

Influence of Reserpine on Cardiovascular and Sympatho-Adrenal Responses to Cyclopropane Anesthesia in the Dog

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The cardiovascular and sympatho-adrenal responses to cyclopropane anesthesia were compared in normal and chronically reserpinized dogs. The results demonstrate that reserpine-treated animals are able to withstand concentrations of cyclopropane as high as those withstood by nontreated animals, even though mean aortic pressure, heart rate and increments in plasma levels of epinephrine were found to be significantly lower in the reserpine-treated animals. On the other hand, ventricular contractile force and aortic flow values were similar in both groups of animals at comparable levels of anesthesia.

SEVERAL reports¹⁻⁴ in recent years have indicated an increased incidence of hypotension during anesthesia in patients who have received *Rauwolfia* compounds. On the other hand, Munson *et al.*⁵ failed to find an increased incidence of hypotension in patients receiving reserpine. Also, Morrow and associates⁶ recently reported no complications in non-hypertensive patients given reserpine experimentally prior to anesthesia with halothane. They concluded that the complications seen by others may be due to the underlying cardiovascular disease rather than to reserpine.

In a recent study⁷ from this laboratory, it was reported that cardiovascular responses to ether anesthesia in dogs are not significantly altered by pre-treatment with reserpine. On the other hand, sympatho-adrenal stimulation, as measured by increments in plasma catecholamines, was greatly suppressed during ether

anesthesia in these animals. The present experiments extend this study to include cyclopropane.

Methods

Twenty-four experiments were performed on 15 mongrel dogs, each weighing approximately 12 kg. (range 11–13 kg.). These animals were selected in this narrow weight range in order to conform to a fixed flowmeter probe size. Five animals received 0.03 mg./kg./day of reserpine (Serpasil) intramuscularly for 2–3 weeks prior to the experiment. Ten animals received no medication and served as controls. Ventricular contractile force was measured with a strain gauge arch⁸⁻¹⁰ and aortic pressures with a Statham transducer. Total aortic flow (cardiac output minus coronary flow) was measured with a square-wave electromagnetic flowmeter.* Heart rate was also computed electronically and all parameters were recorded on a Grass polygraph. Plasma epinephrine and norepinephrine levels were determined by a modification¹¹ of the fluorimetric ethylenediamine condensation method.¹² Arterial blood pH changes † were also monitored periodically in most experiments, and an attempt was made to maintain this parameter at near normal levels by regulating the respiratory minute volume.

All animals were prepared the day preceding the initial experiment by suturing a strain gauge arch to the right ventricle through a thoracotomy made between the fourth and fifth ribs. A flowmeter probe was placed around the ascending aorta and polyethylene cannulae inserted through a femoral artery and

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* Carolina Electronics, Inc., Winston-Salem, North Carolina.

† Instrumentation Labs, Inc., Boston, Massachusetts.

vein into the abdominal aorta and vena cava, respectively. The operation was performed under thiamylal (Surital) anesthesia. The incisions were then closed, penicillin and streptomycin administered, and the animals allowed to recover from anesthesia. On the experimental day, control readings of all parameters were taken while the animals were fully conscious and after they had become accustomed to the surroundings. Arterial samples for catecholamine determinations were also taken at this time. Anesthesia was then induced with 50 per cent cyclopropane in oxygen using a Foregger closed to-and-fro system containing a carbon dioxide absorption canister. Following induction, the tracheas were intubated with cuffed endotracheal tubes and the lungs artificially ventilated with a Harvard respirator at a rate of approximately 12 times a minute with a tidal volume of 20-25 ml./kg. Total gas flows of 500 ml./minute were used throughout. The animals were then placed on a 20 per cent concentration of cyclopropane. This concentration was found in most instances to be the lowest at which the animals could tolerate an endotracheal tube without eliciting tracheal reflexes. The lungs were ventilated with each concentration for a period of 20-30 minutes to allow for stabilization. The reservoir bag was emptied prior to change of concentration.

Results were analyzed using Student's *t* test

or the "test of difference" modification of this test.¹³ A *P* value of less than 0.05 was considered significant.

Results

Figures 1-5 summarize changes in mean aortic pressure, ventricular contractile force, total aortic flow, stroke volume (total aortic flow/heart rate), and heart rate during ventilation with increasing concentrations of cyclopropane. These figures represent average results from 15 experiments on 10 animals receiving no premedication and 9 experiments on 5 animals pretreated with reserpine. The results are also summarized in tabular form in table 1.

Figure 1 depicts changes in mean aortic pressure during cyclopropane anesthesia in control and reserpine pre-treated animals. The control animals showed no significant changes in mean pressure until the concentration of cyclopropane was increased to 75 per cent. At this time, there was a marked drop in pressure; however, on discontinuing the anesthetic, mean pressure returned to levels significantly higher than preanesthetic values. It should be noted that in some animals there was a slight increase in pressure when the animals were placed on 50 per cent cyclopropane. The animals pre-treated with reserpine showed a similar pattern of responses except that the decrease in pressure during

TABLE 1. Summary of Changes in Cardiovascular Dynamics During Cyclopropane Anesthesia in Control and Reserpinized Animals (Values = Mean ± S.E.)

	Conscious		Per cent Cyclopropane						Rebound	
	Control	Reserpine	20		50		75		Control	Reserpine
			Control	Reserpine	Control	Reserpine	Control	Reserpine		
Mean aortic pressure (mm. Hg) ± S.E.	99 5	70* 6	90 8	58*† 5	99 5	58* 9	46† 5	24*† 9	113‡ 7	123‡ 11
Contractile force (grams) ± S.E.	78 7	64 9	62† 7	52† 8	49† 6	36† 7	40† 6	29† 9	85 9	64 7
Aortic flow (ml./min.) ± S.E.	1,402 139	1,197 168	1,170† 116	838† 138	852† 66	629*† 70	589† 90	355† 90	1,574 145	943* 116
Heart rate (beats/min.) ± S.E.	138 10	89* 8	129 7	78* 6	133 8	65* 6	107† 8	60* 7	143 9	94* 7
Stroke volume (ml./beat) ± S.E.	11.43 1.15	14.04 1.94	10.08 1.13	13.11 2.36	6.76† 0.63	9.20 1.55	6.46 1.07	7.30† 1.89	10.54 1.33	11.11 2.01

* Significantly different from control animals at a comparable level of anesthesia.
† Significantly different from values obtained at preceding level of anesthesia.
‡ Significantly different from conscious values.

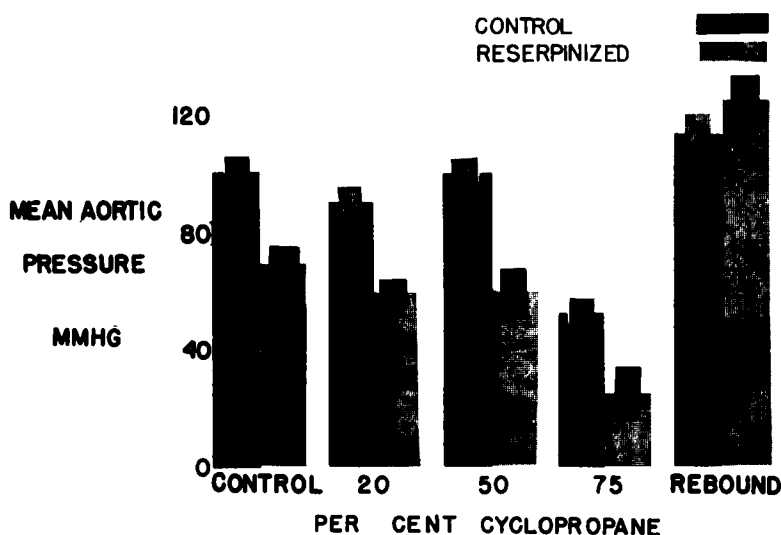


FIG. 1. Changes in mean aortic pressure during inhalation of increasing concentrations of cyclopropane in control (10 animals, 15 experiments) and reserpine pre-treated animals (5 animals, 9 experiments). The reserpine pre-treated animals had received 0.03 mg./kg. of reserpine intramuscularly daily for 2-3 weeks prior to the experiment. Values obtained at each concentration were compared to values at the previous level. Comparisons were also made at each concentration between the mean pressures of the control and reserpine pre-treated animals. The "control" and "rebound" beneath the first and last pairs of bars in this and subsequent graphs represent the preanesthetic and postanesthetic periods, respectively.

inhalation of 20 per cent cyclopropane was of borderline significance ($P < 0.05$). Comparisons made between the two groups of animals demonstrated significantly lower pressures in the animals pre-treated with reserpine both before and during anesthesia.

Contrary to the changes in mean aortic pressure, ventricular contractile force (fig. 2) in both groups of animals was found to be

progressively depressed as the concentration of cyclopropane was increased. On discontinuing the anesthetic, contractile force values of both groups returned to preanesthetic levels. Also, comparisons of results from the two groups of animals revealed no significant differences in contractile force either before, during, or following anesthesia with cyclopropane, although there was a trend for the

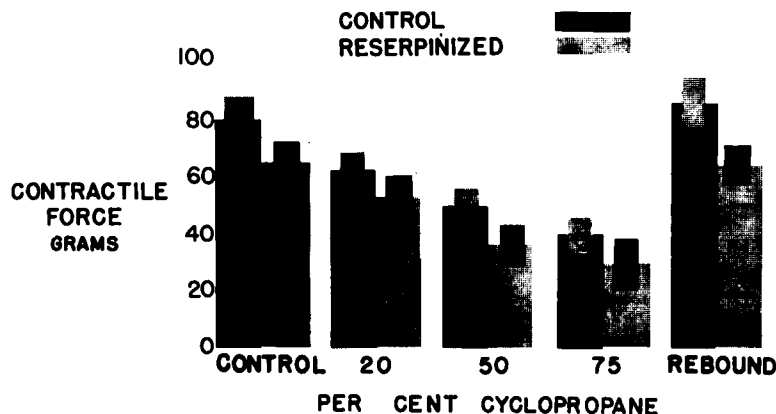
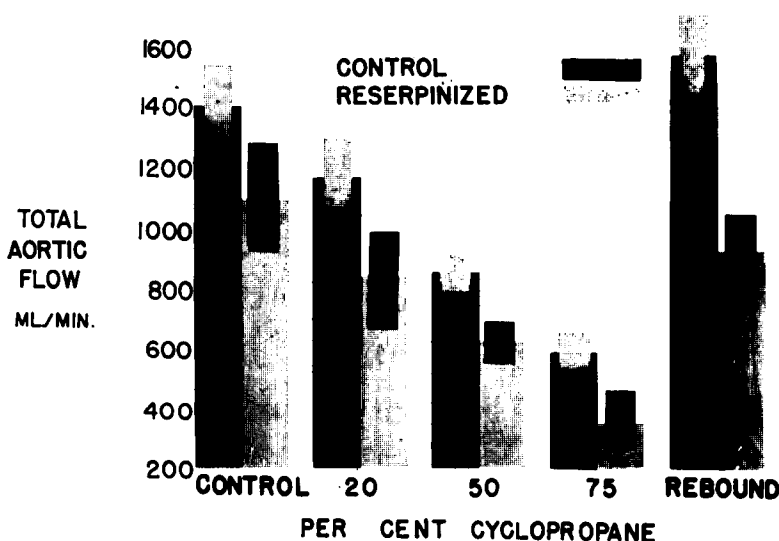


FIG. 2. Changes in ventricular contractile force in control and reserpine pre-treated animals during cyclopropane anesthesia. Experimental conditions in this and subsequent figures are similar to those described in figure 1.

FIG. 3. Changes in total aortic flow (cardiac output-coronary flow) during anesthesia with cyclopropane in control and reserpine-treated animals are illustrated in this graph.



values to be lower in the reserpine pre-treated animals.

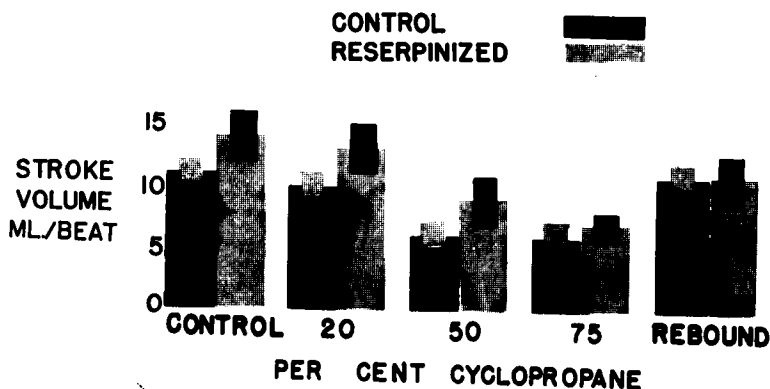
Figure 3 depicts changes in total aortic flow during cyclopropane anesthesia. Similar results were found for both groups of animals. Significant decrements in total aortic flow were found at each concentration of cyclopropane when compared to the preceding concentration. On removing the anesthetic from the inspired air, flow values returned to pre-anesthetic levels. When comparisons were made between the two groups of animals, there was a trend for the mean flow values to be lower in the reserpine-treated animals. However, due to the degree of variation, this difference was only statistically significant during inhalation of 50 per cent cyclopro-

pane and during the postanesthetic "rebound" period.

Figure 4 illustrates changes in stroke volume (total aortic flow/heart rate) during cyclopropane anesthesia. In both groups of animals stroke volume was not significantly altered until deep levels of anesthesia were attained (50-75 per cent). When anesthesia was discontinued the values returned to near pre-anesthetic levels. No significant difference was found between the stroke-volume values of the two groups of animals at any point, although there was a trend for stroke volume to be higher in the reserpine-treated animals.

Figure 5 depicts mean changes in heart rate during inhalation of increasing concentrations of cyclopropane. Heart rate was not signifi-

FIG. 4. Changes in stroke volume (total aortic flow/heart rate) during cyclopropane anesthesia in the two groups of animals.



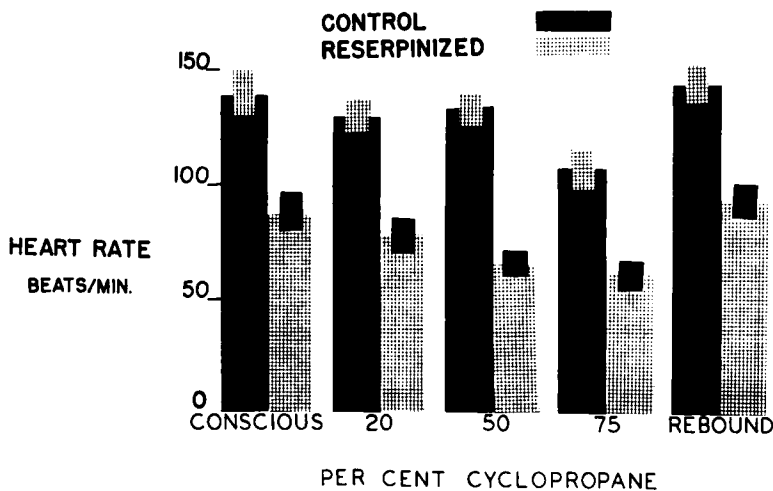


FIG. 5. Changes in heart rate in control and reserpine pretreated animals during inhalation of increasing concentrations of cyclopropane.

cantly changed from preanesthetic values in either group of animals until inhalation of 75 per cent of the agent. When comparisons were made between the two groups of animals, heart rate in the reserpine-treated animals was found to be significantly lower both before and during anesthesia.

In most experiments pH measurements were taken periodically to insure against the development of respiratory acidosis. The mean pH value of both groups before anesthesia was $7.404 \pm \text{S.E. } 0.066$ compared to a mean of 7.409 ± 0.048 during anesthesia.

Changes in circulating catecholamines during cyclopropane anesthesia are summarized in table 2. The conscious levels of both amines were found to be significantly lower in the animals pre-treated with reserpine. During anesthesia, plasma norepinephrine levels were not significantly elevated from preanesthetic values at any time in either the control or the reserpine-treated animals. On the other hand, plasma epinephrine levels were found to be significantly elevated during all levels of anesthesia in the control animals and also during deep anesthesia and the rebound period in the reserpine-treated animals. Also, it should be noted that the increments in epinephrine were significantly greater in the control animals when compared to the increments in the reserpine pre-treated animals at comparable levels of anesthesia.

Discussion

The present series of experiments was designed to compare cardiovascular and sympatho-adrenal responses to cyclopropane anesthesia in normally and chronically reserpine-treated dogs.

Control Studies. The results indicate that in nontreated animals the force of contraction of the myocardium, as measured by the strain gauge arch, is progressively depressed as the concentration of cyclopropane is increased. Boniface and co-workers¹⁴ using this technique with cyclopropane have also reported progressive decrements in contractile force as the depth of anesthesia was increased from stage 3, plane 1.

Mean aortic pressure was found not to be significantly altered until extreme depths of anesthesia were reached. On discontinuing anesthesia, the mean pressure was found to "rebound" to a level significantly higher than the preanesthesia control level. Other investigators have found arterial pressure to be increased significantly from preanesthetic levels in both dog and man during anesthesia with cyclopropane. Price *et al.*¹⁵ attribute these increments to the release of catecholamines. Although an increase in pressure was seen in some experiments, a slight but insignificant decrease was more prevalent in the present study. However, there was a tendency for aortic pressure to increase somewhat when the

TABLE 2. Changes in Plasma Catecholamine Levels During Cyclopropane Anesthesia in Control and Reserpinized Animals

Depth of Anesthesia	Control (12)		Reserpinized (9)	
	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
	μg./Liter of Plasma		μg./Liter of Plasma	
Conscious	2.91 ± .21	.90 ± .08	.89 ± .16*	.14 ± .02*
Values = Mean changes from conscious levels ± S.E.				
Light	0.0 ± .50	2.30 ± .92†	-.23 ± .20	.13 ± .10*
Deep	1.35 ± .97	3.67 ± 1.23†	-.07 ± .20	1.12 ± .13*†
Emergence	1.88 ± 1.40	3.75 ± .98†	.19 ± .41	1.60 ± .52*†

() Number of experiments.

* Significantly different from control animals.

† Significantly different from preanesthetic levels.

animals were placed on a 50 per cent concentration. Millar *et al.*¹⁶ have also noted slight decreases in systolic pressure during cyclopropane anesthesia.

Total aortic flow was found to be progressively depressed as the concentration of cyclopropane was increased. These results differ from those of Robbins and Baxter,¹⁷ who found mean cardiac output in nonpremedicated dogs to be elevated 45 per cent above control during light surgical anesthesia. However, these variations from the present results may be attributed to differences in depth of anesthesia.

Plasma levels of epinephrine were found to be significantly elevated above conscious values during all stages of anesthesia, as well as during the postanesthetic rebound period. Circulating norepinephrine levels were not significantly altered at any time. Other investigators have previously reported increments in catecholamines during cyclopropane anesthesia in both patients^{16, 18-20} and animals.^{16, 21} In general, these results have shown increments in the epinephrine fraction in animals, while in man the norepinephrine fraction is elevated. The present results are qualitatively in agreement with this previous work. On the other hand, Carnes *et al.*²² were unable to demonstrate increments in either amine during cyclopropane anesthesia in animals.

Reserpine Studies. In general, the responses to cyclopropane anesthesia in the reserpinized

animals paralleled those found in the non-treated animals. The most striking difference noted in comparing reserpine-treated animals with the control group was the significantly lower heart rates and aortic pressures seen in the reserpinized animals both before and during anesthesia. Comparison of the differences in other parameters is complex because of their interdependence and because of the variability existing in experiments of this nature. For example, although the differences in total aortic flows and stroke volumes between the two groups of animals were not statistically significant, there was a tendency for the stroke volumes to be higher in the reserpinized animals and a consistent tendency for aortic flows to be lower. It would appear likely that the combined effect of these would equal the significance of the difference observed in heart rate. These results are in general agreement with a similar study reported by Rusy *et al.*²³

In general, plasma catecholamine levels were not significantly altered during light levels of anesthesia in the reserpinized animals. However, during deep anesthesia and during the postanesthetic rebound period, circulating epinephrine levels were significantly elevated above the preanesthetic control values. When the preanesthetic catecholamine levels of the reserpinized animals were compared to those of the control animals, it was found that both amines were significantly

lower in the former. Similar comparisons made during and after emergence from anesthesia showed no significant differences in the norepinephrine fraction at any level, but significantly lower increments in epinephrine were found in the reserpinized animals during both light and deep levels of anesthesia.

Since it is believed that increased sympathoadrenal activity is instrumental in maintaining circulatory homeostasis during cyclopropane anesthesia, one might anticipate that the reserpine-treated animals with diminished sympathetic activity would be affected to a greater degree by anesthesia with this agent. However, this was not found to be true in the present experiments. One possible explanation is that large amounts of circulating amines are not needed to maintain circulation and that catecholamines are still being liberated in effective concentrations at the receptor sites in the myocardium and peripheral vessels. Also, numerous investigators have shown that reserpine pretreatment results in increased sensitivity to catecholamines.

The data from the present experiments demonstrates that reserpine-treated animals are able to withstand concentrations of cyclopropane as high as those withstood by non-treated animals, even though increments in plasma levels of epinephrine and some circulatory parameters are somewhat depressed in these animals.

Summary

Cyclopropane anesthesia produced a uniformly progressive decrease in ventricular contractile force and total aortic flow in non-treated animals as the concentration of cyclopropane was increased. On the other hand, mean aortic pressure and heart rate were not significantly changed until deep levels of anesthesia were reached. Plasma levels of epinephrine were significantly elevated during all stages of anesthesia with cyclopropane, while no consistent changes were found in the norepinephrine fraction.

In general the responses in the reserpine-treated animals paralleled those in the non-treated animals. However, mean aortic pressure and heart rate were found to be significantly lower in the reserpine-treated animals before and during anesthesia. On the other

hand, ventricular contractile force, aortic flow, and stroke volume were not found to be significantly different from values obtained in control animals at a comparable level of anesthesia. Significant increments in plasma epinephrine levels in the reserpine-treated animals were found during deep anesthesia and during emergence. The resting levels of both amines were significantly lower in the reserpine-treated animals when compared to those of the control animals. Similar comparisons made during and after emergence from anesthesia revealed no significant difference in the norepinephrine component at any level, but significantly lower increments in epinephrine were found in the reserpine-treated animals during both light and deep levels of anesthesia.

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URINARY RETENTION Dilatation of the anal sphincter inhibits the detrusor activity of the bladder. Filling the bladder induces micturition contractions; the volume required to do this was greatly increased during anal stimulation. This may account for increases of acute urinary retention following anal operations. (*Kock, N. G., and Pompeius, R.: Inhibition of Vesical Motor Activity Induced by Anal Stimulation, Acta Chir. Scand.* 126: 244 (Sep. 5) 1963.)

HYSTERICAL ANESTHESIA Hysterical anesthesia was present in the left arm of a patient. Electroencephalographic-evoked activity was produced by stimulating the normal arm; no change occurred when the left arm was stimulated. Light barbiturate anesthesia was administered, during which stimuli to either arm produced similar evoked potentials. This suggests that during hysterical anesthesia there is functional blockade of sensory transmission. (*Hernandez-Peon, R., Chavez-Ibarra, C., and Aguilar-Figueroa, E.: Somatic Evoked Potentials in One Case of Hysterical Anesthesia, Electroenceph. Clin. Neurophysiol.* 15: 889 (Oct.) 1963.)