Effects of Acute Hypoxia at Moderate Altitude on Stroke Volume and Cardiac Output During Exercise

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SUMMARY

It has been unclear how acute hypoxia at moderate altitude affects stroke volume (SV), an index of cardiac function, during exercise. The present study was conducted to reveal whether acute normobaric hypoxia might alter SV during exercise.

Nine healthy male subjects performed maximal exercise testing under normobaric normoxic, and normobaric hypoxic conditions (O₂: 14.4%) in a randomized order. A novel thoracic impedance method was used to continuously measure SV and cardiac output (CO) during exercise.

Acute hypoxia decreased maximal work rate (hypoxia; 247 ± 6 [SE] versus normoxia; 267 ± 8 W, P < 0.005) and VO₂ max (hypoxia; 2761 ± 99 versus normoxia; 3039 ± 133 mL/min, P < 0.005). Under hypoxic conditions, SV and CO at maximal exercise decreased (SV: hypoxia; 145 ± 11 versus normoxia; 163 ± 11 mL, P < 0.05, CO: hypoxia; 26.7 ± 2.1 versus normoxia; 30.2 ± 1.8 L/min, P < 0.05). In acute hypoxia, SV during submaximal exercise at identical work rate decreased. Furthermore, in hypoxia, 4 of 9 subjects attained their highest SV at maximal exercise, while in normoxia, 8 of 9 subjects did.

Acute normobaric hypoxia attenuated the increment of SV and CO during exercise, and SV reached a plateau earlier under hypoxia than in normoxia. Cardiac function during exercise at this level of acute normobaric hypoxia might be attenuated. (Int Heart J 2010; 51: 170-175)

Key words: Normobaric hypoxia, Cardiac output, Oxygen uptake, Exercise testing

During ascent to a moderate to high altitude, individuals are exposed to progressive decreases in atmospheric pressure that lead to a reduction in inspired, alveolar, and arterial oxygen pressures. Training at moderate altitude (corresponding to 2000 - 3000 m) is associated with relatively severe hypoxemia during submaximal and maximal exercise, and acute hypoxia of this level decreases VO₂ max as well as exercise capacity. Thus, hypoxia at moderate altitude limits training intensity, which leads to relative deconditioning in elite athletes, although endurance athletes often use hypoxic training to improve sea-level performance. Because VO₂ is the product of cardiac output (CO) and the arterio-venous oxygen content difference (C(a-v)O₂), a decrease in VO₂ max at maximal exercise may be due to a decrease of either factor, or both.

Acute hypoxia may induce abnormalities in cardiac function and redistribution of CO not only at rest but also during exercise. In an animal study, CO at rest increased during acute severe hypoxia (FiO₂ 10% and 5%), and blood flow to all organs increased except for the skin and muscle. In humans under acute hypoxia, heart rate (HR) and CO increase while systemic vascular resistance decreases. Echocardiography also reveals altered mitral flow patterns, suggestive of mild LV diastolic dysfunction. Subacute hypoxia (FiO₂ 12%, simulating an altitude of approximately 4000 m) induced mild diastolic dysfunction in young healthy individuals.

Stroke volume (SV) increases as the work rate increases at low to moderate intensity exercise, but there is conflicting evidence as to whether SV does or does not decrease during maximal exercise in humans. Some previous reports demonstrated that SV did not decrease in young elite endurance athletes and in young healthy persons; whereas other reports demonstrated that SV decreased in older athletes and in young healthy persons. However, it is unclear whether acute hypoxia may induce cardiac dysfunction leading to the deterioration of the SV response to exercise, because it has been difficult to continuously measure SV during exercise.

Although in previous studies researchers investigated the acute effect of hypoxia on the CO response during maximal and/or submaximal exercise at moderate altitude (corresponding to 2500 - 3000 m), in only three studies the SV response was examined during exercise. However, in those investigations, SV was measured at only several time-points during exercise. Therefore, whether acute hypoxia at moderate altitude may alter the SV response during exercise has not been fully investigated.

CO measurement by the impedance method has been improved and can be used to continuously monitor SV, and
thereby CO, during exercise. Using this novel impedance method, previous studies have demonstrated that SV and CO can be continuously and accurately measured during exercise. Indeed, Charloux, et al demonstrated that CO measured by the impedance method was as accurate as that obtained with the Fick method during exercise in patients with chronic obstructive pulmonary disease. We hypothesized that acute hypoxia at a simulated moderate altitude (corresponding to 3000 m) might have a negative impact on cardiac function. The present study was conducted to clarify whether the SV response is altered during exercise under acute normobaric hypoxia.

**METHODS**

We enrolled 9 healthy male subjects (age, 26.9 ± 1.5 years old, height, 170.8 ± 2.1 cm, and body weight, 66.0 ± 1.7 kg). Physical examination and ECG showed they had no symptoms and no evidence of any significant disease. None had a history of pulmonary hypertension or high-altitude pulmonary edema. The present study was approved by the Japan Institute of Sports Sciences Ethics Committee in accordance with the Declaration of Helsinki regarding investigation in human subjects. Informed written consent was obtained from all subjects before their participation in the study.

**Hypoxic exposure:** Subjects were exposed to a normobaric hypoxic gas mixture containing 14.4% O2 (corresponding to an altitude of 3000 m) in a hypoxic chamber for about 15 minutes before and throughout the study. Exercise tests in conditions of normoxia and hypoxia were performed in a randomized order, with an interval of at least 3 days between them.

**Exercise protocol and expired gas analysis:** Before the study the subjects were asked to perform an exercise test, to get familiar with the procedures, during which expired gas was analyzed, and then a symptom-limited exercise test on an electromagnetically braked upright cycle ergometer (Rehcor 500P, Load, Holland) at least 2 hours after a meal. The exercise protocol and gas exchange analysis were performed as previously reported by Matsumoto, et al. In brief, after a 4-minute rest on the cycle ergometer, exercise was started at 50W for a 4-minute warm up and work rate was then increased in 1-W increments every 3 seconds. Blood pressure was measured using an automatic indirect cuff manometer (STBP-780, Colin, Aichi, Japan) every minute. Subjects stopped exercising because of leg fatigue or dyspnea. All subjects stopped exercise at the 19 or 20 level of the 6-20 Borg scale. Expired gases were measured continuously in all subjects on a breath-by-breath basis using an expired gas analyzer (AE-300S, Minato Medical Science, Osaka, Japan). Ventilatory parameters, including VO2, carbon dioxide output, and minute ventilation were calculated. ECG was monitored throughout the test to detect possible ECG signal abnormalities and percutaneous oxygen saturation (SpO2), an index of arterial O2 saturation, was measured continuously in all subjects (WEP-3214, Nihon Koden, Tokyo). The VO2 max was defined as the highest VO2 value at attainment of a plateau of VO2 with increasing intensity, a peak HR at least equal to 90% of age-predicted maximal HR, and respiratory exchange ratio (RER) > 1.10. In the present study, RER at maximal exercise was 1.15 - 1.29 under hypoxia and 1.11-1.27 under normoxia, thus we considered all exercise tests were performed until exhaustion.

**Derived parameters:** (C-a-v)O2 was calculated using the Fick principle: (C-a-v)O2 = VO2/CO. Total peripheral resistance (TPR) was calculated using the equation: TPR = 80 × mBP/CO, where mBP is the mean blood pressure.

**Statistics:** Differences between the means at each time point between groups were evaluated by two-way ANOVA for repeated measures followed by Tukey’s honesty significant difference statistics using JMP 7.0.1 software (SAS Institute, Cary, NC). The level of significance was set at P < 0.05. All data are shown as the mean value ± SE.

**RESULTS**

Under normobaric normoxia, there was an essentially linear increase in VO2 and HR as a function of the work rate. VO2 max was 3039 ± 133 mL/min (46.4 ± 2.5 mL/kg/min) (Figure 1). The percentage of the predicted values of VO2 max for normal Japanese of the same age and sex was 141 ± 7%, suggesting that our subjects were relatively well fit. CO also increased from 7.3 ± 0.5 L/min at rest to 30.2 ± 1.8 L/min at maximal exercise (Figure 2). SV progressively increased until maximal exercise (rest; 107 ± 8 mL, maximal exercise; 163 ± 11 mL, Table). SpO2 remained almost unchanged during exercise.

Under hypoxia, the maximal work rate was lower than that in normoxia (hypoxia; 247 ± 6 versus normoxia; 267 ± 8 W, P < 0.005). However, two of nine subjects (22%) did almost the same level of maximal exercise intensity under hypoxia as that under normoxia.
Table. Summary of Hemodynamic Variables, Oxygen Uptake, and Percutaneous Oxygen Saturation Under Normoxia and Hypoxia at Rest and the Maximal Exercise

<table>
<thead>
<tr>
<th></th>
<th>At rest</th>
<th>At maximal exercise</th>
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<tbody>
<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>70 ± 4</td>
<td>73 ± 4†</td>
</tr>
<tr>
<td>VO2 (mL/minute)</td>
<td>245 ± 11</td>
<td>264 ± 14</td>
</tr>
<tr>
<td>CO (L/minute)</td>
<td>7.3 ± 0.5</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>107 ± 8</td>
<td>103 ± 9</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>119 ± 4</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>72 ± 2</td>
<td>72 ± 5</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>98 ± 0</td>
<td>90 ± 1†</td>
</tr>
</tbody>
</table>

HR indicates heart rate; VO2, oxygen uptake; CO, cardiac output; SV, stroke volume; sBP, systolic blood pressure; dBP, diastolic blood pressure; and SpO2, percutaneous oxygen saturation. *P < 0.05, †P < 0.01, ‡P < 0.005, ¶P < 0.001 versus normoxia.

VO2 max was lower under hypoxia (hypoxia; 2761 ± 99 versus normoxia; 3039 ± 133 mL/min, P < 0.005), but VO2 for a given work rate was comparable with that for the same work rate in normoxia. Delta VO2 / delta work rate in hypoxia was lower than that in normoxia (hypoxia; 10.4 ± 0.3 versus normoxia; 11.0 ± 0.3 mL/min/W, P < 0.05). HR was higher than that in normoxia at rest, and at submaximal and maximal exercise with identical work rate (hypoxia; 181 ± 2 versus normoxia; 176 ± 3 bpm, P < 0.05), but HR at maximal exercise in hypoxia was similar to that in normoxia. RER at maximal exercise was similar to that in normoxia (hypoxia; 1.22 ± 0.02 versus 1.20 ± 0.02, P = NS).

CO at maximal exercise was reduced under hypoxia (hypoxia; 26.7 ± 2.1 versus normoxia; 30.2 ± 1.8 L/min, P < 0.05), but at identical work rate it was comparable with that in normoxia. SV was decreased at submaximal and maximal exercise of identical work rate and at maximal exercise (hypoxia; 145 ± 11 versus normoxia; 163 ± 11 mL, P < 0.05). C(a-v)O2 was comparable with that in normoxia at maximal exercise and at a comparable work load.

Percutaneous oxygen saturation (SpO2) was lower under hypoxia than that in normoxia at rest (hypoxia; 90.4 ± 1.1% versus normoxia; 98.3 ± 0.4%, P < 0.001) and de-
creased as the exercise intensity was increased; in addition, it was lower than that in normoxia (at maximal exercise: hypoxia; 82.1 ± 1.4% versus normoxia; 96.3 ± 1.0%, \( P < 0.001 \)). Acute hypoxia did not alter mBP or TPR during exercise.

Under hypoxia, SVI and CI at maximal exercise tended to correlate with the change in \( \text{SpO}_2 \) from rest to maximal exercise (\( P = 0.098 \) and \( P = 0.087 \), respectively, Figure 3).

The number of subjects who attained their highest SV at maximal exercise was smaller under hypoxia than that in normoxia (4 of 9 versus 8 of 9, \( P < 0.05 \), Figure 4). The %\( \text{VO}_2 \) max at the onset of the decrease of SV was lower than that in normoxia (hypoxia; 91.3 ± 3.3% versus normoxia; 98.2 ± 1.8%, \( P < 0.05 \)). CO progressively increased until exhaustion in all subjects both under normoxia and hypoxia (Figure 5). The variation in SV in relation to HR from 50W to maximal exercise (\( \text{SV}_{\text{max}} - \text{SV}_{\text{50W}} \) / (\( \text{HR}_{\text{max}} - \text{HR}_{\text{50W}} \)) was lower under hypoxia than that in normoxia (hypoxia; 0.28 ± 0.02 versus normoxia; 0.37 ± 0.04 mL/bpm, \( P < 0.05 \), Figure 6). The variation in CO in relation to HR from 50 W to maximal exercise (\( \text{CO}_{\text{max}} - \text{CO}_{\text{50W}} \) / (\( \text{HR}_{\text{max}} - \text{HR}_{\text{50W}} \)) was also lower than that in normoxia (hypoxia; 0.18 ± 0.01 versus normoxia; 0.21 ± 0.01 L/min/bpm, \( P < 0.05 \)).

**Discussion**

In the present study we continuously examined the SV response during exercise under normoxic and hypoxic conditions. Under acute hypoxia corresponding to an altitude of approximately 3000 m, \( \text{VO}_2 \) max as well as CO and SV at maximal exercise decreased. SV and CO also decreased in relation to HR. SV showed a plateau or decreased pattern at maximal exercise decreased. SV and CO also decreased in relation to HR. SV showed a plateau or decreased pattern at maximal exercise decreased.

**Figure 5.** Relation between individual cardiac output and heart rate in all subjects (dotted lines), and mean cardiac output response (solid line) at rest, as well as at 50W, 100W, 150W, 200W, and at maximal exercise under normoxia and hypoxia. Bars show the mean value ± SE.

**Figure 6.** Individual ratio of stroke volume and cardiac output increase in relation to heart rate was significantly lower under hypoxia than under normoxia. Bars show the mean value ± SE. \( P < 0.05 \) versus normoxia.

That in another report. On the other hand, Wasserman, *et al.* reported that an elderly male performed almost the same level of maximal exercise intensity under hypoxia (\( \text{FiO}_2 = 15\% \)) as that under normoxia. This discrepancy might be due to individual differences in the subjects, because 2 of 9 subjects (22%) did almost the same level of maximal exercise intensity under hypoxia as that under normoxia in the present study.

Because \( \text{VO}_2 \) max is the product of CO and C(a-v)\( \text{O}_2 \), the decrease in \( \text{VO}_2 \) max under hypoxia can be due to a decrease in either CO or C(a-v)\( \text{O}_2 \), or both, at maximal exercise. In the present study CO at maximal exercise decreased under acute normobaric hypoxia, confirming the finding of another report. Furthermore, acute hypoxia did not alter CO at a comparable work load during submaximal exercise, which was also in accordance with previous findings. Although under acute hypoxia at higher altitude (corresponding to 4000 - 5000 m) CO increases during low to submaximal exercise, the increase is probably due to a difference in the degree of hypoxia.

Since CO is the multiplication of SV and HR, one possible explanation for the decreased CO at maximal exercise could be a limit on maximal heart rate which decreases progressively with increasing altitude. However, maximal HR under hypoxia was similar to that attained during normoxic exercise in the present study. Moreover, we found that under acute hypoxia the relationship of CO versus HR decreased, suggesting that the decrease of maximal CO was not due to that of HR during exercise in hypoxic conditions.

It has not been clarified yet whether in healthy humans SV does or does not decrease before reaching exhaustion during maximal exercise. In the present study, 89% of the subjects attained their highest SV at maximal exercise, indicating that SV approaching volitional exhaustion does not decrease under normoxia in most young and healthy persons who are relatively well-fit. This finding was in accordance with that of a previous report showing that SV continued increasing until exhaustion in healthy subjects. Others reported that SV did not increase progressively until maximal exercise in healthy untrained subjects, and findings that are in contrast to those of the present study. The discrepancy might be due to differences in cardiac reserve during exercise, because in the present study SV at peak exercise was about 160 - 170 mL, while in others it was about 130 - 145 mL. Endurance-trained subjects have a larger blood volume than untrained subjects, and it is
known that their CO and SV increase when blood volume is augmented. Furthermore, in endurance-trained athletes an enhanced diastolic function allows for a more complete filling during the later stages of vigorous exercise. This continuous increase in SV until exhaustion could be explained by a greater left ventricular filling in well-trained athletes, which allows them to increasingly use the Frank-Starling mechanism throughout incremental exercise.

It is unknown whether acute hypoxia corresponding to that found at moderate altitude may affect the SV response to exercise. Echocardiography performed at rest shows that significant changes in LV filling pattern, as well as in LV myocardial relaxation are induced by high altitude. In the present study the SV response during exercise under acute hypoxia reached a plateau or decreased in more than half of the subjects, whereas in normoxia only 11% of the subjects showed such a pattern. This finding was in accordance with the previous result that SV leveled off at submaximal exercise in acute hypoxia whereas the highest values in normoxia were seen at exhaustion. Furthermore, in the present study the variation in SV as a function of HR, from 50W to maximal exercise, was significantly lower under hypoxia. Taken together these results showed that under acute hypoxia the SV response was attenuated leading to a decreased CO, which suggested that cardiac dysfunction might occur during exercise under acute hypoxic conditions.

We considered several possible mechanisms for this decrease in SV and CO during exercise under hypoxia. One possibility was that myocardial contractility could be depressed under acute hypoxia. However, cardiac contractility remained normal during exposure to altitude-induced hypoxia with preservation of the LV ejection fraction and LV percent fractional shortening during acute or subacute hypoxia. Therefore, the decrease in SV during exercise under hypoxia was not due to depressed myocardial contractility.

Another possibility was that acute hypoxia might have induced left ventricular diastolic dysfunction, and thereby an attenuated SV response during exercise. Bousiges, et al. reported that LV filling was modified under hypoxia in a hypobaric chamber (corresponding to altitudes of 5000, 7000, 8000 m), and that it may have been due to secondary impairment in LV relaxation caused by ventricular interdependence or hypoxia itself. An echocardiography-Doppler study in healthy subjects demonstrated that acute normobaric hypoxia (FiO₂ = 0.14) reduced LV diastolic function, although LV systolic function was well preserved. These results suggested that impaired LV diastolic function might play some role in the attenuated SV and CO response observed during exercise in the present study.

Still another possibility was that impaired right ventricular function due to hypoxia-induced pulmonary vasoconstriction attenuated the SV response during exercise under acute hypoxia. Acute hypoxia equivalent to that found at an altitude of 3000 m induces pulmonary arterial hypertension. Inhalation of 12.5% O₂ decreases arterial oxygen pressure to below 50 mmHg, and increases pulmonary vascular resistance because of constriction of precapillary arteries. Ghofrani, et al. demonstrated that sildenafil, a phosphodiesterase-5 inhibitor, inhibited hypoxic pulmonary vasoconstriction and reduced right ventricular afterload which, in turn, resulted in increased CO during exercise, and that improvement of oxygen transport to the exercising muscles increased the VO₂ max. These findings suggested that impaired right ventricular function due to hypoxia-induced pulmonary vasoconstriction might play a role in this attenuated SV and CO response during exercise.

The present study showed that under hypoxia, SpO₂ decreased as the exercise intensity increased, which was consistent with the findings of another study. The present study also showed that SVI and CI at the maximal exercise showed a positive correlation between the decrease in SpO₂ from rest to maximal exercise under hypoxia, although they did not reach statistical significance. These results suggested that a person who shows a greater decrease in SpO₂ during exercise will tend to have a smaller SVI and CI at maximal exercise. Therefore, acute hypoxia itself will probably lead to decreases in the SV and CO response during exercise.

In conclusion, the increment of SV and CO during exercise under acute normobaric hypoxia corresponding to that found at an altitude of about 3000 m is attenuated. Therefore, acute normobaric hypoxia at this level might affect cardiac function during exercise.

References

33. 1849-54.