

Impaired Reflex Vasoconstriction in Chronically Hypoxemic Patients

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ABSTRACT Acute hypoxia impairs vasoconstrictor responses in normal men. The present study was done to determine whether reflex vasoconstriction is impaired in chronically hypoxemic patients and whether correction of hypoxemia in these patients improves their cardiovascular reflexes. In eight chronically hypoxemic patients, arterial P_{O_2} was increased from an average of 45 mm Hg while breathing room air to 161 mm Hg while breathing 40–100% oxygen, with minimal changes in arterial P_{CO_2} or pH. Correction of hypoxemia did not cause changes in resting arterial pressure or in forearm vascular resistance, but it caused a small increase in resting heart rate. Reflex responses to lower body negative pressure, which causes pooling of blood in the lower part of the body, were observed. When the patients were hypoxemic, lower body negative pressure caused a fall in arterial pressure, slight constriction of forearm vessels, and a small increase in heart rate. When hypoxemia was corrected, the same intervention caused marked vasoconstriction and a greater increase in heart rate, and there was no decrease in arterial pressure. The results indicate that reflex vasoconstrictor responses are depressed in chronic hypoxemia, indicating that adaptive mechanisms which occur in chronic hypoxemia do not include preservation of sympathetic reflexes.

INTRODUCTION

Recent studies have emphasized the frequency of hypoxemia in a variety of clinical problems (2–5). Hypoxemia

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is especially common in shock (6, 7), and it may interfere with blood pressure regulatory mechanisms and contribute to hypotension. It is known that acute hypoxia impairs vasoconstrictor and positive chronotropic responses in normal men (8, 9). During prolonged hypoxia over a period of 36 hr, cardiovascular reflexes in normal men remain impaired and are promptly restored to normal by correction of hypoxia (9).

In this study reflex vasoconstrictor responses were observed in chronically hypoxemic patients. The possibility that adaptive mechanisms in chronic hypoxia might permit restoration of reflex sympathetic responses was considered. The study was done to determine whether reflex vasoconstriction is impaired by chronic hypoxemia and whether correction of chronic hypoxemia improves cardiovascular reflexes.

METHODS

Eight hypoxemic patients with a variety of chronic pulmonary diseases were studied (Table I). The patients were all ambulatory. The criteria for selection of the patients were an arterial P_{O_2} and P_{CO_2} of less than 60 mm Hg at rest and a stable clinical state.

The studies were done with the patient lying supine. Room temperature was maintained at approximately 80°F. The lower half of the body was enclosed in an airtight box to the level of the iliac crest. The left brachial artery was cannulated with a polyethylene cannula (PE 90) after superficial infiltration over the artery with 1% lidocaine. The cannula was introduced about 2 inches into the artery and connected to a pressure transducer and to a syringe for obtaining blood samples.

Blood flow to the forearm was measured with a Whitney mercury-in-silastic strain gauge plethysmograph compensated for temperature variations (10). The gauge was placed around the right forearm 2–3 inches distal to the elbow at a tension of 15 g. The tension and small plastic bridges kept the gauge in the same position during the experiment. The arm was elevated and supported at the wrist so that the

TABLE I
Clinical Data in Patients with Chronic Hypoxemia

Patient	Age	Sex	Diagnosis	Duration of dyspnea	Hemoglobin g/100 ml	Medications*
L. T.	62	M	Chronic pneumonitis	3 months	10.0	None
L. B.	30	F	Alveolar proteinosis, Nocardia pneumonia	2 yr	14.1	None
W. H.	53	M	Chronic obstructive pulmonary disease	Many years	16.2	Theophylline, ephedrine, pheno- barbital, digitoxin, prednisone
R. K.	26	M	Bronchiectasis	5 yr	14.7	None
H. P.	70	M	Chronic obstructive pulmonary disease	6 yr	12.6	Theophylline, ephedrine, pheno- barbital, digoxin, prednisone
V. G.	42	M	Alveolar proteinosis, Nocardia brain abscess	3 months	15.7	Dilantin, Decadron
J. B.	54	M	Chronic obstructive pulmonary disease	Many years	14.8	Theophylline, ephedrine, phenobarbital
R. H.	37	M	Pulmonary fibrosis	7 yr	13.8	None

* Most patients were also receiving antibiotics.

proximal part of the forearm was about 10 cm above the anterior part of the chest wall. A pneumatic cuff was placed around the upper arm and intermittently inflated above venous pressure for 8-9 sec. The rate of increase in volume of the forearm during intermittent venous occlusion is directly related to blood flow (Fig. 1). A second pneumatic cuff was placed around the right wrist and inflated to suprasystolic pressure during the period of measurement to exclude the contribution of hand blood flow to the measurement of forearm flow.

Each patient breathed two levels of oxygen: room air and 40% oxygen in nitrogen. The order of the gases was alternated for the eight patients. When 40% oxygen did not restore arterial P_{O_2} to normal within 5 min, the oxygen concentration was increased so that four patients received 100% oxygen. End-tidal CO_2 was measured continuously

by an LB-1 infrared CO_2 analyzer, with continuous sampling at the mouthpiece. Breathing high oxygen mixtures tended to depress the ventilation of the patients, so that when the end-tidal CO_2 began to rise the patients were asked to hyperventilate to maintain an end-tidal CO_2 similar to that while breathing room air.

After breathing room air and after breathing high oxygen for 5-10 min control measurements were taken. Then the pressure within the suction box surrounding the lower body was reduced to 20 and 40 mm Hg below atmospheric pressure for 1.5 min, with 1.5 min of rest between the two periods of suction. Lower body negative pressure causes pooling of blood in the legs and lower abdomen and produces reflex vasoconstriction and tachycardia (11, 12).

Blood flow to the forearm was calculated from the rate of increase in the volume of the forearm during venous occlusion and expressed in ml/min per 100 ml of forearm. Values were not obtained during the first 30 sec of lower body negative pressure to avoid a rapidly shifting base line and to observe maximum responses. Forearm vascular resistance was calculated from the ratio of mean arterial pressure to forearm blood flow and expressed in mm Hg/ml/min/100 ml forearm.

Statistical comparisons were made by analyses of variance (13), comparing values while breathing room air and 40-100% oxygen.

RESULTS

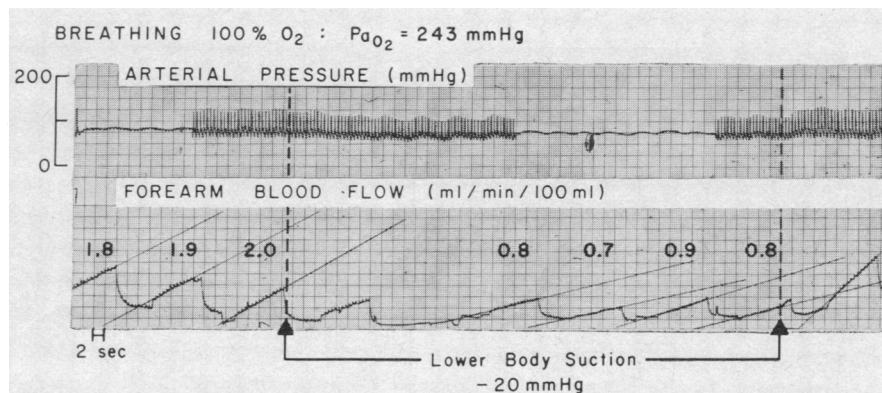
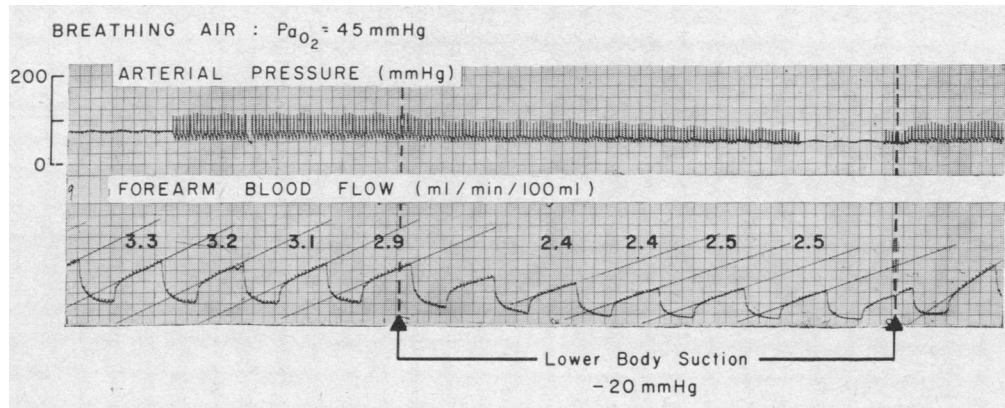
Arterial P_{O_2} , P_{CO_2} , and pH. All patients were markedly hypoxemic at rest. Breathing 40-100% oxygen increased arterial P_{O_2} (Tables II and III). There was no change in arterial P_{CO_2} or pH while breathing oxygen.

Effect of correction of hypoxemia on resting values. Arterial pressure and forearm vascular resistance were unchanged by correction of hypoxemia (Tables IV-VII). There was a small but significant decrease in heart rate when hypoxemia was corrected (Tables VIII and IX).

TABLE II
Arterial P_{O_2} , P_{CO_2} , and pH while Breathing
Room Air and Oxygen*

Patients	Air			40-100% O_2		
	P_{O_2}	P_{CO_2}	pH	P_{O_2}	P_{CO_2}	pH
	mm Hg			mm Hg		
L. T.	44	34.5	7.52	260	35.0	7.53
L. B.	27	34.1	7.57	66	38.2	7.46
W. H.	48	51.0	7.40	88	51.1	7.40
R. K.	51	55.9	7.40	290	64.4	7.38
H. P.	45	38.8	7.50	290	37.8	7.50
V. G.	42	31.4	7.47	78	32.8	7.45
J. B.	60	42.8	7.46	128	43.5	7.46
R. H.	42	28.4	7.47	100	29.2	7.48
Mean	44.9	39.6	7.47	161.2	41.5	7.46
SE	3.3	3.4	0.02	34.5	4.0	0.05

* Values represent the average of two values obtained during each condition.



H.P.

FIGURE 1 Changes in mean and phasic arterial pressure and forearm volume in response to lower body negative pressure while breathing room air and 100% oxygen. The slopes of the forearm volume curves were used to calculate blood flow to the forearm in ml/min per 100 ml of forearm, as indicated by the numbers above the curves.

Effect of correction of hypoxemia on responses to lower body negative pressure. When the patients were hypoxemic, lower body negative pressure caused a significant decrease in arterial pressure, slight vasoconstriction, and a small increase in heart rate (Fig. 2 and Tables IV-IX). When hypoxemia was corrected, lower body negative pressure caused significantly greater vasoconstriction and increase in heart rate, and the decrease in arterial pressure was not statistically significant.

DISCUSSION

This study indicates that reflex vasoconstrictor responses are impaired in chronically hypoxemic patients. Pooling of blood by lower body negative pressure, which is well tolerated by normoxic men (8, 9), caused significant hypotension in these patients. Correction of the hypoxemia caused a prompt improvement in vasoconstrictor responses and prevented hypotension during lower body negative pressure.

TABLE III
Analysis of Variance of Arterial P_{O_2} , P_{CO_2} , and pH while Breathing Room Air and Oxygen

Source of variation	P_{O_2}			P_{CO_2}			pH					
	df	Mean square	F	P	df	Mean square	F	P	df	Mean square	F	P
Patients	7	5,097			7	219			7	0.005		
Oxygen*	1	54,172	12.0	<0.01	1	14.2	3.07	NS‡	1	0.001	1.34	NS
Error	7	4,516			7	4.6			7	0.0007		

* Oxygen refers to variation of values while breathing room air and oxygen.

‡ NS indicates not significant ($P > 0.05$).

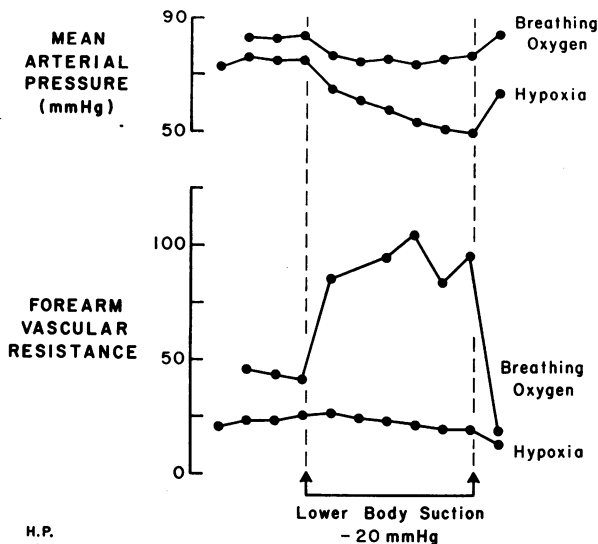


FIGURE 2 Values from Fig. 1 are charted. While the patient was breathing room air and still hypoxemic, lower body negative pressure caused a marked reduction in arterial pressure with no increase in forearm vascular resistance, indicating absence of vasoconstriction. When hypoxemia was corrected by breathing oxygen, lower body negative pressure caused a smaller decrease in arterial pressure and marked vasoconstriction.

Although reflex vasoconstriction is impaired during acute hypoxemia (8, 9), it would not have been surprising if adaptive mechanisms in chronic hypoxemia had permitted restoration and preservation of sympathetic reflexes. Decreased affinity of hemoglobin for oxygen by 2,3-diphosphoglycerate (14) has been demonstrated in chronically hypoxemic patients (15) and appears to be an important compensatory mechanism in hypoxemia.

TABLE IV
Mean Arterial Pressure in Response to Lower Body Negative Pressure while Breathing Room Air and Oxygen*

Patients	Air			40-100% O ₂		
	Con	LBNP ₂₀	LBNP ₄₀	Con	LBNP ₂₀	LBNP ₄₀
	<i>mm Hg</i>			<i>mm Hg</i>		
L. T.	87	84	80	84	83	82
L. B.	99	96	89	96	96	94
W. H.	85	74	74	81	72	70
R. K.	90	86	87	84	84	87
H. P.	74	51	51	82	76	78
V. G.	110	110	101	108	108	103
J. B.	82	77	70	83	83	77
R. H.	68	69	72	67	68	72
Mean	86.8	80.8	78.0	85.6	83.8	82.8
SE	4.7	6.3	5.3	4.2	4.6	4.0

* Con refers to control observations; LBNP₂₀ and LBNP₄₀ refer to lower body negative pressure at 20 and 40 mm Hg below atmospheric pressure.

An increase in red blood cell mass during chronic hypoxemia (16) tends to increase oxygen delivery. Increased cardiac output during acute hypoxemia also increases oxygen delivery (17), but the cardiac output returns to normal levels during prolonged hypoxemia (18). The impairment of vasoconstrictor responses observed in this study suggests that adaptive mechanisms during chronic hypoxemia do not preserve sympathetic reflexes.

There may be at least two mechanisms for decreased reflex vasoconstriction during hypoxia. Studies in animals and man suggest that acute hypoxia inhibits the response of vessels to catecholamines (19, 8). Depressed vasoconstrictor responses to norepinephrine, the neurotransmitter released during reflex vasoconstriction, may therefore be one mechanism by which hypoxia inhibits

TABLE V
Analysis of Variance of Changes in Mean Arterial Pressure during Lower Body Negative Pressure (LBNP) while Breathing Room Air and Oxygen

Source of variation	Effect of oxygen on resting arterial pressure				Effect of oxygen on change in arterial pressure during LBNP			
	df	Mean square	F	P	df	Mean square	F	P
Patients	7	311			7	111		
Oxygen*	1	6.25	0.69	NS†	1	210	13.3	<0.002
LBNP‡	1				1	28.1	1.78	NS
LBNP × oxygen	1				1	8.0	0.50	NS
Error	7	9.11			7	15.8		

* Oxygen refers to variation of resting values, and responses to LBNP, while breathing room air and oxygen.

† NS indicates not significant ($P > 0.05$).

‡ LBNP refers to variation of responses to the two levels of LBNP (reductions of 20 and 40 mm Hg below atmospheric pressure).

|| LBNP × oxygen refers to an interaction between the gas mixture breathed (room air and oxygen) and the level of LBNP (-20 and -40 mm Hg).

reflex vasoconstriction. Acute hypoxia decreases reflex vasoconstrictor responses to a greater degree than responses to norepinephrine, suggesting that hypoxia has additional effects on the reflex vasoconstrictor arc (8). A peripheral neuropathy has been described in patients with chronic obstructive pulmonary disease (20). In the present study, the prompt improvement in vasoconstrictor responses with correction of hypoxemia indicates that the depression of reflex responses during chronic hypoxemia is largely reversible. The reversible impairment suggests interference with central (21) or peripheral (22) neural transmission, rather than an autonomic neuropathy.

Acute hypoxia causes reflex vasoconstriction (23), an increase in heart rate (24), and increased urinary excretion of catecholamines (25), indicating activation of the sympathetic system. Adrenergic activity at rest may have been increased in the patients in the present

TABLE VI
*Forearm Vascular Resistance in Response to Lower Body Negative Pressure while Breathing Room Air and Oxygen**

Patients	Air			40-100% O ₂		
	Con	LBNP ₂₀	LBNP ₄₀	Con	LBNP ₂₀	LBNP ₄₀
	<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>		
L. T.	12	12	14	13	16	19
L. B.	14	18	18	23	32	39
W. H.	14	15	17	15	15	22
R. K.	35	45	48	30	35	46
H. P.	24	21	20	43	95	98
V. G.	12	18	20	17	24	38
J. B.	14	21	26	17	36	31
R. H.	5.0	5.4	5.7	5.7	7.0	7.7
Mean	16.2	19.4	21.1	20.5	32.5	37.6
SE	3.2	4.1	4.4	4.1	9.7	9.7

* See footnote to Table IV.

TABLE VII
*Analysis of Variance of Changes in Forearm Vascular Resistance during Lower Body Negative Pressure (LBNP) while Breathing Room Air and Oxygen**

Source of variation	Effect of oxygen on resting forearm vascular resistance				Effect of oxygen on change in resistance during LBNP			
	df	Mean square	F	P	df	Mean square	F	P
Patients	7	192			7	239		
Oxygen	1	71.0	2.75	NS	1	895	7.01	<0.02
LBNP					1	91.1	0.71	NS
LBNP × oxygen					1	23.5	0.18	NS
Error	7	25.8			7	127		

* See footnotes to Table V.

study, but this was not manifested by vasoconstriction, presumably due to local vasodilator influence of hypoxemia (26) as well as interference with vasoconstriction. The increase in adrenergic activity during hypoxia could contribute to the decreased responsiveness to reflex stimuli. Hypoxia causes neurogenic vasoconstriction, and if the vasoconstriction were near maximal, it could prevent further response. It appears, however, that with the degree of hypoxia present in this study, the vasoconstriction may be slight and, therefore, not contribute significantly to the decreased responses. Black and Roddie (27) reported that blocking the nerves to the forearm did not alter the response to severe hypoxia, suggesting that the adrenergic vasoconstrictor activity of the forearm was slight during hypoxia.

The small increases in heart rate observed in these patients in response to lower body negative pressure

TABLE VIII
*Heart Rate in Response to Lower Body Negative Pressure while Breathing Room Air and Oxygen**

Patients	Air			40-100% O ₂		
	Con	LBNP ₂₀	LBNP ₄₀	Con	LBNP ₂₀	LBNP ₄₀
	<i>beats/min</i>			<i>beats/min</i>		
L. T.	114	118	118	112	116	116
L. B.	102	102	104	92	96	100
W. H.	74	78	82	76	82	85
R. K.	104	104	104	102	105	102
H. P.	96	99	102	90	102	105
V. G.	92	98	104	90	98	106
J. B.	72	78	80	70	84	80
R. H.	92	94	101	84	84	90
Mean	93.2	96.4	99.4	89.5	95.9	98.0
SE	5.1	4.7	4.4	4.7	4.2	4.3

* See footnote to Table IV.

TABLE IX
*Analysis of Variance of Changes in Heart Rate during Lower Body⁺ Negative Pressure (LBNP) while Breathing Room Air and Oxygen**

Source of variation	Effect of oxygen on resting heart rate				Effect of oxygen on change in heart rate during LBNP			
	df	Mean square	F	P	df	Mean square	F	P
Patients	7	380			7	47.4		
Oxygen	1	56.2	7.33	<0.05	1	63.3	7.73	<0.02
LBNP					1	52.5	6.42	<0.02
LBNP × oxygen					1	1.53	0.19	NS
Error	7	7.68			7	8.18		

* See footnotes to Table V.

and the augmentation of increases in heart rate by correction of hypoxemia suggest an impairment of chronotropic reflexes during chronic hypoxemia similar to the impairment seen after shorter periods of hypoxia (9). In addition, the increase in heart rate in response to lower body negative pressure would be expected to have been greater during hypoxia because of the greater decrease in arterial pressure. However, the slightly slower resting heart rate after correction of hypoxemia may have affected the changes in heart rate during lower body negative pressure and precludes a definite conclusion. The decrease in resting heart rate while breathing oxygen suggests increased adrenergic activity during hypoxia, an observation which has been well documented (23-25).

The increase in arterial P_{O_2} while breathing oxygen was variable in these patients. In two patients the arterial P_{O_2} remained below 80 mm Hg while breathing 100% oxygen. Even in these patients the oxygen saturation increased to more than 90%, and vasoconstrictor responses improved. An attempt was made to correlate the level of hypoxemia (resting arterial P_{O_2}) with the increase in vascular responsiveness during administration of oxygen. There was no correlation when responses to lower body negative pressure at -20 mm Hg were analyzed, but at -40 mm Hg the correlation coefficient approached significance ($r = 0.70$; $P < 0.05$ 0.71) suggesting that the improvement in reflex responsiveness while breathing oxygen is greater in more severely hypoxemic patients.

Acute changes in carbon dioxide are known to alter vascular resistance (28). In the present study neither the resting carbon dioxide tension nor the change in carbon dioxide while breathing oxygen appeared to influence the responses to lower body negative pressure. Reflex responses were impaired when the patients were hypoxemic in the presence of hypercapnia or hypocapnia, and were improved by breathing oxygen, despite small increases or decreases in carbon dioxide.

It appears that the depression of reflex responses during chronic, as well as acute (8), hypoxemia is due to changes in arterial oxygen rather than carbon dioxide.

In three patients arterial P_{O_2} was greater than 200 mm Hg while breathing oxygen. The possibility that augmented vasoconstrictor responses were due in part to hyperoxia, as well as correction of hypoxia, should be considered. However, in 12 normal men, we have observed that hyperoxia induced by breathing 100% oxygen did not cause an increase in vasoconstrictor responses to lower body negative pressure: while breathing room air, forearm vascular resistance increased from 23.2 ± 2.7 (SE) mm Hg/ml/min/100 ml sure, and during 100% oxygen the corresponding increase was from 26.3 ± 2.9 to 42.9 ± 7.5 .¹

It appears that reflex vasoconstrictor responses, and probably chronotropic reflexes, are impaired in chronically hypoxemic patients, resulting in an increased susceptibility to hypotensive stimuli. The present study may explain in part the finding (29) that patients with severe chronic obstructive lung disease frequently demonstrate absence of reflex vasoconstriction, with low peripheral vascular resistance, despite hypotension. The prompt improvement in vascular responsiveness which was observed in this study with correction of hypoxemia emphasizes the therapeutic importance of oxygen, particularly in hypotensive patients.

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