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The Effectiveness of Rapidly Infused Intravenous Fluids for Inducing Moderate Hypothermia in Neurosurgical Patients

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Moderate hypothermia is often used for cerebral protection during anesthesia for cerebral aneurysm clipping. No reliable, rapid, and practical noncardiopulmonary bypass methods for the induction of hypothermia to core temperatures <34°C have been reported. We assessed the effects of IV administration of chilled 5% albumin (5 mL/kg at 1–6°C) on core temperature after surface cooling to approximately 34°C. We calculated thermal distribution volume from the change in core temperature after the chilled fluid infusions. We also compared rapid administration (5 mL/kg over 30 min) with very rapid administration (5 mL/kg over 3–5 min). Chilled albumin 5 mL/kg infused over 5 min reduced core temperature by 0.6 ± 0.1°C. The same volume of chilled albumin infused over 30 min reduced core temperature by 0.4 ± 0.1°C. The calculated thermal distribution volume was less than one third of total body volume. Because the thermal distribution volume in these hypothermic patients was much lower than total body volume, the chilled IV fluids in this study were 3 times more effective in inducing hypothermia than suggested by a simple calculation. To achieve maximal effectiveness, however, chilled fluids must be administered very rapidly (>100 mL/min) to avoid heat gains in standard IV tubing that occur even with rapid administration. **Implications:** Chilled IV fluids can be much more effective for the induction of hypothermia than commonly assumed, but they must be administered very rapidly to avoid heat gains in IV tubing.

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Mild hypothermia is often used during anesthesia for cerebral aneurysm clipping in an attempt to provide cerebral protection during the temporary focal ischemia produced by temporary vessel occlusion (1,2). The optimal temperature that balances the risks of hypothermia (3–5) against the benefits of cerebral protection for these procedures has yet to be determined. Animal studies suggest that cerebral protection is substantial with modest reductions of brain temperature (33–35°C) (6–9). These studies also suggest, however, that cerebral protection is increased further as brain temperature is decreased to 31°C (6,9). In humans, brain temperature exceeds body core temperature by 0.5–1.0°C (10). Some clinicians therefore aim for a core temperature of <34°C at the time of temporary vessel occlusion.[1]

Reliable and reasonably rapid reduction in core temperature to <34°C has proven difficult in some patients (1,11,12). The initial rapid decrease in core temperature to approximately 34°C after the induction of general anesthesia is achieved quite readily by passive measures (1). Once core temperature reaches 34°C, however, most patients have reached their vasoconstrictive threshold. This onset of thermoregulatory vasoconstriction coincides with a plateau in core temperature versus time (11), and further reductions in core temperature, even by active means such as surface cooling, are difficult to achieve.

Refrigerated IV solutions have been widely regarded as only moderately effective in active cooling (1,2). Previous investigators used a simple theoretical calculation of total body heat content to show that 1 L of iced IV solutions in a 70-kg patient will only reduce mean body temperature by 0.5°C (1,2). Because the heat content or heat deficit of IV fluids should be distributed throughout the body with tissue blood flow, it is commonly assumed that the thermal distribution volume of the heat deficit in cold IV fluids is equal to whole body volume. The change in core temperature should then reflect the change in mean body temperature. The assumption that thermal distribution volume is approximately equal to whole body

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[1] Craen RA, Gelb AW, Eliasziw M, Lok P. Current anesthetic practices and use of brain protective therapies for cerebral aneurysm surgery at 41 North American centers [abstract]. Anesthesiology 1994;81:209.

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volume therefore predicts that large volumes of chilled IV fluids would be required to produce significant changes in core temperature.

The thermal distribution volume of rapidly infused, chilled IV fluids has not been reported. This is a crucial factor for determining the efficacy of chilled IV fluids, because a distribution volume significantly lower than whole body volume would substantially increase the change in core temperature produced by infused fluids. We administered chilled IV fluids to neurosurgical patients (after core temperature had reached a plateau from passive redistribution and surface cooling) and calculated the apparent thermal distribution volume from the change in core temperature. To assess the effects of heat gains in the IV administration tubing, we also compared the administration of chilled IV fluids at very rapid flow rates with more commonly used rates of administration.

Methods

After approval from our institutional review board, and after receiving written, informed consent, we studied six ASA physical status II or III patients undergoing craniotomy for cerebral aneurysm clipping. Patients were considered for enrollment in the study if deliberate hypothermia was planned as part of the management for the surgical procedure. Patients were not considered for enrollment in the study if they were >65 yr old or had a history of congestive heart failure (CHF), cardiac arrhythmias, or coronary artery disease (CAD). The patients were randomly assigned to one of two treatment regimens: very rapid infusion of chilled (1–6°C) 5% albumin solution (5 mL/kg over 5 min) followed by rapid infusion (5 mL/kg over 30 min) of an equal volume of chilled albumin ($n = 3$); or the 30-min infusion followed by the 5-min infusion ($n = 3$).

Operating room (OR) temperature was maintained at 20°C. A circulating water blanket (Medi-Therm II; Gaymar Industries Inc., Orchard Park, NY) covered by one cotton sheet was placed on the operating table. On arrival in the OR, the patients were connected to routine monitors and given 8–10 mL/kg isotonic sodium chloride solution at room temperature. After insertion of a radial arterial catheter, general anesthesia was induced by the IV injection of thiopental (3–7 mg/kg), fentanyl (2–6 μg/kg), and vecuronium bromide (0.1–0.25 mg/kg). The water circulating blanket was activated and set to 15°C. The water circulating blanket was later turned off at least 30 min before the infusion of the chilled IV fluids. A temperature probe incorporated into an esophageal stethoscope (Coast Medical, Orange, CA) was positioned in the distal esophagus at the position of maximal heart tones (13,14). Adequacy of esophageal temperature probe positioning was confirmed by ensuring that movements of the temperature probe 2 cm in either direction around the final position of maximal heart tones did not result in any change in measured temperature (15). Temperature measured by a properly positioned esophageal probe accurately reflects the temperature of the core compartment (12–14). Temperatures were recorded every 5 min between the induction of anesthesia and initiation of the study. A central venous catheter was inserted via an antecubital or subclavian vein for continuous measurements of central venous pressure (CVP). A large-bore (16- or 14-gauge) IV cannula was placed in a forearm vein. Shortly after the induction of anesthesia, each patient received 1.0 g/kg mannitol IV. Immediately before surgical draping, a full-body disposable forced air blanket (Thermacare; Gaymar Industries) was placed to allow rewarming immediately after the study. No air was circulated through the forced air blanket until the initiation of rewarming.

Anesthesia was maintained with 60%–70% nitrous oxide, 6–8 μg/kg IV fentanyl, and isoflurane in a 0.1%–0.8% end-tidal concentration. During the study, which commenced after the bone flap was raised, the end-tidal isoflurane concentration did not exceed 0.4%. Muscle relaxation was maintained with bolus administration of vecuronium. Patients were hyperventilated to achieve an arterial carbon dioxide partial pressure of 25–28 mm Hg.

Esophageal temperature was monitored until it reached a core temperature plateau, confirmed by a maximal slope of the core temperature-versus-time curve of 0.3°C/h for at least 20 min. Each patient then received two infusions of 5 mL/kg chilled 5% albumin solution: one of the infusions over 3–5 min and the other over approximately 30 min. The infusion times were selected based on preliminary data showing that infusion rates of >100 mL/min were required to maintain the temperature of the IV fluids at the delivery site nearly equal to the temperature in the IV bag. All infusions of chilled albumin were administered through the large-bore peripheral IV, with flow rates adjusted by using a roller clamp. Patients randomly assigned to receive the 30-min infusion first were given 5 mL/kg refrigerated 5% albumin over a period of 30 min. Core temperature was monitored for 10 min after the end of this infusion, then 5 mL/kg refrigerated albumin was administered over 3–5 min. Core temperature monitoring continued for another 25 min. Patients randomly assigned to receive the 5-min infusion first were given 5 mL/kg refrigerated 5% albumin over a period of 3–5 min. Core temperature was monitored for 25 min after this infusion, then 5 mL/kg refrigerated 5% albumin was administered over a period of 30 min. Core temperature monitoring continued for 10 min after this infusion was complete. The investigators administering the chilled fluids were blinded to the patient's core temperatures throughout the study. Rewarming of the patients began at the

conclusion of the study or after placement of the permanent aneurysm clip. The average core temperature at the end of surgery and extubation was 33.9 ± 0.7°C. The average time from beginning of rewarming until core temperature reached 37°C was 195 ± 33 min.

For all infusions of chilled IV fluids, sterilized sheathed thermocouples (0.51 mm diameter, time constant <2 s; Cole-Parmer Instrument Company, Vernon Hills, IL) were inserted via a rubber port into the IV bag and via a rubber injection port into the IV tubing, with the IV thermocouple threaded distally to the end of the IV tubing. IV bag and distal IV temperatures were monitored throughout the infusion (dual input K-type digital thermometer; Cole-Parmer Instrument Company).

Changes in core temperature associated with the 5-min infusion of IV fluids were calculated as the difference between esophageal temperature immediately before fluid infusion and esophageal temperature measured 20 min after the infusion was begun (approximately 15–17 min after the infusion was complete). Changes in core temperature associated with the 30-min infusion of IV fluids were calculated as the difference between esophageal temperature immediately before fluid infusion and esophageal temperature measured 35 min after the infusion was begun (5 min after completion of the infusion).

$$V_{app} = V_{fl} \frac{T_1 - T_{fl}}{T_1 - T_2} \frac{\rho_{fl} C_{pfl}}{C_{pb}} \quad (1)$$

The plateau in core temperature versus time before and immediately after completion of the IV fluid infusions suggests a steady state in core temperature, with the core temperature difference reflecting the apparent distribution volume of the IV fluids. Accordingly, apparent distribution volumes were calculated using Equation 1, which was derived by a thermal balance on body heat content (Appendix 1).

The apparent distribution volume was calculated from the measured IV infusion volume (V_{fl}) and average temperature at the infusion site (T_{fl}), the measured esophageal temperatures before (T_1) and after (T_2) the fluid infusion, a density of water (ρ_{fl}) and heat capacity of water (C_{pfl}) of 0.992 g/cm^3 and 0.998 kcal · kg^{-1} · °C^{-1}, respectively, and an average body heat capacity (C_{pb}) of 0.83 kcal · kg^{-1} · °C^{-1} (16).

Results

Patient demographics are summarized in Table 1. The time from the induction of anesthesia to infusion of the chilled IV fluids was 215 ± 53 min. Volume of fluid infused, temperature in the IV bag, average temperature at the IV site, and CVP data are presented in Table 2. Graphs of esophageal temperature versus time for each patient for the 30-min and the 5-min infusions are shown in Figure 1.

The apparent distribution volumes calculated for each patient for the 30-min and 5-min infusions are shown in Table 3. The average distribution volume for the 5-min infusions was 29% of body volume. The average distribution volume for the 30-min infusions was 30% of body volume. The difference in distribution volume between the two infusions was not significant ($P = 0.85$, paired t-test; power of 0.572 to detect a difference of 0.20).

After an infusion of 5 mL/kg iced fluids, the average change in core temperature for the 3- to 5-min infusions was 0.6 ± 0.1°C. The average change in core temperature for the 30-min infusions after the same volume of fluid was 0.4 ± 0.1°C ($P = 0.0006$, paired t-test).

Discussion

Reducing body core temperature to 34°C in most patients is straightforward and requires little more than the induction of general anesthesia, avoidance of procedures that conserve heat, and avoidance of active surface warming (1). Reduction of body core temperature to 32°C, however, is often difficult and requires alternative, active methods for cooling (1). Few methods for the induction of hypothermia to this level that are both effective and simple to institute have been reported. For example, whole body immersion in iced water has been shown to be very effective at reducing body core temperature, but applying this technique in the OR is logistically challenging (2).

Chilled IV fluids have been generally regarded as only moderately effective for reducing core temperature (1,2). Because heat transfers readily between the vessels of the microcirculation and their surrounding tissue (17), it would be reasonable to assume that the heat deficit in chilled IV fluids is distributed throughout the body after the IV fluids are mixed with the blood volume. If the thermal distribution volume is the entire body volume, the average temperature for total body volume is approximately 34°C, and the temperature of the IV fluid as it enters the patient is 4°C, then Equation 1 predicts that 1 L of iced saline solution administered to a 70-kg patient will reduce core temperature by only 0.5°C.

It is clear from the data in Table 3, however, that the apparent distribution volume of chilled IV fluids was substantially lower than total body volume in our patients. The apparent distribution volume was remarkably consistent among patients and was independent of the rate of administration of the chilled IV fluids.

There are several possible explanations for a reduced apparent distribution in these patients. First,

Table 1. Patient Demographics

Patient	Age	Gender	Height (cm)	Weight (kg)	Location[a]	Grade[b]	ASA physical status
1	59	F	160	62.5	Internal carotid	0	II
2	65	F	160	72	Opthalmic	1	II
3	56	M	185	150	Anterior communicating	0	III
4	46	F	163	51	Anterior communicating	0	II
5	52	F	155	45	Posterior communicating	1	III
6	58	F	170	72	Superior cerebellar	0	III

[a] Location of the aneurysm.
[b] Modified Hunt/Hess grade.

Table 2. Volume of Fluid Infused, Temperature of the IV Bag, Average Temperature at the IV Site, and Central Venous Pressure

		T_{bag} (°C)		T_{site} (°C)		CVP (mmHg)[a]	
Patient	Vol (mL)	Very rapid	Rapid	Very rapid	Rapid	Very rapid	Rapid
1	313	2.1	2.0	4.9	17.8	10/15	8/10
2	360	5.7	2.9	6.5	16.5	5/15	5/14
3	750	1.0	1.8	3.9	11.9	6/10	6/9
4	255	1.0	1.3	4.2	16.2	7/16	7/6
5	225	2.1	2.9	4.2	18.3	10/12	7/9
6	360	0.9	0.9	4.0	15.0	6/8	3/6

[a] Values are before infusion/after infusion.
CVP = central venous pressure.

Equation 1 calculates the volume of an idealized central core compartment at a temperature equal to the core temperature. After the chilled IV fluid mixes with the core compartment, blood flow from the core to the periphery will exchange heat between the core and the cooler peripheral compartment. Any core-periphery heat exchange will increase the measured difference in core temperature before and after the infusion ($T_1 - T_2$ in Equation 1) and decrease the calculated apparent distribution volume. In one article, the mass of the extremities was estimated at 48% of total body mass, and average arm and leg temperatures were typically several degrees cooler than core temperature both before and after the induction of general anesthesia (18). The magnitude of the effect of core-peripheral heat transfer on calculated distribution volume is therefore potentially large. It is not known, however, how rapidly or how efficiently the core compartment is expected to exchange heat with the periphery after the infusion of chilled IV fluids.

It is possible that the apparent distribution volume was influenced by marked kinetic differences between the core compartment and peripheral tissues. For example, in a 70-kg patient, the peripheral mass can be estimated as 34 kg (48% of 70 kg) (18), with a core mass of 36 kg. For a tissue density of 1.065 g/mL (19), the peripheral volume is estimated as 34 L and the core compartment volume as 36 L. If the average normal blood flow to the periphery is the same as resting blood flow to the forearm ($5.3\ mL \cdot 100g^{-1} \cdot\ min^{-1}$) (20) and, during thermoregulatory vasoconstriction, the peripheral blood flow is reduced by a factor of 10 (11), we can estimate the peripheral flow during vasoconstriction as 0.18 L/min. For a cardiac output of 5 L/min, the blood flow to the central compartment would then be 4.82 L/min. If the blood entering the peripheral compartment readily exchanges heat with the entire tissue mass so the whole compartment can be treated as well mixed, the time constant for the peripheral compartment can be estimated as 34 L/(0.18 L/min) or 189 min. The time constant of the core compartment can be estimated as 36 L/(4.82 L/min) or 7.5 min. The kinetics of the peripheral compartment are therefore potentially much slower than the kinetics of the core compartment, and it is possible that the plateau observed 10–20 minutes after the administration of the rapid IV fluids (Fig. 1) reflects a pseudo steady state rather than a true steady state.

From the above considerations, it is clear that if the small apparent distribution volume calculated in these patients results from kinetic differences between core and periphery, then vasoconstriction of the peripheral compartment will have a substantial impact on the apparent distribution volume. Based on the core temperature at the start of the study (13) and on the plateau in core temperature versus time at the start of the study (11), it is likely that most or all of these patients had reached their thermoregulatory threshold and were therefore vasoconstricted peripherally.

A third explanation for the markedly reduced distribution volume is the possibility that heat exchange

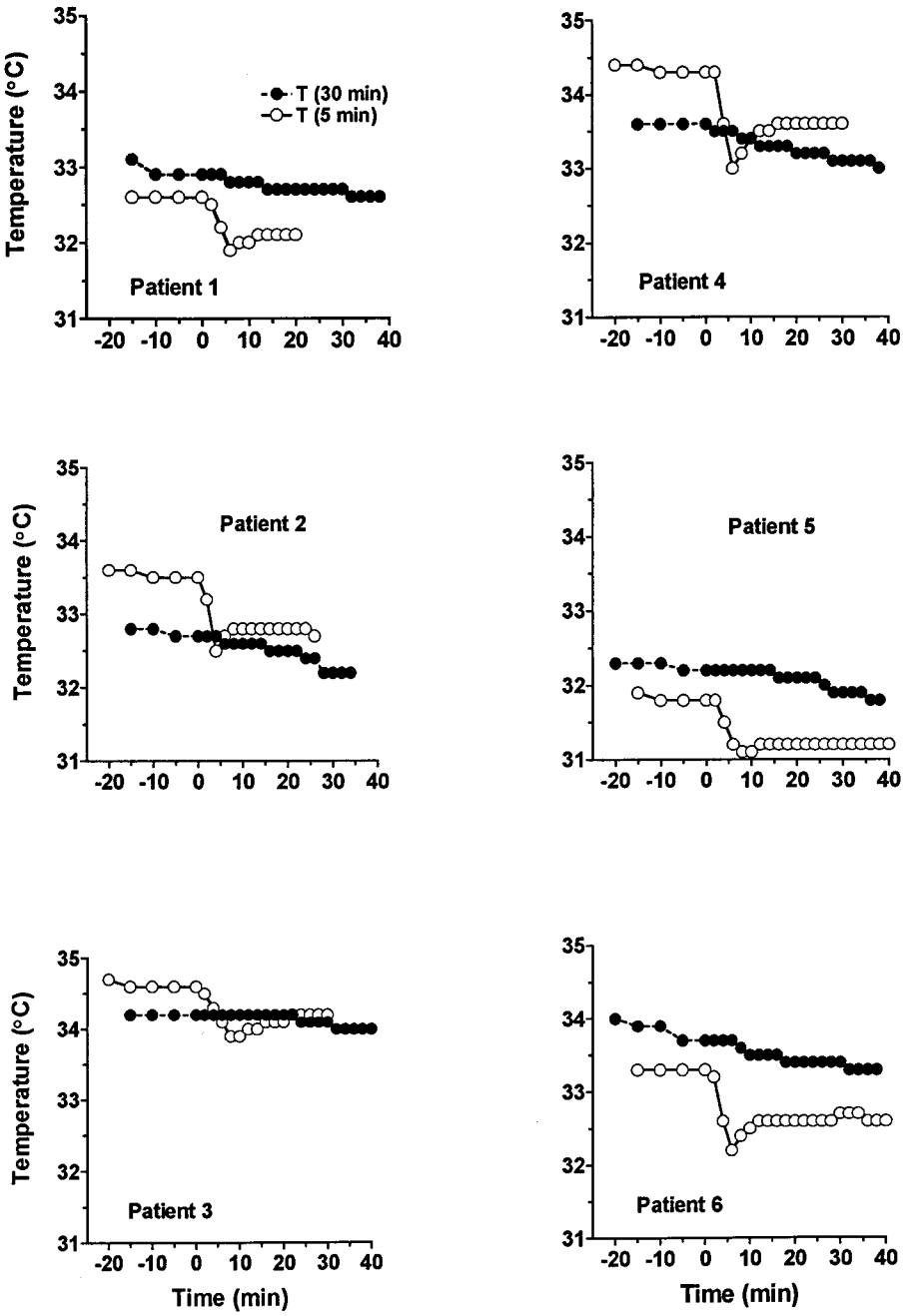

Figure 1. Graphs of core temperature versus time for each patient. Plots for both the 5-min infusions (○) and the 30-min infusions (●) are superimposed for both treatments. Time zero marks the start of each infusion. Patients 1, 5, and 6) were randomized to receive the 30-min infusion first, followed by the 5-min infusion. Patients 2, 3, and 4 received the 5-min infusion first, followed by the 30-min infusion. As an example of the times used to measure core temperatures for use in Equation 1, Patient 4 received the 5-min infusion first: T_1, the temperature at the start of the infusion, was 34.3°C; T_2, the temperature 20 min after the infusion was started, was 33.6°C. The core temperature was 33.6°C 30 min after the start of the 5-min infusion, and the 30-min infusion was started at time zero: T_1, the temperature at the start of the infusion, was 33.6°C; T_2, the temperature at 35 min after the start of the 30-min infusion, was 33.1°C.

between core and extremities was restricted because of countercurrent exchange between the arterial and venous circulations. Classic countercurrent exchange between a single paired artery and vein has long been recognized as a viable way to perfuse cool extremities while minimizing heat losses from the central compartment (21). More recently, it has been suggested that countercurrent exchange plays a significant role in heat transfer in complexly branching, asymmetric vessel networks (22,23). There is considerable evidence in humans that heat transfer between the core and extremities is reduced by countercurrent heat transfer between arteries and veins, especially when the extremity is exposed to a cold environment and blood flow is decreased (24).

A significant limitation of the current study is that the three possible mechanisms described above for the small apparent distribution volume cannot be differentiated solely by measurements of core temperature. Assessment of heat transfer between the central and peripheral compartments would require a measurement of the average temperature in the peripheral compartment (11,18), which is difficult to do in a clinical setting. It is expected that core-to-periphery

Table 3. Apparent Distribution Volumes (as a Fraction of Total Body Volume) of Chilled IV Solutions in Each Patient

Patient	Very rapid infusion	Rapid infusion
1	0.33	0.30
2	0.23	0.19
3	0.37	0.66
4	0.26	0.17
5	0.27	0.21
6	0.29	0.28

Distribution volumes were calculated using Equation 1 as derived in Appendix 1.

heat transfer will vary over time, which could influence the change in core temperature versus time for the 5-minute infusion versus the 30-minute infusion, independent of the infusions of cold fluid. For this reason, we called the distribution volume calculated from Equation 1 the "apparent" distribution volume, recognizing that the relatively slow changes in core temperature before and after the infusions may have represented an approximate steady state in core temperature but that they do not necessarily represent a steady state in terms of heat transfer between the core and periphery. Further work is required to elucidate the mechanisms of the small apparent thermal distribution volume.

Prior impressions of the ineffectiveness of chilled IV fluids for the induction of hypothermia may have resulted from heat gains in the IV tubing that partially negated the benefits of chilling the fluid. It is not widely appreciated how rapidly fluids must be administered to avoid heat gains in standard IV tubing. The data in Table 2 demonstrate that the administration of chilled IV fluids at rates that are commonly used in the OR results in substantial heating of the IV fluid by the time it reaches the IV site (T_{site} for the 30-minute infusions). Even with very rapid administration (>100 mL/min for the 3- to 5-minute infusions), the temperature of the IV fluids increased several degrees. Heat gains could, however, clearly be minimized at lower flow rates if the IV tubing was thermally insulated.

One potential hazard of the use of chilled IV fluids, particularly at rapid infusion rates, is volume overload. All patients in this study had CVP monitoring, and the maximal increase in CVP for a 5-mL/kg fluid load given over 5 minutes was 10 mm Hg (Patient 2); the mean increase in CVP for the 30-minute infusions was 5 mm Hg. The potential for volume overload was reduced both by patient selection (no history of CHF or CAD) and by the routine use of osmotic therapy (mannitol 1.0 g/kg) for cerebral relaxation before the fluid infusions. All fluid infusions were instituted after the diuresis from the mannitol was well underway.

Figure 1 illustrates the characteristic rapid initial decrease in core temperature after a very rapid infusion of iced albumin, followed by a small increase after the nadir in temperature, followed by a return to a plateau in the core temperature-versus-time curve. Compared with surface cooling, using chilled IV fluids for the induction of hypothermia is not associated with a variable "afterdrop" (25) and is characterized by a very predictable time course in core temperature. This represents a significant advantage as a cooling method for cerebral aneurysm clipping because the maximal decrease in core temperature can be precisely timed to coincide with temporary clip placement, and rewarming can begin immediately after placement of the permanent clip with no further afterdrop. Although we did not examine rewarming in the present study, using chilled IV fluids also has the potential advantage of more rapid rewarming, because cooling the core distribution volume, rather than total body volume, produces larger decreases in core temperature for a given whole body thermal deficit.

In summary, the rapid administration of chilled IV fluids is a convenient and effective method for the induction of hypothermia and requires no special apparatus. The technique is especially suited for neurosurgical procedures in which osmotic and diuretic therapy are often used to achieve cerebral relaxation. The potential for fluid overload was minimized in this study by restricting the administration of rapid IV fluids to patients with no history of CHF or CAD. With appropriate timing of the chilled IV fluids and with adequate infusion rates, an infusion of 5 mL/kg provides an average decrease in core temperature of 0.6°C. For 1 L of iced IV fluid in a 70-kg patient, the expected decrease in core temperature would be 1.7°C, and reductions of 2–3°C can be readily obtained.

Appendix 1

Determination of Apparent Distribution Volume

Equation A1 is easily derived from a thermal balance on body heat content. The heat lost by the core compartment after the infusion of IV fluids is given by:

$$\text{heat lost} = V_{appml}\rho_b C_{pb} T_1 - (V_{appml} + V_{flml})\rho_b C_{pb} T_2 \quad \text{(A1)}$$

where V_{appml} is the apparent distribution volume, ρ_b and C_{pb} are the density and specific heat capacity of the core compartment, V_{flml} is the volume of fluid administered, T_1 is the core temperature before fluid administration, and T_2 is the core temperature after

fluid administration. The heat deficit represented by the chilled IV fluids is given by:

$$\text{heat deficit} = V_{flml}\rho_{fl}C_{pfl}(T_1 - T_{fl}) \qquad (A2)$$

where ρ_{fl} and C_{pfl} are the density and specific heat capacity of the fluid and T_{fl} is the fluid temperature. Equating the heat lost with the heat deficit, assuming that the fluid volume is much smaller than the apparent distribution volume, and rearranging, the apparent distribution volume can be calculated as:

$$V_{appml} = V_{flml}\frac{T_1 - T_{fl}}{T_1 - T_2}\frac{\rho_{fl}C_{pfl}}{\rho_bC_{pb}} \qquad (A3)$$

Density of the core compartment (ρ_b) is approximately equal to total body weight divided by total body volume. Therefore, when the fluid volume (V_{fl}) is expressed on the basis of total body weight (mL/kg), the apparent distribution volume as a fraction of total body volume (V_{app}) can be calculated without specification of core density, giving Equation 1.

$$V_{app} = V_{fl}\frac{T_1 - T_{fl}}{T_1 - T_2}\frac{\rho_{fl}C_{pfl}}{C_{pb}} \qquad (1)$$

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