THE EFFECTS OF METHOXYFLURANE (PENTHRANE) ON THE
PERIPHERAL CIRCULATION IN MAN*

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SUMMARY

The peripheral vascular effects of methoxyflurane were studied in eleven adults about
to undergo minor surgical procedures. Although there was a significant fall
in arterial pressure, the inhalation of methoxyflurane caused no significant alteration
in limb blood flow, and hypotension was not of sufficient magnitude to
influence vascular resistance. There was no interference with the effectiveness
of noradrenaline on vascular smooth muscle. It appears that the reactivity
of the circulatory bed remains intact, and that this responsiveness is retained at all
levels of clinical anaesthesia. The evidence suggests that methoxyflurane lowers the
arterial pressure mainly by decreasing the output of the heart, peripheral vaso-
constrictor tone being preserved.

Several studies have been made of the cardiovascular effects of methoxyflurane, but they pro-
vide little indication of the state of the peripheral circulation (Wyant, Chang and Rapicavoli, 1961;
did not include direct measurements of peripheral blood flow, vascular resistance being
calculated from cardiac output data.

The present work was undertaken to determine the peripheral vascular effects of methoxyflurane
under conditions uninfluenced by narcotic or other pre-anaesthetic medication, intermittent
positive pressure respiration and surgical stimulation, factors which have made the findings of
previous studies difficult to interpret.

METHODS

Eleven healthy adults about to undergo surgery
for the treatment of varicose veins were chosen
for the investigation. No subject in the series was
receiving any form of drug therapy and all pre-
anaesthetic medication was omitted.

Anaesthesia was induced with thiopentone
(4 mg/kg) and maintained with nitrous oxide and
oxygen (25 per cent) using a non-rebreathing
system with a Ruben valve. This provided a
control period during which preliminary measure-
ments were made of heart rate, arterial pressure
and limb blood flow. Methoxyflurane was then
added to the mixture of inspired gases from a
Pentec vaporizer (Cyprane Ltd.) until stable
anaesthesia with a vapour strength of 1.0 or 1.5
per cent was obtained.

For convenience under conditions of study in
the operating theatre, limb blood flow was mea-
sured by means of a mercury-in-rubber strain
gauge* as described by Whitney (1953), in pre-
ferece to the method of venous occlusion
plethysmography used in studies of halothane and
cyclopropane (Black and McArdle, 1962;
McArdle and Black, 1963). It was possible to
confirm the work of Clarke and Hellon (1957)
that the two methods were quantitatively com-
parable under the same conditions of study.

Arterial pressure was measured by the auscul-
tatory method, and mean arterial pressure was
calculated as diastolic pressure plus one-third
pulse pressure.

* This gauge consists of fine-bore latex rubber tubing
filled with mercury and it stretches as the limb cir-
cumference is increased during venous occlusion.
Changes in electrical resistance are thus produced and
the variations in current are amplified and recorded
on a direct-writing instrument.

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Laboratories Limited and the Northern Ireland Hos-
pitals Authority.
Vascular resistance was determined by dividing the mean arterial pressure (mm Hg) by the mean blood flow (ml/100 ml/min), and was expressed as "resistance units".

An indwelling needle and a motor-driven syringe were used to infuse noradrenaline intravenously at a rate of 2 μg/min for 2 minutes in each of three subjects.

The Astrup interpolation technique was used to determine arterial Pco₂, samples of capillary blood being taken from a finger stab (Siggaard Andersen et al., 1960).

All observations were made prior to surgery and during stable states of anaesthesia of at least 15 minutes duration.

The Student "t" test was used to determine the significance of differences between results, a difference being considered significant when the P value was less than 0.05.

RESULTS

The data obtained from nine of the subjects studied are shown in table I.

Forearm blood flow. This was not altered significantly by the inhalation of methoxyflurane, the mean values being 4.2 (±0.51) ml/100 ml/min for the control and 4.1 (±0.51) during the administration of the ether.

Arterial pressure. The average mean arterial pressure fell from 89 (± 3.97) to 82 (± 4.71) mm Hg, this difference being significant (P<0.01). Vascular resistance. The hypotension was not of sufficient magnitude to influence vascular resistance, the corresponding means for this parameter being 24 (±2.83) and 23 (±2.84) respectively.

Heart rate. There was a significant reduction in heart rate, the mean control value of 81 (±4.29) falling to 74 (±5.83) beats per minute.

Arterial Pco₂. This was largely within normal limits in the three subjects in whom measurements were made.

The effects of intra-arterial noradrenaline on blood flow. When noradrenaline was infused during the control period there was a rapid fall in calf 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. The magnitude and duration of this response were unaffected by the administration of methoxyflurane (fig. 1).

DISCUSSION

This investigation shows that the inhalation of clinical concentrations of methoxyflurane produces no significant change in limb blood flow, and, therefore, in spite of the significant fall in arterial pressure, the peripheral vascular resistance is unchanged. This consistently unaltered state of the peripheral blood vessels was observed with all concentrations of methoxyflurane up to a maximum of 1.5 per cent.

These findings are at variance with the work of Hudon and his associates (1963), who describe systemic vasodilatation during the first hour of methoxyflurane anaesthesia and report that the cardiac output rises in proportion, so that the arterial pressure is little altered. The measurements were made during surgery, however, which itself was found to reduce vascular resistance (McArdle and Black, 1963). It may well be that a similar effect can occur with methoxyflurane and that the changes described were largely due to this factor. In the present study there was no evidence of vasodilatation at any time during the inhalation of methoxyflurane.

The present work shows that there is no diminution in the ability of noradrenaline to constrict vascular smooth muscle during the administration of methoxyflurane. It seems reasonable to assume, therefore, that the reactivity of the circulatory bed remains intact, and that this responsiveness is retained at all levels of clinical anaesthesia.

Previous work has established that a definite relationship exists between the response of the peripheral circulation to a particular anaesthetic and its effects upon the sympathoadrenal system. For example, the vasodilatation and loss of normal vasoconstrictor tone which occur during halothane anaesthesia indicate diminished sympathetic activity (Black and McArdle, 1962). Although Millar and Morris (1961) showed that plasma catecholamines were not raised in the dog during methoxyflurane anaesthesia, a comparable study has not been undertaken in man. We found that the fall in arterial pressure with 1.5 per cent methoxyflurane (8 per cent reduction), was appreciably less than with 1.5 per cent halothane.
# TABLE I

Changes in mean arterial pressure, heart rate, forearm blood flow and vascular resistance during methoxyflurane anaesthesia.

<table>
<thead>
<tr>
<th>Subject, age, sex</th>
<th>Methoxyflurane per cent</th>
<th>Arterial Pco, (mm Hg) during methoxyflurane</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>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Methoxyflurane</td>
<td>Control</td>
<td>Methoxyflurane</td>
<td>Control</td>
</tr>
<tr>
<td>(1) 32 F</td>
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<td>—</td>
<td>94</td>
<td>85</td>
<td>84</td>
<td>76</td>
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<td>(2) 16 F</td>
<td>1.5</td>
<td>—</td>
<td>76</td>
<td>71</td>
<td>110</td>
<td>115</td>
</tr>
<tr>
<td>(3) 34 F</td>
<td>1.5</td>
<td>—</td>
<td>80</td>
<td>71</td>
<td>88</td>
<td>74</td>
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<td>(4) 40 F</td>
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</tr>
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<td>(5) 44 M</td>
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<td>106</td>
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</tr>
<tr>
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<td>3.97</td>
<td>4.71</td>
<td>4.29</td>
<td>5.83</td>
</tr>
</tbody>
</table>

\[ t = 4.64 \quad t = 3.17 \quad t = 1.70 \quad t = 0.74 \]

\[ P < 0.01 \quad P < 0.02 \quad P < 0.20 \quad P < 0.50 \]
The effect of an intra-arterial infusion of noradrenaline on limb blood flow during methoxyflurane anaesthesia, compared with the control response.

(16 per cent reduction) and that normal vasocostricor tone was preserved. This may be explained by the fact that peripheral vascular resistance is unchanged by methoxyflurane while considerable vasodilatation is produced when halothane is inhaled. Bagwell and Woods (1962) have shown that there is comparable depression of myocardial contractile force during anaesthesia with these two agents. It would appear, then, that methoxyflurane lowers the arterial pressure mainly by decreasing the output of the heart, vascular resistance remaining unaltered. In contrast, the passive and unreactive state of the blood vessels during halothane anaesthesia prevents any effective peripheral vasoconstriction occurring so that profound hypotension may ensue.

ACKNOWLEDGMENTS

We wish to express our thanks to Dr. G. M. Glass for his continued co-operation throughout this investigation. We are grateful to the theatre and ward nursing staff of the Mater Infirnorum Hospital, Belfast.

REFERENCES


LES EFFETS DU METHOXYFLURANE (PENTHRANE) SUR LA CIRCULATION PERIPHERIQUE CHEZ L'HOMME

SOMMAIRE
Onze sujets adultes devant subir une intervention et inhalant du méthoxyflurane, des mesures ont été faites pour connaître les effets vasculaires périphériques de ce produit. Bien qu'il y eut une chute significative de la tension artérielle, l'inhalation de méthoxyflurane n'a pas causé de changement important de la circulation des membres, et l'hypotension n'a pas été d'une intensité suffisante pour influencer la résistance vasculaire. Il n'y a pas eu d'interférence avec l'action de la noradrénaline sur les muscles lisses vasculaires. Il semble que la réactivité du lit circulatoire reste intacte, et que cette absence de réponse se maintient à tous les degrés de l'anesthésie clinique. Ce fait suggère que le méthoxyflurane abaisse la tension artérielle principalement en diminuant le rendement du cœur, le tonus vasoconstricteur périphérique étant conservé.

DIE AUSWIRKUNGEN VON METHOXYFLURANE (PENTHRANE) AUF DEN PERIPHEREN BLUTKREISLAUF BEIM MENSCHEN

ZUSAMMENFASSUNG
An 11 Versuchspersonen wurden kurz vor dem chirurgischen Eingriff und während der Inhalation die Auswirkungen des Methoxyflurane auf den peripheren Blutkreislauf bestimmt. Obwohl es zu einem erheblichen Abfall des arteriellen Blutdruckes kam, verursachte die Inhalation von Methoxyflurane keine signifikante Veränderung der Blutdurchstromung der Gliedmaßen und die Hypotension war nicht ausreichend, um den Gefäßwiderstand zu beeinflussen. Es fand sich keine Beeinträchtigung der Wirkung des Noradrenalin auf die glatte Gefäßmuskulatur. Es scheint, daß die Reaktionsfähigkeit des Strombettes erhalten bleibt und zwar in allen Stadien der klinischen Narkose. Es gibt Hinweise dafür, daß das Methoxyflurane den arteriellen Blutdruck hauptsächlich durch Verminderung des Herzaustrages erniedrigt, der periphere vasokonstriktorische Tonus aber erhalten bleibt.