RESPONSE OF THE DIGITALIZED HEART TO CYCLOPROPANE AND EPINEPHRINE *

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Cyclopropane has been shown to increase the irritability of the dog's heart so that the intravenous injection of .01 mg. epinephrine per kilogram produces ventricular tachycardia. This dose of the amine causes only premature beats or slow ectopic rhythms in unanesthetized animals (1). Cardiac irregularities are often an undesirable side action of digitalis preparations even when used in therapeutic doses. The severity of these arrhythmias increases as the dose is increased. The present report deals with the effects of digitalization on the cardiac response to cyclopropane, to epinephrine and to epinephrine and cyclopropane.

Procedure

The ventricular response to the intravenous injection of .01 mg. epinephrine per kilogram was determined in 13 unanesthetized dogs. The amine was diluted to 5 cc. with normal saline solution and injected into the radial vein at a constant rate of 1 cc. per ten seconds. Electrocardiograms (lead II) were taken before, during, and after the injections; the image of the string was under constant observation for a ten minute period beginning with the injection.

The animals were then anesthetized by rebreathing a cyclopropane-oxygen mixture from a 5 liter bag, intubated with a cuffed endotracheal tube, and connected through a soda-lime carbon dioxide absorber to a 100 liter bag containing a mixture of 30 per cent cyclopropane in oxygen. After equilibration on this constant mixture for thirty minutes, .005 mg. epinephrine per kilogram was injected intravenously and the duration of the resulting ventricular irregularities determined from the electrocardiograms. In several of the animals .01 mg. per kilogram was injected fifteen minutes later.

A week after the above controls had been established 9 of the animals received .05 mg. per kilogram of ouabain, diluted to 20 cc. with normal saline solution and injected intravenously during a fifteen minute period. One hour after the completion of the injection the cardiac response to the test dose of .01 mg. epinephrine per kilogram was determined as on the control. The animals were then anesthetized and the duration of cyclopropane-epinephrine tachycardia determined as above.

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Although the animals showed signs of digitalization as evidenced by an increase in the P-R interval, it was decided to study the effects of higher doses of ouabain. Accordingly, seven to ten days after the first digitalization epinephrine controls were again established on the unanesthetized animals, and 6 were then injected with .07 and 4 with .08 mg. ouabain per kilogram. Two animals received Digalen in doses equivalent to .08 mg. of ouabain per kilogram. The cardiac response to the test epinephrine injections was again determined both before and after anesthetization.

Since 4.5 per cent diethyl ether has been shown to prevent cyclopropane from sensitizing the heart to epinephrine (2), it was next decided to determine if the control dose of epinephrine would cause ventricular tachycardia when digitalized animals were anesthetized with the cyclopropane-ether-oxygen mixture. Five dogs were again digitalized by the intravenous injection of .07 mg. of ouabain per kilogram and the cardiac response to epinephrine determined after the animals had been maintained for thirty minutes on a mixture of 20 per cent cyclopropane and 4.5 per cent ether in oxygen.

RESULTS AND DISCUSSION

The effects of ouabain on cardiac automaticity of the dog are summarized in table 1. Following .05 mg. per kilogram the P–R interval increased in 7 of 8 unanesthetized animals. The heart rate decreased in 5 and remained unchanged in 2. In 7 of the 12 animals receiving .07 mg. or more per kilogram the pacemaker was shifted downward from the SA node, and the rate increased in the same animals. Six of the latter group had ventricular rhythms, and one showed AV rhythm. Two more had numerous premature ventricular contractions.

Central vagal stimulation and depressed conduction, either from direct action or through the vagus, account for the results with the lower dose. Excessive amounts of ouabain increased the irritability of the myocardium and thus caused ectopic beats and ventricular rhythms. Depression of the normal pacemaker also contributed to the appearance of these arrhythmias.

When digitalized animals were anesthetized with cyclopropane, 4 of the ventricular rhythms caused by ouabain reverted to AV and one to SA rhythm. Anesthetization also resulted in the disappearance of ventricular premature contractions in 2 animals. However, this irregularity did occur in dog 12 which had a normal sinus rhythm before cyclopropane. This was the only one of the 21 anesthetizations of 13 digitalized animals in which the pacemaker was displaced downward by cyclopropane.

The tendency for cyclopropane to shift the pacemaker of the overdigitalized heart upward suggests that this anesthetic agent increases the automaticity of supraventricular regions. The cardiac acceleration which occurs when normal unpremedicated dogs are anesthetized

TABLE 1

EFFECT OF OUABAIN ON CARDIAC AUTOMATICITY IN DOGS

Dog No.	Unanesthetized							Cyclopropane		After Ouabain	Cyclo-ether		After Ouabain
	Ouabain	Rate		P-R Interval		Rhythm		Rhythm	Rate	P-R Interval	Rhythm	Rate	P-R Interval
		Before Ouabain	After Ouabain	Before Ouabain	After Ouabain	Before Ouabain	After Ouabain						
	mg./kg.			*sec.*	*sec.*					*sec.*			*sec.*
1	.05	75	60	.14	.14–.20	SA	SA	SA	85	.14			
2	.05	125	63	.12	.16	SA	SA	SA	75	.16			
	.07	133	175	.12	.12	SA	SA+V. Ex.	SA	92	.16	SA	136	.12
3	.05	73	187	.12	—	SA	V	AV	95	—			
	.07	88	214	.12	—	SA	V	AV	167	—			
4	.05	75	75	.12	.14	SA	SA	SA	75	.14			
	.07	80	185	.12	—	SA	V	AV	135	—	SA	107	.14
5	.05	75	65	.12	.15	SA	SA	SA	115	.14			
	.07	68	100	.12	.14	SA	SA+V. Ex.	SA	167	.12	SA	185	.14
6	.05	60	60	.14	.16	SA	SA	SA	60	.16			
	.07	70	190	.14	—	SA	AV	SA & AV	90	.14–.16	SA	107	.16
7	.05	125	94	.11	.16	SA	SA	SA	100	.16			
	.08	88	136	.14	—	SA	V	V	188	—			
8	.08	125	172	.12	—	SA	V	AV	105	—			
9	.05	125	95	.12	.16–.19	SA	SA	SA	100	.21			
	.08	105	158	.16	—	SA	V	AV+V. Ex.	185	—			
10	.07	70	48	.12	.17	SA	SA	SA	100	.14	AV	150	—
11	.08	105	78	.12	.14	SA	SA	SA	50	.16			
	.10	63	167	.12	.16	SA	V	SA	185	.16			
12	.08*	70	80	.14	.16	SA	SA	SA+V. Ex.	167	.12			
13	.08*	75	50	.16	.16–.25	SA	SA	SA	80	.22–.28			

* Digalen equivalent to .08 mg. ouabain per Kilogram. V. Ex. = ventricular extrasystoles.

with cyclopropane supports this. It does not contradict sensitization of the ventricle to epinephrine, for the epinephrine is more specific for the ventricle as shown by ventricular premature contraction following its injection in normal unanesthetized animals.

The effect of digitalization on the cardiac response to epinephrine in unanesthetized animals is shown in table 2. In 21 of the 22 experiments digitalization prolonged the ventricular irregularities resulting from the test dose of epinephrine. In the majority of cases the arrhythmia was also of a more severe character. This confirms the obser-

vations made on the cat's heart by Wiethaup (3), McFarlane and Masson (4), and Zunz and Sanchez de la Cuesta (5). Seevers and Meek (6) reported that in the dog digitalization increased the number of ephedrine irregularities of the ventricular type.

TABLE 2

THE CARDIAC RESPONSE TO THE INJECTION OF 0.01 MG. OF EPINEPHRINE PER KILOGRAM IN UNANESTHETIZED DOGS BEFORE AND AFTER OUABAIN

Dog No.	Ouabain	Cardiac Response to Epinephrine before Ouabain	Cardiac Response to Epinephrine after Ouabain
	mg./Kg.		
1	.05	15" Ventricular rhythm	67" Vent. Ex.
2	.05	No Ventricular effects	25" Vent. rhythm
	.07	15" Vent. rhythm	55" Vent. Tachy.
3	.05	30" Vent. Ex.	VT before injection; AVR after
	.07	16" Vent. rhythm	VT before injection; SA & V after
4	.05	25" Vent. rhythm	46" Vent. rhythm
	.07	23" Vent. rhythm	VR before and after injection
5	.05	30" Vent. Ex.	33" Vent. rhythm
	.07	25" Vent. Ex.	170" Vent. rhythm
6	.05	15" Vent. Ex.; 10" VR	55" Vent. Ex.; 30" Vent. rhythm
	.07	64" Vent. rhythm	44" Vent. rhythm; 60" Vent. Tachy.
7	.05	No Vent. effects	80" Vent. Ex.
	.08	No Vent. effects	53" Vent. rhythm
8	.05	25" Vent. Ex.	No Vent. effects
	.08	No Vent. effects	Vent. rhythm before epinephrine
9	.05	No Vent. effects	30" Vent. rhythm
	.08	35" Vent. Ex.	65" Vent. Tachy.
10	.07	No Vent. effects	100" Vent. rhythm
11	.08	60" 3 SA 3V; 60" V. Ex.	52" VT; 60" VR; 50" V. Ex.
	.10	15" Vent. rhythm	60" Vent. Tachy.
12	.08*	20" Vent. rhythm; 10" V. Ex.	35" Vent. rhythm
13	.08*	No Vent. effects	45" Vent. rhythm

* Digalen equivalent to .08 mg. ouabain per Kilogram.

Epinephrine, in the doses employed in our study, stimulated the ventricles as evidenced by premature ventricular contractions and ventricular rhythm on the control injection. An agent such as ouabain which depresses supraventricular centers and delays conduction increases the duration and severity of the epinephrine irregularities.

In table 3 are summarized the effects of digitalization on the cardiac response to epinephrine in anesthetized animals. In 24 of 27 experiments the duration of cyclopropane-epinephrine irregularities was sig-

TABLE 3

THE CARDIAC RESPONSE TO THE INJECTION OF EPINEPHRINE IN ANESTHETIZED DOGS BEFORE AND AFTER OUABAIN

Dog No.	Epinephrine	Deep Cyclopropane Anesthesia			Cyclo.-ether Anesthesia
		Cardiac Response to Epinephrine before Ouabain	Ouabain	Cardiac Response to Epinephrine after Ouabain	Cardiac Response to Epinephrine after Ouabain
	mg./Kg.		mg./Kg.		
1	.005	15″ VT; 25″ Bigem. (SA+V)	.05	72″ VT	
	.01	55″ VT	.05	Vent. Fib.	
2	.01	25″ VT	.05	62″ VT	
	.005	No Vent. effects	.07	36″ VT	
	.01	25″ VT	.07	93″ VT	No Vent. effects
3	.005	40″ VT	.05	53″ VT	
	.005	40″ VT	.07	Vent. Fib.	
4	.005	No Vent. effects	.05	32″ VR	
	.01	56″ VT	.05	54″ VT	
	.005	No Vent. effects	.07	120″ VT	
	.01	56″ VT	.07	130″ VT	50″ V. Ex.
5	.005	35″ VT	.05	63″ VT	
	.005	35″ VT	.07	105″ VT	No Vent. effects
6	.005	42″ VT	.05	42″ VT	
	.005	42″ VT	.07	73″ VT	No Vent. effects
7	.005	30″ Bigem. (SA & V)	.05	25″ VR	
	.01	40″ V. Ex.	.05	68″ VT	
	.005	30″ Bigem. (SA & V)	.08	Vent. Fib.	
8	.005	45″ Trigem. (2SA & 1V)	.05	17″ VT; 20″ V. Ex.	
	.005	45″ Trigem. (2SA & 1V)	.08	145″ VT	
9	.005	35″ VT	.05	63″ VT	
	.005	35″ VT	.08	Vent Fib.	
10	.01	25″ V. Ex.	.07	71″ VT	5″ V Ex.
11	.01	30″ V. Ex	.08	55″ VT	
	.01	30″ V. Ex.	.10	92″ VT	
12	.005	28″ VT	.08*	73″ VT	
13	.005	22″ VT	.08*	55″ VT	

* Digulen equivalent to .08 mg. ouabain per kilogram. VT = ventricular tachycardia; V Ex. = ventricular extrasystoles; VR = ventricular rhythm; Vent. Fib. = ventricular fibrillation.

nificantly longer after digitalization. Four of the digitalized animals died of ventricular fibrillation when they were anesthetized with cyclopropane and injected with the test dose of epinephrine.

Of the 5 digitalized animals anesthetized with the cyclopropane-ether-oxygen mixture 3 showed no epinephrine arrhythmias. Of the remain-

ing 2 one had five seconds and the other fifty seconds of ventricular extrasystoles. However, when unanesthetized the same dose of epinephrine had caused ventricular rhythm of one hundred seconds' duration in the first animal. The second had a ventricular rhythm as a result of the ouabain alone. This small series suggests that ether prevents cyclopropane-epinephrine tachycardia in the digitalized dog, as has been demonstrated previously for the unpremedicated animal.

SUMMARY

Cyclopropane tends to shift upward the displaced pacemaker in overdigitalized hearts. Four and a half per cent diethyl ether tends to prevent cyclopropane-epinephrine tachycardia in digitalized dogs.

In unanesthetized dogs digitalization increases the severity and duration of ventricular irregularities resulting from the injection of epinephrine. Digitalization has the same effects on cyclopropane-epinephrine arrhythmias.

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