Effect of Reserpine on Cardiac Function During Thiopental-Cyclopropane Anesthesia in the Dog

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The effect of thiopental-cyclopropane anesthesia on cardiac output, heart rate, mean arterial blood pressure, and rate of rise of left ventricular pressure in trained dogs before and after reserpine was investigated. Each dog served as his own control both for the effect of anesthesia (conscious *versus* anesthetized) and the effect of reserpine on the response to anesthesia (pre-reserpine *versus* post-reserpine effects of anesthesia).

Anesthesia caused an increase in mean arterial blood pressure and heart rate both before and after reserpine. The depressant effect of anesthesia on the rate of rise of left ventricular pressure was not altered significantly by reserpine. Cardiac output was depressed by anesthesia. The degree of depression was significantly greater following very large doses of reserpine.

HYPOTENSON during general anesthesia has been reported by Coakley and his associates [1] and others [2] to occur with increased frequency and severity in patients receiving reserpine or similar drugs. In opposition to this, more recent clinical [3, 4] and laboratory [5, 6] studies have shown that the circulatory response to general anesthesia is not significantly altered by reserpine.

Since reserpine is known to inhibit the function of the sympathetic nervous system, there is reason to expect that its use might result in an increased depression of the circulation during anesthesia. Price has stated that the administration of either cyclopropane or ether causes an increased activity of the cardiac sympathetic nerves and that this activity counteracts the direct myocardial depressant effect of these anesthetics.[7] In support of this, he and his associates have shown that blockade of the stellate ganglia during cyclopropane anesthesia causes a reduction in cardiac output, heart rate, and mean arterial blood pressure.[8] Since reserpine is capable of blocking the positive inotropic [9] and chronotropic [10] effects of electrical stimulation of the cardiac sympathetic nerves, pretreatment with this drug would be expected to result in a greater than normal depression of cardiac function during cyclopropane or ether anesthesia.

In the light of this reasoning, further investigation of the effects of reserpinization on the circulatory response to general anesthesia seemed warranted. In the study reported here the effects of thiopental-cyclopropane anesthesia on cardiac function before and after the administration of reserpine were compared.

Methods

Cardiac function was evaluated by measurement of cardiac output, mean femoral arterial blood pressure, left ventricular pressure, and heart rate. Stroke volume was computed. The rate of rise of left ventricular pressure during isovolumetric systole (first derivative of left ventricular pressure) as described by Rushmer,[11] was used, as an index of myocardial "contractility."

The study was carried out in healthy mongrel dogs each weighing about 14 kg. Under sterile conditions a left thoracotomy was performed and a polyethylene catheter with flexible stylet was implanted in the left atrium and exteriorized between the scapulae. Anesthesia for this procedure consisted of pentobarbital sodium (30 mg./kg.) and pulmonary hyperventilation with air. Following wound closure, the animals were allowed to convalesce for two weeks during which they were trained to lie

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quietly on their right sides in the laboratory. Control experiments were then performed. With the animals awake, a pressure sensing catheter was passed via the left atrial catheter through the mitral valve into the left ventricle. This provided a means of recording left ventricular pressure, the electrical analog of which was differentiated to yield the rate of change of pressure in the left ventricle. Under anesthesia with lidocaine (Xylocaine) 1 per cent a polyethylene catheter was passed percutaneously through an external jugular vein to the approximate level of the right atrium. Under local anesthesia, a Cournand needle was placed in a femoral artery for recording of arterial blood pressure and withdrawal of arterial blood. Blood was withdrawn by a Harvard infusion-withdrawal pump at a constant rate of 15.3 ml. per minute through a Waters XC-250A densitometer. One milliliter (2.5 mg.) of indocyanine green (Cardiogreen) was injected via the vena caval catheter for each cardiac output determination. For the standardization of the densitometer Cardiogreen was delivered from the same syringe-catheter setup. Transducers for left ventricular pressure and arterial blood pressure were both Statham type P23Db. The differentiator circuit was calibrated by substituting for the waveform of left ventricular pressure a triangular wave (Hewlett-Packard low frequency function generator) of known rate of rise. Recordings of experimental data were made by an Electronics for Medicine research recorder. Figure 1 illustrates a portion of the record from one experiment.

At least three separate sets of determinations of cardiac output, left ventricular pressure and rate of change of pressure, mean arterial blood pressure and heart rate were made with the dogs awake. Anesthesia was then induced with intravenous thiopental sodium, 225 mg. in all experiments. The trachea was intubated with a cuffed endotracheal tube and 25 per cent cyclopropane in oxygen was administered through a Ruben nonrebreathing valve. Cyclopropane was administered by a nonrebreathing technique in order to assure a predictable and reproduceable concentration of the agent in end-expired air. Respirations were controlled with a Bird automatic ventilator. Minute volume of respiration was adjusted so that the partial pressure of CO_2 in end-expired air was approximately 30 mm. of mercury. The concentration of CO_2 was measured with a Beckman/Spinco infrared gas analyzer calibrated with known mixtures of CO_2 in oxygen. The collision-broadening effect of cyclopropane caused an error of approximately +4 per cent in the measurement of CO_2 and this was accounted for. Cyclopropane was administered in the manner described for 45 minutes following which determinations (3 sets) of cardiac output, left ventricular pressure and rate of change of pressure, mean arterial blood pressure and heart rate were again made. Samples of end-expired air were analyzed for cyclopropane content (Orsatt technique). During anesthesia, lead 2 of the electrocardiogram was monitored. Measurements were not made during periods of irregular rhythm. Arrhythmias were not frequent and occurred most often prior to administration of reserpine.

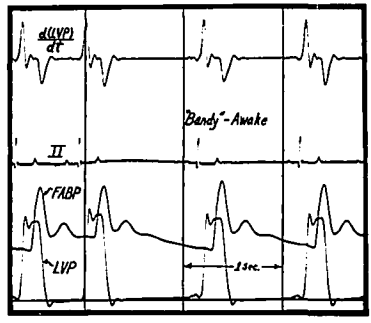

FIG. 1. Portion of record from one experiment, unanesthetized animal. Tracings from above downward: rate of change of left ventricular pressure, ECG-lead 2, femoral arterial blood pressure, and left ventricular pressure. Dye dilution curve for cardiac output not shown.

One day after the control experiment, the intramuscular administration of reserpine (Serpasil), 10 μg./kg./day, was begun and continued for 10 days. For the dog, this amount of reserpine, subsequently to be referred to as the smaller dose, has been found to cause depletion of myocardial norepinephrine [12] and complete inhibition of the cardiac response to electrical stimulation of the car-

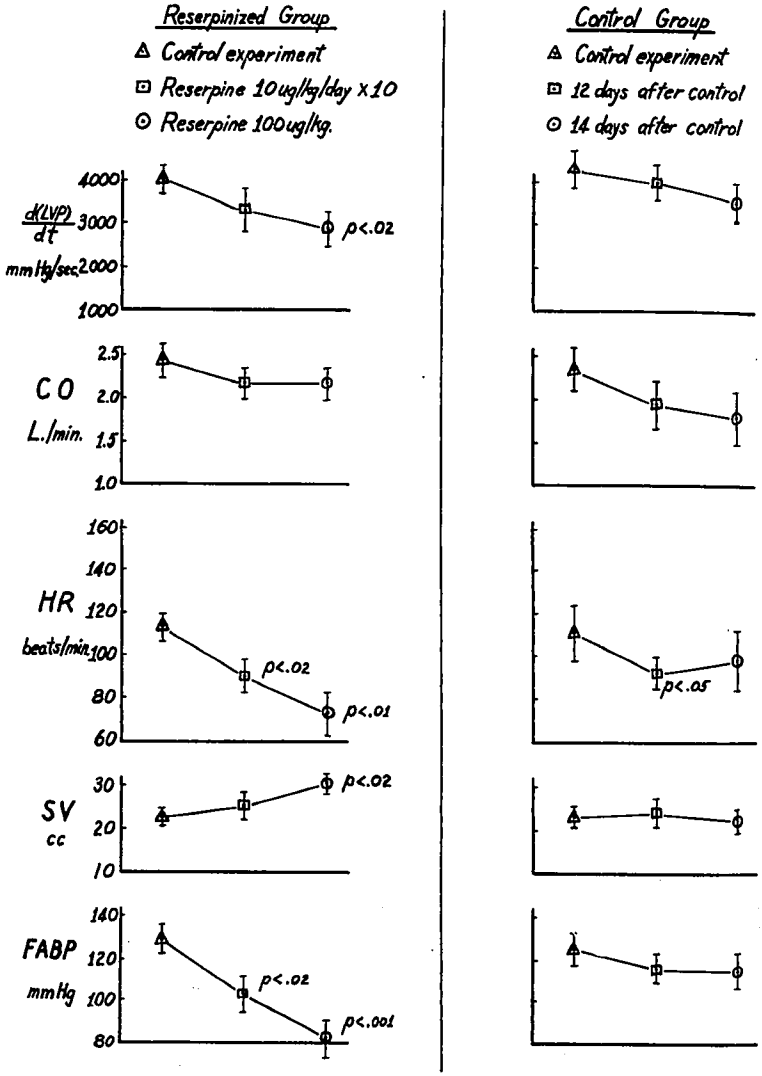

FIG. 2. Effect of reserpine in the treated (reserpinized) group and passage of time in the untreated (control) group. (Values are for conscious animals.) △—control experiment before reserpine or passage of time. ⊡—same animals following reserpine 10 μg./kg./day × 10 or following 12 days without reserpine. ⊙—same animals after additional reserpine (100 μg./kg.) or after 2 more days without reserpine. d(LVP)/dt—rate of rise of left ventricular pressure during isovolumetric systole. C.O.—cardiac output. H.R.—heart rate. S.V.—stroke volume. F.A.B.P.—mean femoral arterial blood pressure. I indicates ± S.E.M. The *P* values indicate significant difference from control (initial) values.

diac sympathetic nerves.[9] Twenty four hours after the final injection, determinations of cardiac output, left ventricular pressure and rate of change of pressure, mean arterial blood pressure, and heart rate were made in the awake animal and again during thiopental-cyclopropane anesthesia administered exactly as in the pre-reserpine control experiment.

Following a day of convalescence, reserpine 100 μg./kg., to be referred to as the larger dose, was administered intramuscularly and in 24 hours cardiac function was again evaluated as before. Nine dogs participated successfully in this part of the study and formed the treated group.

Additional experiments on another group of 8 untreated animals were performed. The protocol for these was the same as that described above except that the administration of reserpine was omitted. These experiments were necessary to evaluate possible changes due to the stress of repeated experimentation.

Results

Cardiovascular Effects of Reserpine Treatment in Unanesthetized Animals. Figure 2 illustrates data gathered from unanesthetized animals. These data demonstrate that reserpine had produced its expected cardiovascular effects prior to anesthesia in the treated group, and that the passage of time or stress of experimentation caused no marked change in the untreated group. The initial data points represent group averages for control experiments. Ensuing points (representing the two groups of experiments which followed) were derived by adding to the control average the average of the individual differences between experiment and control.

In the treated group cardiac output was not significantly different from control following either dose of reserpine. This is in agreement with the findings of others for both animal[13] and man.[14] Stroke volume increased, while heart rate, mean arterial blood pressure, and rate of rise of left ventricular pressure during isovolumetric systole decreased following both doses of reserpine. Significant differences from control are indicated in figure 2. Levels of significance were determined by Student *t* paired sample analysis.

In the untreated group, unanesthetized, there was no significant change in any variable except heart rate from one experiment to the next. The change in heart rate and the small tendency for mean arterial blood pressure, cardiac output, and rate of rise of left ventricular pressure to decrease with time may have been related to a loss of apprehension in the animals following repeated visits to the laboratory.

Cardiovascular Effects of Anesthesia Before and After Reserpine. Figure 3 illustrates the effects of anesthesia. The initial data points are group averages before anesthesia for the control and ensuing experiments. The points representing data gathered during anesthesia were determined by adding to the conscious average the average of the individual differences between the conscious and anesthetized states. Significant differences in responses to anesthesia between the control and ensuing experiments were again sought by paired sample analysis.

The percentage cyclopropane in end-expired air remained quite constant from one experiment to the next. The average concentration in the treated group was 25.4 ± 0.78 (S.D.) volumes per cent. The concentration in the untreated group was 25.0 ± 1.1 volumes per cent. The average end-expired P_{CO_2} for all animals during anesthesia was 32 mm. of mercury, with a range from 29 to 40 mm. of mercury.

Cardiovascular "collapse" during anesthesia did not occur in any animal either before or after reserpine. In the treated group, mean arterial blood pressure rose during anesthesia and the rise, in millimeters of mercury, was approximately the same in the pre-reserpine and post-reserpine experiments. Similarly, the effect of anesthesia in decreasing the rate of rise of left ventricular pressure was not altered by either dose of reserpine. Cardiac output fell during anesthesia. The smaller dose of reserpine did not alter this response. The larger dose, however, caused a significant increase ($P < .01$) in the depression of cardiac output by anesthesia. Heart rate increased during anesthesia in all experiments. The increase was not affected by the smaller dose of reserpine, but it was significantly less ($P < .05$) than control following the larger dose. Stroke volume was decreased a significantly

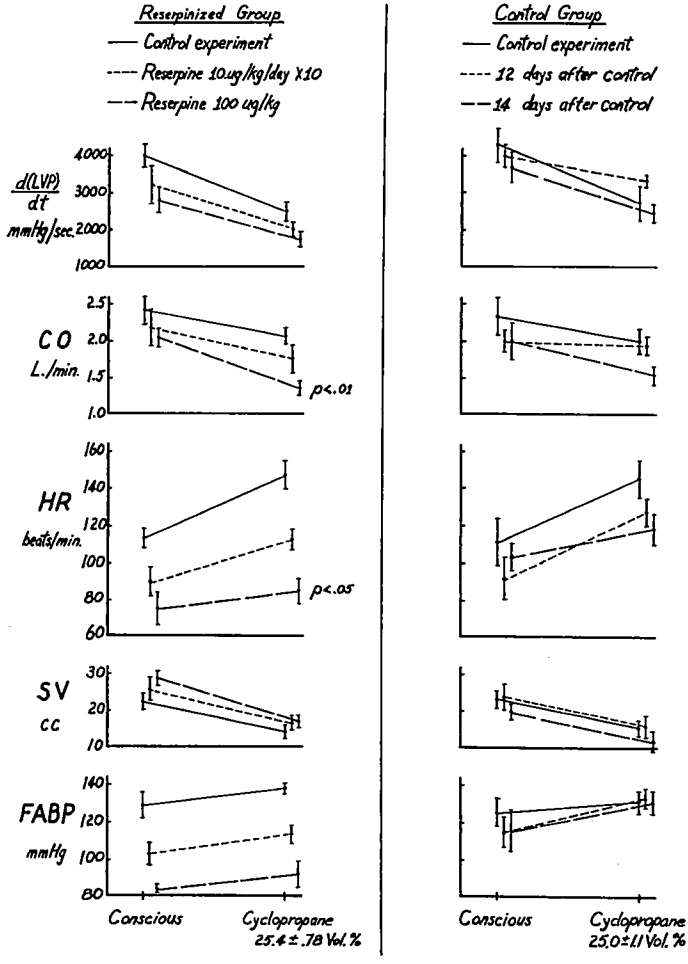

FIG. 3. Effect of anesthesia before and after reserpine in the treated (reserpinized) group, and before and after passage of time in the untreated (control) group. For each group of animals, points on the left represent conscious values and points on the right represent values during thiopental-cyclopropane anesthesia. (Abbreviations are the same as for figure 2). The *P* values indicate significant differences in response to anesthesia between the control and ensuing experiments.

greater ($P < .05$) amount during those anesthetics which followed the larger, but not the smaller dose of reserpine. In summary, the smaller dose of reserpine did not alter, significantly, any of the measured responses to anesthesia. The larger dose caused an exaggeration of the effects of anesthesia on cardiac output, heart rate, and stroke volume.

In the untreated animals, the measured responses to anesthesia did not change significantly from one set of experiments to the next. These responses were similar in magnitude to those observed in the pre-reserpine, treated group.

Discussion

In these experiments, a slow, rather than rapid, technique of reserpinization was chosen to correspond to the ordinary clinical method of administration and to prevent the severe diarrhea and debilitation which often occurs when large doses of reserpine are given to dogs. The smaller dose of reserpine, to which the animals were first subjected, is equivalent on a weight basis, to a daily amount of about 0.7 mg. for the average human being and lies within the therapeutic range. This dose caused a significant fall in mean arterial blood pressure and heart rate in the conscious animal but it did not alter, significantly, any of the measured cardiovascular responses to anesthesia. The larger dose of reserpine was administered after the experiments involving the smaller one were completed. It usually produced signs of overdosage, *e.g.*, moderate to marked sedation, shivering, and diarrhea. Despite these toxic manifestations, the depressant effect of anesthesia on the rate of rise of left ventricular pressure was not exaggerated. While the cardiac output was depressed a significantly greater amount by anesthesia (an average fall of 33 per cent *versus* 13 per cent for the controls) the mean arterial blood pressure rose above the conscious value. The absolute increase in blood pressure was not significantly different from that which occurred during anesthesia prior to the administration of reserpine.

The use of thiopental with cyclopropane coincides with clinical practice. It was thought, initially, that the small dose of thiopental employed for induction would exert little, if any effect 45 minutes after its injection and that the measurements made then would reflect, almost wholly, the actions of cyclopropane. However, a small (unreported) series of experiments demonstrated that in the absence of a thiopental induction, cyclopropane given by nonrebreathing system to produce a concentration of 25 volumes per cent in end-expired air would not maintain anesthesia at a depth sufficient to suppress the lid reflex or prevent swallowing and chewing movements in the non-reserpinized animal. Since the combination of thiopental-cyclopropane completely suppressed this activity, there was clearly a central-nervous-system depressant action of thiopental at 45 minutes. A circulatory effect at this time should probably also be assumed. The fact that cardiac output was depressed by anesthesia in the pre-reserpine experiments supports this assumption since other work [15] has shown that in unpremedicated dogs, cardiac output usually increases during light cyclopropane anesthesia.

The relative importance of sympathetic activity for the maintenance of circulatory homeostasis during thiopental-cyclopropane anesthesia is not known. It is believed that some enhancement of sympathetic activity occurred during anesthesia in our experiments since an increase in mean arterial blood pressure above the conscious value was almost always encountered. That reserpine did little to alter the manifestations of this activity was unexpected. Our results, however, are similar to those of Bagwell *et al.*[5] who found that pretreatment with reserpine did not alter, significantly, the effect of cyclopropane on aortic flow, arterial blood pressure and myocardial contractile force.

Less than the expected effect of reserpine pretreatment on the cardiovascular response to forms of stress other than general anesthesia has been observed by others. Thus, Shapiro [16] has shown that reserpinization of the hypertensive patient does not prevent the pressor response to noxious physical and emotional stimuli and Chidsey and his co-workers [14] have demonstrated a near normal increase in cardiac output during exercise following large doses of syrosingopine (Singoserp).

Our work lends further support to the conclusion of Alper and his associates [17] that "patients on reserpine present few problems that are fundamentally new and that would not be encountered in other patients."

Summary

Thiopental, 225 mg., followed for 45 minutes by cyclopropane, 25 per cent, was administered to trained dogs. Heart function was evaluated by measuring cardiac output, heart rate, rate of rise of left ventricular pressure during isovolumetric systole (an index of myocardial "contractility"), and mean arterial blood pressure. Stroke volume was calculated. Evaluations were made in the conscious and anesthetized animals both before and after the slow administration of reserpine.

Severe hypotension did not occur in any experiment. Mean arterial blood pressure rose during anesthesia both before and after reserpine. The depression of stroke volume and rate of rise of left ventricular pressure by anesthesia was not exaggerated following reserpine. Heart rate increased, while cardiac output decreased during anesthesia. These responses to anesthesia were altered by pretreatment with very large doses of reserpine.

It is concluded that the measured cardiovascular responses to thiopental-cyclopropane anesthesia in dogs were not significantly different following doses of reserpine which were comparable to those used clinically and which had been shown to deplete the canine heart of its norepinephrine content.

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