Short-term potentiation of ventilation after different levels of hypoxia

ASTRYD A. MENENDEZ, THOMAS J. NUCKTON, JOSE´ E. TORRES, AND DAVID GOZAL

Constance S. Kaufman Pulmonary Research Laboratory, Departments of Pediatrics and Physiology, Tulane University School of Medicine, New Orleans, Louisiana 70112

Menendez, Astryd A., Thomas J. Nuckton, Jose´ E. Torres, and David Gozal. Short-term potentiation of ventilation after different levels of hypoxia. J. Appl. Physiol. 86(5): 1478–1482, 1999.—Short-term potentiation of ventilation (VSTP) may be observed in healthy subjects on sudden termination of an hypoxic stimulus. We hypothesized that the level of hypoxia preceding normoxia would modify the duration and magnitude of the ensuing ventilatory decay. Ten healthy adults were studied on two different occasions, during which they were randomly exposed to isocapnic 6 or 10% O2 for 60 s and then switched to an isocapnic normoxic gas mixture. Both hypoxic gases induced significant ventilatory responses, and mean peak minute ventilation before the isocapnic normoxic switch was higher in 6% O2 (P < 0.001). The fast time constant of the two-exponential equation representing the best fit for ventilatory decay was unaffected by the magnitude of the hypoxic stimulus. However, the slow time constant, which is considered to represent VSTP, was markedly prolonged in 6% compared with 10% O2 [106.7 ± 11.3 vs. 38.2 ± 6.1 (SD) s, respectively; P < 0.0001]. This result indicates that VSTP is stimulus dependent. We conclude that the magnitude of hypoxia preceding a normoxic transient modifies VSTP characteristics. We speculate that the independence function of ventilatory stimulus and short-term potentiation is crucial for preservation of system stability during transitions from high to low ventilatory drives.

Methods

Subjects. Ten healthy adults (7 men; age 31.0 ± 3.7 yr) were studied after they signed an informed consent in regard to the experimental protocol, which had received approval from the Institutional Review Board. Pulmonary function tests. To evaluate ventilatory responses adequately, one must initially ensure that no significant mechanical limitation to airflow is present. Therefore, pulmonary function studies were performed in the laboratory, which was located near sea level (mean atmospheric pressure, 761 mmHg). The best forced vital capacity (FVC), forced expiratory volume in 1 s, mean forced expiratory flow (FEF) during the middle half of FVC (FEF25–75%), and maximal expiratory flow-volume curves were obtained from forced expiration into the wedge spirometer (DSIIa; Collins, Braintree, MA) and were corrected for STP. Individual test results were considered abnormal if they were more than ±2 SD from available reference values (6), and these results were thus excluded from the study. Mean FVC was 117 ± 8 (SE)% of predicted value, forced expiratory volume in 1 s was 97 ± 3% of predicted value, and FEF25–75% was 88 ± 5% predicted value. Ventilatory measurements. Subjects were studied while they were awake, sitting comfortably, wearing noseclips, and spontaneously breathing through a mouthpiece. All subjects were visually monitored to ensure that they did not fail...
asleep. O2 saturation was continuously measured by pulse oximetry (Nellcor 3000, Hayward, CA). Subjects were connected via the mouthpiece to a Hans Rudolph pneumotachograph and to a two-way nonrebreathing valve (Hans Rudolph, Kansas City, MO). PCO2 was sampled continuously at the expiratory port of the two-way valve and was analyzed breath-by-breath by using an infrared microcapnometer (Columbus Instruments, Columbus, OH). The gas monitor was calibrated with gas mixtures of known CO2 concentrations. The end-tidal expiratory CO2 tension (PETCO2) was held constant throughout the experiment at ~45 Torr. This was achieved by a custom-made microcomputer assembly (LabCL, National Instruments, Austin, TX), which provided control signals to the gas-flow controllers so that the CO2 composition of the inspired-gas mixture could be adjusted to the desired concentration. The dead space of this system was ~85 ml. During each test, expiratory flow was measured by using a heated pneumotach and a pressure transducer (Validyne, Northridge, CA). The signal was calibrated with a mechanically driven pump yielding 1,000-ml stroke volume at a frequency of 10 strokes/min. Corrections were made for changes in gas viscosity that were caused by warming the inspired-gas mixture, which was warmed and humidified immediately before the inspiratory port of the two-way, nonrebreathing respiratory valve.

Breath-by-breath tidal volume (VT) was obtained by analog integration of the flow signal. Analog-output channels were continuously displayed on-screen and were digitally acquired onto a Macintosh Personal Computer System at 125-Hz sampling frequency, as dictated by the Nyquist theorem (19), by using MacLab Digital Acquisition Software (ADI Instruments, Castle Hill, Australia). During subsequent off-line analysis, VT, inspiratory time (TI), and arterial O2 saturation were measured for each breath. From these measurements, expiratory time (TE), respiratory rate (RR; 60/VT+TE), and minute ventilation (VE) were calculated.

Hypoxic challenges. After an initial 2- to 4-min period of tidal breathing of an isocapnic normoxic gas mixture to establish a baseline, subjects were surreptitiously switched to hypoxic gases (P < 0.05 was considered to achieve statistical significance).

RESULTS

All 10 subjects completed at least three runs with each hypoxic gas mixture. Mean respiratory measurements in isocapnic normoxia as well as peak ventilatory responses to 10 and 6% O2 are shown in Table 1. Dose-dependent VE increases occurred after the switch to hypoxic gases (P < 0.001, ANOVA) and resulted from similar contributions by VT and RR (Table 1). Mean PETCO2 was 44.7 ± 1.7 and 45.1 ± 1.5 Torr at the end of the 10 and 6% O2 hypoxic runs, respectively (Fig. 1; P = not significant).

Table 1. Mean ventilatory measurements in 10 subjects during isocapnic normoxia and during isocapnic hypoxia with 10% and 6% O2

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>10% O2</th>
<th>P Value</th>
<th>Normoxia</th>
<th>6% O2</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>VE, l/min</td>
<td>7.16 ± 1.04</td>
<td>17.30 ± 1.94*</td>
<td>&lt;0.001</td>
<td>7.03 ± 1.17</td>
<td>27.47 ± 2.08*</td>
<td>&lt;0.001</td>
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<tr>
<td>VT, liters</td>
<td>0.52 ± 0.04</td>
<td>0.74 ± 0.12*</td>
<td>&lt;0.001</td>
<td>0.58 ± 0.03</td>
<td>0.94 ± 0.19*</td>
<td>&lt;0.001</td>
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<tr>
<td>RR, breaths/min</td>
<td>13.8 ± 1.2</td>
<td>23.3 ± 1.7*</td>
<td>&lt;0.001</td>
<td>13.1 ± 1.0</td>
<td>29.2 ± 2.8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>44.9 ± 0.73</td>
<td>44.8 ± 0.5</td>
<td>NS</td>
<td>44.9 ± 0.4</td>
<td>45.0 ± 0.3</td>
<td>NS</td>
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<tr>
<td>Ti, s</td>
<td>1.56 ± 0.21</td>
<td>1.12 ± 0.15</td>
<td>&lt;0.01</td>
<td>1.49 ± 0.22</td>
<td>0.92 ± 0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ti/Te</td>
<td>0.358 ± 0.037</td>
<td>0.445 ± 0.046</td>
<td>&lt;0.01</td>
<td>0.326 ± 0.039</td>
<td>0.439 ± 0.049</td>
<td>&lt;0.001</td>
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<tr>
<td>VT/Te, l/s</td>
<td>0.333 ± 0.046</td>
<td>0.661 ± 0.066*</td>
<td>&lt;0.002</td>
<td>0.354 ± 0.015</td>
<td>1.022 ± 0.103*</td>
<td>&lt;0.001</td>
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<tr>
<td>Nadir SaO2, %</td>
<td>98.6 ± 0.7</td>
<td>81.3 ± 2.7*</td>
<td>&lt;0.001</td>
<td>99.1 ± 0.6</td>
<td>74.2 ± 2.8*</td>
<td>&lt;0.001</td>
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</table>

Values are means ± SD; VE, minute ventilation; VT, tidal volume; RR, respiration rate; PETCO2, end-tidal CO2 pressure; Ti, inspiratory time; Te, expiratory time; Ttot, total time; SaO2, arterial O2 saturation; NS, not significant. P values are indicated for comparisons between normoxia and corresponding hypoxic condition. *Significant difference, 10% O2 vs. 6% O2, P < 0.01.
VE after the switch to isocapnic normoxia was best accounted for by a two-order exponential decay equation (Fig. 2). The mean fast time constant ($t_1^{\text{VE}}$) was 6.7 ± 1.3 s for the isocapnic normoxic recovery from 10% O$_2$ and 5.9 ± 1.4 s when 6% O$_2$ was administered (Table 2; $P$ = not significant). In contrast, as shown in Table 2, the slow component of ventilatory decay or VSTP ($t_2^{\text{VE}}$) was markedly prolonged in 6% compared with 10% O$_2$ (106.7 ± 11.3 vs. 38.2 ± 6.1 s, respectively; $P < 0.0001$).

DISCUSSION

In this study, we demonstrate that the magnitude of the excitatory respiratory stimulus that precedes its cessation markedly modifies the slow time constant of ventilatory decay, i.e., VSTP, without affecting the fast time constant.

The exact mechanism of VSTP after hypoxic stimuli has yet to be elucidated, but it is probably mediated by activation of a pontomedullary region(s) that receives afferent information from peripheral chemoreceptors. Centrally received information is then processed and modified to sustain ventilation after gas switches, such that a smooth transition from one condition to the other will occur, and large respiratory oscillations, ranging from apnea to hyperventilation, will be prevented (9, 24).

In this study, we selected 1-min hypoxic runs to minimize the central inhibition of hypoxia. Indeed, Dahan and colleagues (7) have recently shown that if 3- to 5-min hypoxic exposures are allowed, VSTP is significantly attenuated, probably reflecting the inhibitory effect of hypoxia on VSTP. Thus hypoxic duration emerges as an important modifier of the ventilatory expression of STP. Our results with mild hypoxic runs of 1-min duration are in close agreement with those reported by Dahan et al., who found a $t_1^{\text{VE}}$ of 4 s and a $t_2^{\text{VE}}$ of 30 s. The present study shows that, in addition to the duration of the hypoxic period that precedes the normoxic switch, the magnitude of the hypoxic stimulus will markedly modify the VSTP characteristics.

Several studies have examined VSTP in nonisocapnic conditions. Gleeson and Sweer (18) reported that $\dot{V}E$ by 10.2 ± 0.3 on June 8, 2017 http://jap.physiology.org/ Downloaded from

<table>
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<th>Subject No.</th>
<th>$t_1^{\text{VE}, 10% \text{O}_2}$</th>
<th>$t_1^{\text{VE}, 6% \text{O}_2}$</th>
<th>$t_2^{\text{VE}, 10% \text{O}_2}$</th>
<th>$t_2^{\text{VE}, 6% \text{O}_2}$</th>
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<td>36.4</td>
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<tr>
<td>10</td>
<td>6.1</td>
<td>7.0</td>
<td>89.3</td>
<td>37.3</td>
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</table>

Mean ± SD: $6.7 ± 1.3$ (10% O$_2$), $5.9 ± 1.4$ (6% O$_2$), $106.7 ± 11.3$ (10% O$_2$), $38.2 ± 6.1$ (6% O$_2$), *significant difference, 10% vs. 6% O$_2$, $P < 0.0001$. 

Fig. 1. Breath-by-breath minute ventilation ($\dot{V}E$; top) and end-tidal CO$_2$ pressure ($P_{\text{ETCO}_2}$; bottom) measurements in 1 representative subject after transition to isocapnic normoxia (arrow) after 1-min exposure to isocapnic 10% O$_2$ (○) and to 6% O$_2$ (●). Top: lines indicate 2-exponential best curve fit for each condition.

Fig. 2. Ensemble averages of breath-by-breath $\dot{V}E$ decay in 10 subjects after transition to isocapnic normoxia (arrow) after 1-min exposure to isocapnic 10% O$_2$ (○) and 6% O$_2$ (●). Bars, SE.
decreases below baseline after 10% O₂ if hypoxia was terminated with 100% O₂. However, hypoventilation was not present when room air was employed instead of 100% O₂ to terminate the short hypoxic exposure. Discrepant findings were reported by Georgopoulous and colleagues (14), who found no evidence of hypventilation in nine subjects, when they used 8.5% O₂ followed by hyperoxia. One possible explanation for such an apparent discrepancy could reside in the different magnitude of PETCO₂, decrease in the various studies, whereby the larger the PETCO₂ reduction, the more likely is hypventilation to occur in a hyperoxic background (14, 18). Thus the confounding contribution of hypocapnia will adversely affect any effort to obtain a true estimate of VSTP, such that tight control of an isocapnic state is necessary for accurate VSTP assessment (10, 11). In addition, it is difficult to compare the results derived from the present experiments that use a normoxic gas to terminate the hypoxic stimulus with those in which hyperoxia was employed (16), since hyperoxia has been shown to add an excitatory dimension to the ventilatory decay characteristics (7).

On the basis of most of the available animal and human experimental evidence on ventilatory STP, we propose that the central mechanism underlying VSTP is stimulus and state dependent and will also be modulated by the duration of the hypoxic exposure (4, 7, 9–11, 14, 18). For example, increased afferent peripheral chemoreceptor stimulation will induce more pronounced STP activation, which will be counterbalanced by the negative effects of more profound hypocapnia (if the PETCO₂ is not maintained constant) or by sleep (4, 7, 9–11, 14, 18).

Two additional considerations deserve comment. First, the actual PCO₂ in brain stem sites, during ventilatory transients such as those performed in our studies, may not be accurately represented by PETCO₂ measurements. If a linear correlation does not exist between PETCO₂ and brain stem P CO₂, the conclusions derived from the current study would be invalid or at least would be seriously challenged. However, we believe that the tight control of PETCO₂ throughout the experiments will prevent large fluctuations in brain stem P CO₂ levels. Nevertheless, despite such precautions, low arterial P O₂ will independently increase brain blood flow in a dose-dependent fashion and will modify tissue P CO₂ accordingly. Thus an attenuation, rather than an increase, in VSTP would have resulted from the latter consideration when 6% O₂ was employed. This obviously did not happen and suggests that, in our experimental setting, such concerns were of minor consequence, if any, to the magnitude of VSTP. Second, given a lung circulation time of 5–7 s (5, 22) and a respiratory frequency of 14–30 breaths/min, the hypoxic stimulus was effectively withdrawn after ~6–8 s of isocapnic normoxia. However, the real time required in each subject at each fraction of inspired O₂ for complete withdrawal of any residual hypoxic drive during the isocapnic normoxic transition was not measured, and this slightly biases the magnitude of τ Vₑ, albeit without detracting from the validity of our comparisons between 6 and 10% O₂. Finally, short-term exposures to hypoxia (e.g., 10 min) have been shown by Gallman and Millhorn (13) to elicit in the cat a long-term facilitation of respiratory output that appears to be diencephalon dependent and will occur only when milder hypoxic stimuli are applied (arterial P O₂ > 35 Torr). It is unclear whether such mechanisms that underlie long-term facilitation contributed to our findings.

The evolution of Vₑ decay paralleled that of Vₚ, whereas RR seemed to follow a less predictable pattern. Similar findings have been previously described by several investigators in animals (9–11, 25) and in humans (1, 4, 14, 16, 18). In contrast, Fregosi (12) reported that STP was more dependent on RR in a submaximal, steady-state exercise background. Together, these results suggest that pontine locations underlying STP mechanisms may more heavily involve volume- rather than rhythm-related neurons.

Since the original description of VSTP after hyperpnea by Gesell and White (17), this important mechanism has been demonstrated after short-term hypoxia and has been found to be of similar magnitude in young and older humans (1, 14, 24). However, significant reductions in VSTP were reported in adult patients with the obstructive sleep apnea syndrome (15), and, more recently, in patients with congestive heart failure (2, 3). Stimulus dependency of VSTP mechanisms, as shown in the present study, would predict that ventilatory instabilities, such as periodic breathing, would be more likely to occur with more severe O₂ desaturation episodes (3, 4).

In summary, we have shown that τ Vₑ as a measure of VSTP is stimulus dependent. The stimulus dependency of a stabilizing influence on respiratory output such as VSTP will further ensure swift transitions between moment-to-moment changes in excitatory and inhibitory inputs to respiratory drive.

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Address for reprint requests and other correspondence: D. Gozal, Section of Pediatric Pulmonology, SL-37, Tulane Univ. School of Medicine, 1430 Tulane Ave., New Orleans, LA 70112 (E-mail: dgozal@mcpop.tmc.tulane.edu).

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