CHANGES IN TRANSMURAL CENTRAL VENOUS PRESSURE IN MAN DURING HYPERVENTILATION [1, 2]

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(Submitted for publication April 28, 1958; accepted July 24, 1958)

We demonstrated that large amounts of blood shift from the forearm veins during hyperventilation (2). If this effect were generalized in the periphery of the body the volume of blood in the central venous reservoir might increase. An increase in pressure in the central veins would be evidence to support this suggestion. The fall in peripheral venous pressure which occurs during hyperventilation (2, 3), however, implies that central venous pressure also decreases. This makes our thesis less attractive. Still, the *transmural* pressure (4), the net pressure acting to distend the central veins, *could increase* during overbreathing if the pressure surrounding the veins (intrapleural pressure) decreased more than did the pressure within them.

This study was undertaken to assess the nature and magnitude of changes in mean *transmural* central venous pressure during hyperventilation and to see whether the changes were consistent with our suggestion that blood shifts centrally during overbreathing.

METHODS

Subjects were studied in the right lateral decubitus position with the right arm extended downward through an opening in the table. Changes in central venous pressure were measured with a needle in the antecubital vein of the dependent arm according to the method of Gauer and Sieker (5). Changes in intrapleural pressure, measured as changes in esophageal pressure, were obtained by means of a small, open-ended, water-filled polyethylene tube. The tip of this tube was placed in the lower third of the esophagus. It is recognized that esophageal pressure is not identical with intrapleural pressure; however, changes in the two pressures tend to be parallel (6). Cherniak, Farhi, Armstrong and Proctor (6) observed that phasic deviations from this parallelism which did develop during spontaneous breathing resulted in intrapleural pressures which were consistently more negative than esophageal pressures. Even during intermittent positive pressure breathing the mean intrapleural pressure was more negative than the mean esophageal pressure. Thus our recorded values for *transmural* central venous pressure are less than those which actually existed.

Central venous and esophageal pressures were measured with Statham 0 to 5 cm. Hg strain gauges. The difference between these two pressures, the transmural central venous pressure, was measured with a Sanborn differential pressure transducer. The reference point for pressure was the midsternal line. End-expiratory CO_2 concentration was measured with a Liston-Becker CO_2 analyzer and ventilation was monitored with a gas meter (7). All three pressure values and CO_2 concentration were registered simultaneously with a Sanborn direct-writing oscillograph.

After resting values were obtained the subjects, male medical students, were asked to hyperventilate with maximal inspirations and passive expirations. They were prompted in order to keep ventilation above 25 L. per minute and to maintain a reduction of at least 10 mm. Hg in end-expiratory CO_2 concentration. Overbreathing was continued until values became stable. The period of overbreathing usually exceeded two minutes. This procedure was repeated in some experiments with 5 per cent CO_2 in the inspired gas. In some experiments overbreathing with 5 per cent CO_2 was repeated after the intravenous administration of 5 mg. of phentolamine methansulfonate (Regitine®).[4]

Reported mean pressures were obtained by counting squares under the curves registered by electrical integration of the output of the manometers. The sensitivity of the amplifying system was adjusted so that respiratory changes in the electrically integrated pressure curves occupied at least 2 to 3 cm. on the recording paper. In most experiments 1 cm. vertically on the recording paper was equal to 2.0 or 5.0 mm. Hg. Pressures were read to the nearest 0.5 mm. Hg.

Statistical analysis of the data was done by the methods of Fisher (8).

[1] Read in part by title at the Fiftieth Annual Meeting of the American Society for Clinical Investigation in Atlantic City, N. J., May 5, 1958 (1).

[2] Supported by a research grant (H-2644) from the National Heart Institute of the Public Health Service and aided by grants from the Iowa Heart Association and the Tobacco Industry Research Committee.

[3] Established Investigator of the American Heart Association.

[4] Supplied by Ciba Pharmaceutical Products, Inc.

TABLE I

Changes in transmural central venous pressure during air hyperventilation and during CO_2 hyperventilation

Experiment number	Esophageal pressure			Central venous pressure			Transmural central venous pressure			End-expiratory CO_2 tension			Ventilation		
	Rest air	Hyperventilation air	Hyperventilation 5% CO_2	Rest air	Hyperventilation air	Hyperventilation 5% CO_2	Rest air	Hyperventilation air	Hyperventilation 5% CO_2	Rest air	Hyperventilation air	Hyperventilation 5% CO_2	Rest air	Hyperventilation air	Hyperventilation 5% CO_2
	mm. Hg			*mm. Hg*			*mm. Hg*			*mm. Hg*			*L./min.*		
1	1.5	− 4.5		8.5	4.5		6.5	8.0							
2	1.0	− 3.0		5.5	4.0		5.0	7.5							
3	−3.0	− 4.5		9.0	8.5		11.0	12.0		41.4	28.0		11.0	20.0	
4	−4.0	− 7.0		2.5	1.0		7.0	8.0	10.0	40.7	26.2	50.3	6.1	31.5	31.2
5	−4.0	− 8.0	− 6.0	2.0	−4.0	0.0	6.0	3.5	5.5	42.6	24.0	49.4	10.5	42.0	37.0
6	−6.5	−11.0	−10.5	1.5	−2.0	1.0	8.0	9.0	11.0	40.5	22.8	45.7	6.5	32.9	31.8
7	−3.5	−12.0	−11.5	1.5	−4.0	0.0	4.5	8.0	11.0	41.7	27.7	46.7	11.7	36.8	38.3
8	−5.0	− 9.0	−10.0	3.0	0.5	3.5	7.5	8.5	12.5	44.4	28.6	49.9	5.2	32.0	35.8
9	0.0	− 6.5	− 7.5	0.0	−3.5	0.5	0.0	3.5	8.0	37.0	20.0	45.2	7.5	26.6	26.1
10	−9.5	−13.5	−14.0	1.0	−1.0	2.0	9.5	11.5	13.0	44.2	27.7	53.2	5.1	21.8	26.5
11	−5.0	− 9.5	− 9.5	4.0	0.5	3.0	8.5	9.5	12.0	46.8	28.5	51.0	15.9	34.0	27.5
12	−7.5	− 9.0	− 9.0	2.5	1.5	5.0	10.0	11.5	12.0	43.2	26.7	48.2	4.1	26.1	27.4
Experiments 5–12															
Mean difference (between resting and hyperventilation values)		− 4.7	− 4.6		−3.4	−0.1		1.4	3.9		−16.8	6.1		23.2	23.0
Standard error		0.73	0.81		0.59	0.54		0.66	0.93		0.52	0.60		1.80	2.07
Probability		<0.001	<0.001		<0.001	>0.8		<0.1	<0.01		<0.001	<0.001		<0.001	<0.001
Experiments 5–12															
Mean difference (between air and CO_2 hyperventilation values)			0.1			3.4			2.5			22.9			−0.2
Standard error			0.35			0.21			0.46			0.83			1.39
Probability			>0.7			<0.001			<0.001			<0.001			>0.8
Experiments 1–12															
Mean difference (between resting and hyperventilation values)		− 4.3			−2.9			1.4							
Standard error		0.57			0.50			0.45							
Probability		<0.001			<0.001			<0.01							

TABLE II

Changes in transmural central venous pressure during CO_2 hyperventilation before and after phentolamine administration

Experiment number	Esophageal pressure		Central venous pressure		Transmural central venous pressure		End-expiratory CO_2 tension		Ventilation	
	Before	After	Before	After	Before	After	Before	After	Before	After
	mm. Hg		*mm. Hg*		*mm. Hg*		*mm. Hg*		*L./min.*	
8	−10.0	− 8.0	3.5	1.5	12.5	8.5	49.9	49.9	35.8	40.0
9	− 7.5	− 8.5	0.5	−2.0	8.0	7.5	45.2	45.2	26.1	26.3
10	−14.0	−12.0	2.0	1.5	13.0	12.0	53.2	53.2	26.5	22.0
11	− 9.5	−10.0	3.0	−0.5	12.0	9.0	51.0	51.0	27.5	26.2
12	− 9.0	− 8.5	5.0	2.5	12.0	11.0	48.2	48.2	27.4	28.8
13			0.0	−3.5			51.3	51.3	28.0	27.8
14			3.0	0.5			47.5	47.5	23.2	23.3
15			2.5	−3.5			49.6	49.6	29.8	39.7
16			0.0	−2.5			52.2	52.2	40.5	41.7
Mean difference (Experiments 8–12)		0.6		−2.2		−1.9		0.0		0.0
Standard error		0.62		0.49		0.68		0.0		1.44
Probability		>0.3		<0.02		<0.05		>0.9		<0.9
Mean difference (Experiments 8–16)				−2.8				0.0		1.2
Standard error				0.49				0.0		1.33
Probability				<0.001				>0.9		>0.3

RESULTS

Changes in transmural central venous pressure during air hyperventilation

Mean central venous pressure fell in each of 12 experiments during air hyperventilation (Table I); the average change was 2.9 mm. Hg. Mean esophageal pressure fell in each experiment. The average change was 4.3 mm. Hg. In all but one experiment esophageal pressure fell more than central venous pressure. The difference between these two pressures, the transmural central venous pressure, *increased* by a highly significant average value of 1.4 mm. Hg during air hyperventilation ($p < 0.01$). This increase occurred in association with reduction in end-expiratory CO_2 tension which averaged 16.8 mm. Hg and increase in ventilation which averaged 23.2 L. per minute.

In Experiment 5 (Table I) mean central venous pressure decreased more than esophageal pressure during air hyperventilation. This resulted in a fall in transmural pressure. The fact that this experiment differed from the others cannot be explained. Its appearance in the group of eight subjects for which the CO_2 hyperventilation studies apply accounts for the probability value of slightly less than 10 per cent. When the entire group of 12 subjects is considered the probability of air hyperventilation not resulting in increased transmural pressure is less than one per cent.

Changes in transmural central venous pressure during CO_2 hyperventilation

Mean central venous pressure decreased in four and increased in four of eight experiments during CO_2 hyperventilation (Table I). The average change was an insignificant decrease of 0.1 mm. Hg ($p > 0.8$). Mean esophageal pressure fell in each of the eight experiments, the average change being 4.6 mm. Hg. The transmural central venous pressure decreased in one and increased in seven experiments; the average change was a highly significant increase of 3.9 mm. Hg ($p < 0.01$).

Comparison of transmural central venous pressure changes during air hyperventilation with those which occurred during CO_2 hyperventilation

Transmural central venous pressure was higher during CO_2 hyperventilation than during air hyperventilation in each of eight experiments (Table I). The difference between these two pressures was highly significant and averaged 2.5 mm. Hg ($p < 0.001$). This difference occurred because central venous pressure failed to fall appreciably during CO_2 breathing. It could not be attributed to changes in ventilation or esophageal pressure as these were the same during both air and CO_2 overbreathing.

Effect of phentolamine administration on transmural venous pressure during CO hyperventilation

Prior administration of 5.0 mg. of phentolamine methanesulfonate resulted in lower transmural central venous pressure during CO_2 hyperventilation in each of five experiments (Table II). The difference between the pressures measured before and after phentolamine was significant and averaged 1.9 mm. Hg ($p < 0.05$). This difference could not be attributed to changes in esophageal pressure, CO_2 tension or ventilation. The difference occurred because central venous pressure was lower in each instance after phentolamine ($p < 0.02$).

The fact that central venous pressure is lower during CO_2 hyperventilation following phentolamine was confirmed in four additional experiments in which transmural pressure was not measured.

DISCUSSION

Burnum, Hickam and McIntosh (9) found a substantial increase in the cardiac output of supine subjects during air hyperventilation. This was confirmed by Gleason, Berry, Mauney and McIntosh (10) who also demonstrated a similar increase in cardiac output in upright subjects during air hyperventilation. The observed increases were proportionate to the increases in heart rate so that stroke volume was maintained. Weissler, Leonard and Warren (11) found that stroke volume was not maintained in upright subjects during the tachycardia induced by atropine. They also demonstrated that cardiac output did not rise despite the marked increase in heart rate. On the basis of these observations and their own data, Gleason, Berry, Mauney and McIntosh (10) suggested that hyperventilation, unlike atropine, aids in maintaining a more adequate central blood reservoir. The suggestion that reservoir volume increases during overbreathing is consistent with the data and interpretations of these investigators. It is supported strongly (not proven) by our observations that blood shifts from the peripheral veins of part of the body (2) and that transmural central venous pressure increases with hyperventilation.

Hyperventilation could shift blood centrally by the "sucking" effect of inspiration or by the "pushing" effect of peripheral venous constriction. We demonstrated before that active venous constriction during overbreathing does push large quantities of blood from the forearm (2). The same experiments also showed that the amount of blood pushed from the forearm by venous constriction was much greater than the amount sucked from the forearm during the inspiratory efforts. These findings in the limb lead us to suggest that venous constriction may be more important generally than the aspirating effect of inspiration in moving blood into the central reservoir.

The pressure within a fluid-filled container such as the central venous system depends upon the volume within it and the tonic state of its walls. The fact that central venous pressure is greater during CO_2 than during air hyperventilation suggests to us that CO_2 overbreathing is associated with a greater central volume. The only other factor which could explain the increased pressure would be constriction of the central veins. In our opinion central venous constriction of a degree sufficient to account for a major share of the increased pressure with air or CO_2 overbreathing would be rather unlikely if the slope of the resting central venous pressure-volume curve is at all similar to that seen in the peripheral veins.

It is interesting to speculate regarding mechanisms which could explain a greater central volume with CO_2 hyperventilation. If all the peripheral veins respond as do those of the forearm (2) no more blood would be shifted from the periphery with CO_2 than with air hyperventilation. If this is true the only other possible explanation for an increased central volume is that blood is extracted from the reservoir at a slower rate (lower cardiac output) while breathing CO_2. There is some evidence for this in the report of Gleason and coworkers (10) who observed that cardiac output increased less while overbreathing CO_2 than while overbreathing air. The failure of the heart to extract blood from the reservoir as rapidly may result from the fact that the tachycardia of hyperventilation is less while breathing CO_2 than while breathing air (9). On the other hand the failure of the heart to extract blood as rapidly despite a higher transmural central venous pressure may indicate that cardiac filling is reduced because of increased diastolic ventricular tone when there

is a high concentration of CO_2 in the inspired gas.

Tenney (12) found an increased titer of sympatho-adrenal catechol amines in the blood of hypercapneic animals and cited evidence to suggest that CO_2 breathing is attended by an epinephrine-like response of the cardiovascular system in man. Our finding that prior administration of phentolamine results in a central venous pressure response during CO_2 hyperventilation which is similar to that seen with air hyperventilation is additional evidence in man to support this suggestion.

SUMMARY AND CONCLUSIONS

Intrapleural, *i.e.*, esophageal, and central venous pressure and the resultant transmural central venous pressure were measured and registered simultaneously in normal subjects at rest, during hyperventilation while breathing air, during hyperventilation while breathing 5 per cent CO_2 and during hyperventilation while breathing 5 per cent CO_2 after intravenous administration of 5 mg. of phentolamine methanesulfonate. The following observations were made:

1. Mean intrapleural pressure fell about the same amount in each kind of hyperventilation.

2. Mean central venous pressure fell regularly during air hyperventilation but remained essentialy unchanged during CO_2 hyperventilation. Mean central venous pressure, however, fell significantly during CO_2 hyperventilation after phentolamine administration.

3. The pressure distending the central veins, the transmural pressure, increased during hyperventilation in almost all experiments because intrapleural pressure fell more than central venous pressure. The transmural pressure was significantly greater during CO_2 than during air hyperventilation because central venous pressure did not fall appreciably.

4. The increase in transmural central venous pressure supports the suggestion that blood shifts centrally during hyperventilation.

5. The greater transmural central venous pressure during CO_2 than during air hyperventilation is consistent with the suggestion that blood is pumped from the central veins less rapidly. This could be attributed to the slower heart rate with CO_2 hyperventilation than with air hyperventilation. It could mean also that diastolic ventricular tone is increased with the high concentration of CO_2 in the inspired gas.

6. The central venous pressure response to CO_2 overbreathing after phentolamine administration is additional evidence that CO_2 breathing is associated with an increase in the circulating level of catechol amines.

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