THE EFFECTS OF HALOTHANE ON MYOCARDIAL CONTRACTILE FORCE AND VASCULAR RESISTANCE

Direct Observations Made in Patients During Cardiopulmonary Bypass

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HALOTHANE in clinically useful concentrations often produces profound systemic hypotension. The etiology of the decrease in blood pressure has been attributed to direct myocardial depression, alone or in combination with a decline in peripheral vascular resistance. In a comprehensive review by Price[1] the many clinical and experimental studies which have been carried out with halothane are well summarized. Bloodwell and associates, in this clinic, studying the changes in myocardial contractile force and systemic blood pressure produced by halothane demonstrated that myocardial contractile force decreased and arterial pressure fell but that the change in pressure did not necessarily parallel the direct myocardial effect.[2] These observations were made in patients during thoracotomy but prior to complete cardiopulmonary bypass when the circulation was intact. Thus the direct cardiac effects of halothane could not be entirely isolated from its peripheral action. In the present study the myocardial and peripheral effects of halothane were assessed in patients undergoing operations with cardiopulmonary bypass when the heart and peripheral circulation were physiologically separated.

METHODS

Observations were made in 6 patients undergoing direct closure of atrial septal defect. They ranged in age from 5 to 65 years. All had been digitalized preoperatively with digoxin. Premedication consisted of meperidine 40–60 mg., promethazine 25 mg., and scopolamine 0.2–0.6 mg. Anesthesia was induced with thiopental 2 mg./kg., or cyclopropane-oxygen. Relaxation for tracheal intubation was produced with succinylcholine and the drug in 0.4 per cent concentration was administered as a continuous intravenous infusion to provide necessary respiratory control and muscular relaxation. Anesthesia was maintained with nitrous oxide 75 per cent and oxygen 25 per cent in a semiclosed circle system with a Jefferson controller.

Following complete median sternotomy and the placement of the vena caval and femoral arterial cannulae, a Walton-Brodie strain gauge arch[3] was sutured to the anterior surface of the right ventricle. The segment of myocardium between the feet of the gauge was stretched to about 50 per cent of its initial diastolic length to minimize secondary influences introduced by changes in heart size. Records of arterial and central venous pressure were made from catheters placed in the radial artery and inferior vena cava and attached to Statham pressure transducers. These pressures and the myocardial contractile force were continuously recorded on a photographic oscillograph. The intra-esophageal temperature and fronto-occipital electroencephalogram were also recorded.

With the institution of complete cardiopulmonary bypass, pulmonary ventilation was stopped and a mixture of helium 50 per cent and oxygen 50 per cent was supplied to the airway at a constant pressure of 5 cm. of water. After the right atrium had been opened and the residual blood in the heart evacuated, control observations of mean arterial and central venous pressures and myocardial contractility were made for 5–10 minutes. During this time succinylcholine was being administered and no anesthetic agent was being given. Throughout the

Received from the Department of Anesthesiology, The Clinical Center, and the Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda 14, Maryland, and accepted for publication March 6, 1961.

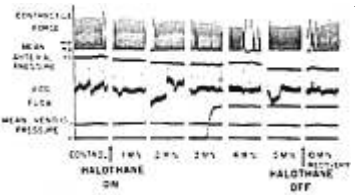

FIG. 1. Segments of the continuous records of myocardial contractile force, mean arterial pressure, electrocardiogram, arterial (pump) flow and central venous pressure obtained in patient P. H. There was a progressive decrease in contractile force during the administration of 2 per cent halothane and the arterial pressure also fell. Little change in either parameter was observed during the 10 minute "recovery" period. Arterial flow was constant throughout the period of study. The deflection in the record of flow shown during the third minute was during the period in which the linearity of the electromagnetic flowmeter was being checked.

control and study periods the perfusion rate was maintained constant at 2 l./minute/m.^{2} body surface area. The gas flow to the oxygenator in all instances was equal to the perfusion rate. After the control period, 2 per cent halothane was added to the mixture of 98.5 per cent oxygen and 1.5 per cent carbon dioxide supplied to the oxygenator unit of the heart-lung machine. The constant 2 per cent concentration of halothane was delivered from a calibrated Fluotec vaporizer for an arbitrary period of exactly five minutes after which it was discontinued and the oxygen-carbon dioxide mixture alone was delivered to the oxygenator. The succinylcholine infusion was not interrupted during halothane administration. The P_{O_2} and total CO_2 of arterialized blood from the extracorporeal circuit were determined during the five minute study period. Observations were continued for 10 minutes after cessation of halothane exposure. Typical segments from the continuous recording obtained in one patient (P. H.) are shown in figure 1.

RESULTS

The changes in heart contractile force and mean arterial and central venous pressure observed in the 6 patients during and following halothane administration are summarized in table 1. The data are expressed as percentage variations from control values. The P_{O_2}, total CO_2 and temperature recorded during each study period are also included. The average percentage changes in contractile force and arterial pressure are shown graphically in figure 2.

Depression of myocardial contractile force occurred in all 6 patients studied. The decreases ranged from 15.8 to 50.0 per cent of control values after five minutes. At the constant 2 per cent halothane vapor concentration employed the degree of depression bore a linear relationship to the time of exposure (fig. 2). The mean arterial blood pressure fell in 5 of the 6 patients studied, the decreases ranging from 2.8 to 77.9 per cent of control level at the end of five minutes. The fall in arterial pressure paralleled the impairment of contractile force during the first two minutes, appeared to be variable during the third minute and again paralleled the contractile force depression during the fourth and fifth minutes. Patient F. D. exhibited a slight increase in mean arterial pressure during the first three minutes but

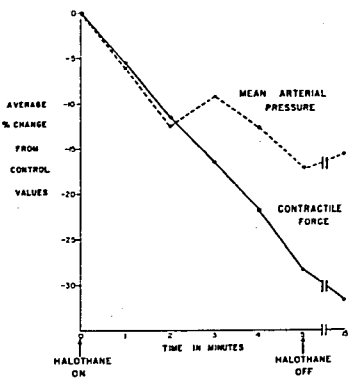

FIG. 2. Average changes in myocardial contractile force and mean arterial pressure observed during and following halothane administration in 6 patients.

TABLE 1

EFFECTS OF HALOTHANE ADMINISTRATION ON MYOCARDIAL CONTRACTILE FORCE AND MEAN ARTERIAL AND CENTRAL VENOUS PRESSURES

Patient	Parameters*	Percentage Change from Control Value						Total CO_2 Vol. %	P_{O_2} mm. Hg.	Blood Temp. °C.
		During Halothane Administration					Recovery			
		Min. 1	Min. 2	Min. 3	Min. 4	Min. 5	Min. 15			
W. B.	C.F.	0	− 9.7	− 12.9	− 16.1	− 35.1	− 16.1	40.5	170	29.5
	MAP	0	− 1.4	− 2.8	− 2.8	− 2.8	+ 5.6			
	MVP	+ 20	+20	+ 40	+ 40	+ 60	+ 40			
R. H.	C.F.	− 9.1	−18.2	− 31.8	− 40.9	− 50.0	− 54.5	48.8	130	28.8
	MAP	− 11.4	−14.8	− 13.7	− 11.4	− 13.7	− 8.0			
	MVP	− 21	−11	− 5	0	0	+ 5.3			
K. J.	C. F.	− 13.6	−18.2	− 13.6	− 9.1	− 20.0	− 20.0	35	180	30.0
	MAP	− 22.2	−55.5	− 55.5	− 55.5	− 77.9	− 41.5			
	MVP	+100	−20	− 10	− 10	0	− 10			
M. L.	C.F.	0	− 8.4	− 16.7	− 25.0	− 25.0	− 25.0	41.2	180	29.8
	MAP	− 3.4	− 3.4	− 3.4	− 4.5	− 5.6	− 9.0			
	MVP	− 38	−25	− 25	0	0	− 38			
F. D.	C.F.	− 4.8	− 9.6	− 14.3	− 23.8	− 23.8	− 4.76	39.4	—	29.0
	MAP	+ 12.3	+12.3	+ 12.3	+ 7.7	+ 7.7	+ 18.5			
	MVP	+ 50	+50	+100	+100	+100	+100			
D. F.	C.F.	− 5.3	− 5.3	− 10.1	− 15.8	− 15.8	− 26.4	40.5	200	29.5
	MAP	− 12.0	−12.0	− 12.0	− 9.7	− 9.7	− 3.6			
	MVP	0	+20	+ 20	+ 20	+ 20	+ 27			

* C.F., MAP and MVP refer to myocardial contractile force, mean arterial pressure and mean central venous pressure respectively.

during the fourth and fifth minutes of exposure to halothane some fall toward the control pressure level was apparent. Mean venous pressure increased over control levels an average of 30 per cent in the 6 patients. The total arterial CO_2 values were all significantly less than the 55 volumes per cent considered as the upper limit of normal for our laboratory and in the usual range observed during bypass. The arterial P_{O_2} values and temperatures were similar in each of the 6 patients.

DISCUSSION

During extracorporeal circulation for the open correction of atrial septal defect, myocardial contractile activity persists and circulation through the coronary and peripheral vascular beds may be maintained at a constant rate by the mechanical action of the pump returning arterialized blood to the patient. When the pump output is constant, alterations in peripheral arterial pressure necessarily reflect alterations in total arterial vascular resistance. Changes in the force with which the heart contracts can be measured by means of the Walton-Brodie strain gauge arch sutured to the surface of the ventricle.[3] Arterial blood pressure can be determined, of course, by direct arterial cannulation. Thus myocardial and peripheral actions of pharmacologic agents may be studied separately while the autonomic innervation of both the cardiac and peripheral systems remains intact.

In the studies presented the administration

of 2 per cent halothane vapor depressed myocardial contractile force. This was usually accompanied by a fall in mean arterial pressure. The extent of these changes varied directly with the time of exposure to the drug for the five minute study period employed. With cessation of halothane administration arterial pressure returned toward its control value in 10 minutes but a further reduction in contractile force was observed during this time. These direct observations, made in hearts hemodynamically isolated from the peripheral circulation, confirm the conclusions previously arrived at from experiments on the intact circulation, that halothane depresses the myocardium directly. The observed decrease in mean arterial blood pressure which occurred during halothane administration in the present experiments proves that the agent also has the effect of decreasing total peripheral arterial resistance. The break in the slope of the average arterial pressure curve during the third minute may represent the effect of some compensating mechanism (fig. 2). No data are presented which would explain the mechanisms involved in the fall in arterial blood pressure or the suggested vascular compensation. The changes in mean central venous pressure in this study may or may not be of physiologic significance. In closing a large atrial septal defect retraction of the intracardiac venous cannulae is necessary and obstruction to inferior vena caval flow, with a rise in inferior vena caval pressure, is often observed. Whether or not the increases in central venous pressure represent an effect of halothane on venous tone requires further study.

The anesthetic and premedicant drugs and dosages used were considered to be the minimum with which these surgical procedures could be carried out. Succinylcholine was employed for relaxation to avoid the possible additive hypotensive effects of halothane and curare. Since every effort was made to discontinue anesthetic administration prior to perfusion and to maintain the rate of succinylcholine infusion constant during the study period, we believe that the influence of these factors was negligible. It was nevertheless possible, however, that normal cardiovascular regulatory mechanisms were impaired to some extent.

The effects of extracorporeal circulation *per se* upon myocardial contractile force and arterial pressure have been studied by Braunwald and associates[4] with a technique of perfusion identical to that employed in these studies. Myocardial contractile force was increased by 8 per cent in one patient and decreased by 5 to 15 per cent of the control values in the other 5 patients. In 12 patients no systemic change in arterial blood pressure occurred when the perfusion rate remained constant. The changes in contractile force and arterial pressure noted in the current study were of sufficiently greater magnitude to substantiate their significance. In the studies described the effects of halothane were necessarily observed while the effects of other pharmacologic agents were operative. However, these agents were in the circulation during both the control and study periods and the only variable introduced was halothane itself.

Summary

The effects of halothane administration upon myocardial contractile force (Walton-Brodie strain gauge arch sutured to the right ventricle) and total vascular resistance were studied in 6 patients during complete cardiopulmonary bypass. The administration of 2 per cent halothane introduced into the oxygenator resulted in a decrease in myocardial contractile force in every patient. The change in contractile force was linear with time and averaged 28 per cent less than the control value at five minutes. Systemic arterial pressure (total vascular resistance) also fell in 5 of the 6 patient and after the period of halothane administration averaged 17 per cent less than the control value. During a ten minute recovery period arterial pressure rose somewhat but a further reduction in contractile force was observed.

The observations, made while the heart and peripheral circulation were physiologically separated, indicate that halothane directly depresses the myocardium and that the agent also decreases total vascular resistance.

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MEGIMIDE Morphine causes a marked narrowing of the margin between the dose of bemegride (Megimide) causing stimulation of respiration and the dose causing convulsions. With pentylenetetrazol (Metrazol) this margin remains unchanged, as the convulsant dose is the same with or without morphine. (*Eckel, D., and Seifen, E.: Comparison of Stimulating and Convulsing Properties of Bemegride and Metrazol after Use of Morphine, Der Anaesthesist 9: 360 (Dec.) 1960.*)

ANTIEMETICS In only 3 per cent of 2,230 patients was vomiting severe enough to indicate drug therapy in the recovery room and in nearly ever case antiemetic therapy was then successful. Three phenothiazine derivatives were employed, all intravenously: promethazine (Phenergan) 12.5 mg.; triflupromazine (Vesprin) 1 to 3 mg.; and fluphenazine (Prolixin) 0.1 to 0.6 mg. All three drugs suppressed vomiting in every case, but produced side actions, most alarming of which was hypotension. The most innocuous was promethazine, which produced no somnolence or hypotension; triflupromazine manifested the most severe side actions. Another drug, trimethobenzamide (Tigan), manifests none of the side-effects characteristic of the phenothiazines. Used intravenously in a 50 mg. dose, it was equally as effective as the phenothiazines and appeared to be devoid of severe hypotensive and somnolent effects. Thus, it appears that the administration of antiemetics should be withheld until they are really needed. (*Adriani, J., and others: Is Prophylactic Use of Antiemetics in Surgical Patients Justified? J. A. M. A. 175: 666 (Feb. 25) 1961.*)

ANTIARRHYTHMIC DRUG Effects of RO 2-5803 and quinidine were compared when given orally and intravenously to 13 patients with chronic cardiac arrhythmias. Both drugs caused quantitatively equal slowing of atrial rate in flutter or fibrillation. They differed mainly in their effect on ventricular rate. In every case, the ventricular rate increased with quinidine but was not accelerated by RO 2-5803. This suggests that RO 2-5803 has no vagalytic activity. (*Kahn, H. R., and others: Some Effects of New Antiarrhythmic Drug, Clin. Pharmacol. Ther. 2: 147 (Mar.-Apr.) 1961.*)