# A Comparison of the Physiological Effects of Hypercapnia and Hypoxia in the Production of Cardiac Arrest*

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CARDIAC ARREST OCCURRED 41 times in the four years 1951 through 1954 at the Cleveland City Hospital, with an over-all mortality of 63 per cent. An increasing appreciation of the problem has resulted in a decrease yearly in the number of such untoward accidents, but their alarmingly high incidence[31] makes it desirable to investigate thoroughly the physiologic mechanisms involved in circulatory arrest during surgery.

Many factors have been implicated and investigated in the causation of cardiac arrest: hypoxia,[1, 7] hypercapnia,[26, 30] overdosage or sensitivity to drugs, hypotension, previously existing disease, and vagal reflexes.[7, 25] Reid *et al.* emphasized that the vago-vagal effects are only operative when one or more of the other agents are present.[29] Recently Dawes and Comroe[11] have reviewed the chemoreflexes from the heart and lung.

In no less than 19 of the 41 cases mentioned there is evidence leading to the belief that inadequate respiratory exchange played a part. Since accurate observations are seldom possible in man because of the unexpected nature and urgency of clinical cardiac arrest, controlled studies of the physiologic responses to each of the contributing variables must be performed in animals.

Experiments were undertaken on the responses of the central nervous and cardiovascular systems of intact animals to pure hypercapnia and to hypoxia. The majority of these experiments were pushed to the point of cardiac arrest. To evaluate the part played by the autonomic nervous system in the production of cardiac standstill under these circumstances, animals in which thoracic sympathectomy or vagectomy had been performed were treated in like fashion. Observations made on patients during anesthesia suggest that the response found in the dog are similar in many respects to those in man. It is the purpose of this paper to present these results, and to demonstrate the very different effects of severe oxygen lack without hypercapnia, and of severe respiratory acidosis without hypoxia.

## METHODS

These experiments on induced severe respiratory acidosis and hypoxia were performed on mongrel dogs, without special preparation other than several days on ordinary kennel diet. Anesthesia was used in each instance. Pentobarbital sodium, 60 mg. per kilogram of body weight, was administered intravenously, at least one hour before the experiment.

In addition to intact animals, a variety of surgical experimental preparations were used, which included vagus section, thoracic sympathectomy, and thoracic sympathectomy plus adrenalectomy. These were operated upon on the day of the experiment, with the exception of animals subjected to

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dorsal sympathectomy, which were allowed three to four weeks to recover fully before the experiments were performed.

Insufflation of the lungs with the desired respiratory gas mixture was done through an endotracheal tube with an attached inflatable cuff, or through a tracheotomy tube with ligatures about the trachea, to insure a completely air-tight connection. The respirator was constructed with rotating valves to insure that only the experimental gas mixture could enter the lungs and at a controlled rate. Furthermore, this made certain that a combination of hypoxia and hypercapnia was not produced. A definite respiratory exchange took place despite depression of the respiratory center, which usually developed in the presence of the severer degrees of acidosis or oxygen lack. Gas mixtures containing low concentrations of oxygen were mixed in a Tissod spirometer at room temperature, using nitrogen and oxygen. The nitrogen tanks contained approximately 0.3 per cent oxygen, to which was added 0.4 per cent oxygen, giving a mixture containing slightly less than 1 per cent $O_2$. This will be referred to as 1 per cent $O_2$ mixture. Other concentrations used were 2 per cent, 4 per cent and 8 per cent oxygen. Similarly, gas mixtures containing abnormally high concentrations of carbon dioxide were made up of $CO_2$ and oxygen. The gas was then stored in Douglas bags, from which it was delivered to the respirator.

Arterial blood pressures were measured by a mercury manometer connected to a cannula in the femoral artery. A water manometer indicated venous pressure through a catheter inserted into a jugular vein, so that its tip lay within the superior vena cava. For convenience in recording pressures and obtaining blood samples, all animals were given sodium heparin, 7 mg. per kilogram of body weight, before each experiment.

The electroencephalograms and electrocardiograms were recorded on a Grass ink writing oscillograph, Model III B. Bipolar leads were used for both E.E.G. and E.C.G. The former was recorded from needles inserted into the frontal and parietal regions of the scalp, using an amplification such that a pen deflection of 6 mm. was produced for each 50 microvolts. The brain wave patterns seen with depression of potential by anesthesia, low oxygen tension or respiratory acidosis were classified according to the pattern types described in a previous publication.[10] The electrocardiogram was obtained from needles inserted into the right foreleg, and into the precordial area of the chest wall near the apex of the heart. The heart rate was determnied from the E.E.G. records.

Arterial blood carbon dioxide and oxygen content were determined from samples obtained in oil-sealed syringes by the method of Van Slyke and Neal.[32] Hydrogen ion content was measured with the Cambridge glass electrode pH meter. Readings were made at room temperature, and corrected to 38° C. Blood potassium, calcium, and magnesium were measured in plasma obtained from centrifuged blood. Samples showing hemolysis were discarded. The Baird flame photometer was employed for determining potassium levels. Calcium and magnesium were measured by a modification of the method of Buckley.[4] The mean laboratory error for the latter technic was found to be ±3.2 per cent.

## PROCEDURE

To test the effects of pure hypercapnia or hypoxia, and the role played by the component parts of the autonomic nervous system in producing cardiac arrest, intact anesthetized animals were compared with groups which had previously undergone bilateral vagotomy, bilateral thoracic sympathectomy, or thoracic sympathectomy plus bilateral adrenalectomy. Pilot experiments indicated that the greatest difference in the time of circulatory failure between the various categories might be expected if respira-

TABLE I. *Effect of Nerve Section and Adrenalectomy on Time of Circulatory Arrest Caused by Hypercapnia and Hypoxia.*

| | | No. of Dogs | Time (Min : Sec) | S. E. |
|---|---|---|---|---|
| Hypercapnia: | Respiratory Mixture: 55% $CO_2$ | | | |
| | Normal | 6 | No arrest | .... |
| | Vagus Section | 5 | No arrest | .... |
| | Dorsal Sympathectomy | 5 | 4 : 16 | ± : 01.1 |
| | Dorsal Symp. + Adrenalectomy | 6 | 4 : 14 | ± : 01.7 |
| Hypoxia: | Respiratory Mixture: 0.5–1.0% $O_2$ | | | |
| | | No. of Dogs | Time (Min : Sec) | S. E. |
| | Normal | 5 | 10 : 17 | ±1 : 01 |
| | Vagus Section | 4 | 9 : 15 | ±1 : 43 |
| | Dorsal Sympathectomy | * | .... | .... |
| | Dorsal Symp. + Adrenalectomy | 5 | 4 : 21 | ±1 : 42 |

*Inadequate number of experiments.

tory gas mixtures contained 55 per cent carbon dioxide or 1.0 per cent oxygen. Therefore, the effects of these mixtures were studied in more detail, and groups of five or six animals from each of the above mentioned four categories were exposed to 55 per cent carbon dioxide insufflation for 20 minutes, or until such time as cardiac arrest occurred. Similarly, five or six of each preparation were given 1.0 per cent oxygen until the onset of circulatory failure.

TABLE II. *Effects of Respiratory Acidosis and Hypoxia on the Plasma Potassium Concentration.*

*Hypercapnia*

| Arterial Blood pH | Shift of K from control level: Meq./liter | | | |
|---|---|---|---|---|
| | 10–30 minutes | | 30–60 minutes | |
| | Mean | S.E. | Mean | S.E. |
| less than 6.5.... | +.08 | ±.12 | +.40 | ±.31 |
| 6.5 to 6.7..... | +.37 | ±.05 | +.55 | ±.25 |
| greater than 6.7. | −.01 | ±.13 | +.16 | ±.13 |

*Hypoxia*

| Arterial Blood $O_2$ content: vols. % | Shift of K from control level: Meq./liter | | | |
|---|---|---|---|---|
| | 10–30 minutes | | 30–60 minutes | |
| | Mean | S.E. | Mean | S.E. |
| less than 3..... | +.60 | ±.21 | —— | —— |
| 3 to 5..... | +.34 | ±.17 | +.10 | ±.18 |
| greater than 5... | +.04 | ±.12 | −.24 | ±.14 |

Following a control period of respiration for ten minutes on room air, arterial blood samples for potassium, pH, $CO_2$ and $O_2$ content were obtained. Similar blood samples were obtained at two, five, ten, and 20 minutes after 55 per cent $CO_2$ respiration was started. If cardiac arrest had not occurred, the mixture of gas was gradually diluted to the consistency of room air to avoid ventricular fibrillation, which invariably followed a sudden shift. The animals were observed for 24 hours further. Electrocardiographic, electroencephalographic, and arterial blood pressure recordings were made every 30 seconds throughout the experiment. Further prolonged experiments using intact animals were conducted on the effects of less intense hypoxia or respiratory acidosis for periods of 90 minutes, or until the development of cardiac arrest. Groups of six anesthetized animals were exposed to each gas mixture. Those tested contained 2 per cent, 4 per cent, and 8 per cent oxygen, or 45 per cent and 35 per cent carbon dioxide.

At the end of each of two control 15 minute periods on room air, arterial blood samples were obtained to determine calcium, magnesium, potassium, hydrogen ion, oxygen and carbon dioxide content. During the exposure to high carbon dioxide or low oxygen, samples were obtained at 15, 30, 60 and 90 minutes. At the termination of this period the mixture was gradually diluted to room air. Throughout the procedure E.E.G., E.C.G., and arterial and venous pressure were recorded.

## RESULTS

### I. RESPONSE TO HYPERCAPNIA

A. *Blood Pressure and Heart Rate.* The response to the severe hypercapnia induced

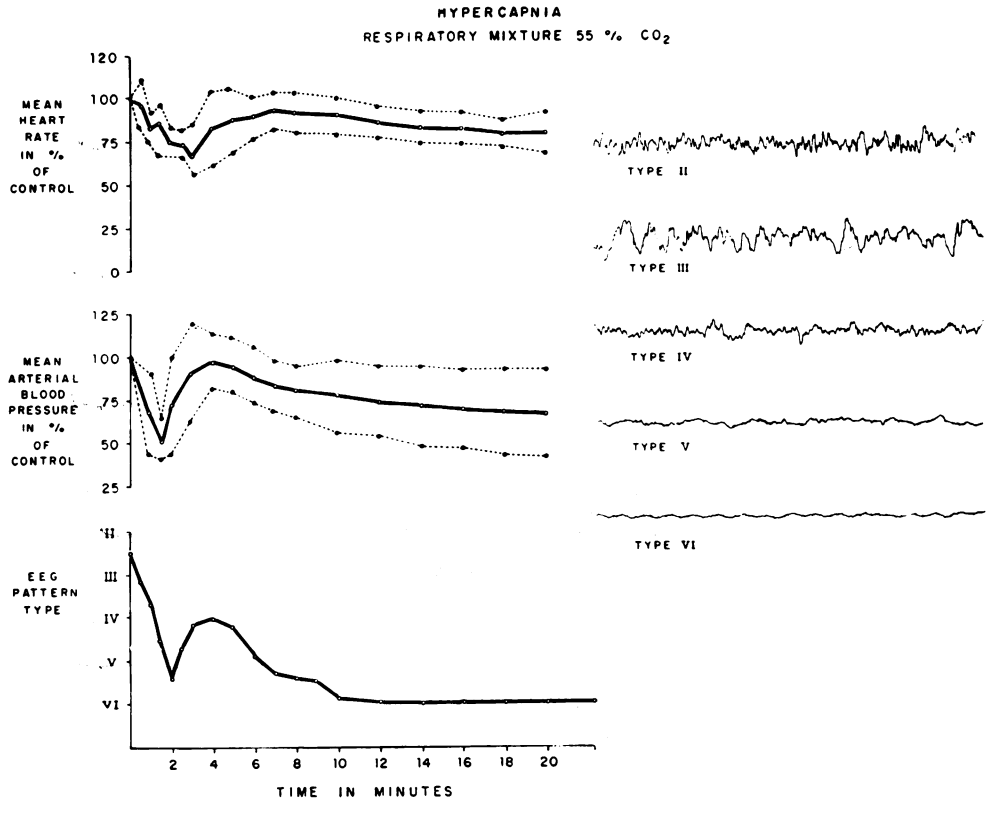


FIG. 1. The mean response of pulse rate, blood pressure and electroencephalographic pattern to the administration of 55 per cent carbon dioxide–45 per cent oxygen mixture. The dashed lines represent standard deviation of pulse and blood pressure. At the right are typical brain wave patterns from one of the six animals in this group.

by 55 per cent $CO_2$ administration, as shown by the curves in Graph I, was characteristically different from that of severe hypoxia shown in Graph II. Respiratory acidosis initially caused a marked but transient hypotension and bradycardia. This was followed by a return of pulse and blood pressure to near control levels, which in turn was succeeded by a gradual decline to the termination of the experiment. Despite the precaution of diluting the respiratory mixture gradually a depression of heart rate and blood pressure invariably occurred. Subsequently the animals slowly returned to a normotensive state. Although marked fluctuations in venous pressure occurred as a result of intense respiratory efforts before depression developed, the mean venous pressure remained nearly unchanged throughout the experiment. There was usually a moderate transient rise of 3 to 4 cm. $H_2O$ immediately following the start and termination of the $CO_2$ exposure.

When carbon dioxide in concentrations of 45 per cent or 35 per cent was administered for 90 minutes to intact animals, there was an initial short depression of heart rate and blood pressure similar to that of dogs given 55 per cent $CO_2$. This is illustrated by the typical examples shown in Graphs III and IV. The subsequent gradual fall of pressure and pulse rate to the termination of the respiratory acidosis was more pronounced in the group which was made to breathe 45 per cent carbon dioxide than those on 35 per cent $CO_2$. Both series showed a post-

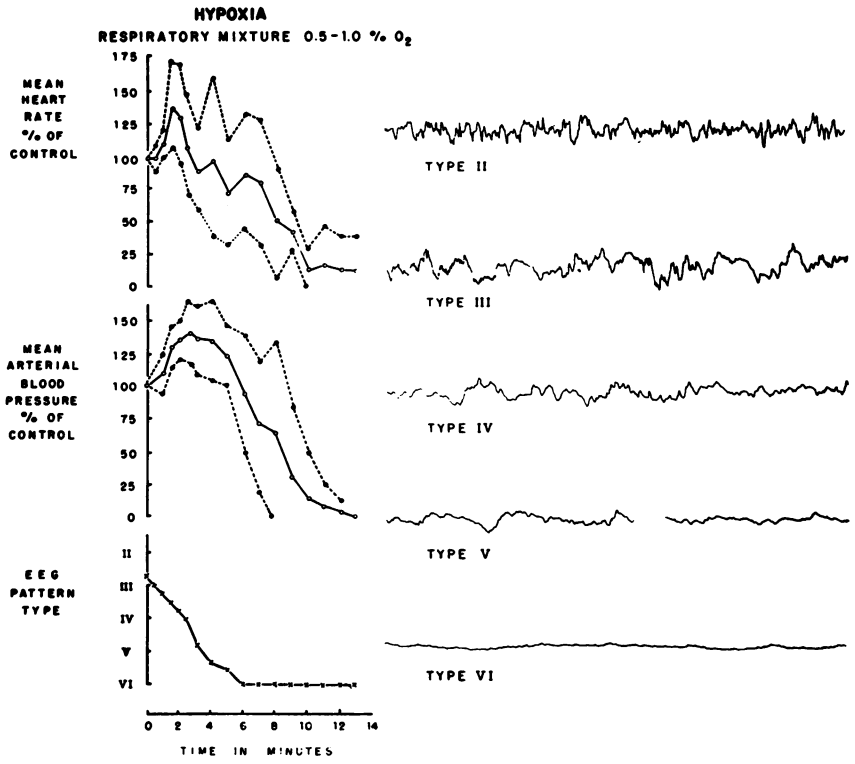


FIG. 2. The mean response of pulse rate, blood pressure and electroencephalographic pattern to severe hypoxia caused by respiration of 1 per cent oxygen–99 per cent nitrogen mixture. The dashed lines represent standard deviation of pulse rate and blood pressure. Typical brain wave patterns from one of the six animals in this group are shown at right.

hypercapnic bradycardia and hypotension with a gradual return toward control values. However, in three of the six animals given 45 per cent $CO_2$ for 90 minutes the blood pressure ultimately fell to very low levels, and they died within four to 12 hours. All of the animals given 35 per cent $CO_2$ survived until sacrificed.

B. *The Effects of Autonomic Nerve Section.* Data on the comparative periods of time required in severe hypercapnia or hypoxia to produce circulatory arrest following vagotomy or sympathectomy are given in Table I. Arbitrarily, the last point at which the pulse rate fell below 25 per cent of the control value was selected as the time of arrest. In each instance blood pressure was absent or nearly so by the time this point was reached. Selection of this arbitrary point became necessary, because infrequent electrocardiographic complexes were recorded in a few instances for as long as 15 minutes after any effective or visible heart beat had ceased.

Vagus section was found to have comparatively little effect on the blood pressure and pulse response in dogs given 55 per cent $CO_2$ when compared to intact animals subjected to the same conditions. Arrest occurred in neither group.

Thoracic sympathectomy and thoracic sympathectomy accompanied by adrenalectomy resulted in a profound fall of blood pressure and pulse rate shortly after the introduction of respiratory mixtures containing 55 per cent $CO_2$. The presence of respiratory acidosis of this degree caused cardiac arrest in five of seven sympathectomized

animals in an average time of four minutes and 16 seconds. The other two did not arrest. This course was in no way influenced by the absence of the adrenals in the animals subjected to 55 per cent $CO_2$ mixtures when the adrenalectomy and thoracic sympathectomy had been performed before the experiment. The mean time of arrest was not significantly different in the two groups.

C. *Blood Chemistry.* The arterial blood pH became stabilized at its lowest value within four to six minutes after 55 per cent $CO_2$ inhalation was started. The administration of 55 per cent $CO_2$ resulted in arterial blood carbon dioxide levels between 84 and 98 volumes per cent, with pH levels ranging from 6.31 to 6.50. The animals on 45 per cent $CO_2$ showed arterial blood pH levels from 6.42 to 6.71, with $CO_2$ contents of 72 to 88 volumes per cent. When 35 per cent $CO_2$ was administered, the arterial blood reached pH levels of 6.70 to 6.82, and the accompanying elevations of $CO_2$ content ranged from 67 to 76 volumes per cent. It is of interest that none of the dogs which survived until sacrificed after 90 minutes of treatment with 45 per cent or 35 per cent $CO_2$ showed arterial pH values of less than 6.40.

Shortly after the start of 55 per cent $CO_2$ respiration, there was a transient rise of plasma potassium which fell to near control levels within eight to ten minutes. The subsequent course of the potassium shift caused by hypercapnia was studied in those animals given less severe degrees of stress for longer periods. Data from these experiments are given in Table II and show that, following the initial rise and fall of potassium, a small but significant secondary rise in potassium took place as a result of acidosis. The plasma calcium shifted rapidly as much as 2 mg. per cent in either direction from control levels as a result of elevated carbon dioxide tensions. Often the calcium rose and fell in the same experiment. The same was found to be true of magnesium. However, with magnesium the changes were usually within 0.5 mg. per cent from the control level, and seldom over 1 mg. per cent. No correlation of these variations in blood level of calcium or magnesium was found with each other or with arterial blood pH. In general, it can be said that at the onset and at the end of the period of hypercapnia a shift of one or both ions occurred. But no relationship was discovered to account for the direction of the shift or for the changes which occurred during the procedure. Furthermore, analysis disclosed no direct association between the observed levels of calcium or magnesium and the pulse or blood pressure response.

D. *The Electroencephalogram.* The electroencephalographic tracings taken from one of the animals of the group given 55 per cent $CO_2$ are reproduced in the right of Graph I. They are quite typical of what may be expected. Starting with the Type II or Type III pattern of light barbiturate anesthesia, depression gradually took place in the presence of this severe hypercapnia to the pattern Type VI in which all recordable potential was absent. The lower curve on each Graph represents the pattern Type found to occur at various stages of the experiment.

The brain wave potential became depressed to a certain level with the various degrees of respiratory acidosis. In general, if the arterial blood pH fell to 6.6, the recordable encephalographic potential fell to zero. A Type V pattern was found to be present when the pH was near 6.7. These reactions are shown by the experiments presented in Figures 1, 3 and 4.

Another important point is illustrated by Figure 3. Although the brain waves of the animal on 55 per cent $CO_2$ and that on 45 per cent $CO_2$ were both depressed to Type VI for part of the time, the latter died in a subsequent state of shock while the former survived. This is related to the length of time the brain waves remained totally depressed. Despite an early apparent recovery, no animal survived, when, as a result of

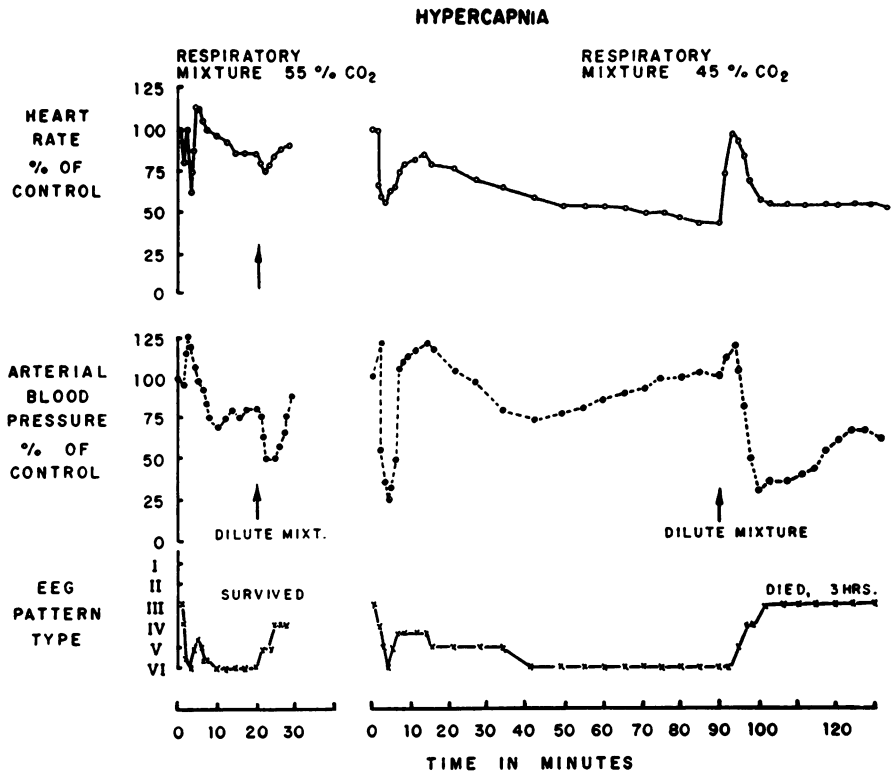


FIG. 3. Typical examples of response of pulse rate, blood pressure and brain wave pattern to hypercapnia; 20 minutes 55 per cent $CO_2$ administration (arterial blood pH: 6.38, $CO_2$: 90 volumes per cent. 90 minutes 45 per cent $CO_2$ administration (arterial blood pH: 6.45, $CO_2$; 87 volumes per cent).

severe respiratory acidosis, the brain waves were absent for more than 20 minutes. Death occurred usually within 12 hours, and often sooner. No animal died when the brain wave pattern remained at Type VI for less than ten minutes, and there were no late deaths if the depression did not progress beyond a pattern of Type V.

### II. RESPONSE TO HYPOXIA

A. *Blood Pressure and Heart Rate.* The characteristic response to severe hypoxia is illustrated in Figure 2. An immediate elevation of blood pressure, or pulse rate, or both, occurred in the animals given 1 per cent oxygen. This was succeeded, as unsaturation progressed, by bradycardia, while the hypertension continued. When the blood pressure fell, it did so precipitously, accompanied by a further fall in pulse rate. Cardiac arrest followed within a few minutes. Venous pressure was found to rise only after the final hypotension occurred.

Animals exposed to less severe degrees of hypoxia showed the same early hypertension and tachycardia. Those given 2 per cent oxygen slowly developed bradycardia as the oxygen content of the arterial blood fell toward 4 volumes per cent. Again, as shown in the second example in Figure 5, which is typical of this group of animals, the blood pressure fell precipitously. Cardiac arrest took place within a short time after the hypotension occurred. Although desaturation of the arterial blood developed more slowly with 2 per cent than with 1 per cent

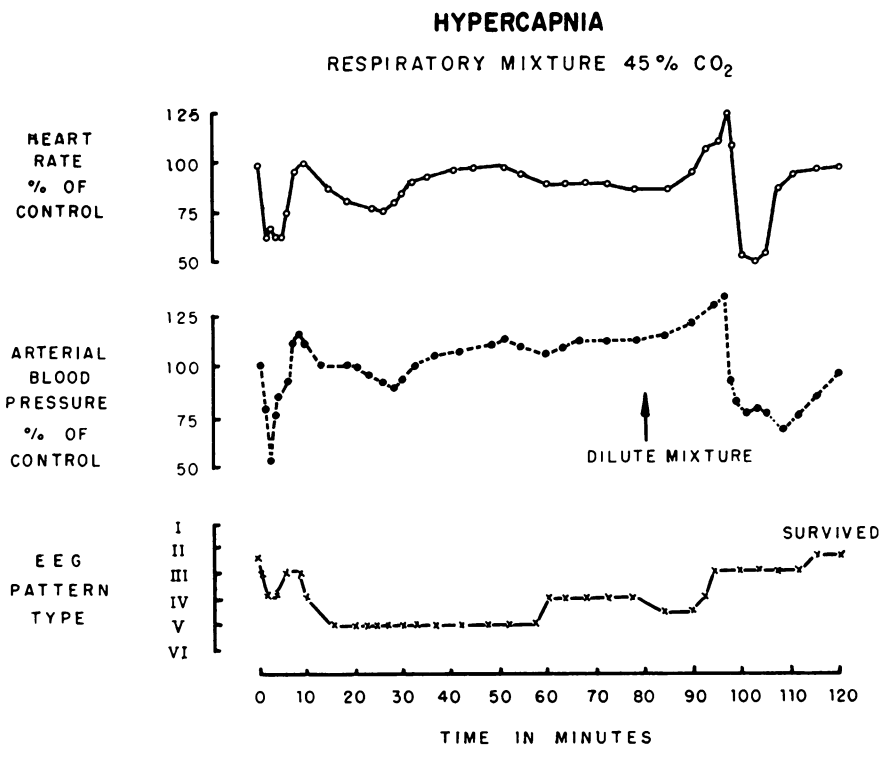


FIG. 4. Typical example of three animals which survived 90 minutes of 45 per cent $CO_2$ administration (arterial blood pH: 6.68, $CO_2$ 81 volumes per cent).

oxygen administration, the arterial blood was found to contain less than 3 volumes per cent of oxygen in all of these animals just prior to circulatory arrest. This event took place in the presence of 2 per cent oxygen inhalation between 24 and 52 minutes.

When given 4 per cent oxygen to breathe, tachycardia and hypertension resulted, as shown in the third example in Figure 5. Bradycardia of a moderate degree, a pulse rate of not less than 85 per cent of control levels, was seen in three of the animals. But circulatory failure occurred in only one of the six in this group. In this one the arterial oxygen was found to be 2.7 volumes per cent shortly before death, whereas in none of the others did it fall below 4 volumes per cent. Despite gradual dilution of the mixture, hypotension developed after the hypoxic period. In two animals shifted rapidly to air, cardiac arrhythmia was observed on the electrocardiogram, promptly followed by ventricular fibrillation.

When an 8 per cent oxygen mixture was administered, there was a mild hypertension and tachycardia, but for the most part blood pressure and pulse rate remained near control levels throughout the experiment.

B. *The Effects of Autonomic Nerve Section.* The data presented in Table I indicate that section of the vagus nerves made no significant difference in the time of cardiac arrest in dogs given 1 per cent oxygen when compared to the intact animals on the same mixture. However, it was observed that the marked fluctuations of pulse and blood pressure commonly seen in the normal dogs under these conditions were greatly diminished in those which had been vagotomized.

In animals previously subjected to dorsal sympathectomy and adrenalectomy, an immediate fall in blood pressure and pulse rate took place when 1 per cent $O_2$ was started. This is in contrast to the normal animals which showed an immediate hypertension and tachycardia. Also, when the time

of arrest of the two groups is compared in Table I, it will be seen that circulatory failure occurred significantly sooner in the sympathectomized animals.

C. *Blood Chemistry.* It was found that four to six minutes were required for the arterial oxygen levels to reach their lowest levels in the presence of 1 per cent oxygen inhalation. These ranged from 0.7 to 2.5 volumes per cent. The critical level of volumes per cent oxygen in the arterial blood following which arrest took place has been described. During the prolonged hypoxia caused by 2 per cent and 4 per cent $O_2$ respiratory mixtures, a gradual fall of pH was noted in the arterial blood. The average fall from control values during the procedure was 0.8 pH. This occurred despite arterial carbon dioxide levels which were normal, or slightly subnormal.

In animals breathing 1 per cent $O_2$ there was an initial progressive rise in the plasma potassium. The average elevation above control values was 2.2 mEq./liter at the time of arrest. Reference to Table II will show that in the less severe states of hypoxia (more than 5 volumes per cent $O_2$ in the arterial blood), a small elevation of potassium occurred during the first half hour. Regardless of the arterial oxygen content, the potassium declined during the second half hour.

Calcium and magnesium shifts in the plasma in response to hypoxia were variable from animal to animal. These ions shifted in both directions, and behaved in most respects in a fashion similar to those described for hypercapnic states.

D. *The Electroencephalogram.* To the right of Figure 2 are reproduced electroencephalographic tracings typical of the various patterns seen as the brain wave potential was depressed by severe hypoxia. In the curves at the bottom of each graph are plotted the pattern types found at various times during the course of each experiment.

In the presence of arterial oxygen levels over 4 volumes per cent, the brain waves were relatively unaffected. When the oxygen content fell below this value, the pattern rapidly was depressed to the flat line of Type VI. Shortly after this, usually within three to four minutes, the blood pressure fell precipitously and circulatory arrest ensued. This is well illustrated in the first and second examples given in Figure 5.

### THE RESPONSE OF MAN TO HYPERCAPNIA

Ten patients, undergoing minor operative procedures with anesthesia limited to thiopental sodium, were given mixtures of gas containing 30 or 35 per cent carbon dioxide. In each, respiration was assisted to insure the complete absence of hypoxia. The periods of induced respiratory acidosis ranged from ten to 26 minutes. Blood pressure, respiratory rate, E.C.G. and E.E.G. were recorded throughout. Arterial blood samples were drawn at intervals.

The course of one such patient is illustrated in Figure 6. The response of blood pressure and heart rate is, in general, quite typical of this series. There was an initial fall, followed by a hypertensive state, followed in turn by a gradual fall of both pulse and blood pressure. Despite extreme care in diluting the $CO_2$ mixture at the end, there was a short but pronounced fall in blood pressure. Four patients received atropine preoperatively, and six did not. There was little difference in the response of the two groups.

Arterial blood $CO_2$ ranged in these patients from 62 to 79 volumes per cent, and the least pH value recorded for each patient ranged from 6.8 to 7.12. As may be seen in Figure 6, this patient's electroencephalographic pattern was gradually depressed to Type V associated with an arterial pH of 6.82. There it remained throughout the procedure. On the right of the graph are reproduced electroencephalographic tracings from this patient, to illustrate the various pattern types recorded as brain depression occurred. Unfortunately the Type V tracing is marred by interference from the electro-

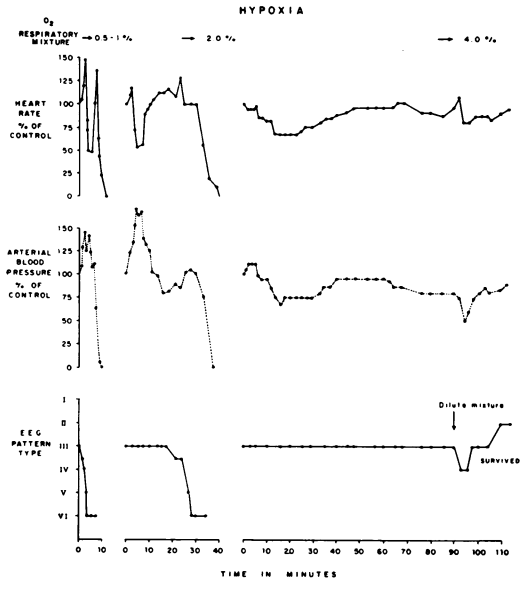


FIG. 5. Typical examples of the response of pulse rate, blood pressure, and the electroencephalographic pattern to respiration of mixtures containing 1 per cent oxygen (arterial $O_2$: 1.6 volumes per cent), 2 per cent oxygen (arterial $O_2$: 2.7 volumes per cent) and 4 per cent oxygen (arterial $O_2$: 4.9 volumes per cent).

cardiogram, but shows the relative absence of recordable potential.

Recovery to the Type II or Type III pattern of anesthesia ocrurred promptly in all instances after relief of hypercapnia. In only one case did the brain waves completely disappear to give a Type VI pattern. The $CO_2$ mixture was then promptly diluted to avoid any of the ill effects associated with prolonged suppression of brain potential in animals.

The blood levels of potassium, calcium and magnesium were followed in three patients. After a brief upward shift of potassium, the average being 0.6 mEq./liter, it promptly returned to control levels in two patients, and showed no further rise in any of them. In each of the three patients there was a short initial depression of magnesium, amounting to no more than 0.5 mg. per cent from the control level. Otherwise the magnesium and calcium levels were variable. The latter shifted no more than 1.2 mg. per cent up or down.

Three patients exhibited a moderate postoperative hypotension, lasting in one instance for 12 hours. Otherwise recovery was without incident except for mild convulsive twitching in one man as he came out of anesthesia. No later sequellae of any sort were observed.

## DISCUSSION

In asphyxia, carbon dioxide accumulation and oxygen want combine to produce cardiac arrest. Yet the mode of action of the two agents is different. This is illustrated by a comparison of the blood pressure and pulse rate response given in Figures 1 and 2.

The observations made on patients subjected to moderately severe degrees of hypercapnia indicate that man and the dog respond to this stress in almost identical fashion, as far as pulse and blood pressure are concerned. Although the elevation of $CO_2$ in these observations exceeded that reported by Maier[24] or Buckley *et al.*[5] during anesthesia, the latter authors report blood pressure responses very similar to those found in these experiments, and those of Miller *et al.*,[26] especially in the posthypercapnic period. Gellhorn's results on man subjected to moderate degrees of hypoxia[15] very much resemble those of dogs on 8 per cent $O_2$ and some of the animals given 4 per cent $O_2$. Obtaining data on the response of man to very severe degrees of pure hypoxia is manifestly impossible with safety, but it is of interest to find that bradycardia accompanied by hypertension was observed prior to onset in four of the cardiac arrest patients mentioned in the introduction. Sealy *et al.*,[30] and Ziegler,[33] also mention this as occurring in several of their patients, which suggests that severe hypoxia may have played an important part in these catastrophes.

The mechanism of the circulatory response to hypercapnia differs in several important respects from that to oxygen lack. Cannon[8] showed that hypoxia was a specific stimulus for the release of epinephrine and sympathin, which account for the initial

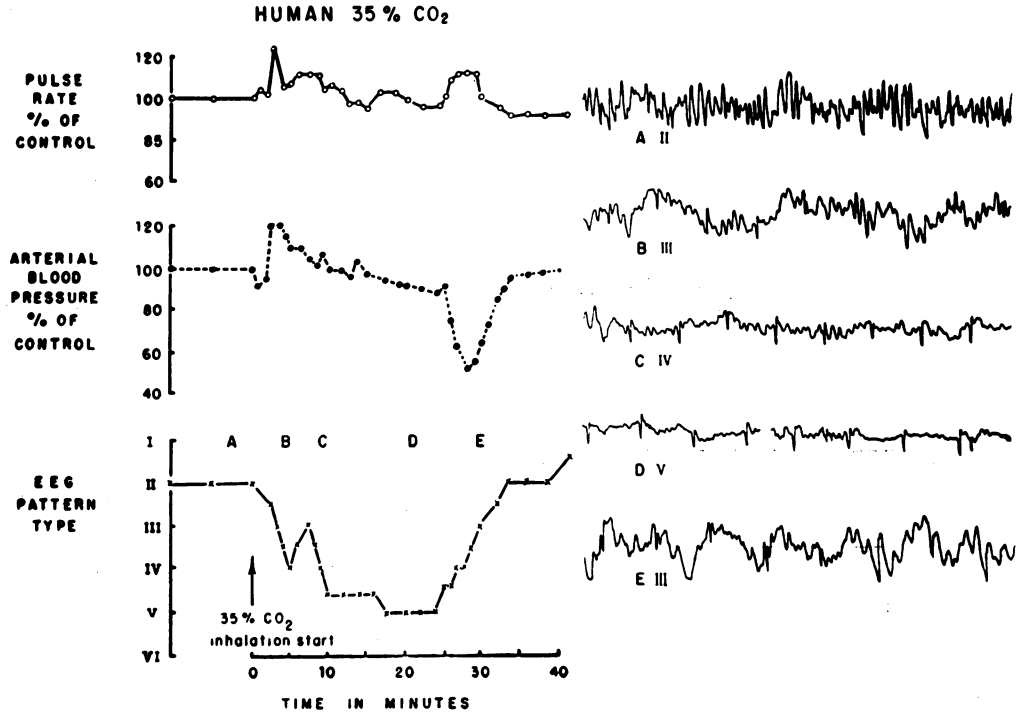


FIG. 6. The response of pulse rate, blood pressure, and electroencephalographic pattern of man to the administration of 35 per cent $CO_2$–65 per cent $O_2$ for 22 minutes (arterial blood pH 6.82, $CO_2$: 78 volumes per cent).

hypertension and tachycardia. Harrison[20] demonstrated that this reaction took place when the arterial oxygen fell below 75 per cent of saturation, which he referred to as the "anoxemic threshold." The immediate fall of both pulse and blood pressure in the sympathectomized, adrenalectomized animals of this series, exposed to 1 per cent oxygen mixtures, supports this view. Harrison, Blalock, Pilcher and Wilson,[20] and Nahas, Mather, Wargo and Adams,[27] reported similar results in milder states of hypoxia caused by 8 per cent $O_2$ inhalation. Both groups found that the increase of cardiac output was less in sympathectomized, adrenalectomized animals than in the controls. From the results obtained when the vagi were severed before hypoxia, it appears likely that vagal activity plays a part in this response. Although the time of cardiac arrest was not significantly different, the marked fluctuations of pulse and blood pressure were eliminated. This may be related to elimination of afferent impulses from the aortic bodies, and other pressor receptors.[21] Mathison[25] observed that vagus section prolonged the course of hypoxia somewhat, but did not protect the animals from arrest.

The fact that venous pressure did not increase until shortly after the critical level of arterial oxygen desaturation (3 volumes per cent) was reached suggests that circulatory arrest was due to a sudden loss of the heart's ability to perform work. Gremel and Starling[18] observed that the isolated heart became dilated swiftly when the $O_2$ saturation of the arterial blood fell to 45 per cent. It became seriously dilated only when the oxygen fell to 12 per cent of saturation in the arterial blood. The work of Harris[19] showed that this is related to failure of conduction in the heart in severe hypoxia.

Excess carbon dioxide, in contrast to the impaired energy supply caused by oxygen lack, has been described as a narcotizing agent by Dripps.[13] Gremel and Starling found that the isolated heart dilated as the pH fell. A similar observation on the contractile force of the heart *in situ* was made by Boniface and Brown.[2] However, the latter authors noted a return of contractile force to near normal after a short period of time, despite a continued elevation of the $CO_2$ tension. This, in part, might account for the subsequent rise of pulse and blood pressure. That the heart *per se* is capable of pumping the blood returned to it is suggested by the finding of normal mean venous pressures throughout the period of hypercapnia in these experiments.

Carbon dioxide is known to dilate vessels in isolated or sympathectomized extremities, and in the brain.[12] But in the intact animal the presence of hypercapnia in moderate amounts results in a peripheral vaso constriction and elevation of peripheral resistance.[23] The immediate and continued fall of both pulse and blood pressure, and early cardiac arrest seen in the sympathectomized animal exposed to 55 per cent $CO_2$, shows that under these conditions the maintenance of blood pressure is dependent upon the vasomotor reflexes mediated by the sympathetic system.

The elevation of plasma potassium seen in these experiments as a result of respiratory acidosis or low arterial oxygen levels has been observed by Civin and Cattell,[9] and by Scaly *et al.*[30] Under conditions of low arterial oxygen tension many investigators, including Calkins, Taylor and Hastings,[6] have demonstrated the outflow of potassium from cells to be greater than inflow below a critical level of 25 per cent arterial $O_2$ saturation. This is supported by the finding in the experiments here reported, in that a progressive rise of potassium was found in the plasma of animals which died of severe hypoxia, and little elevation in the survivors.

That the chemical response of man to hypercapnia is similar to that of the dog is suggested by the observations made on the patients given 35 per cent $CO_2$. Depressions of pH varied from 6.8 to 7.1, which are within the same range as those found in dogs given the same mixture. Potassium showed the same transient rise at the onset of $CO_2$ administration. Although not understood, the same variable shifts of calcium and magnesium were observed in both species.

The depression of the potential and frequency of the brain waves caused by severe respiratory acidosis or oxygen lack are ultimately the same. But there is a distinct difference in the course of events leading up to this depression. Faulconer[14] showed that reproducible electroencephalographic patterns were found at various levels of ether anesthesia. As the degree of narcosis increased the brain wave potential was progressively decreased. Brazier and Finesinger[3] described similar findings in barbiturate anesthesia. Pollock[28] demonstrated that inhalation of 30 per cent $CO_2$ potentiated the depressant action of barbiturates on the E.E.G. of cats. Clowes *et al.*[10] found the same to be true in man, and that the effects are reversible. Thus, as may be seen in Figures 3, 4 and 6, a given elevation of $CO_2$ tension in the blood produces a definite depression of the electroencephalographic pattern under anesthesia.

Hypoxia induced by breathing 1 per cent or 2 per cent oxygen mixtures was also found to cause disappearance of the brain wave potential, as illustrated in Figures 2 and 5. But relatively little change took place in the brain wave patterns until the arterial oxygen content fell to below 35 per cent of saturation. They rapidly then became severely depressed. Gibbs, Williams and Gibbs[16] found that when the $O_2$ tension of the venous blood from the brain fell to 18 mm. Hg, slowing of the E.E.G. frequency occurred, but that this was progressive.

Although death followed only a few minutes of brain suppression by hypoxia, animals could withstand protracted periods of

hypercapnia sufficient to cause absence of any recordable E.E.G. potential with apparent recovery. But as previously reported by Hopkins, Anzola and Clowes,[22] when the brain waves are suppressed by an elevated $CO_2$ tension for more than 20 minutes, the animals die subsequently in a state of shock. This may possibly account for certain of the unexplained hypotensive episodes observed postoperatively as suggested by Buckley.[5]

## SUMMARY AND CONCLUSIONS

1. Severe respiratory acidosis in dogs under anesthesia produces a different response of pulse and blood pressure from that caused by severe oxygen lack.

2. Cardiac arrest from pure hypercapnia did not occur in intact animals breathing mixtures up to 55 per cent $CO_2$. Arrest took place in hypoxia when the arterial oxygen content fell below a "critical level" of 3 volumes per cent.

3. Section of the vagi did not materially affect the response to 55 per cent $CO_2$, or 1 per cent $O_2$ inhalation. Early cardiac arrest resulted in animals exposed to both gas mixtures when sympathectomy and adrenalectomy had been performed. The mechanisms of these reactions are discussed.

4. Suppression of the electroencephalographic potential by low blood oxygen levels was followed shortly by cardiac arrest. Hypercapnia sufficient to abolish the brain waves was tolerated by animals for periods up to one hour, but despite apparent early recovery, all hypercapnic animals died subsequently in a state of shock, if the E.E.G. potential was abolished for more than 20 minutes.

5. The response of plasma potassium, calcium and magnesium to $CO_2$ accumulation and to oxygen lack are described.

6. Observations on man under barbiturate anesthesia rendered acidotic by inhaling 35 per cent $CO_2$ indicate that in the normal man the reaction to hypercapnia is in most respects similar to those observed in the dog.

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DISCUSSION.—DR. WALTER J. BURDETTE, New Orleans, Louisiana: Drs. Clowes, Hopkins and Glover are to be congratulated on these excellent studies concerning the mechanism of cardiac arrest. We have also been interested in changes in cardiac muscle after arrest due to hypoxia, and have studied particularly the amounts of adenosine nucleotides in the muscle under these circumstances, since the contraction mechanism is initiated by one of them (ATP) and transfer of energy in muscle is accomplished through phosphate bond interrelationships.

Cardiac arrest was produced by steadily increasing hypoxia during a period of one hour. Homogenates of the muscle were made immediately, and nucleotides separated by means of formate, ion-exchange columns. In a series of 15 dogs adenosine triphosphate (ATP) was reduced from 18.1 ± 1.50 to 7.1 ± 1.18 M × $10^{-4}$/g.; adenosine diphosphate (ADP) from 10.8 ± 1.2 to 6.1 ± 0.54 M × $10^{-4}$/g.; and adenosine monophosphate from 7.1 ± 0.58 to