Posthyperventilation Hypoxia:

Theoretical Considerations in Man

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The magnitude of CO_2 washout from the body following an increase in alveolar ventilation is time-dependent. Recovery from this depletion in CO_2 content requires relative hypoventilation and is also time-dependent; this leads inevitably to alveolar hypoxia during breathing of air. The model used here predicts that, following hyperventilation ($P_{ACO_2} = 20$ mm. Hg) for several hours, when spontaneous ventilation ($P_{ACO_2} = 40$ mm. Hg) returns alveolar O_2 tension will be 73, 90 and 97 mm. Hg at 10, 30 and 60 minutes, respectively, compared with a value of 101 mm. Hg several hours later.

HYPERVENTILATION immediately lowers alveolar and arterial carbon dioxide tensions and, as a reflection of the diminution of total-body CO_2 content with time, the carbon dioxide tension throughout the body is lowered. The quantity of carbon dioxide lost from reservoirs throughout the body depends upon the magnitude and duration of hyperventilation.[1] Cessation of hyperventilation is followed by apnea or spontaneous hypoventilation. With apnea the amount of carbon dioxide retained may be insufficient to immediately restore the total body CO_2 content to equilibrium. Spontaneous ventilation during this recovery period will be relative hypoventilation until the body has regained all the CO_2 lost during hyperventilation. During breathing of air, this relative hypoventilation inevitably results in a decrease in alveolar oxygen tension. The pattern of these changes has been described in a study in anesthetized dogs.[2] The purpose here is to predict the expected magnitude and time course of posthyperventilation hypoxia as it may occur in man following anesthesia and operation.

Background

Farhi and Rahn [1] have estimated that a man weighing 70 kg. contains approximately 17 liters of CO_2 stored in various tissues of the body. In addition there is estimated to be about 100 liters of CO_2 chemically bound in bone; however, the CO_2 in bone does not enter into alterations that occur over relatively short periods. Vance and Fowler [3] have demonstrated how the duration of hyperventilation in man alters the quantity of CO_2 liberated from the reservoirs. After hyperventilation for 20 minutes the quantity lost was 1.3 ml. CO_2/kg./mm. ΔP_{CO_2}, whereas at the end of one hour of hyperventilation the quantity lost was 2 ml. CO_2/kg./mm. ΔP_{CO_2}. At the end of one hour of steady hyperventilation, with a decrease of P_{ACO_2} (alveolar CO_2 tension) from 40 to 20 mm. Hg, we would expect to lose 2,800 ml. CO_2 (2 ml. × 70 kg. × 20 mm.) from body reservoirs. An ensuing apnea 14 minutes in duration would restore all the CO_2 lost. In anesthetized man during apnea following hyperventilation for one hour, Eger and Severinghaus [4] demonstrated a rise in P_{aCO_2} (arterial CO_2 tension) of approximately 10 mm. Hg in the first minute and 2.5–3.0 mm. Hg/minute therefater. On the average, then, P_{aCO_2} during apnea would be expected to rise from 20 to 40 mm. Hg in about five minutes. In five minutes, however, only (5 × 200) 1,000 ml. of CO_2 would be produced for retention. To reaccumulate all the CO_2 lost during the hyperventilation, an additional nine minutes of apnea would be required, and P_{ACO_2} would have risen to approximately 60 mm. Hg. Because time is required to redis-

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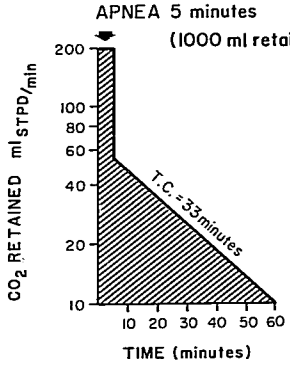

FIG. 1. Recovery of lost CO_2 with time.

tribute the CO_2 retained, the lack of association between alveolar tension and body content is pronounced. When, following artificial hyperventilation, spontaneous respiration is initiated at $P_{A_{CO_2}}$ 40 mm. Hg, the remaining deficit in the CO_2 stores of the body will require alveolar hypoventilation until the CO_2 stores again reach steady-state conditions.

Another study[5] has provided data useful in predicting the changes that will occur when apnea is terminated. It was shown that in anesthetized man following hyperventilation for two hours a stepwise decrease in ventilation resulted in a $P_{A_{CO_2}}$ which approached an equilibrium value in predictable fashion. This change was best represented as the sum of two exponential functions, with time constants (T.C. = 1/2 time/$\log_e 2$) approximately equal to 2 and 33 minutes. By analogy, if at the end of hyperventilation $P_{A_{CO_2}}$ could be changed instantly from 20 to 40 mm. Hg, the recovery of the lost CO_2 would be achieved by a progressive increase in $\dot{V}_A$ (alveolar ventilation) until $\dot{V}_{CO_{2T}}$ (quantity of CO_2 produced by the tissues each minute) was equal to $\dot{V}_{CO_{2R}}$ (quantity of CO_2 eliminated by the lungs each minute). From the dependent relation of $\dot{V}_A$ and $P_{A_{CO_2}}$ we can predict the rate of rise of $\dot{V}_A$ when $P_{A_{CO_2}}$ is constant. After five minutes the fast component (time constant = 2 minutes) in the recovery process will be within 10 per cent of its final value. The assumption that after five minutes the rate of recovery is approximately represented by the slow component (time constant = 33 minutes) appears reasonable, particularly when the intent is to simplify the approach.

Model

Consider mechanical hyperventilation to $P_{A_{CO_2}}$ 20 mm. Hg for one hour in a 70-kg. man. The depletion of CO_2 stores would amount to 2,800 ml. When the ventilator is stopped abruptly, the ensuing apnea of five minutes' duration (until breathing commences at a $P_{A_{CO_2}}$ of 40 mm. Hg) will cause the retention of 1,000 ml. of CO_2 (5×200 ml./min.). The additional CO_2 deficit of 1,800 ml. must be recovered during the period of spontaneous respiration. The quantity of CO_2 retained during the first minute of spontaneous breathing will be 54 ml. With a recovery rate whose time constant equals 33 minutes this is the only value that satisfies 1,800 ml. of CO_2 retention. It is possible to illustrate these calculations by plotting this exponential change semilogarithmically (fig. 1). The value retained in each successive minute can be read directly from this plot and used for the calculation of $P_{A_{O_2}}$.

When hyperventilation has been accomplished with 100 per cent oxygen, the reservoir of oxygen in the lung will prevent the early onset of hypoxia during breathing of air. Initially the ratio of lung volume to the quantity of fresh air presented each minute will determine the oxygen washout. From the size of lung volume (FRC = 2,400 ml.) and magnitude of alveolar ventilation during these first few minutes of breathing air we can expect a 99 per cent change in alveolar oxygen concentration in about three minutes. At the end of the oxygen washout, when oxygen uptake via the lungs is equal to the oxygen consumption of the body, the alveolar air equation[6] describing $P_{A_{O_2}}$ will offer a close approximation (table 1). The data are plotted in figure 2.

Following steady hyperventilation for longer periods, two or more hours, it is likely that the quantity of CO_2 depleted from the body will be greater than 2 ml./kg./mm. ΔP_{CO_2}. For example, with 3 ml. CO_2/kg./mm. ΔP_{CO_2}, hyperventilation ($P_{A_{CO_2}} = 20$ mm. Hg) for two

TABLE 1. 70-kg. Man with CO_2 Depletion of 2,800 ml. (hyperventilation for 60 minutes)

Time after End of Hyperventilation (minutes)	CO_2 Retained (ml.STPD/min.)	$\dot{V}_{CO_2R}$ (ml.STPD/min.)	$\dot{V}_{ABTPS}$ (l./min.)	$P_{A_{O_2}}$ (mm. Hg)
0–5	Apnea (1,000 ml. CO_2 retained)			
5	54	146	3.15	*
6	52	148	3.19	*
7	51	149	3.21	*
8	49	151	3.26	88.5
9	48	152	3.28	88.8
10	46	154	3.32	89.5
15	30	160	3.45	91.4
20	34	166	3.58	93.2
40	25	175	3.77	95.7
40	18.7	181.3	3.91	97.2
50	13.8	186.2	4.02	98.4
60	10.2	189.8	4.09	99.2
∞	0	200	4.31	101.3

CO_2 retained, ml./min.—from semilogarithmic plot (fig. 1).
$\dot{V}_{CO_{2R}} = 200$ ml./min. (tissue production)—quantity retained/min.
$\dot{V}_{ABTPS} = (\dot{V}_{CO_{2R}}|_{STPD}/\text{min.} \times 1.21) \div F_{ACO_2}$ (0.056).
$P_{A_{O_2}} = P_{I_{O_2}} - [0.863\ \dot{V}_{O_2}\ (1 - F_{I_{O_2}})/\dot{V}_A] - [F_{I_{O_2}} \cdot P_{ACO_2}]$.
* See text.

or more hours will result in a loss of 4,200 ml. CO_2 ($3 \times 70 \times 20$). After apnea for five minutes ($P_{ACO_2} = 40$ mm. Hg) 3,200 ml. (4,200–1,000) of CO_2 remain to be retained (table 2). The magnitude of alveolar hypoxia will be more severe (fig. 3). In this case, as in the previous example, the delay in the fall in $P_{A_{O_2}}$ was included in the plot.

During hyperventilation ($P_{ACO_2} = 20$ mm. Hg) with 100 per cent oxygen, $P_{A_{O_2}}$ will be 693 mm. Hg. For purposes of simplification let us assume that no alveolar–arterial P_{O_2} difference exists. In this case the decrease in $P_{A_{O_2}}$ from 693 mm. to 101 mm., reached when the equilibrium with air is completed, will decrease the oxygen content in the circulating blood volume (5 liters, hemoglobin 15 Gm./100 ml.) by approximately 114 ml. O_2. The change in $P_{A_{O_2}}$ from 693 to 101 mm. represents a loss of approximately 1,545 ml. O_2 STPD (FRC 2,400 ml. BTPS). The quantity of oxygen lost from the alveolar gas phase, then, is 13.6 times greater than the quantity of oxygen lost from the circulating blood volume. If the rate of oxygen washout from the circulating blood volume proceeds at the same rate as the lung washout,[6] then this loss of O_2 from the blood appears relatively unimportant. However, if the turnover rate of oxygen in the circulating blood volume is significantly slower, then even this additional quantity of O_2 stored in the blood may tend to prevent the develop-

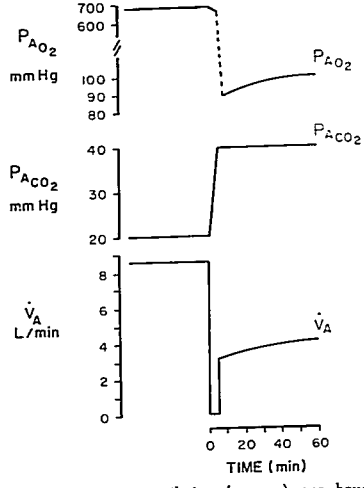

FIG. 2. Hyperventilation (oxygen) one hour (CO_2 depletion 2,800 ml.). Apnea five minutes. Spontaneous air ventilation at P_{ACO_2} 40 mm. Hg, with recovery in P_{ACO_2} and $\dot{V}_A$.

TABLE 2. 70-kg. Man with CO_2 Depletion of 4,200 ml. (hyperventilation for 120 minutes)

Time after End of Hyperventilation (minutes)	CO_2 Retained (ml.STPD/min.)	$\dot{V}_{CO_{2R}}$ (ml.STPD/min.)	$\dot{V}_{A_{BTPS}}$ (L./min.)	$P_{A_{O_2}}$ (mm. Hg)
0–5	Apnea (1,000 ml. CO_2 retained)			
5	96	104	2.24	*
6	93	107	2.31	*
7	91	109	2.37	*
8	88	112	2.42	*
9	85	115	2.47	*
10	83	117	2.52	73.3
15	71	129	2.78	79.6
20	61	139	3.00	84.0
30	45	155	3.34	89.9
40	33	167	3.60	93.5
50	24.5	175.5	3.79	95.8
60	18	182	3.93	97.4
∞	0	200	4.31	101.3

CO_2 retained, ml./min.—from semilogarithmic plot.

$\dot{V}_{CO_{2R}} = 200$ ml./min. (tissue production)—quantity retained/min.

$\dot{V}_{A_{BTPS}} = (\dot{V}_{CO_{2R}}|_{STPD}/\text{min.} \times 1.21) \div F_{A_{CO_2}}$ (0.056).

$P_{A_{O_2}} = P_{I_{O_2}} - [0.863\ \dot{V}_{O_2}(1 - F_{I_{O_2}}/\dot{V}_A] - [F_{I_{O_2}} \cdot P_{A_{CO_2}}]$

* See text.

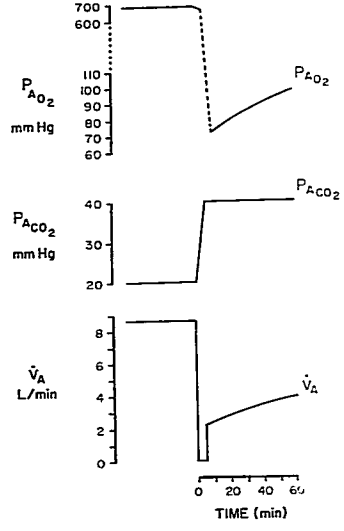

FIG. 3. Hyperventilation (oxygen) two hours (CO_2 depletion 4,200 ml.). Apnea five minutes. Spontaneous air ventilation at $P_{A_{CO_2}}$ 40 mm. Hg, with recovery in $P_{A_{O_2}}$ and $\dot{V}_A$.

ment of hypoxemia. This latter case is not considered in the calculations in this paper.

It should be emphasized that the model presented here deals exclusively with changes that occur in the composition of alveolar gas. In addition to the arterial hypoxemia associated with alveolar hypoxia, a number of other disturbances are capable of producing arterial hypoxemia with or without associated alveolar hypoxia. When a large alveolar–arterial P_{O_2} difference exists, arterial hypoxia will be present. For example, when 20 per cent of the cardiac output (5 l./min.) is passing through pulmonary shunts, Pa_{O_2} will be approximately 280 mm. Hg, compared with $P_{A_{O_2}}$ 693 mm. Hg during hyperventilation with oxygen. When $P_{A_{O_2}}$ returns to 101 mm. Hg during breathing of air, Pa_{O_2} will be about 63 mm. Hg, and in fact is expected to be even lower because of the ventilation–perfusion inequalities present even in the normal lung.

There appears to be little doubt that relative hypoventilation occurs in man following controlled breathing with hyperventilation. To what extent body oxygen stores at full capacity will modify the development of hypoxia remains to be defined in the postoperative patient.

Discussion

Rahn and Fenn have described the alveolar changes that occur during the unsteady states produced by hyperventilation and hypoventilation.[6] The CO_2 stores of the body are large compared with the O_2 stores, with the former mostly in tissues and the latter mostly in blood. As previously stated, the predictions presented here are concerned exclusively with the changes that occur in the alveolar gas during the spontaneous recovery that follows hyperventilation. The prediction of the extent and duration of hypoventilation requires knowledge of the duration of hyperventilation, the extent to which $P_{A_{CO_2}}$ is lowered, and the duration of apnea if it occurs.

As Fink points out, the absence of apnea following hyperventilation in conscious subjects is in marked contrast to the invariable onset of apnea in patients hyperventilated during general anesthesia.[7] The cerebral activity associated with the wakeful state is part of the normal respiratory drive. With this obvious difference between the awake and nonawake state, the question arises whether the phenomenon of posthyperventilation hypoxia will be operative in the relatively awake patient following hyperventilation and general anesthesia. Recently, Bainton has demonstrated that apnea can occur in awake human subjects following hyperventilation.[8]

There is no doubt that there is an increasing respiratory stimulus as alveolar hypoxia increases. In the study of posthyperventilation hypoxia in the anesthetized dog,[2] apnea following breathing of air was terminated when arterial oxygen tension fell to 35 mm. Hg. However, once ventilation has resumed, the role of hypoxia in controlling the ventilatory changes appears to be much less important than the effect of changes in *p*H and P_{CO_2} on the respiratory center.

Mitchell showed that chronic hyperventilation reduces bicarbonate in cerebrospinal fluid and, therefore, increases the sensitivity of central chemoreceptors to P_{CO_2}.[9] This will lower the apneic threshold and the resting P_{CO_2} threshold as well. In this case, less CO_2 retention is required to restore the reservoirs to this new lower P_{CO_2}. On the other hand, when respiration is initiated and maintained at a P_{CO_2} higher than normal, the magnitude of the hypoventilation necessary to produce this accumulation in CO_2 will result in a greater degree of hypoxia.

Dejours studied the effect of voluntary hyperventilation in awake human subjects.[10] Observations were made for 15 minutes following ten minutes of hyperventilation. $P_{A_{CO_2}}$ was lowered to 18 mm. Hg. During the period of spontaneous (air) breathing that followed, $P_{A_{O_2}}$ reached minimal values (50–60 mm. Hg) between three and six minutes. $P_{A_{CO_2}}$ reached a stable level (37–39 mm. Hg) at about seven minutes; however, $P_{A_{O_2}}$ continued to rise during the remainder of the 15 minutes of observation. In other studies the subjects were passively hyperventilated for ten minutes with 33 per cent oxygen. During the period of spontaneous recovery, while continuing to breathe 33 per cent oxygen, a similar pattern of change in $P_{A_{CO_2}}$ and ventilation was observed. $P_{A_{CO_2}}$ appeared to reach a plateau value at about seven minutes, while $P_{A_{O_2}}$ rose progressively. During breathing of 33 per cent O_2, minimal values for $P_{A_{O_2}}$ were reached at three to four minutes. The minimal value, however, was 95 mm. Hg. It appears that the presence or absence of hypoxia does not alter the fact that after $P_{A_{CO_2}}$ has reached a stable level, $P_{A_{O_2}}$ continues to increase with the increase in ventilation.

It has been suggested that during the first few minutes after a change from hyperventilation, whether apnea or a reduction in ventilation ensues, the immediate capacity of the body to store CO_2 is limited by a diffusion barrier to CO_2 between intracellular and extracellular fluid.[11] Others have suggested that delayed chemical buffering explains, at least in part, the small effective tissue volume for the immediate storage of CO_2 following a change in ventilation.[12] In each of the examples presented in this paper where apnea lasted a minimum of five minutes, the slower rate of adjustment would be expected to predominate even from the earliest minutes following the end of apnea. A widely-accepted view is that this slower rate of adjustment is related to tissues with the lowest blood flow, probably flow to skeletal muscle.[13]

Changes in cisternal cerebrospinal fluid *p*H and P_{CO_2} are known to lag behind arterial al-

terations.[14] This lag was also observed in the study of posthyperventilation hypoxia in the dog.[2] The continued rise in ventilation is consistent with the lag in cisternal cerebrospinal fluid CO_2 tension. The question arises whether the hypoxia rather than the continued rise in cisternal cerebrospinal fluid CO_2 tension has the more bearing on the ventilatory changes. This does not appear to be the case, because in the studies where oxygen administration prevented hypoxia, the spontaneous pattern of recovery in arterial CO_2 tension and ventilation was similar to that observed when hypoxia was present.[10] Although the studies of Dejours were of shorter duration, they point out that the pattern of posthyperventilation hypoxia in awake human subjects follows the pattern expected in the presence of anesthesia and narcosis. It is most important to recognize that, following hyperventilation, the pattern of increasing ventilation with constant arterial CO_2 tension is present, with or without hypoxia.

Summary

Hyperventilation lowers $P_{A_{CO_2}}$ and, subsequently, the tension of CO_2 throughout the body. The quantity of CO_2 washed out of body CO_2 stores depends upon the duration of hyperventilation and the extent to which $P_{A_{CO_2}}$ is decreased. When, following hyperventilation, $P_{A_{CO_2}}$ is returned to a normal level, restoration of the depleted CO_2 content of the body can be accomplished only by hypoventilation. Hypoventilation during breathing of air results in an inevitable decrease in $P_{A_{O_2}}$. Alveolar hypoxia persists for as long as an hour, while ventilation on superficial examination appears normal. Posthyperventilation hypoxia is characterized by a normal $P_{A_{CO_2}}$ and a low $P_{A_{O_2}}$.

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