Hyperbaric bradycardia and hypoventilation in exercising men: effects of ambient pressure and breathing gas

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Linnarsson, Dag, Anders Östlund, Folke Lind, and Carl Magnus Hesser. Hyperbaric bradycardia and hypoventilation in exercising men: effects of ambient pressure and breathing gas. J. Appl. Physiol. 87(4): 1428–1432, 1999.—We sought to determine whether hydrostatic pressure contributed to bradycardia and hypoventilation in hyperbaria. Eight men were studied during exercise at 50, 150, and 250 W while breathing 1) air at 1 bar, 2) helium-oxygen (He-O2) at 5.5 bar, 3) sulfur hexafluoride-oxygen (SF6-O2) at 1.3 bar, and 4) nitrogen-oxygen (N2-O2) at 5.5 bar. Gas densities were pairwise identical in 1) and 2), and 3) and 4), respectively. Increased hydrostatic pressure to 5.5 bar resulted in a modest but significant relative bradycardia on the order of 6 beats/min, in both the absence (1) vs. 2), P = 0.0015) and presence (3) vs. 4), P = 0.029) of gases that are both denser than normal and mildly narcotic. In contrast, ventilatory responses appeared not to be influenced by hydrostatic pressure. Also, the combined exposure to increased gas density and mild-to-moderate inert gas narcosis at a given hydrostatic pressure [1] vs. 3), 2) vs. 4)] caused bradycardia (P = 0.032 and 0.061, respectively) of similar magnitude as 5.5-bar hydrostatic pressure. At the same time there was relative hypoventilation at the two higher workloads. We conclude that heart rate control, but not vesatile control, is sensitive to relatively small increases in hydrostatic pressure.

METHODS
Subjects. Eight healthy male subjects were studied. Their age, weight, and height ranged from 27 to 34 yr, 73 to 96 kg and 174 to 186 cm, respectively. All had diving experience and had given their informed consent in agreement with the procedures required for approval by the ethical review board of Karolinska Institutet.

Equipment and procedure. The experimental conditions with four different breathing gas mixtures and three different ambient pressures are shown in Table 1, including partial pressures and densities of inspired gases. All gas mixtures were normoxic and contained either nitrogen (N2-O2), helium (He-O2), or sulfur hexafluoride (SF6-O2) as the inert diluent gas. The SF6 that was used in one of the breathing gas mixtures had undergone a special certification procedure, including batch analysis and bioassay, to ascertain that no toxic impurities were present (Montefluos, Italy). In each condition, the subject exercised continuously at three successive workloads, 50, 150, and 250 W, on an electrically braked cycle ergometer (Siemens Elema, Sweden). The duration of exercise at each workload was 5 min, to attain a physiological steady state. All experiments were performed in an 8-m3 hyperbaric chamber filled with air. Subjects breathed the 37°C humidified premixed gas from a Douglas bag by means of wide-bore tubing, a breathing valve, and a mouthpiece. Exercise was preceded by 15 min washin of the gas mixture. Ventilatory responses were measured as previously reported by Lind et al. (20). In brief, inspired gas flow was measured with a Venturi-type flowmeter, and an
analysis, together with hydrostatic pressure and density, as a possible cause of bradycardia and hyperventilation.

Statistical analysis. Data were analyzed by using a two-way, repeated-measures design of analysis of variance (Statistica 5.1, Statsoft, Tulsa, OK). The experimental design included two factors, exercise intensity (50, 150, and 250 W) and gas pressure condition (1.0-bar air, 5.5-bar He-O₂, 1.3-bar SF₆-O₂, and 5.5-bar N₂-O₂). In case of significant effect of a factor, post hoc pairwise comparisons were tested for significance by using Dunnett's test. Significance was accepted at the P < 0.05 level.

RESULTS

Respiratory and HR responses to exercise with the four different pressure and gas combinations are given in Table 2, and differences in ventilation (V̇I) and HR from air control are shown in Figs. 1 and 2.

HR (Fig. 1) was reduced by ~11 beats/min with 5.5-bar N₂-O₂ and by ~6 beats/min with 5.5-bar He-O₂ and 1.3-bar SF₆-O₂ compared with 1.0-bar air. These pressure and gas effects did not differ at different exercise intensities.

The general pattern of spontaneous ventilatory responses was that the conditions with high-density and inert gas narcosis led to significant and practically identical respiratory responses compared with air control, especially at the two higher exercise intensities. Respiratory data obtained with 5.5-bar He-O₂ on the other hand, were identical to those in air control at 1.0 bar. Therefore, respiratory variables will be analyzed in terms of a comparison between high-density (1.3-bar SF₆-O₂, 5.5-bar N₂-O₂) and normal-density (1.0-bar air, 5.5-bar He-O₂) conditions.

Ventilation (Fig. 2) showed a significant interaction between exercise condition and pressure+gas conditions (P < 0.001), with reductions of 12 and 21% at 150 and 250 W, respectively, in the high-density conditions compared with the normal-density conditions.

Respiratory rate (RR) (Table 2) showed a significant interaction between exercise condition and pressure+gas conditions (P = 0.002), with greater relative reduction in RR in the high-density conditions as exercise intensity was increased from 50 to 150 W (P = 0.013) and 250 W (P = 0.010).

Tidal volume and inspiratory time-to-total time ratio showed no significant differences between pressure+gas conditions, so that differences in V̇I between high-density and normal-density conditions did not reach statistical significance.

Table 1. Physical characteristics of inspired gas mixtures

<table>
<thead>
<tr>
<th>Gas Mixture</th>
<th>Partial Pressures of Inspired Gas, kPa</th>
<th>Density, kg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>He-O₂</td>
<td>5.5</td>
<td>1.11</td>
</tr>
<tr>
<td>SF₆-O₂</td>
<td>1.3</td>
<td>101</td>
</tr>
<tr>
<td>N₂-O₂</td>
<td>5.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

SF₆, sulfur hexafluoride. Partial pressures and densities are at BTPS conditions.

Table 2. Ventilatory variables and heart rate during steady-state dynamic leg exercise at 50, 150, and 250 W

<table>
<thead>
<tr>
<th>Variable</th>
<th>1.0-Bar Air</th>
<th>5.5-Bar He-O₂</th>
<th>1.3-Bar SF₆-O₂</th>
<th>5.5-Bar N₂-O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇I, l/min BTPS</td>
<td>25.1 ± 2.5</td>
<td>50.4 ± 2.9</td>
<td>90.0 ± 14.1</td>
<td>64.6 ± 2.3</td>
</tr>
<tr>
<td>V̇R, l/min BTPS</td>
<td>1.59 ± 0.17</td>
<td>2.71 ± 0.39</td>
<td>3.42 ± 0.44</td>
<td>1.80 ± 0.32</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>16.1 ± 1.9</td>
<td>19.3 ± 3.5</td>
<td>27.2 ± 6.6</td>
<td>15.5 ± 3.3</td>
</tr>
<tr>
<td>MVV, l/min BTPS</td>
<td>193 ± 19</td>
<td>210 ± 15</td>
<td>191 ± 18</td>
<td>210 ± 14</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>85 ± 9</td>
<td>117 ± 12</td>
<td>152 ± 14</td>
<td>78 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SE. V̇I, ventilation; V̇R, tidal volume; RR, respiratory rate; Ti/Tt, inspiratory duration-to-breath duration ratio; P₀.1, inspiratory occlusion pressure after 0.1 s; MVV, maximum voluntary ventilation; HR, heart rate. *Resting before 50 W. †Continued exercise at 250 W after measurements of SR and spontaneous V̇I. For explanation of conditions, see Table 1.
Density and normal-density conditions were entirely due to proportional differences in RR, with equal changes in inspiratory and expiratory durations.

$P_{0.1}$ showed significant interaction between exercise intensity and pressure-gas condition ($P = 0.049$), with increasingly greater differences between normal-density and high-density conditions as exercise intensity was increased from 50 ($P = 0.002$) to 150 ($P = 0.012$) and 250 W ($P = 0.005$).

MVV in the high-density conditions was markedly reduced to $\sim 50\%$ of that in the normal-density conditions ($P < 0.001$). Compared with resting conditions, MVV increased on the average 15–19 l/min during exercise, and there was no difference in this exercise-induced increase between conditions.

**DISCUSSION**

Hydrostatic pressure. The principal finding of this study was that increased hydrostatic pressure per se induced a bradycardia in exercising men (Fig. 1). Such bradycardia was observed both in the presence and in the absence of concomitant mild-to-moderate inert gas narcosis and concomitantly elevated gas density, as evidenced by a comparison between conditions of equal gas density but with different hydrostatic pressures. A hydrostatic pressure of 5.5 times normal ambient pressure represents a very modest elevation compared with the conditions used in most animal and tissue experiments in which hydrostatic-pressure-induced alterations of the function of excitable tissues have been observed (11, 12, 22, 24, 31, 32), but those researchers who have investigated animal models in this relatively low range of hydrostatic pressure (1, 29, 31) have found marked changes in cardiac function at pressures as low as 5 atmospheres.

The observation that the difference in HR between conditions was independent of work intensity suggests that a similar type of bradycardia would also be observed at rest. Indeed, relative bradycardia is also commonly observed in resting divers (16). Bradley et al. (2) found bradycardia of similar magnitude as in the present He-O$_2$ experiments in both resting and exercising subjects breathing 0.3-bar O$_2$ in 4.3-bar He compared with air-breathing control.

Our conclusion that increased hydrostatic pressure induces bradycardia in exercising men rests on the presumption that the two low-density conditions and the two high-density conditions differ in no other way than in hydrostatic pressure. Thus the He atmosphere is presumed to have no narcotic or other pharmacological effects at $\sim 5$-bar partial pressure. This presumption is supported by the fact that He has never been shown to exert any net narcotic effects even at pressures of $>100$ bar in animal models (4). Against this presumption is the observation that unanesthetized rats breathing He at atmospheric pressure have bradycardia compared with air-breathing control animals (19). Our interpretation, however, is strengthened by the observation that a hydrostatic pressure increase from 1.3 bar with SF$_6$O$_2$ to 5.5 bar with N$_2$O$_2$ also causes bradycardia, clearly without any involvement of He.

Also, our conclusion that hydrostatic pressure causes bradycardia in the combined presence of raised gas density and mild-to-moderate inert gas narcosis rests on the presumption that the narcotic effect of 101-kPa SF$_6$ is equivalent to that of 525-kPa N$_2$. Although not studied with respect to possible influences on cardiac function, the narcotic effect of SF$_6$ in terms of psychomotor impairment has been found to be approximately eight times larger than that of N$_2$ per unit partial pressure (27). Thus the degree of inert gas narcosis was similar but not identical in the two high-density conditions.

The present approach, with its comparison of conditions of equal gas density and similar degrees of inert gas sedation, precludes the establishment of a possible dose-response relationship between HR and hydrostatic pressure. An alternative approach, however, has been applied by Bradley et al. (2) and Salzano et al. (30). These authors studied HR responses to exercise in
a wide range of ambient pressures up to 30.6 bar (30), where the gas densities of the near-normoxic He-O₂ breathing mixtures varied with ambient pressure. On the assumption that HR was influenced by the increased density in proportion to the O₂ cost of breathing the dense gas, HR responses were analyzed as a function of Vₒ₂. For a given Vₒ₂ during submaximal exercise, HR was decreased by 6 beats/min at 4.6 bar (2), by 14–16 beats/min at 9.2–18.4 bar (2), and by 25–35 beats/min at 31.6 bar (30). These data support the notion of a dose-dependent effect of hydrostatic pressure on HR.

Reasoning similar to that applied to HR can be used to explain the respiratory responses (Fig. 2, Table 2). Conditions with identical gas density showed practically identical responses at all three workloads despite fivefold differences in hydrostatic pressure. This permits the conclusion that differences in hydrostatic pressure between 1.0-bar air and 5.5-bar He-O₂ and 1.3-bar SF₆-O₂ and 5.5-bar N₂-O₂, respectively, had no effect on respiratory responses. These respiratory responses include exercise hyperpnea, load-compensatory increases in central inspiratory activity, and exercise-induced enhancement of MVV.

Density and inert gas narcosis. The present findings of reduced ventilation at the two higher workloads and reduced MVV in the two high-density conditions agree well with previous data obtained under similar conditions (8, 9, 15, 21). Even though the present experimental design does not allow us to distinguish the specific influences of density and narcotic properties of the respired gas, data from other experiments in which degrees of inert gas narcosis similar to those in the present experiments were obtained with N₂O inhalation while normal gas density was maintained; Bradley and Dickson (3) and Fothergill and Carlson (10) reported slightly increased ventilation in exercising subjects during inhalation of 15–30% N₂O. Fothergill and Carlson also showed that the respiratory response to inspiratory flow-resistive loading was unchanged with 23% N₂O compared with air breathing. During resting conditions, responses to inspiratory loading have been found to be maintained with 39% inspired N₂O (25). In summary, therefore, on the assumption that N₂O results are representative for similar degrees of narcosis with N₂ and SF₆, inert gas narcosis is not likely to have contributed to the relative hypoventilation in the present high-density experiments.

Much less is known regarding possible effects of breathing gas properties on circulatory responses. Apart from possible narcotic influences on central control or effector organ level (6, 26, 28), there are multiple levels on which neural and mechanical outputs of respiration may interact with cardiovascular function with primary or secondary effects on HR. These levels include modulation by central inspiratory activity on the vagal control of HR and effects of breath-synchronous alterations of right ventricular diastolic filling on left ventricular output, with secondary baroreflex-induced HR variations (33). Several studies report data on HR during flow-resistive loading. Dressendorfer et al. (5) found no change in HR when inspiratory flow-resistive loading was imposed on subjects during submaximal exercise. Fothergill and Carlson (10) have shown similar results. Hesser et al. (13) studied bradycardic responses to 6.3-bar N₂ in sitting and standing subjects with and without CO₂-induced hyperpnea. They found the same degree of hyperbaric bradycardia in normocapnic eupnea and hypercapnic hyperpnea, suggesting that the increased respiratory neural and mechanical output had no net effect on the hyperbaric bradycardia during concomitant hypercapnia. Furthermore, they found that the bradycardia associated with inhalation of 6.3-bar N₂ developed gradually over time at a rate suggesting that uptake of N₂ in relatively slowly equilibrating tissues influenced the degree of bradycardia. These observations suggest that, apart from increased hydrostatic pressure, it is the narcotic property of the inert gas rather than the density and its associated effects on respiration that contributes to the hyperbaric bradycardia.

In contrast to these findings with hyperbaric N₂, measurements of steady-state exercise HR during inert gas narcosis with N₂O and normal gas density provide little support for the notion that inert gas narcosis causes bradycardia. Bradley and Dickson (3) found an unchanged HR with 15 and 30% N₂O compared with air in subjects exercising at 65 and 135 W. Fothergill and Carlson found no differences in steady-state-exercise HR values between air and 23% N₂O. In a recent study in our laboratory, subjects exercising at 100-W intensity had identical steady-state HR and blood pressures with and without 30% N₂O in both upright and supine postures (26). In contrast to steady-state HR, HR responses to baroreflex stimuli have been shown to be modified by inhalation of subanesthetic N₂O concentrations. Thus Ebert (6) demonstrated that, in resting humans, tachycardic responses to hypotensive stimuli were attenuated, and Ostlund et al. (28) came to a similar conclusion. In exercising men, Ostlund and Linnarsson (26) found not only attenuations of HR responses to both hyper- and hypotensive stimuli but also a prolongation of the baroreflex response latency with inhalation of 30% N₂O. The observation by Hesser et al. (13) that 6.3-bar N₂ induces a more marked bradycardic effect in the standing than in the sitting position lends further support to the notion that attenuated baroreflex responses of HR contribute to hyperbaric bradycardia. The consistent absence of steady-state bradycardia with N₂O, in contrast to hyperbaric N₂, and, in the present study, also to SF₆, might be explained by the intrinsic sympathostimulatory effect of N₂O (7), which may offset any bradycardic effects arising from baroreflex attenuation.

However, possible intrinsic sympathoexcitatory effects of N₂ and SF₆ have never been directly analyzed. Therefore, the above tentative explanation of the mechanisms for N₂- and SF₆-induced relative bradycardia and the absence of bradycardia in subjects breathing N₂O remains to be established experimentally.

Conclusions. Elevated hydrostatic pressure evoked bradycardia in exercising men. A narcotic influence of
inert gas may contribute further to hyperbaric bradycardia, but this latter effect cannot be separated from possible influences of increased gas density. Ventilatory responses to exercise appear not to be influenced by elevated hydrostatic pressure in the present range.

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