EFFECTS OF CARBON DIOXIDE ON THE CARDIOVASCULAR SYSTEM

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IN discussing effects of carbon dioxide several difficulties are apparent. The most important concern methods of study. Investigations in man are few, and of these not a few are accidental, consisting of reports on patients who were unwittingly exposed to high concentrations of carbon dioxide. These "studies" are necessarily poorly controlled. Studies in animals are complicated by the use of "basal" anesthetics, surgical stimulation, and usually by inadequate control of variables, to say nothing of the problem of species variation. Both in animals and in man the achievement of a steady state during carbon dioxide inhalation is rare. This review has been restricted to information which the author considers descriptive, or at least strongly suggestive, of cardiovascular actions exerted by carbon dioxide in man.

SITES AND TYPES OF ACTION

Hemodynamics responses to carbon dioxide inhalation represent balances among diverse effects exerted in a number of bodily areas. Actions in some areas (cerebral cortex, myocardium) are depressant; elsewhere stimulation results (*e.g.*, chemoreceptors, mesencephalic reticular formation, respiratory "center"). The over-all effect of respiratory acidosis on, for example, arterial pressure can therefore be clearly understood only when its individual actions in a large number of responsive areas are known. Thus it is advantageous to typify cardiovascular effects of carbon dioxide according to site of action. When the effects of drugs or disease are to be investigated, knowledge of those sites of action is invaluable.

Isolated Heart. In isolated dog,[45] rabbit [58] and guinea pig [35] hearts, force of contraction weakened when *p*H was reduced, irrespective of whether acidosis was caused by increased carbon dioxide tension or by other means. Increasing *p*H often increased contractile force. In the absence of external *p*H changes, force of contraction was independent of P_{CO_2}, and the effect of respiratory acidosis therefore apparently depended upon the ability of carbon dioxide to form carbonic acid, thereby reducing *p*H. A decrease of one half unit in the *p*H of arterial blood (or perfusion fluid) reduced contractile force roughly 50 per cent.[38, 45]

Cardiac rate behaved similarly, slowing in the presence of acidosis and, less consistently, increasing during alkalosis.[58] *p*H again appeared to be more important than P_{CO_2} in initiating these changes.

Cardiac rhythm was not usually affected even when the *p*H of the perfusate fell below 7.0.[38, 45, 55]

In summary, increased carbon dioxide tension reduced contractile force and rate of contraction in isolated hearts of various mammalian species. The ability of carbon dioxide to reduce *p*H was believed primarily responsible.

Blood Vessels. Effects of carbon dioxide on isolated or denervated blood vessels appeared analogous to those exerted on cardiac muscle. In the isolated, perfused guinea pig heart coronary flow was found to increase when the *p*H of the perfusate was reduced and to diminish when *p*H was increased.[58] Again these changes were independent of P_{CO_2}, provided that *p*H remained constant. The behavior of cerebral blood vessels was similar both in animals and in man, except that carbon dioxide was more potent than acidosis caused by other means (NH_4Cl, for example) (*cf.* Sokoloff in this symposium). In the nerve-blocked forelimb of dogs anesthetized with pentobarbital the inhalation of carbon dioxide caused a significant reduction in vascular resistance.[22] A similar result occurred in normal man, except that the increase in blood flow on breathing carbon dioxide was transient even after nerve block.[36] Distant release of a hormone causing vasoconstriction was suggested by the authors. Immersion of the

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human hand in water saturated with carbon dioxide markedly increased its rate of heat elimination, indicating local vasodilatation.[15] Intra-arterial injections of acid solutions into the femoral arteries of the dog caused vasodilatation both in skin and muscle; alkaline solutions caused constriction in skin and dilatation in muscle.[16] Perfusion of dog intestine with blood containing increased amounts of carbon dioxide caused vasodilation independently of any alterations in tonus or mobility, while local hypocapnemia caused vasoconstriction.[10] In dogs anesthetized with pentobarbital inhalation of 20 per cent CO_2 in oxygen caused a large decrease in the vascular resistance of denervated kidneys, while hyperventilation with air caused resistance to increase.[21] Pulmonary vessels may be an exception to the general rule that acidosis dilates. More often than not carbon dioxide was found to cause vasoconstriction in isolated lungs, and the suggestion has been made that this results from operation of an intrinsic mechanism which normally acts to shift blood away from poorly ventilated areas.

It was found in limb vessels that carbon dioxide dilated postarteriolar blood vessels more completely than it did arteries and arterioles.[23] The importance of this—assuming it to apply generally—is that most of the vascular capacity in the body resides in capillaries (20 per cent) and veins (60 per cent). Therefore these vessels are, in the aggregate, able to control the availability of venous blood to the heart. In other words, they modify cardiac output by controlling venous return. Thus the direct action of carbon dioxide on vascular elements would favor peripheral pooling of blood and reduced venous return.

In summary, the direct effect of increased carbon dioxide tension on blood vessels with few exceptions consisted of relaxation. Reduced tension caused different effects in various areas. Whether *p*H or P_{CO_2} was more important in causing these changes is not clear. Anatomically, the vessels most affected may be capillaries and veins.

Autonomic Nervous System. In view of the attention given this subject elsewhere in the symposium (*cf.* Tenney and Woodbury), coverage in this section will be minimal. However, hemodynamic effects both of hyper- and hypocapnea depend in large part upon autonomic actions of carbon dioxide, and some discussion of these actions is necessary here.

Aortic and carotid body chemoreceptors are thought to be exquisitely sensitive to carbon dioxide. Some afferent activity was detected at P_{CO_2} levels as low as 30 mm. of mercury,[29] and above this level chemoreceptor impulse activity increased linearly with increasing carbon dioxide tension. It is not clear whether the essential element of the stimulus is decreased *p*H within the chemo-sensitive cells or whether CO_2 acts directly on these tissues.

Chemoreceptor afferent impulses cause stimulation in various subcortical areas, probably including a number in the posterior hypothalamus [25] and the mesencephalic reticular substance [17] in addition to the so-called "respiratory" and "vasomotor" centers farther caudally. Carbon dioxide can also stimulate directly in these and other areas, although its direct actions may be less intense than those exerted reflexly by way of aortic and carotid body chemoreceptors.[9] In addition, chemoreceptors may occur in the medullary respiratory center itself.[56, 57]

The result of these actions resembles that caused by a variety of nociceptive stimuli—namely hyperventilation, cortical activation, increased sympathetic nervous outflow, and increased skeletal muscular activity. The response thus involves several body systems, suggesting that the stimulus is too potent to be dealt with in any discrete manner. Recent evidence indicates that sufficiently potent nociceptive stimuli, no matter how discrete their central representations, can "spill over" to stimulate both somatic and visceral activities in many bodily areas. An important instance of "spill over" may be stimulation of "vasomotor center" discharge by increased activity in the "respiratory center." [32] In this case increased respiratory drive caused sympathetic nervous discharge apparently by means of local spreading of electrical activity from one nervous "center" to another.

Increased sympathetic nervous discharge can, of course, augment the rate and force of cardiac contraction and produce vasoconstriction and arterial hypertension. Thus the central nervous actions of CO_2 are capable, at least potentially, of antagonizing those which

it exerts directly upon the heart and blood vessels. The direction of the response depends on the balance between stimulating and depressing forces.

Ultimately, as P_{CO_2} increases indefinitely, the responses of the body are reduced because acidosis interferes with the ability of the sympathetically innervated cells to respond to the chemical mediator liberated by these nerves. A reduction of roughly 50 per cent at 30 per cent CO_2 is suggested by certain experiments.[54] In addition, acidosis increases the effects of parasympathetic nervous activity, possibly by interfering with the hydrolysis of acetylcholine by acetylcholinesterase. Cardiac arrest has been attributed (without any further evidence) to this effect.

Hemodynamic Effects of Increased Carbon Dioxide Tension

Cardiac Output. Asmussen showed that cardiac output and minute volume of ventilation increased together when normal men breathed CO_2 in air while lying in the supine position.[1] The elevation in cardiac output (+ 60 per cent) was far greater than the increase in oxygen consumption (+ 10 to + 20 per cent) caused by breathing carbon dioxide, indicating that cardiac output did not rise simply as the result of increased metabolic demands made by the muscles of respiration.

In subjects who were tilted head up at an angle of 60 degrees with the horizontal plane, cardiac output increased hardly at all during CO_2 breathing. Asmussen obtained evidence by using pneumatic cuffs that cardiac output failed to increase in the tilted subjects because blood was pooled in their leg veins. He supposed that in the supine subjects this blood was in the splanchnic area and thorax where the excursions of chest and diaphragm were effective in moving it onward toward the heart. He implied that this could not happen when pooling occurred in the legs.

Asmussen concluded that the effect of CO_2 on cardiac output must be due to mechanical forces of hyperventilation and not to a chemical action of CO_2 on the circulation, since "otherwise the difference of the effect in the two positions is unexplained."[4] Of course this is much too sweeping, since we now know that carbon dioxide affects the circulation even in apnea.[53] Besides, in other subjects hyperventilation with 5 per cent CO_2 did not increase cardiac output.[13] This indicates that it is the increase in P_{CO_2} and not the increase in respiratory minute volume which elevates cardiac output during CO_2 breathing. While there is no doubt that hyperventilation can augment venous return, the heart is not obliged to increase its output. Cardiac output is regulated by nervous mechanisms and changes in output imply alterations in regulation.

Honig and Tenney[21] attempted to determine the mechanisms of circulatory alterations which occurred during carbon dioxide breathing in man, laying special emphasis on the role of the sympathetic nervous system in these responses. They employed ballistic measurements of heart force, a lower extremity plethysmograph, a recording teeterboard, and biological assay of circulating blood for catecholamines. They pointed out that ballistic force may not be a direct measure of contractile force of the heart. During CO_2 (6 per cent) breathing in man the mass of the body shifted slightly footward, but the volume of the lower extremity failed to increase. This indicated a small reduction in intrathoracic blood volume (approximately 100 ml.), possibly caused by splanchnic pooling. Despite this, ballistic force increased, suggesting that cardiac contractility increased at least partially as a result of nervous or humoral changes and not simply in response to augmented cardiac filling. The importance of the nervous system in the response was demonstrated in dogs by the finding that increased contractile force did not occur after section of the spinal cord. In fact, force usually decreased during 6 per cent CO_2 inhalation in these animals. Elevated blood concentrations of "epinephrine" could not be demonstrated during hypercarbia in either dog or man, apparently because the method used was relatively insensitive, but they could be shown in cats.

In the author's laboratory and elsewhere elevations both in epinephrine and in norepinephrine concentrations in plasma could be clearly shown during carbon dioxide (7-15 per cent) inhalation by normal men.[7] When sympathetic nervous responses were

blocked (by subarachnoid procaine) carbon dioxide inhalation caused hypotension accompanied by signs of cardiac failure,[24] while plasma catecholamine concentrations remained unchanged.

Aortic and carotid body denervation in the dog usually (but not always) reduced or reversed the increase in ballistic force caused by CO_2 breathing.[24] In view of this, it is tempting to conclude that CO_2 acts as a chemical stimulant leading to sympathetic nervous discharge, and that this explains its effects on cardiac output and ballistic force. It could even be supposed that it acts in part through the respiratory "center," and that vasomotor "center" activation is a consequence of excitation of contiguous nervous elements which predominantly subserve respiration. Since general anesthetics reduce central nervous reactivity, including that of the "respiratory center," the response of cardiac output during hypercarbia could be expected to be abnormally small in anesthetized subjects. Recent evidence suggests that this is true.[22]

In summary, cardiac output increased when normal men breathed carbon dioxide while lying supine. Central nervous actions of carbon dioxide leading to increased sympathetic nervous discharge and hyperventilation probably contributed to this effect.

Peripheral Blood Flow, Pressure and Resistance. During carbon dioxide inhalation increases in cardiac output far exceed those in mean arterial blood pressure. While elevations in output commonly exceed 50 per cent, mean arterial pressure seldom rises more than half as much above the resting level.[50] Calculated total peripheral resistance, consequently diminishes. This suggests that, despite the increase in sympathetic nervous discharge caused by CO_2, more vascular areas are dilated than constricted when the gas is breathed. Presumably this is caused by the predominance of local dilator effects over neurogenically-mediated vasoconstrictor actions.

Vascular resistance diminishes most conspicuously in the cerebral and probably the myocardial circulations. Cerebral vascular resistance is reduced as P_{CO_2} increases, and vice versa. Several studies agree that inhalations of CO_2 (5–7 per cent) which elevate P_{CO_2} to approximately 50 mm. of mercury caused cerebral blood flow to rise roughly 50 per cent.[12, 59] Mean arterial pressure was much less affected in these studies, increasing approximately 5 per cent, while jugular venous pressure rose. Thus, cerebral blood flow increased because cerebral vascular resistance diminished. Smaller increments in P_{CO_2} (4–5 mm. of mercury) affected neither cerebral blood flow nor cerebral vascular resistance.[42] Measurements of coronary blood flow in man are sparse, but from the evidence at hand coronary vessels resemble cerebral ones in their responses to most stimuli. In other words, these vessels respond actively to local changes in the composition of the blood, but feebly or not at all to nervous influences. Consequently they dilate in response to anoxia or acidosis.

In cutaneous, skeletal muscular, splanchnic, and renal circulations local dilating of CO_2 are counterbalanced by its reflex or central effects, with the result that vascular resistance may be little reduced or even increased by respiratory acidosis.[1, 10, 21, 25, 33, 40] However, the local effects often predominate so that vascular resistance tends to diminish with prolonged exposure to high concentrations.[10] On the other hand, very brief exposure may cause vasoconstriction. For example, it has been reported that brief (1–1½ minutes) inhalations of 30 per cent CO_2 in O_2 led to virtual cessation of forearm blood flow.[37] But as a general rule respiratory acidosis causes relatively small changes in vascular resistance in most areas of the body and a marked reduction of resistance in cerebral and myocardial tissues. The over-all effect is to reduce peripheral resistance.

Hyperemia favors loss of plasma ultrafiltrate through capillary walls because arteriolar dilatation causes the mean capillary pressure substantially to exceed colloid osmotic pressure. This in turn causes a net excess of filtration above reabsorption, with the result that plasma is lost during its passage through the tissues. The magnitude of this loss has been estimated in dogs anesthetized with thiopental to approximate 20 per cent of the plasma volume during the first 45 minutes of CO_2 (20 per cent) breathing.[3] In men anesthetized with thiopental, inhalation of 20–30 per cent CO_2 in O_2 for 15 minutes caused a

TABLE 1

BLOOD PRESSURE DURING CARBON DIOXIDE INHALATION

Alveolar P_{CO_2} (mm. Hg)	Arterial Pressures (mm. Hg)			Heart Rate (beats/minute)	Number of Observations
	Systolic	Diastolic	Pulse		
40	129	78	51	64	26
56	146	86	60	85	10
65	161	99	62	96	9
75	170	96	74	98	4
85	165	97	68	127	3

(Data from reference 50.)

reduction in plasma volume averaging 10 per cent and ranging from 3 to 18 per cent.[30]

Arterial hypertension is almost invariable during carbon dioxide inhalation even though it is relatively minor in degree. Sechzer and associates[50] found increases in systolic and diastolic blood pressure and heart rate during carbon dioxide inhalation in each of 12 healthy male volunteers. Systolic, diastolic, and pulse pressures and heart rate tended to increase progressively as P_{CO_2} increased. The mean levels are shown in table 1.

In view of the above it is not surprising that cardiovascular responses to CO_2 are obtunded during general anesthesia.[36, 47] Price and co-workers concluded from their study that—at least during halothane or cyclopropane anesthesia in man—an unexplained increase of 20 mm. of mercury or more in mean arterial pressure was most likely *not* caused by CO_2 retention. Similarly, heart rate, although it usually increased when CO_2 was administered, did so to a far smaller extent than in conscious subjects. These authors concluded that the most reliable circulatory indication of hypercarbia in their anesthetized subjects was the presence of cardiac arrhythmia.

POSTHYPERCAPNEIC HYPOTENSION

Sechzer[50] found that post hypercapneic hypotension failed to occur in conscious subjects unless P_{CO_2} had been elevated above 80 mm. of mercury. Even then it was not pronounced, and the lowest arterial pressure observed at any time in any subject after P_{CO_2} elevations as high as 100 mm. mercury was 84/69 mm. of mercury. Five minutes later arterial pressure in this subject had returned to 105/80. Tachycardia relative to control heart rate was observed in all subjects, and usually persisted for ten or more minutes following cessation of CO_2 inhalation.

Despite the relatively high concentrations of CO_2 breathed in this study the diastolic hypotension noted by Dripps and Comroe[21] and Goldstein and Dubois[26] was not observed. It is possible that hypotension noted by these earlier workers was artifactitious, resulting from the use of auscultatory rather than direct methods for measuring arterial pressure.

Anesthetized men have been exposed to much higher CO_2 concentration than those tolerated by conscious subjects. In Black's study[6] of human beings anesthetized with halothane, P_{CO_2} levels as high as 130–140 mm. of mercury were attained. Hypercarbia persisted for varying periods up to 25 minutes. Even under these conditions posthypercapneic hypotension was remarkable (more than 15 mm. of mercury) in only 3 of 15 cases. Clowes[15] observed "moderate" hypotension in only 3 of 10 anesthetized (thiopental) patients after exposure to 30–35 per cent CO_2. In a similar study during administration of cyclopropane posthypercapneic hypotension was found to be more pronounced, both in frequency and magnitude;[47] the average reduction in blood pressure following CO_2 withdrawal approximated 20 mm. of mercury in these subjects. Posthypercapneic hypotension was even more conspicuous in two other studies of patients anesthetized with cyclopropane,[12, 19] but the patients in both series had been subjected to surgical procedures which may have contributed to the results. Also in both these studies anesthesia and hypercapnea were terminated together, making it difficult to distinguish between the individual effects of cyclopropane and carbon dioxide. It is interesting that in Dripps' study[19] the degree of posthypercapneic hypotension was significantly related to the cyclopropane concentration at the termination of anesthesia as well as to the P_{CO_2} obtaining at this time. Since it is known that hypotension may follow the administration of cyclopropane in the absence of hypercarbia,[12] it is probable that some part of the hypotension observed in these studies resulted

from termination of the anesthetic. Nevertheless from the practical standpoint these data are relevant, for cyclopropane is still frequently given without respiratory assistance. The degree and duration (up to 48 hours) of hypotension which may follow prolonged hypercapnea during anesthesia should not be minimized. From various studies it seems that these sequelae appear with increasing frequency when P_{CO_2} reaches levels approximately twice normal. Levels up to 65–70 mm. of mercury apparently can be tolerated without incident.

The mechanism of posthyperapneic hypotension has intrigued investigators for years. An early suggestion was that it resulted from reduced sensitivity of the medullary vasomotor center caused by narcosis and by long exposure to carbon dioxide. Although Dripps [19] accepted this hypothesis in explaining his own results, there is as yet no direct evidence to support it. Both the usual finding of relative tachycardia during CO_2 blow-off and the fact that hypotension occurs even in the absence of general anesthesia argue against this explanation.

Billings and Brown [5] investigated the role of plasma volume reduction in the causation of posthypercapneic hypotension in the dog. In their animals blood volume was actually greater than normal during the period of most profound hypotension, largely as the result of splenic contraction. The spleen subsequently relaxed, at which time circulating blood volume decreased to, or below, normal. Although these authors appear correct in denying that loss of circulating blood volume contributed to the initial phase of posthypercapneic hypotension in their experiments, the relatively great size and importance of the spleen in dogs makes it hazardous to conclude that their findings can be applied without further study to man.

Heath and Brown,[28] again in dogs anesthetized with thiopental, measured arterial pressure, vena caval pressure, and cardiac output before, during and after inhalation of 30 per cent CO_2 in oxygen. Within ten minutes following P_{CO_2} reduction both cardiac output and arterial blood pressure were reduced to roughly 60 per cent of their initial values. Venous pressure often declined as well. Changes in calculated total peripheral resistance were variable. When the heart and lungs were bypassed by a pump-oxygenator, peripheral resistance consistently declined during CO_2 blow-off. The authors concluded that reduced cardiac output was the principal cause of posthypercapneic hypotension in their animals, and that it might have resulted from a myocardial effect. To establish myocardial incompetence it is necessary, however, to measure cardiac function. In this connection it is disturbing that Heath and Brown fail to mention cardiac rhythm although in previous studies [29] Brown has reported the death of as many as 80 per cent of his animals from ventricular fibrillation during CO_2 blow-off.

One of the most important aspects of CO_2 inhalation is usually overlooked in considering CO_2 "blow-off." This relates to the fact that CO_2 is distributed to the tissues via their respective blood supplies. Areas such as the central nervous system with its high resting blood flow and further, marked increase in flow during CO_2 breathing must equilibrate rapidly with the inspired gas. Therefore CO_2 actions in nervous tissue ought to appear early. Areas with lower flow must take up CO_2 more slowly. It has been shown, for instance, that the CO_2 content of muscle may not reach a plateau for 5 hours following onset of hypercarbia.[41] There is good reason to suppose that wash-out represents saturation in reverse. Therefore the blow-off period probably is one during which CO_2 is cleared rapidly from the central nervous system and more slowly from other tissues. If this is true, hypotension would be expected during CO_2 washout as the result of these differences in CO_2 clearance rate since sympathetic nervous activity would decline more rapidly than did the depressant, local cardiovascular effects of CO_2. Following 30 per cent CO_2 inhalation in man large increases in digital and forearm blood flow were observed.[37] These observations would support the hypothesis of uneven elimination and so would those of Heath and Brown.[28]

Another possibility is that posthypercapneic hypotension is the result of termination of the intense sympathetic nervous activity caused by CO_2 inhalation. It is known that after termination of sympathetic nervous discharge or of intravenous infusions of epinephrine or nor-

epinephrine, hypotension occurs.[21] Although several hypotheses have been advanced, the exact mechanism whereby this results is uncertain.

In summary, then, there are a number of possible causes for posthypercapneic hypotension none of which has been ruled either in or out. Further studies should be carried out in man. Species variation, together with the rather extreme conditions which have been imposed on animals make hazardous the transfer of many experimental findings to man. Human studies have been rare, but they indicate that posthypercapneic hypotension can occur in normal man provided that P_{CO_2} has been sufficiently elevated for a prolonged period.

Circulatory Changes During Respiratory Alkalosis

Circulatory effects of reduced P_{CO_2} have been relatively little studied. Among the regional circulations, most is known concerning the cerebral. Here marked vasoconstriction occurs when P_{CO_2} is reduced and there is some evidence that cerebral anoxia may be produced by this means. This subject is more fully explored in the section by Sokoloff. Vasoconstriction also occurs in skin,[14] intestine,[40] and kidney.[21]

In muscle the effect of lowered P_{CO_2} is one of vasodilatation.[7, 13, 14] Forearm blood flow increased roughly 100 per cent in healthy subjects who reduced their alveolar P_{CO_2} to about 20 mm. of mercury by hyperventilating with air.[14] Hand blood flow diminished. Since arterial pressure declined while venous pressure increased, thus reducing tissue perfusion pressure, the increase in forearm blood flow probably resulted from vasodilatation When the subjects hyperventilated while breathing 6.5 per cent CO_2 in air, thus preventing the occurrence of respiratory alkalosis, a conspicuous increase in flow did not occur. Dilatation was therefore attributable to decreased P_{CO_2} itself rather than to the act of hyperventilation. Nerve block of the extremity failed to prevent the decrease in forearm vascular resistance when P_{CO_2} was reduced.[13] Thus the stimulus was humoral and consisted either of reduced P_{CO_2} in the perfusing blood or of some other chemical change. Since most of the forearm blood flow ordinarily passes through muscle and most of the hand blood flow through skin, the fact that forearm vascular resistance decreased while that in the hand increased suggests that hypocapnea acted by dilating blood vessels in the forearm muscle while constricting those in the skin. In the dog's hind limb alkaline solutions injected intra-arterially caused dilatation of muscle and constriction of skin blood vessels.[16] Reduced P_{CO_2} may thus act merely by causing alkalosis.

Burnum and co-workers [12] measured cardiac output, forearm blood flow, and arterial pressure during hyperventilation in normal subjects and in patients with sympathetic paresis. When P_{CO_2} approximated 20 mm. of mercury, forearm blood flow more than doubled while cardiac output increased by 30 per cent and heart rate by about 70 per cent. Arterial pressure was reduced. These changes were either small or absent when 5 per cent CO_2 was breathed, but they occurred to the same extent as normally during hypocapnea in sympathectomized patients or in individuals exhibiting postural hypotension. Therefore hypocapneic hypotension may not be of central nervous origin as was once assumed. It now appears likely that it results from vasodilatation which is independent of nervous control. Blood vessels in muscle are among those which dilate. Although this is not established, vasoconstriction in the skin, increased cardiac output, and tachycardia can for the moment be viewed as reflex compensatory changes.

It would be pleasant to report that the effects of general anesthetics on these responses had been thoroughly studied, but this is not the case. Twenty years ago Seevers and his associates [51] took the view that "acapnial shock" was "in reality a phenomenon related to narcosis" because, while in anesthetized dogs hyperventilation caused pronounced arterial hypotension, hypotension was not observed in conscious animals under the same conditions. Since then little has been learned, and the remarkably frequent use of hyperventilation during clinical anesthesia thus occurs against a background of nearly complete ignorance. The average anesthetist is now so thoroughly aware of the ability of general anesthetics to depress respiration that respiratory alkalosis is more likely to be present in his patients than

is acidosis. Normal P_{CO_2} is virtually impossible to maintain without monitoring equipment, so the anesthetist errs "on the safe side." But which is the "safe side"?

Cardiac Rhythm

In conscious subjects the effects of carbon dioxide inhalation on cardiac rhythm in various studies were unremarkable up to P_{CO_2} levels approximately twice normal. For example, only two of Seehzer's twelve subjects [50] exhibited either ventricular or nodal extrasystoles and these were infrequent (one in five minutes). Two others showed transient prolongation of the P-R interval. Aside from these changes, electrocardiographic abnormalities were not observed. Altschule [2] found during repeated studies of diffusion respiration in two psychotic subjects that the P-R interval was unchanged despite CO_2 retention sufficient to cause marked acidosis (arterial blood *p*H 6.9). However, A-V nodal beats appeared, ST elevation or depression occurred, and T waves were occasionally inverted. It is not known whether anoxia contributed to these results. MacDonald and Simonson [35] studied the effect of brief (23–63 seconds) inhalations of 30 per cent CO_2 in oxygen in 17 psychiatric patients. QRS changes were not observed, and "only very slight ST depression was noted in an occasional case." "Unusual patterns of auricular and nodal activity" occurred in 11 cases, increased T-wave voltage was noted in 9, and "more or less frequent" ventricular extrasystoles in 5. Auricular tachycardia, P-wave inversion, nodal premature beats, and ventricular bigeminy were also observed in some subjects. Although P_{CO_2} was not measured in either Altschule's [2] or MacDonald's [35] study, it is probable that it approached 100 mm. of mercury in both.

It has been shown in the author's laboratory that the "arrhythmia threshold level" of P_{CO_2} (that at which cardiac arrhythmias occur) can be modified by various anesthetic agents. Cyclopropane reduces the P_{CO_2} threshold at which arrhythmias occur.[46] Halothane elevates it [6] and barbiturates appear to behave similarly (Price and associates, unpublished). On the basis of comparison with studies in anesthetized dogs it has been suggested [2, 35] that the human heart is less "tolerant" to CO_2 than is the canine heart. The reviewer believes that the difference may in part reflect the ability of certain anesthetics to alter the P_{CO_2} arrhythmia threshold.

It is worth noting that most of the types of arrhythmias observed during CO_2 inhalation can be produced directly by stimulation of cardiac sympathetic nerves, or by epinephrine. Further, increased sympathetic activity can be demonstrated during hypercarbia. It can also be shown that anesthetics modify the sympathoadrenal response to CO_2. Anesthetics (like cyclopropane) which increase the response lower the threshold, and the converse also holds.[6, 31, 47] Anesthetics can also increase or decrease the responsiveness of the myocardium to catecholamines. Finally, blockade of cardiac sympathetic nerves can elevate the threshold for ventricular arrhythmias to CO_2 levels which appear almost unattainable in practice (> 120 mm. of mercury). In view of this evidence it is likely that the sympathoadrenal response to CO_2 is concerned in the production of cardiac arrhythmias.

This is not to say that all arrhythmias are so caused. Several other causes are known and more have been postulated. Enhanced effects of vagal stimulation in the presence of acidosis fall into the first category. Young and co-workers [61] found, in dogs anesthetized with pentobarbital, that the duration of cardiac asystole caused by electrical stimulation of the vagus was more than doubled during administration of 20 per cent CO_2 in oxygen. In a similar study, Bohr and Helmendach [8] established the minimum *p*H change necessary to increase the duration of asystole as in excess of 0.4 units, and concluded that the effect was "very modest with decreases in arterial *p*H of the magnitude which could be expected in surgical procedures." However, the effect increases rapidly below *p*H 7, so that it is of paramount importance to know when and if this level is attained. It is equally important to emphasize, despite opinions to the contrary,[19] that hypercarbia does not, by itself, lead to pronounced cardiac slowing or asystole, even though it exaggerates the cardiac response to vagal stimulation. In other words, hypercarbia does not stimulate vagal activity directly [15] but it "sets the stage" for cardiac arrest if such a stimulus is present. It may

be this synergism of actions which renders the combination of hypercarbia and anoxia so effective in causing asystole.

The dramatic changes in cardiac rhythm which follow termination of severe hypercarbia (40 per cent CO_2) of several hours duration in anesthetized dogs have stimulated a considerable literature which may or may not be relevant to clinical practice. Certainly the unwitting duplication of these conditions in man must be extremely rare, if not impossible.[18] Among the cases reported in the anesthesia literature the highest P_{CO_2} levels ever attained approximate 150–200 mm. of mercury.[12, 19, 48, 52]

For these reasons the discussion of posthypercapneic cardiac arrhythmias will be limited to studies carried out under conditions which have some likelihood of occurring clinically. Of these the most complete appear to be those of Sechzer and associates [50] in unanesthetized men, Lurie and co-workers using cyclopropane anesthesia, Black and his associates [6] using halothane, Clowes and associates [15] using thiopental, and Petersen and his coworkers [44] who gave thiopental and nitrous oxide-oxygen. P_{CO_2} levels attained varied from a low of 75 mm. of mercury in Petersen's study [44] to approximately 200 mm. of mercury in Clowes' study.[15] Cardiac arrhythmias were apparently initiated by CO_2 washout in only one of these studies; Lurie noted appearance or exacerbation of ventricular arrhythmias in 6 of 28 subjects. In these 6 subjects P_{CO_2} was exceptionally high preceding blow-off (average P_{CO_2} 120 mm. of mercury) as was the rate of decrease of P_{CO_2} (average 41 mm. of mercury per minute). All arrhythmias disappeared within 5 minutes after termination of CO_2 inhalation. Neither asystole nor ventricular fibrillation was observed. Schultz and associates [48] observed a single case where, because of omission of directional valves from the anesthetic machine, P_{CO_2} reached 238 mm. of mercury three and one fourth hours after the induction of ether anesthesia. During the first 5 minutes of CO_2 washout a few extrasystoles were noted, but the remainder of the washout period was without incident. The rate of reduction of P_{CO_2} was such that it reached 46 per cent of its peak level within 15 minutes after washout began.

Among postulated causes for cardiac arrhythmias during and particularly after hypercarbia are various modifications in the ionic milieu of the heart which depend passively upon variations in *p*H. Despite assumptions to the contrary, none of these has yet been clearly shown to be important. The evidence suggesting hyperkalemia as a cause has been obtained almost entirely from experiments in dogs, a species notoriously ready to exhibit this change in response either to acidosis or its reversal. On the other hand, hyperkalemia was not remarkable in clinical studies although P_{CO_2} was elevated to levels above 200 mm. of mercury [15, 31, 41, 48] and potassium concentration could not be correlated either with P_{CO_2} or with the presence or absence of arrhythmias. In isolated hearts potassium caused bradycardia and slowed conduction; by itself it did not initiate either tachycardia or fibrillation.[27] Changes in the plasma concentrations of ultrafiltrable calcium also have been implicated.[11] There is little doubt that such changes occur provided that *p*H is altered sufficiently, but again it was not demonstrated that they did in fact alter cardiac rhythm. Another possibility which apparently has not been investigated is whether a strong sodium flux similar to that observed in cerebral cortical neurones [60] also occurs in the myocardium during reversal of hypercarbia. Clearly this could result in depolarization of the ventricles and, conceivably, in fibrillation.

Catecholamine liberation is probably involved in initiating posthypercapneic cardiac arrhythmias. The consequences of sudden reduction in P_{CO_2} are such that vagal influences on the heart may be reduced while sympathetic ones are enhanced (see above). Consequently, a subthreshold level of sympathetic activity could become effective in causing arrhythmias during rapid CO_2 elimination. There is evidence that this mechanism is involved; [46] indeed it may be responsible for the observed changes in plasma potassium concentration in the dog at onset and termination of hypercarbia.[49] The latter authors, although they were primarily interested in hyperkalemia as a cause of posthypercapneic cardiac arrhythmias, found considerable evidence that sympathetic nervous activity lay

at the root of their observations. Hyperkalemia may have its most important action in potentiating the effects of catecholamine liberation.[27]

Finally, it is possible that anoxemia contributes to the occurrence of cardiac arrhythmias in studies where marked hypercarbia is terminated by ventilation with air. First, hemoglobin is not completely saturated with O_2 at normal alveolar P_{O_2} when P_{CO_2} is elevated, because of the Bohr effect. Second, alveolar P_{O_2} may be less than normal during washout because P_{CO_2} remains elevated as CO_2 pours out of the pulmonary arterial blood into the alveoli. The latter effect has been labelled "diffusion anoxia," and is a well-recognized hazard following termination of N_2O inhalation, but it can also occur after breathing CO_2.

In summary, various cardiac arrhythmias, of which the most important are ventricular, can occur both during hypercarbia and during its correction. Increased activity of the sympathetic nervous system certainly is, and ionic flux through the myocardial surface may be, involved in these responses. General anesthetics can alter the level at which ventricular arrhythmias first occur when P_{CO_2} is elevated. In the dog, hyperventilation with air or oxygen following prolonged hypercarbia can induce ventricular fibrillation. Whether such posthypercapneic ventricular fibrillation has ever occurred in man is unknown, at least to this author.

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