Ventilatory long-term facilitation in unanesthetized rats


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Ventilatory long-term facilitation in unanesthetized rats. J Appl Physiol 91: 709–716, 2001.—We tested the hypothesis that unanesthetized rats exhibit ventilatory long-term facilitation (LTF) after intermittent, but not continuous, hypoxia. Minute ventilation (Ve) and carbon dioxide production (VCO2) were measured in unanesthetized, unrestrained male Sprague-Dawley rats via barometric plethysmography before, during, and after exposure to continuous or intermittent hypoxia. Hypoxia was either isocapnic [inspired O2 fraction (FiO2) = 0.08–0.09 and inspired CO2 fraction (FiCO2) = 0.04] or poikilocapnic (FiO2 = 0.11 and FiCO2 = 0.00). Sixty minutes after intermittent hypoxia, Ve or Ve/VCO2 was significantly greater than baseline in both isocapnic and poikilocapnic conditions. In contrast, 60 min after continuous hypoxia, Ve and Ve/VCO2 were not significantly different from baseline values. These data demonstrate ventilatory LTF after intermittent hypoxia in unanesthetized rats. Ventilatory LTF appeared similar in its magnitude (after accounting for CO2 feedback), time course, and dependence on intermittent hypoxia to phrenic LTF previously observed in anesthetized, vagotomized, paralyzed rats.

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breathing anesthetized rats (16), we conducted experiments to determine whether ventilatory LTF can be observed in intact, unanesthetized, unrestrained rats. Furthermore, we investigated the dependence of ventilatory LTF on the degree of regulation of arterial CO\textsubscript{2} during hypoxia (isocapnic vs. poikilocapnic hypoxia) and the pattern of hypoxia (intermittent vs. continuous).

**METHODS**

The data reported were collected in two separate, collaborating laboratories, which will be designated as San Diego and Madison in instances when there are differences. Adult, male Sprague-Dawley rats were used (San Diego-Harlan, San Diego, CA; Madison-colony 236, Harlan Teklad, Madison, WI). Ventilatory and metabolic measurements were made using standard barometric plethysmography [San Diego (1); Madison (25)]. In selected rats, blood gases were measured in arterial blood obtained from chronically indwelling femoral artery catheters surgically placed at least 1 wk before sample withdrawal. Surgical, sampling, and analytic procedures for arterial blood-gas analysis have been described previously [San Diego (1); Madison (26, 27)]. Individual rats were placed within the plethysmograph chamber and maintained in normoxia for at least 1 h. Baseline ventilatory and metabolic measurements were then made. After the baseline measurements, one of four hypoxia protocols was followed: 1) isocapnic intermittent hypoxia, 2) isocapnic continuous hypoxia, 3) poikilocapnic intermittent hypoxia, or 4) poikilocapnic continuous hypoxia. Ventilatory measurements were made continuously and metabolic rates [O\textsubscript{2} uptake (V\textsubscript{O\textsubscript{2}}) and CO\textsubscript{2} production (V\textsubscript{CO\textsubscript{2}}) were measured during baseline and posthypoxia conditions].

**Protocols**

**Isocapnic intermittent hypoxia.** In San Diego, seven rats were exposed to the isocapnic intermittent hypoxia protocol, which consisted of five 3-min exposures to inspired O\textsubscript{2} fraction (F\textsubscript{IO\textsubscript{2}}) = 0.08–0.09 and inspired CO\textsubscript{2} fraction (F\textsubscript{ICO\textsubscript{2}}) = 0.04, interspersed with four 2-min exposures to F\textsubscript{IO\textsubscript{2}} = 0.50. Arterial blood drawn from five of the rats during the final hypoxic exposure had a P\textsubscript{O\textsubscript{2}} = 38 ± 1 Torr (mean ± 95% confidence limits) and a P\textsubscript{CO\textsubscript{2}} = 38 ± 2 Torr. In Madison, seven rats underwent a slightly different isocapnic intermittent hypoxia protocol, which was five 5-min exposures to F\textsubscript{IO\textsubscript{2}} = 0.09 and F\textsubscript{ICO\textsubscript{2}} = 0.04, interspersed with four 5-min exposures to F\textsubscript{IO\textsubscript{2}} = 0.21. In San Diego, five of the seven rats exposed to isocapnic intermittent hypoxia were administered supplemental CO\textsubscript{2} (F\textsubscript{ICO\textsubscript{2}} = 0.012–0.026) to reestablish isocapnia 60 min after intermittent hypoxia. Arterial blood drawn at this time from these five rats had a P\textsubscript{O\textsubscript{2}} = 97 ± 7 Torr and a P\textsubscript{CO\textsubscript{2}} = 41 ± 1 Torr.

**Isocapnic continuous hypoxia.** In San Diego, six rats were exposed to 25 min of continuous F\textsubscript{IO\textsubscript{2}} = 0.09–0.10 and F\textsubscript{ICO\textsubscript{2}} = 0.04. In Madison, eight rats were exposed to 120–300 min of F\textsubscript{IO\textsubscript{2}} = 0.10 and F\textsubscript{ICO\textsubscript{2}} = 0.04; the cumulative blood-gas experience for rats under these conditions in Madison is arterial P\textsubscript{O\textsubscript{2}} (P\textsubscript{A\textsubscript{O\textsubscript{2}}}) = 50 ± 1 Torr and arterial P\textsubscript{CO\textsubscript{2}} (P\textsubscript{A\textsubscript{CO\textsubscript{2}}}) = 39.9 ± 0.6 Torr (32 rats).

**Poikilocapnic intermittent hypoxia.** Twenty-four rats underwent five 5-min exposures to F\textsubscript{IO\textsubscript{2}} = 0.11, interspersed with 5-min exposures to F\textsubscript{IO\textsubscript{2}} = 0.21.

**Poikilocapnic continuous hypoxia.** Nine rats were exposed to 50-min of continuous F\textsubscript{IO\textsubscript{2}} = 0.11.

In each of the four protocols, ventilatory and metabolic measurements were made continuously for 1 h after the end of hypoxia while the plethysmograph was normoxic.

**Determination of V\textsubscript{CO\textsubscript{2}}**

In Madison, the flow-through plethysmograph system allowed the determination of V\textsubscript{O\textsubscript{2}} and V\textsubscript{CO\textsubscript{2}} using the difference in the ongoing measurement of O\textsubscript{2} and CO\textsubscript{2} flowing into and out of the chamber (25). In San Diego, V\textsubscript{O\textsubscript{2}} and V\textsubscript{CO\textsubscript{2}} were measured by sealing the plethysmograph for 3–6 min and measuring the decrease in F\textsubscript{IO\textsubscript{2}} and increase in F\textsubscript{ICO\textsubscript{2}} (~0.003) during this period by use of a mass spectrometer (1).

Nine rats were studied in both poikilocapnic continuous hypoxia and poikilocapnic intermittent hypoxia, and seven of these were later studied in isocapnic intermittent hypoxia. In these cases, at least 4 days were allowed between poikilocapnic continuous hypoxia and poikilocapnic intermittent hypoxia and at least 28 days between the poikilocapnic intermittent hypoxia and isocapnic intermittent hypoxia protocols. Sixteen rats were studied repeatedly (2–4 repetitions) using the same protocols: 12 rats in poikilocapnic intermittent hypoxia (some with 1 day recovery between sessions), and 4 other rats in isocapnic continuous hypoxia (at least 16 days recovery between sessions). Data for an individual rat were averaged when repetitive observations were made using the same protocol.

**Data Analysis**

Statistical analyses were performed using commercially available software (SigmaStat, Jandel Scientific, San Rafael, CA; EXCEL 2000, Microsoft). With one exception, two-way repeated-measures analysis of variance revealed no differences between the two laboratories in any ventilatory measurement. There was a significant difference between San Diego and Madison in minute ventilation (V\textsubscript{E}) [although not in tidal volume (V\textsubscript{T}) or frequency] determined during isocapnic continuous hypoxia (P = 0.046). This was most likely due to the somewhat lower F\textsubscript{IO\textsubscript{2}} used in San Diego during hypoxia. However, this difference during hypoxia did not result in any differences between laboratories during the baseline period or during the 1-h period of normoxia after hypoxia. Therefore, all data have been pooled and are presented as average data.

Because each individual rat was studied during baseline conditions before hypoxia and during the hour after hypoxia, we present ventilatory responses after hypoxia as the percent change from baseline. Differences from baseline measurements were determined using one-way repeated-measures analysis of variance. Individual comparisons were made using the Bonferroni t-test (SigmaStat, Jandel Scientific). Although most data were normally distributed, a few instances where the normality test failed are noted.

Data are presented as mean ± 95% confidence limits (with n indicating no. of rats) throughout. In cases where arterial blood-gas analysis was performed, P\textsubscript{ACO\textsubscript{2}} was used to calculate alveolar ventilation (V\textsubscript{A}). The equation used was V\textsubscript{A}/V\textsubscript{CO\textsubscript{2}} = (870 Torr)/P\textsubscript{ACO\textsubscript{2}}.

**RESULTS**

**Blood-Gas Values**

Ventilatory and metabolic rate measurements made in San Diego and Madison were equivalent. Therefore, all data have been pooled and are presented as average data. Blood-gas values were not obtained from the rats.
studied in Madison. In San Diego, arterial blood was obtained from seven rats during normoxic baseline conditions and in normoxia 60 min after isocapnic intermittent hypoxia. Because PaCO₂ significantly decreased from normoxic baseline conditions (41.4 ± 1.4 Torr) to normoxia 60 min after isocapnic intermittent hypoxia (39.4 ± 1.1 Torr) (P < 0.005), intermittent hypoxia initiated a persistent hyperventilation, suggesting LTF. Five of these seven rats exposed to isocapnic intermittent hypoxia were administered supplemental CO₂ 60 min after intermittent hypoxia to bring their PaCO₂ within 0.1 Torr below their original baseline PaCO₂ (40.7 ± 1.5 Torr at baseline, n = 5, vs. 40.6 ± 1.0 Torr 60 min posthypoxia with supplemental CO₂, n = 5). Four of the five rats had substantial increases in Vₑ after supplemental CO₂, with an overall average 29 ± 21% increase over the 60-min poikilocapnic Vₑ (n = 5).

For the 42 rats studied, overall baseline measurements were breathing frequency = 75 ± 3 breaths/min, Vₜ = 0.52 ± 0.04 ml/100 g, Vₑ = 38 ± 3 ml·min⁻¹·100 g⁻¹, VCO₂ = 1.4 ± 0.1 ml·min⁻¹·100 g⁻¹, and Vₑ/VCO₂ = 29 ± 2.

Isocapnic Intermittent Hypoxia

The stimulation of Vₑ, frequency, and Vₜ during isocapnic intermittent hypoxia and for the hour after isocapnic intermittent hypoxia is shown in Fig. 1. There is a significant, approximately fourfold increase in Vₑ during each of the five intermittent periods of isocapnic hypoxia. The Vₑ remained significantly elevated during the intervening periods with either hypoxia (San Diego) or normoxia (Madison). There are equivalent contributions of breathing frequency and Vₜ to the increase in Vₑ during hypoxia, although breathing frequency usually returned to levels that did not significantly differ from baseline during the periods between hypoxic exposures. Vₑ remained elevated 10 and 60 min after the final isocapnic episode (P < 0.05). At 60 min, the Vₑ elevation was primarily due to an elevation in frequency (P < 0.05), with no significant difference in VT.

Isocapnic Continuous Hypoxia

Isocapnic continuous hypoxia (Fig. 2) also produced an approximately fourfold increase in Vₑ, which is sustained for as long as the isocapnic hypoxia continues. Both breathing frequency and Vₜ are significantly elevated during this period, with breathing frequency making a somewhat greater contribution to Vₑ during the initial phase. After exposure to continuous isocapnic hypoxia, ventilatory measurements remained significantly elevated from baseline for ~20 min but were not significantly different from baseline levels for the remainder of the 60 min in normoxia.

Poikilocapnic Hypoxia

In contrast to isocapnic hypoxia, poikilocapnic hypoxia elicited a smaller increase in ventilation. There was a two- to threefold increase in Vₑ during exposure to poikilocapnic hypoxia (Figs. 3 and 4).

Poikilocapnic Intermittent Hypoxia

During the poikilocapnic intermittent hypoxia, Vₑ was significantly elevated over baseline during the four periods of normoxia separating the five hypoxic exposures. Vₑ fell toward baseline 10 min after the exposure to poikilocapnic intermittent hypoxia but was significantly elevated over baseline for the remainder of the 60-min period after poikilocapnic intermittent hypoxia. There appears to be comparable contributions of breathing frequency and Vₜ on the Vₑ time course before, during, and after poikilocapnic intermittent hypoxia. (Fig. 3).

Poikilocapnic Continuous Hypoxia

Figure 4 illustrates the ventilatory effects of poikilocapnic continuous hypoxia. As seen during poikilocap-
nic intermittent hypoxia (Fig. 3), there is a two- to threefold increase in \( \dot{V}E \) during continuous hypoxia. \( \dot{V}E \) fell to levels that were not significantly elevated over baseline by 30 min in normoxia and for the remainder of the 60-min period of normoxia. Although ventilatory frequency was significantly elevated at 50 min posthypoxia and \( V_T \) was significantly elevated at 60 min posthypoxia, there were no consistent effects of poikilocapnic continuous hypoxia on posthypoxic frequency or \( V_T \).

**Ventilatory Dead Space**

Arterial blood gases were only obtained in the isocapnic intermittent hypoxia experiments during baseline conditions and at 60 min posthypoxia. On the basis of these measurements in conjunction with \( V_E \) and \( V_{CO_2} \) measurements, the dead space-to-tidal volume ratio \( (V_{DS}/V_T) = (\dot{V}E/V_{CO_2} - V_A/V_{CO_2})/(\dot{V}E \text{ and } V_{CO_2}) \) (25) was calculated. Baseline \( V_{DS}/V_T \) was \( 0.3 \pm 0.2 \), and 1 h after isocapnic intermittent hypoxia, \( V_{DS}/V_T \) was \( 0.4 \pm 0.4 \) (\( n = 7 \)). There was no consistent significant change in \( V_{DS}/V_T \) before and after isocapnic intermittent hypoxia.

**Ventilation Relative to \( V_{CO_2} \)**

Our equipment design did not allow us to determine \( V_{CO_2} \) during intermittent hypoxia. However, we measured \( V_{CO_2} \) during baseline and during the 1-h period in normoxia after hypoxic exposure. Figures 5 and 6 contrast intermittent vs. continuous hypoxia effects on both \( \dot{V}E \) and \( V_E/V_{CO_2} \) during the 60 min after either isocapnic (Fig. 5) or poikilocapnic (Fig. 6) hypoxia, expressed as a percent change from baseline.

The data presented in Fig. 5 show that \( \dot{V}E \) was significantly elevated above baseline 20 min after exposure to either isocapnic continuous hypoxia or isocapnic intermittent hypoxia. However, at 40 and 60 min after continuous hypoxia, \( \dot{V}E \) was no longer significantly elevated over the baseline level (11 ± 24% at 60 min). In contrast, \( \dot{V}E \) was significantly elevated (22 ± 13%) from baseline 60 min after intermittent hypoxia. Similarly, \( \dot{V}E/V_{CO_2} \) was elevated significantly from baseline 20 min after continuous hypoxia but was no longer significantly elevated over baseline at 40 and 60 min (12 ± 16% at 60 min), whereas \( \dot{V}E/V_{CO_2} \) was not
significantly elevated over baseline 20 min after intermittent hypoxia but was significantly elevated at 40 and 60 min (27 ± 17% at 60 min; \( P < 0.05 \)). Hence, intermittent hypoxia was more effective than continuous hypoxia in inducing ventilatory LTF in unanesthetized rats when \( \text{PaCO}_2 \) was not allowed to decrease during the hypoxic exposure(s).

Responses after poikilocapnic hypoxia are summarized in Fig. 6. The \( \text{VE} \) measurements after poikilocapnic continuous hypoxia failed the test for normality \( (P = 0.003) \). Therefore, significance was assessed using one-way repeated-measures analysis of variance on ranks (SigmaStat, Jandel Scientific). With the use of this conservative approach, \( \text{VE} \) was significantly elevated over baseline 20 min after poikilocapnic continuous hypoxia but did not significantly differ from baseline at 40 and 60 min \( (31 \pm 28\% \text{ at } 60 \text{ min}) \). In contrast, all \( \text{VE} \) measurements made during the 60 min after poikilocapnic intermittent hypoxia were significantly elevated over baseline \( (17 \pm 9\% \text{ at } 60 \text{ min}) \). All \( \text{VE}/\text{VCO}_2 \) measurements made during the 60 min after poikilocapnic intermittent hypoxia are significantly elevated over baseline \( (20 \pm 9\% \text{ at } 60 \text{ min}) \), although not significantly greater than those with poikilocapnic continuous hypoxia \( (12 \pm 11\% \text{ at } 60 \text{ min}, \text{Fig. 6}) \).

In summary, \( \text{VE} \) decreased between 20 and 60 min after continuous hypoxia, whereas \( \text{VE} \) increased or stayed the same between 20 and 60 min after intermittent hypoxia (Figs. 5 and 6). \( \text{VE}/\text{VCO}_2 \) also decreased between 20 and 60 min after continuous hypoxia, whereas it increased over the same time period after intermittent hypoxia. Thus the data demonstrate ventilatory LTF after intermittent hypoxia in unanesthetized rats. The results also suggest that intermittent hypoxia (independent of the \( \text{CO}_2 \) level during hypoxia) is more effective than continuous hypoxia in triggering LTF of at least 60-min duration. However, the shorter period of elevated ventilation after continuous hypoxia \( (i.e., <40 \text{ min}; \text{Figs. 5 and 6}) \) may represent a form of LTF.

**DISCUSSION**

These studies are the first demonstration of ventilatory LTF in unanesthetized rats. In several important
respects (magnitude, duration, pattern), ventilatory LTF in unanesthetized rats is similar to phrenic LTF in anesthetized, vagotomized, and ventilated rats (3, 4, 12, 17) but is unlike the response of anesthetized, spontaneously breathing rats (16).

There are at least two explanations for the discrepancies between the present paper and the Janssen and Fregosi (16) study reporting that LTF cannot be evoked in spontaneously breathing rats. First, in contrast to the present study, Janssen and Fregosi studied anesthetized rats. As pointed out by these authors, anesthetized rats may need to be near the PaCO2 apneic threshold in order for LTF to be observed (16). Second, the Janssen and Fregosi study reporting that LTF cannot be evoked in anesthetized, vagotomized, and ventilated rats (3, 4, 12, 17) but is unlike the response of anesthetized, spontaneously breathing rats (16).

Figures 1–4 show that intermittent and continuous hypoxia have dramatically different effects on the time-course patterns of VE, VT, and breathing frequency. The absolute values of VE, VT, and frequency depend on the parallel metabolic activity of the rats and are therefore inherently more variable than ventilation expressed relative to an index of metabolic rate (for example, VE/VCO2 as shown in Figs. 5 and 6). It is not clear why some groups of rats have a higher baseline metabolic activity than others, but this variability explains the somewhat different levels of baseline VE occasionally observed (compare Figs. 1 and 2). For the most part, the presentation of the time courses of VT and frequency in Figs. 1B–4B demonstrates a balance between these two ventilatory parameters in generating the overall changes in VE.

Expressing the posthypoxia ventilatory data as a percent change from baseline (see Figs. 5 and 6) is analogous to previously published phrenic LTF data from anesthetized, paralyzed, vagotomized rats (3, 4, 12, 17), allowing a more direct comparison. With this normalization procedure, ventilatory LTF in unanesthetized rats has some of the same properties as phrenic LTF in anesthetized rats and has some differences. Specifically, ventilatory LTF in unanesthetized rats appears to have at least partial dependence on the pattern of hypoxia (intermittent, but not continuous) (4). The same pattern dependence is observed in unanesthetized ducks (24) and goats (8, 29). The time course of the ventilatory LTF that we observed in unanesthetized rats, a constant or slightly increasing VE/VCO2 during the 60 min after intermittent hypoxia (see Figs. 5 and 6), is similar to the progressively increasing time course of phrenic LTF after intermittent hypoxia (3, 4, 12, 17) but is notably longer than phrenic LTF after carotid sinus nerve stimulation in the same preparation (15, 18) or the minimal diaphragmatic LTF in anesthetized but spontaneously breathing rats after intermittent hypoxia (16).

There are some apparent differences between ventilatory LTF and phrenic LTF. The increase in phrenic amplitude 60 min after intermittent hypoxia in anesthetized rats has been reported as 63% (3), 37% (17), 78% (4), and 57% (13). In contrast, we observed an average increase of 22% in ventilation 60 min after intermittent hypoxia in unanesthetized rats. These apparent quantitative differences in LTF between continuous hypoxia elicits phrenic LTF (4). Phrenic LTF requires 5-HT-receptor activation (3, 17) during but not after intermittent hypoxia (13). The relevant 5-HT receptors are located in the spinal cord (6). Furthermore, phrenic LTF requires spinal protein synthesis (5), although the identity of the relevant spinal protein is not yet clear. Given the rapid pace of progress in understanding phrenic LTF in anesthetized rats, and reports that awake animals (21, 24, 29) or even anesthetized, spontaneously breathing rats (16) exhibit relatively small or short manifestations of LTF, it seemed important to determine whether rats, in fact, exhibit ventilatory LTF under more physiological conditions.
anesthetized, vagotomized rats vs. unanesthetized rats could reflect an inhibitory feedback in intact, spontaneously breathing rats, or could be related to differences inherent in our direct measurement of ventilation vs. assessment of phrenic nerve activity. We suggest that the major cause of quantitatively smaller ventilatory LTF in unanesthetized rats is the hypocapnic condition allowed posthypoxia. Specifically, with no inspired CO₂, Paco₂ would decrease due to ventilatory LTF, thereby reducing CO₂ chemoreceptor feedback and constraining ventilation. In support of this hypothesis, five of the seven rats exposed to isocapnic intermittent hypoxia (San Diego) were administered supplemental CO₂ 60 min after intermittent hypoxia to bring their Paco₂ within 0.1 Torr below their original baseline PaCO₂. Four of the five rats had substantial increases in ventilation, with an overall 29% increase over the 60-min poikilocapnic ventilation, indicating that our measurements of ventilatory LTF were low. A 29% increase, superimposed on the preexisting 22% increase, suggests an overall increase in ventilation of 57% above baseline under isocapnic conditions. A 57% ventilatory LTF is well within the range of values reported for phrenic LTF (3, 4, 13, 17).

There was an approximately fourfold increase in V˙E during isocapnic hypoxia (Figs. 1 and 2) vs. an approximately two- to threefold increase during poikilocapnic hypoxia (see Figs. 3 and 4). Nevertheless, ventilatory LTF after intermittent exposure to either isocapnic (Fig. 5) or poikilocapnic (Fig. 6) hypoxia was equivalent. Therefore, the magnitude of the ventilatory increase during hypoxia does not appear to be a critical determinant of ventilatory LTF. This conclusion is similar to the relative Pao₂ independence of phrenic LTF in anesthetized rats (11) but contrasts with the correlation between the hypoxic phrenic response and phrenic LTF magnitude (11). We are not aware of other laboratories having systematically compared ventilatory LTF after exposure to isocapnic or poikilocapnic intermittent hypoxia.

The evidence demonstrating ventilatory LTF in anesthetized rats is a significant, prolonged increase in V˙E and V˙E/CO₂ for at least 60 min after intermittent hypoxia (see Figs. 5 and 6). Although V˙E and V˙E/CO₂ were always significantly elevated over baseline at 60 min after intermittent hypoxia, V˙E and V˙E/CO₂ at this time were seldom significantly elevated over their respective values 60 min after continuous hypoxia. Thus it is difficult to clearly differentiate between these patterns of hypoxia. However, the time course of ventilation after hypoxia differs. Ventilation after continuous hypoxia is highest immediately after the hypoxia ends and then decreases progressively (Figs. 5 and 6). In contrast, immediately after intermittent hypoxia, ventilation is at its lowest (although still above baseline) and progressively increases with time. The peak ventilation after intermittent hypoxia occurs at least 30 min posthypoxia. This ventilatory pattern after intermittent hypoxia is a hallmark of phrenic LTF in the rat (4).

Previous studies have shown that there is an acute increase in V˙E/VT during continuous hypoxia (25). Nevertheless, V˙E/VT calculations presented in RESULTS, as well as previous experience, support the premise that an acute increase in physiological V˙E during hypoxia will have returned to normal within 60 min after return to normoxia (E. B. Olson, Jr., unpublished observation). Therefore, differences seen in V˙E/CO₂ values were not considered to be distorted by V˙E changes caused by hypoxia.

Ventilatory LTF after intermittent (usually isocapnic) hypoxia has been reported in several unanesthetized models including awake dogs (7), goats (28), and ducks (24) and in some sleeping humans (2). There have been equivocal findings in humans (21), and the existence of LTF in spontaneously breathing animals is not universally accepted (16). Our study is the first demonstration of ventilatory LTF in an unanesthetized animal that can be directly compared with anesthetized results from the same species and strain (3, 4, 12, 17). We are not aware of other laboratories having systematically compared ventilatory LTF after exposure to isocapnic or poikilocapnic intermittent hypoxia.

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