

Ventilatory and Pulmonary Vascular Responses to Acute Hypoxia in Patients with Chronic Obstructive Lung Disease

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The present study was undertaken to examine the pulmonary vascular and ventilatory responses to acute hypoxia in chronic obstructive lung disease. Pulmonary hemodynamics, minute ventilation (V_E) and oxygen uptake (VO_2) were serially measured during inhalation of 13% O_2 for 15 min. There was a wide variability in the pulmonary vascular response to acute hypoxia. The initial increase in V_E and the magnitude of change in VO_2 were significantly lower in subjects developing a 25% or greater increase in mean pulmonary arterial pressure during hypoxic breathing. These results suggest that the ventilatory response to acute hypoxia plays a significant role in the pulmonary vascular response to acute hypoxia, and blunted initial ventilatory response to acute hypoxia may be a physiological adaptation to enhanced responses of pulmonary vessels.

Introduction

A rapid fall in alveolar oxygen tension causes constriction of pulmonary vessels and elevation of pulmonary arterial pressure. Since first reported in 1946 by Von Euler and Liljestrand¹⁾, this phenomenon, i. e., hypoxic pulmonary vasoconstriction (HPV), has been studied by several investigators. However, the mechanism underlying HPV is still unclear. The response of pulmonary vessels to acute alveolar hypoxia exhibits marked interspecies and intraspecies differences^{2,3)}. These differences have been attributed to the quantity of smooth muscles in the media of the pulmonary arteries⁴⁾, to differences in the release of mediators induced by the direct effect of acute hypoxia⁵⁾ or to a restricted collateral ventilation^{6,7)}. Although various studies investigated the response of pulmonary vessels to acute hypoxia in healthy individuals⁸⁻¹⁶⁾, the magnitude of the resultant rise in pulmonary arterial pressure varied among different reports. Abraham et al.¹⁷⁾, who studied patients with chronic bronchitis, reported a negative correlation between arterial oxygen saturation and pulmonary arterial pressure during hypoxic inhalation. Weitzenblum et al.¹⁸⁾, who studied patients with the same disease, reported that the response of pulmonary vessels to acute hypoxia varied among individual patients, and that some patients showed little rise in pulmonary arterial

pressure despite a marked reduction in arterial oxygen saturation.

High-altitude pulmonary edema (HAPE) develops when healthy individuals without a past history of cardiopulmonary disease rise rapidly to high altitudes. Factors involved in the onset of HAPE include hypoxia, hypobaric, cold environment and exercise (factors prevailing in high altitudes), in addition to other predisposing factors. Of these factors, hypoxia has been the focus of attention, and its effect on the living body has been studied extensively. It has been recognized that the intensity of HPV plays a major role in the development of HAPE. Previous studies examining the hypoxic ventilatory response (HVR) in HAPE-susceptible subjects revealed a significantly reduced HVR in HAPE-susceptible subjects compared with control subjects¹⁹⁻²²⁾. This finding suggests that low HVR could be a predisposing factor for HAPE.

The present study was undertaken to serially measure pulmonary hemodynamics and ventilation in patients with chronic obstructive lung disease (COLD) during inhalation of a hypoxic gas mixture. The protocol allowed assessment of the relationship between the response of pulmonary vessels and ventilatory function.

Subjects and Methods

Subjects

The subjects consisted of 21 patients (15 males and 6 females) with COLD such as chronic pulmonary emphysema or diffuse panbronchiolitis (excluding bronchial asthma) diagnosed based on physical findings, chest X-ray films, pulmonary function test, selective alveolar bronchography, transbronchial lung biopsy or open lung biopsy. The condition of each patient was clinically stable at the time of this study. Table 1 summarizes the age distribution, pulmonary function tests and arterial blood gases. All subjects gave informed consent.

Methods

In the evening before the day of the planned examination, drugs that affect the circulation or central nervous

TABLE 1. Characteristics of subjects

	COLD
n	21
Age, yr	63.3±2.5
FEV ₁ /FVC, %	57.5±3.2
VC, % predicted	93.0±5.6
DLco, % predicted	68.8±5.0
PaCO ₂ , Torr	34.5±0.7
PaO ₂ , Torr	77.2±2.4
SaO ₂ , %	94.9±0.4
pH	7.403±0.005

EFV₁/FVC, percent of forced VC expired in 1s; VC, vital capacity; DLco, CO diffusing capacity; PaCO₂ arterial CO₂ tension; PaO₂, arterial O₂ tension; SaO₂, arterial O₂ saturation;

system were suspended. No food or premedication were given in the morning on the days of examination. Right heart catheterization was performed with the subject in the supine position, using a Swan-Ganz catheter (Model TF002H-7F, Baxter Healthcare Corporation) introduced via the femoral vein. Arterial pressure measurements and arterial blood sampling were made through an introducer in the femoral artery. Intravascular pressure was measured relative to atmospheric pressure with a zero reference point at the mid-axillary line. We measured the mean pulmonary capillary wedge pressure (PCWP), mean pulmonary arterial pressure (MPAP) and mean arterial pressure (MAP). In addition, cardiac output (CO) was determined by the thermodilution technique, using REF-1 ejection fraction/cardiac output computer (Edwards Critical Care Division). Total pulmonary resistance (TPR) was calculated, using the following equation:

$$\text{TPR} = \text{MPAP}/\text{CO} \times 80 \text{ (dyne} \cdot \text{sec} \cdot \text{cm}^{-5}\text{)}.$$

Arterial blood gases were measured with a Ciba-Corning pH/blood gas analyzer fitted with a co-oximeter. Minute ventilation (\dot{V}_E) and oxygen uptake ($\dot{V}O_2$) was measured using a respirometer (RM-300 System DHC, Minato Medical Corporation). Using a Douglas bag fitted with a unidirectional valve, it was possible to change the composition of inspired air from that of room air to a hypoxic gas mixture of 13% O₂ in N₂. Pulmonary function tests were examined one week prior to the measurement of ventilation and hemodynamics, using an Autspirometer System 9.

Protocol

When the Swan-Ganz catheter was checked to be in the proper position, the subject was connected to the respirometer via a tightly fitting face mask. A period of ten minutes was allowed for adaptation to the recording system and stabilization of measurement of hemodynamic and ventilation variables during room air breathing. Measurement of MPAP, MAP, CO commenced thereafter,

TABLE 2. Hemodynamics and blood gases

	FIO ₂	21 %	13 %	p
HR, beats/min		73.9±2.7	87.8±5.0	< 0.01
CO, L/min		5.4±0.3	6.2±0.3	< 0.001
SV, ml		74.1±3.5	73.5±2.6	NS
MPAP, mmHg		15.3±0.7	19.0±1.2	< 0.001
PCWP, mmHg		3.9±0.8	3.7±0.8	NS
MAP, mmHg		96.1±4.3	99.7±4.7	NS
TPR, dyne·sec·cm ⁻⁵		241±19	259±21	< 0.05
PaCO ₂ , Torr		34.5±0.7	32.1±0.8	< 0.01
PaO ₂ , Torr		77.2±2.4	43.5±1.3	< 0.001
SaO ₂ , %		94.9±0.4	79.7±1.4	< 0.001

FIO₂, fractional inspiratory oxygen; HR, heart rate; CO, cardiac output; SV, stroke volume; MPAP, mean pulmonary arterial pressure; PCWP, mean pulmonary capillary wedge pressure; MAP, mean arterial pressure; TPR, total pulmonary resistance;

in addition to \dot{V}_E and $\dot{V}O_2$. Blood samples were simultaneously withdrawn from the femoral and pulmonary arteries. After measurements in room air were completed, FIO₂ was lowered to 13% and MPAP, MAP, \dot{V}_E and $\dot{V}O_2$ were monitored. After 15 minutes, when ventilation and vascular pressures were again steady, measurements of MPAP, MAP, \dot{V}_E , $\dot{V}O_2$ and CO were repeated and blood samples were withdrawn again. The patients were then disconnected from the respirometer.

Statistics

Values are expressed as mean ± SEM. A paired t-test was used to compare measurements within groups while unpaired t-test was used to compare measurements between groups. Comparisons were considered significant at $p < 0.05$.

Results

During room air inhalation, HR, CO, MPAP, PCWP and MAP were 73.9±2.7 beats/min, 5.4±0.3 L/min, 15.3±0.7 mmHg, 3.9±0.8 mmHg and 96.1±4.3 mmHg, respectively. Table 2 summarizes the changes in hemodynamic parameters and blood gases during hypoxia. Reduced arterial oxygen tension and arterial oxygen saturation levels significantly augmented CO and increased HR. However, stroke volume and MAP remained unchanged during hypoxia, while MPAP and TPR were significantly elevated.

Subjects developing a 25% or greater increase in MPAP during hypoxic breathing (i. e., % Δ MPAP \geq 25%) were classified as responders, while those developing < 25% increase in this parameter were classified as non-responders. The magnitude of change in TPR (Δ TPR) was significantly greater in responders compared with

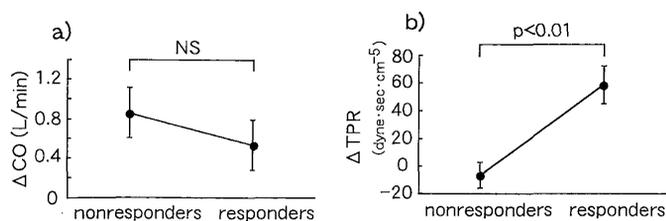


Fig. 1. Comparison of the increase in CO (Δ CO) and the magnitude of change in TPR (Δ TPR) between nonresponders and responders

nonresponders, while the change in CO (Δ CO) did not differ significantly between the two groups (Fig. 1). There were no significant differences in pulmonary function tests, arterial blood gases, hemodynamic parameters, \dot{V}_E or $\dot{V}O_2$ between responders and nonresponders during room air breathing (Table 3). On the commencement of breathing of hypoxic gas mixture, \dot{V}_E increased initially but gradually declined to a steady state. When the difference between the baseline \dot{V}_E and peak \dot{V}_E was expressed as $\Delta \dot{V}_E$ and the magnitude of change in $\dot{V}O_2$ was expressed as $\Delta \dot{V}O_2$, $\Delta \dot{V}_E$ and $\Delta \dot{V}O_2$ were significantly lower in responders than in nonresponders (Table 3).

Discussion

The findings of the present study suggest that the pulmonary vascular response to hypoxia varied among subjects and that it could not be predicted using tests performed during resting ventilation. In addition, our results suggested that ventilatory response to acute hypoxia plays an important role in the pulmonary vascular response to acute hypoxia.

It is generally accepted that the rise in pulmonary arterial pressure during acute hypoxia in healthy subjects is due to the combined effect of increased pulmonary vascular resistance and increased CO^{8,10,16}. In COLD patients with pulmonary hypertension, Saadjian et al.²³ showed that hypoxic breathing further increased MPAP but did not affect CO. A significant elevation in MPAP, TPR and CO was observed during hypoxic breathing in our subjects. Δ TPR was significantly high in responders compared with nonresponders, while Δ CO was not different between the two groups (Fig. 1). This finding suggests that the magnitude of rise in pulmonary arterial pressure during hypoxia depends on pulmonary vascular reactivity.

There was a wide variability in pulmonary vascular response to acute hypoxia in the present study. Sixty-two percent of subjects appeared to be nonresponders to hypoxia. Similarly, a wide variability in pulmonary vascular response was also observed, ranging from a complete lack of response to a marked elevation of pulmonary arterial pressure. In 11 normal subjects investigated

TABLE 3. Comparison of main functional and hemodynamic data between nonresponders and responders

	nonresponders	responders
n	13	8
Age, yr	61.2±3.8	66.8±1.6
FEV ₁ /FVC, %	57.4±4.4	57.7±5.0
VC, % predicted	86.3±5.8	103.9±10.7
DLco, % predicted	71.7±5.5	65.0±9.9
PaO ₂ , Torr	77.3±2.9	76.9±4.5
SaO ₂ , %	95.0±0.5	94.7±0.8
PvO ₂ , Torr	38.4±0.9	37.5±1.1
SvO ₂ , %	71.8±1.5	70.0±1.8
CO, L/min	5.4±0.4	5.4±0.3
MPAP, mmHg	14.6±0.8	15.1±1.7
TPR, dyne·sec·cm ⁻⁵	241±27	241±25
\dot{V}_E , L/min	10.83±0.6	9.99±0.8
$\dot{V}O_2$, ml/min	216.7±16.8	225.8±18.6
$\Delta \dot{V}_E$, L/min	3.66±0.50	2.05±0.22*
$\Delta \dot{V}O_2$, ml/min	19.0±14.8	-37.3±16.22*

\dot{V}_E , minute ventilation; $\dot{V}O_2$, O₂ uptake; $\Delta \dot{V}_E$, early increase in ventilation; $\Delta \dot{V}O_2$, early change in O₂ uptake; *p < 0.05 in responders compared with nonresponders

by Beard et al.⁸, 28 % failed to respond to hypoxia (FIO₂ = 12 %). In addition, 36 % of 17 normal subjects studied by Fritts et al.¹¹ were also nonresponders to hypoxia (FIO₂ = 12-14 %). Furthermore, 50 % of 10 normal subjects investigated by Fishman et al.¹⁰ also failed to respond to hypoxia (FIO₂ = 12-14 %). In chronic bronchitis, nearly 50 % of the patients studied by Weitenblum et al.¹⁶ appeared to be nonresponders to hypoxia (FIO₂ = 13 %). However, such variability in hemodynamic response to acute hypoxia was not observed by Doyle et al.⁹ when testing eight normal subjects where all subjects responded to hypoxia (FIO₂ = 10 %).

Our results indicated that there were no significant differences in pulmonary function tests, arterial blood gases, hemodynamics, \dot{V}_E and $\dot{V}O_2$ during resting breathing, between responders and nonresponders (Table 3). Thus, differences in the response of pulmonary vessels to hypoxic breathing could not be predicted by test performed before hypoxic inhalation. The response of pulmonary vasculature to acute hypoxia also varied among individual subjects, suggesting that this response is closely related to predisposing factors.

The measurement of HVR often employs maintenance of a stable isocapnia, as first described by Weil et al.²⁴. We measured \dot{V}_E during 13 % O₂ inhalation and analyzed $\Delta \dot{V}_E$ as an index of chemostimulation. PaCO₂ was measured under poikilocapnic conditions in our experiment, without adding CO₂ to the breathing circuit. Since the change in PaCO₂ was minimal, CO₂ seemed to be less affected by hypoxic breathing. In this regard, Easton et al.²⁵ reported

that hypoxic ventilatory depression, when assessed under isocapnic conditions, did not differ from that measured under poikilocapnic conditions.

Matsuzawa et al.²¹⁾ reported that HAPE-susceptible subjects showed significantly lower HVR than control subjects. Furthermore, Hackett et al.¹⁹⁾ demonstrated that HAPE patients had significantly lower HVR during their illness compared with control subjects. In the present study, $\Delta \dot{V}_E$ were significantly lower in responders than in nonresponders. These results support the view that a blunted ventilatory response to acute hypoxic stimulation makes constriction of pulmonary vessels more likely to occur. It would seem, therefore, that the ventilatory response to acute hypoxia plays an important role in the pulmonary vascular response to acute hypoxia.

Hypoxia basically elevates ventilation by stimulating the respiratory center (the medulla oblongata) mediated by peripheral chemoreceptors. However its direct action on the central nervous system (CNS) or its indirect CNS action mediated by an increased cerebral blood flow leads to suppression of ventilation²⁶⁾. Ventilatory responses to hypoxia are therefore a total of these effects (respiratory stimulation via peripheral chemoreceptors + respiratory suppression due to its effects on the CNS). In the present study, $\Delta \dot{V}_E$ were significantly lower in responders than in nonresponders. This means that HVD was more marked in responders than in nonresponders. Neonatal or juvenile warm-blood animals are more likely to develop HVD and tend to show a reduction in metabolic rate or $\dot{V}O_2$ when exposed to hypoxia^{27, 28)}. In the present study, $\Delta \dot{V}O_2$ was lower in responders than in nonresponders. Suppression of ventilation in response to hypoxic stimuli appears to be quite unnatural when viewed from the standpoint of oxygen supply and seems to be inappropriate from the viewpoint of homeostasis in the living body. However, analyses of the manner by which cells adapt themselves to hypoxia indicate that it fits the purpose of survival to suppress metabolism so that the energy needed for the membranous ion gradient (most important to keep the cell viable) can be minimized. The blunted initial ventilatory response to acute hypoxia, observed in the present study, may be a physiological adaptation to enhanced responses of pulmonary vessels.

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