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

E. E. Bagwell, Ph.D., E. F. Woods, Ph.D., R. P. Linker, M.D.

There have been several reports in recent years dealing with patients on long-term therapy with Rauwolfia compounds who exhibited a profound bradycardia and an inability to maintain an adequate blood pressure when given a general anesthetic. Reports such as these have led to the recommendation by many anesthesiologists that treatment with Rauwolfia compounds be discontinued at least two weeks prior to elective surgery. However, in a recent study, Munson et al. found that the incidence of hypotension occurring during induction of anesthesia was just as high in patients in whom reserpine had been discontinued as in those in whom treatment was continued up to the time of surgery.

Experiments in animals have shown that animals pre-treated with reserpine are more prone to become hypotensive following the administration of thiopental. There have been no detailed studies on the effects of reserpine on cardiovascular responses to anesthesia with the commonly used inhalational agents; however, preliminary studies of this nature with cyclopropane have recently been reported. The objective of the present study was to observe the effects of ether anesthesia on several cardiovascular parameters and then to compare the results with those obtained from similar experiments performed on reserpine pre-treated animals.

Methods

Acute Experiments

Twenty-one mongrel dogs ranging in weight from 10–16 kg. were used in these experiments. Ten animals received 0.1 mg./kg. of reserpine (Sertral) intramuscularly for two consecutive days prior to the experiment. Ventricular contractile force was measured with a strain gauge arch and aortic pressure with a Statham transducer. Total aortic flow (cardiac output-crown flow) was measured with a square-wave electromagnetic flowmeter. All parameters were recorded on a Grass oscillograph. Plasma epinephrine and norepinephrine levels were determined by a modification of the fluorimetric ethylenediamine condensation method. Arterial blood $P_{CO_2}$ and $pH$ changes were also monitored periodically in most experiments, and an attempt was made to maintain these blood parameters at near pre-anesthetic levels.

All animals were prepared the day preceding the experiment for measuring contractile force and aortic pressure. This preparation consisted of anesthesia with thiamylal (Surital) and the suturing of a strain gauge arch to the right ventricle through a thoracotomy made between the fourth and fifth ribs. Polyethylene cannulas were also placed through a femoral artery and vein into the abdominal aorta and vena cava, respectively. The incisions were then closed, antibiotics administered, and the animals allowed to recover.

On the experimental day, control readings of contractile force and aortic pressure were taken after the animals had become accustomed to the surroundings. Arterial samples for catecholamines were also taken at this time. The animals were then anesthetized with ether in oxygen using a semiclosed technique with a Foregger anesthesia machine.

* Carolina Electronics, Inc., Winston-Salem, North Carolina.
† Instrumentation Labs, Inc., Boston, Massachusetts.

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The authors are in the Department of Pharmacology and Anesthesiology, Medical College of South Carolina, Charleston, South Carolina.
**CHRONIC EXPERIMENTS**

Seventeen experiments were performed on 10 dogs weighing approximately 12 kg. Four of the animals received 0.03 mg./kg. reserpine intramuscularly daily for two to three weeks prior to the experiment.

Preparations and procedures similar to those described for the acute animals were also used in these experiments, with the following exceptions. In addition to implanting the strain gauge arch and cannuhas on the day prior to the initial experiment, a chronic flowmeter probe was also placed around the ascending aorta. This procedure facilitated the recording of total aortic flows before and during anesthesia and also allowed the use of each animal for several days since the chest was not opened on the experimental day. Heart rate was also recorded with an electronic tachometer. None of the animals in this group received atropine prior to anesthesia.

Mean aortic pressure, ventricular contractile force, total aortic flow and stroke volume (total aortic flow/heart rate) were found to be linearly related to the concentration of ether in the inspired gas, and the results are expressed as regression lines.\(^\text{15}\) Regression lines from the control and reserpine-treated animals were compared as to slope and elevation by the method of “covariance.”\(^\text{16}\) Heart rate changes were analyzed by the Student’s t test.\(^\text{17}\) A P value of less than 0.05 was considered significant.

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CONTROL  
RESERPINIZED

150

100

MEAN
AORTIC
PRESSURE
MM. Hg.
50

0  3  6  9  12  15

PER CENT ETHER

Fig. 3. Comparison of regression lines in control (9 experiments, 6 animals) and reserpinized (8 experiments, 4 animals) animals formed by plotting mean aortic pressure (mm. of mercury) against the concentration of ether in the inspired gas. All of the animals did not receive each concentration of the anesthetic. However, the points on the graph represent the number of animals studied at each concentration. The reserpinized animals had received 0.03 mg./kg. of reserpine intramuscularly daily for two weeks prior to the experiment. These animals were chronic preparations (see Methods) and were used on more than one day. The regression coefficients for the control and reserpine-treated animals were -2.71 and -2.37, respectively.

Results

Acute Experiments

Figure 1 depicts the effects of increasing concentrations of ether on mean aortic pressure in control and reserpine pre-treated animals. The regression coefficient for the control animals was found to be -3.92 as compared to -2.97 for the reserpine-treated group. When the slopes of these two lines were compared by covariance no significant difference was found. On the other hand, a comparison of the elevations of the two lines revealed that the regression line representing the reserpine-treated animals was significantly lower than that of the control animals (P < 0.01). The effects of ether on ventricular contractile force in control and reserpine-treated animals are shown in figure 2. The regression coefficients for control and reserpine-treated animals were -5.72 and -4.24, respectively. When the slopes of the two lines were compared no significant difference was found; however, as with blood pressure, the difference between the elevations was of statistical significance (P < 0.01).

Total aortic flow was also recorded in these experiments. However, the flow measurements in these early experiments were variable and inconclusive due largely to an inadequate selection of probe sizes and other technical difficulties which were corrected in the later series of experiments. Arterial pH and P_{\text{CO}_2} values were monitored periodically in most experiments, and an attempt was made to maintain these parameters at near preanesthetic levels. Mean pH values before anesthesia were 7.41 as compared with 7.37 during anesthesia, and the mean P_{\text{CO}_2} values prior to and during anesthesia were 26.13 and 25.16, respectively.
Fig. 4. Comparison of regression lines in control and reserpine-treated animals formed by plotting changes in ventricular contractile force (grams) against the concentration of ether in the inspired gas. Experimental conditions are the same as in figure 3. The regression coefficient for the control animals was \(-3.47\) compared to \(-3.16\) for the reserpine-treated animals.

**Chronic Experiments**

Figures 3 and 4 summarize changes in mean aortic pressure and ventricular contractile force during ether anesthesia in control and reserpine pre-treated animals. The results of these experiments correlated statistically with the results obtained from the acute preparations. The slopes of the regression lines are similar, while the elevations are significantly lower in animals which had received reserpine. However, it should be noted that the initial levels of contractile force, necessarily, are dependent on the manner in which the arch is attached and adjusted in length. (It has been previously shown that each 1 per cent stretch beyond the initial diastolic length, there is about 2–4 per cent increase in force.)\(^{12}\) The uniformity which has been attained in this manipulation, however, is demonstrated by the observed figures. For the control group of animals, the mean initial contractile force in grams was 96.4 with a standard error of \(\pm 9.4\); for the reserpine-treated animals the mean initial contractile force in grams was 69 with a standard error of \(\pm 8.3\). The regression coefficients are indicated in the legends of the respective figures. Changes in total aortic flow during increasing concentrations of ether are depicted in figure 5. It can be seen that the elevations as well as the slopes of these two regression lines are similar, indicating similar aortic flows in the control and reserpine-treated animals both before and during anesthesia. Figure 6 shows the regression lines depicting changes in stroke volume during ether anesthesia in the control and reserpine-treated animals. Contrary to the findings with the other parameters, the slope of the regression line was found to be greater in the reserpine-treated animals (\(P < 0.01\)). Mean changes in heart rate are summarized in figure 7. In the control animals, heart rate increased significantly during light levels of anesthesia, but began to decrease toward preanesthetic levels as anesthesia was deepened. On the other hand, the reserpine-treated animals exhibited a somewhat different pattern of changes. Heart rate increased significantly from preanesthetic levels during light anesthesia, and remained elevated throughout the experiment even when anesthesia was deepened. However, absolute heart rate was
Fig. 5. Comparison of regression lines in control and reserpine-treated animals formed by plotting changes in mean aortic flow (ml./minute) against percentage concentration of ether in the inspired gas. Experimental conditions are described in figure 3. The regression coefficient for the control animal was −37 compared to −38 for the reserpine-treated animals.

Fig. 6. Comparison of regression lines in control and reserpine-treated animals formed by plotting stroke volume (ml./beat) against the concentration of ether in the inspired gas. Experimental conditions are the same as in figure 3. Regression coefficients for the control and reserpine-treated animals were −0.315 and −0.675, respectively.
found to be significantly less in the reserpine-treated animals when compared to the control animals except in deep levels of anesthesia (12–15 per cent).

Changes in circulating catecholamines during ether anesthesia are summarized in table 1. This table includes values obtained from both acute and chronic experiments since statistical analysis revealed no significant difference between the values obtained from the two groups. Plasma levels of epinephrine in the control animals were found to be significantly elevated from resting levels during all depths of anesthesia with ether. Norepinephrine levels were also significantly increased during light anesthesia and during emergence from anesthesia. Strikingly different results were obtained from the animals pre-treated with reserpine. Plasma levels of circulating amines were found to be significantly elevated above resting levels in only one instance. This elevation occurred in the epinephrine fraction during light anesthesia. Comparisons were also made between changes from conscious values obtained in the control and reserpine-treated animals at each level. Norepinephrine levels were found to be significantly lower in the reserpine pre-treated animals during the conscious state and during emergence from anesthesia. Significantly lower increments in epinephrine levels were found in the reserpine-treated animals during all stages of anesthesia. However, the levels of epinephrine during consciousness in the two groups of animals were found to be similar.

Arterial pH and Pco2 values were also monitored and an attempt made to maintain these values at near preanesthetic values. The mean pH values prior to anesthesia were 7.44 as compared to 7.51 during anesthesia, and the mean Pco2 values before and during anesthesia were 42.66 and 29.03, respectively.

Discussion

Control Group. The results of the present experiments show that in non-premedicated (control) animals there is a progressive and linear depression of ventricular contractile force, mean aortic pressure, total aortic flow, and stroke volume as the concentration of ether in the inspired gas is increased. Heart rate was found to be significantly elevated above conscious values during light anesthesia, but as the depth of anesthesia was
increased heart rate returned toward pre-anesthetic values. Plasma levels of epinephrine were found to be significantly elevated above conscious levels during all stages of anesthesia. Circulating norepinephrine levels were more variable, but they were also significantly elevated during light anesthesia and during emergence. Other investigators have previously reported increments in catecholamines during ether anesthesia in both animals and man.

Several studies have shown that ether depresses the myocardium in the isolated preparation. Boniface et al. and Etten and Li using the strain gauge arch have also shown that ether depresses ventricular contractile force in the intact animal. The present results are in agreement with this previous work. Malt has recently recorded force changes during ether anesthesia in volunteers with an ultra-low frequency ballistocardiogram and has also found the force of contraction to be depressed during light anesthesia.

Previous studies in animals have generally shown an increase in cardiac output during light ether anesthesia. In the present experiments, total aortic flow has been used as an index of cardiac output and in all but one experiment flow was depressed during light surgical levels of ether anesthesia. It is felt that this depression is due primarily to a decreased stroke volume resulting from a depressed myocardium. During deep levels of anesthesia, the increased heart rate seen during light levels of anesthesia returned toward pre-anesthetic levels, and this probably contributed to the aortic flow decrements seen at this time.

**Reserpine-treated Group.** Results obtained from animals pre-treated with reserpine differ in several respects from those of the nontreated animals. The rate of depression of both aortic pressure and ventricular contractile force, as indicated by the slope of the regression lines, was similar in both groups of animals. However, the absolute values at any given time, as indicated by the elevation of the lines, were found to be lower in the reserpine-treated animals. On the other hand, regression lines representing changes in total aortic flow in the two groups almost co-incident. Therefore, although aortic pressure and contractile force are lower in the reserpine-treated animals before and during anesthesia, aortic flow is still maintained at levels compa-
rable to those of the control animals. Since aortic flow is related to the product of heart rate and stroke volume, further analysis of these two parameters was necessary to provide an explanation for aortic flow being maintained in the reserpine-treated animals. From figure 6 it can be seen that during light ether anesthesia stroke volume is higher in the reserpine-treated animals. However, at the same time, heart rate (fig. 7) is lower than in the control animals. Therefore, it appears that during light ether anesthesia a higher stroke volume in the reserpine-treated animals is primarily responsible for maintaining total aortic flow at a level comparable to the control animals. In deep levels of anesthesia, stroke volume in the reserpine-treated animals was found to be depressed to a level equal to that of the control animals. However, at this time heart rate in the control animals was also depressed to values near the reserpine-treated animals, so that again the difference in total aortic flow between the two groups was insignificant.

In general plasma catecholamine levels were not significantly elevated during ether anesthesia in the reserpine-treated animals. Since Brewster et al. have shown that a functional sympathetic nervous system is instrumental in maintaining circulatory homeostasis during ether anesthesia, one might expect the reserpine-treated animals with diminished sympathetic activity to be affected to a greater degree by ether. However, in general this was not found to be true in the present experiments. One possible explanation for this finding could be that catecholamines are still liberated in about normally effective concentrations at the nerve endings in the myocardium and peripheral vessels but are not generated in the amounts which escape and raise blood levels. Also, there is evidence to indicate that animals pretreated with reserpine are more sensitive to catecholamines.

The data from the present experiments demonstrate that the reserpine-treated animals were generally able to withstand concentrations of ether as high as those withstood by the non-treated animals even though plasma catecholamine levels and some circulatory parameters were significantly depressed in the reserpine-treated animals. The numerous reported clinical observations of marked circulatory depression during general anesthesia in reserpine-treated patients appear to be based on factors not existing in these experiments with healthy, vigorous dogs.

Summary

Changes in several cardiovascular parameters were measured during anesthesia with increasing concentrations of ether in control and reserpine pre-treated animals.

Ventricular contractile force, mean aortic pressure, total aortic flow and stroke volume in both groups of animals were found to be progressively depressed as the concentration of ether was increased. The following differences were noted between the responses obtained in the control and reserpine-treated animals:

1. The rate of depression of mean aortic pressure and ventricular contractile force, as indicated by the slopes of regression lines, was similar in both groups of animals. However, the absolute values both before and during anesthesia, as indicated by the elevation of the lines, were found to be lower in the reserpine-treated animals.

2. Regression lines depicting changes in total aortic flow were almost identical in the two groups of animals both in slope and elevation, indicating similar aortic flows both before and during anesthesia.

3. Stroke volume was higher in the reserpine-treated animals during light anesthesia, but this difference disappeared during deep levels due to a greater rate of depression.

4. Heart rate in the control animals was significantly increased during light anesthesia, but as the depth was increased the rate returned to near preanesthetic levels. In the reserpine-treated animals, heart rate increased significantly during both light and deep anesthesia. However, the absolute rate in the reserpine-treated animals was significantly less than in the control animals except during deep levels of anesthesia.

5. In general, plasma levels of catecholamines were significantly elevated during ether anesthesia in the control animals; whereas, in the reserpine-treated animals, the only elevation observed was that of epinephrine during light anesthesia.
These results indicate that reserpine pre-treatment does not markedly alter the cardiovascular responses of animals to ether anesthesia even though some sympathetic factors are significantly depressed.

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References

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EXPERIMENTAL EPHYSEMA Partial expiratory obstruction produced by implanting a ball valve in a bronchus of dogs produced histologic changes resembling changes in human emphysema. Only in those animals with superimposed infection were there detectable changes in blood gas and lung function. (Frayer, R.: Experimental Pulmonary Emphysema in Dogs, Amer. Rev. Resp. Dis. 87: 666 (May) 1963.)

INTRATHORACIC PHEOCHROMOCYTOMA Fourteen pheochromocytomas occurring as intrathoracic tumors have been described. During operation for removal, the patients' blood pressure rose; after removal it fell. Vasopressor drugs were required during operation and for three days after. Halothane was used without difficulty. (Luna, R., Katz, I., and Ernst, R. W.: Intrathoracic Pheochromocytoma, Arch. Surg. 87: 369 (Sept.) 1963.)

ASTHMA There may be impairment in the distribution of an inert gas in the lungs of patients with bronchial asthma at a time when the disease appears to be in remission. Maximal ventilatory airflow may also be reduced in the absence of symptoms. In 6 of the 12 patients studied, the residual impairment of gas distribution was found to follow a zonal rather than a diffuse, uniform pattern. The patients showing this defect had a significantly greater degree of impairment of forced expiratory volume, maximal mid-expiratory flowrate, and helium mixing efficiency than did those not showing this abnormality. The findings indicate that the residual ventilatory impairment in patients with bronchial asthma in remission must be seen as a zonal or possibly lobar phenomenon. Such regional ventilatory impairment does not seem to be accompanied by a corresponding reduction in perfusion. (Bentivoglio, L. G., and others: Regional Pulmonary Function Studied with Xenon in Patients with Bronchial Asthma, J. Clin. Invest. 42: 1193 (Aug.) 1963.)