Incidence of Catechol-Amine-Induced Arrhythmias During Halothane Anesthesia

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HALOTHANE increases the bathmotropic effect of epinephrine on the myocardium. Premature ventricular beats and ventricular tachycardia have been described as a major hazard if these two drugs are administered together.[1]

It has been indicated that there is little difference between norepinephrine and epinephrine in this respect during cyclopropane anesthesia in dogs,[2] while it has been stated that norepinephrine can be used safely with halothane in man.[3]

It has been shown in cyclopropane-anesthetized dogs [2] and in man [4] that catechol amines can be infused in physiologic concentrations without producing serious and irreversible arrhythmias. The present clinical study was undertaken to compare the effect of epinephrine and norepinephrine on the cardiac irritability during halothane anesthesia. Other pertinent observations made during the experiment will be described and discussed.

Method

Fifty-one patients were studied. Thirty-one patients received norepinephrine, 15 received epinephrine, and in five patients, first epinephrine and subsequently norepinephrine were given in order to make a direct comparison of the catechol amines. The patients were unselected and underwent major surgical procedures of the following categories: abdominal, vascular, pulmonary, and orthopedic operations. The distribution according to sex was 21 males and 30 females. The age grouping was: 13–40 years, eight patients; 40–60 years, 20 patients, and 60–83 years, 23 patients. Durations of the operations were: 60–119 minutes, 12 patients; 120–179 minutes, 16 patients; 180–239 minutes, nine patients; 240–359 minutes, six patients; 360–479 minutes, two patients, and 480–580 minutes, three patients.

The patients were premedicated with atropine or scopolamine (0.2–0.5 mg.) alone (five patients) or in combination with morphine (6–12 mg.) or meperidine (25–75 mg.) and anesthetized for the surgical procedures with concentrations of halothane that would produce a lowering of the preoperative systolic blood pressure of 40–60 per cent. A Fluotec Mark II vaporizer was used. All patients had their tracheas intubated following a sleeping dose of thiopental (200–300 mg.) and 75 mg. of succinylcholine iodide. No other muscle relaxant was administered during the anesthesia, which was maintained with halothane. The mean halothane concentration as determined by the Fluotec setting during catechol-amine infusions was 1.4 per cent (0.5–1.25 per cent in 20 patients, 1.5–1.75 per cent in 16 patients, and 2.0–2.5 per cent in 14 patients) and nitrous oxide-oxygen in a nonrebreathing system with flows of not less than 8 liters/minute. The respiration was controlled mechanically with a Lundia respirator. The blood pressure was measured by auscultation at least every five minutes. The electrocardiogram was monitored continuously and recorded intermittently.

When the systolic blood pressure had decreased 40–60 per cent and had stabilized, the concentration of halothane was kept constant, and an infusion of either epinephrine or *l*-norepinephrine base (2 μg./ml. in 5 per cent glucose in water) was started and continued during the operation. The durations of the catechol-amine infusions were: 4–59 minutes, 14 patients; 60–119 minutes, 18 patients; 120–179 minutes, eight patients; 180–299 minutes, five patients; 300–360 minutes, four patients; 480 minutes, one patient; 535 minutes, one patient.

The infusion rate in μg./minute was noted at the various stages of the cardiovascular re-

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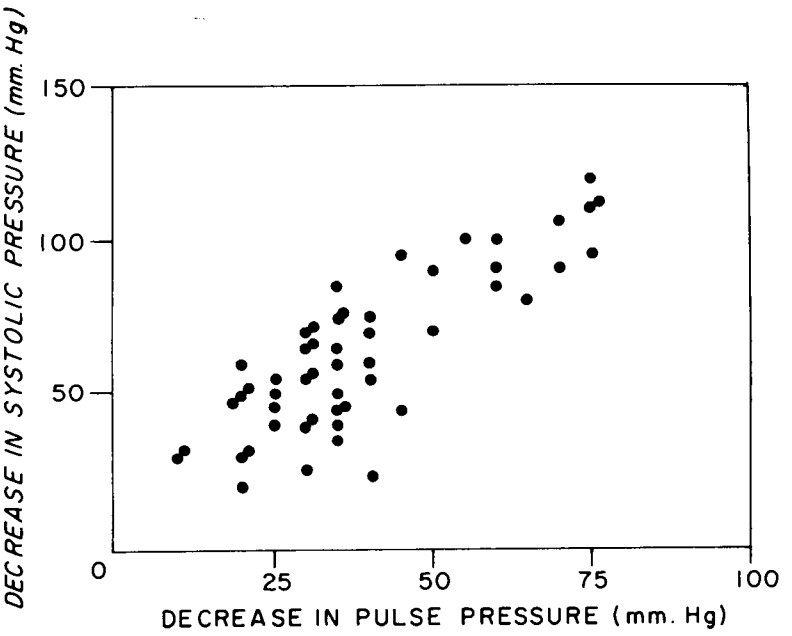

FIG. 1. The relationship between the decrease of systolic blood pressure (*e.g.*, 160/100 − 95/65 = 65); and the decrease of pulse pressure (*e.g.*, 160/90 − 100/60 = 30) from preoperative values to the values during halothane anesthesia.

sponse. The infusion rate of epinephrine averaged 6μg./minute, ranging from 2.5 to 16.3. The infusion rate for norepinephrine averaged 6.2 μg./minute, ranging from 2.0 to 19.0.

The catechol amines were always given into one vein, while another was reserved for routine administration of blood and other fluids.*

Results

Clinical evidence of severe circulatory insufficiency did not occur during the hypotensive period or during the infusion of catechol amines. A careful postoperative follow-up revealed no signs of myocardial damage, impaired renal function, or cerebrovascular accidents. No death attributable to anesthesia occurred in the patients studied.

On no occasion was it difficult to wean the patients from catechol-amine infusion at the end of the surgical procedure. It was accomplished by simultaneously decreasing the concentration of halothane and the rate of infusion of catechol amines. Hypotension, such as has been described after prolonged catechol-amine administration, was not encountered in the postoperative period.

The circulatory responses to the catechol amines were judged by the response of systolic blood pressure and by electrocardiographic evidence of augmented myocardial excitability. The systolic blood pressure was preferred to the mean pressure, since it is more easily defined with the auscultatory method and because a direct relationship was found between systolic pressure and pulse pressure as seen in figures 1 and 2. In figure 2 the responses to epinephrine and norepinephrine are plotted separately.

Blood Pressure

It was found that the hypotension in most patients could be corrected and that the systolic pressure could be brought to 80 per cent of the preoperative systolic pressure (80 per cent correction) without the occurrence of electrocardiographic evidence of arrhythmias.

Epinephrine. With epinephrine 80 per cent of the preoperative systolic blood pressure was obtained in 18 of the 20 administrations at some time during the administration. Two patients developed ventricular arrhythmias before an 80 per cent correction could be

* *Complications of the method.* In one instance the needle was flushed with the catechol-amine solution by error, which gave rise to ventricular tachycardia. On two occasions the flow rate increased suddenly because position of the needle was altered accidentally or because of decreased venous tone. In one case perivenous infiltration occurred. This was followed by a period of myocardial irritability of several minutes' duration.

reached; one had severe arteriosclerotic heart disease, and one cor pulmonale incipiens. Beside these patients, 11 patients developed ventricular arrhythmias at infusion rates exceeding those necessary for 80 per cent correction.

Norepinephrine. With norepinephrine an 80 per cent blood pressure correction was obtained in 34 of the 36 administrations. Again, two patients developed arrhythmias below this level; one had arteriosclerotic heart disease with spontaneous ventricular extrasystoles, and one was the patient mentioned above with cor pulmonale incipiens. Beside these two patients, nine patients developed arrhythmias when pressed beyond 80 per cent correction.

Pulse Rates

The rates tended to be higher during epinephrine infusion. A rate of 80 to 100 beats/minute was usual as compared to a rate with norepinephrine normally ranging from 60 to 90. A rate of more than 120 was observed once in a patient who was given epinephrine, and a rate less than 60, in three patients who received norepinephrine.

Arrhythmias

As mentioned above, arrhythmias accompanied the infusion of both the catechol amines. Data from the 13 patients who developed arrhythmias during epinephrine infusion are shown in table 1. It is seen that, with the exception of one, these patients either: (1) received more epinephrine than 10 μg./minute, (2) exhibited severe blood loss treated with not only blood transfusion but also with increased infusion rates of catechol amine, (3) were brought back to systolic pressure equal to or above the preoperative, or (4) suffered from cardiac disease. Data from the 11 patients who developed arrhythmias with norepinephrine are seen in table 2. As with epinephrine, all patients but one had infusion rates of about 10 μg./minute, severe blood loss, systolic blood pressure driven to above preoperative findings, or cardiac disease.

The arrhythmias observed were of the same kind and degree with epinephrine and norepinephrine: premature ventricular beats, bigeminal and trigeminal rhythm, and rarely, a short burst of ventricular tachycardia (fig. 3). The arrhythmias could be induced and ended at will by adjustments in the infusion rate and could be made to disappear in one-half to two minutes. The arrhythmias never lasted long enough or were severe enough to produce hypotension lasting for more than one to two minutes. Out of 14 patients who received infusion rates of more than 10 μg./minute, six patients with norepinephrine and two patients with epinephrine did not develop arrhythmias.

When much blood was lost during operation, blood was administered, and at the same

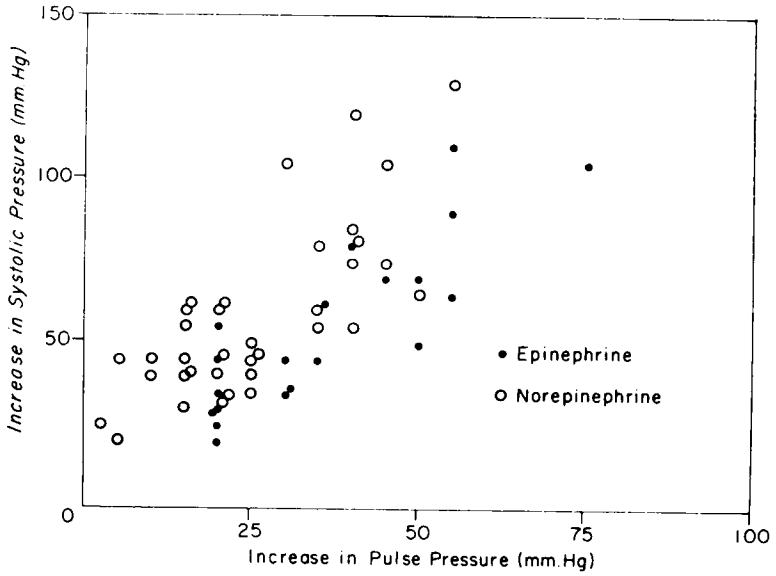

Fig. 2. The relationship between the increase of systolic blood pressure and the increase of pulse pressure associated with the administration of epinephrine and/or norepinephrine during halothane anesthesia.

TABLE 1. The Occurrence of Ventricular Arrhythmias During Epinephrine Infusion in Relation to: (1) Infusion Rate, (2) Increase in Infusion Rate Concomitant with Severe Bleeding and Blood Transfusion, (3) Instances of Correcting Systolic Blood Pressure to or Above the Preoperative Level, and (4) the Presence of Manifest Cardiac Disease

Patient Number	Infusion Rate (>10 μg./minute)	Severe Bleeding	Corrected Blood Pressure ≧ Preoperative Blood Pressure	Cardiac Disease
2	+		+	
3			+	
4	+	+		
5			+	
6		+		
7				+
8			+	
9			+	
47		+		
48				
49		+		
50		+		+
51			+	

time, the infusion rates were speeded up for experimental reasons.

In all patients but the three mentioned with cardiac disease, the arrhythmias developed at higher infusion rates than were necessary to restore the systolic blood pressure to 80 per cent of the control value. In one patient with cardiac disease, the infusion had to be discontinued after four minutes. Only twice with norepinephrine and once with epinephrine was it possible to exceed the lowest preoperative systolic blood pressure without the occurrence of ventricular arrhythmias.

Six patients out of eight with cardiac disease all characterized by hypertrophy developed ventricular extrasystoles or tachycardia.

The arrhythmias with epinephrine occurred at infusion rates of 4.4–13.2 μg./minute with an average of 7.2 μg./minute.

The arrhythmias with norepinephrine occurred at infusion rates of 5.5–13.2 μg./minute with an average of 8.7 μg./minute.

EPINEPHRINE FOLLOWED BY NOREPINEPHRINE

In the five patients in whom a direct comparison between the two catechol amines was attempted, epinephrine produced arrhythmias in all five at an average infusion rate of 6.5 μg./minute, norepinephrine in only three at an average infusion rate of 7.3 μg./minute. The blood pressure response was similar with the two amines in all five patients.

In 11 hypertensive patients with a preoperative systolic blood pressure of more than 150 mm. of mercury or a diastolic blood pressure of more than 100 mm. of mercury, the mean infusion rate of catechol amines necessary to produce a systolic blood pressure increase of 5 mm. of mercury after a 40–60 per cent decrease was 0.4 μg./minute (0.2–0.8), while 0.8 μg./minute (0.3–2.2) produced the same changes in the rest of the patients after a similar decrease. The mean halothane concentration administered to this patient group during catechol-amine infusions was 1.3 per cent.

In figure 4 it is seen that the higher the halothane concentration inhaled, the higher the infusion rate necessary to increase the systolic blood pressure by 5 mm. of mercury. However, most patients breathed halothane at concentrations of 1–2 per cent.

Discussion

We chose to give premedication to the patients and to control the ventilation according to clinical judgment so that the effect of epinephrine and norepinephrine in combination with halothane anesthesia might be compared

TABLE 2. The Occurrence of Ventricular Arrhythmias During Norepinephrine Infusion in Relation to: (1) Infusion Rate, (2) Increase in Infusion Rate Concomitant with Severe Bleeding and Blood Transfusion, (3) Instances of Correcting Systolic Blood Pressure to or Above the Preoperative Level, and (4) the Presence of Manifest Cardiac Disease

Patient Number	Infusion Rate (>10 μg./minute)	Severe Bleeding	Corrected Blood Pressure ≧ Preoperative Blood Pressure	Cardiac Disease
19	+		+	
24		+		+
25				
26			+	
27	+			
29				+
30	+			
40				+
48	+			
49		+		
50		+		+

under usual clinical conditions. All patients were slightly hyperventilated (8–10 liters/minute) to avoid an increased carbon dioxide tension, which in itself may precipitate ventricular arrhythmia with cyclopropane anesthesia as shown by Price *et al.*[4] The anesthetic gases were passed through the Fluotec Mark II vaporizer into the reservoir bag of a Lundia nonreturn respirator. Thus, the halothane concentrations delivered to the patients were assumed to correspond to the dial setting on the Fluotec vaporizer.

From our observations there did not seem to be much difference between epinephrine and norepinephrine in their tendency to increase myocardial excitability during halothane anesthesia. Admittedly, fewer instances of arrhythmias occurred in the norepinephrine group, which would be in accordance with von Euler's experience,[5] but the arrhythmias occurred at nearly identical infusion rates in our patients. This corresponds well with the findings of Price *et al.*,[4] who infused epinephrine and norepinephrine intravenously during cyclopropane anesthesia, producing arrhythmias at infusion rates from 4 to 26 μg./minute.

Mahaffey and associates [6] have demonstrated a depression of the contractile force of the heart and the blood pressure with concentrations of 1.2 per cent halothane. In unanesthetized persons, the blood pressure easily rises beyond the normal level during infusion of catechol amines [7] even in the presence of heart disease. Price and Price [8] have published observations relative to a diminution of the vasoconstrictor activity of the catechol amines by halothane. The fact that the blood pressure in the present experiment was seldom restored to the preoperative level without the occurrence of cardiac arrhythmias is in accordance with the above-mentioned publications. The direct relationship found between the increase in systolic blood pressure and pulse pressure indicated that an increase in stroke volume was primarily responsible for the effects exerted by the catechol amines in this study.[9] For the same increase in systolic pressure, epinephrine showed a slight but definite tendency to cause a larger increase in pulse pressure than norepinephrine (fig. 2).

Epinephrine and norepinephrine in equipotent doses exert an equally positive inotropic effect on the heart.[10, 11] The importance of an intact sympathetic nervous system in the anes-

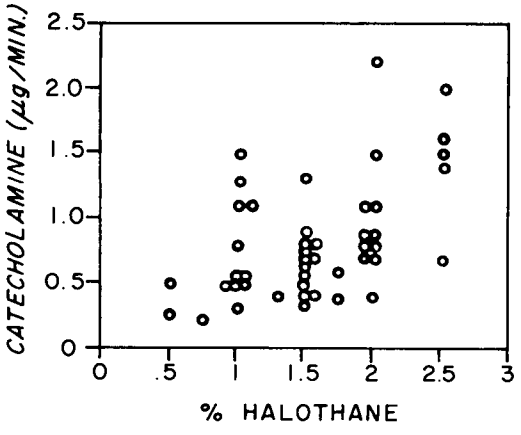

FIG. 3. The amount of epinephrine or norepinephrine necessary to increase the systolic blood pressure by 5 mm. of mercury in μg./minute in relation to the percentage of halothane administered at the time. (Five out of 51 patients not included because of incomplete data.)

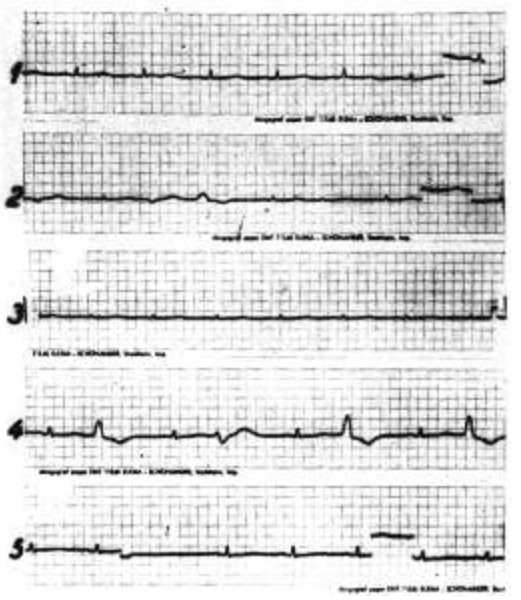

FIG. 4. Electrocardiographic evidence (lead 2) of increased myocardial excitability during infusion of epinephrine under halothane anesthesia (2 per cent) Patient number 2, 38 years old. (1) Before start of infusion, (2) during infusion of 10 μg./minute, (3) three minutes later at infusion rate of 6 μg./minute, (4) 100 minutes later at infusion rate increased to 12 μg./minute, and (5) three minutes later at infusion rate decreased to 8 μg./minute.

thetized state has been demonstrated.[12] Price and associates [13] found that the administration of halothane failed to evoke the increase in plasma catechol-amine concentration which accompanied anesthesia with ether, and, even more so, with cyclopropane. Consequently, compensation with catechol amines appears logical when halothane is administered in concentrations which produce undesired hypotension. Evidence of myocardial excitability, however, seriously limits the use of this theoretically advantageous combination.

Patients with hypertensive cardiovascular disease developed arrhythmias more easily and at lower levels of blood pressure than the group as a whole. Goldenberg and co-workers [10] found that hypertensive individuals were more sensitive than normotensive to intravenous infusion of catechol amines. Our results tend to confirm this for patients anesthetized with halothane.

Continuous infusions of epinephrine and norepinephrine in the majority of cases can only partly correct the hypotensive action of halothane if cardiac arrhythmias are to be avoided. An infusion rate of more than 10 μg./minute of either catechol amine or a blood pressure correction beyond 80 per cent of the lowest preoperative value constitutes a greatly increased risk of cardiac arrhythmias.

It can be concluded from our findings that if local anesthetics are employed together with halothane anesthesia, the addition of norepinephrine for vasoconstrictor purposes carries the same risk as the addition of an equal dose of epinephrine.

Summary

Infusion of the catechol amines epinephrine and norepinephrine during halothane anesthesia in man has demonstrated that for practical clinical purposes, increased myocardial excitability occurs as readily with one amine as with the other.

The hypotension of halothane anesthesia can only be partly corrected by an infusion of epinephrine or norepinephrine if ventricular arrhythmias are to be avoided.

The risk of evoking ventricular arrhythmias is increased with infusion rates of more than 10 μg./minute and in the presence of arteriosclerotic cardiac disease.

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