THE EFFECTS OF TRICHLOROETHYLENE ON LIMB BLOOD FLOW IN MAN

BY
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SUMMARY
Limb blood flow was studied in twelve subjects, during trichloroethylene anaesthesia, using venous occlusion plethysmography. There was no significant alteration in blood flow or vascular resistance in the series as a whole. In some cases there was evidence of peripheral vasodilatation which was not abolished by nerve block. This was associated with tachypnoea and it was considered to be the result of the action of trichloroethylene on the blood vessel wall. Vasodilatation during trichloroethylene anaesthesia was replaced by vasoconstriction when the tachypnoea was abolished by means of intravenous pethidine. It is suggested that this is a compensatory vasoconstriction in response to a fall in the cardiac output, brought about by the combined effects of the narcotic and the anaesthetic agent.

Since halothane was introduced in 1956, the use of trichloroethylene in anaesthesia has tended to diminish. However, its powerful analgesic action (Hewer, 1953) still assures it a place in modern anaesthetic practice. At the present time trichloroethylene is used mainly to produce pain relief in obstetrics (Wylie and Churchill-Davidson, 1966), or in an anaesthetic sequence to exploit its analgesic properties. In this respect, it may be employed as an adjunct to nitrous oxide and oxygen anaesthesia as one part of the triad of Gray, when the relaxant technique is used (Lee and Atkinson, 1964). Also, it is valuable as an induction agent before ether anaesthesia, or as a supplement to nitrous oxide and oxygen for superficial surgical procedures (Tunstall, 1963).

Trichloroethylene may have undesirable side effects, the most common of which are the production of cardiac arrhythmias (Orth, 1958) and tachypnoea (Dundee, 1953), but it would seem that these can be regarded mainly as signs of overdosage, either relative or absolute (Ballantine and Jackson, 1960). When minimal concentrations are inhaled, however, untoward effects are rare, and anaesthesia with this agent is associated with a considerable degree of cardiovascular stability.

As there are no previous reports of quantitative peripheral vascular studies of trichloroethylene in the literature, it was felt that such an investigation was desirable.

In the present study the maximum concentration used was 1 per cent, a vapour strength unlikely to be associated with a high incidence of side effects. Also, it has been shown that it is not possible to maintain a concentration of trichloroethylene in excess of 1 per cent with a Boyle-type vaporizing bottle and Magill rebreathing attachment (Mapleson, 1957), the method most commonly employed in clinical practice.

METHODS
The subjects chosen for the study were twelve adults, awaiting operation for varicose veins or minor gynaecological conditions. Their ages ranged from 21 to 45 years, and a careful physical examination was carried out to exclude cardiovascular or other systemic disorders. The nature of the investigation was explained to each subject and consent was obtained prior to anaesthesia. Pre-anaesthetic medication was omitted but a short-acting hypnotic was given the night before operation.

Anaesthesia was induced with minimal dose of thiopentone (4 mg/kg), and during the control period, while preliminary measurements were made, it was maintained with nitrous oxide and oxygen (25 per cent) using a non-rebreathing system.

The forearm blood flow was measured by means of venous occlusion plethysmography...
using a mercury-in-rubber strain gauge (Whitney, 1953; see Appendix).

The arterial pressure was estimated by the auscultatory (Riva-Rocci) method and the mean arterial pressure was calculated as diastolic plus one-third of the pulse pressure.

Vascular resistance was determined by dividing the mean arterial pressure by the mean blood flow, and expressed as "resistance units".

The electrocardiogram was continuously monitored with an oscilloscope (Videograph), using chest electrodes.

The Astrup interpolation technique was used to determine the arterial Pco$_3$, samples of capillary blood being taken from a finger stab (Siggaard-Andersen et al., 1960).

The respiratory rate was noted at 5-minute intervals in all the subjects studied.

Trichloroethylene was then added from a calibrated temperature-controlled vaporizer until stable anaesthesia with a vapour strength of 1 per cent was obtained. Measurements of forearm blood flow, arterial pressure, heart rate, arterial Pco$_3$, and respiratory rate were then repeated.

All observations were carried out prior to surgery and during stable states of anaesthesia of at least 20 minutes duration.

In two subjects the brachial plexus was blocked with 30 ml of 1 per cent lignocaine, using the transaxillary approach, in order to remove vasoconstrictor tone from the vessels of the limb.

The Student t test was used to determine the significance of difference 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 in this investigation are summarized in table I.

Forearm blood flow.

Although in three instances there was a definite increase in forearm blood flow during trichloroethylene anaesthesia (nos. 1, 2 and 6), in the series as a whole the difference was not statistically significant (P<0.30), the mean control value being 3.8 (±0.37) ml/100 ml/min, while during the inhalation of trichloroethylene it was 4.8 (±0.64) ml/100 ml/min.

It was found that if an increase of blood flow did occur during trichloroethylene anaesthesia it was not abolished by nerve block. Figure 1 illustrates how this increase in blood flow was apparent in both the normal and the nerve-blocked arm during trichloroethylene anaesthesia.

Arterial pressure.

It can be seen from table I that the inhalation of trichloroethylene had no effect on the mean

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<th>Subject, age, sex</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Forearm blood flow (ml/100 ml/min)</th>
<th>Forearm vascular resistance (units)</th>
<th>Arterial Pco$_3$ (mm Hg)</th>
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$ t_1 = 0.77  \quad t_2 = 1.50 \quad t_3 = 1.35 \quad t_4 = 1.39  \quad P < 0.50 \quad P < 0.20 \quad P < 0.30 \quad P < 0.20$
EFFECTS OF TRICHLOROETHYLENE ON LIMB BLOOD FLOW

769

Control
Trichloroethylene

Effect of trichloroethylene on limb blood flow

arterial pressure, the control value being 85
(±1.98) mm Hg, and 87 (±1.69) mm Hg during
anaesthesia with trichloroethylene (P<0.50).

Vascular resistance.
Since the increases in forearm blood flow were
not significant and the mean arterial pressure was
relatively unaltered, there was no significant
change in the vascular resistance, the correspond-
ing means being 25 (±2.93) units for the control
period and 20 (±2.15) units for trichloroethylene
anaesthesia (P<0.20).

Heart rate and rhythm.
Although bradycardia was observed in two of
the subjects (nos. 2 and 5), and in the series the
heart rate fell from a mean control value of 72
(±3.90) to 65 (±3.56) beats/min, this was not
statistically significant (P<0.20). Apart from one
subject who developed transient auricular extra-
systoles, no electrocardiographic abnormalities
were encountered during the investigation.

Arterial Pco₂.
This was found to be within normal limits in
the four subjects in whom it was measured
(table I).

THE EFFECTS OF INTRAVENOUS PETHIDINE ON THE
FOREARM BLOOD FLOW DURING TRICHLORO-
ETHYLENE ANAESTHESIA
It was observed that a considerable degree of
tachypnoea was associated with an increase in
forearm blood flow during trichloroethylene
anaesthesia. In the three subjects in whom this
was seen, the respiratory rate was restored to that
of the control period by means of a dilute solution
of pethidine given intravenously, the average dose
required being 30 mg. In each case this had the
effect of reducing the forearm blood flow to a
value less than in the control period (fig. 2).

The relationship between forearm blood flow and res-
piratory rate, during the control period, trichloro-
thylene anaesthesia, and trichloroethylene + pethidine.
Representative case.

THE EFFECTS OF INTRAVENOUS PETHIDINE ON
FOREARM BLOOD FLOW DURING NITROUS OXIDE
AND OXYGEN ANAESTHESIA
In three subjects the forearm blood flow was
measured during stable anaesthesia with nitrous
oxide and oxygen. Pethidine 30 mg was then
given intravenously and the blood flow measure-
ments repeated. It was found that there was no
change in the forearm blood flow after the injec-
tion of pethidine.

THE EFFECTS OF SURGERY ON FOREARM BLOOD
FLOW DURING TRICHLOROETHYLENE ANAESTHESIA
In three subjects, the studies were continued after
surgery was commenced. In two of these cases a
well-marked increase in forearm blood flow
occurred in association with surgical manipulation.
Plethysmographic records obtained from one
patient during trichloroethylene anaesthesia to-
gether with the effects of surgery are shown in
figure 3.

DISCUSSION
The results of this investigation show that tri-
chloroethylene produces no significant alteration
Control

Trichloroethylene

Trichloroethylene + surgery

Time (min)

FIG. 3

Plethysmographic records showing the increase in blood flow produced by surgery during trichloroethylene anaesthesia.

See appendix for full explanation of tracing and method of calibration.

in forearm vascular resistance, mean arterial pressure or heart rate.

It has been demonstrated in studies of other anaesthetics (Black and McArdle, 1962, 1965; McArdle and Black, 1963; McArdle, Black and Unni, 1968) that there is a close relationship between the peripheral vascular effects produced by different agents and their effects upon the sympathoadrenal system. Marked increases in vascular resistance take place in the limb vessels when cyclopropane or diethyl ether are inhaled, and this is associated with significant increases in the plasma noradrenaline levels (Price et al., 1959; Hamelberg et al., 1960). During anaesthesia with halothane, and methoxyflurane, however, such increases are not seen (Price et al., 1959; Hamelberg et al., 1960; Millar and Morris, 1961), and vasoconstriction is not encountered. It was found in a study of other aspects of trichloroethylene anaesthesia (work in progress) that the plasma noradrenaline level remained within normal limits with vapour strengths of up to 1 per cent. This is in keeping with the finding that increases in forearm vascular resistance are absent when the agent is inhaled.

Some workers have reported that trichloroethylene produces an increase in the arterial pressure (Johnson, 1945; Bernstine, 1952), while others (Love, 1937; Haworth and Duff, 1943) detected a decrease. The finding that there was no alteration in the arterial pressure in the present investigation is in agreement with the majority of previous studies (Hewer and Hadfield, 1941; Griffiths, 1942; Gordon and Shackleton, 1943; Wagner, 1946).

It is of interest that vasodilatation of the forearm blood vessels occurred in those patients who developed a severe degree of tachypnoea, evidence suggestive of relative overdosage (Dundee, 1953). In three such instances the increase in the forearm blood flow was considerable, and as the mean arterial pressure was unaltered, the vascular resistance fell. When this occurred, the increase in forearm blood flow was not abolished by nerve block, suggesting that it was the result of a direct effect of trichloroethylene on the blood vessel wall or the action of a humoral agent in the circulating blood. It has been shown that voluntary over-breathing is associated with a marked increase in forearm blood flow which is not abolished by nerve block (Roddie, Shepherd and Whelan, 1957), and it was first thought that the increase in blood flow associated with the tachypnoea of trichloroethylene was similar. However, these workers attributed the vasodilatation produced by over-breathing to the effects of hypocarbia, a factor not demonstrated in the present study. This finding is in agreement with the work of Nowill, Stephen and Searles (1953), who found that there was no change in arterial pH or Pco₂ in human subjects anaesthetized with trichloroethylene. It may well be that if vasodilatation takes place in a subject inhaling trichloroethylene it is due to the direct effect of a high concentration of the anaesthetic acting on the blood vessel wall. Since this response was not consistent and the data presented are limited, it is felt that this aspect will require more investigation to establish whether or not hypocarbia can be completely excluded as a factor in the production of vasodilatation.

Abolition of tachypnoea due to trichloroethylene by means of intravenous pethidine reduced the forearm blood flow to less than that in the control period, and, as there was no alteration in the mean arterial pressure, vascular resistance was increased. This finding indicates that the fall in blood flow produced by pethidine resulted from a vasoconstriction in the limb blood vessels. There is no evidence to suggest that pethidine has of itself a vasoconstrictor action and in the present
study there was no alteration in forearm blood flow when it was given intravenously during nitrous oxide and oxygen anaesthesia. It may be that the reduction in blood flow produced by pethidine during trichloroethylene anaesthesia is the result of a compensatory vasoconstriction in response to a fall in the cardiac output. Previous investigators have found that normal anaesthetic concentrations of trichloroethylene produce little or no change in the cardiac output in dogs (Dobkin, Harland and Fedoruk, 1962). However, as tachypnoea indicates a state of relative overdosage of trichloroethylene, it seems reasonable to suggest that the superimposed action of a narcotic would be sufficient to affect the output of the heart. Depression of myocardial activity and hypotension have been demonstrated in dogs anaesthetized with pentobarbitone, when pethidine is administered (Sugioka, Boniface and Davis, 1957), and the increase in cardiac output produced by cyclopropane is abolished by the administration of morphine (Jones et al., 1960).

A well-marked increase in forearm blood flow was observed when surgery was commenced during trichloroethylene anaesthesia. Since this was not associated with alteration in the mean arterial pressure, the vascular resistance was reduced, indicating that it was due to vasodilatation. This vasodilatation was similar to that observed when surgery was performed under light cyclopropane anaesthesia (McArdle and Black, 1963), but the scope of the present investigation did not allow for study of the precise mode of production of this response.

APPENDIX

Principles of the Method

The percentage change in the volume of a cylinder, to a close approximation, is equal to twice the percentage change in its circumference if only small changes in the latter are considered. The linear relationship between changes in volume and circumference may, therefore, be expected to apply for a segment of a limb subject to volume changes of vascular origin. Changes in limb circumference following, for example, venous occlusion may be quite small—less than 1 per cent—and these small changes have to be measured accurately over easily deformable tissues.

The strain gauge is a fine-bore silicone rubber tube (bore 0.5 mm, wall thickness 0.8 mm) completely filled with mercury, the ends of the tube being closed by copper plugs which are in electrical continuity with the mercury. If this mercury-filled tube is always in slight extension, the change in electrical resistance between the copper plugs is directly proportional to change in the length of the tube with further extension. If the tube is arranged to encircle a limb completely, changes of limb circumference are reliably recorded as corresponding changes in electrical resistance. A suitable Wheatstone bridge circuit, using the strain gauge as one of the resistances, is employed, while a second variable resistance is used to bring the bridge into balance. The gauge itself is all that needs to be mounted on the limb with a lead to the recording apparatus.

The gauge used was approximately 7 inches long (18 cm) looped to form a two-strand type, and it was mounted on the arm by means of a Velcro strap, which allowed its rapid application and removal. The electrodes were built into a perspex block and a similar block was attached to the strap with two fine screws. These two blocks could be approximated by means of a micrometer screw which allowed the gauge to be extended by a known amount during calibration. The output from the Wheatstone bridge was fed into a transistorized preamplifier, and the tracing was recorded on a slow-speed pen writer (Minewriter; Watman Instrument Co.), with the paper speed set for 1 mm/sec. A collecting cuff was applied to the upper arm and this could be inflated to 50–60 mm Hg from a reservoir, while an occlusion cuff on the wrist excluded hand blood flow during recording. Inflation of the collecting cuff arrests the venous outflow from the limb, and as the arterial inflow continues unchecked the limb increases in volume. These changes cause extension of the gauge and a change in its electrical resistance which is recorded as a slope on the paper.

When the investigation was completed, with the collecting cuff deflated, the apparatus was calibrated. The writer was run to draw a baseline, the gauge was extended by 1 mm using the micrometer screw and then the writer started again to draw a baseline; this process was repeated several times. The height of this calibration line $X$ was measured in cm. When the gauge was removed, the circumference of the forearm at the level where it had been applied was measured in cm; this is the value $C$. By substitution of these values $X$ and $C$ together with $M$ (the paper speed in cm/min) in the formula $t = (200 M/XC)$, a value $t$ is obtained. This is expressed in seconds and it is measured along the baseline of the tracing from the point where a tangent drawn to the blood flow slope intersects it. A vertical line is drawn from the other end of $t$ to intersect with the tangent. This line (measured in cm) is the blood flow expressed in ml/100 ml/minute.

REFERENCES


**LES EFFETS DE TRICHLOROETHYLENE SUR LE FLUX SANGUIN DES MEMBRES**

**SOMMAIRE**

Le flux sanguin des membres a été étudié à l'aide de la plethysmographie avec occlusion veineuse, chez douze sujets sous anesthésie au trichloroéthylène. On n'observait pas de modification significative du flux sanguin ou de la résistance vasculaire dans l'entité du groupe. Dans certains cas, on notait des signes de vasodilatation périphérique, qui ne disparaissait pas sous block nerveux. Celle-ci s'accompagnait de tachypnée qui était considérée comme la conséquence de l'action du trichloroéthylène sur la paroi vasculaire. La vasodilatation durant l'anesthésie au trichloroéthylène était remplacée par une vasoconstriction, lorsque la tachypnée était combatue à l'aide de pethidine par voie intraveineuse. L'auteur suppose que cette vasoconstriction compense la chute du débit cardiaque, qui est causée simultanément par le narcotique et l'agent anesthésique.

**ZUSAMMENFASSUNG**