MODERATE HYPOTHERMIA IN MAN: HAEMODYNAMIC AND METABOLIC EFFECTS

BY

JOHN D. MICHENFELDER, ALFRED UIHLEIN, EDWARD F. DAW AND RICHARD A. THEYE

Section of Anesthesiology and of Neurologic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A.

SUMMARY

Studies were performed on four patients undergoing intracranial operation during the induction and reversal of surface hypothermia to 30°C. Oxygen uptake decreased an average of 26 per cent from 34° to 30°C to a mean value of 48 per cent of predicted basal uptake. At the same time, cardiac output decreased only 11.5 per cent, resulting in a consistent rise in calculated mixed venous oxygen saturation from a mean of 76 to 81 per cent at 30°C. As a result of this and the effect of cooling on oxygen dissociation, the estimated tension of oxygen in mixed venous blood remained virtually unchanged. When shivering was allowed to occur in two patients, oxygen uptake increased approximately 50 per cent without any concomitant increase in cardiac output. Observed right atrial and SVC oxygen saturations correlated well with calculated mixed venous oxygen saturations with regard to direction and magnitude of change with change in temperature.

Lowering of body temperature to 30°C by surface cooling is generally believed to be advantageous during certain surgical procedures (Little, 1959). This belief is based almost entirely on observations from the experimental laboratory and on "clinical impression". Its validity has been questioned in recent reports comparing morbidity and mortality after operations for intracranial aneurysm, with and without hypothermia (Hale, Collis and King, 1962; Hamby, 1963). The physiology of moderate hypothermia in man has not been thoroughly studied, perhaps because, as Rose and co-workers (1957) have stated it, "... uniform physiologic responses to hypothermia cannot be expected in the experimentally uncontrolled operating room setting". Hoping to clarify this situation, we performed metabolic and haemodynamic studies, during the induction and reversal of hypothermia to 30°C, on patients undergoing intracranial operations.

PROCEDURE AND MATERIAL

Four adults without apparent pre-operative abnormalities of nutrition, hydration, or cardiopulmonary function were studied. The intracranial pathology differed as follows: one patient had a grade 3 astrocytoma of a temporal lobe, one had a parasagittal meningioma, one had a meningioma of the tuberculum sellae, and one had a chromophobe adenoma of the pituitary gland. Preoperative neuroradiological contrast studies were carried out on three patients under local anaesthesia.

Two patients (cases 1 and 3) underwent carotid angiography 2 days prior to operation, and pneumoencephalography was done on the day of operation in case 2. All patients were operated on in the supine position with a slight (5°) head-up tilt. Premedication in three cases consisted of pethidine 75 mg, or morphine 10 mg, with atropine 0.4 mg, given 1 to 2 hours pre-operatively. Patient 3 received no premedication. After induction with thiopentone, 350 to 500 mg, endotracheal intubation with an armoured latex tube was accomplished with the
aid of suxamethonium 80 mg. Anaesthesia was maintained with 0.5 to 1.5 per cent halothane in an analyzed mixture of oxygen (35 per cent) and nitrogen. A non-rebreathing system was used with collection of expired gases as previously described (Theye and Tuohy, 1964). All patients were intentionally hyperventilated (Bird ventilator) with peak inspiratory airway pressures of 18 to 22 cm H₂O and minute volumes of 8 to 9 l./min.

Cooling and rewarming were accomplished by circulating cold or hot water through modified Therm-O-Rite blankets placed above and below the patient. Shivering during cooling was manifest on the e.c.g. (case 4) and was controlled with gallamine triethiodide (Flaxedil) 80 mg. During rewarming, brief periods of shivering in cases 1 and 3 were permitted for purposes of the study. Two patients (cases 1 and 2) were given urea, 60 to 90 g, to improve intracranial exposure. Blood was transfused in amounts from 500 to 4250 ml in order to replace the surgical loss. At 31°C, brief episodes of ventricular arrhythmias occurred in cases 2 and 3 and were controlled by procaine amide, 200 to 600 mg. Cooling to 30°C required 2½ to 3½ hours, and rewarming to 35°C required 2 to 3½ hours. Temperatures were maintained at 30°C for 1 to 3 hours.

The majority of the studies were done while body temperatures were between 34° and 30°C, both during cooling and rewarming. A few isolated observations were available at temperatures between 36° and 34°C during the cooling phase.

After induction of anaesthesia, two polyethylene catheters were passed centrally via the medial antecubital veins and positioned by electrocardiographic means (Robertson and associates, 1961). In cases 1 and 4, the tips of the catheters were located in the superior vena cava and right atrium, and in cases 2 and 3, both catheters were placed in the superior vena cava. A Teflon needle was placed in a peripheral artery (brachial, radial, or femoral). At approximately 30-minute intervals, cardiac output (dye-dilution technique with SVC injection), central venous and arterial pressures (strain gauges), oxygen uptake and expired halothane concentrations (timed collection of expired gases and analysis by gas chromatography), and central venous and arterial oxygen saturations (reflection oximetry) were determined as previously described in detail (Theye, 1964; Theye and associates, 1964; Theye and Tuohy, 1965). The effect of temperature on light-transmission characteristics of blood and blood-dye solutions was handled by the preparation and use of multiple densitometer calibration curves covering the range of temperatures encountered. P O₂, P CO₂, and pH were determined by electrodes maintained at the temperature of the patient. Haemoglobin was determined by the cyanmethaemoglobin method. The electrocardiogram (lead 2) was monitored throughout for the detection of shivering and arrhythmias. Oesophageal and nasopharyngeal temperatures were followed by thermistors.

With the above determinations, it was possible to calculate mixed venous oxygen levels by means of the rearranged Fick equation:

\[
CvO₂ = Cao₂ - \frac{Vo₂}{Q}
\]

This can be solved for saturation:

\[
SvO₂ = SaO₂ - \frac{10}{1.34\text{Hgb}} \left( \frac{Vo₂}{Q} - 10 C(a-v)O₂D \right)
\]

In our calculations, we chose to ignore the effect of dissolved oxygen (10 C(a-v)O₂D). In the range of O₂ values with which we were dealing (75 to 114 mm Hg), the dissolved A-V oxygen difference amounted to about 0.2 volume per cent; and, with cooling to 30°C, it increased to less than 0.3 volume per cent (Sendroy, Dillon and Van Slyke, 1934). When this is taken into account, the calculated \(SvO₂\) is systematically increased by about one saturation unit.

RESULTS

All patients survived the procedure and no cardiopulmonary abnormalities were apparent in the postoperative period. Table I includes acid-base data obtained early in cooling and late in rewarming. No abnormalities are evident other than the expected respiratory alkalosis. The relatively low P O₂ values in cases 1 and 3 are consistent with a spread in ventilation-perfusion ratios similar to that described by Bendixen, Hedley-Whyte and Laver (1963) during con-
TABLE I
Oxygen levels, acid-base data and haemoglobin concentration of arterial blood and concentration of expired halothane at beginning and end of study.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr) and sex</th>
<th>Temp. (°C)</th>
<th>Po₂ (mm Hg)</th>
<th>Pco₂ (mm Hg)</th>
<th>pH</th>
<th>BB* (m.equiv/L)</th>
<th>Haemoglobin (gm/100)</th>
<th>Expired halothane (per cent)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>54 M</td>
<td>36†</td>
<td>75</td>
<td>29</td>
<td>7.58</td>
<td>53</td>
<td>13</td>
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<td>35‡</td>
<td>78</td>
<td>27</td>
<td>7.57</td>
<td>52</td>
<td>12</td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>2</td>
<td>55 M</td>
<td>35†</td>
<td>114</td>
<td>32</td>
<td>7.49</td>
<td>49</td>
<td>12</td>
<td>1.19</td>
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<tr>
<td></td>
<td>35‡</td>
<td>98</td>
<td>31</td>
<td>7.53</td>
<td>51</td>
<td>12</td>
<td></td>
<td>.26</td>
</tr>
<tr>
<td>3</td>
<td>53 F</td>
<td>36†</td>
<td>86</td>
<td>27</td>
<td>7.57</td>
<td>50</td>
<td>11</td>
<td>.65</td>
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<tr>
<td></td>
<td>35‡</td>
<td>81</td>
<td>26</td>
<td>7.57</td>
<td>50</td>
<td>12</td>
<td></td>
<td>.05</td>
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<td>4</td>
<td>35 F</td>
<td>35†</td>
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<td>24</td>
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<td>14</td>
<td>.55</td>
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<tr>
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<td>35‡</td>
<td>395§</td>
<td>25</td>
<td>7.57</td>
<td>49</td>
<td>14</td>
<td></td>
<td>.30</td>
</tr>
</tbody>
</table>

♦ Buffer base.
† Cooling.  ‡ Rewarming.
§ Patient breathing 100 per cent oxygen.

Changes in oxygen uptake, expressed as per cent of predicted basal uptake, are shown in relation to changes in oesophageal temperature between 34° and 30°C. Smooth curve representative of all observations (10 to 12 for each patient) has been drawn. Individual observations are indicated only at 34°, 32°, and 30°C. Symbols: △, case 1; o, case 2; x, case 3; ●, case 4.

trolled ventilation with constant minute and tidal volumes. Haemoglobin and expired halothane concentrations in table I are representative of the ranges encountered.

Oxygen uptake decreased in each patient during cooling and returned to control levels with rewarming (fig. 1). The wide range of values observed is indicative of individual variation as well as of probable error inherent in choosing one temperature (oesophageal) as representative of “body temperature”. At 36°C (not included in the figure) oxygen uptake averaged 75 per cent of predicted basal uptake consistent with premedication, thiopentone induction, halothane anaesthesia, and a 2°C drop in temperature. Between 34° and 30°C, oxygen uptake decreased an average of 26 per cent to a level of 48 per cent of predicted basal
uptake. This correlates well with observations in dogs (Bigelow and associates, 1950), and observations in man during extracorporeal perfusion at 30°C (Theye and Kirklin, 1963). The rate of decrease in oxygen uptake with decrease in temperature is also in agreement with the findings of Otis and Jude (1957); they reported in dogs a 6 per cent decrease in oxygen uptake with every 1°C decrease in temperature.

A consistent decrease in cardiac output and mean arterial pressure was observed during cooling from 34°C to 30°C (fig. 2). With rewarming, cardiac output was seen to overshoot somewhat, probably as a result of decreasing halothane concentrations. The average decrease in cardiac output from 2.15 l./min/sq.m (litres per minute per square metre of body surface) to 1.9 l./min/sq.m is equivalent to an 11.5 per cent change. As with oxygen uptake, a wide range of values was observed. There was, however, individual consistency in that the lowest cardiac outputs were observed in those patients (cases 3 and 4) with the lowest oxygen uptakes. Likewise, the rate of decrease of cardiac output and oxygen uptake in each patient correlated well. Thus, in case 3, where oxygen uptake decreased 35 per cent, cardiac output decreased 18 per cent; whereas in the patients (cases 2 and 4) showing a decrease in oxygen uptake of 18 and 28 per cent, cardiac output decreased only 8 and 6 per cent, respectively. Changes in calculated systemic peripheral resistance were insignificant, as is apparent from the mean arterial pressure and cardiac output curves. Only a slight change in heart rate was observed during cooling, decreasing from an average of 75 beats/min at 34°C to 70 beats/min at 30°C. Likewise, venous pressure decreased minimally from 11 cm H2O to an average of 9 cm H2O at 30°C. Thus, there was no evidence of significant change in either stroke index or myocardial contractility with cooling.

The significance of the relationship between cardiac output and oxygen uptake is emphasized in figure 3, in which these curves are compared.
to the mean calculated mixed venous oxygen saturation curve ($S\text{v}\text{o}_2$). The increase in calculated $S\text{v}\text{o}_2$ from a mean of 76 per cent at 34°C to 81 per cent at 30°C and then back to 77 per cent with rewarming reflects the fact that cardiac output did not change at the same rate or to the same degree as did oxygen uptake. This calculation also confirmed the apparent consistency in the individual observations of cardiac output and oxygen uptake. Thus, with cooling, $S\text{v}\text{o}_2$ increased from 74 to 80 per cent in case 2; 72 to 77 per cent in case 3; and 80 to 85 per cent in case 4. Since cardiac output was not determined in case 1, this calculation was not possible; however, the observed right atrial oxygen saturation increased from 68 to 73 per cent, suggesting that cardiac output did maintain the same relationship to oxygen uptake as was seen in cases 2, 3, and 4. This is in contrast to the observations of Brendel, Albers and Usinger (1958) in dogs of a 50 per cent decrease in cardiac output at 30°C, identical to the expected decrease in oxygen uptake. On the other hand, an increase in $S\text{v}\text{o}_2$ with cooling has been previously observed by both Bigelow and associates (1950) and Hegnauer and D'Amato (1954) in dogs. The data of Hegnauer and D'Amato also showed a greater fall in oxygen uptake than in cardiac output, even at 17°C (15 and 19 per cent of normal, respectively).

The validity of using right atrial or SVC saturation as an index of mixed venous saturation has been discussed previously (Theye and Tuohy, 1965). It is apparent from figure 4 that in this study the observed saturations were consistently 7 to 9 saturation units lower than the
calculated \(\text{Sv}_0\). This difference probably results from a failure to sample true mixed venous blood which can only be reliably obtained from the pulmonary artery. Nonetheless, the direction and magnitude of change in the observed saturations reflected accurately the changes in calculated \(\text{Sv}_0\) with change in temperature.

This observation was used in interpreting the data obtained during shivering in two patients (cases 1 and 3) as shown in Table II. Each patient was permitted to shiver midway through the rewarming period, while controlled ventilation and halothane anaesthesia still were maintained. In each case, shivering was controlled as

<table>
<thead>
<tr>
<th>Case</th>
<th>Temp. (°C)</th>
<th>Shivering</th>
<th>Oxygen uptake (ml/min/sq.m)</th>
<th>Central venous blood*</th>
<th>Arterial blood</th>
<th>Cardiac output (l./min/sq.m)</th>
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<tbody>
<tr>
<td>1</td>
<td>31.2</td>
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<td></td>
<td>32.3</td>
<td>Yes</td>
<td>116</td>
<td>36</td>
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<tr>
<td></td>
<td>32.6</td>
<td>No†</td>
<td>—</td>
<td>66</td>
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<td>32.7</td>
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<td>72</td>
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<td>No†</td>
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<td>55</td>
<td>99</td>
<td>1.99</td>
</tr>
</tbody>
</table>

* Case 1, right atrium; case 3, superior vena cava. † Suxamethonium administered.

desired by the intermittent administration of suxamethonium 40 mg. In case 1, oxygen uptake was observed to increase 45 per cent with shivering. Although no values for cardiac output were available for this patient, the observed right atrial saturation decreased immediately from 66 to 36 per cent. Since there were no changes in arterial oxygen content, this is strong indirect evidence that cardiac output failed to increase to a level sufficient to meet the increased tissue demands for oxygen. When the patient was then paralyzed, right atrial saturation returned to the control level of 66 per cent. This sequence of events was repeated, and again an immediate decrease and return of right atrial saturation were observed. In case 3, shivering produced a 50 per cent increase in oxygen uptake with a concomitant decrease in SVC oxygen saturation from 59 to 49 per cent. At this point the cardiac output was determined and the patient was then paralyzed, resulting in an appropriate decrease in oxygen uptake and increase in SVC saturation. Cardiac output was again determined and showed no significant change (6 per cent increase) from that obtained during shivering. With these latter observations, it was possible to calculate \( S_{\text{Vo}} \), which increased from 68 to 77 per cent when shivering was terminated. In this instance, SVC blood was quantitatively less representative of mixed venous blood than was expected; nonetheless, changes in SVC saturation did reflect changes in \( S_{\text{Vo}} \).

**DISCUSSION**

Although this study was performed on a relatively small number of patients and under uncontrolled conditions, certain consistencies were apparent in the observations. During cooling from 34° to 30°C, oxygen uptake decreased an average of 26 per cent. At the same time, cardiac output was observed to decrease at a rate of half or less than that of oxygen uptake. This was true of the individual observations as well as of the mean values. In calculating \( S_{\text{Vo}} \), all values were normal or high normal, indicating the adequacy of cardiac output in relation to oxygen uptake. Furthermore, with cooling, \( S_{\text{Vo}} \) increased 5 to 6 saturation units in each patient, reflecting the relative maintenance of cardiac output as compared to oxygen uptake. The observed increase in \( S_{\text{Vo}} \) would tend to minimize any fall in mixed venous \( P_{\text{O}} \) resulting from the effect of cooling per se on the oxygen dissociation curve. Since cooling shifts the dissociation curve "to the left", if \( S_{\text{Vo}} \) had remained the same, mixed venous oxygen tension would have decreased as the temperature fell. In order to examine the magnitude of this effect, the mean calculated \( S_{\text{Vo}} \) values were translated into tension by taking into account changes both in temperature and pH (Dill and Forbes, 1941). This manoeuvre, although lacking in absolute accuracy, indicated that during both cooling and rewarming mixed venous oxygen tension remained virtually level, whereas, had \( S_{\text{Vo}} \) not increased with cooling, the tension of the mixed venous blood would have decreased approximately 10 mm Hg at 30°C.

The effects of shivering on oxygen uptake were of the order expected. The apparent failure of cardiac output to keep pace with the increased tissue oxygen demands points out the potential hazard of this situation. Should shivering be allowed to continue, anaerobic metabolism and increased acid metabolites would likely result. This is possibly one of the mechanisms responsible for the so-called rewarming shock (Blair, Montgomery and Swan, 1956). No data are available regarding the effect of shivering between 35° and 37°C during emergence from anaesthesia. Such information would be of value not only in the management of induced hypothermia but also in the common postoperative problem of unintentional hypothermia.

This study did not reveal any untoward physiological effects resulting from the induction and reversal of moderate hypothermia in man. If, however, the technique is improperly conducted and the patient is permitted to shiver, the beneficial effect of hypothermia is negated and a potentially harmful situation results. No conclusion can be made with regard to individual organ function during hypothermia. Such information, particularly regarding cerebral function, will be required in order to conclude that induced moderate hypothermia in man is a physiologically sound technique.

**ACKNOWLEDGMENTS**

The authors wish to express appreciation for the co-operation of Sister Mary Alanna, and the technical assistance to these studies provided by Jim Milde and Jean O'Haver.
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REFERENCES


