Original article

Variability of cardiovascular responses to hypercapnia in Man

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Abstract: This study was conducted to assess the significance of the difference between forearm and finger blood flow responses to hypercapnia in man. Forearm and finger blood flows, arterial blood pressure and pulse were recorded in ten normal subjects, ages 19-22 years, while inhaling air and 8% CO_2 in air containing 20% O2. Flow in the forearm decreased by 14.99 to 35.15% in three (3/10) subjects and increased by 5.15 to 25.50% in seven (7/10) subjects. In the finger, it decreased by 2.22 to 80.61% in six (6/10) subjects and increased by 1.63 to 27.86% in four (4/10) subjects. The overall test mean forearm blood flow (4.53 ± 0.52ml/100ml) differed from the overall control mean forearm blood flow (4.32 ± 0.4 ml/100ml) only slightly (Mean difference = 0.209, P>0.50). On the other hand, the overall test mean finger blood flow (28.15 ± 5.24ml/100/min) differed from the overall control mean finger blood flow (33.08 ± 2.83ml/100/min) relatively more considerably (mean difference = -4.934, P>0.05). The individual variations are marked and equivocal in the forearm and less so in the finger thus showing that forearm blood flow response to hypercapnia is obscured by cholinergic activation of vasodilator nerves found in the forearm and not in the fingers. Any difference of response in the two vascular beds may probably be more evident in subjects who are more apprehensive and have muscular forearm. Unlike forearm blood flow, arterial blood pressure and pulse rate increased significantly and unequivocally in response to hypercapnia (P<0.05-0.001). This probably reflects an increased release of catecholamines and sympathetic activation with a respiratory "pacemaker" involvement. [*Ethiop. J. Health Dev.* 2000;14(2):135-141]

Introduction

The mechanism of vasomotion in the extremities under various conditions has been studied and elucidated for more than a century now. The regulation of the circulation through the skin and through the skeletal muscle were reviewed by Fox and Edholm (1) and Roddie and Shepherd (2), respectively. Blood flow in the forearm seems to be under three different mechanisms of vasomotion. Flow in the muscle is regulated by adrenergic vasoconstrictor and cholinergic vasodilator nerves of the sympathetic nervous system while that in the skin may be only under adrenergic influence. The adrenergic vasoconstrictor fibres are activated by stimuli like passive body tilt, hypercapnia and Valsalva manoeuvre

and inhibited by blocker drugs and anaesthetics. The cholinergic vasodilators are activated by emotional stress leading to the release of catecholamines with adrenaline having the preponderant action; they are inhibited by atropine. The vasodilator mechanism in the forearm skin which is dependent on rich vascularization is activated by heating and unaffected by atropine (1). This reflects that the regulation of flow in the forearm is complex and its interpretation subject to confounding.

Blood flow through the hand and the fingers is influenced by adrenergic sympathetic nerve fibres which induce vasoconstriction on activation and vasodilation on inhibition. The regulation in these vascular beds, therefore, appears to be relatively simpler as elucidated by several examples of of vasomotion relating to ventilation and the peripheral circulation. It

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is now understood that an increase in $PaCO_2$ supplying the vasomotor centre potentiates the activity of the latter and consequently, induces vasoconstriction in the limbs. It is, however, shown by several workers that the inhalation of a hypercapnic mixture may not affect the circulation consistently. Lennox et at (3) pointed out that breathing 4% to 8% CO_2 did not affect the blood flow through the legs consistently except perhaps the heart (11) and the brain (4, 5). Abramson et al (6) found that the forearm blood flow was either increased or unchanged during the inhalation of 7% CO_2. Roddie et al (7) observed little or no change in the forearm blood flow with the inhalation of 5% CO_2 in O_2. Richardson et al (8) obtained small and inconsistent changes in limb blood flow during the inhalation of 5-7% CO_2 for 5-10 minutes. They also found that 10 normal subjects inhaling 7% CO_2 for seven minutes showed a 45% increase in cardiac output accompanied by a rise in arterial blood pressure. Schneider et al (9) found an average flow reduction of 44.4% in the hand in six subjects following a stepwise increase of inhaled CO_2 concentration from 3% to 7% in air containing about 30% O_2. McArdle et al (10) also showed that two subjects inhaling 30% CO_2 in O_2 for less than two minutes had an intense vasoconstriction in the muscles of the calf and forearm and equivocal changes in hand blood flow. Inconsistent changes in heart rate and cardiac output in response to systemic hypercapnic were observed by several other workers (11, 12, 13, 14).

Subjects inhaling hypercapnic mixtures become apprehensive as they progressively feel the brunt of hypercapnia. In effect, both the cholinergic and adrenergic components of the sympathetic nervous system are activated (15, 16, 17, 18, 19, 20). Cholinergic activation induces an increase in the release of catecholamines into the circulation (21) leading to vasodilation of forearm muscle. This probably obscures, at least, partially the concurrent sympathetic vasoconstricting effect of hypercapnia on the forearm blood flow.

For reasons stated previously (1, 2), the regulation of blood flow is apparently less complex in the hands and fingers than in the forearm. The flow response to hypercapnia in the forearm and finger are, therefore, probably different. The present study was conducted to try and see if further clearing could be made on this issue by comparing the forearm and finger blood flow responses of ten normal subjects inhaling 8% CO_2 in air containing 20% O_2. Recording of arterial blood pressure and pulse rate was also included in this study to see if there was any obscurity in the hypercapnia-induced responses of these variables.

Methods
Forearm and finger blood flows, arterial blood pressure and pulse rate were studied in ten normal subjects, two females and eight males, ages 19-22 years while inhaling air and 8% CO_2 in air containing 20% O_2. The subjects were breathing at the rate of 12-14 and 15-18 breaths/min while inhaling air and the hypercapnic mixture, respectively in a room with an ambient temprature of 22-23°C. They were allowed to habituate to 3-5% CO_2 mixtures for about 10 minutes before the investigation started with 8% CO_2 in air which they could tolerate only for 3-4 minutes. This level of inspired CO_2 was understood to produce a significantly high $PaCO_2$ by inference from previous works (5, 12, 16).

A Whitney mercury-in-rubber resistance strain gauge with a balancing unit (22) coupled to a Devices setup of preamplifier and pen recorder was used to record blood flow through the former while the subject was inhaling air or CO_2 - O mixtures. This method is a well established innovation found to be accurate, convenient, and more sensitive than the conventional plethysmographs in measuring flow through the extremities (22, 23). It is easy to use for measuring flow through the penis (24) and also to record blood flow and pulses from the digits (25).

The flow to the hand was occluded at a pressure of about 200 mmHg. Then 4-5 inflow curves (Figure 1) were recorded for 3-4 minutes in each subject with the strain gauge wound on the forearm and with a pneumatic cuff placed on the upper arm at a pressure of about 60 mmHg to occlude the venous outflow for about 15 seconds. At the end of flow recording, the girth of the forearm under the strain gauge was measured and the strain gauge calibrated for each subject. The slope value per minute of the inflow curve was multiplied by the calibration factor formulated by Whitney (22) to approximate the forearm blood flow.

Loops of narrow silactic tube filled with mercury and fitted to Model 270 parks plethysmograph connected to Devices pen recorder via a CD preamplifier were used to measure finger blood flow (25, 26). Gauging of blood flow change in this setup is based on Whiney's principle which states that flow change is twice the percentage change in the girth of the extremity. Finger cuffs of 22-24 cm in diameter were used for venous tamponade during the recording of finger inflow curves. Then 4-5 control inflow curves were recorded from the middle phalanx of the index or middle finger while each subject was inhaling air or 8% CO_2 in air containing 20% O_2 (Fig 1). Finger blood flow was computed from each inflow curve using the method adopted by Birch (27). Arterial blood pressure and pulse rate were also recorded using the sphygmom-anometer and electrocardiograph, respectively. Mean +/-SD of reading taken from each subjec under the control and testing conditions was determined. Then the overall mean±sem was computed and test of significance for paired means performed using student t test as shown in Tables 1 and 2.

Results

The results show that the forearm blood flow response to hypercapnia studied in ten subjects is considerably equivocal (Tables 1 and 2). It was markedly decreased in one subject (-35.5%; Fig. 1) and less so in two others (-16.67%, -14.99%). Equivocally, it showed variable increase in seven subjects (5.15% to 25.5%, Table 1). The overall mean difference was only 0.209ml. The finger blood flow response to the CO_2-O_2 mixture, on the other hand, looked relatively less equivocal. The subject that showed strong forearm blood flow response to hypercapnia and was breathing relatively easily also showed very strong finger blood flow response (-80.61%, Table 1) to same CO_2-O_2 mixture. The vasoconstricting response in the finger was significant in four other subjects (-49.5%, -45.91%, -24.84%, -18.80%) and only slight in one subject (-2.22%). Equivocally, the finger blood flow was variably increased in four subjects (+27.86, 17.0%, +1.88%, +1.63%). The

Table 1: **The relative effect of 8% CO_2 in air containing 20% O_2 on forearm and finger blood flows (ml/100ml/min).**

| | Mean Forearm Blood Flow | | %Δ | Mean Finger Blood Flow | | |
	Air	8%CO₂		Air	8%CO₂	%Δ
	4.29±0.53	4.75±0.53	10.72	36.28±12.30	18.3 7.88	-49.56
	5.67±0.69	4.82±0.34	-14.99	35.17±11.53	34.39 7.95	-2.22
	5.75±0.78	6.44±0.94	12.00	36.79±14.21	37.48±5.1	1.88
	6.35±0.52	7.37±1.05	16.06	28.67±3.01	33.56±9.52	17.06
	4.32±0.71	5.11±0.22	18.29	26.05±8.19	14.09±4.35	-45.91
	2.39±0.36	1.55±0.51	-35.15	33.01±17.06	6.4±1.32	-18.61
	3.90±0.73	3.25±0.42	-16.67	50.51±6.21	4.18±8.72	27.86
	4.47±0.52	4.70±0.79	5.15	39.47±6.8	32.05±9.69	-18.80
	2.98±0.55	3.74±0.54	25.50	27.60±4.75	28.05±8.65	1.63
	3.10±0.71	3.58±0.38	15.48	17.27±2.73	12.98±1.66	-24.84
OM±SEM	4.32±0.41	4.53±0.52		33.08±2.83	28.15±5.24	
MD	0.209			-4.934		
P	>0.50			>0.05		

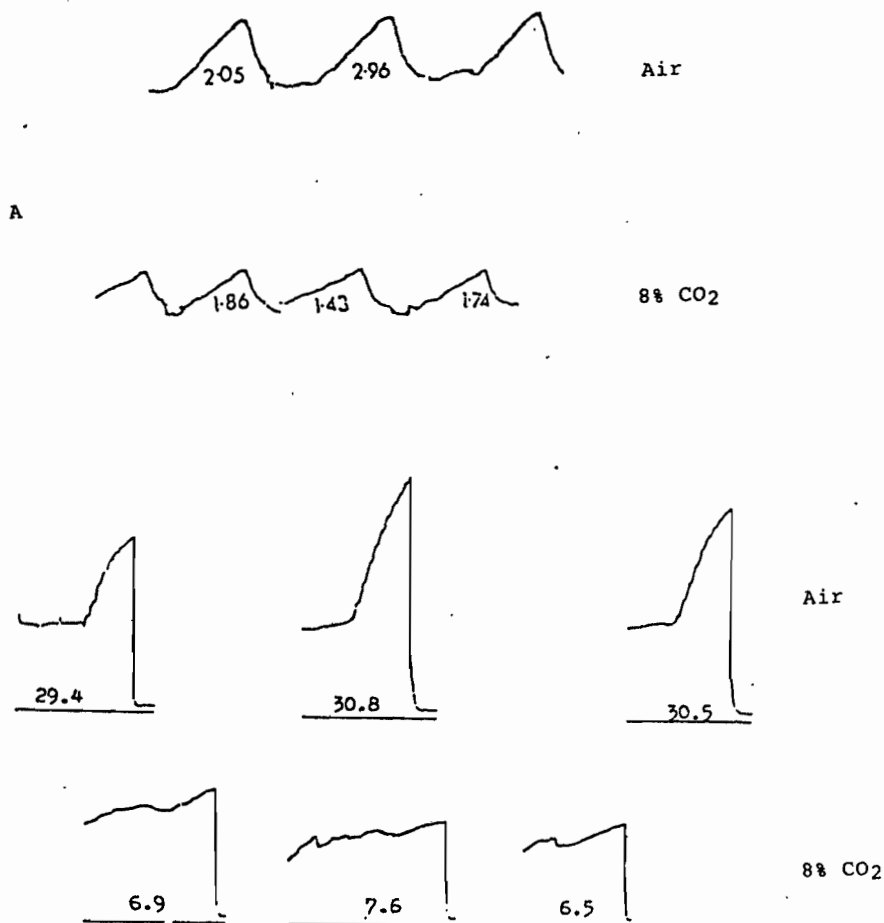OM = overall mean   SEM = standard error of mean   MD = mean difference

Figure 1: Forearm (A) and finger (B) inflow curves recorded in a normal subject inhaling air and 8% CO_2 in air containing 20% O_2

Table 2: The relative effects of 8% CO_2 in air on arterial blood pressure (mmHg) and pulse rate (beats/min)

| | Air | | 8% CO_2 | |
	MPR	MBP	MPR	MBP
	64	93.9	73	105.7
	75	98.5	77	122.9
	82	84.7	89	93.2
	66	82.8	79	86.1
	75	93.5	83	103.3
	60	79.5	75	89.6
	57	79.7	69	96.7
	79	92.3	90	107.4
	82	89.8	92	106.3
	58	88.5	68	97.0
OM ± SEM	69.80 ± 3.133	88.32 ± 0.042	79.50 ± 2.75	100.82 ± 3.371

Comparison:		MD		P value
MPRc vs MPRt		+9.70		<0.05
MBPc vs MBPt		-12.50		<0.001

MPRt = Control mean pulse rate (beats/min)   MPRt = Test mean pulse rate   MBPc = control mean blood pressure (mmHg)
MBPt = Test mean blood pressure, MD = Mean difference

overall mean difference in finger blood flow response to the inhalation of the hypercapnic mixture was - 4.934ml apparently indicating that the vasoconstricting effect of hypercapnia is more appreciable and less obscure in the finger than in the forearm.

As shown in Table 2, arterial blood pressure (P<0.001) and pulse rate (P<0.05) increased significantly and unequivocally in response to the inhalation of 8% CO_2 in air.

Discussion

The magnitude of blood flow response to a certain stimulus is dependent on the change in the sympathetic vasoconstrictor or vasodilator nerve activity and on the release of hormonal or other chemical substances into the blood stream. The human forearm blood flow is mainly regulated by a vasodilator mechanism (cholinergic deep in the muscle) with only a small component of adrenergic vasoconstrictor activity in the muscle (28).

This is in sharp contrast with the hand (or finger) in which control is effected mainly by the release of vasoconstrictor tone. As noted previously, cholinergic vasodilator nerve fibres are activated by emotional stress while the vasoconstrictor tone is influenced by different stimuli like passive body tilt (25) and hypercapnia (8,14). When hypercapnic mixtures are inhaled, forearm blood flow decreases in some subjects and shows little or no increase in others. The increase in flow appears to be more common in subjects who are relatively more apprehensive and hyperventilate strongly. This could be explained in at least two ways. When a person is apprehensive and quite stressed, it is likely that the vasodilator nerve fibres are activated thus inducing the release of adrenaline into the blood stream (1, 29, 30, 31, 32). Other possible factors affecting the flow response to hypercapnia are genetic variability (33) and the washing out of CO_2 during vigorous hyperventilation. Since the blood flow in the fingers is controlled mainly by sympathetic vasoconstrictor fibres, it is possible that finger

blood flow response is free of the effect of apprehension and, therefore, less obscure.

In the present study, the forearm blood flow response to hypercapnia was considerably equivocal with percentage changes ranging between -35.15 and +25.50 and a negligible overall mean difference of only 0.209ml. The increase in mean forearm blood flow in seven subjects (% ∆ =5.15-25.5) indicates that cholinergic activation secondary to apprehension predominates the vasoconstricting effect of hypercapnia. In three of the ten subjects, on the other hand, there was a response to hypercapnia as reflected by vasoconstriction (% ∆ =-14.99 to -35.15). This shows that the subjects in this category were not apprehensive. In both cases, the magnitude of cholinergic and adrenergic responses appear to be variable. The finger blood flow response, on the other hand, was relatively less equivocal with an overall mean difference of -4.934 ml. This apparently indicates that the vasoconstriction inducing effect of hypercapnia is more evident in the finger than in the forearm (Table 1). The responses in the two vascular beds are not much different statistically because some of the subjects with relatively small forearm muscle and minimal apprehension would show similar flow variations in the forearm and the finger. The variation in flow may apparently be more evident in subjects with larger forearm muscle and greater apprehension. In both cases, since the subject inhaling a hypercapnic mixture is hyperventilating, the concurrent increase in $PaCO_2$ would be relatively less while the removal of CO_2 from the brain tends to increase (15). This probably contributes to minimizing the vasoconstricting effect of hypercapnia on the peripheral circulation which is observed to be evident in some of the subjects in this study.

In two male subjects who were hyperventilating strongly the finger blood flow showed quite a considerable increase (27.86%, 17.06%). This is probably a normal fluctuation potentiated by the metabolic effect of increased

breathing. A CO_2 concentration of over 7.5% produces a moderate increase in cardiac output (4). The fact that hyperventilation secondary to inhalation of hypercapnic mixtures can produce an increase in cardiac output is also shown by Richardson et al (18). In these subjects, the increase in cardiac output is probably high enough to obscure the vasoconstricting effect of hypercapnia and even induce a moderate increase in blood flow. The increase in finger blood flow observed mainly in two of the ten subjects can not be attributed to cholinergic activation. The considerable reduction in finger blood flow in some of the subjects may be accounted for by not only the absence of vasodilator nerve fibres in the finger to be activated by stress but also probably by the vasoconstrictor tone which is relatively stronger in the finger than in the forearm.

Unlike the flow response, the hypercapnia-induced changes in arterial blood pressure ($P < 0.001$) and pulse rate ($P < 0.05$) were clearly unequivocal. Both of these variables increased significantly in all subjects inhaling the hypercapnic mixture. This finding is in agreement with other studies (21, 15, 18, 14) and the changes are attributable to the increase in sympathetic activity and the release of catecholamines. The efferent sympathetic activation probably interacts with respiratory "pacemakers" in the central nervous system in response to the increase in $PaCO_2$.

In conclusion, the overall results appear to be in favour of the hypothesis and suggest that a confounding factor like apprehension must be avoided to study the effect of hypercapnia on cardiovascular variables.

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