Pethidine and Skin Warming to Prevent Shivering During Endovascular Cooling

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SUMMARY
We tested the efficacy of pethidine and cutaneous warming to prevent shivering during percutaneous cooling in unanaesthetized patients. Ten patients scheduled for cranial neurosurgery received pethidine infusion and skin warming. The Setpoint™ internal heat-exchanging catheter was inserted and cooling to 33.5°C was started. Clonidine and chlorpromazine were given as “rescue medication” to treat shivering. General anaesthesia was planned to be induced after cooling was complete. Rewarming was initiated at dural closure. Three patients successfully completed the protocol, cooling to 33.8°C at a median rate of 3.6 (range: 3.4-3.8) °C/h. Two patients cooled to 33.8°C but required treatment for shivering (cooling rate: 2.9 [2.8-3.1] °C/h). Four patients failed to cool adequately because of refractory shivering (cooling rate: 2.0 [1.5-2.9] °C/h). One patient did not shiver and yet failed to cool adequately (cooling rate: 0.76 °C/h). Rewarming was at a rate of 2.6 (1.2-4.3) °C/h. There were no significant complications arising from catheter placement. The combination of skin warming and pethidine was not reliable enough to be recommended for use during endovascular cooling in unanaesthetized patients.

Key Words: TEMPERATURE: thermoregulation, hypothermia, pethidine, cooling. BRAIN: protection

There is considerable interest in mild hypothermia to reduce brain injury after stroke1-2 and aneurysmal subarachnoid haemorrhage3. This interest is largely based on copious and convincing animal data4-7, as the efficacy of mild hypothermia for brain protection in humans is yet to be confirmed8-9, except after cardiac arrest10,11.

Mild hypothermia has several potential limitations as a therapeutic modality following brain injury12-15. In particular, it is difficult to induce hypothermia in awake or sedated patients without inducing shivering. Shivering must be prevented if hypothermia is to be induced rapidly and without provoking adverse haemodynamic consequences. One approach is skin-surface warming, which reduces the core temperature triggering shivering16. In addition, numerous drugs ablate thermoregulatory responses including clonidine17-18, chlorpromazine19, pethidine20,21 and general anaesthetics22.

Pethidine prevents and treats shivering far better than equi-analgesic doses of other µ-receptor agonists23, but may produce sedation, hypoventilation and nausea24. Mokhtarani et al25 reported that pethidine (target plasma concentration 400 ng/ml) combined with buspirone (a 5-HT1A partial agonist) caused minimal sedation yet reduced the shivering threshold as much as pethidine at a plasma concentration of 800 ng/ml. Buspirone must be given orally and has a time to peak effect of at least an hour25, which may delay induction of hypothermia. We therefore tested the efficacy of pethidine (400 ng/ml) combined with skin warming for prevention of shivering in unanaesthetized patients. Intravenous clonidine and chlorpromazine were used, as necessary, as rescue medication.

METHODS
The Royal Melbourne Hospital Ethics Committee approved recruitment of 20 patients to this pilot trial. With written informed consent, patients aged 18 to 60 years presenting for elective intracranial surgery were recruited, as it was considered reasonable to induce hypothermia in these patients for potential brain protection. Exclusion criteria included 1) a contraindication to deliberate hypothermia (e.g., myo-
cardiac ischaemia or infarction, cardiac arrhythmia, systemic or local infection, immune deficiency, or coagulopathy; 2) allergy to or intolerance of pethidine, clonidine, or chlorpromazine, or treatment with a monoamine oxidase inhibitor; 3) height less than 1.5 m; or 4) inadequate English language comprehension (due to language barrier, confusion, dementia or intellectual disability).

A 16 gauge cannula was inserted into a forearm vein and warmed 0.9% NaCl was infused at 100 ml/h. A 20 gauge cannula was inserted into the left radial artery for continuous arterial pressure monitoring and blood sampling. Routine anaesthetic monitoring was applied, and specific study monitoring started (see below). Oxygen 4 l/min was delivered via a Hudson mask.

Participating patients were covered with a full-body, forced-air warming blanket, and the blower was set to “high.” A variable-rate infusion of pethidine, targeting a plasma concentration of 400 ng/ml, was then started. The infusion profile was based on a modification of the method of Kruger-Thiemer25 and published data26. The pethidine infusion continued until induction of general anaesthesia.

Core hypothermia was induced before induction of anaesthesia. Hypothermia was induced using the Setpoint™ endovascular temperature management system (Radiant Medical Inc., Redwood City, CA). This device is approved by the Therapeutic Goods Administration (Australia). The details of this system have been described previously27. Briefly, the Setpoint™ catheter was inserted under local anaesthesia into the inferior vena cava, via a 10 Fr introducer sheath in the femoral vein. Care was taken to position the catheter tip in the upper inferior vena cava. We achieved this by measuring the distance from the insertion point on the patient’s groin to the tip of the xiphoid process before the catheter was inserted. During the operation, sterile water was circulated by the Setpoint™ controller through a helically wound balloon mounted on the catheter, thereby heating or cooling the blood by means of counter-current heat exchange. The balloon has a diameter of 9 mm and a length of 25 cm during system operation. The controller continuously monitors patient core temperature, comparing this to the target temperature chosen by the operator.

After catheter positioning, cooling was started at the maximal rate with the target temperature set to 33.5°C. Shivering, if observed, was treated with clonidine 75 µg IV. If clonidine did not arrest shivering within 10 minutes, chlorpromazine 50 mg IV was added. When the target temperature was reached or if the anti-shivering protocol failed, patients were moved to the operating room and anaesthesia was induced. The target core temperature of 33.5°C was maintained until the critical part of the operation (i.e., aneurysm clipping or tumour removal) was complete. Rewarming was then started at the maximal rate to a target core temperature of 36.5°C. Patients were awakened from anaesthesia and tracheal extubation performed after the core temperature reached 35°C. Rewarming ceased when the core temperature reached 36.5°C. At this point, the catheter was removed. Adverse events which could be attributed to the catheter or to induced hypothermia were recorded in the recovery room, during the hospital stay, and after one month.

During cooling and rewarming, anaesthetic and study parameters were monitored continuously and recorded at 0.5°C intervals between 37°C and 33.5°C. Core temperature was measured at the tympanic membrane of both ears with Mon-a-therm thermocouples (Tyco-Mallinkrodt, St Louis, MO) that interfaced with the Setpoint™ controller. The patients inserted the aural probe until they felt it next to the tympanic membrane; appropriate placement was confirmed when patients easily detected gentle rubbing of the attached wire. The aural canal was occluded with cotton wool, the probe securely taped in place, and a gauze bandage positioned over the external ear. Skin temperature was measured with adhesive probes (Tyco-Mallinkrodt, St Louis, MO) at four sites: the upper arm, chest, thigh and lower leg. Mean skin temperature was calculated with the formula: [0.3 (chest+arm)+0.2 (thigh+leg)]28.

Thermal comfort was recorded by patients using a 100 mm visual analogue scale (50 mm=completely comfortable; 0 mm=extreme cold; 100 mm=extreme heat). Shivering was recorded on a four-point scale (1=no shivering, 2=mild shivering, 3=moderate shivering, 4=vigorous shivering) by a blinded observer. The core temperature when the shivering score first exceeded 1 identified the threshold. The EEG was monitored continuously (BIS-XP; Aspect Medical Systems Inc, Newton, MA, U.S.A.). The level of sedation was scored using the Observer’s Assessment of Alertness/Sedation (OAA/S) rating scale29, and blood was sampled for gas analysis at 30-minute intervals.

Arterial blood for pethidine was sampled at intervals of 0.5°C at core temperatures between 36°C and 33.5°C. Blood samples were centrifuged at 4°C and then frozen at –20°C until assayed as previously described30,31. This method is linear to at least 10 µg/ml, with a limit of quantification of 20 ng/ml.
Nonparametric statistics were selected because of the small sample size. Results are presented as median (range) unless otherwise specified. The relationship between median pethidine concentration and final core temperature achieved was determined using Spearman rank correlation (ρ). Linear regression was used to calculate individual core-temperature cooling and rewarming rates. Because the Setpoint™ system is programmed to slow the cooling rate when core temperature is within 0.3°C of the target, we excluded measurements within 0.3°C of the target from these analyses; \( P<0.05 \) was considered statistically significant.

RESULTS

This pilot trial was discontinued after ten patients were recruited, because of failure of the anti-shivering protocol. Seven women and three men, aged 48 (24-61) years and weighing 67 (60-90) kg were included in the data analysis. Six patients were presenting for neurovascular procedures and four for intracranial tumour surgery. The Setpoint™ catheter was inserted without difficulty in all cases. The cooling protocol lasted 43 minutes (28-118 min).

Three patients successfully completed the protocol, cooling to 33.8°C at a median rate of 3.6 (range: 3.4-3.8) °C/h; \( r^2=0.96 \) (0.95-0.98). Two patients cooled to 33.8°C but required treatment for shivering (cooling rate: 2.9 [2.8-3.1] °C/h; \( r^2=0.97 \) [0.95-0.99]). One received clonidine to treat shivering at a core temperature of 34.0°C and another received clonidine at 34.0°C and chlorpromazine at 33.8°C.

Four patients failed to cool adequately because of refractory shivering (final core temperature: 35.2 [34.0-35.8] °C; cooling rate: 2.0 [1.5-2.9] °C/h; \( r^2=0.95 \) [0.68-0.98]). In these patients, clonidine and chlorpromazine arrested shivering briefly, but general anaesthesia was required to completely abolish it. One patient did not shiver and yet failed to cool adequately over a period of 2h (final core temperature: 35°C; cooling rate: 0.76 °C/h; \( r^2=0.98 \)).

After general anaesthesia was induced, these five patients were cooled to 33.8°C at a rate of 2.2 (2.0-3.0) °C/h. Rewarming in all patients was achieved during anaesthesia at a rate of 2.6 (1.2-4.3) °C/h (\( r^2=0.99 \) [0.90-0.99]).

Respiratory, cardiovascular, and temperature data are reported in Table 1. Median total pethidine doses were 82 mg (range: 75-184 mg). Median pethidine concentration was 292 (101-895) ng/ml, and there was no correlation between median pethidine concentration and final core temperature (ρ=0.35; \( P=0.32 \)). The median core temperature triggering shivering was 34.9 (34.1-36.0) °C at a median pethidine con-
These rates of cooling are greater than those achieved by Doufas et al. in anaesthetized patients (2.0±0.5 °C/h). Rewarming rates were also similar to those achieved by Doufas et al. (3.9±1.6 °C/h)27. Rewarming rates were similar to those achieved by Doufas et al. in anaesthetized patients.

Suppression of shivering in induced hypothermia in the face of thermoregulatory vasoconstriction14 because the system removes heat directly from the central compartment. One patient failed to cool well despite the absence of shivering. This patient was tall (1.9m), and we questioned whether the balloon was positioned sufficiently high in the inferior vena cava although advancing the catheter further did not improve the cooling rate. There were no other apparent catheter-related issues in this study and no adverse events that were unequivocally associated with induced hypothermia. This trial was not powered to assess the safety of the catheter or induced hypothermia. Large trials are currently underway which will provide more comprehensive safety information.

For reasons that remain unclear, pethidine is more effective at suppressing shivering than other opioids and most non-opioid agents35. However, substantial concentrations (~1200 ng/ml) are required to suppress shivering when pethidine is used alone, and these concentrations produce sedation and hypventilation36. The addition of buspirone substantially reduces the target concentration of pethidine required (to 400 ng/ml), but buspirone must be given orally and, due to its slow onset of action, for efficacy its administration must be appropriately timed before induced hypothermia and pethidine administration are started33,34.

In patients who were cooled successfully, the cooling rates compared favourably with those achieved by Doufas et al. in anaesthetized patients (3.9±1.6 °C/h)39. Rewarming rates were also similar to those achieved by Doufas et al. (2.0±0.5 °C/h). These rates of cooling are greater than those reported for other methods such as skin surface cooling30 or cold intravenous fluid infusion23. Confirmation of this possible faster cooling with the Setpoint™ system compared to other methods awaits evaluation in a randomized trial.

Induced hypothermia was well tolerated in all patients in this study, with no adverse cardiorespiratory consequences. Visual analogue scales for thermal comfort indicated that patients were generally completely comfortable, with only a modest deterioration in comfort during the study. Even patients who shivered did not complain of feeling cold. This is likely to be due to the high mean skin temperatures maintained using forced-air warming16 and the fact that thermal comfort is 50% determined by skin temperature31 whereas autonomic thermoregulatory control is only 20% based on skin temperature16. In terms of thermal comfort, the Setpoint™ system may have an advantage over other methods, particularly when skin temperature is maintained.

VAS thermal comfort=100 mm visual analogue scale (50 mm =completely comfortable; 0 mm=extreme cold; 100 mm=extreme heat).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation (%)</td>
<td>99.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Respiration rate (breaths per min)</td>
<td>12 (11-14)</td>
<td>0 (-3.4-3.4)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>63 (5-71)</td>
<td>-9 (-14--4)</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>86 (72-100)</td>
<td>9 (1-17)</td>
</tr>
<tr>
<td>Ambient temperature (°C)</td>
<td>23.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean skin temperature (°C)</td>
<td>36.1</td>
<td>0.4</td>
</tr>
<tr>
<td>VAS thermal comfort (mm)</td>
<td>50 (42-58)</td>
<td>-17 (-28--7)</td>
</tr>
</tbody>
</table>

Results are reported as median (95% confidence intervals). Median values were calculated for the entire cooling period for each patient and the grand median is reported. Change=the difference between the variable at the end and start of cooling. VAS thermal comfort=100 mm visual analogue scale (50 mm =completely comfortable; 0 mm=extreme cold; 100 mm=extreme heat).
In this study, the combination of skin warming and pethidine, at a target concentration of 400 ng/ml, was only effective at preventing shivering in four of the ten patients, but one of these did not cool adequately and failed to complete the protocol. Median arterial pethidine concentrations were lower than the target concentration, although there was considerable inter-individual variability and concentrations were generally stable. These results are similar to previous studies using the same infusion protocol. Greater concentrations of pethidine, or drug combinations, may be more effective for preventing shivering.

Shivering thresholds were greater in our patients than in previous studies, despite the fact the skin temperature was relatively warm. There was considerable variability in pethidine concentrations at the shivering threshold, but no relationship between the threshold temperature for shivering and plasma pethidine concentration. A stress response induced by hypothermia or anxiety may explain these findings, although the patients were comfortable from a thermal perspective, without tachycardia, hypertension, or other evidence of anxiety.

Clonidine and chlorpromazine proved to be inadequate rescue medications. Clonidine has a dose-dependent effect on the shivering threshold temperature, 75 µg being the minimal effective dose to treat shivering in postoperative patients. We chose a low dose of clonidine in order to avoid sedative or haemodynamic side-effects. This dose was inadequate for treatment of shivering in our setting. Similarly, chlorpromazine has been used to prevent and treat shivering in a variety of situations, but was also ineffective in this study.

In conclusion, the Setpoint™ endovascular temperature management system was an effective method for inducing and reversing hypothermia. The combination of forced-air skin warming and pethidine (at a target plasma concentration of 400 ng/ml) was insufficient to prevent shivering during induction of hypothermia in unanaesthetized patients, and clonidine and chlorpromazine were not uniformly effective for rescue.

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FOOTNOTE

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REFERENCES


