Actions of Halothane and Norepinephrine in the Isolated Mammalian Heart

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DESPITE the great interest in the cardiovascular actions of the volatile anesthetic halothane (1,1,1-trifluoro-2-chloro-2-bromoethane), no reports of its action in the isolated mammalian heart have appeared since the presentation of preliminary data by Burn and coworkers in 1957.[1] Although myocardial depression by halothane has been demonstrated unequivocally in studies in intact animals and in open chest preparations, more extensive evaluation of the cardiac effects of halothane in the dog heart-lung preparation is justified for several reasons. First, distribution equilibrium can be expected to proceed faster in the heart-lung preparation, thus making it possible to relate the observed effects to a maintained arterial or tissue concentration of the drug. Secondly, experimental variables such as arterial resistance and cardiac output can be controlled easily and can be altered at will. Finally, the isolated heart is free from reflex nervous and hormonal effects. This permits the investigation of the drug effect as such, free from modifying influences.

The present report deals with the inotropic and chronotropic actions of halothane in the isolated normal dog heart, in the heart pretreated with reserpine, and in the heart under the influence of a continuous infusion of norepinephrine. It has been suggested that the depressant effect of halothane upon the circulation may be related, at least partly, to an antagonism by halothane of the action of norepinephrine.[2, 3] In the present experiments, special attention was therefore given to the interaction of halothane and norepinephrine.

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Methods

Thirty-six heart-lung preparations were set up by the method of Starling as modified by Krayer.[4] Mongrel dogs of either sex with an average weight of 11.5 kg. were used. Defibrinated blood, obtained from donor dogs under ether anesthesia, was used throughout. In 30 experiments, anesthesia was induced and maintained with halothane and oxygen during the preparation. The anesthetic was discontinued at the time of isolation of the heart. Thereafter, the lungs were ventilated with 95 per cent oxygen and 5 per cent carbon dioxide. At least 45 minutes were allowed to elapse between the discontinuation of the halothane and the beginning of observations. Ventilation was maintained with a constant-volume pump at a tidal volume of 250 ml. at a rate of 20/minute. In six of the experiments, the dogs were anesthetized with sodium pentobarbital, 40 mg./kg. given intraperitoneally.

The arterial resistance was set to give a mean arterial pressure of about 100 mm. of mercury as measured with a mercury manometer. Left atrial pressure was monitored from a cannula inserted into the left atrial appendage, right atrial pressure from the inferior vena cava. The systemic output was measured with a Shipley-Wilson recording rotameter and was initially set at an average of 700 ml./minute. The heart rate was determined from electrocardiographic records on a Grass direct-writing oscillograph. The total blood volume averaged 1,050 ml.

The level of blood in the venous reservoir was maintained at a constant height of approximately 12 cm. above the right atrium. In order to test the competence of the heart, the venous inflow was increased by raising the reservoir blood level in measured steps of 50 mm. each. The blood temperature ranged between 38.2° C. and 39.2° C. in all experi-

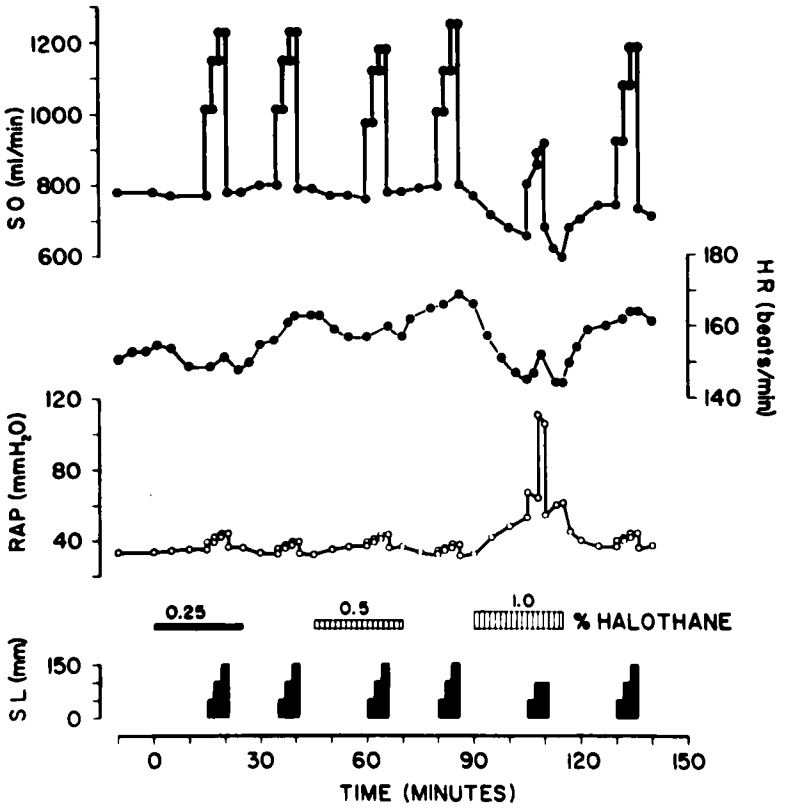

FIG. 1. Effect of halothane on the normal heart. *From top to bottom:* systemic output; heart rate; right atrial pressure; time of administration of halothane and concentrations in inspired gas; SL = change in supply level of venous reservoir at times of competence tests (each step represents a rise of 50 mm.). Dog heart-lung preparation, 10 kg., male. Temperature range 38.7–38.8° C.

ments. The variation in any one experiment did not exceed ± 0.1 degree centigrade.

Halothane was vaporized by a flow and temperature-compensated, calibrated vaporizer (Fluotec Mark II) into a 20-liter reservoir bag. Each concentration of halothane was administered to the heart-lung preparation for at least 15 minutes before cardiac competence was tested. To minimize loss of anesthetic vapor, the venous reservoir was made airtight with a soft rubber glove. Norepinephrine, in the form of l-norepinephrine bitartrate, was administered by a constant infusion pump into the tubing leading into the right atrium. Doses of norepinephrine refer to micrograms of the base.

In three experiments, dogs were pretreated with two subcutaneous injections of lyophilized reserpine phosphate in a dose of 0.5 mg./kg., 48 and 24 hours prior to operation. This dose of reserpine has been shown to reduce the norepinephrine content of the dog heart to less than 2 per cent of normal.[5]

Results

Effects of Halothane in Heart-Lung Preparations

Inotropic Action. The effect of different concentrations of halothane on the ability of the heart to cope with an increased volume load was determined by observing the response of systemic output to raising the level of the venous reservoir in measured steps. In eight experiments, the administration of 0.25 per cent or 0.5 per cent halothane did not significantly diminish the ability of the heart to increase its output. However, 1 per cent halothane invariably resulted in severe impairment of myocardial contractility with a rapid rise in atrial pressure and fall in systemic output. An illustrative experiment is shown in figure 1. In every case, when halothane administration was ended, recovery of competence, even after severe impairment, was rapid and complete. Similar observations were made in three heart-lung preparations from

reserpine-pretreated dogs. Despite the depletion of norepinephrine stores by the reserpine, there was no increase in sensitivity of the heart to the depressant action of halothane.

Chronotropic Action. It is apparent from figure 1 that halothane administration is associated with a fall in heart rate. The effect of different concentrations of halothane on the heart rate was observed in 20 normal heart-lung preparations. The average magnitude and time course of heart rate change in these experiments is depicted in figure 2 (left). Atropine, in doses up to 2 mg., given ten minutes before beginning the administration of halothane did not alter this fall in heart rate. In the three experiments carried out after reserpine pretreatment, the negative chronotropic action of halothane was not different from that observed in the normal hearts.

Interaction of Halothane and Norepinephrine

Inotropic Effects. When halothane, in increasing concentrations, was administered to the normal heart-lung preparation during the continuous infusion of norepinephrine, at rates varying from 3 to 11.2 μg./minute, the tolerance to halothane was increased. The concentration of halothane which just caused a rise in atrial pressure and a concomitant fall in cardiac output was increased to 1.5–2.0 per cent (fig. 3). Figure 4 shows the result of the administration of 3 per cent halothane during the continuous infusion of norepinephrine at a rate of 3 μg./minute. At the end of eight minutes, the heart was in severe failure with elevated right atrial pressure and diminished output. In spite of the marked myocardial depression, recovery upon discontinuation of the anesthetic was rapid and complete. Within the first minute, both atrial pressure and systemic output returned to the pre-halothane levels. The heart rate, on the other hand, had not returned to its starting level at the end of eight minutes.

In four experiments, the attempt was made to reverse the negative inotropic effect of halothane by a continuous infusion of norepinephrine. It was found that complete restoration of cardiac competence was possible only with concentrations of 1.5 per cent halothane or less in the inspired gas. During administration of halothane at concentrations of 2.5 per cent or higher, the induced failure could not be reversed despite infusion of norepinephrine at rates as high as 78 μg./minute.

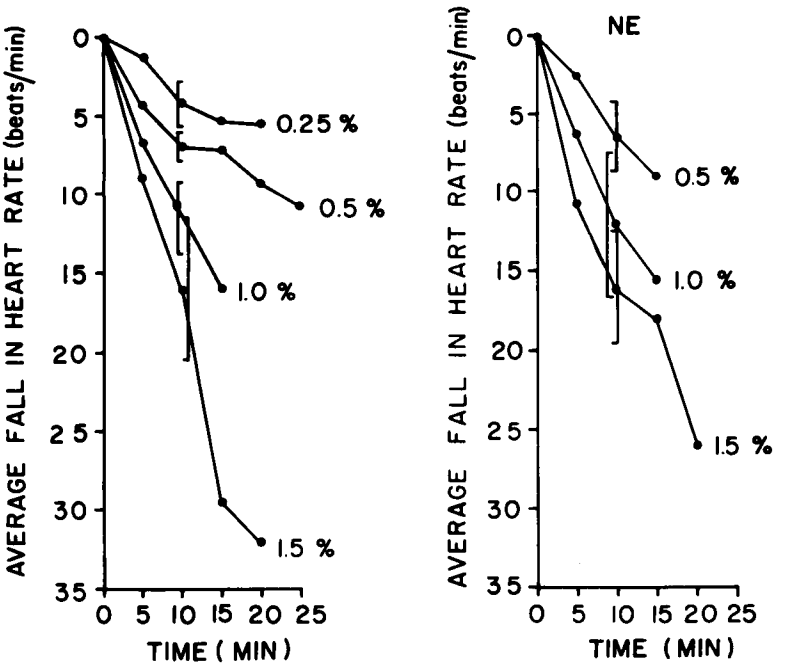

Fig. 2. Chronotropic action of halothane in normal heart-lung preparation and during infusion of norepinephrine. *Left side:* normal hearts. *Right side:* during infusion of norepinephrine at rates between 1.2–3.0 μg./minute. Each point represents a mean of from three to 13 observations. The vertical bars represent the standard error.

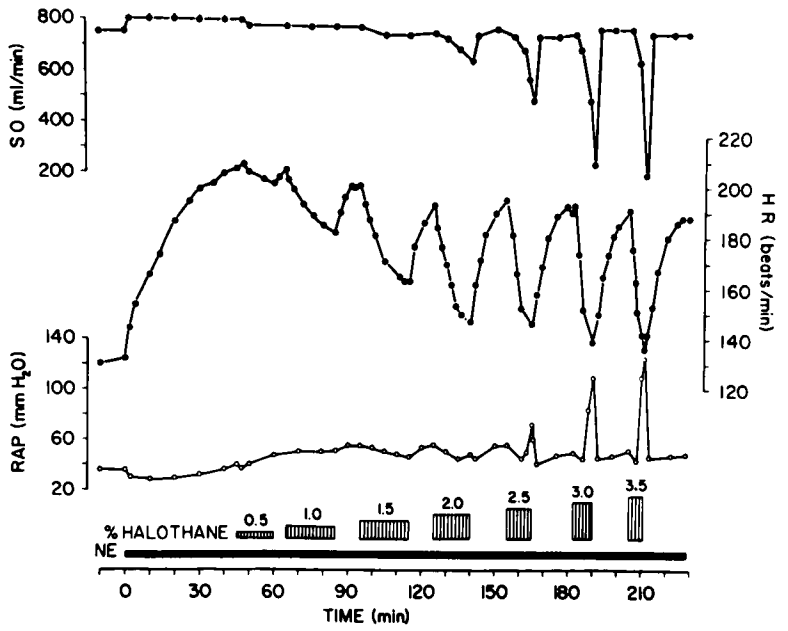

FIG. 3. Effect of halothane on the heart during continuous infusion of norepinephrine. *From top to bottom:* systemic output; heart rate; right atrial pressure; time of administration of halothane and concentrations in inspired gas. Horizontal black bar labelled NE represents continuous infusion of norepinephrine at a rate of 3 μg./minute. Dog heart-lung preparation, 9.5 kg., male. Temperature 39.0° C.

The high rates of norepinephrine infusion during these experiments were accompanied by high heart rates (see below). It appeared possible that the tachycardia as such might limit cardiac diastolic filling and thus diminish cardiac output. In order to test this possibility, veratramine was used to reduce the rate effect of the catechol amine. Veratramine antagonizes the positive chronotropic action of catechol amines but leaves their effect on myocardial contractility unaltered.[6] The result is shown in figure 5. The reduction of heart rate by veratramine did indeed improve the competence as shown by the decrease in left atrial pressure and the increase of cardiac output. That it did not, however, completely reverse the negative inotropic action of halothane was demonstrated during a volume load test.

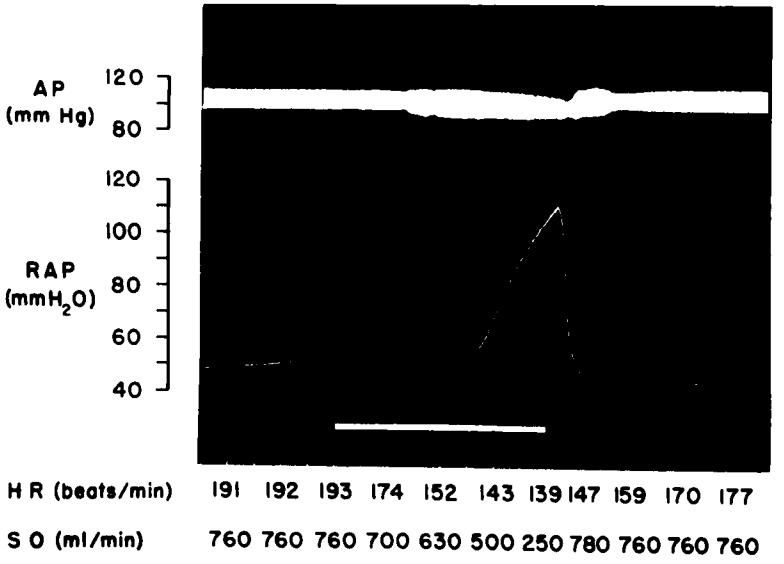

FIG. 4. Effect of 3 per cent halothane on the heart during continuous infusion of norepinephrine. *From top to bottom:* arterial pressure; right atrial pressure; white bar represents time of administration of 3 per cent halothane; time marks at intervals of one minute; HR and SO are the heart rate and systemic output values at the times indicated. Norepinephrine was infused at a rate of 3 μg./minute throughout (from experiment of figure 3).

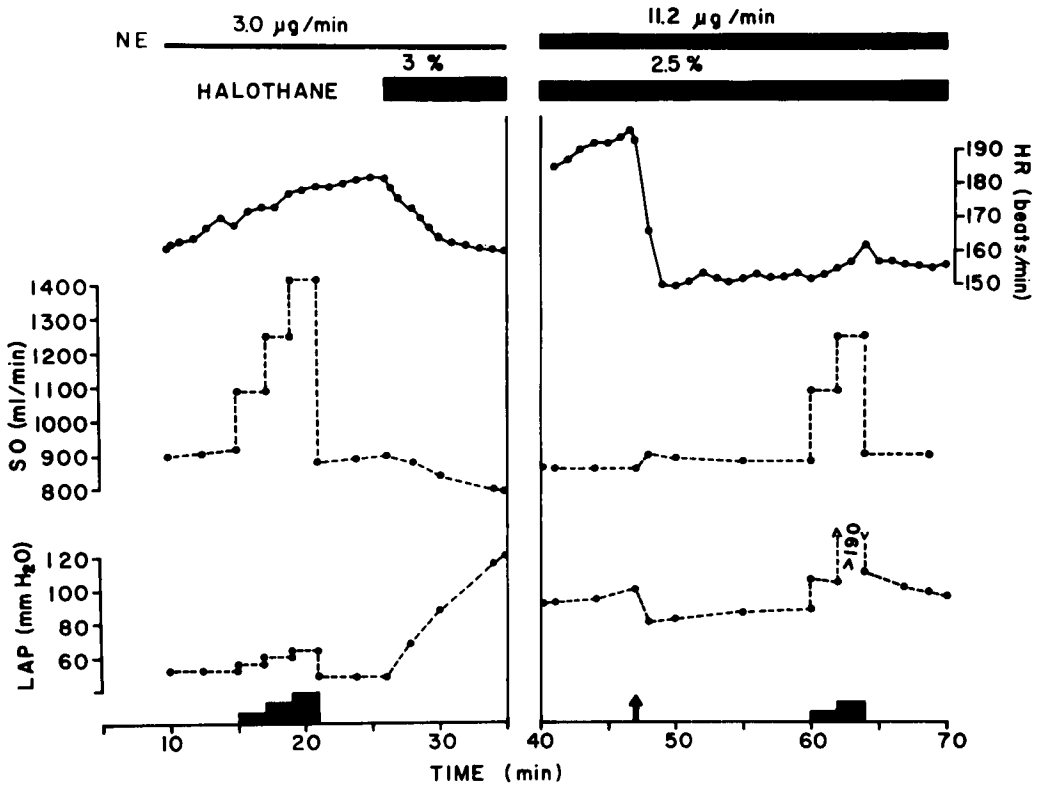

FIG. 5. Effect of veratramine during cardiac failure induced by halothane. *From top to bottom:* NE and black bars represent times of norephinephrine infusion at 3 and 11.2 μg./minute; times and concentrations of halothane administration; heart rate; systemic output; left atrial pressure; times of competence tests (each step represents 50 mm. rise in venous reservoir level). At the arrow, 0.6 mg. of veratramine was injected. Dog heart-lung preparation, 10.5 kg., male. Temperature range 39.1–39.3° C.

Thus, the inability of norepinephrine to antagonize the depressant effect of halothane on the myocardium is only partly due to the high heart rate associated with the administration of large doses of norepinephrine.

Chronotropic Effects. In experiments such as depicted in figure 3, it was observed that even during norepinephrine infusion with a moderately elevated heart rate, each concentration of halothane resulted in a prompt fall in heart rate. Different concentrations of halothane were administered to eight heart-lung preparations during the infusion of 1.2 to 3.0 μg./minute of norepinephrine. As shown in figure 2 (right), the absolute fall in heart rate under these conditions was not different from that observed in the absence of exogenous norepinephrine.

During high rates of norepinephrine infusion, a quite different effect of halothane was observed (fig. 5). Here, 0.5 per cent halothane resulted in a rise in heart rate which was sustained throughout the administration of the halothane, whereas 2 per cent halothane caused an initial rise in rate followed by a prompt fall. One per cent halothane produced an initial rise in rate followed by a decrease and a similar biphasic response upon its discontinuation. This phenomenon was studied by obtaining complete norepinephrine dose-response curves of heart rate during the administration of 1.5 per cent halothane.

Despite the continued administration of 1.5 per cent halothane, which, by itself, had marked rate-decreasing action (fig. 2), the smallest effective infusion rate of norepinephrine (0.43 μg./minute) was the same as in the controls (fig. 7). In the lower range of

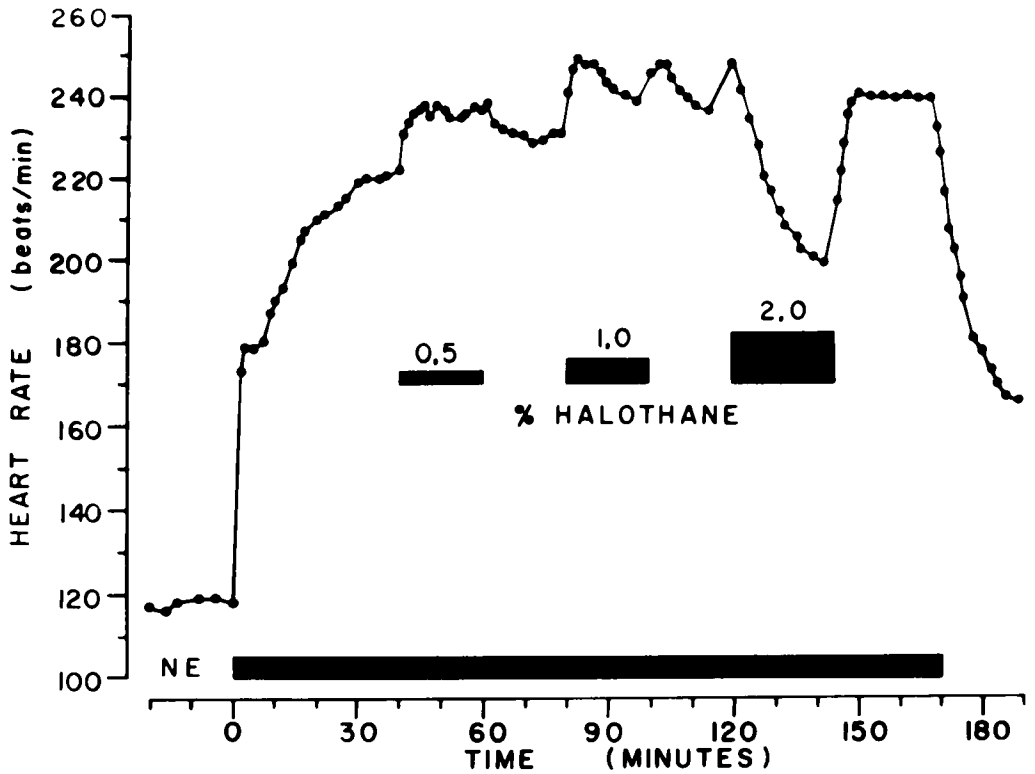

FIG. 6. Effect of halothane on heart rate during high rate of infusion of norepinephrine. *Upper horizontal bars:* times and concentrations of halothane administration. *Lower bar (NE):* continuous infusion of norepinephrine at a rate of 11.2 μg./minute. Dog heart-lung preparation, 12 kg., male. Temperature 38.8° C.

norepinephrine infusions, the average heart rate response was not different from that observed in five control experiments. With increasing rates of norepinephrine infusion in the presence of halothane, the slope of the dose-response curve becomes steeper. At the highest infusion rates of norepinephrine (31, 78, and 136 μg./minute), the mean rate increase in the presence of halothane is significantly greater than in the controls ($P < 0.05$). The average maximal rate and maximal-rate increase during administration of halothane were greater than in the controls. The initial rates of the two groups were not different (table 1).

Discussion

These experiments confirm the observation that halothane has direct negative inotropic and chronotropic actions in the normal mammalian heart. Other investigators who determined ventricular function curves [7, 8] or measured contractile force with the strain gauge arch [9, 10, 11] have found significant myocardial depression occurring with inspired concentrations of halothane of 1 per cent and above. In our experiments, this was also found to be the case in the isolated heart.

In both intact animals and in man, halothane has variable effects on heart rate. The most common observation is a fall in heart rate which is reversed, at least partially by atropine. In the isolated heart, halothane invariably exhibited negative chronotropic action that was not affected by the prior administration of atropine. This direct action of halothane on the cardiac pacemaker was also demonstrated in the chronically denervated dog heart [12] and can undoubtedly be masked in the intact animal by compensatory reflexes.

Several observers have suggested the potential importance of an antagonism between halothane and norepinephrine in the mechanism of the hemodynamic changes during halothane anesthesia. In the toad heart [2] and in rabbit aortic strips,[3] a decreased responsiveness to norepinephrine was observed in the presence of halothane. Similarly, Millar and Morris [13] found increased circulatory depression in dogs with induced hypercarbia during halothane anesthesia despite increased levels of circulating catechol amines. In man, halothane anesthesia was associated with diminished pressor response to norepinephrine [14] and lessened vasoconstriction in the forearm upon intra-arterial injection of norepinephrine.[15]

The present studies demonstrate that the interaction between halothane and norepinephrine in the heart is not a simple antagonism and that its nature may differ in different tissues. Both the negative inotropic and the negative chronotropic effects of halothane were present in the hearts pretreated with reserpine and thus largely depleted of endogenous catechol-amine stores. In fact, the sensitivity of these hearts to halothane was not increased in the absence of norepinephrine. These ob-

TABLE 1. Maximal Chronotropic Action of Norepinephrine in the Heart-Lung Preparation of the Normal Dog and in the Presence of 1.5 Per Cent Halothane

Type	Number of Experiments	Initial Rate beats/min. mean ±S.D.	Maximal Rate beats/min. mean ±S.D.	Maximal Rate Increase beats/min. mean ±S.D.
Control	5	135±13	269±20	134±13†
Halothane 1.5%	5	134±20 124±12*	285±16	161±13†

* Rate after 10 minutes of halothane and before beginning infusion of norepinephrine (used for calculation of maximal rate increases).
† $P < 0.025$.

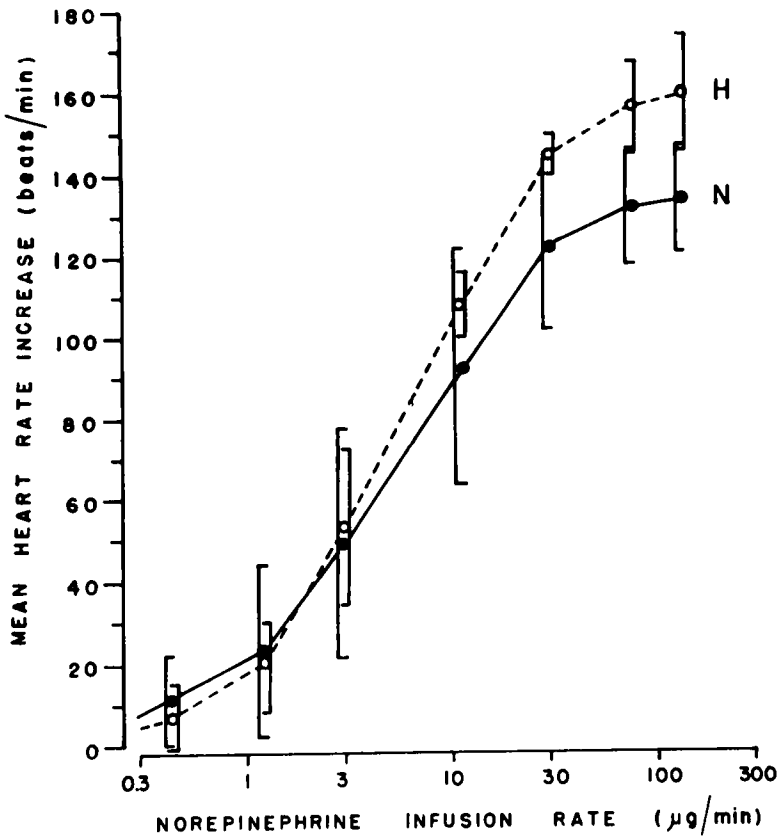

FIG. 7. Influence of halothane on the norepinephrine dose-response curve of heart rate. *Curve N:* normal hearts; *Curve H:* during administration of 1.5 per cent halothane. Each point represents the mean of five experiments; the vertical bars represent the standard deviation.

servations confirm the findings of Morrow and associates [12] in the chronically denervated, catechol-amine-depleted dog heart and those of Beaton [16] who found no change in sensitivity to halothane after blockade of the sympathetic outflow. It must be concluded that the effect of halothane on the heart is not, or at least not entirely due to an antagonistic action of the agent to the transmitter substance of the sympathetic nervous system.

Quantitative evaluation of changes in myocardial contractility in the heart-lung preparation in terms of dose-response curves is difficult since contractility is not related in a linear fashion to the observed parameters, atrial pressures and systemic output. Factors such as heart rate and conduction velocity may be influenced simultaneously and may affect the competence of the heart. Thus, it will be stated only that the power of norepinephrine to reverse halothane-induced myocardial depression in the heart-lung preparation is limited to concentrations of the anesthetic agent below 2 per cent.

Quantitative evaluation of effects on heart rate is far less complex. The factors mentioned above, which complicate evaluation of contractility changes, do not bear on the action upon the cardiac pacemaker. These experiments show that halothane decreases the rate of the mammalian heart. This effect occurs equally in the absence of endogenous norepinephrine and in the presence of moderate amounts of the hormone. It is, therefore, not due to a pharmacological antagonism between halothane and norepinephrine. Over a limited range of concentrations, the interaction of the two agents with opposing effects on the pacemaker results in an antagonism of the physiological type. Each agent exerts its characteristic effect on heart rate despite the presence of the other. Simultaneously, in the presence of halothane, the effect of high infusion rates of norepinephrine on heart rate is enhanced, resulting in a steepening of the dose-response curve and a greater maximal response.

This interaction of the two agents on the pacemaker is different from their interaction with regard to contractility. No amount of norepinephrine can overcome the depression of the myocardium caused by high concentrations of halothane. This fact may point to a difference in the site or mechanism of action of the agents on the two parameters of cardiac function. It also implies that, in clinical anesthesia, no degree of sympathetic reflex response is able to compensate fully for the effect on the heart of too great a concentration of halothane.

Summary

The cardiac action of halothane and interaction with norepinephrine were investigated in the heart-lung preparation of the dog. Halothane depressed myocardial contractility and heart rate in the normal heart, in the heart depleted of its catechol-amine stores by reserpine, and in the presence of exogenous norepinephrine.

The depressant effect of halothane on cardiac competence was antagonized by norepinephrine. However, complete reversal by norepinephrine of this depression was possible only with concentrations of halothane of 2 per cent or less.

The negative chronotropic action of halothane was undiminished during infusion of norepinephrine (1.2 to 3 μg./minute), and the positive chronotropic effect of norepinephrine was not depressed in the presence of halothane (1.5 per cent in the inspired gas). High rates of infusion of norepinephrine (31 μg./minute and above), in the presence of 1.5 per cent halothane, resulted in heart rate increases significantly greater than in the controls.

It is concluded that the depressant effects of halothane and the stimulant actions of norepinephrine on the heart are independent and that the two drugs do not interact at the same receptor. Over a limited range of concentrations, an antagonism of the physiological type results from the opposing actions of the two agents on the heart. The fact that the power of norepinephrine to reverse halothane-induced myocardial depression is limited makes it likely that the effect of an overdose of halothane on the heart cannot be completely counteracted by any degree of reflex sympathetic response.

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