THE EFFECTS OF HALOTHANE ON THE PERIPHERAL CIRCULATION IN MAN

BY

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Many aspects of the effects of halothane on the cardiovascular system have been studied but its action on peripheral blood vessels has received little attention. During halothane anaesthesia the limbs are red and warm with prominent superficial veins, a clinical picture strongly suggestive of vasodilatation (Johnstone, 1956).

The present study was undertaken to determine what changes occurred in limb blood flow and vascular resistance during the inhalation of halothane. Further, it was felt that such an investigation might contribute to a better understanding of the general circulatory effects of this anaesthetic.

METHODS

The cases selected for this investigation were healthy subjects about to undergo minor surgical procedures. Thirteen females and two males were studied, their ages ranging from 20 to 45 years. In order to obtain data as unbiased as possible it was decided to omit pre-anaesthetic medication.

Anaesthesia was induced with thiopentone (4 mg/kg) and maintained with nitrous oxide 75 per cent and oxygen 25 per cent, using a non-rebreathing system incorporating a Ruben valve. A control state was thus obtained during which preliminary measurements of arterial pressure, heart rate and limb blood flow were made. Halothane was then added from a Fluotec vaporizer, Mark 2, and the concentration was gradually increased until a steady level of anaesthesia with stable blood pressure and heart rate was produced. The concentration of inspired halothane ranged from 1 to 4 per cent, the average being 2.3 per cent.

Blood flow measurements were obtained by means of venous occlusion plethysmography using temperature controlled mechanically stirred plethysmographs with water temperature at 35°C (Greenfield, 1954). The forearm blood flow was studied in ten subjects, the calf flow in two subjects and the hand flow in three subjects. In several instances the forearm and hand or forearm and calf blood flows were recorded simultaneously.

Systemic blood pressure was measured by the auscultatory (Riva-Rocci) method and mean arterial pressure was calculated as diastolic pressure plus one-third pulse pressure. In some instances direct measurements were obtained from a manometer connected to a needle in the brachial artery.

Vascular resistance was determined by dividing the mean arterial pressure (mm Hg) by the mean blood flow (ml/100 ml/min), and expressed as “resistance units”.

The electrocardiogram, lead 2, was continuously registered on a Mingograf 24 variable speed, direct writing recorder.

Atropine 0.65 mg was given intravenously to four subjects in order to determine what changes occurred in the peripheral vessels following the reversal of bradycardia and hypotension.

End-tidal Pco₂ was measured by means of a Stanley Cox time phased analyzer (Nunn and Pincock, 1957).

By means of an indwelling needle and a motor-driven constant rate syringe, noradrenaline was infused intra-arterially at a rate of 2 µg/min for 2 minutes in three instances.

Using the same technique, atropine 0.65 mg in 20 ml of saline was infused into the brachial artery for 5 minutes in four subjects.

The brachial plexus was blocked on one side in three subjects, using 30 ml of 1 per cent lignocaine with 1/100,000 adrenaline, in order to
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remove sympathetic vasoconstrictor tone from the vessels of the limb.

All observations were made prior to surgery and during stable states of anaesthesia of at least 10 minutes duration.

Standard statistical methods were used to determine the significance of differences between results, a difference being considered significant when the P value was less than 0.05.

RESULTS

Typical circulatory changes during halothane anaesthesia.

The data obtained from an individual case are shown in figure 1, and the results obtained from eight of the subjects studied are summarized in table I.

Forearm blood flow. This was increased from a control mean of 2.6 (±0.20) ml/100 ml/min to a mean of 4 (±0.10) ml/100 ml/min, a difference which was highly significant (P<0.001).

There was no obvious correlation between the extent of the increase in blood flow and the concentration of inspired halothane.

Arterial pressure. The administration of halothane resulted in hypotension in each subject. The average mean arterial pressure fell from 84 (±1.87) mm Hg to 70 (±2.88) mm Hg, this difference being highly significant (P<0.001).

Vascular resistance. When the increases in forearm blood flow during halothane anaesthesia are considered with the accompanying fall in arterial pressure, marked and consistently significant reductions in vascular resistance are revealed (P<0.001). The average mean control value of 34 (±2.94) units fell to 18 (±1.80) units.

Heart rate and rhythm. Although bradycardia often accompanied hypotension during the inhalation of halothane this was not an invariable finding. No electrocardiographic abnormalities were observed during the studies.

End-tidal Pco₂. When end-expiratory Pco₂ was
Changes in mean arterial pressure, heart rate, forearm blood flow and vascular resistance during halothane anaesthesia.

<table>
<thead>
<tr>
<th>Subject age/sex</th>
<th>Halothane per cent</th>
<th>End-tidal Pco₂ (mm Hg) during halothane</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats per min)</th>
<th>Forearm blood flow (ml/100 ml/min)</th>
<th>Forearm vascular resistance (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 30F</td>
<td>2.0</td>
<td>—</td>
<td>85</td>
<td>72</td>
<td>3.1</td>
<td>4.2</td>
</tr>
<tr>
<td>(2) 32M</td>
<td>1.5</td>
<td>—</td>
<td>80</td>
<td>74</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>(3) 31F</td>
<td>1.5</td>
<td>—</td>
<td>75</td>
<td>77</td>
<td>3.3</td>
<td>2.4</td>
</tr>
<tr>
<td>(4) 40F</td>
<td>3.5</td>
<td>—</td>
<td>65</td>
<td>72</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>(5) 32F</td>
<td>1.5</td>
<td>40</td>
<td>60</td>
<td>87</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>(6) 23M</td>
<td>3.5</td>
<td>36</td>
<td>65</td>
<td>108</td>
<td>1.7</td>
<td>4.7</td>
</tr>
<tr>
<td>(7) 20F</td>
<td>4.0</td>
<td>37</td>
<td>71</td>
<td>80</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>(8) 32F</td>
<td>1.5</td>
<td>47</td>
<td>67</td>
<td>81</td>
<td>3.1</td>
<td>3.8</td>
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<td></td>
<td></td>
<td>84</td>
<td>81</td>
<td>2.6</td>
<td>4.0</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td></td>
<td>4.93</td>
<td>7.60</td>
<td>0.56</td>
<td>0.28</td>
</tr>
<tr>
<td>S.E.</td>
<td></td>
<td></td>
<td>1.87</td>
<td>2.88</td>
<td>0.20</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*t = 9.30  
P < 0.001

The effects of nerve block on forearm blood flow. Blood flow through the normal and nerve blocked forearm was compared in three subjects during halothane anaesthesia. Successful brachial plexus block was indicated by a high blood flow through the forearm during the control period. In each subject when halothane was inhaled there was an increase in blood flow through the normal forearm but this did not occur on the nerve-blocked side. The data obtained from one of these subjects are shown in figure 3. As hypotension was minimal in this case there was no fall in blood flow on the nerve-blocked side.

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The effects of intravenous atropine.

In the four subjects studied the injection of atropine 0.65 mg intravenously during stable halothane anaesthesia resulted in a reversal of bradycardia and hypotension. These changes were accompanied by an increase in forearm blood flow and little alteration in vascular resistance (fig. 2) The results were reproducible and are summarized in table II.
Changes in forearm blood flow, arterial pressure, vascular resistance and heart rate produced by intravenous atropine during halothane anaesthesia.

A comparison of the effect of halothane on blood flow through the normal and nerve-blocked forearm.
The effects of intra-arterial atropine on forearm blood flow.

In the four subjects studied the increase in forearm blood flow produced by halothane was unaffected by the infusion of atropine into the brachial artery (fig. 4).

![Plethysmographic records showing that forearm blood flow was unaltered by the intra-arterial infusion of atropine.](image)

Top: Pre-infusion. Centre: During infusion into the right brachial artery. Bottom: 10 minutes after infusion. 

R=right arm. L=left arm.

The effects of intra-arterial noradrenaline on forearm blood flow.

When noradrenaline was infused during the control period there was a rapid fall in forearm blood flow to an unrecordable level. This reduction in blood flow was still apparent after the termination of the infusion but it was followed by a swift return to pre-infusion levels. During halothane anaesthesia, however, although the infusion of noradrenaline diminished forearm blood flow the magnitude and duration of this reduction was strikingly modified, and a detectable blood flow pattern remained throughout. The data obtained from an individual case are shown in figures 5 and 6. Calculation of vascular resistance showed that noradrenaline increased resistance to infinity during the control period compared with a two-fold increase during the inhalation of halothane. Comparable results were obtained in the other two subjects studied.

Hand and calf blood flow.

Increases occurred in two of the three subjects in whom hand blood flow was studied during the administration of halothane but in the third, where the control blood flow was high, no change was detected (table III). Halothane increased calf blood flow in both subjects studied, in one from 2.2 to 6 ml/100 ml/min, and in the other from 3 to 5.2 ml/100 ml/min.

DISCUSSION

The results of this investigation show that halothane increases blood flow and reduces vascular resistance in the limbs. These findings indicate considerable vasodilatation and substantiate the impression gained from clinical observation.

This vasodilatation may be due to the localized action of halothane on the blood vessel wall as suggested by Burn and Epstein (1959). Again, it may be mediated through the sympathetic nervous system either by reduction of normal vasoconstrictor tone or by stimulation of sympathetic cholinergic vasodilator fibres (Blair et al., 1959; Uvnas, 1960).

During halothane anaesthesia an increase in blood flow was found in the normal forearm but not in the forearm in which the vasoconstrictor tone had been removed by nerve block. An increase in blood flow in the normal forearm, not greater than that produced by successful nerve block, could be due to either activation of cholinergic fibres or to release of vasoconstrictor tone. In order to obtain unequivocal evidence of the participation of cholinergic fibres in this vasodilatation it would be necessary to demonstrate a greater blood flow through the normal than the nerve blocked forearm and further, active cholinergic vasodilatation can often be reduced or abolished by atropine (Blair et al., 1959; Uvnas, 1960). However, in no case was blood flow through the normal forearm greater than that in the nerve-blocked side and, in
A plethysmographic record comparing the effect of an intra-arterial infusion of noradrenaline on forearm blood flow during the control period and during halothane anaesthesia.

A graphic representation of figure 5, illustrating the changes in forearm blood flow during halothane anaesthesia compared with the control response.

**Table III**

Changes in hand blood flow produced by halothane anaesthesia.

<table>
<thead>
<tr>
<th>Subject age/sex</th>
<th>Halothane per cent</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Hand blood flow (ml/100 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Halothane</td>
</tr>
<tr>
<td>(1) 20F</td>
<td>40</td>
<td>87</td>
<td>71</td>
</tr>
<tr>
<td>(2) 45F</td>
<td>20</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>(3) 32F</td>
<td>1.5</td>
<td>82</td>
<td>67</td>
</tr>
</tbody>
</table>
addition, the increase in forearm blood flow produced by halothane was unaffected by atropine. These findings suggest that it is the release of vasoconstrictor tone which is responsible for the vasodilatation during halothane anaesthesia, although excitation of cholinergic fibres cannot be excluded completely.

From the foregoing evidence it is reasonable to expect the action of halothane to be most marked on the blood vessels of muscle and of the skin of the hand, areas where resting vasoconstrictor tone is known to be high (Greenfield, Shepherd and Whelan, 1951; Barcroft and Swan, 1953; Roddie and Shepherd, 1955). The increase in blood flow in the forearm and calf produced by halothane was, in most cases, greater than could be accounted for by release of vasoconstrictor tone in skin only. Since resting vasoconstrictor tone is low in the skin of the forearm and calf (Roddie, Shepherd and Whelan, 1957), full release of this could account for only part of the change in total limb blood flow. This means that a proportion of the increase in blood flow caused by the inhalation of halothane is the result of vasodilatation in muscle. Although the data on hand blood flow presented here are limited, they show that halothane diminishes the vasoconstrictor tone of skin vessels. When a low blood flow was present in the hand during the control period halothane anaesthesia produced a well-marked increase.

Changes in the peripheral blood vessels may play a part in the production of hypotension and it is well known that the blood pressure may fall to a greater extent with halothane than with other anaesthetic agents. It does not follow that the reductions in vascular resistance which have been demonstrated in the limbs during halothane anaesthesia reflect comparable changes throughout the body. It might be thought that compensatory vasoconstriction would occur in other areas. However, what little work has been done regarding regional blood flow through the main organs of the body provides no evidence of this. Indeed, Fabian (personal communication, 1961) has observed that halothane increases renal blood flow and work by Price (personal communication, 1961) suggests that cerebral vasodilatation also occurs. In all probability widespread vasodilatation is the rule when halothane is administered. In addition to changes in the peripheral blood vessels, hypotension may be initiated by alteration in the output of the heart. Moderate reductions in cardiac output have been shown to result from the inhalation of clinical concentrations of halothane (McGregor et al., 1958; Severinghaus and Cullen, 1958; Wyant et al., 1958). It seems reasonable to assume that such decreases become a factor in the production of hypotension as they occur in conjunction with widespread vasodilatation.

The present investigation shows that the reversal of bradycardia and hypotension following the injection of atropine intravenously during halothane anaesthesia was accompanied by an increase in forearm blood flow. It would seem that the tachycardia induced by atropine increased the output of the heart and that the resultant rise in arterial pressure, acting on vessels largely devoid of vasomotor tone, was responsible for this increase in blood flow. The fact that atropine reversed the fall in arterial pressure while vasodilatation persisted emphasizes the importance of changes in cardiac output in the production of halothane-induced hypotension.

A possible explanation for the peripheral vascular response to the administration of halothane may be obtained from its effect upon the sympathetic nervous system. Little sympatho-adrenal activity is evoked by halothane, as evidenced by the fact that increases in the concentrations of plasma adrenaline and noradrenaline do not occur, irrespective of the level of anaesthesia (Price et al., 1959; Hamelberg et al., 1960). This is in keeping with the uniform peripheral vascular picture of diminished sympathetic tone observed with clinical concentrations of halothane.

In contrast to this, it is interesting to recall that Kitchin and his associates (1953) demonstrated that although vasodilatation accompanied light cyclopropane anaesthesia the inhalation of high concentrations reduced forearm blood flow. This latter response was probably due to the high titre of circulating noradrenaline during deep anaesthesia with this agent (Price et al., 1959; Hamelberg et al., 1960).

Although no increases in plasma catecholamine concentrations are detectable during uncomplicated halothane anaesthesia, when hypercarbia is present the level of circulating noradrenaline
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rises (Millar and Morris, 1960; Price et al., 1960). In the present studies $P_{co_2}$ was maintained within normal limits in order to avoid any such complicating factor in the interpretation of plethysmographic findings.

Catecholamines influence not only the state of the peripheral blood vessels but also the cardiac output, by the extent of their liberation at the cardiac sympathetic nerve endings (Anzola and Rushmer, 1956). During the administration of halothane, compensatory increases in these amines are absent, so that the direct depressant effects of the anaesthetic on the heart may become more obvious. In a study of subjects undergoing thoracotomy Thrower and his colleagues (1960) and Bloodwell and his associates (1961) found reductions in ventricular contractile force during halothane anaesthesia, presumably due to decreased noradrenaline stimulation. Naylor (1959) reported that adrenaline and noradrenaline produced only small increases in the contractile force of the isolated heart when halothane was added to the perfusate, as compared with the control response. Price (1960) has demonstrated that noradrenaline failed to constrict strips of rabbit aorta in the presence of halothane.

It was in order to study the localized effects of noradrenaline on the blood vessels of the forearm in a precise manner that this substance was infused into the brachial artery. The results reveal that halothane strikingly reduced the ability of noradrenaline to diminish the blood flow through the forearm. This provides strong evidence that halothane modifies the action of noradrenaline on the peripheral blood vessels. It may well be that the activity of noradrenaline released at the cardiac sympathetic nerve endings into the myocardium is reduced in a comparable manner.

In addition to a poor sympatho-adrenal response during halothane anaesthesia, it would appear that the noradrenaline which is present in the myocardium and peripheral vessels is prevented from exerting its normal action.

In consequence a picture of cardiovascular depression presents when halothane is administered.

SUMMARY

Studies of limb blood flow were made in fifteen subjects during halothane anaesthesia using venous occlusion plethysmography. Halothane increased peripheral blood flow and reduced vascular resistance.

Vasodilatation was shown to be nervously mediated, as it was abolished by nerve block. The evidence suggests that it resulted from a reduction of normal vasoconstrictor tone.

The findings indicate that halothane interferes with the ability of noradrenaline to constrict the peripheral blood vessels.

It is assumed that the administration of halothane results in a deficient sympatho-adrenal response not only in a quantitative, but also in a qualitative, sense.

The fall in arterial pressure which occurs during halothane anaesthesia is considered to be due to diminished cardiac output associated with widespread vasodilatation.

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REFERENCES


EDITORIAL NOTE

TRANSLATION SERVICE

The proper content of the summary of each paper can be debated endlessly. Some feel that a full summary discourages casual readers from studying the paper completely. Others complain that the short summary too frequently gives no useful information whatsoever.

Hitherto the Journal has to a large extent left the summary to the individual choice of the contributor. Now it is hoped to introduce an innovation, about the middle of this year, in the form of foreign language summaries at the end of each main paper. To make this possible summaries of about one hundred words containing the main substance of the paper will in future be required of contributors.

It is hoped that this service will enhance the value of the Journal to many of our overseas readers.