CIRCULATORY EFFECTS OF CONTROLLED ARTERIAL HYPOTENSION WITH TRIMETAPHAN DURING NITROUS OXIDE/HALOTHANE ANAESTHESIA

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SUMMARY
Studies were made in ten patients of the circulatory changes occurring during the administration of trimetaphan to produce hypotension during nitrous oxide/halothane anaesthesia. Ventilation was spontaneous throughout. There were significant falls in arterial pressure and peripheral resistance. Cardiac output was relatively unaffected. Heart rate sometimes increased and this was associated with a fall in stroke volume. Central venous pressure fell in all but one patient, but the change did not reach statistical significance. It is felt that the safety of this hypotensive technique is related to the fact that cardiac output is not seriously reduced when lying horizontal. Patients tilted into the head-up posture, however, usually exhibit a lowered cardiac output.

Although controlled hypotension has been a standard anaesthetic technique for many years, there appear to be few data on its effects upon central haodynamics. Theye and Tuohy (1965) studied a group of patients anaesthetized with halothane and artificially ventilated, and reported little or no fall in cardiac output. Didier, Clagett and Theye (1965), however, reported from the same centre falls of up to 50 per cent in cardiac output in spontaneously ventilating patients undergoing mastectomy. We have investigated the haemodynamic effects of trimetaphan in 10 patients receiving controlled hypotension during nitrous oxide/halothane anaesthesia.

METHODS
All patients were studied immediately before undergoing surgery for which hypotension was to be induced. Seven cases were for vaginal repair of prolapse and three for operation on the middle ear. Their ages ranged from 26 to 67 years.

Premedication was given 1 hour before anaesthesia and consisted of papaveretum 20 mg and atropine 0.6 mg. Anaesthesia was induced with thiopentone 400 mg (16 ml 2.5% solution) and endotracheal intubation was performed after injection of suxamethonium 50 mg. Anaesthesia was maintained with nitrous oxide 3 l./min, oxygen 1 l./min and halothane 1–1.5% from a Fluotec vaporizer using a semiclosed circuit with absorber, respiration being spontaneous throughout.

A central venous catheter (E-Z Cath) was passed via a cubital fossa vein and its position checked by the pressure tracing. An arterial cannula was inserted percutaneously into the brachial or radial artery.

It is our practice to use intra-arterial pressure recordings during controlled hypotension but we do not strive unduly to place a catheter if arterial puncture is not successful at the first or second attempt. Consequently 4 of the 10 patients did not have an indwelling arterial cannula. In these cases arterial pressure was measured by sphygmomanometry and cardiac output by an earpiece (Waters 302).

Intravascular pressures were measured by pressure transducers, either Sanborn 267A or Bell and Howell 4327–L221. Cardiac output was calculated using the dye dilution method with indocyanine green and a Waters 302 cuvette (except in the 4 patients without an arterial cannula). Injections of dye were made with a semi-automatic injector and the cardiac output was monitored with a Sanborn cardiac output computer. The heart rate was taken from the electrocardiogram which was running continuously. All recordings were made on a Sanborn 6-channel or Devices 4-channel pen recorder.

Experimental protocol.
By the time cardiac output measurements were begun all patients were breathing quietly and spontaneously, and were lying horizontal and supine.

Peripheral resistance, central venous pressure, heart rate, mean arterial pressure, stroke volume and peripheral resistance, the mean of the lowest figures during trimetaphan administration in individual cases are compared with the mean of the control figure and given as the "mean maximum change". With the cardiac output computer which did not indicate variations in excess of ±5%.

Trimetaphan 0.5 mg/ml was now infused by intravenous drip until the arterial pressure had fallen to around 60 mm Hg systolic pressure. The pressure was maintained at this level either by stopping the infusion or running it slowly. Four further cardiac output measurements were made. In 4 patients the effects of posture were then studied by tilting into a 5-degree reverse Trendelenburg position and making further measurements also at 2-min intervals.

RESULTS

The means of the observations on cardiac output, mean arterial pressure, heart rate, systemic vascular resistance, stroke volume and central venous pressure before and after infusing trimetaphan are shown in Table I.

Cardiac output. The individual results are shown in figure 1. It will be seen that the mean cardiac output fell in 5 cases and rose in 5 following the administration of trimetaphan. The maximum fall in any patient was 27%. Taking the group as a whole, the observed changes after giving trimetaphan were not statistically significant. In no patient did the cardiac output fall to a dangerous level.

Arterial pressure. This, of course, fell in every case, the individual results being shown in figure 2. The mean maximum fall in mean arterial pressure was 23 mm Hg (34%) and this was statistically significant. It is of interest that the 2 patients whose mean pressure fell by more than 50% suffered a maximum fall in cardiac output of 24% and 27% respectively. In the other cases the maximum fall in pressure was in the range of 25–37% and such falls were associated with changes in cardiac output of +13 to −20%.

Heart rate. Following the onset of hypotension the heart rate rose in 3 patients and was virtually unchanged in the rest (fig. 3). The maximum rise was 24 beats/min.

Central venous pressure. This fell in all but 1 patient (fig. 4). The mean maximum fall was 2.2 mm Hg. In spite of the consistency of the change, statistical significance was not reached.

Stroke volume. This parameter fell in 7 patients and rose in 2, the mean maximum falling being 6 ml (fig. 5). The maximum fall in any patient was 18 ml (30%). It appears that the falls in cardiac output were mainly in terms of stroke volume, those patients who raised their heart rates being better able to maintain output in spite of a reduced stroke volume.

Peripheral resistance. This was decreased on average by a maximum of 33% (fig. 6) and this fall was statistically significant. It appears, therefore, that the main factor in reducing arterial pressure is a reduction in peripheral resistance.

Postural change. The effects of a 5-degree head-up tilt were studied in 4 patients and the results are shown in figure 7. A decrease in cardiac output occurred in each patient, the maximum fall varying from 9 to 29%. Mean arterial pressure only fell minimally, as did heart rate. It should be noted that the trimetaphan infusion tended to be slowed or stopped after tilting and this may account for the rises in peripheral resistance.

Table I. Mean results from 10 patients before and during the administration of trimetaphan. In the case of cardiac output, arterial pressure, central venous pressure, stroke volume and peripheral resistance, the mean of the lowest figures during trimetaphan administration in individual cases are compared with the mean of the control figure and given as the “mean maximum change”. With the cardiac output computer which did not indicate variations in excess of ±5%, the highest figure is used for comparison.

<table>
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<tr>
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<th></th>
<th></th>
<th>Trimetaphan</th>
<th></th>
<th></th>
<th></th>
<th>Mean max change</th>
<th>t/P</th>
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<td>Cardiac output (l./min)</td>
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<td>4.5</td>
<td>4.5</td>
<td>4.6</td>
<td>4.5±0.2</td>
<td>4.7</td>
<td>4.5</td>
<td>4.4</td>
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<td>70</td>
<td>68</td>
<td>69±2.4</td>
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<td>50</td>
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<td>81</td>
<td>80</td>
<td>81±3.0</td>
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<td>Central venous pressure (mm Hg)</td>
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<td>6.4</td>
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<td>Stroke volume (ml)</td>
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<td>Peripheral resistance (dyne/cm/sec-²)</td>
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<td>1270</td>
<td>1210</td>
<td>1240±62</td>
<td>940</td>
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<td>980</td>
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</table>

<0.001 | <0.001
CONTROLLED ARTERIAL HYPOTENSION WITH TRIMETAPHAN

FIG. 1. Cardiac output in 10 patients before and during the administration of trimetaphan. On the right the lowest measurement during trimetaphan is compared with the mean of the control period in individual patients.

FIG. 2. Mean arterial pressure in 10 patients before and during the administration of trimetaphan. On the right the lowest measurement during trimetaphan is compared with the mean of the control period in individual patients.

FIG. 3. Heart rate in 10 patients before and during the administration of trimetaphan. On the right the highest measurement during trimetaphan is compared with the mean of the control period in individual patients.

FIG. 4. Central venous pressure in 10 patients before and during the administration of trimetaphan. On the right the lowest measurement during trimetaphan is compared with the mean of the control period in individual patients.

FIG. 5. Stroke volume in 10 patients before and during the administration of trimetaphan. On the right the lowest measurement during trimetaphan is compared with the mean of the control period in individual patients.

FIG. 6. Peripheral resistance in 10 patients before and during the administration of trimetaphan. On the right the lowest measurement during trimetaphan is compared with the mean of the control period in individual patients.
Discussion

Controlled hypotension has had a somewhat chequered career. Following its introduction into anaesthesia over 20 years ago, there were several reports of deaths occurring and the technique was abandoned by many as being unsafe. However, when used by those experienced in the method, the results are very good (Enderby, 1955) and, indeed, many forms of surgery, for example operative procedures on the middle ear, are greatly facilitated by the dry field without risk to the patient.

The fact that patients can have their arterial pressure reduced to very low levels and recover without any evidence of tissue hypoxia indicates that the circulation must remain adequate in spite of hypotension. Such a state would arise if the fall in arterial pressure was due in the main to a reduction in peripheral resistance leaving cardiac output relatively unaffected.

The results of the present investigation appear to support the view that this, in fact, is the case. The falls in cardiac output seen in our patients were of little clinical significance and would be unlikely to affect adversely the supply of oxygen to the tissues of normal subjects.

Trimetaphan, like other ganglion blocking drugs, is not thought to have a direct myocardial depressant action. However, a fall in cardiac output could occur by eliminating an existing beta-receptor stimulation in much the same way as beta-blocking drugs do during halothane anaesthesia (Stephen, Davie and Scott, 1971). This would depend upon the sympathetic-parasympathetic balance existing at the time of administration.

It could be argued that a reduction in mean arterial pressure and an increase in venous capacitance would cause a fall in cardiac output by reducing the “mean systemic pressure” (Kelman, 1971). This, however, does not appear to be the case. Previous work with epidural block also showed that a marked fall in arterial pressure can occur without change in cardiac output (Stephen, Lees and Scott, 1969). The venous return is obviously a key factor in any change in cardiac output. Vasodilatation of arterioles reduces peripheral resistance and, therefore, arterial pressure, but blood arrives at the capillaries at near normal pressures. The pressures affecting the venous return (i.e. the gradient between the venous end of the capillary bed and the right atrium) cannot then be greatly changed, and little reduction in venous return will occur unless posture is used to produce venous pooling. The loss of tone on the venous side of the circulation will also reduce any resistance to flow offered by the veins and would account for the diminution in central venous pressure seen in our cases.

If posture acts adversely upon the venous return then a fall in cardiac output is to be expected and this was seen in the patients who were tilted into a reverse Trendelenburg position. Our results, however, are not strictly applicable to the clinical situation as we tilted our patients after they were hypotensive and we believe most anaesthetists would tilt them before lowering the blood pressure. However, it seems obvious that a head-up tilt will reduce the venous return and a fall in cardiac output is to be expected.

It was noteworthy that during this investigation trimetaphan frequently caused a prolonged fall in arterial pressure (up to 30 min) after discontinuing the drug. This has been seen many times in clinical practice and detracts from the main advantage put forward for this drug, namely the rapid reversibility of its action when the drip is stopped. In our experience it is inferior in this respect to sodium nitroprusside and often has little advantage over longer-acting drugs such as hexamethonium.

The present work supports the findings of Theye and Tuohy (1965) who studied the effects of trimetaphan in healthy patients undergoing varicose vein operations. Their patients were given halothane, were artificially ventilated and lying supine. The maximum fall in cardiac output seen was 29%
in one patient in whom the lower output was maintained even after recovery of the arterial pressure near to the control value. Their results in regard to stroke volume and peripheral resistance were very similar to ours.

It is, therefore, difficult to explain the difference that was found in the same hospital when patients undergoing mastectomy were studied (Didier, Clagett and Theye, 1965). These patients were breathing spontaneously, some receiving halothane and others nitrous oxide with pethidine and thiopentone supplements. Large falls in cardiac output were measured and, indeed, the authors stated that the operative field was only considered satisfactory when the output did fall. One of the most surprising results was that in some patients the peripheral resistance increased when trimetaphan was given. Unfortunately it is not stated whether the patients were lying supine or were head-up. The large falls in cardiac output would indicate a considerable degree of venous pooling and it may be that the patients were tilted head-up to obtain the most satisfactory operating conditions.

ACKNOWLEDGEMENTS
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REFERENCES

EFFETS SUR LA CIRCULATION D'UNE HYPOTENSION ARTERIELLE CONTROLEE OBTENUE PAR LE TRIMETAPHAN AU COURS D'UNE ANESTHESIE AU PROTOXYDE D'AZOTE ET A L'HALOTHANE

SOMMAIRE
Des études ont été effectuées chez dix malades en vue de noter les modifications circulatoires survenant au cours de l'administration de trimétophan et visant à obtenir une hypotension pendant une anesthésie au protoxyde d'azote et à l'halothane. Les malades ont présenté une respiration spontanée tout au long de l'anesthésie. On a observé des chutes significatives de la pression artérielle et de la résistance périphérique. Le débit cardiaque n'a été que relativement peu influencé. La fréquence cardiaque s'est accrus parfois et ce, en liaison avec un abaissement du débit systolique. La pression veineuse centrale a chuté chez tous les malades sauf un, mais ce changement n'a pas été significatif sur plan statistique. On a l'impression que la sécurité de cette technique d'hypotension contrôlée provient du fait que le débit cardiaque n'est pas sériusement abaissé lorsque les malades sont en position de décubitus. Les malades ayant reposé sur un plan incliné, la tête en position surélevée ont cependant présenté habituellement un débit cardiaque plus abaissé.

DIE KREISLAUFWIRKUNGEN KONTROLLIERTER ARTERIELLER HYPOTONIE MIT TRIMETAPHAN Während LACHGAS/HALOTHAN-NARKOSE

ZUSAMMENFASSUNG
10 Patienten wurden auf Kreislaufveränderungen untersucht, die während der Anwendung von Trimetaphan zur Erzielung einer Hypotonie während der Narkose mit Lachgas/Halothan auftraten. Die Patienten atmeten während der ganzen Narkose spontan. Der arterielle Druck und der periphere Widerstand fielen bedeutend ab. Das Herzschlagvolumen war verkleinert und die Frequenz erhöht. Der Herzschlag wurde manchmal schneller und dies hatte ein verkleinertes Schlagvolumen zur Folge. Der zentrale Venendruck fiel bei allen ausser bei einem Patienten, aber die Änderung war nicht von statistischer Bedeutung. Die Sicherheit dieser hypotensiven Technik ist der Tatsache zu verdanken, dass das Herzschlagvolumen nicht ernstlich abnimmt beim horizontal liegenden Patienten. Das Schlagvolumen vermindert sich jedoch gewöhnlich bei Patienten, die in eine Kopfhochlage gekippt werden.

EFECTOS CIRCULATORIOS DE LA HIPOTENSION ARTERIAL CONTROLADA CON TRIMETAFANO DURANTE LA ANESTESIA POR OXIDO NITROSO/HALOTANO

RESUMEN
Fueron efectuados estudios en diez pacientes sobre los cambios circulatorios que tienen lugar durante la administración de trimetafano para producir hipotensión durante la anestesia por óxido nitroso/halotano. La ventilación siempre fue espontánea. Hubo caídas significativas en la presión arterial y resistencia periférica. El gasto cardíaco quedó relativamente constante. La frecuencia cardíaca aumentó algunas veces y esto estaba asociado con una disminución en el volumen sistólico. La presión venosa central disminuyó en todos los pacientes excepto uno, pero este cambio no alcanzó una significación estadística. Se cree que la seguridad de esta técnica hipotensora está relacionada con el hecho de que el gasto cardíaco no está severamente reducido en decúbito horizontal. Sin embargo, los pacientes inclinados en posición con cabeza hacia arriba exhiben generalmente una disminución del gasto cardíaco.