APNEIC OXYGENATION IN MAN

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This report deals with prolonged suppression of respiratory function in man while full oxygenation and other vital functions are maintained. This phenomenon has been studied extensively in dogs and other laboratory animals, and was termed "diffusion respiration" by Draper, Whitehead and their collaborators[1, 2] and "apneic diffusion oxygenation (ADO)" by Holmdahl[3] who also reviewed the extensive literature in this subject.

The descriptive term "apneic oxygenation" first employed by Nahas[4] is used here instead of the other titles to avoid the misconception that the process of molecular diffusion in the conducting air passages brings oxygen to the alveoli from the outside environment. This misconception regarding mechanism was strengthened by an incomplete description of the process in an early report by Draper *et al.*[1] even though in a later report[2] it was stated that the *en masse* movement of gas down the trachea is responsible for the sustained high alveolar and blood oxygen levels. However, the exact mechanism responsible for this bulk movement was not presented explicitly. Objections to the term "diffusion" have been raised by Joels and Samueloff[5] and by Bartlett *et al.*[6] They have emphasized the interpretation accepted in this study of the mechanism responsible for this mass movement and Bartlett *et al.*[6] proposed the title of "aventilatory mass flow (AVMF)" for this phenomenon.

An impetus for carrying out this study is the widespread interest in respiratory acidosis during anesthesia and operation. There seems to be little agreement as to what constitutes a "toxic" level of carbon dioxide. Furthermore, the frequent use of skeletal muscle relaxants during anesthesia may, under certain circumstances such as in bronchoscopy, result in apnea which cannot easily be relieved until the operative procedure is completed.[7] Finally, the provocative work of Brown and Miller[8] regarding posthypercapneic arrythmias in dogs appeared to be in conflict with the findings of Holmdahl.[3] It, therefore, seemed to be important to study this phenomenon in man.

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Methods

Eight essentially healthy patients scheduled for a variety of minor operations served as subjects. In four instances, the apneic period was produced while the surgical procedure was being performed, while in the remainder the operation was completed first. The subjects received 50–100 mg. of meperidine and 0.4 mg. of scopolamine approximately one hour before the induction of anesthesia. In all cases but one, 100 per cent oxygen was administered with a circle anesthesia apparatus for five minutes, then an hypnotic dose of 2.5 per cent thiopental was given intravenously followed by approximately 100 mg. of succinylcholine chloride. When relaxation was complete, a cuffed endotracheal catheter was inserted and a tight seal obtained by inflation of the cuff. Denitrogenation was accomplished by administering 100 per cent oxygen for a minimum of 30 minutes with the circle apparatus at a flow rate of at least 8 liters per minute. To insure unconsciousness throughout the study, additional doses of thiopental were given until the total amount was approximately 1.0–1.5 Gm. Immobility was obtained by additional intermittent doses of succinylcholine or *d*-tubocurarine chloride. Artificial respiration during the denitrogenation process was performed by intermittent compression of the reservoir bag of the circle apparatus. In the first patient studied, the 30 minute exposure to 100 per cent oxygen occurred before induction of anesthesia.

Following denitrogenation, the endotracheal tube was left connected to the circle apparatus filled with 100 per cent oxygen and intermittent compression of the reservoir bag stopped.

Apnea was allowed to persist for the desired period, usually between 30–55 minutes. The bag was observed visually or manually for any sign of spontaneous respiration. When movement was observed, more muscle relaxant was given intravenously. The usual fractional dose was 100 mg. of succinylcholine or 9–12 mg. of *d*-tubocurarine. The total dose of the relaxant varied somewhat according to the size of the subject and the duration of the apnea, but was on the average approximately 500 mg. of succinylcholine or 50 mg. of *d*-tubocurarine. As the reservoir bag gradually emptied during the course of the study, it was periodically refilled with oxygen and required approximately 2–3 liters every 15 minutes.

Arterial blood samples were obtained from an indwelling needle in the brachial or femoral artery and collected anerobically in greased syringes containing small amounts of heparin, sodium fluoride and a droplet of mercury. Oxygen saturations were determined spectrophotometrically in duplicate.[9] The *p*H was determined potentiometrically with the Cambridge micro glass electrode using a thermostatically controlled air bath.[10] The plasma carbon dioxide content was determined with the Kopp-Natelson microgasometer.[11] Samples for oxygen saturation and *p*H were obtained every five minutes, while carbon dioxide content analyses were carried out on samples drawn every ten minutes. The arterial carbon dioxide tension and the buffer base were estimated from the nomogram of Singer and Hastings [12] or from the Henderson-Hasselbalch equation for the higher carbon dioxide tension values. The epinephrine and norepinephrine concentrations in arterial plasma were determined by the technique of Cohen and Goldenberg.[13, 14] The arterial plasma sodium and potassium levels were obtained by flame photometry using an internal standard Baird apparatus. The arterial pressure was determined by auscultation and the mean arterial pressure was estimated as the diastolic pressure plus ⅓ of the pulse pressure. Lead 2 of the electrocardiogram was recorded with a Cambridge direct writing apparatus. The arterial pressure and the electrocardiogram were determined either continuously or at intervals no greater than five minutes, while the pulse was monitored continuously by palpation. This was done in order to detect any dangerous circulatory changes.

Results

Table 1 summarizes the data on the duration of apnea and the arterial oxygen saturation, *p*H and carbon dioxide tensions. The duration of apnea was 30 minutes or longer in all cases but one. In 6 of 8 subjects, the time of termination of the apneic period by artificial respiration was planned prior to the beginning of the study. In the remaining two patients, apnea was terminated in one at 17 minutes and in the other at 53 minutes because of the appearance of ventricular premature contractions or other ectopic beats. Although arterial samples for oxygen saturation were obtained every 5 minutes during the apneic period, only the lowest values obtained in each subject are shown. In all instances, the blood was virtually fully saturated with oxygen throughout the apneic period. This table also gives the *p*H and the calculated carbon dioxide tension of the last sample obtained in

TABLE 1

Apneic Oxygenation in Man

Subject Number	Duration of Apnea (minutes)	Lowest Arterial Saturation (per cent)	Lowest Arterial pH	Highest $PaCO_2$ (mm. Hg)	Average Rate of Rise of $PaCO_2$ (mm. Hg/minute)
1	30	100	—	—	—
2	45	100	—	—	—
3	55	100	—	—	—
4	45	100	6.88	160	3.0
5	18	99	6.97	130	4.9
6	45	98	6.87	160	3.0
7	53	98	6.72	250	3.5
8	38	100	6.96	130	2.7

TABLE 2

ARTERIAL pH, SODIUM AND POTASSIUM CHANGES DURING APNEIC OXYGENATION

Subject 6

Time (minutes)	pH	Na mEq/L	K mEq/L
Control	7.36	128	3.8
10	7.13	—	4.0
20	7.06	128	—
30	6.95	129	4.0
40	6.87	133	4.3
6 post apnea	7.13	127	4.8

5 subjects during the apneic period. The *p*H usually fell below 7.00 within 30 minutes. The lowest *p*H observed was 6.72 in a subject who began the apneic phase with a moderate respiratory acidosis and in whom the apnea was maintained for 53 minutes with an estimated maximum carbon dioxide tension of 250 mm. of mercury. The maximum carbon dioxide tensions in each of the other subjects were not less than 130 nor more than 160 mm. of mercury. The average rate of rise in the carbon dioxide tension was approximately 3 mm. of mercury per minute with a range of 2.7 to 4.9 mm. of mercury per minute. The serial changes in *p*H at 10 minute intervals in an individual are shown in table 2.

The arterial pressure changes are summarized in table 3. During the apnea, a moderate to severe hypertension was usually seen with the systolic pressure rising as much as 100 mm. of mercury. The average of the maximum rises in mean arterial pressure for the entire series was 26 per cent. In one instance the mean pressure declined, due primarily to a fall in the diastolic value. In the period immediately following the apnea, the arterial pressure always fell, usually below the control values, with the lowest observed systolic value at 90 mm. of mercury. The average of the maximum post apneic fall in pressure from the preapneic values was 14 per cent.

In 6 of the 8 subjects no cardiac irregularities were observed. Figure 1 shows the typical serial electrocardiographic patterns found in one of these subjects. The duration of apnea in this subject was the longest in the series, 55 minutes. Normal sinus rhythm with an essentially constant rate persisted both during and after the apnea. There was virtually no change in the shape of the complex from control. In two subjects, ventricular extrasystoles were observed. The serial tracings in one of these subjects, in which this arrhythmia appeared after 53 minutes of apnea, are presented in figure 2. After a few ventricular premature contractions were noted, we decided to terminate the apnea. The institution of artificial respiration with oxygen was accompanied within 15 seconds by ventricular tachycardia, lasting less than one minute. Then the rhythm became normal spontaneously.

The plasma sodium and potassium concentrations during and after the apnea in a typical case are shown in table 2. During the apnea in the other two cases in which arterial

TABLE 3

ARTERIAL PRESSURE CHANGES DURING AND AFTER APNEIC OXYGENATION

Subject Number	Duration Apnea (minutes)	Arterial Pressure (mm. Hg)			Per Cent Change, Mean Arterial Pressure	
		Before	Highest During	Lowest After	Maximum Rise During	Maximum Fall After
1	30	110/80	160/100	120/80	33	−4
2	45	120/80	150/90	90/75	18	14
3	55	100/85	200/100	90/60	47	21
4	45	110/70	170/90	105/60	46	10
5	18	120/80	180/110	110/80	43	4
6	45	110/70	160/40	90/50	−4	24
7	53	120/80	150/80	100/80	11	7
8	38	130/100	170/100	90/60	12	36
Average					26	14

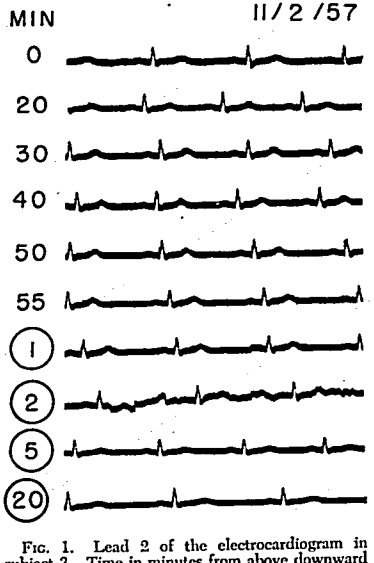

FIG. 1. Lead 2 of the electrocardiogram in subject 3. Time in minutes from above downward refers to the duration of apnea; encircled figures are time in minutes following institution of manual artificial ventilation.

samples were drawn every 10 minutes for determination of sodium and potassium, the maximum increase in plasma potassium concentration from the control value was 0.4 mEq./l. with a further rise of 0.6 mEq./l. or less noted in the immediate posthypercapneic period. The plasma sodium changes were relatively small with a maximum rise during the

TABLE 4

ARTERIAL BUFFER BASE CHANGES DURING HUMAN APNEIC OXYGENATION

Subject number	Duration Apnea (minutes)	Arterial pH Lowest During	Buffer Base (mEq./l.) Preapnea	Lowest During	Change
4	45	6.88	46.0	37.5	−8.5
5	18	6.97	43.8	40.2	−3.6
6	45	6.87	44.5	36	−8.5
7	53	6.72	44.0	35	−9.0
8	38	6.96	47.0	39.8	−7.2

TABLE 5

ARTERIAL EPINEPHRINE AND NOREPINEPHRINE LEVELS DURING HUMAN APNEIC OXYGENATION

Subject number		Control	10 Minutes	20 Minutes	30 Minutes
6	E	0.3	—	0.9	—
	N	0.4	—	1.2	—
	BP	110/70	—	160/70	—
7	E	0.1	0.25	0.4	0.6
	N	0.4	0.4	0.6	0.8
	BP	120/80	120/80	120/70	150/80
8	E	—	0.1	0.3	0.6
	N	—	0.4	0.3	0.8
	BP	130/100	140/80	150/100	170/100

E—Arterial Plasma Epinephrine (μg./l.).
N—Arterial Plasma Norepinephrine (μg./l.).
BP—Arterial Blood Pressure (mm. Hg.)

apnea in one case of 7 mEq./l. The changes in the arterial buffer base are shown in table 4 and indicate a fall amounting to as much as 9 mEq./l. in the apneic period.

The arterial plasma epinephrine and norepinephrine concentrations in 3 subjects are shown in table 5. The concentration of both substances increased as the apnea progressed with a maximum rise in one instance of 0.6 and 0.8 μg./l. of epinephrine and norepinephrine, respectively. These changes are outside the range of error of the method (± 0.1 μg./l.).

DISCUSSION

The mechanism by which gas moves into the lungs from the external environment during apnea will be considered first. Respiration is thought of usually as the simultaneous extraction of oxygen from the alveoli by blood and the addition of an equal or nearly equal volume of carbon dioxide to the alveoli by the blood. If these conditions obtained during apnea and if one assumes an R.Q. of 1.0 and oxygen consumption and carbon dioxide production of 300 ml. and an alveolar volume of 2,000 ml., then all of the alveolar oxygen would have been replaced by carbon dioxide in about 7 minutes. Therefore, the concept of the "hemoglobin pump" of Draper *et al.* cannot account for the maintained oxygenation. However, this view of respiration with the assumptions made above fails to take into account the distribution of carbon dioxide.

The outstanding feature of apneic oxygena-

tion is that only a small fraction of metabolically produced carbon dioxide enters the alveoli even though carbon dioxide production may equal the oxygen consumption in the metabolizing tissues. The reason for this distribution of carbon dioxide is the equilibration or near-equilibration of carbon dioxide throughout the body, *i.e.*, in the blood, tissues and lungs. It is impossible for all of metabolically produced carbon dioxide to enter the alveoli since the blood and tissues would have to remain at their pre-apneic levels while the alveolar level rose precipitously. Holmdahl [3] has estimated that the carbon dioxide which is produced is so partitioned that approximately 90 per cent remains in the blood and tissues while only 10 per cent enters the alveoli. The buffering of carbon dioxide in the body tissues and fluids is, therefore, considerably greater than that in the alveolar compartment.

In addition, there is a simultaneous reduction of barometric pressure in the alveoli resulting from a smaller transfer of carbon dioxide from the blood to alveoli than of oxygen to the blood from the alveoli. Thus, a pressure gradient is created between the upper airway and the alveoli, which moves gas from the outside, down the trachea to the alveoli. The only other significant gaseous transport which can go on is the transfer of nitrogen from the blood to the alveolus. The solubility of nitrogen in the body fluids makes possible the transfer of only relatively small amounts during this period. Quantitative data on this point have been presented by Holmdahl.[3]

The volume of gas moved down the trachea has been observed and measured in dogs by Draper and Whitehead [2] and by Holmdahl.[3] It has also been measured spirometrically in man as an incidental finding during compliance studies [15] and by the body plethysmograph technique.[6] The gradual emptying of the reservoir bag during the present study provided semiquantitative confirmation of these earlier findings.

Most of the observations made here have been previously described in laboratory animals. The important point of interest in this study was to define the limits of applicability of these results to man. For example, the rate

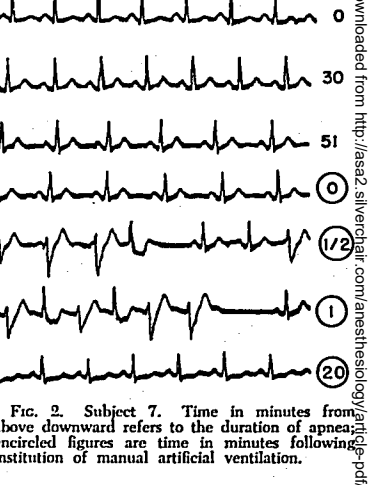

FIG. 2. Subject 7. Time in minutes from above downward refers to the duration of apnea; encircled figures are time in minutes following institution of manual artificial ventilation.

of rise in carbon dioxide tension is about half of that found in dogs.[2] Also, the human subjects maintain full oxygen saturation for periods lasting more than 30 minutes whereas dogs show a progressive desaturation after this time.[3]

The present study clearly indicates that severe respiratory acidosis (without anoxia), as produced by apnea lasting over 30 minutes, can easily be tolerated by lightly anesthetized normal man with complete recovery. Similar findings have been reported in other studies in man under a wide variety of circumstances. Survival without apparent sequelae in man anesthetized by thiopental was found by Clowes *et al.*[16] following the inhalation of 30 per cent carbon dioxide for 10–26 minutes; in studies producing a respiratory acidosis and lowering of the arterial *p*H to 6.8–7.1. Altschule and Sulzbach [17] produced 10–20 minutes of apnea in 2 subjects with curare and recorded arterial *p*H values of 6.81–7.03 with apparently uneventful recovery. Jooste [7] produced complete paralysis with succinylcholine and an apnea which lasted 30 minutes while tracheal insufflation of oxygen was carried out. The arterial *p*H fell to 6.97 and the arterial

carbon dioxide tension rose to 115 mm. of mercury and there were no postoperative complications. Taylor and Roos [18] reported a pH of 6.86 and a carbon dioxide tension of 170 mm. of mercury during ether anesthesia for intrathoracic surgery. Respiratory acidosis with carbon dioxide tensions as high as 120 mm. of mercury during cyclopropane anesthesia was produced by both exogenous and endogenous carbon dioxide by Lurie *et al.*[19]

Dripps and Comroe [20] insufflated oxygen endotracheally in two apneic comatose terminal patients for periods as long as three hours. The arterial pH fell as low as 6.67 and the carbon dioxide tensions rose to over 300 mm. of mercury. The arterial oxygen saturations were not maintained as well as in the present study. According to Holmdahl's findings in dogs,[3] tracheal insufflation is comparable to apneic oxygenation with respect to carbon dioxide accumulation and, therefore, their results should be similar to those in the present study. Since these subjects never regained consciousness from the primary neurosurgical disease, it was impossible to assess any long-term deleterious effects of such massive carbon dioxide accumulation.

Busse *et al.*[21] on the other hand, produced apnea by barbiturates for 11–22 minutes. They reported that one of their 3 subjects died 12 hours after the study was completed. The exact mechanism of death was not clearly stated, but may have been related to the large doses of thiopental required when relaxant agents were not used to supress respiratory movements.

In addition to complete recovery after exposure to high carbon dioxide tensions, this study demonstrates the ability of a mass movement of gas to produce full oxygen saturation for at least approximately 45 minutes in man. The uniformly high oxygen saturation in man may be contrasted to the progressive fall in saturation usually seen in dogs when the apnea progressed beyond 30 minutes.[3, 22] The maintenance of excellent oxygen saturation values in the present study probably contributed to the long-term survival without sequelae of these subjects in contrast to the 30 per cent mortality rate in dogs.

The sodium and potassium changes (table 2) were not striking. The potassium changes were similar to those described in man during a milder acidosis with either cyclopropane,[19] thiopental [16] or thiopental-nitrous oxide-succinylcholine.[23] These findings are similar although not as marked as those described in animals during respiratory acidosis.[24] The further elevation of the plasma potassium in the posthypercapneic period which was observed here has been reported previously in dogs.[25, 26] However, it appears from these small shifts that little insight will be gained from the arterial potassium changes as to the mechanism of the posthypercapneic events such as hypotension or arrhythmias. The potassium changes in subject 7 in whom the ventricular tachycardia was demonstrated were similar to those in subjects 6 and 8 who had normal rhythms when respirations were resumed.

The rises in arterial pressure (table 3) are consistent with the results of many other studies of carbon dioxide retention. The hypertension during the apnea may be mediated by reflexly induced sympathetic discharge as judged by the rise in catecholamine levels. Although the action of carbon dioxide in stimulating the medullary centers is well established, the time course of the changes in this study differ from those observed by Joels and Samueloff [27] during apneic oxygenation in cats. They concluded that the medullary respiratory and vasomotor centers were stimulated early in the apneic period since they observed an increased discharge over the recurrent laryngeal nerve and the cervical sympathetic trunk at this time. However, the central discharge diminished after 25 minutes and was absent after 47 minutes of apnea while in the present studies the hypertension usually continued to increase as the apnea persisted and the carbon dioxide tension rose. When moderate to severe hypercarbia of 90–120 mm. of mercury was produced during cyclopropane anesthesia by Lurie *et al.*[19] the mean arterial pressure rose to 99 mm. of mercury from a control level of 88 mm. of mercury, an elevation considerably less than that observed in the present study.

The detection of increased plasma levels of epinephrine and norepinephrine constitutes direct evidence for increased sympathetic and adrenal medullary function during respiratory

acidosis in man. Presumptive evidence for a similar response to prolonged apnea in cats was presented by Tenney [28] on the basis of an *in vivo* bioassay technique.

The relationship of the plasma catecholamine concentrations to the observed arterial pressures is not a direct one, and, therefore, the data require interpretation. Although increased medullary secretion reflects itself directly in increased plasma catecholamine levels, increased sympathetic discharge, on the other hand, results in increased plasma catecholamines in a less direct manner. Only a fraction of the pressor amines secreted at the sympathetic nerves reach the circulation and then over an as yet unknown time period. What is observed in plasma is the overflow from the neuroeffector sites which has escaped metabolic transformation or binding to other tissues. It is, therefore, evident that the arterial hypertension need not be due to the circulating pressor amines but that the circulating pressor amines may reflect indirectly the sympathetic activity which caused the hypertension.

Further difficulties in exact interpretations result from the fact that circulating epinephrine and norepinephrine produce hypertension by different mechanisms, *i.e.*, epinephrine hypertension is associated with tachycardia, increased cardiac output and decreased total peripheral resistance while norepinephrine hypertension is associated with bradycardia, no change in cardiac output and increased total peripheral resistance.[28] Thus, the pressor effects of these two catecholamines should not be considered additive.[29] Therefore, no attempt was made to correlate plasma catecholamine levels with the observed arterial pressures in the present study. The need for caution in interpreting plasma catecholamine levels is well illustrated by the data of Price *et al.*[30] They showed that in order to produce by infusion of these amines a degree of hypertension equivalent to that observed as the result of hypercarbia during cyclopropane anesthesia, a 5 to 10-fold greater plasma catecholamine level was produced in the former.

The electrocardiographic changes in lead 2 during the apneic period were relatively slight in 6 of the 8 subjects. Figure 1 shows a remarkable constancy of the pattern in the face of an undoubted hypercarbia, *i.e.*, 55 minutes of apnea and a severe degree of arterial hypertension. The constancy of rate was also surprising in view of the marked hypertension. Altschule and Sulzbach [17] noted somewhat different findings, *i.e.*, an elevation in the ST segment in lead 1 and a depression in lead 3 together with an inversion of the T wave. The pattern of ventricular irritability in one subject during apnea reverted promptly to normal with the reestablishment of ventilation and carbon dioxide excretion. Since a few ventricular premature contractions were noted in the other subject (fig. 2) during the last minute of the apnea, it is difficult to decide whether the bout of ventricular tachycardia during the early washout period was due solely to the abrupt reduction of carbon dioxide tension or whether it was a continuation of the irritability noted earlier during the apnea.

It should not be concluded that the usual occurrence of normal rhythms in the present study would be as frequent in clinical situations in which apnea was deliberately produced, because conditions are then encountered which might provoke ectopic beats. In this study, there were no endobronchial manipulations, traction on dura, ocular or extraocular structures or other maneuvers resulting in vagal stimulation. These might be expected to increase the frequency of arrhythmias. Furthermore, Bohr and Helmendach [31] show that the duration of cardiac asystole resulting from vagal stimulation in dogs increased during apneic oxygenation when the *p*H fell 0.4 units or more.

The occurrence of a severe metabolic acidosis accompanying the acute respiratory acidosis has been noted in man previously.[32] Holmdahl [3] and Joels and Samueloff [5] have described similar findings in dogs during apneic oxygenation. The apparent severity of the metabolic acidosis, however, seems to be somewhat greater than might be expected from the relatively brief exposure. It should be noted that Joels and Samueloff [5] and others have pointed out the limitations in the application of the Singer-Hastings nomogram which was used in the present study for estimating these changes.

The circulatory phenomena during the post-

hypercapneic period are particularly interesting. When the apnea was terminated and the carbon dioxide tension was returning towards normal, a moderate arterial hypotension with a systolic pressure falling to approximately 90 mm. of mercury was observed. This finding resembles the observations of Lurie *et al.*[19] in man during carbon dioxide washout accompanying recovery from cyclopropane anesthesia.

The infrequent occurrence of posthypercapneic arrhythmias when apneic oxygenation is terminated confirms the finding of Holmdahl[3] in the dog. Also, none of the investigators who produced relatively short term acidosis (usually under 30 minutes) in man mention arrhythmias as a complication when artificial respiration was resumed.

These findings appear to be in conflict with those of Brown and Miller[8] who reported ventricular fibrillation in the posthypercapneic period. However, Brown[26] pointed out that if the blood *p*H fell to approximately 6.7 when the dog breathed 40 per cent carbon dioxide for only 15 to 30 minutes, the rapid reversal of this hypercapneic acidotic state was not followed by the cardiac arrest or fibrillation which follows the hypercapnea which has lasted 2 or more hours.

Nevertheless, the pattern observed in subject 7 at the start of the washout closely resembles that described by Brown[26] in dogs following termination of prolonged carbon dioxide administration. Furthermore, the plasma potassium changes are also in the same direction. Although in both the present series and that of Brown[26] plasma potassium rose during the hypercapneic phase and rose still further with the resumption of ventilation, the magnitude of the rise in plasma potassium was considerably less in the present study. Even though there seems to be a distinct parallel between the results in man and dog it is necessary to point out that arrhythmias were noted only once in the present series. The other case which showed arrhythmias did so within 7 minutes of the start of apnea and they terminated with the end of the apnea. In all other cases, no arrhythmias were noted when breathing was resumed.

After this experimental work was completed, Nahas[21, 22] described the use of an intravenously administered amine buffer during prolonged apnea in dogs which kept the arterial *p*H normal while carbon dioxide tension rose 45 mm. of mercury and presented most of the accompanying circulatory and electrolyte alterations seen with untreated apneic oxygenation. He also reported elevations of the plasma epinephrine and norepinephrine to maximal values of 27 and 23 μg./l. as estimated by the Weil-Malherbe and Bone technique during 45–60 minutes of unmodified apneic oxygenation. The striking contrast between these catecholamine levels in dogs and those obtained in this study in which the trihydroxyindole technique was employed may be due to differences in species, sampling sites, carbon dioxide tensions or perhaps specificity of the two analytical techniques.[14, 24]

Summary

Apneic oxygenation was carried out in 8 human subjects for periods between 15 and 55 minutes. The mechanism by which oxygenation was maintained during the period of increasing respiratory acidosis was described. A moderate to severe arterial hypertension usually developed followed by a mild hypotension when artificial respiration was resumed. The increases in plasma sodium, potassium, epinephrine and norepinephrine concentrations during the apnea were described and their relationship to the hypertension and the electrocardigraphic changes were discussed. The electrocardiographic patterns were usually unchanged during the production of profound acidosis with arrhythmias noted only twice, once after 7 minutes and once after 53 minutes of apnea. In the latter instance, ventricular tachycardia lasting one minute accompanied the institution of artificial respiration and carbon dioxide elimination. A severe metabolic acidosis accompanied the respiratory acidosis.

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CLINICAL RESEARCH All knowledge of patient reaction to clinical treatment must ultimately be derived from clinical trial. The three pillars of clinical trial are: (1) control with randomization of subjects and consideration of ethical problems; (2) mensuration properly done with no attempts to measure incommensurables; and (3) analysis of results with statistical validation and listing and weighing of factors besides those under study that might have influenced the results. (*Atkins, H. J. B.: Three Pillars of Clinical Research, Brit. Med. J. 2: 5112 (Dec. 27) 1958.*)

SPINAL ANESTHESIA After the administration of 2,016 spinal anesthetics with xylocaine the incidence of lumbar-puncture headache was 0.9 per cent. This low incidence was attributed to the use of 26 gauge spinal needles. One serious neurological sequela was noted—paralysis and anesthesia of one leg from which there has now been 95 per cent return of function. (*Phillips, O. C., and others: Spinal Anesthesia for Vaginal Delivery, Obst. & Gynec. 13: 437 (April) 1959.*)

OBSTETRIC ANESTHESIA With the organization of an obstetric anesthesia service manned by trained anesthesiologists, in a private hospital the uncorrected fetal mortality was reduced at Women's Hospital in Baltimore, Maryland, from 28 to 20.4 per thousand during the first complete year of the service. Advantages also include reduced morbidity for the mothers, better training in obstetric anesthesia for the obstetric residents and better anesthesia coverage for other patients in the hospital since one anesthesiologist is now in the hospital at all times. (*Nelson, A. T., Phillips, O. C., and Savage, J. E.: Obstetric Anesthesia Care, Obst. & Gynec. 13: 426 (April) 1959.*)