

Effect of Acute Hypoxia on Vascular Responsiveness in Man

I. RESPONSIVENESS TO LOWER BODY NEGATIVE PRESSURE AND ICE ON THE FOREHEAD

II. RESPONSES TO NOREPINEPHRINE AND ANGIOTENSIN

III. EFFECT OF HYPOXIA AND HYPOCAPNIA

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ABSTRACT An effect of hypoxemia on vascular responsiveness and blood pressure regulation has not been demonstrated in man. The response of forearm resistance vessels to several vasoconstrictor stimuli was compared during normoxia and acute hypoxia. Forearm vasoconstrictor responses to lower body negative pressure and to the application of ice to the forehead, which are neurogenic stimuli, were decreased during acute hypoxia. Lower body negative pressure caused a decrease in mean arterial pressure during hypoxia, but not during normoxia. Because norepinephrine is the neurotransmitter released during reflex vasoconstriction, we considered the possibility that decreased responsiveness to norepinephrine might be one mechanism for diminished responses to lower body negative pressure and ice on the forehead during hypoxia. Hypoxia decreased the response of forearm resistance vessels to infusions of norepinephrine and angiotensin into the brachial artery. In addition, the effectiveness of intravenous infusions of norepinephrine in elevating mean arterial pressure was decreased during hypoxia. Since exposure to acute hypoxia stimulates hyperventilation and hypocapnia, experiments were done to determine the contribution of hypocapnia during hypoxia to the decreased vasoconstriction. The results indicate that hypocapnia may diminish the vascular response to some stimuli, but the reduction in oxygen appears to be the primary mechanism for decreased vasoconstrictor responses during acute hypoxia.

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INTRODUCTION

Hypoxemia is commonly observed in patients with pulmonary disease, patients in shock, after a myocardial infarction (2), and in normal persons at high altitude. Observations in animals indicate that hypoxia may interfere with adrenergic responses. Skinner and Costin (3), using a perfused dog gracilis muscle preparation, found decreased responses to sympathetic nerve stimulation during hypoxia. Gowdey (4) reported that the pressor response of the cat to intravenous norepinephrine was greatly reduced at a simulated altitude of 20,000 feet. Indirect evidence in man suggests that hypoxia may alter blood pressure regulation (5). Reduced responsiveness to adrenergic stimuli similar to that demonstrated in animals might contribute to the hypotensive states observed in man in association with hypoxia.

The present experiments were done to test the hypothesis that hypoxia may interfere with the pressor and vasoconstrictor effects of adrenergic stimulation in man. Three studies were carried out. The first was done to observe the effect of hypoxia on responsiveness to lower body negative pressure and to the application of ice to the forehead. We found that hypoxia decreased the vasoconstriction induced by lower body negative pressure or by the application of ice to the forehead. These stimuli are mediated primarily through neurogenic reflexes (6, 7). Since norepinephrine is the neurotransmitter released during neurogenic vasoconstriction, in the second study we considered the possibility that hypoxia reduces responsiveness to norepinephrine. In the third study we assessed the contribution of hypocapnia, which is associated with the hyperventilation of hypoxia, to the altered responsiveness.

I

Responsiveness to lower body negative pressure and ice on the forehead

METHODS

We studied 12 healthy men, 19–24 yr of age. The studies were done with the subject lying supine in a warm room (80°F). The lower half of the body was enclosed in an air-tight box to the level of the iliac crests.

Blood pressure was determined by auscultation at 30-sec intervals. Forearm blood flow was measured with a water plethysmograph (8). The segment of the forearm within the plethysmograph was at heart level. The water surrounding the arm was at 33°C. A pneumatic cuff was placed around the upper arm and inflated intermittently above venous pressure for 8–12 sec. An increase in volume of the forearm within the plethysmograph displaced water in an open tube at the top of the plethysmograph, so that changes in arm volume were measured by a Statham strain gauge as a change in hydrostatic pressure. The rate of increase in volume of the forearm during intermittent venous occlusion indicates blood flow. In 8 of the 12 subjects blood flow to the hand was measured on the same arm, using a water plethysmograph. A second pneumatic cuff was placed around the wrist between the two plethysmographs. The wrist cuff was inflated at the same time as the upper arm cuff, and at the same pressure. The cuff produced venous occlusion at the wrist, allowing measurement of the rate of increase of volume in the hand and also preventing return of blood from the hand to the forearm during the period of forearm blood flow measurement (Fig. 1). In the four subjects in whom hand blood flow was not measured, a pneumatic cuff was placed around the wrist and inflated to suprasystolic pressure during the period of measurement to exclude con-

tribution of hand blood flow from the measurement of forearm flow.

Each subject breathed three gas mixtures through a Rudolph valve: room air, 12% oxygen (in nitrogen), and 10% oxygen. Since the three gas mixtures can be given in six possible sequences, 2 of 12 subjects received each sequence. The gases were breathed for 16 min, with a 10-min rest period between each gas. After breathing each gas for 5 min, control measurements were taken for 3 min, and then the response to reflex vasoconstrictor stimuli was studied. The pressure within the suction box surrounding the lower body was reduced to 40 mm Hg below atmospheric pressure, and maintained for 1.5 min. Lower body negative pressure induces constriction of forearm resistance vessels (7, 9, 10), apparently by pooling of blood in the lower extremities. Lower body negative pressure was applied twice while breathing each gas mixture, separated by a 1.5-min rest period, and after a 2 min rest period a plastic bag of ice was applied to the forehead for 1 min.

Blood flow to the forearm and hand were calculated from the rate of increase in the volume of the forearm or hand during venous occlusion and expressed in milliliters per minute per 100 ml of forearm or hand. About four blood flow curves were obtained each minute. Values were not obtained for blood flow (or blood pressure) during the first 30 sec of lower body negative pressure or of application of ice to the forehead, to avoid a rapidly shifting base line and to observe maximum responses. Values were averaged for the two periods of lower body negative pressure while breathing each gas. Forearm vascular resistance was derived by dividing mean arterial pressure by forearm blood flow and expressed in mm Hg per milliliter per minute per 100 ml. Mean arterial pressure was derived by adding one-third of the pulse pressure to the diastolic pressure (11).

Statistical comparisons were made by paired *t* test analyses, comparing values while breathing air or 12% oxygen, and air or 10% oxygen.

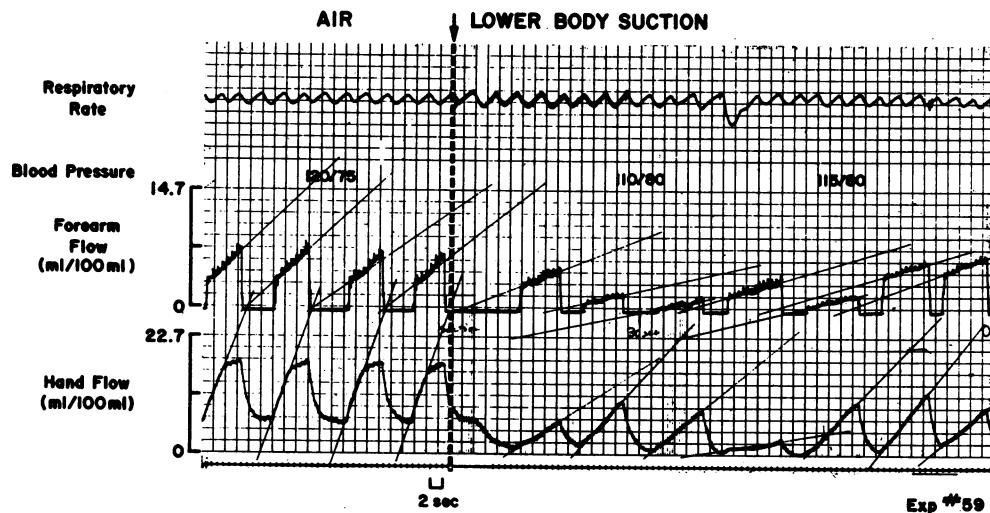


FIGURE 1 Changes in respiratory rate, systemic arterial pressure, forearm volume, and hand volume before and during lower body negative pressure while breathing room air. The slopes of the forearm and hand volume curves were used to calculate forearm and hand blood flow in milliliters per minute per 100 ml of forearm or hand. Lower body negative pressure caused a minimal increase in mean arterial pressure (with a narrowing of pulse pressure) and decreased forearm and hand blood flow.

TABLE I
*Mean Arterial Blood Pressure in Response to Lower Body Negative Pressure, and Ice on the Forehead while Breathing Air, 12% Oxygen, and 10% Oxygen**

Subjects	Air			12% O ₂			10% O ₂		
	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice
	<i>mm Hg</i>			<i>mm Hg</i>			<i>mm Hg</i>		
W. C.	95	95	97	88	75	95	83	73	95
T. Ki.	78	84	97	82	82	97	85	83	102
J. R.	82	83	102	83	81	93	83	79	88
J. J.	83	77	93	85	79	92	83	73	93
T. T.	82	85	107	96	95	107	90	90	97
E. S.	85	91	95	83	84	95	95	82	103
G. M.	90	93	105	90	85	103	95	83	108
D. R.	87	89	92	88	85	92	82	74	93
W. H.	85	85	92	87	87	92	87	80	90
L. B.	94	95	95	95	87	102	90	51	103
T. Ks.	90	91	95	90	87	97	93	70	102
J. I.	90	99	103	93	96	103	103	98	110
Mean	86.7	89.0	97.6	88.4	85.3	97.2	89.2	78.0	98.7
SE	1.5	1.8	1.5	1.4	1.7	1.5	1.9	3.4	2.0
P†				>0.05	<0.001	>0.05	>0.05	<0.001	>0.05

* Con refers to control (or "resting") observations, LBNP refers to lower body negative pressure, and Ice to application of Ice to the forehead.

† P values for control values refer to significance of difference of control values while breathing 12% or 10% oxygen from control values while breathing air. P values for LBNP and Ice refer to significance of difference between change in mean arterial pressure caused by LBNP or Ice while breathing air or 12% oxygen and air or 10% oxygen.

TABLE II
*Forearm Vascular Resistance in Response to Lower Body Negative Pressure and Ice on the Forehead while Breathing Air, 12% Oxygen, and 10% Oxygen**

Subject	Air			12% O ₂			10% O ₂		
	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice
	<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>		
W. C.	33	87	64	37	54	56	26	32	34
T. Ki.	21	42	42	20	30	7	13	22	20
J. R.	26	56	60	19	38	35	17	34	24
J. J.	31	77	41	29	49	34	36	46	29
T. T.	20	47	34	21	40	29	20	35	22
E. S.	14	27	23	12	18	16	21	22	20
G. M.	35	52	55	39	42	30	34	35	23
D. R.	30	41	33	25	37	31	23	23	27
W. H.	23	28	37	22	32	14	21	38	18
L. B.	24	40	30	26	34	28	23	23	26
T. Ks.	11	26	14	16	31	17	15	19	20
J. I.	15	24	22	16	19	18	17	21	20
Mean	23.6	45.4	37.9	23.5	35.4	26.1	22.2	29.1	23.5
SE	2.2	5.8	4.5	2.4	3.1	3.7	2.0	2.4	1.4
Mean of individual % change from Con		92.2	58.8		28.8	38.8		36.0	11.6
SE of % change		13.6	10.1		8.3	11.2		10.3	7.4
P†				>0.05	<0.01	<0.01	>0.05	<0.01	<0.001

* See footnote to Table I.

† See footnote † to Table I.

TABLE III
Forearm and Hand Blood Flow While Breathing Air,
12% Oxygen, and 10% Oxygen*

Subject	Forearm blood flow			Hand blood flow		
	Air	12% O ₂	10% O ₂	Air	12% O ₂	10% O ₂
	<i>ml/100 ml</i>			<i>ml/100 ml</i>		
W. C.	2.9	2.4	3.2			
T. Ki.	3.7	4.2	6.4			
J. R.	3.1	4.3	5.0			
J. J.	2.7	2.9	2.3			
T. T.	4.1	4.6	4.4	23.0	16.8	16.9
E. S.	5.9	7.0	4.6	10.4	9.0	5.3
G. M.	2.6	2.3	2.8	9.3	11.1	5.4
D. R.	2.9	3.5	3.6	14.9	14.2	17.3
W. H.	3.7	4.0	4.1	10.7	9.6	11.4
L. B.	3.9	3.7	3.9	26.8	29.1	21.7
T. Ks.	8.2	5.6	6.1	18.4	9.5	8.6
J. I.	5.9	5.8	6.1	16.3	14.4	14.9
Mean	4.13	4.19	4.38	16.22	14.21	12.69
SE	0.49	0.41	0.38	2.22	2.35	2.12
P†		>0.05	>0.05		>0.05	<0.05

* Values are averages of 3 min of resting values while breathing each gas mixture.

† Values refer to significance of difference of forearm or hand blood flow while breathing air or 12% oxygen and air or 10% oxygen.

RESULTS

Effect of hypoxia on resting blood pressure and vascular resistance. Mean arterial pressure and forearm vascular resistance were not significantly different while breathing air, 12% oxygen, or 10% oxygen (Tables I and II). Blood flow to the hand decreased during hypoxia; the reduction was statistically significant during the administration of 10% oxygen (Table III).

Responses to lower body negative pressure. Mean arterial pressure increased minimally during lower body negative pressure while breathing air, and fell during lower body negative pressure while breathing 12% or 10% oxygen (Table I). The increase in forearm vascular resistance during lower body negative pressure was significantly greater during normoxia than during either level of hypoxia (Table II).

Responses to application of ice to the forehead. The increase in mean arterial pressure during ice on the forehead was not significantly different while breathing air, 12% oxygen, and 10% oxygen (Table I). The increase in forearm vascular resistance which occurs during ice on the forehead while breathing air was markedly reduced during hypoxia (Table II).

DISCUSSION

These experiments indicate that constriction of forearm resistance vessels in response to lower body negative

pressure is reduced during hypoxia. Reduction in vasoconstrictor responsiveness might explain the fall in arterial pressure observed with lower body negative pressure during hypoxia.

There may be an alternative to the interpretation that hypoxia reduces forearm vasoconstriction. We observed that hypoxia reduced blood flow to the hand, and tended to increase blood flow to the forearm, in agreement with previous studies (12-15). If the hand and the cutaneous portion of the forearm respond similarly to hypoxia, then it appears that cutaneous vasoconstriction occurs during hypoxia with dilatation of the vessels supplying the muscle bed, so that a greater proportion of blood flow to the forearm is distributed to the muscular portion of the forearm during hypoxia. If the vasoconstrictor response of vessels to muscle is less than that of cutaneous vessels in response to lower body negative pressure, the apparent decrease in forearm vasoconstriction by hypoxia might be due simply to the greater proportion of blood flow to the less responsive bed, the muscle. For this reason, we compared the changes in blood flow to the hand, which consists predominantly of skin flow (16), to the changes in the forearm, which consists of both skin and muscle flow. The decreases in flow during lower body negative pressure are virtually identical in the hand ($-38 \pm 5\%$ SE) and forearm ($-37 \pm 5\%$), suggesting that the proportion of skin and muscle flow

does not affect the response to lower body negative pressure. Thus the shift of blood flow within the forearm from cutaneous to muscular vessels during hypoxia would not account for the decreased forearm vasoconstrictor response to lower body negative pressure.

In response to application of ice to the forehead, blood flow to the hand decreased more ($-35 \pm 7\%$) than blood flow to the forearm ($-21\% \pm 3\%$), confirming the greater responsiveness to ice of cutaneous vessels than vessels to muscle. Therefore, part of the reduction in responsiveness to ice during hypoxia might be caused by shifting of blood flow from skin to muscle by hypoxia. However, for shifts of blood flow during hypoxia to virtually abolish the forearm vasoconstriction during ice, as was observed in these experiments, the shifts would have to be much greater than those observed.

Intra-arterial guanethidine blocks the vasoconstrictor response to the application of ice to the forehead (6) and also to lower body negative pressure (in two experiments). Intra-arterial guanethidine is known to interrupt the transmission of neurogenic stimuli, but does not block the effects of circulating catecholamines. This suggests that the responses to the application of ice to the forehead and to lower body negative pressure are mediated predominantly through neurogenic reflexes (6, 7). Therefore the major new finding in this study is that hypoxia decreases the vasoconstrictor response to neurogenic reflexes.

The interference with neurogenic vasoconstriction by hypoxia causes a fall in arterial pressure during lower body negative pressure. Since the pooling of blood in the

lower extremities during negative pressure simulates postural changes, the failure to maintain arterial pressure during negative pressure suggests the possibility of diminished postural compensatory mechanisms in the many diseases associated with hypoxia. In addition, decreased neurogenic vasoconstriction during acute hypoxia has important implications concerning compensation for acute blood loss, which is a neurogenic vasoconstrictor stimulus, during hypoxia associated with general anesthesia, pulmonary disease, and after a myocardial infarction.

II

Responses to norepinephrine and angiotensin

METHODS

We did 24 experiment on 15 healthy young men. The studies were done with the subject lying supine in a warm room (80°F).

In 12 subjects the brachial artery was cannulated with a polyethylene cannula (PE 90) after superficial infiltration of the antecubital area over the artery with 2% xylocaine. The cannula was introduced approximately 2 inches into the artery, and connected to a pressure transducer and to a syringe for infusions of norepinephrine and angiotensin.

Forearm and hand blood were measured as described in the previous study in this report.

Each subject breathed three gas mixtures: room air, 12% oxygen, and 10% oxygen with a 10 min rest period between each gas. Since the three gases can be given in six possible sequences, 2 of the 12 subjects received each sequence.

TABLE IV
Arterial Blood Gas Oxygen and Carbon Dioxide Tension and pH While Breathing Air, 12% Oxygen, and 10% Oxygen*

Subjects	PO ₂			PCO ₂			pH		
	Air	12% O ₂	10% O ₂	Air	12% O ₂	10% O ₂	Air	12% O ₂	10% O ₂
		<i>mm Hg</i>			<i>mm Hg</i>				
R. W.	84.4	28.4	26.0	39.1	31.7	34.5	7.39	7.43	7.43
T. Ki.	83.5	36.7	28.0	37.7	32.5	37.0	7.39	7.42	7.43
J. R.	90.8	42.3	31.6	40.5	34.7	26.2	7.41	7.44	7.47
J. J.	88.2	41.0	33.4	41.3	31.5	35.7	7.43	7.45	7.45
T. T.	89.0	40.2	34.4	30.0	35.8	31.0	7.38	7.43	7.46
R. S.	82.5	41.0	32.6	41.5	34.8	32.2	7.38	7.42	7.44
D. R.	94.6	37.8	39.3	34.2	21.8	17.8	7.40	7.42	7.46
G. M.	88.5	44.5	38.0	37.2	34.1	23.5	7.38	7.43	7.45
L. B.	97.5	46.4	36.0	30.7	31.0	25.9			
M. R.	95.9	39.5	31.1	30.2	31.1	27.2	7.44	7.44	7.47
D. M.	91.0	51.0	51.7	30.8	19.4	20.2	7.47	7.46	7.50
Mean	89.6	40.8	34.7	35.8	30.8	28.3	7.407	7.434	7.456
SE	1.5	1.7	2.1	1.4	1.6	1.9	0.010	0.004	0.007

* PO₂ and PCO₂ refer to arterial blood oxygen and carbon dioxide tension.

TABLE V
Forearm Blood Flow in Response to Norepinephrine and Angiotensin into the Brachial Artery While Breathing Air, 12% Oxygen, and 10% Oxygen*

Subject	Air					12% O ₂			10% O ₂				
	Con†	NE ₁	NE ₂	A ₁	A ₂	Con	NE ₁	NE ₂	Con†	NE ₁	NE ₂	A ₁	A ₂
	ml/100 ml					ml/100 ml			ml/100 ml				
R. W.	1.4	1.0	1.1	1.0	0.7	1.9	1.5	1.6	1.6	1.1	1.5	1.7	1.7
T. K.	3.0	1.8	1.6	1.7	1.4	3.4	2.6	2.4	5.2	3.1	3.1	2.9	3.1
J. R.	4.4	3.1	2.8	2.5	2.5	3.9	2.6	2.6	4.4	2.8	3.2	3.2	3.1
J. J.	3.9	2.4	2.2	2.1	2.9	3.4	2.5	2.4	4.5	3.4	3.3	3.2	2.5
T. T.	3.2	2.1	1.7	2.2	1.8	6.1	4.7	3.4	5.1	4.5	3.7	2.9	2.6
R. S.	4.1	3.9	3.4	2.7	2.4	5.4	5.2	4.5	4.0	3.7	4.0	3.2	3.8
G. M.	3.4	2.1	1.9	2.6	2.2	2.8	1.7	1.9	3.1	2.2	2.3	2.4	2.4
D. R.	2.6	2.2	2.0	2.2	2.1	3.1	2.9	2.4	3.4	3.7	2.6	2.7	2.9
W. H.	4.8	3.3	3.3	3.1	2.8	6.5	4.4	3.6	6.7	5.8	4.3	4.9	4.8
L. B.	3.7	2.6	2.6	2.1	1.6	4.6	4.2	2.9	2.8	2.6	2.2	2.9	2.6
M. R.	3.5	2.3	1.4	2.5	1.4	3.7	2.7	2.3	4.0	2.1	2.4	1.7	1.7
D. M.	3.4	2.3	2.2	2.6	2.9	3.8	3.6	3.4	4.3	3.3	2.3	3.3	3.2
Mean	3.45	2.42	2.18	2.28	2.06	4.05	3.22	2.78	4.09	3.19	2.91	2.92	2.78
SE	0.26	0.22	0.21	0.16	0.20	0.39	0.34	0.23	0.38	0.35	0.24	0.24	0.23
Mean of individual % change from Con		29.8	36.3	33.0	40.4		20.8	29.5		21.9	26.8	25.4	28.6
SE of % change		2.9	3.6	2.8	4.2		3.5	3.2		4.7	3.9	5.2	5.2

* Con refers to control (or "resting") observations. NE₁ and NE₂ refer to the doses of norepinephrine and A₁ and A₂ to the doses of angiotensin: 75 and 150 ng/min respectively.

† Individual control values during air and 10% O₂ are averages of the two control periods before norepinephrine and angiotensin infusions.

After breathing each gas for 5 min, control measurements were made for 3 min, and then either *l*-norepinephrine-bitartrate or angiotensin was infused into the brachial artery. The drug was infused with a Harvard constant infusion pump at a dose of 75 μg/min (as the base) for 3 min and then at 150 μg/min for 3 min. The drugs were diluted in 5% dextrose in water and infused at 1.0 and 2.0 ml/min. Norepinephrine was infused while each subject was breathing air, 12% oxygen, and 10% oxygen, and angiotensin was infused while breathing air and 10% oxygen. In six subjects

norepinephrine was infused before angiotensin, and in six subjects the order was reversed.

An arterial blood sample was obtained after 6 min of breathing each gas. Po₂ (oxygen tension), Pco₂ (carbon dioxide tension), and pH were determined by a Corning model 16 blood gas system.

In 12 other experiments a No. 17 Intracath was inserted about 3 inches into the basilic vein and connected to a syringe for infusion of norepinephrine. Calf blood flow was measured with a water plethysmograph (17). A pneumatic cuff was placed around the ankle and inflated to suprasystolic pressure during the measurements to exclude the contribution of venous return from the foot to changes in calf volume. A pneumatic cuff was placed around the thigh and inflated intermittently for 10-15 sec to pressures sufficient to produce venous occlusion. Blood pressure was determined by auscultation.

The subjects breathed room air, 12% oxygen, and 10% oxygen twice: 3 and 6 μg/min of norepinephrine (as the base) were infused into the basilic vein while breathing each gas mixture. The norepinephrine was diluted in 5% dextrose in water and infused with a Harvard pump. Statistical comparisons were made by analysis of variance.

RESULTS

Arterial blood oxygen and carbon dioxide tensions. Average arterial blood Po₂ decreased from 90 mm Hg while breathing air to 41 mm Hg during 12% oxygen and 35 mm Hg during 10% oxygen (Table IV). Accompanying the decrease in Po₂ during hypoxia was a fall in Pco₂ and a rise in pH.

Effect of hypoxia on responsiveness to intraarterial norepinephrine and angiotensin The doses of norepi-

TABLE VI
Analysis of Variance of Forearm Responses to Norepinephrine and Angiotensin While Breathing Air and 10% Oxygen*

Source of variation	Decrease in forearm blood flow			
	df	Mean square	F	P
Subjects	11	780		
Oxygen†	1	2035	9.37	<0.025
Drug dose	1	724	15.69	<0.005
Drug‡	1	241	1.37	>0.05
Error	11	53.8		

* Analysis of variance was done on the per cent decrease in forearm flow to consider resting values as well as absolute reductions as described in the text.

† Oxygen refers to variation among responses to drugs while breathing air and 10% oxygen.

‡ Drug refers to difference between responses to norepinephrine and angiotensin.

TABLE VII
*Mean Arterial Blood Pressure in Response to Intravenous Norepinephrine While Breathing Air, 12% Oxygen, and 10% Oxygen**

Subject	Air			12% O ₂			10% O ₂		
	Con	NE ₁	NE ₂	Con	NE ₁	NE ₂	Con	NE ₁	NE ₂
	<i>mm Hg</i>			<i>mm Hg</i>			<i>mm Hg</i>		
W. C.	93	14	26	99	16	20	96	15	17
T. K.	94	15	20	100	14	24	96	3	24
J. R.	86	11	8	89	9	21	82	9	17
T. T.	90	11	16	88	1	8	91	6	10
J. J.	83	7	15	85	7	13	86	3	10
F. T.	85	12	18	90	5	9	90	10	21
G. M.	91	11	21	88	8	19	97	10	16
D. R.	96	20	34	95	22	31	87	14	30
L. B.	94	17	24	94	17	22	90	7	20
M. R.	90	4	9	94	6	10	97	4	10
D. M.	82	12	18	86	11	15	88	6	14
R. P.	100	13	22	97	7	16	111	5	12
Mean	90.4	12.2	19.2	92.2	10.2	17.3	92.5	7.7	16.8
SE	1.6	1.2	2.1	1.5	1.7	2.0	2.2	1.2	1.8

* Control values indicate actual values; NE₁ and NE₂ values are the increase in mean arterial pressure from the control values during infusion of two doses of norepinephrine: 3 and 6 µg/min.

nephrine and angiotensin were insufficient to cause detectable changes in blood pressure or heart rate. The reduction in blood flow to the forearm during both norepinephrine and angiotensin was significantly less during hypoxia than during normoxia (Tables V and VI).

Effect of hypoxia on blood pressure response to intravenous norepinephrine. Resting mean arterial pressure was not significantly different while breathing air, 12% oxygen, and 10% oxygen (Table VII). The increase in blood pressure in response to intravenous norepinephrine was significantly less during hypoxia than during normoxia (Tables VII and VIII).

Effect of hypoxia on calf response to intravenous norepinephrine. Resting calf vascular resistance was not significantly altered ($P > 0.05$) by hypoxia (Fig. 2). The increase in calf vascular resistance during two doses of intravenous norepinephrine was not significantly different during normoxia and hypoxia.

DISCUSSION

These experiments indicate that hypoxia decreases the constrictor response of forearm resistance vessels to infusions of norepinephrine and angiotensin into the brachial artery. In terms of relative potency, twice the dose of norepinephrine and angiotensin were required during hypoxia to give the same vasoconstriction occurring during normoxia. The absolute levels of flow

achieved during infusions of norepinephrine and angiotensin were lower during normoxia than those during hypoxia. The absolute reductions in flow during norepinephrine and angiotensin were similar during normoxia and hypoxia. However, at high levels of resting blood flow the absolute reduction in blood flow was greater (Fig 3), so that similar absolute reduction in flow does not mean that responsiveness did not change because, if this were the case, one would have expected greater reductions in flow at the higher resting flows during hypoxia.

We considered the possibility that shifts of flow within the forearm from skin to muscle during hypoxia might contribute to the decrease in responses to norepinephrine. The response of the hand to norepinephrine was greater than that of the forearm (Fig. 4), indicating greater response of the skin than muscle. However, the shift of flow from skin to muscle during hypoxia appeared to be of small magnitude, particularly during 12% oxygen, and not sufficient to explain the decrease in forearm responses during hypoxia. The response to angiotensin was similar in the hand and forearm, so that shifts of blood flow from skin to muscle would not account for the diminished response to angiotensin during hypoxia. Therefore, the small shift of flow from skin to muscle within the forearm during hypoxia does not appear to account for the decreased forearm vascular responsiveness to norepinephrine and angiotensin during hypoxia.

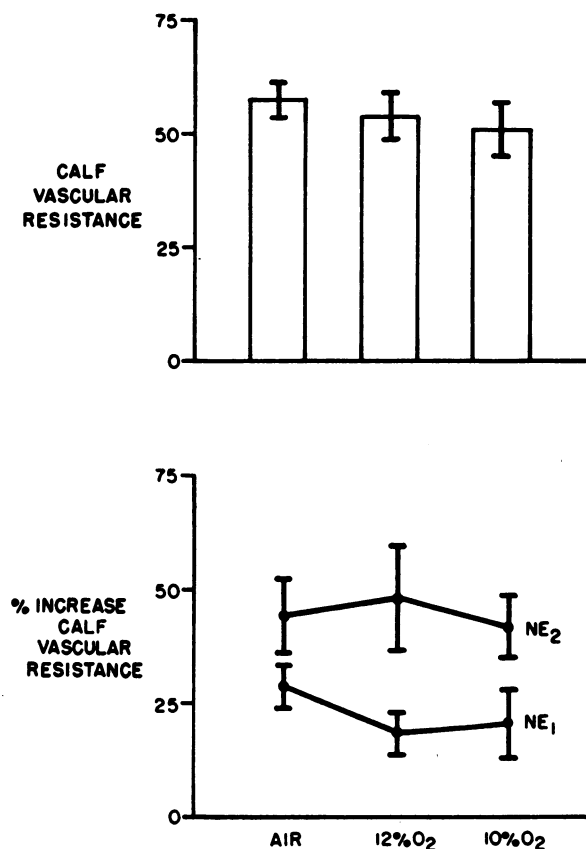


FIGURE 2 Mean (± 1 SE) resting calf vascular resistance in mm Hg/ml/min/100 ml calf (upper half) and per cent increase in calf vascular resistance in response to an intravenous infusion of 3 and 6 μ g/min norepinephrine (lower half), while breathing air, 12% oxygen, and 10% oxygen.

Hypoxia decreased the response to intravenous as well as intra-arterial norepinephrine, as the increase in mean arterial pressure during intravenous norepinephrine was

significantly less during hypoxia than during normoxia. Although the pressor response to intravenous norepinephrine was diminished during hypoxia, the increase in calf vascular resistance during norepinephrine was not significantly different during normoxia and hypoxia. The similar increase in calf vascular resistance, but with a greater increase in distending pressure during normoxia, suggests a greater increase in vasoconstrictor tone during norepinephrine infusion during normoxia than hypoxia.

Detar and Bohr (18) have reported that hypoxia decreases the response of aortic strips to epinephrine, suggesting that hypoxia limits oxidative pathways, with diminished high-energy phosphate production. Whether systemic hypoxia in man actually causes hypoxia in the vascular smooth muscle is not answered at the present time.

The effect of hypoxia in reducing vasoconstrictor responses to norepinephrine, the neurotransmitter released during reflex vasoconstriction, appears to be one mechanism by which hypoxia decreases reflex vasoconstriction. However, it appears that hypoxia decreases reflex vasoconstrictor responses to a greater degree than the responses to norepinephrine, suggesting that hypoxia has additional effects on the reflex vasoconstrictor arc.

III

Effect of hypoxia and hypocapnia

METHODS

We studied 12 healthy men. Responses to lower body negative pressure and the application of ice to the forehead were compared during four conditions.

- (a) Normoxia and normocapnia: while breathing air.
- (b) Hypoxia and hypocapnia: while breathing 12% oxygen.

TABLE VIII
*Analysis of Variance of Mean Arterial Pressure Responses to Intravenous Norepinephrine While Breathing Air, 12% Oxygen, and 10% Oxygen**

Source of variation	Effect of oxygen on resting mean pressure				Effect of oxygen on increase in mean pressure during norepinephrine			
	df	Mean square	F	P	df	Mean square	F	P
Subjects	11	85			11	147		
Oxygen†	2	15.7	1.09	>0.20	2	75.5	4.98	<0.025
Dose					1	1073.0	108.05	<0.001
Error	22	14.4			22	9.0		

* Analysis of variance was done on the absolute values of resting mean arterial pressure and on the absolute values for change in mean pressure during norepinephrine.

† Oxygen refers to variation in resting pressure and responses to norepinephrine while breathing air, 12% oxygen, and 10% oxygen.

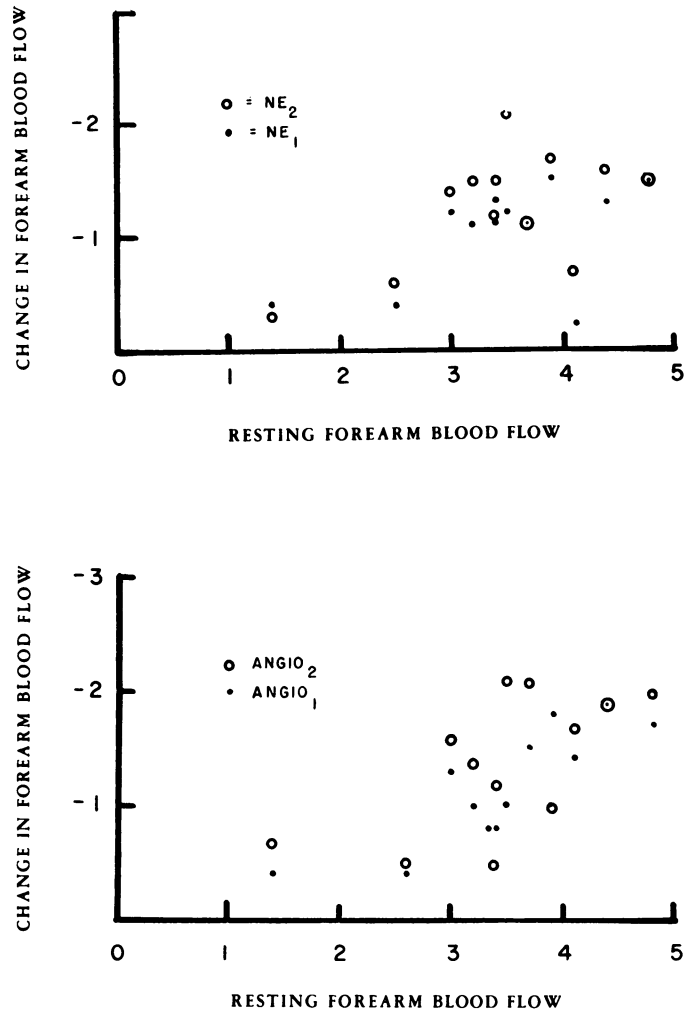


FIGURE 3 Relationship between resting forearm blood flow and the decrease in forearm flow (expressed in ml/min/100 ml forearm) in response to 75 and 150 $\mu\text{g}/\text{min}$ of norepinephrine (upper half) and angiotensin (lower half) infused into the brachial artery, while breathing air. A positive correlation exists between resting forearm flow and the decrease in forearm flow: in response to 75 μg norepinephrine (NE_1) $r = 0.54$ ($P > 0.05$); in response to 150 μg norepinephrine (NE_2) $r = 0.58$ ($P = 0.05$); in response to 75 μg angiotensin (Angio_1) $r = 0.83$ ($P < 0.01$); in response to 150 μg angiotensin (Angio_2) $r = 0.62$ ($P < 0.05$).

(c) Hypoxia and normocapnia: while breathing 10.5% oxygen with carbon dioxide replacement. End-tidal CO_2 was measured directly by an LB-1 infrared CO_2 analyzer, with continuous sampling at the mouthpiece. Additional carbon dioxide was added to the inspired 10.5% oxygen at flow rates sufficient to maintain end-tidal CO_2 at values similar to those obtained while breathing air. 300–500 cc of carbon dioxide was necessary to maintain normal end-tidal CO_2 . Since addition of carbon dioxide stimulates further hyperventilation and increases Po_2 during hypoxia (14), 10.5%

oxygen was inspired during carbon dioxide replacement in an attempt to approximate the Po_2 during 12% oxygen.

(d) Normoxia and hypocapnia: during hyperventilation while breathing room air. The subject adjusted his respiration to maintain an end-tidal CO_2 similar to the level achieved while breathing 12% oxygen.

In addition to continuously monitoring end-tidal CO_2 , alveolar samples were obtained with a Rahn-Otis sampling valve after breathing each gas mixture for 6 and 14 min. The alveolar gas samples were analyzed for Po_2 and PCO_2 .

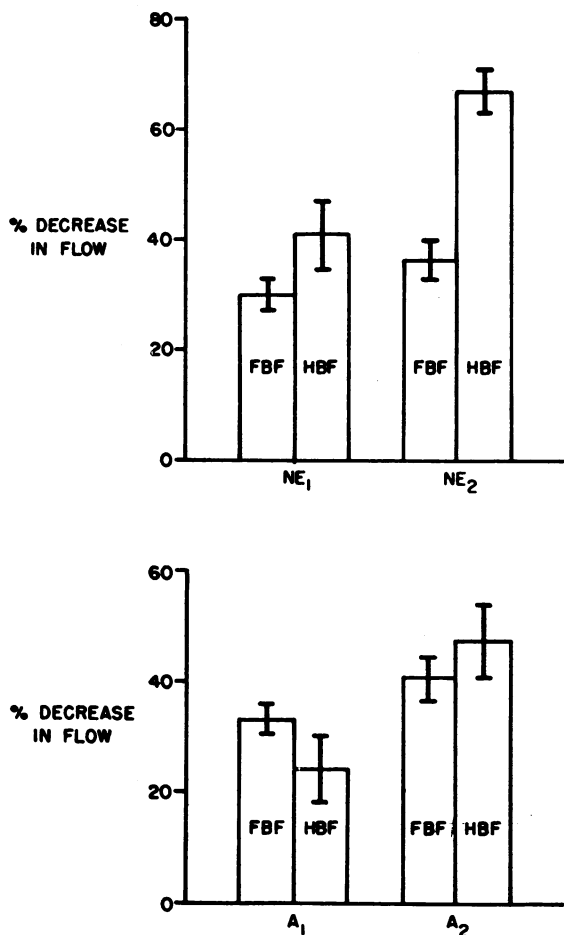


FIGURE 4 Mean per cent decrease in forearm (FBF) and hand (HBF) blood flow in response to 75 and 150 µg/min of norepinephrine (upper half) and angiotensin (lower half) infused into the brachial artery. Measurements were obtained while breathing room air.

with an IL Ultramicro Gas Analyzer. Expiratory minute volume was collected and measured.

Forearm and hand blood flow were measured with water plethysmographs, and blood pressure determined by auscultation.

RESULTS

Alveolar oxygen and carbon dioxide tensions. Alveolar P_{CO_2} was reduced to virtually identical levels while breathing 12% oxygen and during hyperventilation while breathing air (Table IX). Alveolar P_{CO_2} was similar while breathing air and while breathing 10.5% oxygen with carbon dioxide replacement. The alveolar P_{O_2} was reduced to similar levels while breathing 12% oxygen and while breathing 10.5% oxygen with carbon dioxide replacement.

Effect of hypoxia and hypocapnia on blood pressure and vascular resistance. Mean arterial pressure and forearm vascular resistance were not significantly altered by hypoxia or hypocapnia (Tables X and XI). Hand blood flow was significantly greater ($P < 0.05$) while breathing air (20.4 ± 2.5 SE) than during either the hypoxic or hypocapnic periods (14.8 ± 2.6 during 12% oxygen, 16.2 ± 2.5 during 10.5 O_2 with CO_2 replacement, and 15.9 ± 2.4 during hyperventilation.).

Effect of hypoxia and hypocapnia on responses to lower body negative pressure. Lower body negative pressure causes a similar fall in mean arterial pressure during hypoxia with and without carbon dioxide replacement (Tables X and XII). The lower body negative pressure caused a negligible fall in mean arterial pressure during the hypocapnia of hyperventilation. Therefore, hypocapnia appears to contribute minimally to the hypotensive effect of lower body negative pressure during acute hypoxia. The increase in forearm vascular resistance in response to lower body negative pressure was diminished during hypoxia with and without carbon dioxide replacement (Tables XI and XII).

Effect of hypoxia and hypocapnia on responses to application of ice to the forehead. The increase in mean arterial pressure during application of ice to the forehead was not significantly altered during hypoxia or hypocapnia (Tables X and XIII). The increase in forearm vascular resistance which occurs during application of ice to the forehead while breathing air was markedly reduced during hypoxia, with and without carbon dioxide replacement, and by the hypocapnia of hyperventilation (Tables XI and XIII).

DISCUSSION

In a previous study (13), addition of carbon dioxide to the inspired mixture during exposure to acute hypoxia decreased the forearm vasodilatation which occurs during severe hypoxia, suggesting an important role of hypocapnia in the cardiovascular response to hypoxia. However, addition of carbon dioxide stimulates further hyperventilation and significantly increases the P_{O_2} during hypoxia (14). When hypocapnia was eliminated during acute hypoxia without a change in P_{O_2} , the circulatory response to acute hypoxia was not altered (14).

These experiments indicate that hypoxia, but not hypocapnia, decreases the vasoconstrictor response to lower body negative pressure, with a fall in arterial pressure. In contrast to the primary role of oxygen in the response to lower body suction, both hypocapnia and hypoxia decreased the forearm vasoconstrictor response to the application of ice to the forehead. The diminished vasoconstrictor response to norepinephrine during hypoxia appears to be unrelated to hypocapnia. In Part II

TABLE IX
Alveolar Carbon Dioxide and Oxygen Tension*

Subject	Pco ₂				Po ₂			
	Air	Hyper	12% O ₂	10.5% O ₂ and CO ₂	Air	Hyper	12% O ₂	10.5% O ₂ and CO ₂
			<i>mm Hg</i>				<i>mm Hg</i>	
J. R.	37.8	36.0	36.8	40.8	104.3	109.7	54.8	56.7
L. H.	40.1	35.7	37.4	39.0	103.3	108.1	58.0	58.6
D. O.	41.5	32.0	32.8	40.1	98.4	108.8	50.7	50.0
T. T.	35.0	31.2	28.6	37.0	114.2	111.2	63.6	50.0
R. J.	39.4	37.5	34.0	38.0	104.6	107.2	54.6	52.4
R. R.	37.8	29.0	35.0	41.0	107.0	115.6	49.8	53.4
R. A.	42.6	32.5	33.5	37.7	107.6	112.9	52.4	55.8
B. S.	36.0	33.4	29.2	39.6	111.8	113.8	57.6	52.4
E. W.	37.8	31.8	31.6	37.6	105.4	112.4	54.2	51.6
D. R.	36.7	35.6	33.8	41.4	114.6	112.4	54.0	55.2
J. S.	35.8	30.0	29.2	39.8	127.0	120.0	54.5	53.2
G. M.	33.9	29.4	30.0	37.2	114.2	119.6	54.7	53.6
Mean	37.9	32.8	32.7	39.1	109.4	112.6	54.9	53.6
SE	0.8	0.8	0.9	0.5	2.2	1.2	1.0	0.8

* Hyper refers to hyperventilation while breathing air. 10.5% O₂ and CO₂ refers to breathing 10.5% oxygen with replacement of carbon dioxide to normal values. Each value represents the average of two values obtained during each condition.

of this study, in 4 of the 24 periods of exposure to hypoxia the arterial blood Pco₂ was higher during hypoxia than while breathing air (Table IV) and in all four the vasoconstrictor response to intra-arterial norepinephrine was reduced during hypoxia. It therefore

appears that, although hypocapnia may alter the response to some neurogenic stimuli, the reduction in oxygen is the primary mechanism for decreased vascular responsiveness during acute hypoxia.

The levels of hyperventilation used in this study did

TABLE X
Mean Arterial Blood Pressure in Response to Lower Body Negative Pressure and Ice on Forehead during Alteration of Oxygen and Carbon Dioxide*

Subject	Air			Hyperventilation			12% O ₂			10.5% O ₂ and CO ₂		
	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice
			<i>mm Hg</i>			<i>mm Hg</i>			<i>mm Hg</i>			<i>mm Hg</i>
J. R.	85	85	103	88	89	90	88	82	93	89	87	102
L. H.	79	77	85	80	85	90	80	81	90	84	83	88
D. O.	102	95	115	103	100	117	99	89	108	97	88	112
T. T.	87	89	102	85	86	102	87	88	110	83	84	103
R. J.	84	82	95	87	84	95	86	85	95	84	83	92
R. R.	82	81	102	83	83	105	83	74	90	87	80	88
R. A.	90	89	100	91	83	105	90	86	110	93	87	103
B. S.	86	89	100	85	85	97	85	77	93	80	76	87
E. W.	81	85	100	93	93	102	88	84	95	90	93	102
D. R.	78	74	90	83	76	92	86	75	90	80	73	90
J. S.	94	99	123	97	96	125	93	87	110	95	87	113
G. M.	92	95	113	94	94	113	94	90	120	107	98	120
Mean	86.7	86.7	102.3	89.1	87.8	102.8	88.2	83.2	100.3	89.1	84.9	100.0
SE	2.0	2.2	3.0	1.9	1.9	3.2	1.5	1.6	3.0	2.3	2.0	3.2

* See footnote to Table I and IX.

TABLE XI
Forearm Vascular Resistance in Response to Lower Body Negative Pressure and Ice on the Forehead during Alteration of Oxygen and Carbon Dioxide*

Subject	Air			Hyperventilation			12% O ₂			10.5% O ₂ + CO ₂		
	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice	Con	LBNP	Ice
	<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>			<i>mm Hg/ml/min/100 ml</i>		
J. R.	8.6	11.0	17.8	12.6	18.5	12.7	12.1	13.4	11.1	8.7	11.6	17.9
L. H.	11.0	20.3	15.7	12.5	21.2	16.1	11.1	17.6	15.0	11.7	16.0	13.8
D. O.	17.3	20.2	19.5	18.1	27.0	23.9	16.2	18.5	16.9	12.3	9.2	14.4
T. T.	31.1	46.8	48.6	31.5	57.3	42.5	30.0	38.3	36.7	23.7	33.6	32.2
R. J.	31.1	41.0	33.9	36.2	49.4	22.1	23.9	30.4	27.9	28.0	34.6	30.7
R. R.	23.4	31.2	44.3	30.7	46.1	36.2	22.4	25.5	22.0	30.0	30.8	29.3
R. A.	14.3	26.2	45.5	13.4	22.4	30.0	16.1	26.1	47.8	16.6	25.6	57.2
B. S.	24.6	111.2	29.4	19.8	42.5	20.2	19.8	30.8	13.5	18.6	34.5	10.7
E. W.	38.6	85.0	50.0	46.5	77.5	60.0	24.4	38.2	29.7	26.5	56.4	35.2
D. R.	22.9	41.1	21.4	31.9	69.1	32.9	30.7	34.1	30.0	29.6	45.6	30.0
J. S.	25.4	47.1	58.6	32.3	60.0	40.3	32.1	37.8	42.3	30.6	29.0	33.2
G. M.	30.7	41.3	40.4	34.8	49.5	20.5	30.3	34.6	25.0	34.5	28.0	21.8
Mean	23.2	43.5	35.4	26.7	45.0	29.8	22.4	28.8	26.5	22.6	28.8	27.2
SE	2.7	8.2	4.2	3.2	5.6	3.9	2.1	2.5	3.4	2.5	3.4	3.7
Mean of individual % change from Con		84.7	63.9		68.9	18.1		30.8	22.3		29.9	32.7
SE of % change		25.8	19.3		7.7	12.2		6.1	16.9		10.3	22.1

* See footnote to Table X.

not alter resting forearm resistance or blood pressure. Previous studies have indicated that the hypocapnia associated with hyperventilation increases forearm blood flow (19, 20). However, those studies employed levels

of hyperventilation far greater than ours, in which minute volume increased from an average of 5.6 liters/min while breathing air to 6.8 liters/min during hyperventilation.

TABLE XII
Analysis of Variance and Calculation of Critical Difference of Responses to Lower Body Negative Pressure during Alteration of Oxygen and Carbon Dioxide*

Source of variation	Effect of O ₂ and CO ₂ on change in mean arterial pressure during negative pressure				Effect of O ₂ and CO ₂ on % change in forearm vascular resistance during negative pressure			
	df	Mean square	F	P	df	Mean square	F	P
Subjects	11	32.5			11	5612		
Treatments†	3	68.8	8.02	<0.001	3	9144	5.70	<0.005
Error	33	8.57			33	1605		

* To avoid doing multiple *t* test analyses on the same data, critical difference was calculated using the mean square error term, with *t*_{0.05} taken from a table by Tukey for the number of means involved (21). The critical difference for change in mean arterial pressure during lower body negative pressure was 3.2 mm Hg; from Table X it is evident that the response during air differs significantly from the response during 12% oxygen and from 10.5% oxygen with CO₂, and that the response during 12% oxygen differs from that during hyperventilation. The critical difference for change in forearm vascular resistance during lower body negative pressure was 44.3. From Table XI the response during air differs significantly from the response during 12% oxygen and from 10.5% oxygen with CO₂.

† Treatment refers to variation among responses to lower body negative pressure while breathing air, 12% oxygen, 10.5% oxygen with replacement of CO₂, and during hyperventilation.

TABLE XIII

*Analysis of Variance and Calculation of Critical Difference of Responses to Ice on the Forehead during Alteration of Oxygen and Carbon Dioxide**

Source of variation	Effect of O ₂ and CO ₂ on changes in mean arterial pressure during ice				Effect of O ₂ and CO ₂ on % change in forearm vascular resistance during ice			
	df	Mean square	F	P	df	Mean square	F	P
Subjects	11	96.3			11	12,587		
Treatments†	3	50.8	2.01	>0.05	3	5,152	5.24	<0.005
Error	33	25.3			33	983		

* See footnote to Table XII. Critical difference was not calculated for change in mean arterial pressure during ice on the forehead since analysis of variance indicated no significant differences were present. The critical difference for change in forearm vascular resistance during ice on the forehead was 34.7. From Table XI the response during air differs significantly from the response during 12% oxygen and from hyperventilation. † Treatment refers to variation among responses to ice on the forehead while breathing air, 12% oxygen, 10.5% oxygen with replacement of CO₂, and during hyperventilation.

It was again evident in these experiments, as in the other experiments in this report, that levels of hypoxia which do not consistently alter resting vascular resistance and arterial pressure nevertheless markedly decrease vasoconstrictor responsiveness. Although it is clear that resistance vessels exhibit significant "resting" tone, the finding that hypoxia decreases vasoconstrictor responses without altering vascular resistance appears to support the hypothesis (18) that oxygen is more likely to be rate limiting in the vascular smooth muscle during vasoconstriction.

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