THE CARDIOVASCULAR EFFECTS OF HALOTHANE[1, 2]

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ONE OF THE INTERESTING and disturbing properties of halothane—$CF_3CHClBr$ (Fluothane®)—is the ease and rapidity with which it can produce hypotension which is sometimes of an alarming degree. It has been variously speculated that this might be due to either peripheral vasodilatation or myocardial depression, or to a combination of both. Hitherto, experimental evidence for either viewpoint has been lacking. This study was undertaken to elucidate the effects of halothane upon the cardiovascular system.

METHOD

The experiments were carried out on healthy male volunteers. The men were instructed not to breakfast on the day of the experiment. After admission to the Recovery Room, blood and urine specimens were taken. Haemoglobin, packed cell volume, total and differential white counts, and a routine urinalysis, including reaction, specific gravity, sugar, acetone, protein, and microscopic examination, were done. Liver function was evaluated by the thymol flocculation, thymol turbidity and zinc sulphate flocculation tests and by blood albumen-globulin determinations, including electrophoresis for the various globulin fractions. These tests were repeated the day following the experiment.

No premedication was administered. A cardiac catheter was passed, under fluoroscopic control, from the left median cubital vein into the pulmonary artery. An intravenous needle was placed into the median cubital vein of the other arm, and a 20-gauge Riley needle was inserted into either the brachial or the femoral artery. Electrocardiographic and electroencephalographic leads were applied.

Cardiac output. Cardiac output was determined by the indicator-dilution technique, using the venous injection of Cardio-Green[4] with arterial sampling through a cuvette oximeter (1, 2). The exact method has been described in a separate publication, which should be consulted for details (3). The advantages of using Cardio-Green and oximetry, as opposed to other dye methods, are that (*a*) there is no significant blood loss, (*b*) results are almost immediately available, (*c*) the method requires a minimum of the technicians' time for the calculation of output, (*d*) any number of determinations can be carried out without accummulation of dye, and without toxic effects, and (*e*) variations of percentage of oxygen saturation have no effect on the output curves.

Peripheral arterial pressure. By means of the indwelling arterial needle, con-

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tinuous arterial pressure tracings were recorded in a manner similar to that described in a previous publication (4).

Pulmonary artery pressure. The same recording devices were used for pulmonary artery pressure as for peripheral arterial pressure. The cardiac catheter was connected to a Statham strain gauge and thence to a recording device which allowed continuous monitoring and recording of these pressures.

Electrocardiogram. A third channel on the recording device was used for continuous monitoring and recording of the electrocardiogram.

Electroencephalogram. Continuous tracings were taken during the experiment by means of an Edin Anesthograph.

Vein-to-artery circulation time was the "appearance time" of the cardiac output curve: that is, the time which elapsed from injection of the dye into the vein to its appearance in the arterial blood, as this was drawn through the oximeter cuvette.

Total peripheral resistance was calculated from the following formula:

$$R = \frac{B(F)A_m - O}{CO} \times 1{,}332$$

where R = total peripheral resistance (Dynes/sec./cm.$^{-5}$)
$B(F)A_m$ = brachial (or femoral) arterial mean pressure (mm.Hg)
CO = cardiac output (ml./sec.)
O = approximation of left ventricular end-diastolic pressure
1,332 = 980 (gravity factor) $\times$ 1.36 (specific gravity of Hg) for conversion to absolute units.

Total pulmonary resistance was calculated from a similar formula, substituting PA_m (pulmonary mean arterial pressure in mm. Hg) for $B(F)A_m$.

Control values were recorded over a period of not less than ten minutes, and at least two control cardiac ouput measurements, closely similar to one another, were obtained. Anaesthesia was then induced with small incremental doses of 2.5 per cent thiamylal sodium. This was done in order to avoid the subjective unpleasantness of a slow inhalation induction, and to prevent the excitement stage during which the many needles might have been dislodged. The amounts of thiamylal used were never sufficient to produce either apnoea or hypotension. Halothane was then administered from a Fluotec® vaporizer in a semi-closed (partial rebreathing) system using a flow of 10 L./min. of oxygen. The concentration of halothane was gradually increased during the first ten minutes or so to the maximum of 3 per cent. This concentration was maintained until all vital signs had become stabilized. An oropharyngeal airway was inserted as soon as it could be tolerated. Endotracheal tubes were not used. When the blood pressure had been stable for at least five minutes, halothane was administered in a closed system with carbon dioxide absorption, a reduced flow of oxygen and controlled respiration—the vaporizer being left full on—until the maximum hypotension compatible with safety had been attained. In one or two patients blood pressure was allowed to fall as low as 30 mm. Hg

[4]Kindly supplied through the courtesy of Dr. John H. Brewer, Director of Biological Research, Hynson, Westcott & Dunning, Inc., Baltimore, Maryland, U S.A.

systolic. Cardiac output determinations were done at various stages of anaesthesia. After cardiac output determinations had been completed at the maximum hypotension, halothane was discontinued, oxygen administered in a semi-closed system at 10 L./min., and the subject allowed to waken spontaneously. Cardiac output determinations were done again during various stages of awakening, the last one just before the subject answered to verbal command, but when he was still lying quietly.

At various stages of the experiment, the effects of a number of agents on blood pressure, cardiac output, etc., were observed. Atropine was given to two subjects after moderate hypotension had been reached. In four subjects phenylephrine was administered intravenously when the blood pressure had reached its lowest level. One volunteer, who had had neither atropine nor phenylephrine, was given Lanatoside C when a moderate degree of hypotension with a nodal rhythm existed during awakening.

Results

Subject I (Fig. 1)

Induction was smooth, but the systemic arterial pressure rose from 125/75 mm. Hg to 160/85 mm. Hg and the pulmonary artery pressure from 21/8 mm. Hg to 26/16 mm. Hg. A concentration of 3 per cent halothane was attained within 12 minutes.

Anaesthesia was maintained at this level for 20 minutes during which time some peripheral vasodilatation was noted, and the blood pressure fell rapidly to 80–90 mm. Hg systolic and then levelled off. Similarly the pulmonary artery pressure fell to 17/9 mm. Hg, and stabilized at its induction level. The cardiac output by this time had fallen from a control value of 9 L./min. to 7 L./min and the vein-to-artery circulation time had increased from 11 to 13 seconds. The total peripheral resistance had declined somewhat, but the total pulmonary resistance was markedly raised.

When these observations had been completed, the administration of halothane was continued in a closed system with carbon dioxide absorption. It quickly became necessary to assist and then control ventilation. There was now a slowly progressive further fall of pressure. But neither the cardiac output nor the vein-to-artery circulation time had changed significantly at a time when the systemic blood pressure had reached 60/40 mm. Hg. The total peripheral resistance declined, and total pulmonary resistance fell again.

When the systemic blood pressure had fallen to 45/30 mm. Hg, the cardiac output had also fallen to 5 L./min. Meanwhile, the pulmonary artery pressure had steadily declined to 14/6 mm. Hg, vein-to-artery circulation time had increased to 14 seconds, the total peripheral resistance had risen slightly and total pulmonary resistance markedly.

The systemic blood pressure rose sharply to 130/80 mm. Hg as soon as halothane was discontinued.

No abnormalities were seen in the electrocardiogram during the experiment.

Subject II (Fig 2)

During the induction, which was smooth, there was a temporary fall of systemic blood pressure from 140/70 mm. Hg to 120/70 mm. Hg, accompanied by a fall of pulmonary artery pressure from 25/15 mm Hg to the control level (18/9 mm. Hg). A concentration of 5 per cent halothane was reached within 8 minutes.

The blood pressure dropped sharply 8 minutes later to 100 mm. Hg systolic and then rose to a steady level of 110/50 mm. Hg. At the same time the pulmonary artery pressure rose to 28/15 mm. Hg and then stabilized at 24/15 mm. Hg At this time the cardiac output had fallen to 7.7 L./min. from pre-anaesthetic values of 11

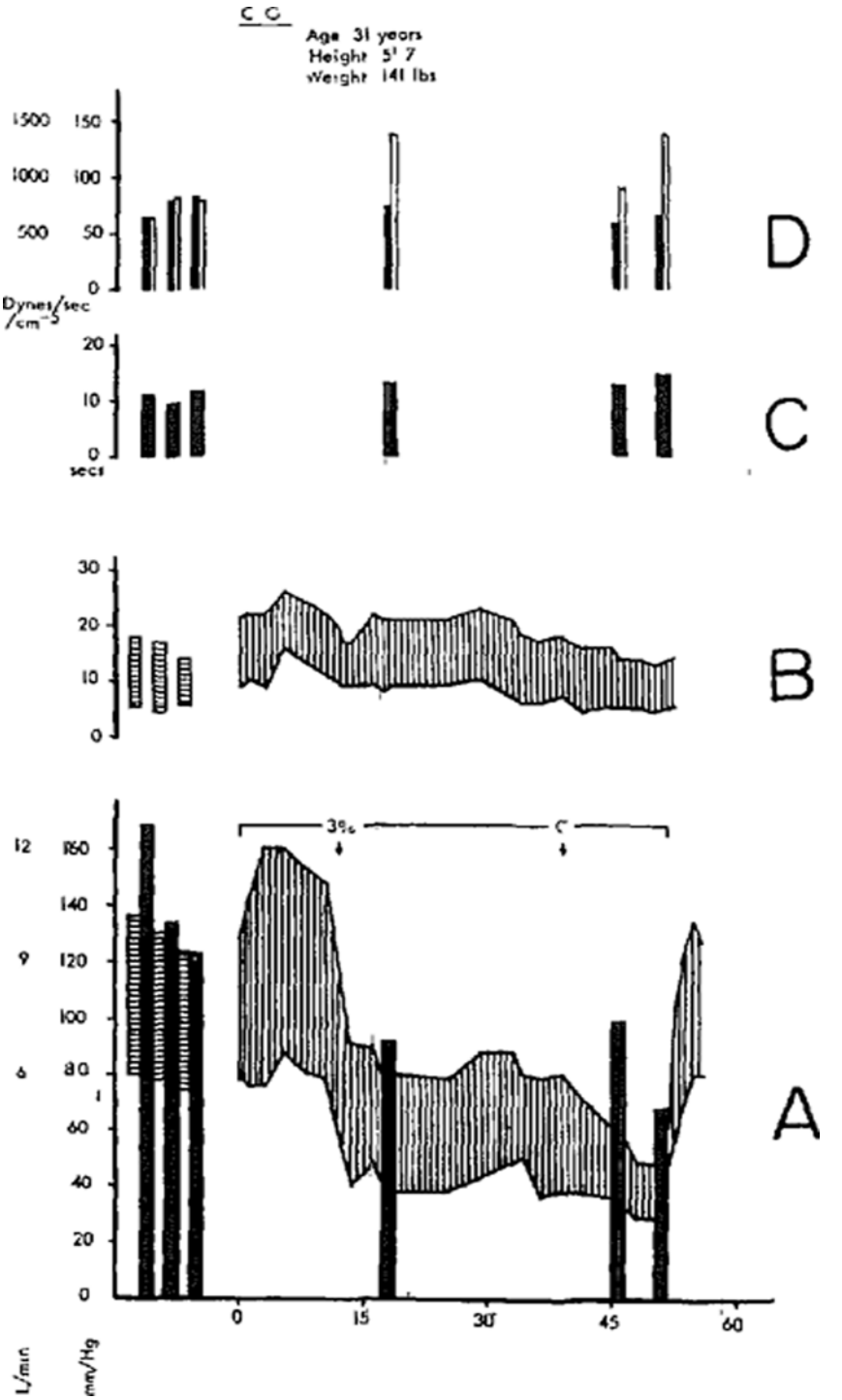

FIGURE 1 *A*, systemic blood pressure in mm Hg (pulse pressure shaded) Cardiac output (black bars) in L/min Bracket denotes duration of administration of halothane, the time when 3% concentration was reached and when the system was closed is marked by "3%" and "C" respectively *B*, pulmonary artery pressure in mm Hg *C*, vein-to-artery circulation time in seconds *D*, total systemic resistance (black bars, scale on left), total pulmonary resistance (white bars, scale on right), both—Dynes/sec /cm $^{-5}$

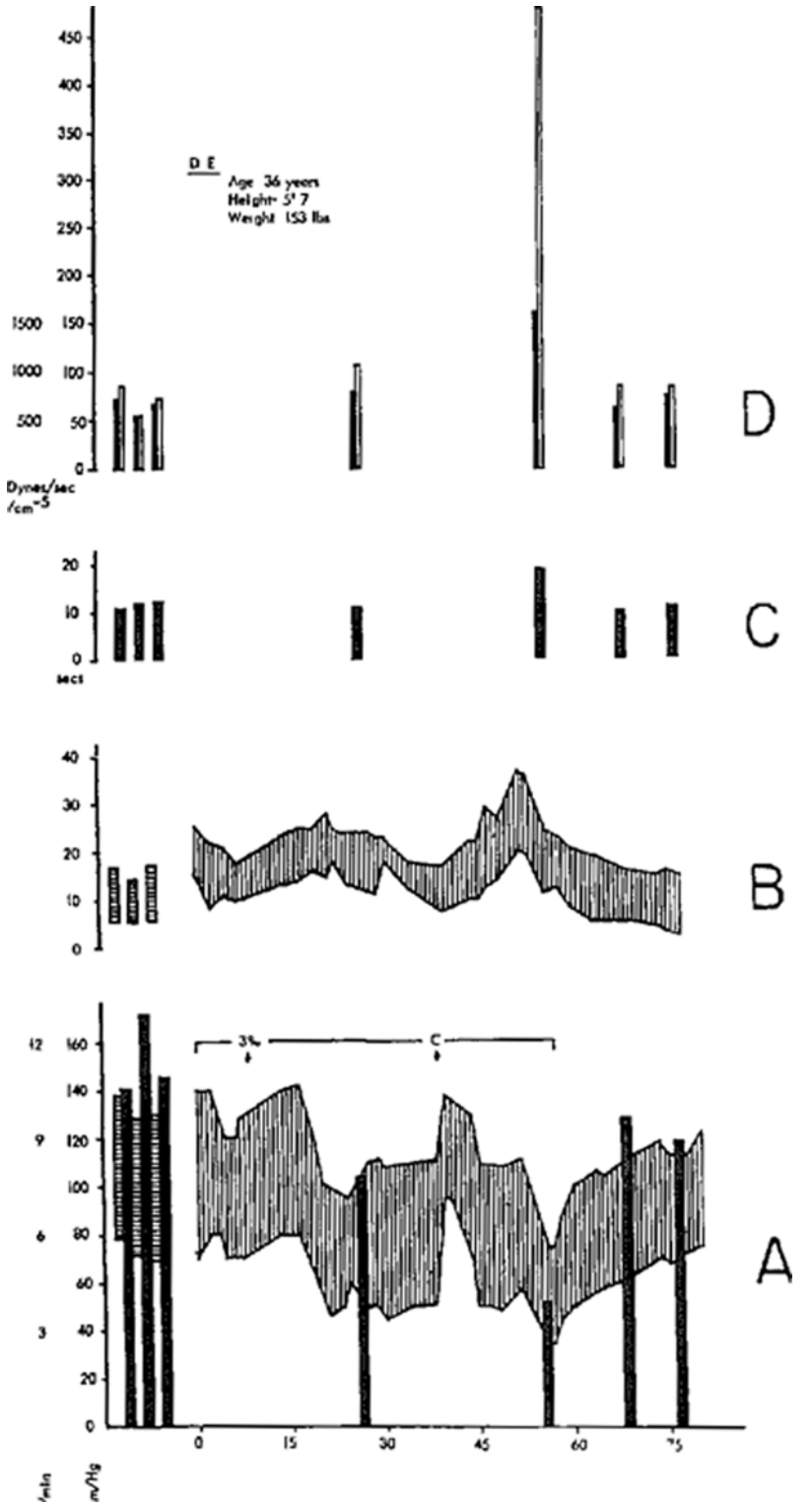

FIGURE 2 Same as Figure 1.

L /min The vein-to-artery circulation time was unchanged at 11 seconds, the total peripheral resistance had risen slightly and the total pulmonary resistance markedly

There was some technical difficulty while the change to a closed system was being made, so that anaesthesia lightened rapidly and the blood pressure rose to 135/95 mm Hg, meanwhile the pulmonary artery pressure had steadily fallen to pre-induction levels Following this, the systemic blood pressure fell slowly and steadily with a concomitant rise in pulmonary artery pressure Respiration was controlled When a systolic pressure of 75 mm Hg had been reached the cardiac output had fallen to 3 9 L/min , and the pulmonary artery pressure to 23/13 mm Hg The vein-to-artery circulation time had increased to 19 seconds There was a substantial increase of total peripheral resistance, but the most striking feature was the great rise of total pulmonary resistance A nodal rhythm was observed as the systemic blood pressure reached its nadir

After halothane had been discontinued, the systemic blood pressure rose gradually to 120/75 mm Hg, and the pulmonary pressure fell to 15/2 mm Hg The cardiac output was measured twice during the recovery period and found to have risen to the control level Circulation time and systemic and pulmonary resistances were also back to normal

Subject III (Fig 3)

Induction was as previously described, the 3 per cent concentration being reached in 5 minutes The subject was moaning and struggling a little during this time, and the electrocardiogram showed some ventricular extrasystoles As anaesthesia deepened, these disappeared and the blood pressure fell rapidly from 160 mm Hg to a little over 100 mm Hg systolic, the pulmonary artery pressure rose briefly from 23/9 mm Hg to 32/15 mm Hg and then stabilized at 25 mm Hg systolic, and the cardiac output fell from 12 L /min to 7 8 L /min There was no significant change in the vein-to-artery circulation time, but the total peripheral resistance increased slightly and the total pulmonary resistance markedly As soon as the systemic blood pressure had reached a stable level, a nodal rhythm, alternating with an inverted T wave, was observed in Lead II of the electrocardiogram These abnormalities persisted on and off throughout the experiment

When the circulatory parameters had been stable for 10 minutes, the anaesthetic system was closed and respiration was first assisted and then controlled The systemic blood pressure now fell abruptly to 24/16 mm Hg, at which level halothane administration was stopped The S-T segment in Lead II of the electrocardiogram was now depressed, the pulse rate was 48/min , the pulmonary artery pressure was 15/7 mm Hg, and the cardiac output had fallen to 5 8 L /min The vein-to-artery circulation time had increased from 13 seconds to 16½ seconds The total peripheral resistance had fallen to pre-anaesthetic levels, but a further marked rise in the total pulmonary resistance had occurred

After halothane had been discontinued, the systemic blood pressure rose spontaneously Within 10 minutes it had reached 90/50 mm Hg and the pulmonary artery pressure had returned to 20/5 mm Hg The cardiac output was now 8 2 L /min , the vein-to-artery circulation time had returned to normal, the peripheral resistance had increased somewhat and the total pulmonary resistance had fallen Nodal rhythm was again noted intermittently

Lanatoside C 0 4 mg was administered intravenously after the output determination had been completed This seemed to have no immediate effect on the course of events, other than that the nodal rhythm disappeared

Twenty minutes later the systolic blood pressure had risen to 140/80 mm Hg and the output had reached pre-induction levels

Subject IV (Fig 4)

Anaesthesia was induced in the usual manner and after some struggling and coughing a concentration of 3 per cent halothane was reached after 17 minutes The systemic

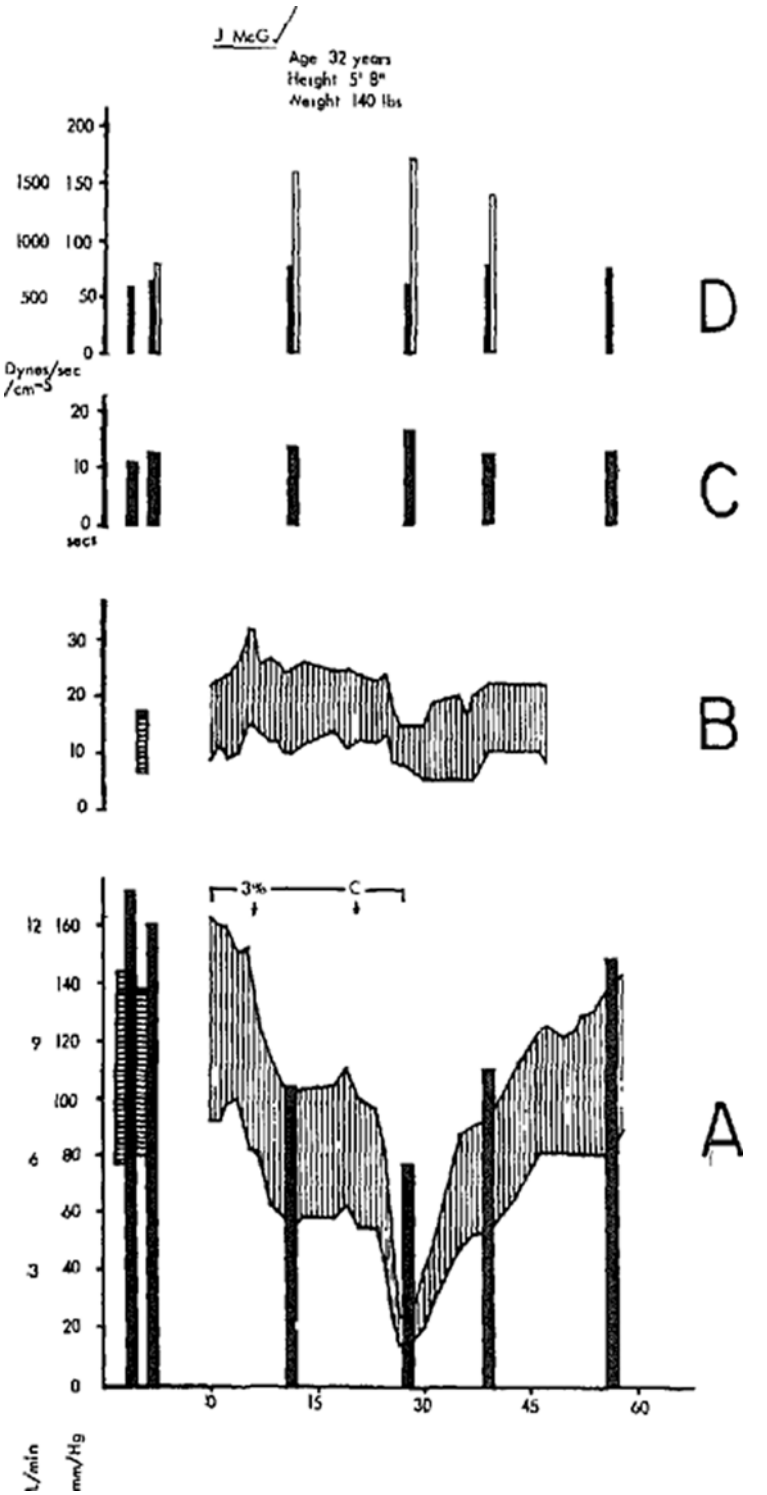

FIGURE 3 Same as Figure 1 L, Lanatoside C given

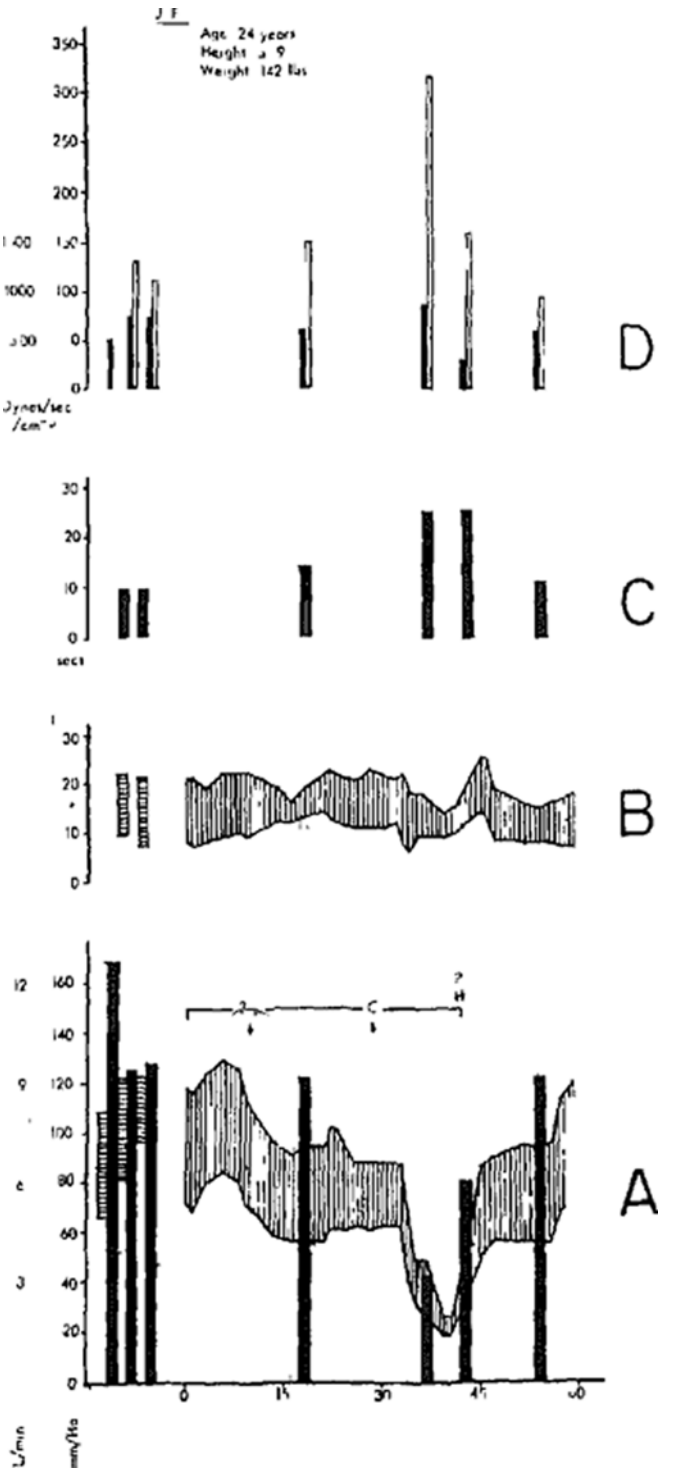

FIGURE 4 Same as Figure 1 P, phenylephrine given

blood pressure rose from 120/70 mm Hg to 130/80 mm Hg during this rather stormy induction, but the pulmonary artery pressure was unchanged

Following this, the systemic blood pressure fell to, and became stable at 90/55 mm Hg systolic and the pulmonary artery pressure fell to 16/12 mm Hg from 22/10 mm. Hg The cardiac output was unchanged, but the vein-to-artery circulation time increased from 9 to 14 seconds The total peripheral resistance fell and the total pulmonary resistance was markedly increased

When the blood pressure had been stable for a little over 15 minutes, the anaesthetic system was closed and respirations were controlled Nodal rhythm soon appeared, and after 3 minutes the systemic pressure fell steeply to 48/30 mm Hg There were occasional ventricular extrasystoles and the pulse rate had declined to 55/min The cardiac output now had fallen to 3 1 L /min , the vein-to-artery circulation time was 24 seconds, the total peripheral resistance was increased a little and the total pulmonary resistance had risen greatly

Meanwhile, the systemic blood pressure had fallen still further to 25/20 mm Hg and the pulmonary artery pressure to 15/9 mm Hg The administration of phenylephrine 0 25 mg intravenously, followed 3 minutes later by another 0 5 mg , raised the systemic blood pressure to 85/45 mm Hg Administration of halothane was now discontinued Immediately following this, the cardiac output was found to have risen to 6 L /min A nodal rhythm persisted although ventricular extrasystoles were seen no longer The pulmonary artery pressure had risen to 16/10 mm Hg, from a low of 13/9 mm Hg at the time of greatest systemic hypotension The vein-to-artery circulation time was unchanged, but the peripheral resistance was markedly diminished and the total pulmonary resistance, although much reduced from the previous reading, was still significantly elevated above the controls

During the next 10 minutes, the blood pressure rose steadily to 99/55 mm Hg, the nodal rhythm disappeared, and the pulmonary artery pressure declined gradually to 15/8 mm Hg At the end of this time the cardiac output was 9 1 L /min , the circulation time was normal and the peripheral and pulmonary resistances more nearly normal

Subject V (Fig 5)

This was a smooth induction, a concentration of 3 per cent halothane being attained within 5½ minutes As anaesthesia progressed, the systemic blood pressure fell steeply from 130/85 mm Hg to 62/30 mm Hg and then rose gradually to stabilize at 70/40 mm Hg, the pulmonary artery pressure declined from 22/11 mm Hg to 13/5 mm Hg immediately after induction, the pulse rate from 60/min to 48/min When the circulatory parameters were stable at these levels, the cardiac output was found to be 5 9 L /min and the vein-to-artery circulation was unchanged at 23 seconds, but the total peripheral resistance had fallen slightly and the total pulmonary resistance moderately

Soon after the cardiac output measurement had been done, the subject's pulse rate fell to 36/min The injection of atropine 0 4 mg intravenously raised the rate to 68/min within 1 minute and caused the systemic blood pressure to rise to 100/60 mm Hg The pulmonary artery pressure rose to 19/6 mm Hg At this time the cardiac output had increased to 7 8 L /min , and the vein-to-artery circulation time had decreased to 11 seconds The total peripheral resistance had risen slightly and the total pulmonary resistance had fallen a little

Halothane was then administered from a modified Boyle bottle with the lever at 10, the oxygen flow being unchanged Respiration was assisted and later controlled There followed a sharp drop of systemic blood pressure, which reached 40/25 mm Hg after 7 minutes, accompanied by a slower fall of pulmonary artery pressure to 10/2 mm Hg The cardiac output at this time had fallen to 6 2 L /min , the vein-to-artery circulation time had increased to 22 seconds and both peripheral and pulmonary resistances had fallen further

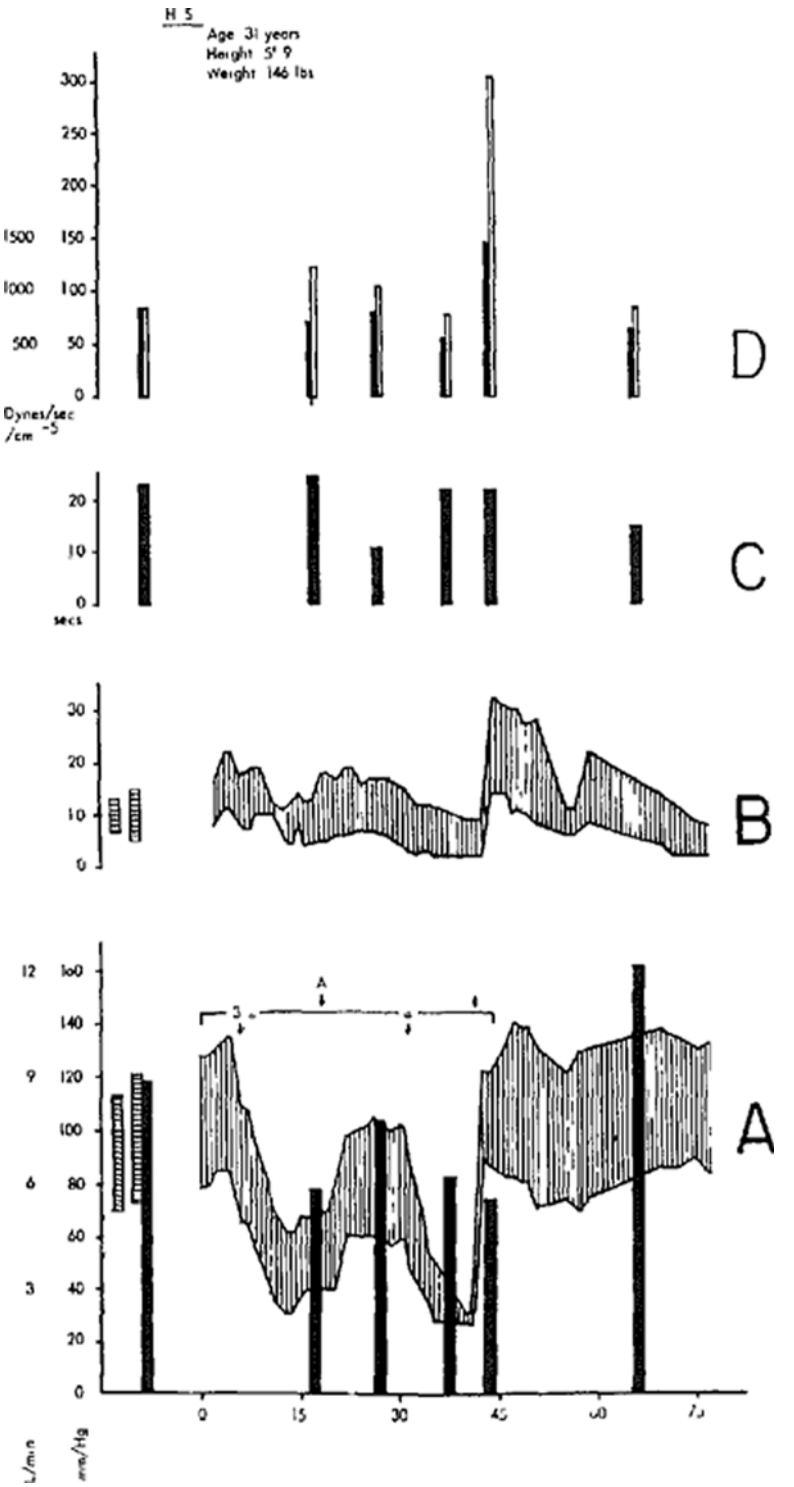

FIGURE 5 Same as Figure 1 B, change from Fluotec to Boyle vaporizer, A, atropine sulphate 0 4 mg given, P, phenylephrine given

Two minutes after these determinations had been completed the systemic blood pressure had fallen to 30/25 mm Hg and the pulmonary artery pressure to 9/2 mm Hg At this time phenylephrine 2 5 mg, was injected intravenously There was an immediate sharp rise of the systemic blood pressure to 122/86 mm Hg and of the pulmonary artery pressure, after a delay of 30 seconds, to 33/14 mm Hg The cardiac output now had fallen to 5 5 L , the vein-to-artery circulation time had not changed, but the total peripheral resistance had risen sharply and the total pulmonary resistance greatly The P wave on the electrocardiogram became inverted in Lead II at this time Halothane was now discontinued

During the next 10 minutes the systemic blood pressure rose to 140/80 mm Hg and then fell slowly to 120/75 mm Hg, while the pulmonary artery pressure fell gradually to 11/6 mm Hg

Seven minutes later, the systemic blood pressure had risen slowly to 130/80 mm Hg and the pulmonary artery pressure was 16/5 mm Hg The cardiac output now had risen to over 12 L /min , the vein-to-artery pressure circulation time had returned to normal, and both peripheral and total pulmonary resistances had returned to control levels

Ten minutes later, as the subject awoke, the systemic blood pressure had remained unchanged, but the pulmonary artery pressure had fallen to 8/2 mm Hg

Subject VI (Fig 6)

This was a smooth induction in the usual manner, 3 per cent halothane was attained within 4 minutes During this time the blood pressure dropped steeply to 64/40 mm Hg and then gradually rose again to 80/45 mm Hg Pulmonary artery pressure was essentially unchanged at 17/5 mm Hg after it had risen momentarily to 20/4 mm Hg after induction The cardiac output had fallen from 9 3 L /min to 8 4 L /min with an increase in the vein-to-artery circulation time from 12 seconds to 15 seconds The total peripheral resistance fell, but the total pulmonary resistance was unchanged

When the systolic blood pressure had risen to 85/60 mm Hg, atropine 0 4 mg was given intravenously During the next 15 minutes the systemic blood pressure fell slowly to 60/45 mm Hg During the same period the pulmonary artery pressure averaged 15/8 mm Hg Two minutes after the injection of atropine, the cardiac output had risen to its pre-induction level, the vein-to-artery circulation time and total peripheral resistance had risen to control values, and the total pulmonary resistance had not changed The fall of systemic blood pressure was followed by a spontaneous rise to 80/55 mm Hg within the next 5 minutes

At this point, rebreathing was instituted The systemic blood pressure fell rapidly to 48/40 mm Hg The pulmonary artery pressure rose at first to 22/14 mm Hg and then fell to 11/7 mm Hg At this time the cardiac output had fallen to 5 7 L /min , the vein-to-artery circulation time had increased to 15 seconds, the total peripheral resistance had fallen, and the total pulmonary resistance had risen steeply The intravenous injection of phenylephrine 2 5 mg was followed by an immediate rise of the systemic blood pressure to 125/105 mm Hg and a rise of pulmonary artery pressure to 38/22 mm Hg Halothane administration was discontinued Three minutes later a cardiac output determination was done The resultant curve was flat and prolonged and did not lend itself to accurate measurements Undoubtedly, however, the output was extremely low The vein-to-artery circulation time was increased to 20 seconds There was a run of ventricular extrasystoles followed by sinus rhythm and return of more ventricular extrasystoles

Both systemic and pulmonary pressures returned to pre-anaesthetic levels during the next 30 minutes Cardiac outputs, measured on two occasions, had returned to normal levels, as had the vein-to-artery circulation time and the total peripheral resistance The total pulmonary resistance remained elevated at the first reading but had returned to pre-anaesthetic levels on the second

Just before the patient wakened, his systemic blood pressure was 115/80 mm Hg and his pulmonary pressure 12/6 mm Hg, all other parameters were normal

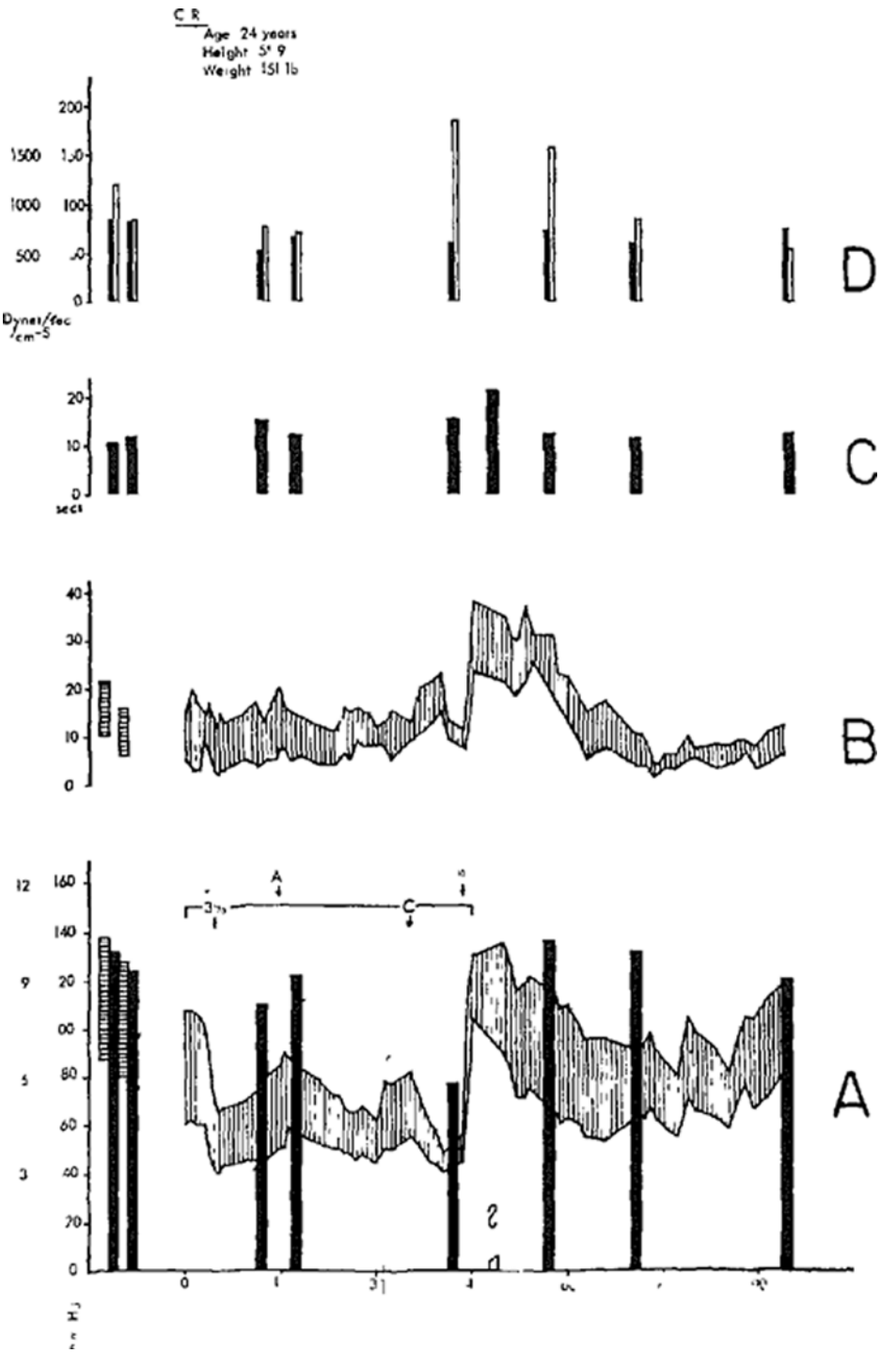

FIGURE 6 Same as Figure 1 A, atropine given, P, phenylephrine given

Subject VII (Fig 7)

Anaesthesia was administered in the routine manner, but the induction was somewhat more stormy than usual with much breath-holding and coughing, it took 9 minutes to reach a concentration of 3 per cent Even then, the subject was holding his breath, coughing, and struggling a little Meanwhile the systemic blood pressure had risen from 145/85 mm Hg to 160/110 mm Hg and had then fallen to 130/80 mm Hg, while the pulmonary artery pressure had risen from 16/7 mm Hg to 20/8 mm Hg Three minutes later succinylcholine 10 mg was administered to smooth anaesthesia Thereafter, the systemic blood pressure fell gradually until it had reached a plateau at 105/64 mm Hg and the pulmonary artery pressure stabilized at 20/10 mm Hg, having previously risen to 25/11 mm Hg When the plateau had been reached, the cardiac output was found to be 10 L /min The total peripheral resistance had diminished somewhat and the total pulmonary resistance had increased

Rebreathing was now instituted with controlled respiration and the halothane concentration gradually reduced to 0 5 per cent Within 7 minutes the blood pressure had fallen to 60/40 mm Hg The pulmonary artery pressure, which had initially fallen to 17/7 mm Hg, returned to 20/12 mm Hg The cardiac output at this time had fallen to 4 L /min with an increase in the vein-to-artery circulation time from 10 seconds to 13 seconds The total peripheral resistance had increased to pre-induction levels and the total pulmonary resistance had risen markedly While the cardiac output was being done, anaesthesia became a little lighter This was reflected by a slight rise of systemic blood pressure

Further deepening of the anaesthesia brought the blood pressure down to 40/30 mm Hg, the pulmonary artery pressure remaining essentially unchanged The cardiac output was the same as before but the vein-to-artery circulation time was much prolonged at 19 seconds, the total peripheral resistance was reduced, and the pulmonary resistance remained high

The intravenous administration of phenylephrine 2 5 mg was followed, within one minute, by a return of the systemic blood pressure to 130/90 mm Hg, and a steep rise of pulmonary artery pressure to 41/21 mm Hg The cardiac output failed to keep pace with these changes and was only 5 7 L /min The vein-to-artery circulation time had fallen slightly to 17 seconds, the total peripheral resistance had risen markedly, and the total pulmonary resistance had risen further

Halothane was now discontinued and within 10 minutes the cardiac output had returned to 10 2 L /min , neither systemic nor pulmonary pressures having changed The vein-to-artery circulation time was now normal at 10 seconds, the total peripheral resistance had fallen and the total pulmonary resistance, although still markedly elevated, had returned to more acceptable levels The pulmonary artery pressure was still elevated at 42/11 mm Hg and remained high until the subject awoke

No cardiac arrhythmias were noted during the experiment

Discussion

Systemic Blood Pressure

There is a progressive, sometimes rapid, fall of blood pressure as anaesthesia is deepened with halothane A plateau is established at a level which depends upon the concentration employed Sometimes this plateau is established at a level somewhat higher than that reached during the initial fall, probably because of compensatory readjustments in the peripheral vascular bed

If the concentration is further increased, for example, if rebreathing is permitted, the pressure falls further Often this fall begins after a very short period of time, and may be precipitous in the presence of controlled respiration This

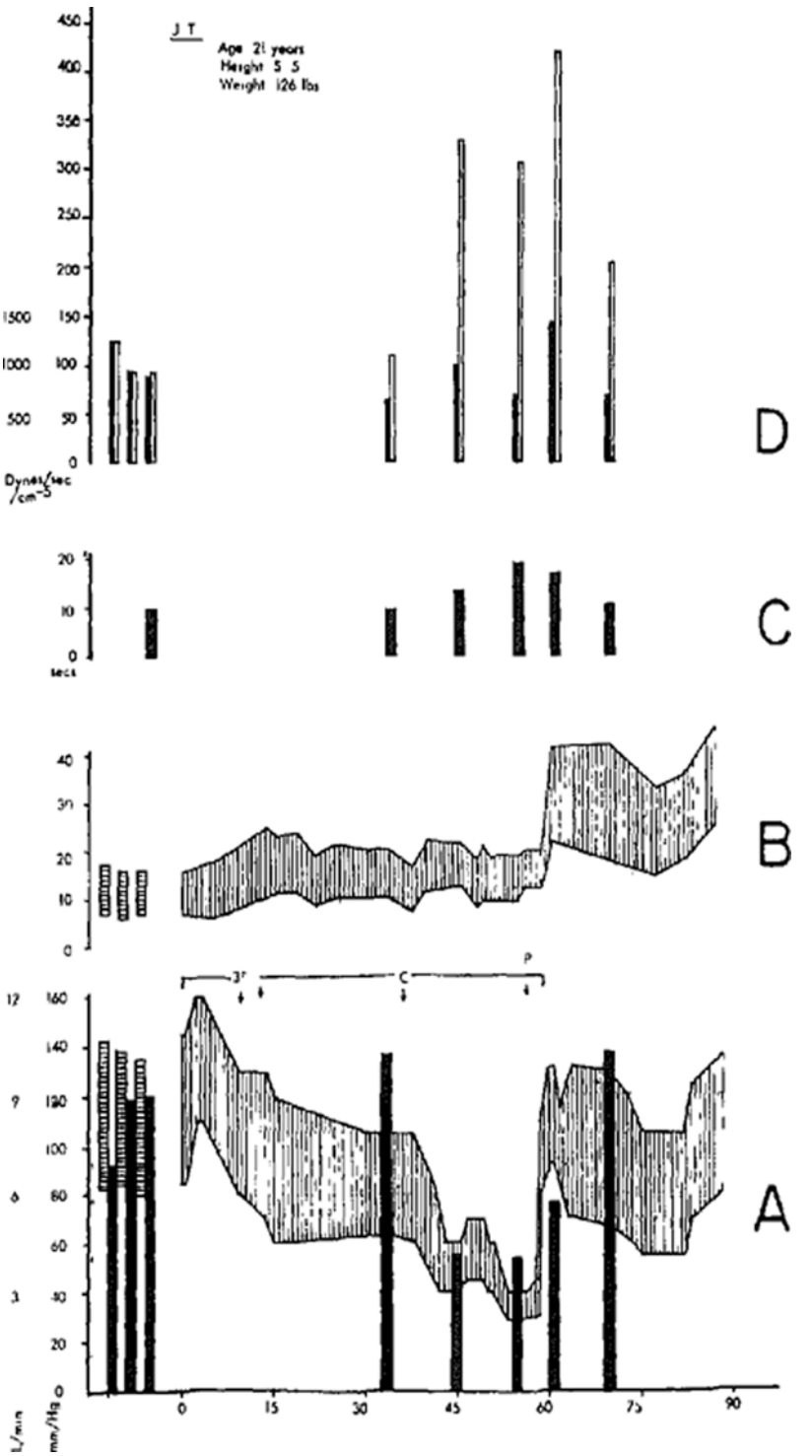

FIGURE 7 Same as Figure 1 S, succinylcholine 10 mg given, P, phenylephrine given

second fall of pressure, due to a deliberate overdose, results in marked narrowing of the pulse pressure.

The blood pressure quickly rises to pre-anaesthetic levels when the administration of halothane is stopped.

Pulmonary Artery Pressure

There is usually a slight elevation of pulmonary artery pressure, which persists until the systemic pressure falls to very low levels. This fall is usually associated with a concomitant fall of pulmonary artery pressure which remains low even though the systemic pressure returns to normal.

Cardiac Output

The cardiac output falls with the systemic blood pressure until the plateau of pressure is reached. If further hypotension is produced by an overdose of halothane, the cardiac output falls to the point where it becomes inadequate. The cardiac output rises *pari passu* with the spontaneous rise of blood pressure which occurs after halothane administration is discontinued.

Vein-to-Artery Circulation Time

A comparison of the appearance times of the various cardiac output curves indicates clearly a progressive slowing of circulation related to the degree of hypotension and reduction of cardiac output.

Total Peripheral Resistance

This is the sum of the pressure-flow relationships in all parts of the peripheral circulation. A change in the total peripheral resistance indicates that vasoconstriction or dilatation in one area or areas exceeds the opposite reaction in another field. It does not necessarily mean that vasoconstriction or dilatation is general; nor does it indicate which parts of the vascular tree are predominantly affected.

The peripheral resistance declines as the blood pressure falls and settles to the plateau, indicating that this moderate hypotension may be the result of peripheral vasodilatation. The presence, in some subjects, of a definite skin flush supports this conclusion. The severe hypotension produced by an overdose of halothane is accompanied by a substantial increase of peripheral resistance. This presumably is a defensive reaction on the part of the vascular system, tending to maintain circulation in the face of hypotension and a low cardiac output.

Towards the end of the experiment, as the level of anaesthesia lightens, the peripheral resistance, together with the other parameters, returns to pre-anaesthetic levels.

Total Pulmonary Resistance

Total pulmonary resistance invariably increases, often quite sharply, as the plateau of hypotension is reached. Total pulmonary resistance is the sum of the resistance across the pulmonary arterioles and the resistance of the left heart to the inflow of blood from the pulmonary circulation. It is a matter of speculation whether this increased total pulmonary resistance is due to an increased

pulmonary arteriolar constriction, as a direct effect of halothane, or to an elevated left ventricular diastolic pressure associated with the diminished output of the left heart.

As the cardiac output falls with an overdose of halothane, the total pulmonary resistance increases markedly, and may reach very high levels. This increase is almost certainly due to the resistance offered by the left heart, which is unable to propel the blood offered to it.

Total pulmonary artery resistance returns to pre-anaesthetic levels as halothane is eliminated from the body.

Effect of Drugs

Phenylephrine was administered when the blood pressure had reached its lowest levels in four of the seven subjects. Large doses of phenylephrine raised the systemic pressure immediately to pre-anaesthetic levels, and the pulmonary artery pressure to very high levels. Smaller doses caused a more gradual rise in Subject IV. The cardiac output either fell further or was unchanged, indicating that the myocardium was sufficiently affected by halothane to be unable to cope with the increased peripheral resistance against which it had to work. Ventricular extrasystoles were seen in two subjects at this time.

The cardiac output returned to pre-anaesthetic levels and severe cardiac irregularities ceased within a few minutes of stopping the administration of halothane.

Atropine sulphate, given twice during the initial fall of systemic blood pressure towards the plateau, caused reversal of the hypotension for a period of time in one subject in whom it also helped to raise the pulmonary artery pressure. Atropine reversed bradycardia promptly. The cardiac output increased and vein-to-artery circulation time shortened. In both subjects following administration of atropine, total peripheral resistance increased, but total pulmonary resistance was not significantly affected. These observations raise some interesting problems as to the action of atropine.

Lanatoside C given only once during the spontaneous return of pressure following hypotension seemed to have little if any effect, other than that of abolishing a nodal rhythm. Whether this was due to the drug or merely a coincidence remains a matter of speculation, since nodal rhythm tended to disappear spontaneously in other subjects as the level of anaesthesia became lighter.

Cardiac Rhythm

The electrocardiogram (Lead II) was unchanged in two subjects.

The P wave inverted in one subject soon after induction; a nodal rhythm appeared when the plateau of systemic blood pressure was reached. Nodal rhythm was present in two others when the systemic pressure reached its nadir and in one the P wave inverted after the administration of phenylephrine.

Ventricular extrasystoles occurred in three subjects: once early in the experiment, once as the systemic blood pressure reached its lowest level, and once after phenylephrine. The S-T segment was depressed in one subject at the time of maximum hypotension.

Cardiac Rate

Bradycardia invariably occurred during halothane anaesthesia. It could be reversed by the use of atropine. If it was permitted to persist, the bradycardia often culminated in nodal rhythm.

Electroencephalogram

There was no correlation between the apparent depth of anaesthesia and the electroencephalographic pattern. Even when marked hypotension was produced, the electroencephalogram gave the appearance of relatively light levels of surgical anaesthesia. Presumably then, severe cardiovascular depression occurs in light planes of anaesthesia long before anaesthesia is deep enough to cause burst suppression.

Laboratory Investigations

Laboratory investigations were carried out not only to check the effects of halothane following an acute experiment, but also to exclude any harmful effects on parenchymatous function of repeated dye injections.

The only consistent finding was a mild leucocytosis on the day following the experiment. This was no doubt due to the trauma inflicted and the administration of drugs. All subjects showed a slight increase of haemoglobin and packed cell volume on the day following the experiment. Probably this was due to dehydration since they had only had one meal in 30 hours.

One subject who had had a pre-anaesthetic elevation of gamma globulin, thymol turbidity, and zinc sulphate turbidity had a further rise of zinc sulphate turbidity on the day following the experiment and at that time had also a double plus thymol flocculation test. His liver function tests, repeated six days later, had returned to pre-experimental levels.

The urinary tests always gave essentially normal results.

Neither administration of large doses of halothane for periods up to one hour, nor the repeated injection of Cardio-Green, exerted any deleterious effect on parenchymatous functions in these seven subjects.

Summary and Conclusions

The administration of controlled concentrations of halothane lowers the systemic blood pressure. This hypotension tends to reach a plateau and does not seriously affect cardio-vascular efficiency. There is good evidence that this hypotension is due to peripheral vasodilatation; it is associated with increased total pulmonary resistance.

Overdoses of halothane can easily be administered if either a closed system or a poorly calibrated vaporizer is used. The hypotension thus produced may reach profound levels in a very short period of time and seriously impairs circulatory efficiency. It is associated with some peripheral vasoconstriction. The increased total pulmonary resistance indicates that the hypotension is most likely due to myocardial impairment.

Bradycardia invariably occurs and becomes pronounced when excessive doses of halothane are administered. It can be reversed by atropine sulphate, which may also raise the blood pressure from its early plateau.

The profound hypotension produced by overdoses of halothane reverts spontaneously when the administration of the drug is stopped. It is imperative that the hypotension be recognized early because of the severe effect it has on myocardial efficiency. The hypotension can also be reversed by vasopressors, but these must be used cautiously since they may produce ventricular extrasystoles. The most frequent electrocardiographic abnormalities produced by halothane are inversion of the P wave and nodal rhythm. Ventricular extrasystoles may occur early or when hypotension becomes extreme.

Halothane does not seriously affect the circulation provided its concentration it rigorously controlled by means of a suitable vaporizer. Its administration in a closed system or from unsuitable vaporizers is fraught with grave potential hazard. The potentially adverse effects of halothane upon the cardiovascular system are such that the use of this drug must be restricted to those familiar with its properties.

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Résumé

Nous avons fait des expériences sur des volontaires du sexe masculin dans le but d'étudier les effets de l'halothane sur le système cardiovasculaire.

Nous avons mesuré la pression artérielle périphérique directement au moyen d'une aiguille à demeure dans une artère; nous avons mesuré la pression artérielle pulmonaire au moyen d'un cathéter pour le cœur. Nous avons déterminé le débit cardiaque un certain nombre de fois, durant chaque expérience au moyen d'une méthode de dilution en employant une nouvelle teinture verte—Cardio-vert®—comme indicateur; nous avons fait l'échantillonnage artériel au moyen d'un oxymètre cuvette. Des données obtenues, nous avons calculé le temps de circulation veine à artère, la résistance totale périphérique et la résistance pulmonaire totale.

Continuellement, nous avions comme contrôle: l'électroencéphalogramme et un électrocardiogramme en deuxième dérivation.

Avant et après les expériences, nous avons fait subir des tests hépatiques et rénaux.

Nous avons constaté que l'administration d'halothane à des concentrations contrôlées fait baisser la pression sanguine systémique. Cette hypotension a tendance à atteindre un plateau et n'affect pas sérieusement l'efficacité du système cardiovasculaire. Nous avons raison de croire que cette hypotension est occasionnée par une vasodilatation périphérique; elle s'accompagne d'une augmentation de la résistance pulmonaire totale.

Nous avons constaté aussi qu'il est facile de faire du surdosage avec l'halothane, soit en employant un circuit fermé, soit en employant un vaporisateur dont la calibration n'est pas précise. En ces circonstances, l'hypotension constatée peut

atteindre très rapidement des niveaux très bas et réduire sérieusement l'efficacité de la circulation. Elle s'accompagne d'une certaine vasoconstriction périphérique. L'augmentation de la résistance pulmonaire totale nous porte à croire que l'hypotension observée serait attribuable à des troubles myocardiques.

Nous avons noté l'apparition constante d'une bradycardie s'accentuant quand les doses d'halothane augmentent. On peut faire disparaître cette bradycardie en administrant de l'atropine ce qui a pour effet également d'élever la pression artérielle à son plateau initial.

L'hypotension marquée produite par des surdosages d'halothane disparaît spontanément si l'on cesse l'administration du médicament. Il s'impose de dépister précocement l'hypotension à cause des effets sérieux qu'elle produit sur l'efficacité myocardique. On peut corriger l'hypotension en employant également des vasopresseurs, mais il faut être prudent en les employant, car ils peuvent provoquer des extrasystoles. Les anomalies électrocardiographiques les plus fréquemment observées ont été une inversion de l'onde P et un rythme nodal. Nous avons observé que des extrasystoles ventriculaires peuvent apparaître précocement ou encore quand l'hypotension devient très marquée.

Pourvu que sa concentration soit contrôlée de façon rigoureuse au moyen d'un vaporisateur approprié, l'halothane n'affecte pas sérieusement la circulation. Si on l'administre en circuit fermé ou au moyen d'un vaporisateur inadéquat, l'halothane peut constituer un risque sérieux. L'halothane peut avoir sur le systéme cardiovasculaire des effets tellement nuisibles que son emploi devrait être réservé à ceux qui connaissent bien ses propriétés.

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Errata

Sodium Methitural: A Clinical Study, by Gordon M. Wyant *et al.*, this Journal, Volume 5, page 265 (July, 1958), Table V: the following should be the times for the mean duration of operation.

	Mean
Thiopental c	12 min. 40 sec.
Methitural c	9 min. 41 sec.
Methitural s	8 min. 45 sec.
Methitural (exp.) s	10 min. 31 sec.