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Apneic Thresholds in Anesthetized Subjects with Chronic Obstructive Pulmonary Disease

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Hypocapnic apnea is common in overventilated anesthetized patients. The threshold Pa_{CO_2} for resumption of ventilation under these circumstances has been reported for healthy subjects,[1, 2] but not for patients who have chronic obstructive pulmonary disease. In this study we measured the Pa_{CO_2} threshold for return of ventilation in anesthetized patients with chronic obstructive pulmonary disease following prolonged hyperventilation.

METHODS

Elderly male patients with histories of chronic obstructive pulmonary disease who were scheduled for elective lower abdominal surgery (inguinal herniorrhaphy, suprapubic prostatectomy, hydrocelectomy) were screened for study after obtaining informed consent. To confirm the presence of chronic obstructive pulmonary disease and to evaluate its severity, a slight modification of the criteria of Paskin *et al.*[3] was used. We reviewed each patient's medical history, electrocardiogram, and roentgenograms of the chest. Pulmonary function studies were then performed with the patient in a sitting position. The patient's tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), inspiratory capacity (IC), vital capacity (VC), maximum voluntary ventilation (MVV) and forced expiratory volume in one second ($FEV_{1.0}$) were determined with a 13.5-l spirometer. Functional residual capacity (FRC) was measured with the helium closed-circuit technique and total lung capacity (TLC) was calculated by adding FRC and IC. Residual volume (RV) was determined by subtraction of ERV from FRC. Predicted values, corrected for age, were obtained from the tables of Berglund *et al.*[4]

Only those eight patients whose MVV's were less than 60 l/min and whose RV/TLC's were greater than 45 per cent were accepted for study. Heparinized arterial blood samples were drawn the day before operation with the patient supine, at rest, breathing air. Five additional blood samples were obtained preoperatively on the day of operation, and one sample was obtained postoperatively. Pa_{O_2}, Pa_{CO_2}, and pH_a were measured with appropriate electrodes at 37 C. Patient temperature was measured with an esophageal thermistor probe, and blood-gas and *p*H values were corrected for patient temperature variations from 37 C.[5]

On the day of operation, each patient received 0.5 mg of atropine im. Forty to 65 minutes later, arterial blood was drawn for analysis (sample 1). Anesthesia was induced

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by an iv injection of sodium thiopental (average dose, 175 mg, range 50–350 mg). Each patient was given 80 mg succinylcholine, iv, to facilitate tracheal intubation with a cuffed endotracheal tube. Anesthesia was maintained with 1 per cent halothane, which was delivered in a nitrous oxide–oxygen mixture (N_2O 3 l: O_2 2 l) via a semiclosed system containing a carbon dioxide absorber. After 30 minutes of anesthesia, arterial blood (sample 2) was drawn and control blood–gas values were obtained; expired minute volume was measured with a Wright respirometer.[6] The stability of alveolar ventilation in the spontaneously-breathing subject was assumed when three consecutive Pa_{CO_2} values obtained at 2- to 3-minute intervals were within 1.5 torr of each other.

Then, Pa_{CO_2} was lowered rapidly by vigorous (18.8 ± 2.9 l/min, mean $\pm$ SD) manual hyperventilation. Ten minutes later another blood sample (sample 3) was obtained. Ventilation was then decreased (3.6 ± 1.1 l/min) to permit CO_2 to accumulate without allowing hypoxemia. Blood sample 4 was obtained as soon as spontaneous ventilation returned (manually determined); sample 5 was drawn when the ventilatory pattern became regular, and sample 6 was obtained an hour postoperatively.

The same protocol was followed in six additional patients without pulmonary disease in order to compare manually-determined return to spontaneous ventilation with previously-reported determinations of apnea threshold obtained by electromyography of the diaphragm.[1,2] These studies were performed by anesthesiologists not privy to the nature of the experiment.

Results

The average age of the patients with chronic obstructive pulmonary disease was 69.9 ± 6.4 years; average height, 67.3 ± 6.2 inches; average weight, 157.4 ± 18.2 pounds. The results of preoperative pulmonary function studies are shown in table 1. They indicated that our patients were in Stage II (moderately severe obstructive disease) of the criteria of Bendixen *et al.*[7] for chronic obstructive pulmonary disease.

The post-atropine preinduction blood–gas values (table 2, Pa_{CO_2} 47.9 ± 1.7 torr) are not significantly different ($P > 0.1$) from the blood–gas values of the unpremedicated patients (table 1, Pa_{CO_2} 48.0 ± 2.0 torr). After 30 minutes of unassisted ventilation breathing 1 per cent halothane in nitrous oxide–oxygen, Pa_{CO_2} had risen to 61.9 ± 6.9 torr. Ten minutes of manual hyperinflation lowered Pa_{CO_2} to 27.6 ± 4.4 torr. The first spontaneous breath returned (post-hyperventilation apneic threshold) in 4.9 ± 0.3 minutes, when Pa_{CO_2} was 42.3 ± 2.1 torr, a value significantly less ($P < 0.001$) than the preoperative value (table 2).

The ages of the six patients without pulmonary disease averaged 60.4 ± 7.1 years; heights, 66.2 ± 4.1 inches; weights, 161.6 ± 11.4 pounds. The post-atropine, preinduction Pa_{CO_2} was 42.3 ± 3.1 torr. After 30 minutes of unassisted ventilation breathing 1 per cent halothane in nitrous oxide–oxygen, Pa_{CO_2} had risen to 50.8 ± 3.9 torr. Following hyperventilation, spontaneous respiration was initiated at a Pa_{CO_2} of 45.2 ± 3.2 torr, a value quite similar to that reported by Fink *et al.*,[1] who determined return to spontaneous ventilation by electromyography of the diaphragm.

Discussion

The apneic threshold (Pa_{CO_2}) of our subjects was 5.6 torr less than the resting value, a magnitude of difference consistent with the findings of others.[8–12] From the data of Edelist and Osorio, it is apparent that the drive to resume ventilation in passively hyperventilated dogs and humans is the result of the return of the *p*H of CSF to normal even though the blood is well oxygenated, extremely alkalotic, and hypocapnic.[11] This is compatible with the findings of Mitchell and Singer that the CSF *p*H, acting through the central chemoreceptor, contributes approximately 80 per cent of the response to inhaled CO_2, while the peripheral chemoreceptor contributes 20 per cent.[13] The decrease in bicarbonate accompanying hyperventilation has been ascribed by Severinghaus and co-workers to active transport across the blood–brain barrier, which adjusts the CSF bicarbonate to maintain a constant *p*H.[14]

TABLE 1. Preoperative

	Vital Capacity (l)		Functional Residual Capacity (l)		Residual Volume (l)		Total Lung Capacity (l)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
Subject 1	3.3	3.6	3.8	3.7	3.1	1.6	6.4	5.3
Subject 2	3.6	4.1	3.7	3.5	2.9	1.9	6.5	6.0
Subject 3	3.3	3.7	4.0	3.9	3.2	1.7	6.5	5.4
Subject 4	2.1	2.5	3.2	3.1	2.6	1.1	4.7	3.6
Subject 5	4.3	4.6	4.5	4.3	3.6	2.1	7.9	6.7
Subject 6	4.0	4.5	5.7	5.8	3.8	2.0	7.8	6.6
Subject 7	3.9	4.1	3.4	3.6	3.0	1.8	6.9	5.9
Subject 8	2.5	2.9	2.5	2.8	2.3	1.3	4.8	4.2
MEAN	3.4	3.8	3.9	3.8	3.2	1.7	6.8	5.5
± SD	0.8	0.8	1.0	0.9	0.8	0.3	1.0	1.1

It appears that the relationship between resting Pa_{CO_2} and apnea-threshold Pa_{CO_2} is set, and that the CO_2 dose–response curves of patients with mild hypercarbia are shifted to the right on the horizontal axis. Further evidence for this is that during light halothane anesthesia our patients had the same degree of Pa_{CO_2} change (12 torr increase) as healthy volunteers.[12]

The problems with this interpretation of our data are: 1) our subjects were not severely hypercapnic; 2) they were mildly acidotic preoperatively, and thus not wholly (chronically) compensated; 3) the levels of halothane anesthesia were variable following hyperventilation.

In a study of patients with severe chronic obstructive pulmonary disease who were anesthetized with nitrous oxide–oxygen, Utting *et al.*[8] found that spontaneous ventilation returned during a state of relative respiratory alkalosis. They suggested that their results would not have been obtained had more potent anesthetic agents been used. Our study demonstrates that during anesthesia with 1 per cent halothane patients with chronic ob-

TABLE 2. Pre-, Intra- and Postoperative

	Sample 1 Preoperative (post-atropine) F_{IO_2} = 0.21			Sample 2 30 Minutes Anesthesia F_{IO_2} = 0.4			Sample 3 Post-hyperventilation F_{IO_2} = 0.4		
	Pa_{O_2}	$Paco_2$	pH	Pa_{O_2}	$Paco_2$	pH	Pa_{O_2}	$Paco_2$	pH
Subject 1	55	47	7.33	120	60	7.35	127	26	7.45
Subject 2	52	46	7.35	161	56	7.33	168	32	7.44
Subject 3	62	51	7.34	114	75	7.31	123	34	7.46
Subject 4	51	47	7.35	106	68	7.33	110	25	7.42
Subject 5	64	51	7.38	133	57	7.39	129	28	7.40
Subject 6	58	47	7.36	108	59	7.30	103	31	7.43
Subject 7	55	48	7.34	95	55	7.31	99	22	7.41
Subject 8	59	46	7.34	98	65	7.35	97	23	7.40
MEAN	57.0	47.9	7.35	116.9	61.9	7.33	119.5	27.6	7.43
± SD	4.6	1.7	0.02	21.6	6.9	0.03	23.3	4.4	0.02

Pulmonary Function

RV/TLC Per Cent	Maximum Voluntary Ventilation (l/min)		Forced Expiratory Volume in 1 Second (l)		Pao_2 (torr)	$Paco_2$ (torr)	pH
	Observed	Predicted	Observed	Predicted			
51	46	110	1.9	2.6	55	46	7.33
46	48	123	2.3	2.9	50	47	7.36
53	60	123	2.0	2.8	59	53	7.32
61	51	80	1.1	1.8	53	46	7.33
48	50	140	2.6	3.4	61	50	7.35
79	58	130	1.8	3.2	58	48	7.36
50	60	130	2.3	3.0	57	47	7.34
48	52	94	1.9	2.1	52	47	7.32
55	53	116	2.0	2.7	56	48	7.34
11	6	20	0.5	0.6	4	2.0	0.02

structive pulmonary disease will readily resume spontaneous ventilation after hyperventilation.

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Blood-Gas Results

Sample 4 Post-hyperventilation Apneic Threshold FIO_2 = 0.4			Sample 5 Ventilatory Pattern Stable FIO_2 = 0.4			Sample 6 Postoperative 1 Hour FIO_2 = 0.21		
Pao_2	$Paco_2$	pH	Pao_2	$Paco_2$	pH	Pao_2	$Paco_2$	pH
102	43	7.40	118	48	7.38	56	43	7.34
151	44	7.35	158	53	7.39	55	48	7.35
111	45	7.40	112	56	7.36	60	42	7.34
103	42	7.34	103	49	7.33	50	49	7.33
110	40	7.36	136	47	7.36	65	48	7.36
96	44	7.34	110	43	7.37	58	50	7.38
100	41	7.39	98	46	7.35	53	52	7.34
97	39	7.37	104	48	7.34	61	47	7.35
108.8	42.3	7.37	117.4	48.8	7.36	57.3	47.4	7.35
17.9	2.1	0.03	20.1	4.1	0.02	4.8	3.4	0.02

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The Effect of Forane on Hemoglobin Function *in Vitro*

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Methoxyflurane,[1] halothane, nitrous oxide, and enflurane[2] do not alter the affinity of hemoglobin for oxygen. The lack of effect of halothane was recently reconfirmed by Weiskopf *et al.*[3] No data for Forane† (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) are presently available. This study quantitates the effects of Forane on hemoglobin function (P_{50}) at *p*H 7.4 and on the acid Bohr shift.

METHODS

Paired venous blood samples from six healthy adults were subjected to open-circuit tonometry according to the technique of Edwards and Martin.[4] Each sample was divided, placed in two flasks, and equilibrated with humidified gas for 45 minutes at 37 C. The gas phase was varied (table 1) so that one flask contained blood fully saturated with oxygen and the other, blood fully desaturated. Using a previously calibrated syringe, fixed-volume samples with a known ratio of saturated to unsaturated hemoglobin may be taken. The hemoglobin saturation of the resulting mixture is the ratio of the volume of oxygenated blood to the total volume of the sample.[4] The P_{O_2} and *p*H of these samples were measured. The O_2 electrode was standardized with gas of known P_{O_2} before and after each measurement.

TABLE 1. Composition of Gases Used for Tonometry (Percentages)

Study	Gas	Flask 1 (Deoxygenated)	Flask 2 (Oxygenated)
Control (*p*H 7.4)	O_2	—	20.55
	CO_2	6.05	6.02
	N_2	93.95	73.43
Bohr shift (*p*H < 7.3)	O_2	—	19.97
	CO_2	10.31	11.21
	N_2	89.69	68.82

The gas contents listed are dry gas. All gas phases were fully humidified at 37 C before entering the flasks. (The Forane was vaporized into the listed gas mixtures.)

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