Relation of Sympathetic Activation to Ventilation in Man at 4300 m Altitude

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Background: The sympathetic nervous activity increases at high altitude but is not maximal initially when hypoxemia is most severe. ***Hypothesis:*** The sympathetic activation would correlate better to the ventilatory response to chronic hypoxia than to the severity of hypoxia per se. ***Methods:*** Eleven healthy male volunteers (27 ± 1 yr) had measurements from the abdominal aorta of pressure, catecholamines, and blood gases at sea level, on arrival at 4300 m, and after 21 d of residence. Additionally, we measured 24-h urinary catecholamine excretion at sea level and each day at altitude, and made serial measurements of resting ventilatory parameters. ***Results:*** Arterial norepinephrine (NE) concentrations on arrival at 4300 m were little changed from sea level, but were increased following acclimatization at 21 d. Arterial oxygenation was decreased on arrival, but improved with acclimatization. Arterial epinephrine (E) concentrations were increased on arrival, and returned to an intermediate level by 21 d. The urinary NE excretion was increased along with the increase in V_E ($p < 0.01$) and the fall in end-tidal P_{CO_2} ($p < 0.001$), but not with the decrease in end-tidal P_{O_2} during the sojourn at 4300 m. Excretion of E did not relate to any ventilatory parameters. Propranolol (240 $mg \cdot d^{-1}$), which was given to 6 of 11 subjects, did not affect any relationships. ***Conclusion:*** The sympathetic activation was related to the ventilatory response but not to measures of hypoxemia at 4300 m. We conclude that factors related to ventilatory acclimatization, possibly increased chemoreceptor activity, contribute to the development of sympathetic activation at high-altitude.

THE SYMPATHO-ADRENAL systems are activated when humans go to high altitude (3–9,13,16,17). We have previously reported that activation of the adrenal system, as manifested by the development of tachycardia (5) and an increase in arterial epinephrine (E) (7–9) occurs on arrival (i.e., when the hypoxemia is most severe), and it diminishes over time as ventilatory acclimatization lessens the hypoxemia. Thus, hypoxia per se has been considered to mediate the adrenal activation. However, a slower activation (over 7 to 10 d) of the sympathetic system, as manifested by increases in arterial pressure and urinary excretion of norepinephrine (NE) (9,17) suggests that control of the sympathetics differs from those of the adrenal system. In our previous report of arterial pressure changes (17), we suggested that factors related to hypocapnia, rather than hypoxemia, affected norepinephrine excretion at high altitude, but detailed evidence was not presented. In addition, the interaction between ventilatory and sympathetic responses, which is well demonstrated during acute hypoxia (4,12,14), has not been examined with chronic hypoxia.

Therefore, we examined in detail the relationships between the sympathetic and the ventilatory response to chronic altitude by analyzing simultaneously obtained data, some of which has been reported separately (7–9,17). We measured the urinary NE excretion daily as a noninvasive index of sympathetic activation, along with the ventilation and end-tidal gases as indices of hypoxemia and ventilatory parameters. The measurements were made at sea level and over 21 d at 4300 m. Arterial catecholamine, gas tension, and pressure measured at sea level and twice at altitude were also presented to help establish the effects of hypoxia at altitude acutely and after acclimatization. Whether the sympathetic activation at high altitude relates more closely to hypoxic stimulus per se or to development of ventilatory acclimatization, could provide insight into mechanisms of sympathetic activation at high altitude.

METHODS

Conditions of altitude sojourn: Subjects were 11 healthy male sea-level residents (26.7 ± 1.2 yr, 71.4 ± 3.2 kg) who volunteered for this study. All signed informed consents approved by the Human Subject Committees at the University of Colorado Health Sciences Center, the Palo Alto Veterans Administration Hospital, and the University of California at Berkeley. Because concomitant studies (5,7–9,17) required dense β-adrenergic blockade, 6 subjects received oral propranolol, 240 $mg \cdot d^{-1}$ (propranolol

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group), and 5 were given placebo (placebo group) in a single blind study design. The treatments were begun 3 d before the sea-level measurements performed at the Palo Alto Veterans Administration Medical Center (Palo Alto, CA, P_B 751 mm Hg), and continued throughout residence at altitude. The subjects were transported by air to Denver, and were taken by car to Manitou Springs, CO (1954 m), where they spent one night. The following day they were taken by car to the U.S. Army Maher Memorial Laboratory on the summit of Pikes Peak (4,300 m, P_B 461–463 mm Hg), where they remained for 21 d. Caloric and water intake was controlled throughout the study, as previously reported (2).

Arterial blood measurements: Arterial catheterization was performed at sea level, within 4 h of arrival at 4300 m, and again day 21 at 4300 m. The femoral artery was cannulated using standard percutaneous techniques and the catheter was positioned in the distal abdominal aorta as previously described (7–9,16). Following catheterization, the subjects rested quietly while seated in a semirecumbent position for at least 45 min, following which two measurements were made 15 min apart. Resting arterial blood gas tension and arterial pressure were measured as previously described (7–9). Blood samples for catecholamine analysis were collected in heparinized tubes containing reduced glutathione. The plasma was stored frozen at −80°C for subsequent catecholamine analysis.

Ventilatory parameters: Resting ventilatory measurements were made at sea level and on days 1 (immediately upon arrival), 2, 3, 4, 5, 7, 10, 15, and 20 at 4300 m. The subjects, fasted for at least 2 h, were seated in a quiet room and breathed through a mouthpiece with a nose clip in place for at least 10 min before data were collected. End-tidal CO_2 ($P_{ET}CO_2$) and O_2 ($P_{ET}O_2$) tension, and expired ventilatory volume were measured as previously described (17).

Urine collection: For urinary catecholamine (CA) measurements, 24-h urine samples were collected at sea level and during each day of the sojourn at high altitude. The urine collection at sea level and at altitude day 20 at 4300 m preceded the arterial catheterization. However, the catheterization on arrival at 4300 m was performed during the initial 24-h urine collection and could have affected CA excretion for this day. For all other days at 4300 m, the exercise activity was monitored and a log kept to match metabolic requirements at 4300 m to those at sea level. After determination of the daily urine volume, a 10-ml aliquot was taken, reduced glutathione (10 $mmol \cdot L^{-1}$) was added to prevent catecholamine oxidation, and the aliquot was stored frozen until analysis.

Catecholamine (CA) analysis: CA (NE, E, and dopamine) levels of the plasma and urine were determined by high-performance liquid chromatography (HPLC-BioRad Model 1330 pump, Model 1340 electrochemical detector; Richmond, CA) with electrochemical detection, as previously described (6–9). The arterial measurements of CA levels provided relatively instantaneous values soon after arrival at altitude and after acclimatization compared with the more time-integrated urinary CA excretion.

The relevance of urinary CA excretion as noninvasive indices of sympathetic activation was supported in these subjects by the good relation of NE excretion to arterial

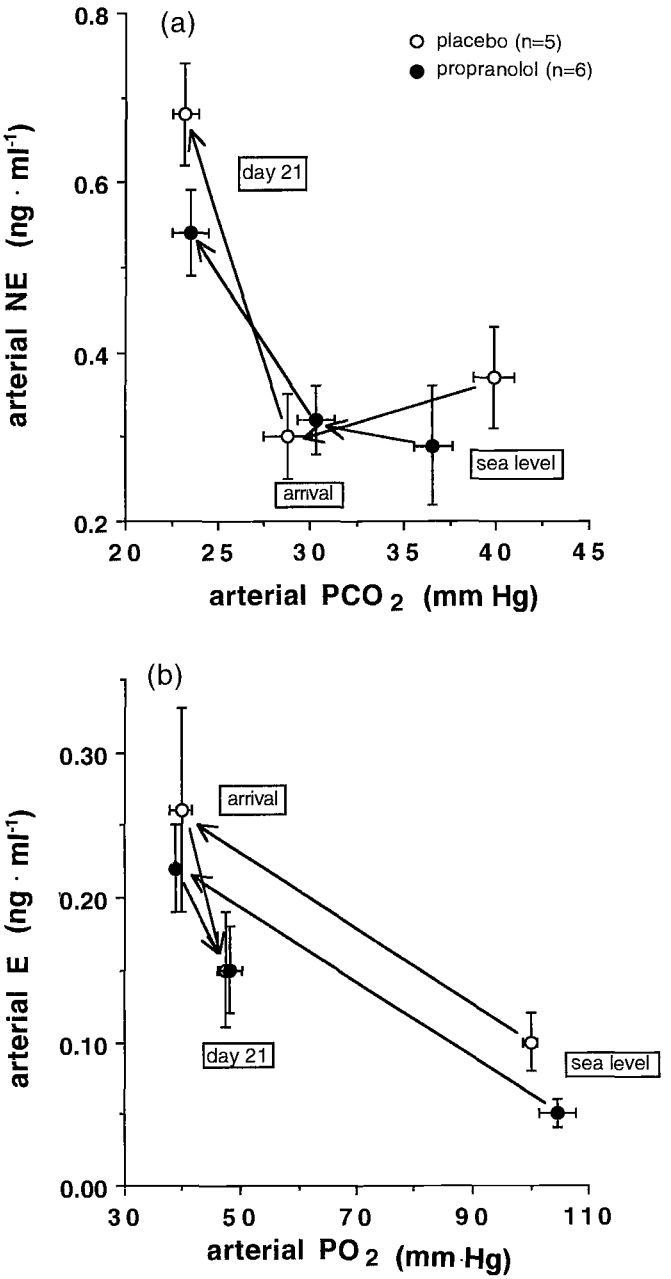

Fig. 1. (Panel a) Relation of arterial norepinephrine (NE) concentration to arterial Co_2 tension (Pco_2) and, (Panel b) relation of epinephrine (E) concentration to arterial O_2 tension (Po_2) at sea level, on arrival, and after 21 d at 4,300 m as indicated.

NE concentration (9), the relation of arterial NE concentration to muscle sympathetic activity (8), the relation of arterial pressure to NE excretion (9), and the relation of 24-h ambulatory blood pressure to NE excretion at altitude (17). Because the urine volume tended to decrease in the placebo but not the propranolol group while total CA (dopamine + NE + E) excretion did not significantly change in either group at high altitude, the difference in urine volume between the two groups might affect plasma CA clearance which could increase noise within the data. Therefore, although the absolute amounts per 24 h were reported in the previous papers (9,17), in the present data analysis we expressed NE and E excretions

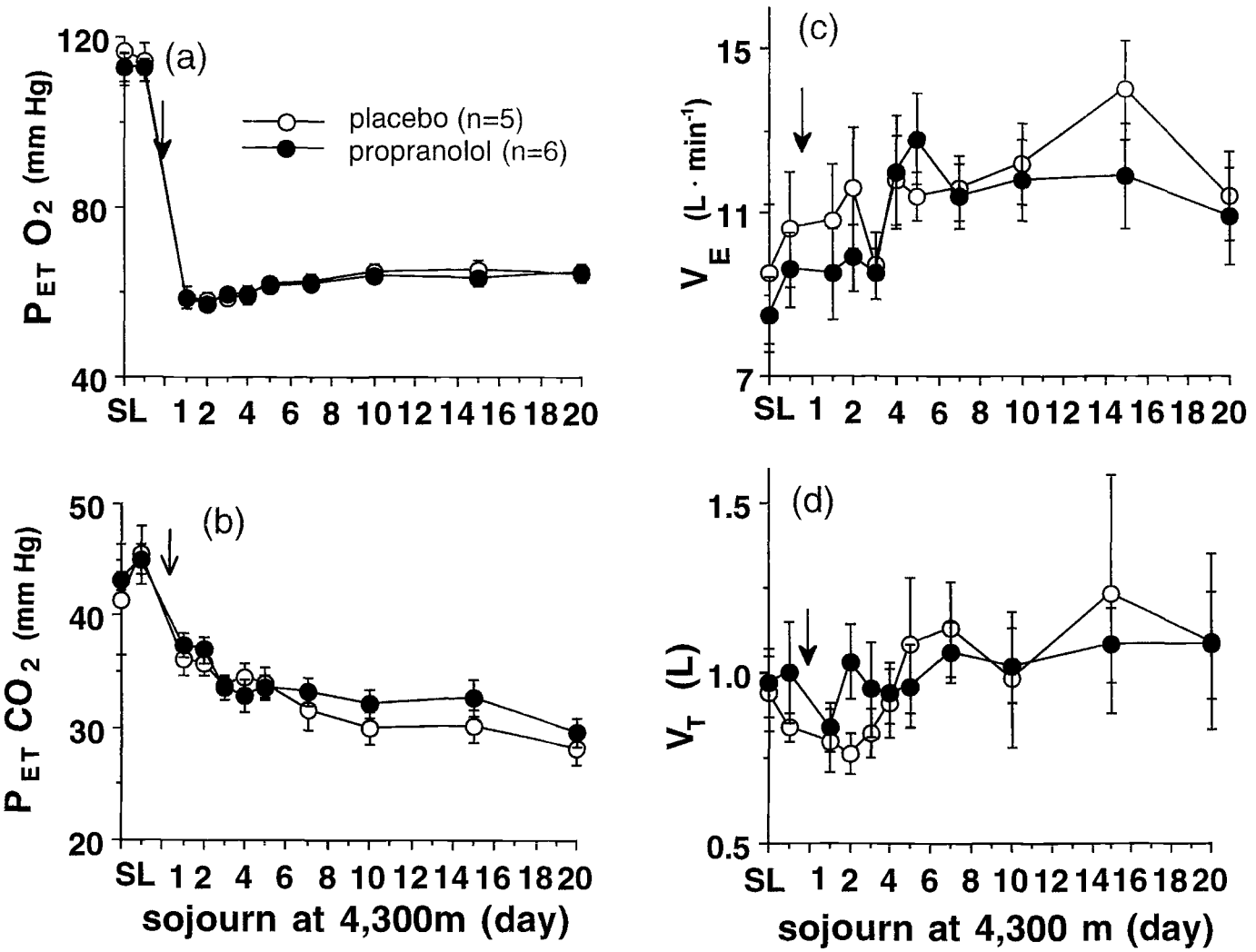

Fig. 2. Time course of the changes in (Panel a) end-tidal O_2 (P_{ETO_2}), (Panel b) end-tidal CO_2 (P_{ETCO_2}), (Panel c) minute ventilation (V_E), and (Panel d) tidal volume (V_T) at sea level and during sojourn at 4300 m. There were no significant differences between the placebo (n = 5) and the propranolol (n = 6) groups in any of the parameters. In this and subsequent figures, data are expressed mean ± SE, SL = sea level, and arrows indicate arrival at high altitude.

as fractions of total CA (i.e., the ratio of NE to CA (NE/CA) and E to CA (E/CA) as indices of relative metabolic activity producing the NE and E from dopamine) independent of urine volume, and subsequent references to excretion are in terms of these ratios.

Statistics: Data are expressed as mean and one standard error (SE). An analysis of variance (ANOVA, repeated measures) was used to test the effects of sojourn at high altitude and the difference between the placebo and the propranolol group. Pearson's simple linear regression analysis was used to examine the relationships of measurements on the same days between urinary NE or E excretion and ventilatory variables. Differences were considered statistically significant when $p < 0.05$. Because of the possible effects of drug treatment, the data for placebo and propranolol groups are indicated separately in the figures, and the analyses are presented for the groups separately and combined.

RESULTS

Arterial blood measurements: Compared to sea level, both $PaCO_2$ and PaO_2 were decreased within 4 h of arrival at 4300 m. Following 21 d of acclimatization, there was a further decrease in $PaCO_2$ (**Fig. 1a**) accompanied by a lessening of hypoxemia (Fig. 1b). Arterial norepinephrine (NE) levels on arrival at 4300 m were not different from those at sea level, but they were increased after 21 days at 4300 m accompanied by the fall in $PaCO_2$ (Fig. 1a), but by a rise in PaO_2. Arterial epinephrine (E) levels were increased above sea-level values on arrival and then fell to an intermediate value by 21 d, a pattern of response which was shared by PaO_2 (Fig. 1b). As found previously (6), arterial pressures followed a time course similar to that for NE, with mean values (mmHg) for the placebo and propranolol groups, respectively, of 91 ± 3 and 82 ± 3 at sea level, 84 ± 6 and 84 ± 3 on arrival, and 104 ± 6 and 94 ± 1 after 21 d.

Resting ventilatory parameters: The end-tidal gas tensions were comparable to those in arterial blood, and in addition provided a detailed time course of changes. As expected, the end-tidal oxygen pressure (P_{ETO_2}) decreased sharply on arrival at 4300 m, and then partially but significantly returned toward the sea level value, reaching a stable plateau by 7–10 d at 4300 m (**Fig. 2a**).

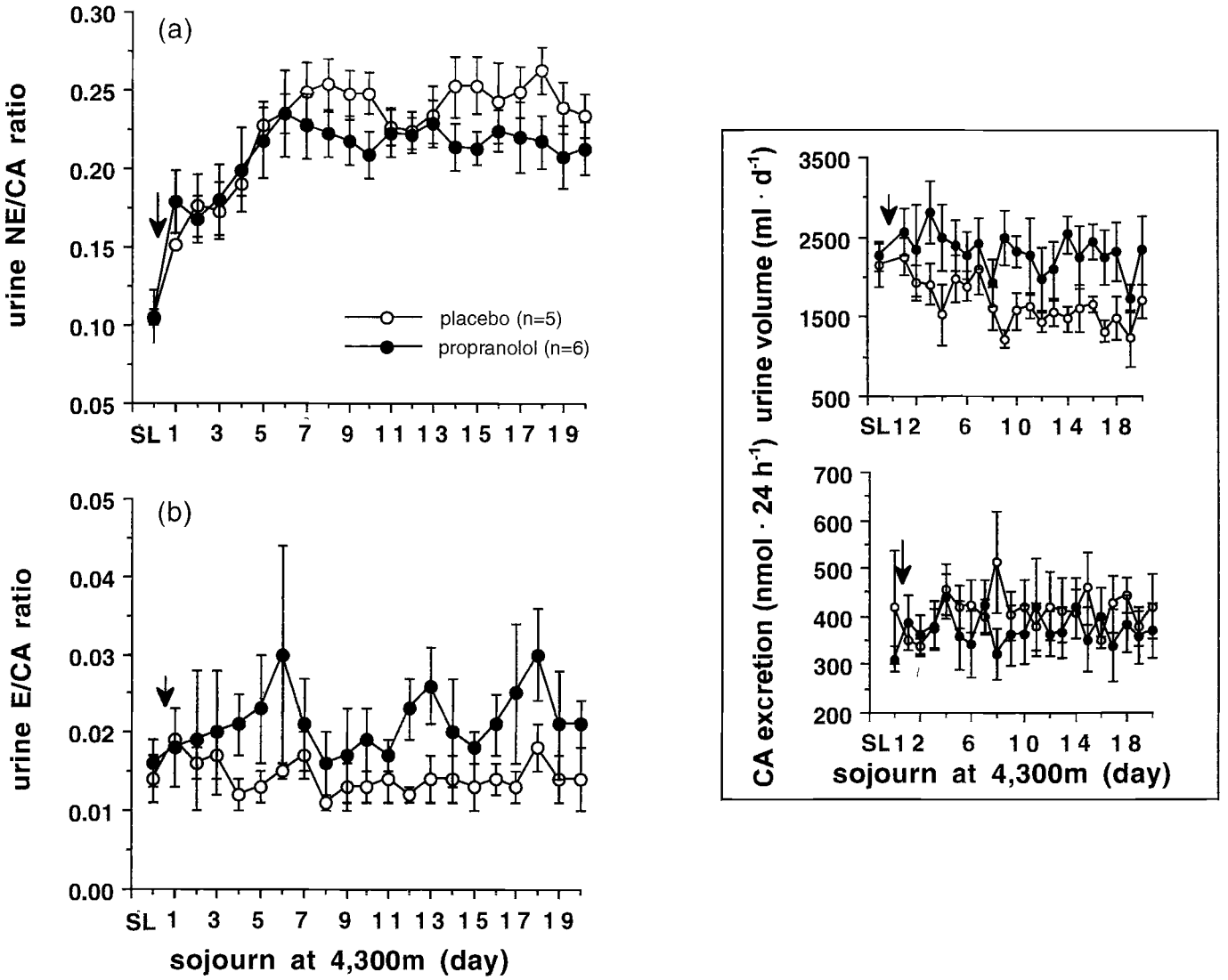

Fig. 3. Time course for the placebo and propranolol groups at 4300 m altitude of the changes in (Panel a) fractional urinary excretion of norepinephrine/total catecholamines (NE/CA) and (Panel b) fractional excretion of epinephrine/total catecholamines (E/CA). Inset shows time course of the changes in 24-h urine volume (upper) and total (dopamine + norepinephrine + epinephrine) catecholamine (CA) excretion (lower) at 4,300 m.

The end-tidal CO_2 pressure (P_{ETCO_2}) decreased on arrival, but significantly decreased further during the sojourn at 4300 m altitude (Fig. 2b). Minute ventilation (V_E) gradually but significantly increased during the sojourn at altitude (Fig. 2c). Tidal volume tended to increase (Fig. 2d) and frequency (not shown) was not significantly changed at altitude. As previously reported (10), there were no significant differences between the placebo and the propranolol groups for any of these measurements.

CA excretions: Excretion of NE increased on day 1, and increased further during the sojourn at 4300 m altitude in both placebo and propranolol groups (**Fig. 3a**). Although ANOVA showed no difference between the placebo and propranolol groups, there was a significant interaction between altitude sojourn and drug treatment, suggesting that propranolol affected NE excretion at altitude. Excretion of E did not significantly increase during the sojourn in either group (Fig. 3b), and there was no significant difference between the placebo and propranolol groups by ANOVA.

Relation of NE and E excretion to ventilatory measurements: The 24-h CA excretions were related to ventilation for the days when both were obtained. NE excretion positively correlated to P_{ETO_2} ($r = 0.86$, $p < 0.001$) in the combined placebo and propranolol groups at high altitude (**Fig. 4a**). However, sea-level data did not fall near the regression line, and if sea-level data were included in the analysis, the positive correlation disappeared.

Excretion of NE inversely correlated to P_{ETCO_2} ($r = -0.78$, $p < 0.001$) in the combined group at high altitude (Fig. 4b). Furthermore, the sea-level data fell near an extrapolation of the regression line, and including the sea-level data in the analysis improved the goodness of fit (combined group $r = -0.90$).

P_{ETCO_2} findings were reflected in minute ventilation (V_E). Excretion of NE showed a significant, positive cor-

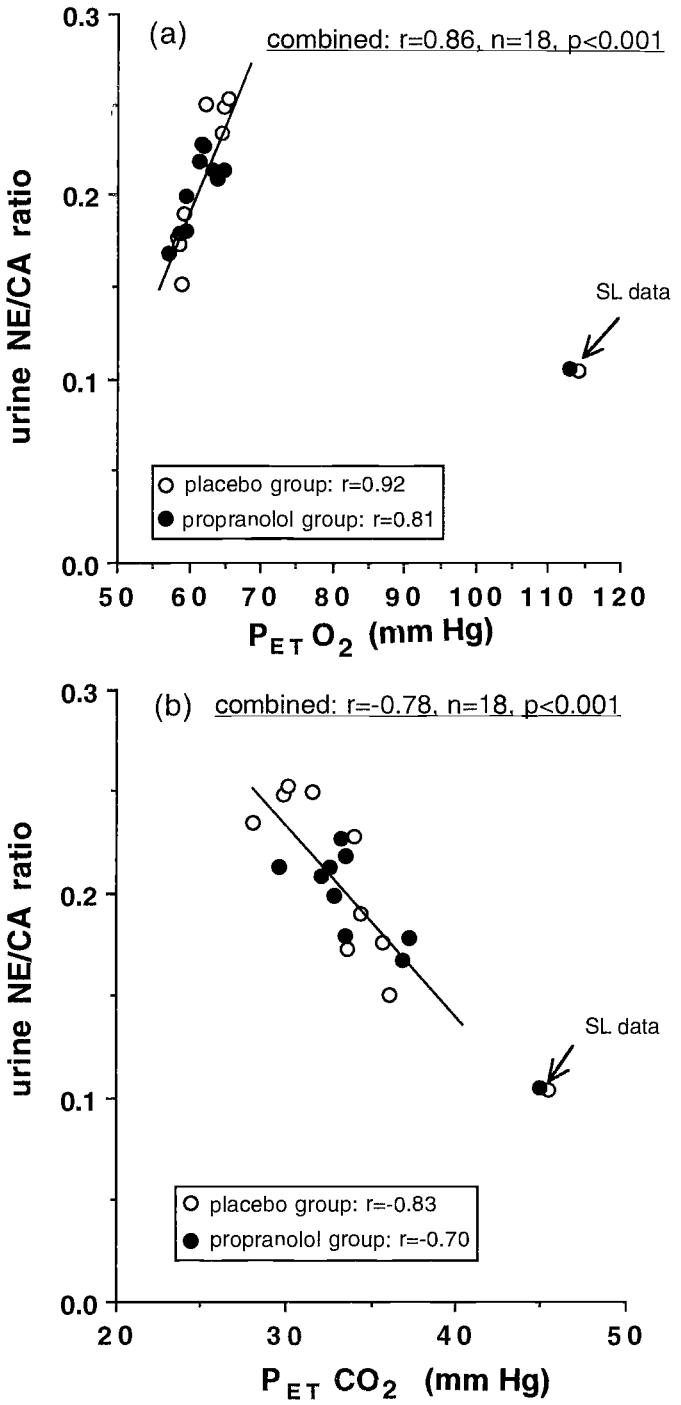

Fig. 4. (Panel a) Relation of daily mean excretion of norepinephrine (NE/CA) to daily mean end tidal O_2 pressure (P_{ETO_2}). (Panel b) Relation of daily mean excretion of norepinephrine (NE/CA) to daily mean end tidal CO_2 pressure (P_{ETCO_2}). Shown is the regression line and the correlation coefficient for the altitude data only.

relation to V_E ($r = 0.68$, $p < 0.01$) at high altitude for the combined group (**Fig. 5a**). The sea-level data fell sufficiently near the regression line that when they were included in the analysis, the correlations remained significant (combined group $r = 0.67$). Excretion of NE showed a significant positive correlation to V_T ($r = 0.83$, $p < 0.001$) at high altitude for the combined groups (Fig. 5b). The correlation remained significant (combined group $r = 0.65$) when the sea-level data were included.

As shown in Fig. 5, the propranolol treatment did not affect any relationships between NE excretion and venti-

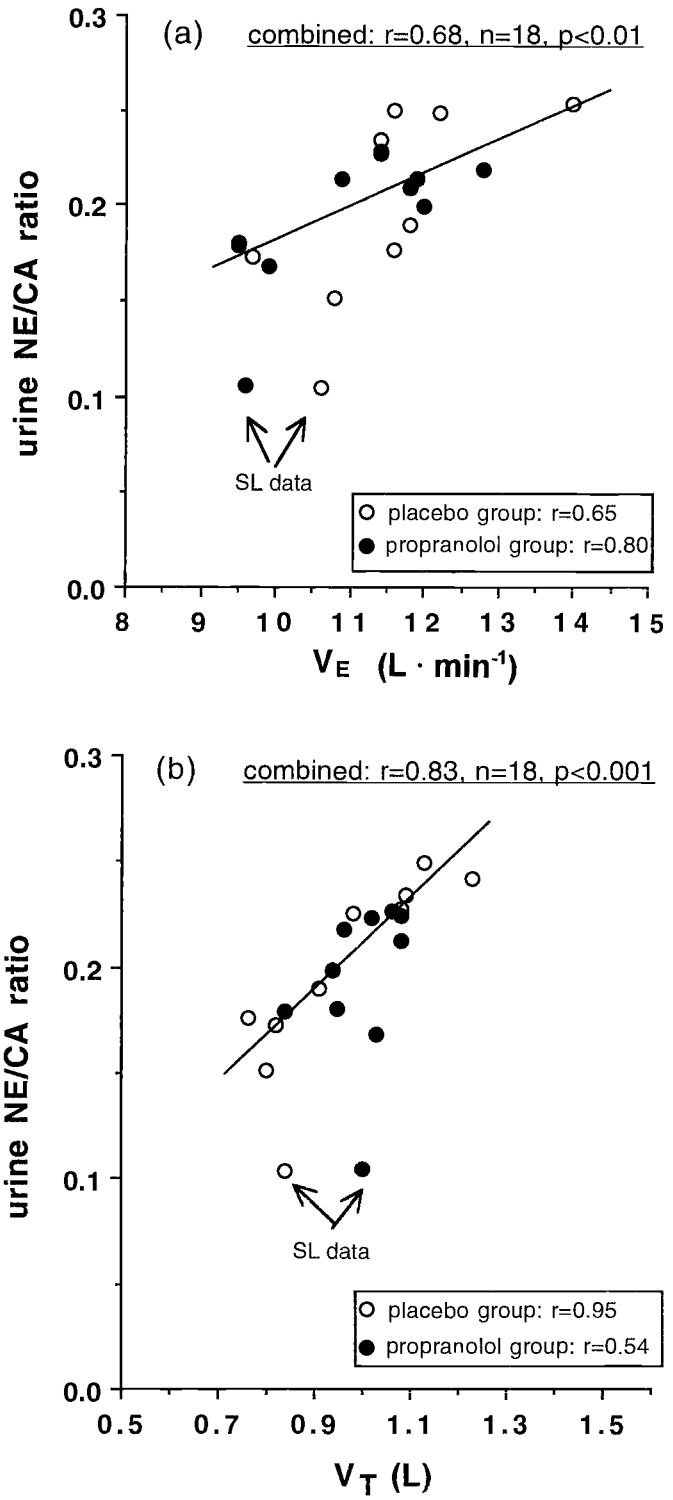

Fig. 5. (Panel a) Relation of daily mean excretion of norepinephrine (NE/CA) to daily mean minute ventilation (V_E). (Panel b) Relation of daily mean excretion of norepinephrine (NE/CA) to daily mean tidal volume (V_T). Shown is the regression line and the correlation coefficient for the altitude data only.

latory parameters, regardless of inclusion of the sea-level data.

There were no significant correlations of E excretion to any ventilatory parameters at altitude when the groups were examined separately or combined with regard to the propranolol treatment, or when the sea-level data were included (data not shown).

DISCUSSION

We studied the relationships between urinary catecholamine excretion and ventilatory acclimatization in normal subjects having measurements at sea level and repeatedly over time during a 21-d sojourn at 4300 m altitude. The main findings were that norepinephrine (NE) but not epinephrine (E) excretion rose progressively with the rising ventilation and falling $P_{ET}CO_2$ during the sojourn at high altitude.

Since acute hypoxia is known to induce both sympathetic activation and an increase in ventilation (1,4,12,14), hypoxia presumably contributed to the overall sympathetic activation indicated by an increase in NE excretion from sea level which was observed in the altitude sojourn. However, the hypoxic stimulus per se does not account for the progress of sympathetic activation seen from arrival to day 21 at altitude, because the hypoxic stimulus was decreasing; i.e., arterial PO_2 and $P_{ET}O_2$ were increasing, as a result of ventilatory acclimatization during the altitude sojourn. The resultant positive correlation of NE excretion to $P_{ET}O_2$ at altitude (Fig. 4a) was opposite to that expected if hypoxia itself determined the development of sympathetic activation at 4300 m. The main focus of present study was to explore why sympathetic activation further developed during 21 d at altitude despite the decreasing hypoxic stimulus.

The relevant findings for this question were that NE excretion correlated positively to V_E and V_T, and inversely to $P_{ET}CO_2$ during the altitude sojourn. The findings that the above relationships were maintained by including the sea-level data, unlike the relation for $P_{ET}O_2$, supported the much closer relationship of sympathetic activation to an increasing effective ventilation than to the hypoxic stimulus per se. Excretion of E did not correlate to any ventilatory parameters, suggesting unique relationships of NE excretion to ventilation. Thus, NE excretion was uniquely and closely related with two key ventilatory parameters (V_E and $P_{ET}CO_2$) independent of β-blockade, whether or not the sea-level data are included.

The correlations observed in the present study were consistent with a novel concept, namely, that progressive sympathetic activation and ventilatory acclimatization at high altitude may be related via some common regulatory mechanisms. Supporting evidence for such a concept from the literature should be stated. Sympathetic activity and ventilation are simultaneously increased by the acute stimulation of peripheral and central chemoreceptors (1,4,12,14). Also, in experimental animals chemoreceptor activation is known to stimulate neurons in the rostral, ventral, lateral medulla, which project to exclusive terminations on sympathetic preganglionic neurons in the thoraco-lumber portions of the spinal cord, which in turn, are thought to be primarily responsible for basal vasomotor tone (11). Thus, links exist between the sympathetic and ventilatory responses to acute hypoxia. During acclimatization to chronic hypoxia, ventilation further increases by opposing the restraints of hypocapnia resulting from the initial response to the acute hypoxic stimulus. Thus, ventilation increases as hypoxemia lessens. This phenomenon is considered to reflect increasing sensitivity of peripheral chemoreceptor to hypoxia (15), and to reflect potential central chemoreceptor activation which is manifested by the left-shift of the P_{CO_2}-ventilation relationship to a lower P_{CO_2} intercept such that the inhibitory effect of hypocapnia on ventilation is reduced (1,15). From the above, we postulate that the increasing drive from the chemoreceptors, despite the lesser hypoxic stimulus, is potentially responsible for both the ventilatory acclimatization and the development of sympathetic activation during the altitude sojourn.

The concept of a link between sympathetic activation and ventilatory acclimatization is speculative for two reasons. First, the experimental evidence presented is based on correlations which cannot establish cause and effect. Second, increasing sympathetic and chemoreceptor activity during acclimatization were assumed from indirect evidence. However, to our knowledge, the present study suggests for the first time that norepinephrine excretion (sympathetic neural output) at high altitude and the process of ventilatory acclimatization may be related to each other by complicated mechanisms which bear further investigation.

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