

Effects of Guanethidine and Reserpine on the Cardiac Responses to Halothane

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GUANETHIDINE (Ismelin)* and the Rauwolfia alkaloids, including reserpine, are employed extensively in the treatment of patients with essential hypertension.¹⁻⁵ It has been well documented in laboratory animals that the administration of these compounds reduces the levels of stored tissue norepinephrine in the heart.^{6,7} Further, reserpine-pretreatment has been shown to deplete the catecholamine stores of vessel walls,⁸ and the adrenal medulla,⁹ and to abolish two adrenergic responses important in circulatory regulation: the positive chronotropic response to cardio-accelerator nerve stimulation,¹⁰ and the arteriolar constrictor response to lumbar sympathetic stimulation.¹¹ Although the effects of guanethidine on the levels of norepinephrine stores have not been determined in man, it has been shown that the administration of reserpine reduces atrial norepinephrine levels in patients.¹² This latter observation lends support for the assumption that the decrease in systemic arterial pressure which is seen clinically when these drugs are administered is related to their pharmacologic effects on adrenergic reflexes.¹³

It is generally agreed that the induction and maintenance of general anesthesia in *hypertensive* patients receiving reserpine may be complicated by severe bradycardia and hypotension,^{14,15} and it might be anticipated that hypertensive patients receiving guanethidine could exhibit similar difficulties during anesthesia. Since the physiologic responses to anesthesia have not been reported in patients receiving guanethidine, the present studies were performed to evaluate the effects of halo-

thane on heart rate, myocardial contractile force, and systemic arterial pressure in dogs pretreated with guanethidine, as compared with similar responses in control dogs and dogs pretreated with reserpine.

Methods

Nineteen adult mongrel dogs averaging 12.2 kg. in weight were studied. Control observation were made in five mongrel dogs. Seven dogs were studied 24 hours following the single intravenous injection of guanethidine 100 mg./kg., and seven dogs were studied following the intraperitoneal injection of reserpine 0.1 mg./kg., on each of the two days preceding the experiment. These pretreatment schedules were selected because each has been shown to produce significant depletion of atrial norepinephrine.^{6,7} Each animal was anesthetized with an intravenous injection of warmed chloralose, 100 mg./kg., and endotracheal intubation was performed. Respirations were controlled with a Harvard laboratory pump utilizing 100 per cent oxygen at a total flow of 5 liters/minute in a nonbreathing circuit. Each animal was studied as an open-chest preparation following a right thoracotomy. Right ventricular myocardial contractile force was estimated with a Walton-Brodie strain gauge arch.¹⁶ Arterial blood pressure was continuously measured from a polyethylene catheter in the right femoral artery utilizing a pressure transducer. The heart contractile force and blood pressure responses were recorded on a direct writing polygraph. The heart rate was counted from the arterial pressure pulse record.

Fifteen minutes following the intravenous injection of 2 mg. atropine sulphate, halothane in sequential concentrations of 0.5, 1.0, 1.5, and 2.0 per cent was added to the inspired oxygen from a Fluotec Mark II vaporizer. Inhala-

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tion of the drug was continued at each vaporizer setting until the maximal effects on heart rate, myocardial contractile force and arterial pressure had been obtained. The duration of administration of each halothane concentration ranged from five to ten minutes.

The results were analyzed for statistical significance utilizing Students' *t*-test.¹⁷ *P* values less than 0.05 were considered significant. Variability is expressed as the standard error of the mean.

Results

Heart Rate and Mean Arterial Pressure. The control heart rates in the seven guanethidine-pretreated dogs (150 ± 10), and seven reserpine-pretreated dogs (145 ± 11) were slightly, but not significantly less than those observed in the five normal dogs (167 ± 7). The control mean femoral artery pressures in the seven guanethidine-pretreated dogs (127 ± 14), and the seven reserpine-pretreated dogs (113 ± 9) were lower, but not significantly lower than those observed in the three normal dogs (142 ± 13) in which complete arterial pressure data were obtained (table 1).

All concentrations of halothane administered resulted in a clear-cut decrease in heart rate in each group of animals (table 1). Consistently greater negative chronotropic responses were obtained at each halothane dose in the guanethidine- and reserpine-pretreated animals as compared with control. The absolute reduction in heart rate was significantly greater in the reserpine- and guanethidine-pretreated dogs at both the 0.5 and 1.0 per cent concentrations.

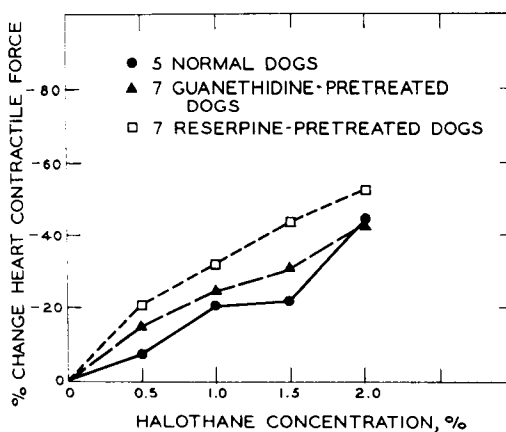


FIG. 1. Percentage change in heart contractile force from control of normal, guanethidine-pretreated and reserpine-pretreated dogs. 0 = contractile force response measured 15 minutes after 2 mg. atropine.

Parallel decreases in mean arterial pressure were produced by each concentration of halothane in the three groups of animals (table 1). The absolute pressure decrements were uniformly greater in the guanethidine- and reserpine-pretreated dogs than in the normal dogs and were significantly greater in the reserpine-pretreated dogs at halothane concentrations of 0.5 and 1.0 per cent, and in both the guanethidine- and reserpine-pretreated groups at 2.0 per cent.

Heart Contractile Force. The administration of each of the four concentrations of halothane produced a striking negative inotropic effect in each of the three groups of animals. The maximal decrements in contractile force from control were produced by 2 per cent

TABLE 1. Observations of Heart Rate and Blood Pressure in Normal Dogs, and in those Pretreated with Guanethidine and Reserpine

	Normal		Guanethidine-Pretreated		Reserpine-Pretreated	
	M.H.R.**	M.A.P.†	M.H.R.	M.A.P.	M.H.R.	M.A.P.
Control*	167 ± 7	142 ± 13	150 ± 10	127 ± 14	145 ± 11	113 ± 9
Halothane 0.5%	161 ± 7	135 ± 13	130 ± 6	109 ± 11	127 ± 10	90 ± 9
Halothane 1.0%	148 ± 6	130 ± 15	115 ± 7	94 ± 13	113 ± 6	83 ± 9
Halothane 1.5%	140 ± 18	114 ± 11	113 ± 6	87 ± 10	106 ± 6	84 ± 10
Halothane 2.0%	134 ± 18	85 ± 5	109 ± 5	59 ± 7	101 ± 5	57 ± 8

* Control = values measured 15 minutes after 2 mg. atropine.

** M.H.R. = mean heart rate, ± 1 S.E.

† M.A.P. = mean atrial pressure, ± 1 S.E.

halothane and averaged -44 ± 11.5 per cent in the normal dogs, -43 ± 8 per cent in the guanethidine-pretreated dogs, and -53 ± 8 per cent in the reserpine-pretreated dogs (fig. 1). There were no significant differences in the contractile force responses to halothane among the three groups of dogs except that difference produced at the 0.5 per cent concentration in the control and reserpine-pretreated dogs.

Comments

These observations extend the conclusions drawn from a previous study in this laboratory in which it was shown that depletion of myocardial catecholamines by chronic cardiac denervation does not increase the sensitivity of the dog heart to the negative inotropic effects of halothane.¹⁸ In addition, they provide evidence that the dose response relationship between halothane and myocardial contractile force is not altered by guanethidine, reserpine, or the pharmacologic effects of these drugs, a conclusion which is supported by the observations of Flacke and Alper who have reported similar effects of halothane on myocardial contractility in heart lung preparations made from normal and reserpine-pretreated dogs.¹⁹

The observation that halothane in concentrations of $\frac{1}{2}$ and 1 per cent produces a consistent negative chronotropic effect and a reduction in arterial pressure in both the guanethidine- and reserpine-pretreated atropinized dogs, in contrast to the variable responses measured previously in the cardiac denervated dogs, indicates that guanethidine and reserpine increase the sensitivity of the intact dog to the negative chronotropic and arterial pressure reducing effects of halothane in low concentrations.

Summary

The effects of halothane on myocardial contractile force, heart rate and systemic arterial pressure were studied in dogs after the administration of 2 mg. atropine intravenously. Observations were made in normal dogs and in dogs pretreated with either guanethidine or reserpine. The anesthetic agent, in concentrations ranging from $\frac{1}{2}$ to 2 per cent, produced decreases in heart contractile force which did not differ significantly among the

three groups of animals. In concentrations of $\frac{1}{2}$ and 1 per cent, halothane had a significantly greater negative chronotropic effect, and reduced arterial pressure more in the the guanethidine- and reserpine-pretreated dogs than in the control dogs while comparable decrements were produced in these responses at the $1\frac{1}{2}$ and 2 per cent halothane concentrations. These observations indicate that the negative inotropic effects of halothane are not modified by guanethidine, reserpine or the depletion of myocardial catecholamines which they produce, while the negative chronotropic and hypotensive effects of halothane at lower concentrations are augmented by pretreatment with these drugs.

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FEMORAL VENIPUNCTURE Two infants lost part of a lower extremity following femoral venipuncture. Both infants apparently developed marked arterial spasm, followed by complete thrombosis of the distal arteries of the leg. Management of similar problems must include early sympathetic block, restoration of normal blood volume, normal hydration and replacement of electrolyte losses and possibly the intravenous administration of low molecular weight dextran. If, after a brief period of such treatment, it becomes clear that the viability of all or part of the limb is seriously threatened and palpable pulsations are missing, direct surgical exploration at the site of the venipuncture may be indicated. (*Nabseth, D. C., and Jones, J. E.: Gangrene of the Lower Extremities of Infants After Femoral Venipuncture, New Engl. J. Med.* 268: 1003 (May 2) 1963.)

NEONATE ACIDOSIS Newborns were examined with Astrup capillary blood method 15 minutes, 35 minutes and 3 hours after birth. During the first 10 minutes of life, blood is acidotic but becomes normal in another 10 minutes provided respiration and renal function become normal. Premature infants sometime remain acidotic for days. At birth P_{CO_2} is lower in infants delivered by uterine section. Children of primiparas have a more intense metabolic acidosis for a longer duration than those of multiparas. If the mother received barbiturates the P_{CO_2} is raised considerably and for longer times, sometimes with development of secondary metabolic acidosis. Males had retarded regulation and uncompensated metabolic acidosis persisted longer than in girls. Slowing of the heart rate during delivery lead to considerable metabolic and respiratory acidosis even in normal children with uncomplicated births. (*Weidtmann, V.: Influence on the Acid-Base Balance in the First Hours of Life, Arch. Kinderheilkunde* 168: 35 (Mar.) 1963.)