Epinephrine-Induced Arrhythmias Effect of Carbon Dioxide and Acid-Base Changes

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WHILE the subject of arrhythmias occurring during cyclopropane anesthesia has attracted considerable investigation, controversy still exists regarding the role of carbon dioxide, acidosis, and catechol amines. Price and his co-workers [1] have shown in man that arrhythmias encountered during cyclopropane anesthesia with hypercarbia were coincident with an increase in plasma concentrations of catechol amines. They concluded that the arrhythmias were caused by liberation of catechol amine from sympathetic nerve endings in the myocardium. Robbins and Thomas [2] reported that excess carbon dioxide itself was the cause of cardiac irregularities during cyclopropane anesthesia in cats. In dogs, on the other hand, other authors have reported a protective effect of carbon dioxide against cardiac irregularities induced by epinephrine administered during cyclopropane anesthesia.[3,4] Graff *et al.*[3] concluded that the above protection resulted from a direct depressive effect of carbon dioxide on the myocardium.

Results of the above studies appear contradictory in that hypercarbia during cyclopropane anesthesia leads to cardiac arrhythmias from endogenously liberated catechol amines [1,5] and that hypercarbia affords protection from arrhythmias induced by exogenous epinephrine.[3,4] Price *et al.*,[1] however, have suggested that differences in arrhythmia producing mechanisms may exist between species.

This study proposes that the protection to epinephrine induced arrhythmias during prolonged hypercarbia [3,4] may have resulted from release of endogenous catechol amines producing a catechol amine tachyphylaxis; with development of tachyphylaxis, the animals would be protected from arrhythmias during subsequent injections of epinephrine. Tachyphylaxis, defined by Seevers and Woods as "a rapidly developed short lived tolerance resulting from the oft repeated administration of a drug . . . ," has been noticed with sympathomimetic amines.[6] Gilbert and associates [7] have shown that sympathomimetic amines induce partial tachyphylaxis to induction of ectopic beats in electrically-driven dog hearts.

The present report demonstrates that arrhythmia tachyphylaxis to exogenously administered epinephrine develops in dogs anesthetized with pentobarbital. Ligou and Nahas [8] reported that elevation of plasma catechol amines during carbon dioxide inhalation was prevented if the hydrogen ion concentration was buffered by an infusion of tris (hydroxymethyl) aminomethane (THAM).

To determine if protection from epinephrine induced ventricular arrhythmias can develop during pentobarbital anesthesia in this study, dogs were either (1) respired with 15 per cent carbon dioxide mixtures, (2) subjected to "diffusion respiration," or (3) infused with acid solutions. To investigate whether hypercarbia itself or the accompanying acidosis protects against epinephrine-induced arrhythmias, another series of animals was given THAM to prevent a fall in *p*H during inhalation of carbon dioxide mixtures. To determine whether acidosis itself *or* liberation of catechol amines is the cause of the protective effect of carbon dioxide, this study also included animals pretreated with catechol amine-depleting doses of reserpine.

Method

Mongrel dogs weighing from 10 to 20 kg. were anesthetized with 25 mg./kg. of sodium pentobarbital intravenously. Respiration was provided by a Palmer volume controlled res-

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TABLE 1. Tachyphylaxis from Repeated Administration of Epinephrine

Dose of Epinephrine, μg./kg.	Dog										
	1	2	3	4	5	6	7	8	9	10	11
5	Big	ST	ST	VES	ST	ST	Big	MVR	ST	VT	VT
5	ST			Big			VES	Big		VT	VT
5				ST			Big	ST		VES	VT
5							Big			VES	VES
10	Big	ST	ST	ST	VES	VT	ST	ST	VES	ST	ST
10	ST				ST	VT			Big		MVR
10						ST			ST		ST
15	ST	ST	VES	ST	ST	ST	ST	ST	ST	ST	VES
15			ST								ST
20	Big	Big	ST	ST	ST	ST	ST	ST	ST	ST	ST
20	ST										
30	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST
40	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST
80	ST	ST	ST	ST	ST	ST		ST			

ST: Sinus tachycardia; MVR: Multifocal ventricular rhythm; Big: Bigeminy; VES: Occasional ventricular extrasystole; VT: Ventricular tachycardia.

Repeated injections of epinephrine were administered to the same dog. (A larger dose was given if the previous dose did not produce arrhythmias.)

pirator through an oral cuffed endotracheal tube. Gallamine triethiodide was administered intermittently for muscular relaxation. End-tidal P_{CO_2} was measured by an infrared carbon dioxide analyzer, Beckman LB1 model. The femoral artery and vein were each cannulated with a polyethylene catheter. Arterial pressure was measured by means of a pressure transducer connected to the indwelling catheter. The electrocardiogram and blood pressure were recorded with a Visicorder and a multichannel monitoring system (ENSCO). Arterial blood samples were collected anaerobically at regular intervals and measured for *p*H with a glass electrode and a Beckman GS *p*H meter at 37° C. in a constant temperature water bath.

Hypercarbia was induced by inhalation of 15 per cent carbon dioxide in oxygen or by "diffusion respiration" following a period of 30 minutes respiration with 100 per cent oxygen with a nonrebreathing system. Lactic acid 0.3 *M* and hydrochloric acid 0.15 *M* were diluted from stock solutions and administered by intravenous drip. THAM was prepared as 0.3 *M* solution of tris (hydroxymethyl) aminomethane containing sodium chloride 1.75 Gm. and potassium chloride 0.37 Gm. per 1,000 ml. according to Millar *et al.*[9]

TABLE 2. Effect of 15 Per Cent CO_2 Inhalation

Dog	Control		Blood *p*H Change From CO_2 Inhalation						ECG, after Epinephrine, 20 μg./kg. I.V.
			Time in Minutes						
	*p*H	P_{CO_2}	5	10	15	20	25	30	
1	7.36	38.0	7.29	7.12	7.08	7.05	7.01	7.00	ST
2	7.43	38.0	7.28	7.12	7.06	7.03	6.99	6.96	ST
3	7.38	38.5	7.26	7.19	7.11	7.07	7.02	7.01	ST
4	7.36	38.5	7.28	7.14	7.08	7.05	7.00	6.99	ST
5	7.41	38.0	7.29	7.18	7.10	7.06	7.03	6.99	ST

ST: Sinus tachycardia.

TABLE 3. Effect of Acid Infusion

Dog	Control				Acid Infusion					ECG, after Epinephrine, 20 μg./kg. I.V.	After 30 Minutes Recovery			
													Epinephrine I.V.	
	pH	P_{CO_2}	Epinephrine, μg./kg.	ECG	Type Infused	Time (minutes)	Total Dose (ml)	pH	P_{CO_2}		pH	P_{CO_2}	μg./kg.	ECG
1	7.42	35.8			0.3 M Lactic acid	50	500	7.02	30.0	ST				
2	7.38	31.2			0.3 M Lactic acid	50	500	7.00	31.0	ST				
3	7.42	34.0			0.3 M Lactic acid	60	430	6.97	30.0	ST	7.40	32.0	20	Big
4	7.45	32.0			0.15 M HCl	60	350	6.98	30.0	Big				
5	7.35	36.0	20	VT	0.15 M HCl	65	450	6.96	31.5	ST	7.33	35.0	20	VES
6	7.37	39.0	20	VT	0.3 M Lactic acid	70	500	7.00	35.5	ST	7.35	35.0	20	MVR
7	7.38	33.0	20	VT	0.3 M Lactic acid	85	520	7.00	31.0	ST				
8	7.39	39.0	20	VT	0.3 M Lactic acid	75	530	7.03	35.0	ST	7.35	37.0	20	VT
9	7.38	39.5	20	VT	0.3 M Lactic acid	85	650	6.95	33.5	ST	7.36	37.5	20	VES
10	7.37	36.5			0.3 M HCl	55	400	7.01	38.5	ST	7.35	36.5	20	VT

ST: Sinus tachycardia; Big: Bigeminy; VT: Ventricular tachycardia; VES: Occasional ventricular extrasystole; MVR: Multifocal ventricular rhythm.

Epinephrine (Adrenaline chloride solution 1:1000) was diluted with normal saline to appropriate volume just before use. It was given in a single dose through an indwelling catheter in the femoral vein and subsequently washed in with minimal amounts of normal saline.

Results

REPEATED INTRAVENOUS INJECTIONS OF EPINEPHRINE (Table 1). Epinephrine was given in increasingly larger doses starting from an initial dose of 5 μg./kg. Each injection was given at 10 minute intervals. The blood pressure which rose with administration of epinephrine returned to the preinjection level during this period. The dosage of epinephrine was increased when the preceding dose did not induce ventricular beats. Ventricular arrhythmias did not occur when the animals were finally challenged with 80 μg./kg. (after 9 to 10 repeated epinephrine injections totaling approximately 120 μg./kg.). When a single injection of 80 μg./kg. of epinephrine was administered to each of three dogs not pretreated with epinephrine, ventricular tachycardia occurred. Ventricular tachycardia was noted in all animals in another series when 20 μg. kg. of epinephrine was administered initially (table 3).

CARBON DIOXIDE (15 PER CENT) INHALATION. Five dogs were subjected to inhalation of a mixture of 15 per cent carbon dioxide and oxygen for 30 minutes. At the end of 30

TABLE 4. Effect of 15 Per Cent CO_2 Inhalation During 0.3 *M* THAM Infusion

Dog	Control		*p*H Changes During CO_2 Inhalation — Time in Minutes						Epinephrine I.V.	
	*p*H	P_{CO_2}	5	10	15	20	25	30	Dose μg./kg.	ECG. Effect
1	7.38	39.0	7.25	7.35	7.38	7.38	7.37	7.38	20	MVR
2	7.36	39.0	7.30	7.28	7.26	7.29	7.32	7.42	20	Big
3	7.35	39.0	7.33	7.30	7.25	7.35	7.35	7.35	20	Big
4	7.40	39.0	7.36	7.34	7.30	7.34	7.37	7.37	20	VES
5	7.38	39.0	7.35	7.31	7.33	7.33	7.36	7.39	20	VES

MVR: Multifocal ventricular rhythm; VES: Occasional ventricular extrasystole; Big: Bigeminy.

minutes, arterial *p*H had dropped from 7.39 ± 0.02 to 6.99 ± 0.02. Ventricular irregularities were not observed in any animals with single administrations of 20 μg./kg. of epinephrine given just prior to termination of carbon dioxide inhalation (table 2). Injection of 20 μg./kg. of epinephrine in the absence of respiratory acidosis in controls uniformly resulted in ventricular tachycardia (table 3).

INTRAVENOUS ACID INFUSIONS. Five of the ten dogs receiving acid infusions were given 20 μg./kg. of epinephrine 30 minutes prior to acid infusion. This control injection was given to only one half of the animals in order to limit the possibility that tachyphylaxis could be induced by the initial injections of epinephrine. All five dogs given 20 μg./kg. of epinephrine developed ventricular arrhythmias (table 3).

When three dogs were infused with 0.15 *M* hydrochloric acid at approximately 0.4 ml./kg./minute, arterial *p*H dropped from 7.39 ± 0.04 to 6.99 ± 0.04. End-expiratory P_{CO_2} was maintained within the normal range by hyperventilation. Arterial blood *p*H was maintained at approximately 7.00 for 30 minutes with hydrochloric acid infusion. When the animals were challenged with 20 μg./kg. of epinephrine, one dog showed bigeminy and two dogs developed sinus tachycardia.

When seven dogs were infused with 0.3 *M* lactic acid at the rate of 0.4 ml./kg./minute, the arterial blood *p*H fell from 7.39 ± 0.04 to 6.99 ± 0.04. End-tidal P_{CO_2} was again maintained within the normal range by hyperventilation. With the administration of 20 μg./kg. of epinephrine after 30 minutes of acidosis, none of the animals manifested ventricular irregularities.

After termination of the lactic acid infusion, arterial *p*H returned to normal limits (7.36 ± 0.03) within 30 minutes. Six dogs were given 20 μg./kg. of epinephrine intravenously after return of *p*H to normal; all of the animals showed ventricular arrhythmias.

THAM WITH HYPERCARBIA. (1) Five dogs were ventilated with a mixture of 15 per cent

TABLE 5. Effect of Apneic Oxygenation During 0.3 *M* THAM Infusion

Dog	Control		*p*H Change During Apneic Oxygenation — Time in Minutes						Epinephrine I.V.	
	*p*H	P_{CO_2}	10	20	30	40	50	60	Dose μg./kg.	ECG. Effect
1	7.40	39.0	7.38	7.49	7.50	7.50	7.40	7.42	20	Big
2	7.38	39.0	7.38	7.45	7.45	7.43	7.42	7.40	20	Big
3	7.36	39.0	7.35	7.27	7.28	7.30	7.34	7.40	20	VES
4	7.41	39.0	7.40	7.45	7.41	7.43	7.40	7.39	20	VES
5	7.36	39.0	7.35	7.35	7.38	7.38	7.37	7.38	20	Big

Big: Bigeminy; VES: Occasional ventricular extrasystole.

TABLE 6. Effect of Reserpine Pretreatment and 15 Per Cent CO_2 Inhalation

Dog	Control		pH Change During 15 Per Cent CO_2 Inhalation			Epinephrine I.V.	
			Time in Minutes				
	pH	P_{CO_2}	10	20	30	Dose μg./kg.	ECG Effect
1	7.36	39.5	7.20	7.08	7.00	20	VES
2	7.35	38.0	7.15	7.09	7.01	20	VT
3	7.37	36.0	7.17	7.10	7.01	20	VT
4	7.36	36.0	7.13	7.05	6.98	20	VT
5	7.36	37.0	7.20	7.09	7.00	20	VT

VES: Occasional ventricular extrasystole; VT: Ventricular tachycardia.

carbon dioxide and oxygen. It was found by repeated *p*H determinations that an infusion of approximately 1.0 ml./kg./minute of 0.3 *M* THAM was sufficient to prevent a change in *p*H. After a 30 minute period of carbon dioxide inhalation and THAM administration 20 μg./kg. of epinephrine was administered. Ventricular arrhythmias were manifested in all animals (table 4).

(2) Five dogs were subjected to diffusion oxygenation after 30 minutes denitrogenation by respiration with 100 per cent oxygen. THAM was infused after respiration was arrested by gallamine triethiodide administration. The drip rate of THAM was regulated so that the arterial *p*H was maintained at a normal level. When 20 μg./kg. of epinephrine was given intravenously after one hour of diffusion respiration, all animals developed ventricular irregularities (table 5).

RESERPINE PRETREATMENT. Five dogs were pretreated with reserpine 0.1 mg./kg. intraperitoneally 24 and 48 hours prior to the experiments. An intraperitoneal administration of reserpine 0.1 mg./kg. has been shown to deplete the total myocardial catechol amines.[10] When 15 per cent carbon dioxide with oxygen was administered for 30 minutes, arterial *p*H dropped to 7.00 ± 0.03. Injection of 20 μg./kg. of epinephrine induced ventricular arrhythmias in all animals in spite of existing respiratory acidosis (table 6).

Discussion

The finding that inhalation of 15 per cent carbon dioxide for 30 minutes provided protection against epinephrine induced irregularities, is in agreement with results obtained by previous workers.[3,4] However, protection was not afforded when arterial *p*H was kept within the normal range by THAM infusion. This observation suggests that *p*H change is the predominant factor in development of protection. Results obtained by acid infusions provide further evidence for the above assumption. Animals with increased hydrogen ion concentration by acid infusions were shown to have developed protection against epinephrine-induced ventricular irregularities in spite of normal end-tidal P_{CO_2} levels.

Reduced vasopressor reaction to systemically administered catechol amines during acidosis has been reported.[11,13] Seehzer *et al.*[15] assumed that there is a depression in the vasopressor response at the tissue receptor level during acidosis. The possibility of development of similar depression at the cardiac receptor level during acidosis cannot be refuted. This present experiment does not eliminate the possibility of direct inhibition of metabolism during acidosis as has been suggested by Nahas, Ligou, and Mehlman[14] in their study of the effects of epinephrine on oxygen consumption in dogs. Working with *Escherichia coli*, Weiner and Draskoczy[15] demonstrated a correlation between the inhibitory effect on oxidative mechanisms and concentration of unionized molecules of organic acid. Inhibition of oxidative metabolism of cell-free supernatants was found to be proportional to the concentrations of dissociated molecules. Presumably intracellular *p*H had a predominant effect on oxidative metabolism. A previous report from this laboratory[16] showed that pretreatment with sodium fluoride, an inhibitor of glycogenolysis, decreased the incidence of ventricular irregularities induced by epinephrine. It is possible that metabolism is inhibited by acidosis to such a degree that it may protect from induced cardiac irregularities.

Price *et al.*[1] and Ligou and Nahas[8] demonstrated that the level of circulating endogenous catechol amines was increased during respiratory acidosis. It has also been shown[8] that the level of circulating endogenous catechol amines was also increased during acid infusions when *p*H dropped below 7.00, but was not increased during hypercarbia if arterial

*p*H was buffered within the normal range with a THAM infusion. The present study shows that protection to epinephrine-arrhythmias occurs during acidosis, a condition in which endogenously liberated plasma catechol amine levels have been reported to be elevated.[1,8] Furthermore, when liberation of endogenous catechol amines was prevented by catechol amine depleting doses of reserpine, acidosis which otherwise protects the heart from epinephrine-arrhythmias failed to do so. Since tachyphylaxis rapidly developed with exogenously administered epinephrine, it is plausible that tachyphylaxis, developed by endogenous catechol amine liberation, provided protection rather than acidosis itself.

The subject of supersensitivity after pharmacological or surgical denervation of neurotransmitter substances has been reviewed by Emmelin.[17] Whether supersensitivity to epinephrine after reserpinization occurred in the present study is open to question. The development of supersensitivity was observed in the nictitating membrane of the cat by Flemming and Trendelenburg[18] after daily reserpine administration of 0.1 mg./kg. for 7 to 14 days. Supersensitivity of the cardiac pacemaker and the circulatory system to epinephrine required at least three days of reserpine 0.1 mg./kg. administration. However, since studies of supersensitivity to epinephrine-arrhythmias after reserpine have not yet been reported, it is impossible to refute in our study the occurrence of supersensitivity to epinephrine counteracting a protective action of acidosis. A supersensitive state may apparently develop from interruption of a relative tachyphylaxis present in the normal state. Burn and Rand[19] suggest that catechol amines are released continuously from the combined form of tissue stores, thereby partially occupying receptors available for the transmitters. According to the above authors "sensitivity" to catechol amines is low in the normal state. After depletion of stores of catechol amines by surgical denervation or reserpine pretreatment, termination of catechol amine leakage leaves receptor sites totally open and "sensitivity" increases. Winder, Anderson and Parke[20] working with a series of sympathomimetic amines on their capacity to constrict nasal mucosa, suggested that the development of tachyphylaxis is caused by progressive receptor occupation. By plotting cumulative effects of decongestant activity of sympathomimetic amines on a probability scale against a logarithm of cumulative doses, they obtained a linear relationship. The concept of Burn and Rand[19] mentioned above can be interpreted that there exists a relative tolerance to catechol amines in the normal state. In our experiment absence of protection during acidosis, after reserpinization, seems best explained by lack of development of tachyphylaxis at the receptor site.

Recovery of sensitivity after termination of acidosis demonstrated in the present study could be explained by the diffusion of epinephrine from active myocardial sites and dilution by circulating blood or by metabolism of catechol amine near the myocardial receptor. Price *et al.*[1] reported the existence of discrepancies between endogenously liberated plasma catechol amine levels at the time of initiation of ventricular irregularities during respiratory acidosis and the plasma levels needed to produce irregularities during exogenous infusions. Measuring blood catechol amine levels they found that ten times higher catechol amine levels were necessary on infusion of exogenous epinephrine to induce ventricular arrhythmias as compared to the endogenously liberated plasma catechol amine levels during ventricular arrhythmias initiated by respiratory acidosis. The above authors assumed that during hypercarbia higher catechol amine concentrations existed at the myocardium than catechol amine levels in the plasma, *i.e.*, a concentration gradient presumably existed from myocardium toward plasma. On the other hand Bacq[21] showed that administered epinephrine leaves the circulation but if O-methyl transferase were inhibited by pyrogallol, nearly maximal response of the denervated nictitating membrane was demonstrated even after blood catechol amine was undetectable. We are inclined to believe that termination of tachyphylaxis was attributable to metabolism of catechol amines near the site of liberation and action.

Summary

Inhalation of a mixture of 15 per cent carbon dioxide with oxygen resulted in a decreased incidence of ventricular irregularities

from epinephrine injection in dogs anesthetized with pentobarbital.

When the arterial *pH* was kept within the normal range by THAM infusions during hypercarbia induced either by 15 per cent carbon dioxide inhalation or apneic oxygenation, protection against epinephrine-arrhythmias was not observed.

Infusion of 0.15 *M* hydrochloric acid or 0.3 *M* lactic acid provided protection against epinephrine-arrhythmias, although end-expiratory P_{CO_2} levels were kept within normal range by hyperventilation.

When the animals were pretreated with catechol amine depleting doses of reserpine, respiratory acidosis did not provide protection against epinephrine-arrhythmias.

With repeated injections of increasingly larger doses of epinephrine given at ten-minute intervals, tachyphylaxis developed; arrhythmias did not occur even with doses of epinephrine 16 times larger than those doses which in animals not pretreated with epinephrine produced arrhythmias.

The role of tachyphylaxis to catechol amines in providing protection to arrhythmias during acidosis was discussed.

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