PREVENTION AND CORRECTION OF VENTRICULAR ARRHYTHMIAS BY DICHLOROISOPROTERENOL IN DOGS ANESTHETIZED WITH CYCLOPROPANE

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THE occurrence of epinephrine induced ventricular arrhythmias in animals anesthetized with cyclopropane was reported by Meek, Hathaway and Orth in 1937.[1] Orth, Stutzman and Meek [2] and Orth, Leigh, Mellish and Stutzman [3] found that arterenol epinine, cobefrin and kephrine also caused arrhythmias when given to dogs anesthetized with cyclopropane but tertiary amines with the catechol nucleus did not produce these cardiac arrhythmias. Stutzman and Pettinga [4] found that methoxamine and phenylephrine did not produce arrhythmias when given dogs anesthetized with cyclopropane. Evidence has been presented that these arrhythmias are not due to the pressor effects of the drugs themselves.[3, 5] Morris, Noltensmeyer and White [6] demonstrated that the injection of 9.7 μg. of epinephrine per kilogram produced ventricular tachycardia in animals anesthetized with either trichloroethylene or cyclopropane. Deterling, Ngai and co-workers [7] found that in comparable doses, norepinephrine produced arrhythmias more frequently than epinephrine when given to dogs anesthetized with cyclopropane.

Moran and Perkins [8] reported on the adrenergic blockade of the mammalian heart by a dichloroanalogue of isoproterenol (β-hydroxy-N-isopropyl-3,4-dichlorophenethylamine hydrochloride (Lilly 20522).[9] They noted that dichloroisoproterenol (DCI) would block the effect of epinephrine and norepinephrine on the contractile force, heart rate and blood pressure of the intact dog which seemed to indicate that this drug would be of interest in the study of arrhythmias produced with the combination of norepinephrine and cyclopropane. This paper will present the results of such a study.

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METHODS

Mongrel dogs varying in weight from 8 to 15 kg. and without premedication were studied. Anesthesia was induced with a 50 per cent mixture of oxygen-cyclopropane and intubation of the trachea was carried out under direct vision with a no. 8 cuffed McGill tube. This was connected to a circle filter Heidbrink gas machine. Cyclopropane concentration was maintained at that flow necessary to keep the animal in surgical anesthesia, plane 2. The femoral artery was cannulated with a Courand needle which was connected to a Statham strain gauge for measuring arterial pressure. This was recorded on a Grass multichannel polygraph. A polyethylene tube was placed in the femoral vein for the injection of drugs. Both systems were intermittently irrigated with normal saline containing heparin. Arterial blood samples were drawn using sealed, oiled syringes and the blood content of carbon dioxide, oxygen and cyclopropane were determined by using the method of Orcutt and Waters.[10] Norepinephrine solutions were prepared as to give a concentration of 8 or 16 μg. of free base of norepinephrine per milliliter. DCI was prepared for each experiment so as to give a concentration of 10 mg./ml. in normal saline. The electrocardiogram was recorded both on the Grass multichannel polygraph and also on the Sanborn direct writer cardioscope. Respirations were assisted for pulmonary ventilation. After the dog had reached a steady state, plane 2, approximately 30 to 40 minutes post-induction, blood samples were drawn and infusion of norepinephrine was begun in a regulated drip into the femoral vein. The norepinephrine infusion was kept at a constant, measured rate during each experiment. When ventricular multifocal extrasystoles occurred, the norepinephrine solution was discontinued and the time required to return to a normal sinus rhythm was ob-

served and recorded. This challenge was repeated after a rest of 10 minutes.

In 3 dogs, DCI was given after a rest period of 10 minutes, norepinephrine was again infused and the presence or absence of arrhythmias noted and blood samples for gas analyses drawn. In the remainder of the dogs (5), at the time of the second infusion of norepineph-

TABLE 1A

SHOWING THE TYPE OF ARRHYTHMIA, DOSE OF NOREPINEPHRINE TO PRODUCE ARRHYTHMIA, AND TIME TO RETURN TO NORMAL SINUS RHYTHM; INCLUDES CONCENTRATIONS OF CARBON DIOXIDE, OXYGEN AND CYCLOPROPANE

Number of Dog	Weight of Dog, kg.	Type of Arrhythmia*	Number of Trials	Dose of Norepinephrine, μg.	Time in Sec. to Produce Arrhythmia	Time in Sec. to Return to Sinus Rhythm	Blood* Pressure, mm. of Hg	Pulse	CO_2, Vol.%	O_2, Vol.%	C_3H_6, mg.%
1	15	V.T.	2	16	60	60	200/110	grossly irreg.	36.7	18.03	11.3
2	18	V.F.	1	16	60	Died	170/110	grossly irreg.	31.98	19.9	17.7
3	12	V.F.	1	30	30	Died	200/130	grossly irreg.	32.6	21.3	17.1
4	8.1	M.F.V.ex.	2	20	30	70	170/130	grossly irreg.	33.5	21.5	21.2
5	8	M.F.V.ex.	2	20	30	80	225/80	grossly irreg.	34.14	19.5	17.9
6	10.5	M.F.V.ex. V.T.	2	16	20	60	210/110	grossly irreg.	34.3	19.1	17.1
7	14.9	M.F.V.ex.	2	40	60	60	200/180	grossly irreg.	41.5	18.3	11.0
8	10.5	M.F.V.ex.	2	24	30	120	220/160	grossly irreg.	40.9	17.6	17.7
9	15	M.F.V.ex.	2	22	15	120	220/120	grossly irreg.	32.1	18.1	21.5
10	15	M.F.V.ex.	2	50	50	50	200/110	grossly irreg.	37.7	19.5	19.4
10	Two hours after anesthesia: no arrhythmia								30.6	17.7	15.8

* Following infusion of norepinephrine.
V.T.: Ventricular Tachycardia.
V.F.: Ventricular Fibrillation.
M.F.V.ex.: Multifocal Ventricular Extrasystoles.

TABLE 1B

SHOWING THE AMOUNT OF DICHLOROISOPROTERENOL TO PREVENT OR CORRECT ARRHYTHMIAS AND THE AMOUNT OF NOREPINEPHRINE GIVEN WITHOUT ARRHYTHMIA; INCLUDES CONCENTRATIONS OF CARBON DIOXIDE, OXYGEN AND CYCLOPROPANE

Number of Dog	Dose of DCI in mg.		Time in Sec. to Return to Sinus Rhythm	Blood* Pressure, mm. of Hg	Pulse	Norepinephrine in mg. After DCI Without Arrhythmia	CO_2, Vol.%	O_2, Vol.%	C_3H_6, mg.%
	To Prevent Arrhythmia	To Stop Arrhythmia							
1	15			180/110		1	35.3	15.7	16
2									
3									
4	8			240/140	120	.5	32.9	20.6	18.5
5	20			180/100	220	.4	30.5	19.28	16.11
6		20	24	180/100	108	.1	32.9	18.8	18.2
7		28	30	180/80	130	.2	35.9	17.0	14.4
8		20	20	200/120	144	.1	38.5	18.2	18.4
9		30	30	220/120	144	.5	30.5	16.10	19.2
10		28	10	220/120	120	.4	37.3	18.9	18.3

* Following infusion of norepinephrine.

rine, DCI was given intravenously at the height of arrhythmia and the time required to return to normal sinus rhythm was again observed and recorded and blood samples taken. Following the return to normal rhythm, norepinephrine infusion was begun and absence or presence of arrhythmias noted. In 3 of these dogs, cyclopropane concentration was increased and after 15 minutes norepinephrine given again at the same rate and for the same duration as previously. If arrhythmias occurred, DCI was again given to convert the heart action to a normal sinus rhythm. Blood samples were drawn.

RESULTS

The results of these experiments are shown in table 1a and 1b. In all dogs, ventricular multifocal extrasystoles or ventricular tachycardia were produced by the infusion of 0.8 μg. to 3 μg./kg. of free base of norepinephrine per minute. Two animals, numbers 2 and 3,

died of ventricular fibrillation before norepinephrine infusion could be discontinued. In animals, 1, 4 and 5, following an intravenous injection of 1–2 mg./kg. of DCI, arrhythmias were not produced by the infusion of norepinephrine in amounts up to 1 mg. In one animal, number 1, a single injection of 1 mg. of undiluted norepinephrine failed to produce arrhythmias.

Following the injection of DCI there was a decrease in the arterial pressure in the three animals, 1, 4 and 5. These were of the order of 160/90 to 120/70; 190/110 to 110/60; and 190/150 to 140/110. These decreases in pressure lasted approximately 60 seconds and the pressure then returned to normal levels. In each of these cases a pressor response followed when norepinephrine was given after DCI. This is shown in figure 1. In the 5 animals given DCI at the height of the arrhythmias, the time required to return to a normal sinus rhythm was reduced 50 per cent as shown in figure 2. Figure 2(b) also shows that the pressor response remained elevated after the DCI was given and after the rhythm had returned to normal.

In the 5 animals given DCI at the height of arrhythmias, the time required to return to a normal sinus rhythm was reduced 50 per cent as shown in figure 2. Infusions of norepinephrine following the reversion to a sinus rhythm failed to produce arrhythmias. A pressor response to norepinephrine was present in all cases. Figure 3 shows typical electrocardiograms in this series. In some dogs it was necessary to give an additional dose of DCI to convert from a nodal sinus rhythm to a normal sinus rhythm. This is included in the total dosage and the time recorded is the time necessary to return to a normal sinus rhythm. One animal (10, table 1) after a resting period of 2 hours without anesthesia, was again anesthetized and norepinephrine infusion again begun. Arrhythmias failed to appear. The average dose of DCI to stop arrhythmias was approximately 1.9 mg.

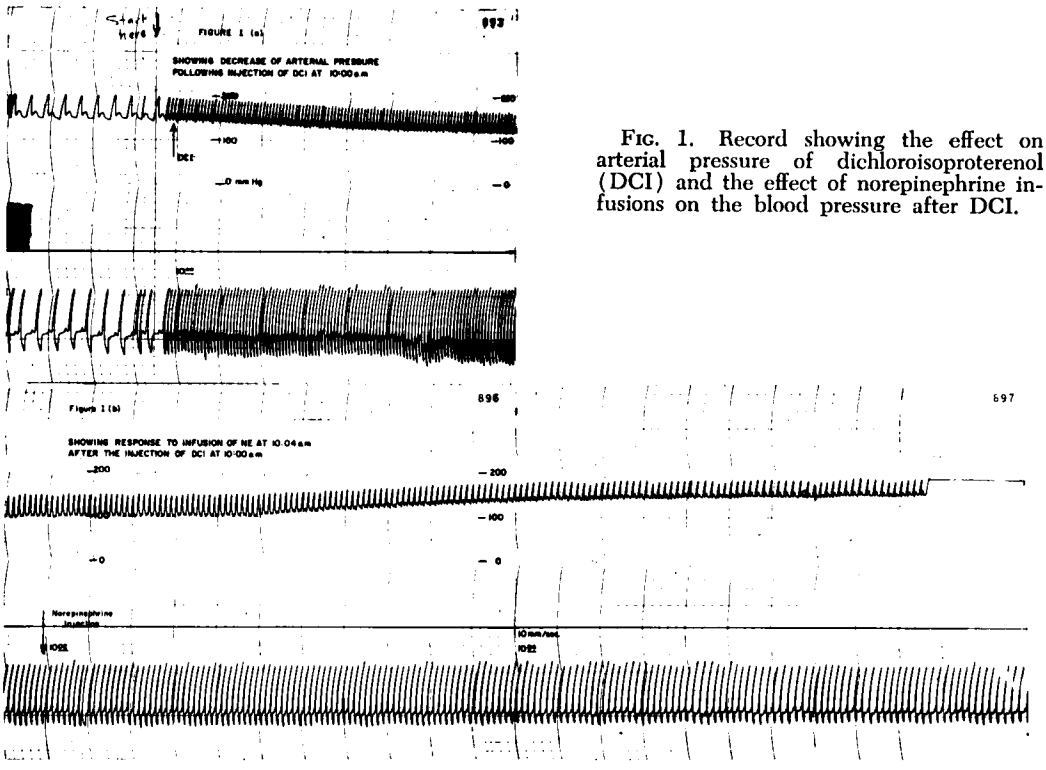

FIG. 1. Record showing the effect on arterial pressure of dichloroisoproterenol (DCI) and the effect of norepinephrine infusions on the blood pressure after DCI.

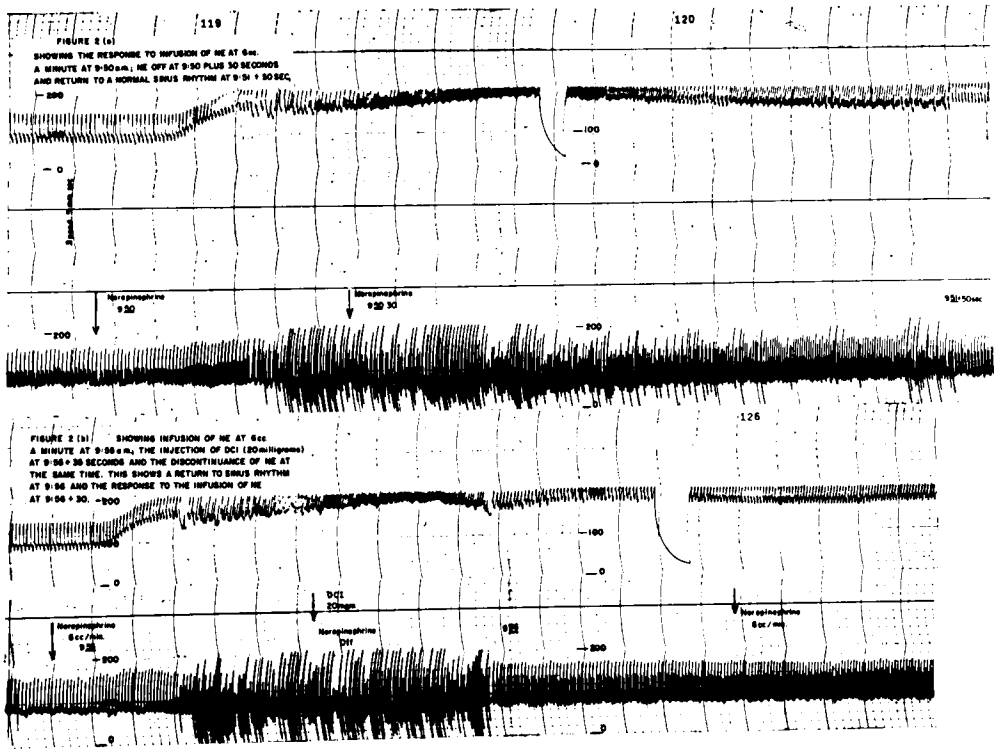

FIG. 2. Record showing the difference in time to return to a normal rhythm following termination of norepinephrine infusion and the time taken to return to normal when dichloroisoproterenol was given.

/kg. Table 2 shows the data from 3 animals, 8, 7 and 5 of table 1, in which infusions of norepinephrine up to 0.4 mg. after DCI failed to produce arrhythmias. After breathing a 50 per cent mixture of cyclopropane for approximately 15 minutes, the same amount of norepinephrine was again infused and in 2 cases multifocal ventricular extrasystoles, and in one case, bigeminal rhythm occurred. These were converted to a normal sinus rhythm with additional amounts of DCI in doses of 1.1 mg./kg.

TABLE 2A

SHOWING THE AMOUNT OF DCI GIVEN AND OF NOREPINEPHRINE INFUSED AND THE CONCENTRATION OF GASES THAT PRODUCED NO ARRHYTHMIAS

Number of Dog	Weight of Dog	DCI Dose, mg.	Norepinephrine Dose, mg.	CO_2, Vol.%	O_2, Vol.%	C_3H_6, Vol.%
7	14.9	28	.2	35.0	17.0	14.4
8	10.5	20	.1	32.9	18.8	18.2
5	8	28	.4	30.5	19.28	16.1

DISCUSSION

The prevention of cardiac arrhythmias in animals anesthetized with cyclopropane and challenged with epinephrine or norepinephrine and the prevention of spontaneous arrhythmias occurring in man anesthetized with cyclopropane have been investigated by several workers. Nickerson and Smith [11] found that Dibenamine in dosages of 20 mg./kg. would prevent arrhythmias which had been previously produced by the injection of epinephrine into a dog anesthetized with cyclopropane. They found the dose necessary to prevent cardiac irregularities to be greater than that to block the pressor response. Later, Nickerson and Brown [12] found in 20 adult males that 5 to 6 mg./kg. of Dibenamine caused a slight reduction in spontaneous arrhythmias with cyclopropane, a dose of 7 to 7.5 mg./kg. prevented the occurrence of these spontaneous

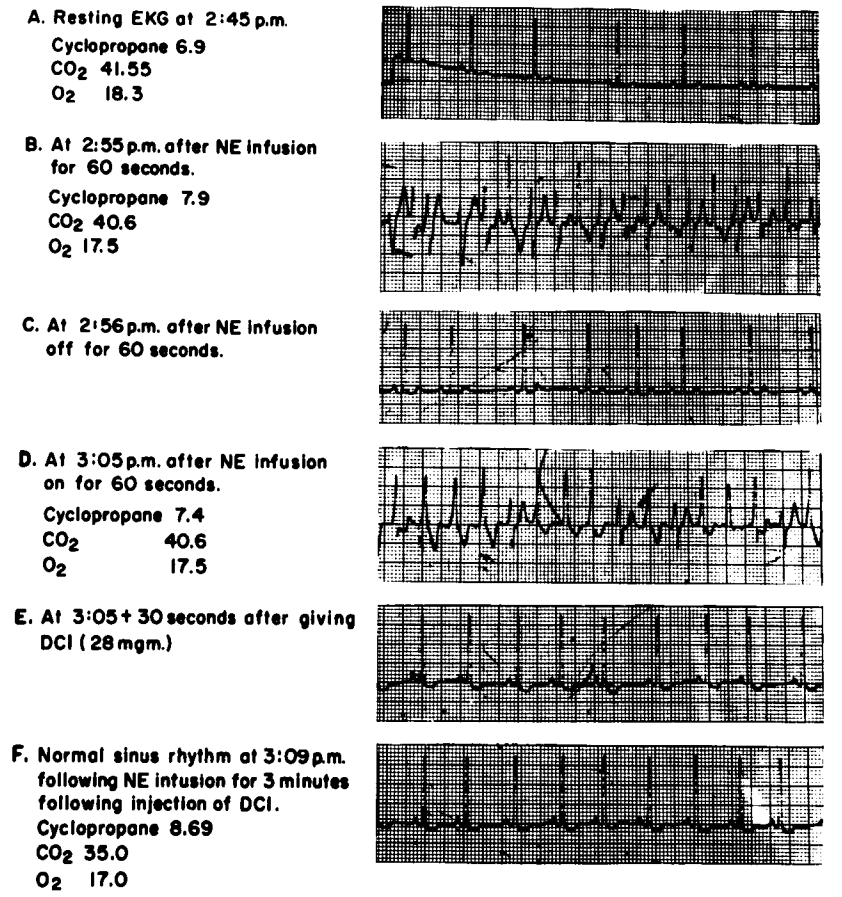

FIG. 3. Changes in cardiac rhythm with infusion of norepinephrine and the time of return to normal and effect of dichloroisoproterenol on this time. These are related to concentrations of cyclopropane, oxygen, and carbon dioxide.

arrhythmias. In neither of these studies was the Dibenamine able to correct an arrhythmia once it had been established. McMillan, Hampton and Drill [13] were also able to show that 20 mg./kg. of Dibenamine in dogs anesthetized with cyclopropane increased by tenfold the amount of epinephrine needed to produce arrhythmias. Drill and Hays,[14] in studying the effect of halogenated ethylamine in cardiac arrhythmias, found 3 drugs that offered some protection against epinephrine-cyclopropane arrhythmias and raised the

TABLE 2B

SHOWING THE AMOUNT OF NOREPINEPHRINE, CONCENTRATION OF GASES AFTER CYCLOPROPANE INCREASED TO 50–50 MIXTURE AND AMOUNT OF DCI TO CORRECT ARRHYTHMIAS

Norepinephrine Dose, mg.	Arrhythmia	CO_2, Vol.%	O_2, Vol.%	C_3H_6, Vol.%	DCI in mg.	Time in Sec. to Return to Sinus Rhythm
.176	M.F.V.ex.	41.6	16.4	18.7	20	30
.1	M.F.V.ex.	41.97	17.2	26.9	10	35
1	Bigeminy	46.5	20.0	31.0	10	31

threshold to injected epinephrine. Morris and co-workers [15] found that in animals, phenatolamine (Regitine) would prevent arrhythmias in 5 of 7 dogs anesthetized with cyclopropane and challenged with epinephrine; but that it was ineffective in reducing the spontaneous arrhythmias occurring in human subjects anesthetized with cyclopropane. Corssen, Eggers, Gadermann and co-workers,[16] studying myocardial irritability in dogs anesthetized with cyclopropane, showed that in 16 dogs given a phenothiazine derivative, mepazine (Pacatal), that the occurrence of arrhythmias was decreased or prevented when this phenothiazine compound was given before the challenging dose of epinephrine. Winbury, Martin, Hausler and Wolf,[17] in testing four phenothiazine derivatives, found that one, perphenazine, was most effective of the four drugs—perphenazine, chlorpromazine, promazine and mepazine.

The observation of Moran and Perkins [8] indicate that the site of action of DCI is to block the receptors of the Beta type according to the Ahlquist terminology for catechol amines.[18] They believe that these receptors, which are inhibitory in other organs, are excitatory in the heart and have to do with the inotropic and chronotropic effect of the catecholamines. It would seem that from this study, these receptors have also to do with the excitability of the myocardial tissue. Lucchesi [19] has found that DCI will correct arrhythmias produced by ouabain both in intact dogs and in the dog heart-lung preparation. Kukovetz and Hess and co-workers [20] attempted to relate the increase of inotropic effect of epinephrine and norepinephrine to the conversion of phosphorylase B to phosphorylase A in the myocardium. Mayer and Moran [21] believe that DCI prevents the activitation of myocardial phosphorylase by epinephrine as it blocks the inotropic effect of epinephrine. Further studies on this are being carried out at the present time.

DCI has not been made available for clinical use. If this drug is effective in preventing arrhythmias in man with the combination of cyclopropane and norepinephrine, it might prove useful from three standpoints. One, in correcting the spontaneous arrhythmias that occur under cyclopropane anesthesia; two, by its specific action it will be a valuable tool for the study of the etiology of these arrhythmias; and three, to make it possible to use norepinephrine with cyclopropane.

Summary

Dogs anesthetized with cyclopropane have been given challenging doses of norepinephrine. In 3 dogs following the administration of dichloroisoproterenol (DCI), it was possible to infuse large amounts of norepinephrine without altering a sinus rhythm. In all dogs the pressor effect of norepinephrine was still present. In 5 dogs, multifocal ventricular extrasystoles or ventricular tachycardia were stopped by the intravenous injections of DCI, 1.9 μg./kg., and in each case the subsequent infusion of norepinephrine failed to produce arrhythmias. A pressor effect was present. When the concentration of cyclopropane was increased and the same challenging dose of norepinephrine which had previously failed to produce arrhythmia was given, arrhythmias did occur. These were reverted to a normal sinus rhythm by subsequent injections of DCI.

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HYPOTHERMIA Cardiac arrest by hypothermia, and 30 minutes of ischemia, resulted in little impairment of ventricular function in animals. It was necessary to keep the temperature of the heart below the level at which ventricular fibrillation occurs. General body hypothermia to 15 C. was found more satisfactory than coronary perfusion with cold solutions. (*Willman, V. L., and others: Ventricular Function After Hypothermic Cardiac Arrest, A. M. A. Arch. Surg. 82: 120 (Jan.) 1961.*)

HYPOTHERMIA Animals cooled to 10 C. had oxygen consumption reduced to one sixth of normal. A low-flow perfusion, however, was unable to furnish enough oxygen. Oxygen tension of cerebrospinal fluid drops to zero in 2 minutes at normal temperature; at 10 C. this takes 18 minutes to occur. During rewarming, metabolic acidosis was proportional to the duration of hypothermia. Cooling below 20 C. was survived by 3 out of 4 patients. (*Neville, W., and others: Profound Hypothermia and Complete Circulation Interruption, A. M. A. Arch. Surg. 82: 108 (Jan.) 1961.*)