Elbrus.

All subjects were tested in the morning, on an empty stomach. Initially, venous blood was drawn from the median antecubital vein

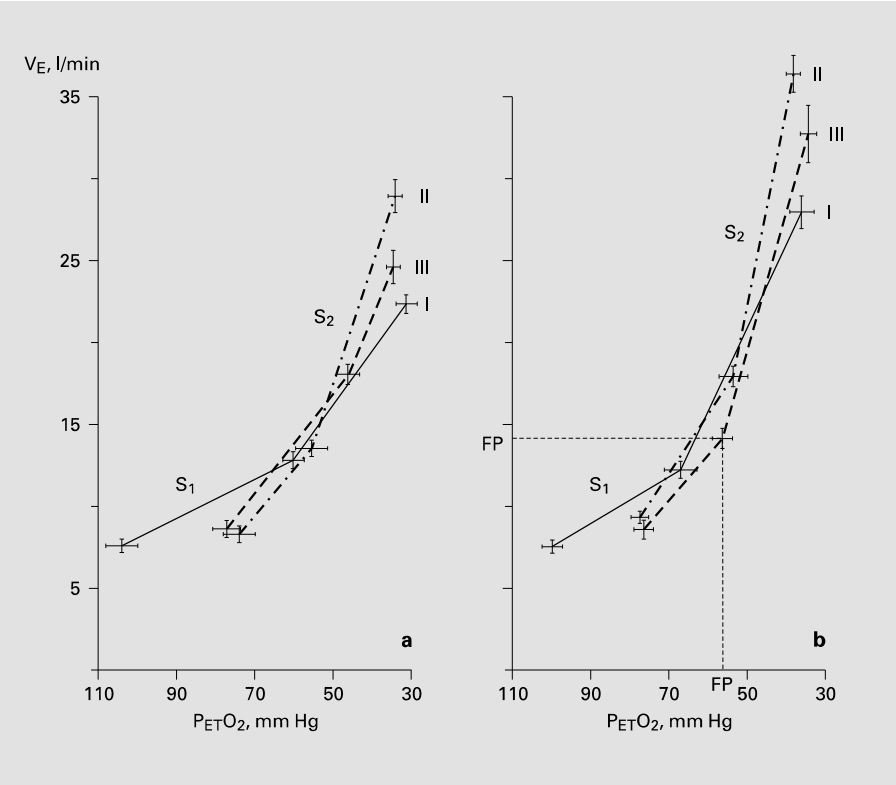

Fig. 1. Ventilatory responses to isocapnic progressive hypoxia at sea level and altitude in old (**a**) and young climbers (**b**). I = Sea level, II = 2,200 m altitude, day 3 after arrival; III = 2,200 m altitude, day 14 after arrival.

to measure NE, DA and DOPA content as described by Jakobowich and Richardson [26]. A fluorescence spectrophotometer (FMA-2A, Hitachi) was used for catecholamine measurements. Secondly, blood from the finger was drawn for measurement of hematological indices, i.e. hemoglobin (Hb) concentration, platelets (PLTs) and differential white blood cell (WBC) count. After 30 min of rest, the pulmonary function test was carried out in a sitting position using a pneumotachograph (Renaissance Spirometry System from Puritan-Bennett Company). Spirometric indices were derived automatically from the volume-time tracing produced by the microprocessor of the spirometer. All recordings were made by the same technician and the spirometric values were corrected for body temperature, atmospheric pressure and saturation.

After a 30-min rest, HVS was tested. Hypoxic ventilatory response (HVR) to isocapnic, progressively hypoxic rebreathing, in the sitting position was studied. Partial pressures of expiratory oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) were continuously monitored at the mouth with a medical mass spectrometer (MX62-02, USSR) which was calibrated before and after each test with standardized gases that had been assayed by the Scholander technique. Subjects breathed into a spirometer in which the O_2 concentration fell with body utilization over time. Initial inspired gas composition (F_i) was 20.9% O_2 and 79.1% N_2. Rebreathing continued for 5–6 min until an F_iO_2 of 8–7% was reached. The period of severe hypoxia (F_iO_2 of 10–7%) lasted no more than 1.5 min. Subjects easily endured the severe hypoxia without any side effects. For the isocapnic hypoxic response measurements, $P_{ET}CO_2$ was maintained at atmospheric pressure level by a special device which gradually diminished the volume (quantity) of CO_2 absorbed as hyperventilation increased thereby preventing an unwarranted decrease ('washing out') in PCO_2 level.

HVR Calculation

Ventilatory responses were analyzed using the subject's values for relative minute ventilation ($\dot{V}_E$) with respect to $P_{ET}O_2$. Curves were hyperbolic in shape. Usually, ventilatory and chemoreceptor responses to hypoxia are measured as a shape parameter A, which described the hyperbolic relationship between $P_{ET}O_2$ and ventilation or carotid sinus nerve activity. This shape parameter has the advantage of describing the response over the entire range of PO_2 values studied and produces a good description of raw data over a wide range of hypoxic responses from attenuated to broad [27]. An alternative method for estimation of HVRs was employed in this research; the piecewise linear approximation technique. This method, which we have described in previous studies [28, 29], allows comparison of ventilatory responses to weak (S_1) and severe (S_2) hypoxia, and to define the threshold (point of inflection) for maximum ventilatory rate increase (fracture point coordinates; FP) (fig. 1).

Statistical Tests

Statistics were performed using the analysis of variance (ANOVA) and Tukey's test. Comparisons of young vs. old data were made using Wilcoxon's unpaired test. All values were expressed as means ± SD. Correlations were identified by the least-squares method and expressed as linear regression slopes. Differences were considered significant when p ! 0.05.

Table 1. Old men at altitude: respiratory and hematological indices

a Lung ventilation

Parameters	(1) Sea level		(2) 2,200 m, day 3		(3) 2,200 m, day 14		p (1 vs. 2)		p (1 vs. 3)	
	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2
$\dot{V}_E$/kg, ml/min	112±7.0	132±6.3*	122±7.3	161±10.4**	128±5.6	158±9.2**	NS	0.05	NS	NS
f, min^{-1}	13.4±1.6	15.0±1.34	13.8±1.49	13.2±0.74	14.0±0.94	15.8±0.76	NS	NS	NS	NS
V_T, ml	572±52	480±63	605±40	665±69	628±54	544±77	NS	NS	NS	NS

b Spirometric indices

FVC, l	4.64±0.32	3.9±0.24	4.33±0.34	4.13±0.30	4.20±0.52	4.39±0.22	NS	NS	NS	! 0.05
FVC/kg, ml	67±5.4	72±3.6	63±4.8	76±5.2	61±5.4	81±5.0**	NS	NS	NS	! 0.05
FEV_1, l/s	3.57±0.65	2.8±0.18	3.57±0.67	3.95±0.36	3.99±0.43	3.87±0.28	NS	! 0.01	NS	! 0.01
MLV, l/min	139±42	122±31	158±37	161±32	163±29	168±28	NS	NS	NS	NS
MLV/kg, l/min	2.02±0.18	2.24±0.13	2.29±0.21	2.95±0.17*	2.36±0.23	3.08±0.20*	NS	! 0.01	NS	! 0.01

c Hematological indices

Hb, g/dl	120±5.4	128±4.9	139±6.5	143±3.9	129±7.4	139±5.3	! 0.05	! 0.05	NS	NS
PLTs, ! 10^3/ml	212±17	215±20	261±31	267±23	319±32	280±36	! 0.01	! 0.05	! 0.01	NS
WBCs, ! 10^3/ml	4.71±0.66	5.4±0.48	6.12±0.82	6.6±0.52	6.16±0.70	7.62±0.71	NS	! 0.05	NS	! 0.05
Band, %	3.3±0.73	3.1±1.1	4.5±0.9	5.25±0.91	6.6±1.2	6.75±1.3	NS	! 0.05	! 0.05	! 0.01
Neutrophils, %	59.3±6.0	58±3.5	60±5.1	61±2.9	61.3±8.1	59.1±4.8	NS	NS	NS	NS
Lymphocytes, %	28.8±3.7	31.4±4.8	31.2±4.5	29±3.4	29.2±3.4	30.1±2.8	NS	NS	NS	NS
Monocytes, %	3.0±0.8	3.8±0.71	3.27±0.91	3.1±0.62	2.2±0.71	2.9±0.9	NS	NS	NS	NS
Eosinophils, %	3.8±0.7	2.5±0.15	2.09±0.60	1.5±0.1	2.0±0.22	1.0±0.07**	! 0.05	! 0.01	! 0.05	! 0.01
Basophils, %	1.1±0.33	0.75±0.15	0.45±0.20	0.85±0.15	0.78±0.20	0.85±0.1	NS	NS	NS	NS

* p ! 0.05; ** p ! 0.01, group1 vs. group 2.

Results

The initial sea level investigation revealed differences between young and old alpinists. Parameters of resting respiratory frequency (f) and tidal volume (V_T) were not significantly different, but the mean value for specific lung ventilation (V_E/kg) was 18% less in veterans (table 1a). We did no find marked differences in basic spirometric indices (table 1b). Significant differences in hypoxic ventilatory sensitivity were found (fig. 1). Though responses to a weak hypoxic stimulus (S_1) did not differ between groups 1 and 2 (0.15 ± 0.01 and 0.15 ± 0.8 liters/min/mm Hg), there was a significant 47% mean HVR decrease in the severe hypoxia range (S_2) in the older subjects (group 1: 0.31 ± 0.06 liters/min/mm Hg; Gr. 2: 0.59 ± 0.09 liters/min/mm Hg; p ! 0.01). The diminution by 21% of maximal ventilation during the rebreathing test (V_E, max) and the shift of the abscissa FP coordinate to lower levels of $P_{ET}O_2$ also indicate a decrease in VHS in group 1. The low hypoxic sensitivity was accompanied by higher levels of blood DOPA and DA content (300 and 37%, respectively). A tendency toward increased levels of NE content (by 23%) was also found in old alpinists (fig. 2). Thus sea level DA and DOPA concentrations showed a strong positive correlation with age (r = 0.63; p ! 0.05 and 0.76; p ! 0.01, respectively) and a negative correlation with initial HVR (r = –0.61 and –0.65, respectively; p ! 0.05) in groups 1 and 2 (fig. 3). At sea level, no significant differences were observed in hematological indices between old and young subjects (table 1c).

Passive transport to middle altitude (2,200 m) provoked considerable shifts in most investigated parameters in both old and young alpinists. Three days after arrival, lung ventilation at rest in group 2 increased by 22%, with only a trend for V_E increase in group 1. During the whole stay at 2,200 m, V_E/kg was significantly lower in old alpinists. Some differences were found in spirometric indices. FVC rose by 13% (490 ml) in young alpinists by the 14th day at 2,200 m while decreasing by 10% (440 ml) in veterans over the same period. A similar shift occurred in group 2 for forced expiratory volume at 15 (FEV_1) and maximal lung ventilation (MLV), producing a rise of 41 and 32%, respectively, with no significant change in group 1 (table 1). Living at 2,200 m for 3 days increased

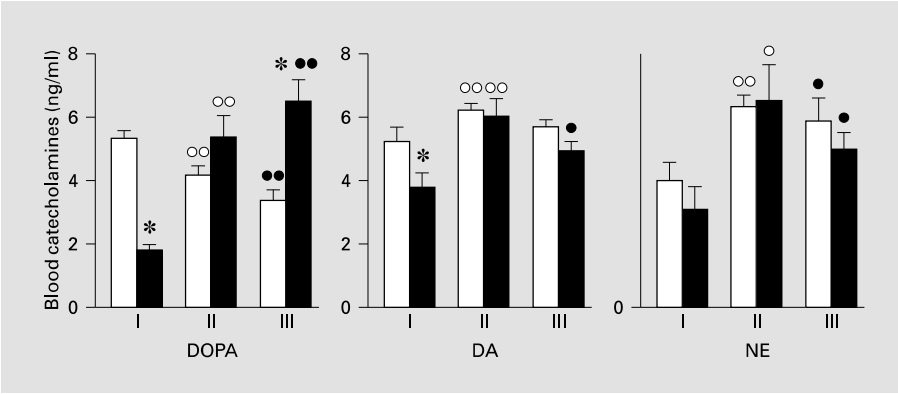

Fig. 2. Blood catecholamines at sea level and altitude in old ()) and young ($) climbers. I = sea level, II = 2,200 m altitude, day 3 after arrival; III = 2,200 m altitude, day 14 after arrival. *p ! 0.05, ** p ! 0.01, statistically significant difference between group 1 and group 2; ◦ p ! 0.05, ◦◦ p ! 0.01, statistically significant difference between I and II; • p ! 0.05, •• p ! 0.01, statistically significant difference between I and III.

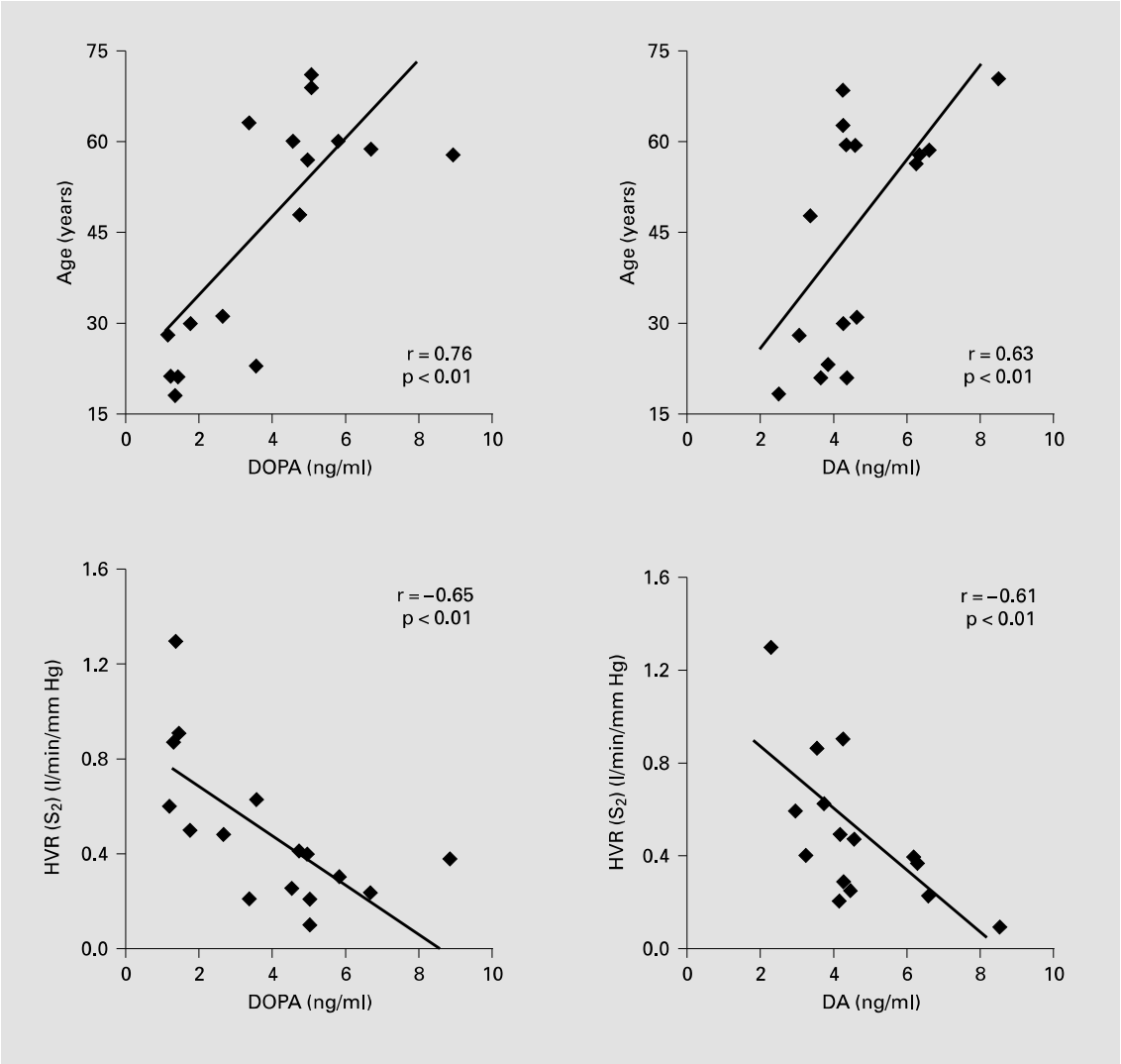

Fig. 3. Relation of baseline blood DOPA and DA content with age and hypoxic ventilatory response in group 1 (old) and group 2 (young) climbers. HVR(S_2) = HVR, slope of sharp increase in ventilation; r = coefficient of correlation.

HVS, doubling S_2 for both group 1 (from 0.31 ± 0.06 to 0.73 ± 0.08 liters/min/mm Hg; p ! 0.01) and group 2 (from 0.59 ± 0.09 to 1.17 ± 0.10 liters/min /mm Hg; p ! 0.01), and producing an increase of $V_{E,max}$ during the isocapnic rebreathing test of 29 and 28%, respectively. After the 2 week adaptation, HVRs decreased slightly in both groups (fig. 1).

The most impressive differences between the two groups were observed in blood catecholamine content. On the 3rd day after arriving at 2,200 m, blood DOPA content increased by 300% in group 2 and decreased by 22% in group 1. DA increased in both groups, by 57% in group 2 and by 18% in group 1 making DA concentration equal in young and old groups at 2,200 m for 3 days. Two weeks of active adaptation produced a further rise in group 2 and fall in group 1 DOPA content. DA content decreased slightly in both groups at 2,200 m for 14 days. When compared to sea level values, DA concentration finished higher by 28% in group 2, with no significant difference in group 1. On the 3rd day at 2,200 m, NE content increased by 200% in young subjects and by 56% in old subjects. By the 14th day, this parameter slightly decreased in both groups. When compared to sea level values, the final concentration was 63% higher in group 2 and 48% higher in group 1 (fig. 2). Hematological factors of Hb, PLTs, WBCs, and band leukocyte count all increased while eosinophils decreased in both groups. There was no significant difference between group 1 and group 2 in hematological parameters at altitude, except for enhanced PLTs in the older climbers (table 1c).

Discussion

Healthy sexagenarian alpinists in this investigation climbed high altitudes successfully. The effects of high altitudes on climbers included the observation of a reciprocal relationship between changes in HVS and blood DOPA content in old age and youth. Initially, veterans did not differ from young subjects in spirometric and hematological indices, but were characterized by lower specific lung ventilation at rest and lower HVS accompanied by higher venous blood DOPA and DA content. These differences were assumed to be the result of aging. Adaptation to a 2,200-meter altitude provoked augmentation in HVRs both in old and young climbers, but this increase was accompanied by a great increase in DA and NE blood content in group 2 while group 1 demonstrated only a slight increase. The most striking differences were found in DOPA concentration shifts: swift augmentation in young climbers just after arriving at altitude with further increase during the 2 week period of adaptation, and significant decrease in old subjects with a further reduction over time. As a result, DA content remained higher in group 1 compared to group 2, but there was an inversion in DOPA concentration between the two groups in proceeding from sea level to 2,200 m. Spirometric differences at altitude for group 2 included a gradual rise in forced vital capacity (FVC), FEV_1 and MLV but no significant spirometric changes occurred in group 1. There were no hematological differences between group 1 and group 2 at sea level or altitude except for an augmentation of PLT count in group 1.

The fact that short-term exposure to high-altitude hypoxia results in increases in HVS in humans and animals is well established and summarized in many reviews [18, 30, 31]. The mechanisms responsible for this increase have remained unclear, but could involve events happening on both central and peripheral levels. Data suggest that carotid chemoreceptor activity plays a key role in ventilatory acclimatization to hypoxia [10, 12, 32]. Released acutely from type I glomus cells in the CB by hypoxic stimuli, DA has been postulated as the excitatory transmitter for sinus nerve endings [11, 17, 33, 34]. However, intravenous or intra-arterial infusion of DA induced transient inhibition of both sinus nerve action potential conduction and lung ventilation [24, 35–37], supporting the concept of an inhibitory role for DA in the regulation of respiration. Previous studies in normal humans have shown that aging is associated with a reduced ventilatory response to hypoxia [7–9, 38]. Although our earlier investigation did not find a decrease in HVRs in 5 older male subjects [39], the present study recorded a significant decrease in HVS with age at both sea level and 2,200 m altitude. The fact that this depression was accompanied by an increased DA and DOPA blood content at sea level should corroborate the theory of an inhibitory action for DA on ventilation. However, we found no significant correlation between individual DA and DOPA content changes during high-altitude adaptation when compared to changes in HVRs in groups 1 and 2. DA released by CB type I cells and the high DA concentration in the synaptic cleft probably does not significantly influence DA blood concentration [40]. Furthermore, exogenously administered DA flowing to the CB could provoke DA autoreceptor-mediated inhibition of endogenous DA release which would produce the decreased HVR in subjects with high blood DA concentration by the principle of autoregulation. Venous blood DA probably does not reflect events happening at the synaptic cleft between type I cells (releasing dopamine) and postsynaptic receptors on the afferent nerve terminals.

In the present study, we observed a higher level of blood DA and a trend to higher NE content in the older subjects. Age-related increases in plasma catecholamine concentration are well documented in healthy humans [41–43]. This phenomenon is explained in part by the decrease in neuronal reuptake [44–46]. As Esler et al. [47] suggest, reduced NE reuptake increases the overflow of the neurotransmitter to plasma from the aging heart during stimulation of the cardiac sympathetic outflow. Some authors have suggested that hypoxia activates the sympathoadrenal system and enhances the blood catecholamine content in young persons [48]. This augmentation could lead to smooth muscle relaxation in the respiratory tract, and thus explain the increase in FEV_1 and $V_{E,max}$ at altitude in young persons. Our data, however, showed no significant differences in NE blood content between old and young subjects at 2,200 m. Ng et al. [46] also reported that plasma NE responses to stress did not differ in old when compared with young subjects.

As Gonzalez-Guerrero et al. [17] reported, isolated CBs cultured under hypoxia for 8 days in vitro, synthesized DA twice as fast as in control animals. Moreover, the content of tyrosine hydroxylase (TH), was gradually increased in rat CBs after adaptation to hypoxia, and the turnover of DA and NE in in vitro CB culture was increased by 15- and 5-fold, respectively [49]. The activity of the plasma enzyme dopamine-ß-hydroxylase has been reported to be increased due to exposure to altitude hypoxia [50]. DOPA level in the plasma is maintained by spontaneous output from chromaffin cells of the adrenal medulla and from the sympathetic nervous system, and is approximately proportional to the rates of NE turnover [22, 51]. The limiting factor of DOPA synthesis is TH. Aging is associated with decreased TH activity and therefore we would expect a decrease in DOPA content with age. However, we registered a 3-fold increase in this amine in the blood of the older subjects when challenged hypoxically at sea level, but a 22% decrease at 2,200 m. These sea level data are confirmed by our observations on 8 older nonalpinist sea level residents [52]. Furthermore, the urinary excretion of DOPA in group 1 exceeded that in young subjects. TH is an O_2-dependent enzyme [53]. TH gene expression starts within hours after hypoxia [23] and can be provoked by increased intracellular Ca^{2+} and/or increased firing rate of catecholaminergic neurons [22, 54]. In rats, adrenal gland DOPA content increased 2.3 times after a 7-day exposure to hypoxia [53]. The above-mentioned mechanism could explain the enhancement of blood DOPA and subsequent DA concentration in young subjects during their stay at 2,200 m. Activation of the sympathoadrenal system can also promote an increase in DOPA output into blood [22]. The decrease in blood DOPA content in older subjects at 2,200 m remains unclear. We speculate that the relationship between HVR and the reciprocal DA/DOPA values seen in groups 1 and 2 is associated with age, producing both decreased DA receptor sensitivity and enhanced DA reuptake during adaptation to high altitude.

Summary

This investigation shows that old alpinists can successfully climb up to high altitudes such as 5,642 m in spite of measurably decreased HVS. At sea level, this decreased sensitivity was associated with high venous DOPA and DA contents. There were quantifiably significant differences in sea level versus 2,200-meter catecholamine values in both group 1 and group 2 subjects. DOPA values were markedly different in group 1 and group 2 at sea level and after 14 days at 2,200 m, but there was an inversion of these two measurements. Group 1 had higher values than group 2 at sea level and lower values than group 2 at the 14-day 2,200-meter sampling. This difference is thought to be due to aging-related phenomena.

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