Effect of Acute Hypoxia and Hypercapnic Acidosis on the Development of Acetylstrophanthidin-Induced Arrhythmias

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ABSTRACT The effect of acutely induced hypoxia, hypercapnic acidosis, and the combination of the two on the amount of acetylstrophanthidin (AS) required to produce cardiac arrhythmias was determined in anesthetized dogs. Each animal was studied during ventilation with room air and again during ventilation with gas mixtures of appropriate concentrations; 24 hr separated the study periods. AS was infused intravenously at a rate of 5 μg/kg per min.

Significantly less AS was required to produce arrhythmias during hypoxia and hypercapnic acidosis together than during the period with normal arterial Po_2, Pco_2, and pH (10 animals). Included in this group were two animals which had undergone previous bilateral adrenalectomy and four animals in which heart rate was maintained at the same frequency during both study periods. A significant reduction in the toxic dose of AS also was demonstrated in eight animals, two with constant heart rate, during hypoxia with normal arterial Pco_2 and pH. Hypercapnic acidosis alone (eight animals) did not significantly alter the toxic dose of AS. After the administration of propranolol (six animals) or hexamethionium (six animals), no significant difference was observed between the toxic dose of AS during hypoxia and that during ventilation with room air. Thus although hypoxia and hypercapnic acidosis together do reduce the amount of AS required to produce arrhythmias, it is the hypoxia which exerts the predominant effect on the development of this increased sensitivity to AS. Furthermore, this effect of hypoxia occurs primarily as a result of reflexly augmented sympathetic stimulation of the heart.

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INTRODUCTION

The development of digitalis-induced arrhythmias undoubtedly is modified by many conditions and previous studies have defined clearly a number of factors which can exert such an effect (for review, see reference 1). The frequent occurrence of cardiac arrhythmias in patients with chronic lung disease who are receiving a digitalis preparation has led to the belief that these patients are unduly sensitive to the arrhythmia-producing effects of the glycosides and that the alterations in blood gases, which commonly occur in such patients, may contribute to this increased sensitivity. Baum, Dick, Blum, Kaupe, and Carballo observed that 8 of 29 patients with chronic lung disease developed cardiac arrhythmias after receiving a single injection of 1.2 mg of acetylstrophanthidin (2). They reported that this represented increased sensitivity to the aglycone which was related more significantly to the reduction in arterial Po_2 than to the elevation of Pco_2. Recently preliminary reports of two studies have appeared in which hypoxia was observed to decrease the amount of acetylstrophanthidin required to produce arrhythmias (3, 4), whereas, in one of these studies, hypercapnic acidosis permitted the administration

of a larger amount of acetylstrophanthidin before arrhythmias occurred (3). In neither study was the effect of the combination of hypoxia and hypercapnic acidosis observed nor was the mechanism by which hypoxia effected the development of the aglycone-induced arrhythmias determined.

It has been demonstrated that acutely induced hypoxia reflexly increases sympathetic stimulation of the heart (5–7), adrenal catecholamine release (8), and catecholamine release from isolated muscle preparations (9, 10). In addition, hypercapnic acidosis also results in sympathoadrenal stimulation and increased plasma catecholamine levels (11–13). Since catecholamines have been shown to adversely effect the development of glycoside-induced arrhythmias (14–17), it seemed possible that the action of hypoxia and hypercapnic acidosis on the sympathetic nervous system could play a significant role in their effect on the development of digitalis arrhythmias.

The following study was performed to provide more definitive information as to whether hypoxia, hypercapnic acidosis, or the combination of the two effect the development of acetylstrophanthidin-induced arrhythmias and, if so, whether the effect is mediated by increased catecholamine stimulation of the heart.

METHODS

Mongrel dogs weighing between 14 and 25 kg were anesthetized with sodium pentobarbital, 35 mg/kg, intubated, and ventilated with a positive pressure displacement pump (Harvard Apparatus Co., Dover, Mass.). Femoral arterial pressure and a standard limb lead of the electrocardiogram were recorded continuously on a multichannel oscillograph (Sanborn Co., Waltham, Mass.). Pressure measurements were made with a Statham P23 Db pressure transducer (Statham Instruments, Inc., Los Angeles, Calif.). Each animal was studied on two occasions separated by 24 hr. During one study period, the animal was ventilated with room air and during the other period with various concentrations of O_2, CO_2 and N_2. In consecutive animals, the order of study was reversed. After arterial P_{O_2}, P_{CO_2} and pH, as determined with a direct reading electrode instrument (IL Meter No. 102, Instrumentation Laboratories, Boston, Mass.), had remained constant for 30–45 min, an intravenous infusion of acetylstrophanthidin (AS),[1] 5 μg/kg per min, was begun and continued until toxic cardiac arrhythmias occurred. Plasma potassium was determined by flame photometry and blood samples were obtained before AS administration and again at the time of the arrhythmias. During study periods in which the concentration of gases in the inspired air was altered, blood samples for plasma potassium also were drawn before ventilation with the appropriate gas mixture. Arterial P_{O_2}, P_{CO_2}, and pH were measured intermittently throughout the study. The animals were divided into five groups.

Group 1 consisted of 10 animals in which hypoxia and hypercapnic acidosis were produced by ventilation with 7% O_2–5% CO_2–88% N_2. The occurrence of marked respiratory efforts necessitated the administration of 2.5–4.0 mg of decamethonium bromide to obtain the desired level of arterial gases. This dose of decamethonium has been reported not to produce significant hemodynamic effects (18). Comparable amounts of decamethonium were also administered during the period in which the animal was ventilated with room air. Two animals had undergone previous bilateral adrenalectomy and were receiving maintenance doses of corticosteroids. In four other animals, heart rate was maintained at the same frequency during both study periods by means of electrical stimulation of the right atrium with a bipolar electrode catheter inserted through a femoral vein.

Group 2 included eight animals made hypoxic by ventilation with 7% O_2–93% N_2. In two of these animals, heart rate also was maintained constant during each study period as described above.

Group 3 consisted of eight animals in which hypercapnic acidosis was produced by ventilation with 20% O_2–10% CO_2–70% N_2.

Group 4 included six animals ventilated with 7% O_2–93% N_2 which had received 1.5 mg/kg of propranolol[2] intravenously during each study period before the administration of AS. The completeness of beta adrenergic blockade was verified in each animal at the conclusion of the experiment by failure to observe an increase in heart rate after the injection of 20 μg of isoproterenol.

Group 5 consisted of six animals ventilated with 7% O_2–93% N_2 to which 4 mg/kg of hexamethonium chloride[3] was administered intravenously during each study period before the infusion of AS and repeated after approximately one-half the arrhythmia-producing dose of AS had been given. The effectiveness of ganglionic blockade was determined in each animal by infusing norepinephrine at the end of the experiment. In each instance, heart rate increased as systemic arterial pressure rose.

Statistical analyses were performed using Student's *t* test with paired observations (19).

RESULTS

Individual values for arterial P_{O_2}, P_{CO_2}, pH, and the amount of AS required to produce toxic arrhythmias during both study periods are presented

[1] Acetylstrophanthidin was supplied by Dr. G. C. Chiu, Eli Lilly & Co., Indianapolis, Ind.

[2] Propranolol was supplied by Dr. Alex Sahagian-Edwards, Ayerst Laboratories, New York.

[3] Hexamethonium chloride was provided by the Warner-Lambert Pharmaceutical Co. Morris Plains, N. J.

in Tables I–V. Average values for heart rate, mean arterial pressure, and plasma potassium at various periods during the study are presented in Table VI.

Group 1 (Table I)

During ventilation with room air, arterial Po_2 averaged 103.1 ± 3.4 SEM mm Hg, Pco_2 37.2 ± 1.5 mm Hg, and pH 7.39 ± 0.01 and an average of 74.2 ± 4.1 μg/kg of AS was required to produce toxic arrhythmias. With 7% O_2–5% CO_2 in the inspired gas, pO_2 averaged 30.5 ± 2.2 mm Hg, Pco_2 66.9 ± 2.4 mm Hg, pH 7.14 ± 0.03 and an average of 58.8 ± 3.3 μg/kg of AS produced arrhythmias; 9 of the 10 animals required a lesser amount of AS during this period ($P < 0.01$). During both study periods, toxicity was characterized by the appearance of ventricular tachycardia, herein defined as three consecutive premature ventricular contractions. In three of the four animals in which heart rate was maintained constant during both study periods, lesser amounts of AS were required to produce arrhythmias during the administration of 7%O_2–5% CO_2. Similarly in the two adrenalectomized animals, 16.0 and 17.2 μg/kg less of AS produced ventricular tachycardia when breathing 7%O_2–5% CO_2 than when breathing room air. In four animals breathing room air, the infusion of AS was stopped with the appearance of sustained ventricular tachycardia. Once sinus rhythm had been restored, ventilation was

TABLE I

Arterial Po_2, Pco_2, pH, and Amount of AS Required to Produce Toxicity during Ventilation with Room Air (A) and 7% O_2–5% CO_2 (B) in Group 1

Animal	Inspired gas	Po_2	Pco_2	pH	Amount of AS to toxicity
		mm Hg	*mm Hg*	*U*	*μg/kg*
463	A	93	35	7.43	54.8
	B	30	67	7.19	39.0
444	A	84	40	7.37	69.6
	B	24	71	7.07	60.4
472	A	105	41	7.44	82.3
	B	27	67	7.17	57.9
509	A	119	32	7.40	80.0
	B	31	70	7.17	60.3
523*	A	108	41	7.35	71.8
	B	33	72	7.14	59.6
515*	A	112	38	7.40	58.3
	B	30	71	7.03	72.7
505*	A	111	31	7.37	90.4
	B	30	70	7.09	56.3
522*	A	105	41	7.39	91.4
	B	32	74	7.01	71.3
391‡	A	104	30	7.35	81.3
	B	21	57	7.26	65.3
354‡	A	90	43	7.44	62.1
	B	47	50	7.30	44.9
Mean ± SEM	A	103.1 ± 3.4	37.2 ± 1.5	7.39 ± 0.01	74.2 ± 4.1
	B	30.5 ± 2.2§	66.9 ± 2.4§	7.14 ± 0.03§	58.8 ± 3.3§

* Animals in which heart rate was maintained constant.

‡ Adrenalectomized animals.

§ Mean significantly different from that during ventilation with room air ($P < 0.05$).

begun with 7% O_2–5% CO_2 and in each animal ventricular tachycardia recurred within 1–2.5 min. In three of these animals, the infusion of AS was continued with the appearance of the arrhythmia during the study period with 7% O_2–5% CO_2, but the animal was immediately ventilated with room air. In each instance sinus rhythm was restored and an additional amount of AS averaging 10.6 μg/kg was infused before ventricular tachycardia recurred.

Group 2 (Table II)

With room air, arterial Po_2 averaged 97.1 ± 4.3 mm Hg, Pco_2 35.3 ± 2.0 mm Hg, pH 7.42 ± 0.01, and an average of 56.9 ± 2.8 μg/kg of AS was infused before the appearance of an arrhythmia. With 7% O_2, arterial PO_2 averaged 31.2 ± 2.3 mm Hg, Pco_2 35.8 ± 1.0 mm Hg, pH 7.41 ± 0.01, and a lesser amount of AS was required to produce toxicity in each animal, averaging 49.0 ± 3.5 μg/kg ($P < 0.001$). Ventricular tachycardia was the toxic arrhythmia in each animal in both study periods. In each animal, the infusion of AS was discontinued with the appearance of the arrhythmia, whereas, ventilation with 7% O_2 was continued. Normal sinus rhythm always recurred.

Group 3 (Table III)

With room air, arterial Po_2 averaged 105.0 ± 5.6 mm Hg, Pco_2 34.0 ± 1.1 mm Hg, pH 7.42 ± 0.01, and an average of 65.1 ± 2.8 μg/kg produced ventricular tachycardia in seven animals and nodal tachycardia in one. With 20% O_2–10% CO_2, arterial Po_2 averaged 104.6 ± 4.3 mm Hg, pCO_2 77.0 ± 7.0 mm Hg, pH 7.13 ± 0.03, and a similar amount of AS, averaging 66.4 ± 3.9 μg/kg, produced the same arrhythmia in each animal as occurred with room air.

TABLE II

Arterial Po_2, Pco_2, pH, and Amount of AS Required to Produce Toxicity during Ventilation with Room Air (A) and 7% O_2 (B) in Group 2

Animal	Inspired gas	Po_2	Pco_2	pH	Amount of AS to toxicity
		mm Hg	*mm Hg*	*U*	*μg/kg*
370	A	98	26	7.44	57.9
	B	37	36	7.40	48.3
350	A	97	43	7.44	45.6
	B	24	36	7.40	40.0
424	A	81	35	7.42	49.9
	B	31	34	7.42	40.7
380	A	101	35	7.42	56.3
	B	41	40	7.45	45.5
336	A	82	42	7.42	52.9
	B	33	38	7.41	50.8
331	A	118	37	7.40	57.1
	B	30	33	7.39	40.1
511*	A	94	33	7.39	66.3
	B	21	31	7.38	59.3
485*	A	106	31	7.39	69.1
	B	33	38	7.44	67.5
Mean ± SEM	A	97.1 ± 4.3	35.3 ± 2.0	7.42 ± 0.01	56.9 ± 2.8
	B	31.2 ± 2.3‡	35.8 ± 1.0	7.41 ± 0.01	49.0 ± 3.5‡

* Constant heart rate.
‡ $P < 0.05$.

TABLE III

Arterial P_{O_2}, P_{CO_2}, pH, and Amount of AS Required to Produce Toxicity during Ventilation with Room Air (A) and 20% O_2–10% CO_2 (B) in Group 3

Animal	Inspired gas	P_{O_2}	P_{CO_2}	pH	Amount of AS to toxicity
		mm Hg	*mm Hg*	*U*	*μg/kg*
292	A	108	30	7.40	65.0
	B	112	63	7.16	75.1
346	A	106	37	7.45	79.2
	B	82	100	7.02	76.3
338	A	93	33	7.38	55.0
	B	97	100	7.05	53.6
342	A	119	33	7.40	68.7
	B	98	65	7.16	50.4
318	A	119	34	7.47	70.4
	B	118	73	7.14	77.5
303	A	124	35	7.44	59.6
	B	114	100	7.08	58.8
330	A	92	31	7.45	57.5
	B	115	59	7.28	73.8
272	A	79	39	7.39	65.0
	B	101	56	7.18	65.4
Mean ± SEM	A	105.0 ± 5.6	34.0 ± 1.1	7.42 ± 0.01	65.1 ± 2.8
	B	104.6 ± 4.3	77.0 ± 7.0*	7.13 ± 0.03*	66.4 ± 3.9

* $P < 0.05$.

Group 4 (Table IV)

Mean arterial P_{O_2}, P_{CO_2}, and pH averaged 94.3 ± 2.6 mm Hg, 37.7 ± 1.1 mm Hg, and 7.38 ± 0.01, respectively, with room air after propranolol and an average of 57.8 ± 4.8 μg/kg of AS was infused before the appearance of arrhythmias. With 7% O_2, arterial P_{O_2} averaged 26.3 ± 2.1 mm Hg, P_{CO_2} 38.2 ± 1.6 mm Hg, and pH 7.37 ± 0.02 and a comparable amount of AS averaging 60.8 ± 2.3 μg/kg was required to produce toxicity after the administration of propranolol. In both periods, ventricular tachycardia occurred in each animal.

Group 5 (Table V)

After the administration of hexamethonium, mean arterial P_{O_2}, P_{CO_2}, and pH averaged 93.7 ± 3.0 mm Hg, 35.8 ± 1.2 mm Hg, and 7.42 ± 0.01, respectively, with room air. Ventricular tachycardia occurred in five animals and rapid nodal tachycardia in one animal after an average of 45.8 ± 3.1 μg/kg of AS has been infused. Ventilation with 7% O_2 produced a mean P_{O_2}, P_{CO_2}, and pH which averaged 28.7 ± 2.1 mm Hg, 36.7 ± 1.0 mm Hg, and 7.41 ± 0.01, respectively. After hexamethonium, an average of 47.6 ± 4.3 μg/kg of AS was infused before the development of toxicity. In each animal, the arrhythmia was similar to that which occurred with room air.

Mean arterial pressure, heart rate, and plasma potassium (Table VI). Mean arterial pressure was somewhat elevated in each group during both control periods. Within any group, control values were similar. Ventilation with low concentrations of O_2 always resulted in a relatively rapid increase in mean arterial pressure. Excluding the group which received hexamethonium, mean arterial pressure thereafter declined to a relatively stable value which, however, remained above control values before AS infusion. The administration of hexamethonium during hypoxia resulted in a precipitous fall in arterial pressure necessitating the administration of 100–250 ml of normal saline to each animal to restore arterial pressure to satis-

TABLE IV

Arterial P_{O_2}, P_{CO_2}, *pH, and Amount of AS Required to Produce Toxicity during Ventilation with Room Air (A) and 7% O_2 (B) After Propranolol in Group 4*

Animal	Inspired gas	P_{O_2}	P_{CO_2}	pH	Amount of AS to toxicity
		mm Hg	*mm Hg*	*U*	*μg/kg*
416	A	97	37	7.35	43.8
	B	21	41	7.30	68.0
415	A	101	42	7.40	50.8
	B	30	36	7.37	57.1
397	A	89	39	7.36	77.9
	B	30	34	7.44	53.9
422	A	89	38	7.44	63.4
	B	25	41	7.35	65.9
409	A	102	36	7.35	54.0
	B	20	34	7.38	63.3
406	A	88	34	7.37	56.9
	B	32	43	7.35	56.7
Mean ± SEM	A	94.3 ± 2.6	37.7 ± 1.1	7.38 ± 0.01	57.8 ± 4.8
	B	26.3 ± 2.1*	38.2 ± 1.6	7.37 ± 0.02	60.8 ± 2.3

* $P < 0.05$.

TABLE V

Arterial P_{O_2}, P_{CO_2}, *pH, and Amount of AS Required to Produce Toxicity during Ventilation with Room Air (A) and 7% O_2 (B) after Hexamethonium in Group 5*

Animal	Inspired gas	P_{O_2}	P_{CO_2}	pH	Amount of AS to toxicity
		mm Hg	*mm Hg*	*U*	*μg/kg*
486	A	96	32	7.41	52.3
	B	25	36	7.36	49.6
510	A	93	37	7.40	38.1
	B	24	34	7.46	44.1
490	A	96	36	7.45	37.5
	B	32	36	7.44	34.9
498	A	95	37	7.41	54.3
	B	24	41	7.39	61.8
492	A	80	33	7.45	51.2
	B	31	37	7.39	57.2
483	A	102	40	7.39	41.3
	B	36	36	7.41	38.1
Mean ± SEM	A	93.7 ± 3.0	35.8 ± 1.2	7.42 ± 0.01	45.8 ± 3.1
	B	28.7 ± 2.1*	36.7 ± 1.0	7.41 ± 0.01	47.6 ± 4.3

* $P < 0.05$.

TABLE VI

Mean Values ± SEM for Heart Rate, Mean Arterial Pressure, and Plasma Potassium at Various Periods during the Study

State	Period	Heart rate	Mean arterial pressure	Plasma potassium
		beats/min	*mm Hg*	*mEq/liter*
Group 1				
Room air	C	168 ± 7.4	121 ± 7.2	4.1 ± 0.21
	T	143 ± 10.5*	143 ± 9.3*	4.6 ± 0.15*
7% O_2–5% CO_2	C	151 ± 12.0	120 ± 5.0	3.7 ± 0.23
	AS	165 ± 7.2	139 ± 7.0*	4.1 ± 0.23*
	T	147 ± 8.6	146 ± 6.6‡	4.8 ± 0.33‡
Group 2				
Room air	C	154 ± 9.4	128 ± 7.8	4.0 ± 0.26
	T	125 ± 13.4*	148 ± 8.8*	4.4 ± 0.17
7% O_2	C	138 ± 18.8	118 ± 5.5	4.0 ± 0.13
	AS	178 ± 13.0	132 ± 6.9*	3.7 ± 0.13*
	T	145 ± 8.5‡	149 ± 6.7‡	4.3 ± 0.22‡
Group 3				
Room air	C	141 ± 13.7	130 ± 6.7	4.4 ± 0.17
	T	108 ± 11.9*	149 ± 5.7*	4.9 ± 0.21*
20% O_2–10% CO_2	C	154 ± 12.4	124 ± 8.2	4.7 ± 0.14§
	AS	148 ± 10.4	124 ± 10.7	5.3 ± 0.18*
	T	126 ± 12.0‡	153 ± 7.9‡	5.7 ± 0.23‡
Group 4, propranolol				
Room air	C	163 ± 8.4	123 ± 6.4	3.9 ± 0.38
	AS	128 ± 6.0*	125 ± 5.6	—
	T	127 ± 3.8	156 ± 10.0‡	4.3 ± 0.46*
7% O_2	C	165 ± 10.9	120 ± 9.9	3.9 ± 0.23
	AS	141 ± 7.5*	133 ± 9.9	4.4 ± 0.25*
	T	139 ± 7.6	173 ± 10.3‡	5.9 ± 0.79
Group 5, hexamethonium				
Room air	C	146 ± 13.7	124 ± 8.2	3.4 ± 0.13
	AS	128 ± 2.1	98 ± 2.5*	—
	T	123 ± 2.8‡	148 ± 4.4‡	3.7 ± 0.11*
7% O_2	C	148 ± 9.2	125 ± 5.7	3.5 ± 0.10
	AS	134 ± 4.2‖	103 ± 10.0‖	3.1 ± 0.08‖
	T	133 ± 6.1	124 ± 9.9‡	3.4 ± 0.12‡

C, denotes period during ventilation with room air before any intervention; AS, just before infusion of acetylstrophanthidin; T, just prior to appearance of toxic arrhythmia. Mean values for heart rate in groups 1 and 2 do not include aninals in which heart rate was maintained constant.

* Mean value significantly different from respective control ($P < 0.05$).

‡ Mean value significantly different from AS value.

§ Mean control value significantly different from control with room air.

‖ Statistical significance of difference between mean AS and control values not determined since animals received normal saline to maintain arterial pressure.

factory levels. No significant change in mean arterial pressure occurred in the group breathing 20% O_2–10% CO_2. The infusion of AS in each group always produced a gradual increase in arterial pressure.

Each group demonstrated sinus tachycardia during the control periods with considerable variations among groups. However, there were no significant differences between control reart rates within groups. In each group which received low concen-

trations of O_2 in the inspired air, heart rate rose rapidly. In groups 1 and 2, heart rate thereafter declined somewhat but remained above control levels before the infusion of AS. However in groups 4 and 5, heart rate fell below control values after the administration of propranolol or hexamethonium. An insignificant decrease in heart rate occurred in group 3 ventilated with 20% O_2–10% CO_2. During the infusion of AS, heart rate gradually decreased except in those receiving propranolol or hexamethonium. In these latter animals, no significant change occurred.

There was only slight variation in the average control plasma potassium concentrations among groups 1, 2, and 4, whereas, the values in group 3 were simewhat higher and in group 5, slightly lower. With the exception of group 3, there were no statistically significant differences between control plasma potassium concentrations within any group. An increase in plasma potassium occurred in both groups in which hydrogen ion concentration and Pco_2 increased. The administration of 7% O_2 to group 2 resulted in a slight fall in plasma potassium, while an increase was observed in group 4 to which propranolol was given during hypoxia. With two exceptions, the infusion of AS produced a statistically significant increase in plasma potassium concentrations in each group during both study periods. In group 2, the infusion of AS during ventilation with room air did result in an increase in the average plasma potassium concentration which, however, was not statistically significant ($0.10 < P > 0.05$). Infusion of AS in group 4 during hypoxia resulted in a greater average increase in plasma potassium concentrations than during either period in any other group. However, this was due primarily to an increase of 4.0 mEq/liter in one animal and the average increase also just failed to attain significance at the 5% level.

DISCUSSION

The present study has demonstrated that the combination of acutely induced hypoxia and hypercapnic acidosis reduces the amount of acetylstrophanthidin required to induce arrhythmias. Furthermore, the results indicate that this occurs primarily as a result of the decrease in arterial Po_2 since hypoxia with normal arterial pH and Pco_2 increased the sensitivity of the heart to the arrhythmic effects of AS, whereas, hypercapnic acidosis with normal arterial Po_2 exerted no significant effect on the development of AS arrhythmias.

Although hypoxia of the degree produced in this study undoubtedly results in widespread metabolic and physiologic changes, the results in group 4, in which pretreatment with propranolol abolished the increased sensitivity to AS during hypoxia, would indicate that this effect of hypoxia occurred primarily as a result of increased catecholamine stimulation of the heart. Furthermore, the observation that during hypoxia previous adrenalectomy did not reduce the increased sensitivity, which was abolished by pretreatment with hexamethonium, provides evidence that the increased sensitivity was not related predominately to increased adrenal catecholamine release or a direct effect of hypoxia on myocardial catecholamine stores, but occurred as a result of reflexly induced sympathetic stimulation of the heart. In addition, the observations with hexamethonium provide further evidence that the effect of propranolol in this study was mediated primarily by its beta adrenergic blocking action and not by "quinidine-like" or nonbeta blocking effects which it may exert (20, 21).

In view of these results, it is perhaps surprising that hypercapnic acidosis alone did not increase the sensitivity to AS since this is also a stimulus to the sympathetic nervous system (11–13). However, there may well have been quantitative differences in the extent to which sympathetic activity was increased by the degree of hypoxia and hypercapnic acidosis produced in this study. Furthermore, other effects of hypercapnic acidosis would tend to inhibit the development of digitalis arrhythmias. Among these latter effects would be included carbonic acid interference with the action of catecholamines (12) and an increase in plasma potassium concentration, as occurred in this study. Thus the effect of hypercapnic acidosis on the development of digitalis arrhythmias undoubtedly represents the interplay of several factors. Such may account for the difference between the results of this study and that of Tisa and Moser in which hypercapnic acidosis increased the amount of AS required to produce arrhythmias (3). In the present study, hypercapnic acidosis did not exert a "protective" effect against the development of AS arrhythmias nor prevent the increased sensitivity to AS during hypoxia. In fact, the average toxic

dose of AS was reduced to a greater extent by the combination of hypoxia and hypercapnic acidosis than by hypoxia alone, 21 and 14%, respectively. Although these results would suggest that hypoxia and hypercapnia exert a synergistic effect on the sympathetic nervous system, as observed by others (22), these values are not significantly different statistically ($P > 0.30$).

A number of experimental precautions were taken to exclude other factors from significantly influencing these results. Each animal served as his own control. Study periods were separated by 24 hr in each animal, a time interval well beyond that required for complete dissipation of AS (23). Furthermore in consecutive animals, study periods were reversed. Heart rate was maintained constant in four animals in group 1 and two in group 2 since suggestive evidence has been presented that the rate of development of the arrhythmic effect of the glycosides is related to the frequency of electrical depolarization (24); a situation analogous to the relationship between the rate of development of the positive inotropic effect and the number of cardiac contractions (25). To be certain that the arrhythmias which occurred during hypoxia in group 2 were AS induced and did not result solely from hypoxia, the infusion of AS was discontinued with the appearance of the arrhythmia, whereas ventilation with the hypoxic gas mixture was continued. In each animal sinus rhythm recurred.

It is somewhat more difficult to exclude an effect from changes in myocardial potassium gradients. There was some variation in control plasma potassium concentrations among groups; the lowest values occurring in group 5 which also required the least amount of AS to produce arrhythmias. However, excluding group 3, there were no statistically significant differences between these values within groups. In group 3, control plasma potassium was slightly higher before ventilation with 10% CO_2 than during the control period with room air. Although plasma potassium is a poor reflector of total body potassium, it would not appear that major differences in potassium stores occurred between study periods in any group. It is, of course, not possible to determine to what extent the relationship of extracellular to cardiac intracellular potassium concentration was altered during the various study periods and there is reason to suspect that hypoxia and hypercapnic acidosis may exert different effects on this relationship (26. 27). Nevertheless, it does not seem reasonable to attribute these results solely to a direct effect of the altered blood gases and pH on myocardial potassium gradients.

This study was not designed to determine the extent to which arterial Po_2 must be reduced to affect the development of AS arrhythmias. However, it is of interest that in two animals not included in this series, arterial Po_2 could be reduced to only 51 and 53 mm Hg during ventilation with 7% O_2–5% CO_2 without the use of decamethonium. Both animals required an amount of AS comparable to that during ventilation with room air to produce toxicity. Also it is possible, if not probable, that more gradual changes in arterial gases and pH might produce different effects or act by different mechanisms than occurred in this study. Certainly, these results may not be applicable to humans with chronic disturbance of arterial gases and pH, pulmonary hypertension, and heart disease. They may have relevance, however, to patients in whom severe hypoxia develops more rapidly, e.g., patients with chronic lung disease and acute respiratory insufficiency. If digitalis-induced arrhythmias should occur in such patients, relief of hypoxia might be effective in rapidly terminating the arrhythmia. Although these studies would indicate that blockade of sympathetic activity of the heart also might be beneficial in such patients, it must be appreciated that withdrawal of sympathetic stimulation to the heart may aggravate or precipitate congestive heart failure (28), and propranolol may increase pulmonary artery pressure (29) and airway resistance (30).

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