Enhanced Hypoxic Pulmonary Vasoconstriction in Hypertension

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In this study, we tested the hypothesis that hypoxic pulmonary vasoconstriction may be enhanced in systemic hypertension. The hypothesis took origin from the following two considerations: alveolar hypoxia constricts the pulmonary vessels by enhancing the Ca²⁺ penetration across sarcolemma of the smooth muscle cells and systemic high blood pressure is associated with an elevation of tone and reactivity of the lung vessels, which seems to depend on an excessive cytosol free Ca²⁺ concentration due to alterations in sodium handling and in the Na⁺-Ca²⁺ exchange system. These considerations suggest the possibility that the disorders in the biochemistry of smooth muscle contraction in hypertension facilitate the rise of cytosol Ca²⁺ concentration during alveolar hypoxia, thus resulting in a potentiation of the vasoconstrictor properties of this stimulus. In 43 hypertensive and 17 normotensive men, pulmonary arteriolar resistance has been evaluated during air respiration and after 15 minutes of breathing 17%, 15%, and 12% oxygen in nitrogen. Curves relating changes in pulmonary arteriolar resistance to oxygen breathing contents had similar configuration in the two populations but in hypertension were steeper and significantly shifted to the left, reflecting a lower threshold and an enhanced reactivity. This pattern was not related to differences in severity of the hypoxic stimulus, plasma catecholamine concentration, or hypocapnia and respiratory alkalosis induced by hypoxia and probably was not mediated through α-receptor activation. Calcium channel blockade with nifedipine was able to almost abolish both the normotensive and the hypertensive pulmonary vasoconstricting reaction. These findings support the hypothesis that hypoxic pulmonary vasoconstriction may be enhanced in systemic hypertension. As to the mechanism of this effect, findings are consistent with the interpretation that hypoxic vasomotion is mediated by an increased availability of calcium ions for the contractile elements of the lung vessels, which is facilitated with hypertension. The association of high blood pressure with enhanced pulmonary vasoactivity to alveolar hypoxia could have clinical implications in patients who are chronically hypoxic and have systemic hypertension. (Circulation 1989;79:337–343)

Alveolar hypoxia is a physiologic stimulus that causes local vasoconstriction of the pulmonary arteries, probably by affecting excitation, contraction, or the coupling of the two.¹ A role of increased slow channel calcium entry into vascular smooth muscle in mediating pulmonary vasoconstriction is suggested by the observation that verapamil inhibits such vasoconstriction² and that nifedipine reduces pulmonary vascular resistance in patients with respiratory failure.³,⁴

Systemic primary hypertension is another clinical condition in which handling of Ca²⁺ by the smooth muscle cell seems to be involved in the enhancement of the contractile activity of the lung vessels. In fact, the elevation of vascular pressure and resistance of the lesser circulation,⁵,⁷ compared with normalª; the hypersensitivity to catecholaminesª; and the hyperreactivity of the lung vessels to sympathetic nervous system activation¹⁰,¹¹ that characterize systemic high blood pressure seem to depend on an excessive free calcium availability for smooth muscle contraction.¹²,¹³ Abnormalities in Na⁺ transport in essential hypertension would lead to intracellular Na⁺ accumulation causing a decrease of movement of Ca²⁺ out of the cell through the Na⁺-Ca²⁺ exchange system resulting in an increase in intracellular Ca²⁺ and contractility.¹⁴ Thus, hypertension might be seen as a background facilitating the increase in the cytosol free Ca²⁺ concentration during alveolar hypoxia and augmenting the vasoconstricting potency of this stimulus.

In the present study, we investigated the vaso-
motor responses to breathing of low oxygen mix-
tures in hypertensive and normotensive subjects
and proved that hypoxic pulmonary vasoconstric-
tion is enhanced in systemic hypertension and that
calcium channel blockade with nifedipine greatly
weakens this effect.

Methods

Subjects

Forty-three hypertensive men (mean age, 47±4.2
years; mean weight, 74.5±5 kg) and 17 healthy
normotensive men (mean age, 45±3.7 years; mean
weight, 72.2±4.3 kg) were the subjects of the present
study. Hypertensive individuals showed repeated
supine diastolic pressure values between 95 and 110
mm Hg and had never received antihypertensive
therapy. None of them had urgent need for treat-
ment; evidence of lung, cardiac, or cerebrovascular
disease; or renal or endocrine cause of hyperten-
sion. Respiratory gases and pH of the arterial blood
were normal, and none had symptoms or signs
referred to sleep apnea syndrome.15 Normotensive
men were subjects with precordial systolic murmur
or atypical chest pain in whom coronary or cardiac
valve diseases were excluded by appropriate diag-
nostic procedures. They were not receiving any

treatment. The scientific purposes of the program
and the investigative procedures were explained in
detail to each patient.

Hemodynamic Procedures

For the right-sided pressure and cardiac output
measurements, a triple lumen 7F thermodilution
balloon-tipped catheter (Edwards Laboratories,
Irvine, California) was inserted percutaneously into
an antecubital vein and advanced to the pulmonary
artery or, when necessary, to the pulmonary wedge
position. Systemic arterial pressure was derived
from the right brachial artery through insertion of a
Teflon catheter needle. Catheters were introduced
under local anesthesia. Pressures were determined
with Statham strain gauge transducers (Cleveland,
Ohio), with the zero reference level 5 cm below the
equatorial angle. The pulmonary artery wedge pressure
was characterized by a distinct A and V waveform,
with the V wave occurring after the T wave of the
electrocardiogram. Cardiac output was determined
by the thermodilution method. Systemic vascular
resistance (SVR) and pulmonary arteriolar resistance
(PAR) were derived from the following formulas:

\[
SVR = \frac{(AP - RAP \times 1,332 \times 60)}{CO} \text{ (ml/min)}
\]

\[
PAR = \frac{(PAP - PWP \times 1,332 \times 60)}{CO} \text{ (ml/min)}
\]

where AP, RAP, PAP, and PWP are, respectively,
mean systemic right atrial, pulmonary artery, and
pulmonary wedge pressures, and CO is cardiac
output. The circulatory variables were recorded on
a Gould-Brush eight-channel recorder (Model 480,
Saddle Brook, New York). Arterial oxygen and
carbon dioxide tension and pH were determined by
the methods reported previously.7 Plasma catechol-
amine concentration was evaluated by high-
performance liquid chromatography with electro-
chemical detection.16

Most of the testing sessions occurred in the morn-
ing, 1 week after admission to the hospital and after
the patients had been familiarized on 3 consecutive
days with the investigators, equipment, and environ-
ment. They were instructed to not smoke or ingest
alcohol or caffeine-containing foods for 24 hours
before testing. Observations were started 30 minutes
after completion of right heart catheterization.

Methods

For convenience in presentation, the study has
been subdivided into three parts.

Part 1. Observations were made on 21 hyperten-
sive and 10 normotensive subjects. They consisted
of a comparison of the systemic and pulmonary
hemodynamic pattern of the two groups before and
during breathing of low oxygen mixtures. An open

circuit was used to administer ambient air or spe-
cific mixtures and consisted of a mouthpiece; a
three-way, low dead space valve; and a Tissot
gasometer. Each study consisted of five consecu-
tive periods: ambient air breathing (control period)
and four periods of 15 minutes of breathing 20%,
17%, 15%, and 12% oxygen in nitrogen. Between
periods, the subjects were disconnected from the
open circuit for 15–20 minutes of relaxation and
ambient air breathing. Continuous records of heart
rate (cardiotachograph) and systemic and pulmo-
nary pressures were obtained throughout the stud-
ies. Cardiac output and pulmonary wedge pressure
were measured, and systemic and pulmonary arte-
riolar resistance were calculated immediately before
and at the end of each of the five periods. Hemo-
dynamic variables between each breathing step
returned to levels similar to those recorded at the
beginning of the study, which indicated that between
tests the steady state could be reestablished. During
cardiac output evaluation, samples of peripheral
arterial blood were withdrawn for the determination
of the gaseous composition, pH, and concentration
of catecholamines.

Part 2. In 16 other hypertensive and seven other
normotensive subjects, we investigated the hemo-
dynamics of the lesser circulation during low oxy-
gen breathing, before and after nifedipine. The
calium antagonist was administered sublingually
(20 mg), and the repeated series of tests were begun
at least 30 minutes later, a time at which a known
hemodynamic effect (decrease in arterial pressure)
had occurred. The sequence of administration of
specific breathing mixtures as well as the hemody-
namic and humoral measurements in these patients
were identical with those described above, with the
exception of the 20% oxygen step.
Part 3. In six other hypertensive subjects, a sequence of procedures identical with those reported in part 1, with the omission of plasma catecholamine determination, was carried out before and after phenoxybenzamine. This α-adrenergic receptor blocker, in a dose of 1 mg/kg diluted in 200 ml normal saline, was infused over a 10-minute period into the pulmonary artery. After 1 hour, the effectiveness of the pharmacologic blockade was tested before starting and after completing the low oxygen tests, during breathing of ambient air, by challenging the patient with a standard cold pressor test. The test caused a rise of 30% or more, above control level, in mean systemic arterial pressure before blockade but only a rise of 15% or less after administration of phenoxybenzamine. Although the blockade was probably not complete, it was judged to be as effective as feasible for that particular experimental condition.

Statistical Analysis

Data were expressed as mean±SD. Significance of differences from the air breathing values and between the normotensive and hypertensive groups at each phase of the breathing tests was assessed by either one-way or two-way analysis of variance, as appropriate.

Results

Responses to Hypoxic Stimulus

Figure 1 refers to subjects reported in part 1 and shows values of arterial oxygen tension recorded during respiration of ambient air and after 15 minutes breathing 20%, 17%, 15%, and 12% oxygen in nitrogen. At the 20% oxygen step, arterial PO₂ was identical with the air breathing period, and then it fell significantly in parallel with the diminution in the oxygen content of the gaseous mixture; at no step was the group difference statistically significant. The decrease in arterial PCO₂ and the rise in pH were also very similar in the two populations.

In neither group (Table 1) did the 20% oxygen mixture modify the hemodynamic parameters from the air breathing period. At subsequent steps, variations in the systemic circulation were similar in normotension as in hypertension and consisted of a tendency of heart rate, blood pressure, and vascular resistance to rise under the stimulus of hypoxia, with minimal changes in cardiac index. In the lesser circulation, hypoxia significantly increased vascular pressure and resistance in both groups: in normotension, only the lowest (12%) oxygen content showed a distinct vasoconstrictor efficacy; in high blood pressure, on the contrary, a vasoconstrictor, hypertensive effect was consistently recorded starting from the 17% oxygen mixture. In the latter group of patients, baseline pulmonary pressure and arteriolar resistance were higher than in normotensive subjects and remained so during hypoxia; it is noteworthy, however, that group differences, at each low oxygen breathing step, were almost twice as great as those in the baseline, reflecting an enhanced vasoconstrictor reactivity in high blood pressure. There was not a correlation between the degree of pulmonary vascular reactivity and the level of systemic hypertension.

Hyperreactivity appears even more impressive if changes from the air breathing phase at each hypoxic step are presented graphically (Figure 2); the curves of mean pulmonary arterial pressure and arteriolar resistance have similar-shaped configurations in the two populations, but those for the hypertensive group are steeper and shifted to the left. Variations in either parameter of all hypertensive patients exceeded the normal values at each level of hypoxia. Both in the subjects with the normal and with high blood pressure the hemodynamics of the lesser circulation varied in the absence of significant changes in cardiac index (Table 1 and Figure 2) as well as of the epinephrine and norepinephrine plasma concentrations (Table 1).
**Table 1.** Hemodynamic Parameters, Plasma Catecholamine Concentration, Arterial Carbon Dioxide Tension, and pH During Air and Low Oxygen Mixture Breathing in Normotensive and Hypertensive Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive (n=10)</th>
<th>Hypertensive (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air 10</td>
<td>20</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>89 (11)</td>
<td>(13)</td>
</tr>
<tr>
<td>Cardiac index (ml/min/M²)</td>
<td>4,340 (320)</td>
<td>4,338 (305)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec/cm⁻⁵)</td>
<td>892 (120)</td>
<td>910 (112)</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>10 (1.2)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure (mm Hg)</td>
<td>5 (2.5)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance (dynes/sec/cm⁻⁵)</td>
<td>48.8 (12)</td>
<td>47.6 (11)</td>
</tr>
<tr>
<td>Epinephrine plasma concentration (pg/ml)</td>
<td>62 (31)</td>
<td>66 (36)</td>
</tr>
<tr>
<td>Norepinephrine plasma concentration (pg/ml)</td>
<td>127 (29)</td>
<td>134 (30)</td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>33 (2.5)</td>
<td>34 (2.8)</td>
</tr>
</tbody>
</table>

*Differences from the air breathing period significant at p<0.01. Values are mean (±SD).

**Calcium Channel Blockade**

These observations were made on patients described in part 2 of “Methods.” Before nifedipine, the finding was duplicated of enhanced hypoxic pulmonary vasoconstriction in hypertension, with increases in pressure and resistance (left side of Figure 3) significantly greater than in normotension at each step of low oxygen breathing. About 30 minutes after the administration of nifedipine (Table 2), systemic blood pressure, vascular resistance, and plasma epinephrine concentration had diminished significantly; heart rate, cardiac index, and concentration of plasma norepinephrine had risen; and arterial blood gases and pH were unchanged in each group. Under the influence of the calcium channel blocker, pulmonary arterial pressure in hypertensive patients had fallen from an average of 16.2 to 12.7 mm Hg and arteriolar resistance from 84 to 52 dynes/sec/cm⁻⁵; their variations in normotensive subjects were minimal and statistically not significant. In each group, the curves representing changes from baseline of these variables during the hypoxic tests became flatter, and those of hypertension were almost superposable on those of normotension (right side of Figure 3), indicating that resistance of lung vessels was reduced to similar levels after nifedipine. Hypoxic variations of blood flow through the lungs were minimal and similar to those before calcium channel blockade.

Although blood viscosity and lung mechanics were not studied, it is likely that neither varied importantly because hematocrit (44±3%) did not change and the amplitude of swings in the intrathoracic pressure, as measured in pulmonary wedge pressure recordings, after nifedipine was identical with that during the control period (12±2 mm Hg).

**α-Adrenergic Receptor Blockade**

This part of the study was performed on only six hypertensive subjects in consideration of the reproducibility of our findings. In the control condition, mean pulmonary arterial pressure rose by an average of 2.5±2, 3.9±1.8, and 6.1±2.2 mm Hg at the 17%, 15%, and 12% oxygen breathing periods, respectively; the corresponding average changes in pulmonary arteriolar resistance were +12±7, +18±8, and +32±6 dynes/sec/cm⁻⁵. After phenoxybenzamine, cardiac index augmented by an average of 550 ml/min/M², pulmonary arteriolar resistance was 19 dynes/sec/cm⁻⁵ lower than in the control condition and mean pulmonary arterial pressure remained steady. Without exception, the hypoxic pulmonary vasomotor response persisted and increases in pressure and resistance were comparable to those recorded before α-adrenergic receptor blockade.

**Discussion**

The major finding in this study is that hypoxic pulmonary vasoconstriction is enhanced in high blood pressure and the threshold of the constrictor reaction is lowered. This suggestion is based on the
following points. Hypoxia raised pulmonary artery pressure without affecting blood flow and the pulmonary wedge pressure.\textsuperscript{17,18} Curves relating increases in mean pulmonary artery pressure and arteriolar resistance to the oxygen content of the breathing mixtures were steeper and shifted to the left of normotensive curves. In hypertensive patients, a vasoconstrictor response was consistently detected at 17% oxygen content, whereas in normotensive patients, pressure and resistance started to significantly rise at 12% oxygen content. The same observations were duplicated in two consecutive series of experiments.

There are several mechanical and chemical factors, which, although potentially involved, can be excluded as responsible for this particular pattern. It is unlikely that the rise in resistance reflected passive adaptation to changes in flow\textsuperscript{1} because variations in cardiac index were quite small and, more importantly, the resistance rose in parallel with variations in oxygen content and not in cardiac output. A mechanical effect related to the open circuit seems also excludable because the methods used to administer the gaseous mixtures were the same in hypertension as in normotension and because breathing of the 20% oxygen mixture did not elicit any hemodynamic response. Similar arterial oxygen tension at each hypoxic step suggests that the severity of the stimulus was comparable in the two groups; furthermore, the degree of hypocapnia and respiratory alkalosis induced by hypoxia did not account for the differences in the hemodynamic responses. As far as catecholamine plasma concentrations may reflect the activity of the sympathoadrenal system,\textsuperscript{19,20} the pulmonary vasmotion in normotension during hypoxia,\textsuperscript{21} as well as the enhanced vasoconstriction in hypertension, do not seem to be related to the sympathetic nervous system and endogenous catecholamines. In fact, plasma catecholamines at each of the hypoxic steps

\textbf{FIGURE 2.} Plots of changes from the air breathing control phase in mean pulmonary arterial pressure (MPAP), pulmonary arteriolar resistance (PAR), and cardiac index (CI) in 10 normotensive and 21 hypertensive subjects at various low oxygen breathing steps. Mean±SD of normotensives and hypertensives are indicated by open circles and squares, respectively. *Differences from the control phase significant at p<0.01; ▲, Differences from the corresponding value in the normotensive group significant at p<0.01.

\textbf{FIGURE 3.} Plots of changes from the air breathing control phase in seven normotensive and 16 hypertensive subjects during low oxygen breathing, before and after nifedipine. Mean±SD of normotensives and hypertensives are indicated by open circles and squares, respectively. *Differences from the control phase significant at p<0.01; ▲, Differences from the corresponding value in the normotensive group significant at p<0.01.
TABLE 2. Hemodynamic Parameters, Plasma Catecholamine Concentration, Arterial Carbon Dioxide and Oxygen Tension, and pH in the Control Condition and After Nifedipine in Normotensive and Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 7)</th>
<th>Hypertensive (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Heart rate</td>
<td>73 (beats/min)</td>
<td>77</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>87 (11)</td>
<td>81* (9.5)</td>
</tr>
<tr>
<td>Cardiac index (ml/min/M²)</td>
<td>4,590 (280)</td>
<td>4,820 (310)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec/cm⁻³)</td>
<td>904 (129)</td>
<td>787* (134)</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>10.3 (2)</td>
<td>9.8 (1.7)</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure (mm Hg)</td>
<td>6 (2.1)</td>
<td>5.5 (1.8)</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance (dynes/sec/cm⁻³)</td>
<td>41.7 (22)</td>
<td>36.1 (25)</td>
</tr>
<tr>
<td>Epinephrine plasma concentration (pg/ml)</td>
<td>101 (28)</td>
<td>67* (29)</td>
</tr>
<tr>
<td>Norepinephrine plasma concentration (pg/ml)</td>
<td>134 (31)</td>
<td>205* (28)</td>
</tr>
<tr>
<td>P⁰₂ (mm Hg)</td>
<td>94 (1.5)</td>
<td>95.5 (1.6)</td>
</tr>
<tr>
<td>P⁰₁₂ (mm Hg)</td>
<td>35 (2)</td>
<td>36 (1.8)</td>
</tr>
<tr>
<td>pH</td>
<td>7.423</td>
<td>7.425</td>
</tr>
</tbody>
</table>

*Differences from the control condition significant at p<0.01. Values are mean (+SD).

did not vary significantly from the ambient air breathing period, in both the normal and the high blood pressure groups.

Norepinephrine release and α-adrenergic receptor activation mediate the pressure rise during cold stimulation. This test was deemed suitable for an approximate estimation of α-receptor blockade because α-blockers have been shown to abolish peripheral vasoconstriction during cold pressor test. The pressor reaction to cold after phenoxybenzamine was reduced by 50–80%, suggesting that a substantial blockade of the α-receptor had been obtained. If pulmonary hypoxic vasoconstriction in normal subjects and its enhancement in hypertensive patients depended on the α-receptor activity, phenoxybenzamine should restrain the vasoconstriction in normotension and, to a larger extent, in hypertension. On the contrary, the pulmonary vasomotor reaction persisted identically with those before the α-blocker. This observation leads to the same conclusion achieved by Thilenius and collaborators in dogs and by Silve and Grovers in calves that hypoxic pulmonary vasoconstriction in humans is not mediated through adrenergic receptors and that its magnification in high blood pressure is also independent of them.

In hypertension, structural alterations may occur in the systemic circulation leading to an increase of the wall:lumen ratio, which can have a progressive pressor effect and accentuate the response to superimposed vasoconstrictor stimuli. If similar anatomic changes involved the lung vessels, they could explain the enhancement of hypoxic pulmonary vasoconstriction during hypoxia observed in this study. However, although an increase of the pulmonary artery medial thickness has been reported in spontaneous hypertensive rats, there is no information in human subjects concerning the structure of the vessels in the lesser circulation in hypertension. Therefore, the question of whether an increased wall thickness and a reduced arterial lumen may be the cause of the augmented hypoxic vasoconstrictor reaction in hypertension remains basically unanswered.

From these considerations the reasons for the enhancement of the hypoxic pulmonary vasoconstriction in hypertension seem referable to a potentiation of the contractile mechanisms of the pulmonary vascular smooth muscle rather than to neurogenic effects, mechanical factors, α-adrenergic receptor activation, or structural changes of the arterial wall.

We interfered with the vascular contractile activity through the calcium channel blocker nifedipine. This drug substantially reduced the vasomotor response to the hypoxic stimulus in both the normotensive and hypertensive subjects and abolished almost completely the differences in vasoconstriction between the two groups. However, we failed to identify, through this method, the exact mechanism by which hypertension enhances the potency of the hypoxic stimulus. In fact, the depression produced...
by nifedipine might reflect either an interference of the calcium channel blocker2-4,28 with the basic factors that mediate the rise in pulmonary vascular resistance, thus preventing any possibility of potentiation, whatever the mechanism through which hypertension causes this effect, or a nonspecific result of two opposing influences, vasodilating by nifedipine and vasoconstricting by hypoxia, on the vascular smooth muscle tone, or an antagonistic action on Ca2+, whose transport across sarclemma is facilitated by the hypoxic stimulus and whose availability for contraction is potentiated in hypertension. Our experiments neither support nor refute each of these interpretations.

Despite this limitation, the observation that patients with systemic hypertension have enhanced pulmonary vasoreactivity to acute alveolar hypoxia may have clinical significance for patients who have systemic hypertension and are chronically hypoxic.

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References


KEY WORDS • calcium flux • low oxygen breathing
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