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Blood warming: current applications and techniques

K.V. ISERSON AND D.W. HUESTIS

THERE WAS NO NEED to think of warming blood when direct donor-to-patient and immediate indirect transfusions were used. After World War II, indirect, delayed transfusions of preserved, anticoagulated blood became the norm,[1,2] and preservation technology based on refrigeration arose. Blood banking and the storage of blood still require that collected blood units be kept refrigerated, for the most part in the liquid (unfrozen) state. This allows prolonged storage time, delays the metabolic deterioration of red cells (RBCs) and other components, and inhibits the growth of any accidentally introduced pathogens.[3] Currently, units of RBCs and whole blood (WB) are stored at 1 to 6°C,[4] a temperature predominantly determined by the requirements for the preservation of RBC functional integrity.[5,6]

A unit of WB, as collected from the donor, consists of approximately 450 mL of donor blood plus 63 mL of adenine-supplemented citrate phosphate dextrose anticoagulant (CPDA-1). An RBC unit is derived from that donation by the removal of 200 to 220 mL of anticoagulated plasma. Whereas, through the early 1970s, most transfusions involved WB,[7] current practice is to store RBCs for this purpose and to use the other components separately.

Blood components other than RBCs and WB are stored differently: plasma and cryoprecipitate are frozen, platelets are kept at room temperature, and purified derivatives such as albumin or immunoglobulins are stored as specified by the manufacturer. But the sterility and functional integrity of RBCs and WB depend on refrigeration, and every transfusionist could tell horror stories of the consequences of refrigerator failure or of the misguided actions of those who allow blood to reach and remain at ambient temperature. Thus, on the one hand, the blood banker wants blood to stay cold until actually transfused, and on the other, the bedside clinician is trying to devise ways of protecting the patient from the possibly harmful effects of hypothermia.

Both are right. Warming does indeed accelerate the deterioration of stored RBCs and may permit rapid growth of contaminating microorganisms. A few severe reactions and even deaths resulting from such growth continue to be reported. At the same time, the resuscitation of trauma patients necessitates rapid, massive transfusions, and significant hypothermia can be fatal. In taking the balanced view, one should avoid warming blood except for specific clinical indications, but reasonably safe, convenient, and effective methods must be available when those indications exist.

Warming blood for transfusion has been a common practice since the early 1960s, when a group of papers appeared on the dangers of hypothermia following cold blood transfusions.[8-12] Since Russell published the last major review of blood warming and blood warmers in 1974,[13] transfusion practices and equipment have changed dramatically, especially for acutely hypovolemic patients.[14-18] Whereas a maximum flow rate of 150 mL per minute was acceptable in the mid-1970s, current techniques for rapid transfusion allow, and current practice dictates, flow rates near to 1 L per minute in patients critically in need of blood replacement.[14-18] A transfusion is generally considered massive when 1 blood volume is transfused within 24 hours.[19] However, that definition pales beside the case of a patient who received 12 units of blood components per hour for 30 hours and lived to return to work.[20]

Practices in transfusion medicine have also changed. In 1974, WB was the most commonly transfused substance, but economics and the need for specialized components now make WB nearly unavailable for regular clinical use.[7] RBC units are the blood component currently used for patients who are exsanguinating. An increased awareness of the potential for transmitting infections through blood transfusions has also decreased the use of blood when clinical indications are marginal. This has shifted a larger proportion of blood use toward acutely hypovolemic patients who are likely to require rapid, massive transfusion. This shift in blood use in

Abbreviations: DEHP = di(2-ethylhexyl)phthalate; IV = intravenous; MEHP = monoethylhexylphthalate; RBC(s) = red cell(s); WB = whole blood.

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turn requires new consideration of methods of warming blood, which is usually provided for transfusion in an ice-cold state.

In this review, we try to define the various clinical situations in which cold blood transfusion may be of serious clinical import and those in which it is of trivial or no significance. We shall also review the effects of warming on the RBC and provide a critical outline of blood-warming methodology.

Hypothermia

Hypothermia is defined as a core body temperature below 35°C.[21] In the context of blood transfusions, hypothermia occurs in three types of patients: 1) patients not initially hypothermic who need large amounts of blood fast; 2) hypothermic trauma patients needing blood; and 3) surgical (often cardiac or neurosurgical) patients with induced (controlled) hypothermia who need blood. Because this last category of patients is normally in a well-controlled situation, often on a bypass pump capable of delivering large amounts of warmed fluid and blood, only the first two categories will be discussed.

Hypothermic physiology

The physiologic changes produced by hypothermia include impairments in the stress response and immune system, impaired drug clearance, hypovolemia due to cold diuresis, exacerbation of lactic acidosis, cardiac arrhythmias, and coagulopathies.[22-27] The last two may be caused acutely by cold transfusions.[8-10,12,27,28] Bigelow[29] noted the increased irritability of the hypothermic heart and suggested that when the blood is warmed to proper temperature levels, the heart does not show undue irritability. Dybkjaer and Elkjaer[8] reported that, in a 5-year period during which large amounts of cold blood were transfused for neurosurgical procedures, 13 patients experienced cardiac arrest, and 11 died. During a subsequent 2-year period, during which only warmed blood was used, there were no cardiac arrests.[8] Figure 1 shows one concept of the vicious cycle of effects induced by hypothermia.[30]

Arrhythmias, too, are presumably induced by the direct hypothermic effect of cold blood on the right atrium and ventricle.[31-33] Ozinsky[31] reported that, in a large series of patients with known cardiac defects who were undergoing induced hypothermia, the first incident of ventricular fibrillation occurred at 35°C. Because cold blood causes a fall in core body temperature,[29] the aim should be to keep the core temperature at or above 35°C and never to let it fall below 33°C.[11]

Warming 10 L (20 units) of WB from 4 to 37°C requires nearly 300 kcal,[34] equivalent to perhaps 30 minutes of heavy muscular work. The temperature of the intravascular space drops appreciably with the transfusion of just 2 units of cold blood. Assuming the vascular space to be a closed system for the first 2 minutes while blood is rapidly transfused, the final intravascular temperature would theoretically be the addition of the two simple proportions, as described in the equation:

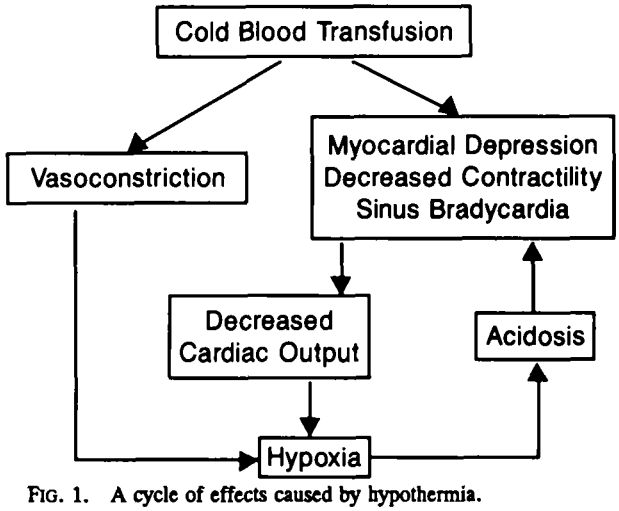

FIG. 1. A cycle of effects caused by hypothermia.

$$F = (V_A/V_T \times T_A) + (V_B/V_T \times T_B),$$

where F = final fluid temperature; V_A = remaining intravascular fluid volume; V_B = replacement fluid volume; V_T = normal intravascular fluid volume; T_A = temperature of the intravascular fluid; and T_B = temperature of the replacement fluid.

Let us apply this formula to a simplified example. A person with a blood volume of 5 L loses 1.5 L of blood via hemorrhage. He receives in replacement 1.5 L of 4°C blood at maximal flow rate. Therefore:

$$\begin{aligned} F &= (3.5\ L/5\ L \times 37°C) + (1.5\ L/5\ L \times 4°C) \\ &= (0.7 \times 37°C) + (0.3 \times 4°C) \\ &= 25.9°C + 1.2°C \\ &= 27.1°C. \end{aligned}$$

In actual fact, patient body temperature does not fall to this degree, probably because the vascular space is not fixed, heat exchange begins at once, and many other poorly understood factors affect temperature. Also, rather than cold WB, cold RBCs and room-temperature crystalloid are normally transfused. However, regardless of the accuracy of the mathematical expression, such heat equilibration must still be accomplished through a large expenditure of caloric energy, which is needed elsewhere.

Hypothermia-induced coagulopathies of various origins[27] appear to disrupt clotting in three general ways. First, enzyme function in coagulation is retarded, slowing the initiation and propagation of both the platelet plug and fibrin clot.[35] Second, there is enhanced plasma fibrinolytic activity, possibly due to the release of a heparin-like compound that produces a syndrome similar to

disseminated intravascular coagulation.[36,37] Finally, there are hypothermia-induced morphologic changes and decreased activity in platelets, possibly due to an imbalance in arachidonic acid metabolite production.[38,39]

Rapid massive transfusions

The terms "rapid" and "massive" as descriptors of blood transfusion have been defined differently over the years, and these definitions have changed with the advent of newer technology. The standards[4] of the American Association of Blood Banks define a massive transfusion as one in which a patient's total blood volume is replaced within 24 hours. In 1974, an infusion flow rate of 150 mL per minute through one intravenous (IV) line was considered the maximum flow necessary, but now, commercially available equipment allows a blood flow of 850 mL per minute or more through a single IV line.[40,41] Standard trauma protocols now require the initial placement of at least two large-bore (14-gauge or larger) IV lines to resuscitate the severely injured patient. These techniques have also been adopted to resuscitate patients with intraoperative and non-trauma-induced bleeding. Deaths due to hypothermia frequently follow the administration of cold blood even at the earlier, slower, maximum available flow rate.[8,9,12,42] Thus, adequate blood-warming systems are essential.

Trauma

Severely injured patients are a special group who need rapid, often massive, transfusions. These patients often are already hypothermic when they arrive at the emergency department.[43-45] Both the degree of hypothermia on arrival at the hospital and the lowest core temperature reached during resuscitation correlate with the degree of injury, volume deficit and hemorrhage, number of cold blood units transfused, and subsequent mortality.[43-46] Hypothermia is exacerbated by the removal of clothing for examination and therapy; the transport time; the administration of unwarmed crystalloids; a decrease in thermogenesis due to shock, drugs, or anesthesia; alcohol-induced vasodilatation; central nervous system injury with subsequent poor thermoregulation; and environmental exposure of large body surfaces during surgery.[43-45] The rapid addition of cold blood worsens the hypothermia. There has been some discussion in the past about a possible protective effect of hypothermia on trauma patients, but any beneficial effect seems to apply only to cerebral edema. All other systems deteriorate with lowered body temperature. Patients who are kept warm have a lower mortality rate.[43-45]

Infants

The ability to maintain core body temperature is severely compromised in full-term and premature newborn infants. A key element in both the support and resuscitation of infants is the maintenance of body temperature, usually through external means. Infants have a large ratio of surface area to body mass, poor thermal insulation because of thin subcutaneous fat, and an inability to prevent blood stream convection of heat from core to body surface.[47] Transfusion with cold blood is known to produce profound changes in body temperature and other metabolic responses with significant morbidity,[48] including cold stress and increased metabolic demands and oxygen requirements.[47]

Situations in Which Transfusion of Cold Blood is of Relatively Minor Importance

A conventional unit of RBCs weighs approximately 300 g, and the process of raising its temperature from 4 to 37°C consumes close to 10 kcal. This figure can sometimes be helpful in an evaluation of the potential effects of cold transfusions on patients in a variety of circumstances.

Elective transfusions

The transfusion of 2 units of RBCs drop-by-drop to an adult patient in 2 to 4 hours will require about 20 kcal. For most patients, the effect will be negligible. But just as eating ice cream or rapidly drinking an ice-cold beverage can cause chills and shivering, so can a cold transfusion (in some patients). This is by no means a rare occurrence in hospitals, where rooms may be cold and patients scantily covered. Despite the absence of fever, such events are sometimes reported to the blood bank as transfusion reactions and may therefore interfere with the completion of transfusions and result in wastage of blood.

Blood warming is neither necessary nor desirable in this setting. Simple nursing measures, such as making sure the patient is adequately covered, suffice. If the room is chilly, additional covering should be provided. It is not desirable to allow the blood to warm to room temperature before starting the transfusion. In short, it is easier and certainly safer to warm the patient than the blood.

Likewise, blood warming should not be necessary in the replacement of a few units of RBCs at regular rates during or after surgical operations. But in major procedures, as quantities and flow rates of transfused blood increase, transfusional hypothermia may be anticipated. We can give no definite guidelines as to when blood warming becomes necessary. The decision should be clinical and should be based on the size and clinical status of the patient, expected blood loss, replacement needs, rate of transfusion, and available warming systems.

Cold agglutinins

Autoagglutination of RBCs at low temperatures is a common observation in the blood bank and may interfere

with crossmatching. Most such antibodies react only at or near refrigerator temperatures and are of no clinical importance. A few stronger examples may react at a wider thermal range, even near 37°C, and may occasionally cause hemolytic anemia. When cold agglutinins are known to be present in a patient needing transfusion, it is tempting to think that blood should be warmed. But there is no evidence that warming is needed in these circumstances, and in our experience the usual elective transfusions (e.g., 2 units of RBCs at regular rates of transfusion) are accepted without complications. Blood entering the patient's vein drop-by-drop is warmed immediately and any agglutinates are dispersed.

With high-titer cold autoantibodies causing hemolytic anemia, opinions as to warming differ,[49-52] but relevant data are lacking. This being the case, it seems prudent to use a blood warmer for transfusions to seriously ill patients and to warm the patient as well. The same procedure could be used for patients with cold agglutinin disease and Raynaud's phenomenon or other cold vasoactive effects, although data are lacking here too.

Effects of Heat on RBCs

Heating RBCs produces various effects, depending on the temperature, the duration of exposure, and other less well-defined influences. RBCs are damaged irreversibly by vesiculation and fragmentation when heated to 49 to 50°C for short periods,[53-57] although keeping RBCs at 46°C for up to 1 hour produces no change in osmotic fragility,[58] and keeping them at 45°C does not increase hemolysis.[59] The elastic properties of the RBC membrane have been shown to alter around 49°C,[60,61] which may reflect increased fluidity and decreased cohesion of cell membranes.[62] Subsequent membrane fragmentation may be due to extensive intramolecular and intermolecular disulfide bonds that result in the crosslinking of spectrin and the formation of high-molecular-weight aggregates.[63] Spectrin, composing about 25 percent of RBC membrane protein, is thought to play a large part in maintaining the RBC's shape.[64] With 4 minutes' incubation at temperatures increasing from 46°C, there is a progressive decrease in membrane deformability, such that, at 50°C, the cells are rigid. The ability of RBCs to deform and change shape permits them to pass through capillaries of a diameter smaller than their own and is an important determinant of the life span of circulating RBCs.[62]

The incubation of RBCs at temperatures lower than 46°C can also cause changes: 30 minutes' incubation at 40°C decreases osmotic fragility, whereas more than 180 minutes' incubation at 40°C increases it. At 42 and 44°C, there is a decreased osmotic fragility after 1-hour incubation; osmotic fragility returns to normal after an additional hour of incubation. There is no change in the plasma pH, Na^+ or K^+ concentration, or intracellular potassium concentration for incubation temperatures up to 44°C.[65] Some degree of heating may decrease the immunogenicity of RBC antigens.[66,67]

Heat-damaged RBCs are removed from the circulation by three mechanisms. In the first 10 minutes after transfusion, liver uptake is important. From 10 to 30 minutes, pooling in the spleen is primary. After 30 minutes, irreversible splenic uptake is the major process.[68]

Shear stress occurs during the transfusion of RBCs at high rates of flow. As the temperature of RBCs increases, less shear stress is required to cause hemolysis.[69] Between 2 and 45°C, RBCs deform from biconcave discs to teardrop shapes when subjected to shear stresses under 2 dyne per cm^2. For shear stresses up to 4.5 dyne per cm^2, the cell's body length (the teardrop-shaped portion of a shear stressed-cell, not including any "tethers" or other abnormal processes) varies by no more than 10 percent.[62] Heating to 48 to 50°C causes marked irregularity in the cell membrane, and the cells become highly deformable, to the point of disintegration, even with shear stress as low as 1 dyne per cm^2. If RBCs are warmed to 50°C and subsequently subjected to shear stress at body temperature, they are less deformable than normal. Overall, however, RBC deformability increases gradually between 2 and 24 to 37°C and then increases dramatically between 48 and 50°C, at which point the RBCs may be pulled apart by shear stresses.[62]

After RBCs are stored in ACD for 1, 10, and 21 days, their passage through a dry-heat in-line warmer (Fenwal R4301, Fenwal Laboratories, Deerfield, IL) produces a rise in plasma hemoglobin, a very slight increase in plasma pH, and no change in potassium or sodium concentration.[70] Storage of RBCs in CPD for 1 to 23 days at 4°C with subsequent warming in electromagnetic units (microwave and radiowave) decreases plasma sodium and glucose and increases plasma potassium, lactic acid dehydrogenase, free hemoglobin, and dipeptidyl aminopeptidase III (RBC membrane enzyme), all of which represents an acceleration of the cell changes normally occurring during storage.[71] This is one reason that warmed but unused RBCs should not be returned to storage for use by another patient.

Specifications for a Blood-Warming System

Besseling et al.[33] and Russell[13] (in his review of blood warmers) described the specifications for an acceptable blood-warming device. These stringent specifications continue to be used, with appropriate modifications, in evaluating new systems.

Any such system must warm blood (both WB and RBC units) effectively, safely, and conveniently. This entails warming uniformly without damage to RBCs and

rapidly enough to accommodate the maximum expected flow rate. Appropriate monitors and alarms are essential. Electrical safeguards must protect both the patient and staff. Convenience implies compact size, ease of use, minimal training for proficiency, and the capability of regular staff to operate the system.

Current standards[4] stipulate that in-line blood warmers be equipped with a visible thermometer and, ideally, an audible warning system. Blood is not to be warmed above 38°C.[4] This standard seems unnecessarily restrictive, because, as already noted, brief exposure of RBCs to temperatures less than 46°C causes no observable cell damage.[58,59,64]

Another desirable feature in systems that warm the entire container is a mechanism for marking the container in such a way as to make it obvious that the unit has been warmed. Thus, in the event that such a unit is not used and is returned to the blood bank, it will not inadvertently be replaced on the shelf for reissue, to be given to another patient.

In addition to the foregoing criteria, cost is an important factor in equipment purchasing. When various effective options are available, expense guides the decision-making process.

Blood-Warming Methods

Blood can be warmed either before it passes into the delivery system or during its passage through the IV tubing. Both systems have been used successfully. In the United States (US), in-line warming now predominates. Future changes in technology may alter this.

Pretransfusion warming

Blood can be warmed before transfusion, and over the years, passive rewarming of blood to room temperature, warm-water baths, and radiant and microwave ovens have been used to accomplish this. Some of those methods are still in use. Warming by admixture with room-temperature or body-temperature saline is common. We recently developed a system of warming with 70°C saline.[72-76]

Pretransfusion warming is effective only for rapid transfusions. During transfusion, the circulating blood temperature is inversely related to the rate of transfusion of a cold liquid. At slower rates, or if transfusion is delayed, the blood remaining in the bag cools rapidly toward room temperature. But at such rates, warming is probably not required anyway. Blood warmed to 37°C and kept at room temperature (21°C) falls 3°C in 5 minutes and 5°C in 15 minutes.[77]

In general, pretransfusion warming is less expensive than in-line warming, because one central warmer can meet the warming needs of several patients or of multiple IV lines in one patient.

Ambient temperature (slow transfusions). Warming blood by allowing it to sit at ambient temperature is a common but undesirable practice for slow transfusions. It is discouraged because warming is generally unnecessary for slow transfusions, and slow warming may allow bacterial growth. Also, it is easy for staff to forget such a unit and allow it to sit for longer than intended. When transfusions are prolonged over several hours per unit (another procedure that is not generally recommended), there is a gradual rise in the temperature of the blood. This passive warming is of dubious value, because we can prevent chilling more easily by warming the patient during such elective transfusions.

Allowing blood to warm to ambient temperature may be suitable for small-volume transfusions and exchange transfusions in infants, as the aliquots of blood in syringes used for transfusions to infants are not easily adaptable to conventional warmers. Here, too, the risks of hypothermia must be balanced against those of bacterial growth, and aseptic techniques are essential. With such small transfusions, the priming and tubing volumes and subsequent waste of blood in in-line warmers and the open system and the possible contamination of the RBCs in a syringe transfusion complicate the application of most warming systems, which are primarily set up for adult transfusions.[47]

In a syringe kept in a 35°C isolette, 12.5 mL of 12°C blood reaches 28°C in 30 minutes and 34°C in 90 minutes. The same blood kept in a room-temperature environment of 22 to 24°C reaches 21°C at 30 minutes and 32°C at 90 minutes. Because total transfusion time, including set-up, generally should not exceed 2 hours, the warming already achieved can usually be maintained, and perhaps additional warming can be achieved, through keeping the syringe in the warmed isolette during the transfusion.[47]

Overheating of blood during transfusion has occurred in this setting when blood tubing was exposed either to a phototherapy unit being used to treat hyperbilirubinemia or to an infrared radiant warmer. The result of the former exposure was a hemolytic reaction, with hemoglobinuria, increased indirect serum bilirubin, and no rise in the blood hemoglobin level after transfusion. This outcome may be explained not only by the effect of overheating, but also by a direct hemolytic effect of phototherapy on the RBCs.[78] Exposure to the infrared energy source caused cellular damage, abnormal function, and a fall in pH, with temperatures approaching 45°C. However, infrared radiation causes cellular damage even at lower temperatures (e.g., 34.8°C).[79]

Water bath. Immersion of entire blood units in a water bath is still used sometimes to warm blood before transfusion.[77,80,81] We encountered one instance of a physician at our institution dunking blood units into hot water in a hospital sink before emergency transfusion.

In this setting, warming may be incomplete, local overheating may occur, warmed units may be left unused while pathogens grow at the higher temperature, and the outlet port may be contaminated. In general, this method is nearly impossible to control or to document. The technique, though, is simple, inexpensive, and seemingly effective.

In a more elaborate system with a water bath thermostatically controlled at 39.5°C with continuous agitation, the temperature of whole blood units held at 5°C rises to 35°C in 6.6 minutes.[77] This is effective and harmless to RBC units.[80]

Electromagnetic. Electromagnetic units, both radiowave and microwave, are no longer sold in the US, although many are still in use elsewhere in the world.[82] A relatively new microwave unit (Infusotherm 608, Infusotherm, Göttingen, Germany) was introduced in Europe in the mid-1980s.[83] Electromagnetic units have appeal because they warm blood rapidly, and one warmer can be used for many patients. The possibility of contamination and shear damage to RBCs may be less than that encountered in running blood through a heat-exchange coil.[84] Depending upon a substance's molecular configuration, the electromagnetic beam is variably absorbed and converted to heat. Factors affecting the absorption include the wavelength of the radiation, the duration of exposure, the composition and thickness of the walls of the bag, and environmental factors such as temperature, humidity, and convection currents.[71]

Blood is a fluid tissue, composed of cells with solid, high-resistivity membranes, suspended in and containing fluids of relatively high conductivity that themselves carry a large number of ions in solution. Therefore, the conductivity of blood depends on the beam frequency and current density,[33] with energy absorption and distribution inversely proportional to the beam frequency and the tissue water content. With frequencies of less than 500 mHz (radiowave warmer range), absorption is more diffuse and uniform. Between 1000 and 3000 mHz (microwave warmer range), it is more variable.[71]

One reason for the decline of the radiowave warmer in the US may have been the rather negative review that it received from Russell in his influential article.[13] However, he grouped together the two types of electromagnetic warmers (radiowave and microwave) and mistakenly reported complications from microwave devices as complications from radiowave devices.[13] Even those working with electromagnetic warmers often felt it was impractical to attempt to warm blood to body temperature.[85]

Radiowave warmer. Radio frequency blood warming was first reported by Besseling et al. in 1965.[33] The blood warmer subsequently available commercially (Taurus, Plessey Group, Capetown, South Africa) warmed a plastic bag containing 400 to 600 mL of 7°C whole blood to 33°C in 2 to 3 minutes or a glass bottle of whole blood from 4°C to 33°C in about 4 minutes.[13,86] Warming was by high-frequency electromagnetic oscillations that induced electrical eddy currents in the blood. Separate units were required for bottles and bags. The energy of the currents was converted to heat.[13] A manually adjusted automatic switch set the level to which the blood was to be warmed. The switch had to be reset once a month.[84] A saline solution test pack containing a calibrated thermometer was used as a standard of reference. A thermistor probe in contact with one side of the plastic bag measured the temperature at that site and activated the switch controlling the warming process. A mechanical agitator continuously shook the blood during warming.[84]

The Taurus warmer reached its preset temperature ±1°C, independent of the hematocrit or volume of the unit being warmed. When functioning properly, it could not warm WB above 39.3°C. The agitator was inadequate with units smaller than 300 mL or with hematocrits over 0.75. Attempts to heat small units led to local overheating and slight hemolysis, which would obviate the warmer's use with undiluted RBC units. More hemolysis occurred in WB than in RBCs admixed with saline. Both plasma hemoglobin and plasma potassium levels were higher after radiowave warming than in previously warmed controls.[87] The unit was not foolproof, in that overheating and hemolysis occasionally occurred, apparently because of operator error.[84]

Microwave. Medical microwave warmers (Ohio 987, Ohio Medical Products, Madison, WI; Haemotherm, Robert Bosch Elektronik GmbH, Berlin, Germany; and Infusotherm 407) use a higher-frequency radiation than do radiowave warmers. The Ohio 987 heated a standard WB unit of no less than 425 mL. During warming, metal

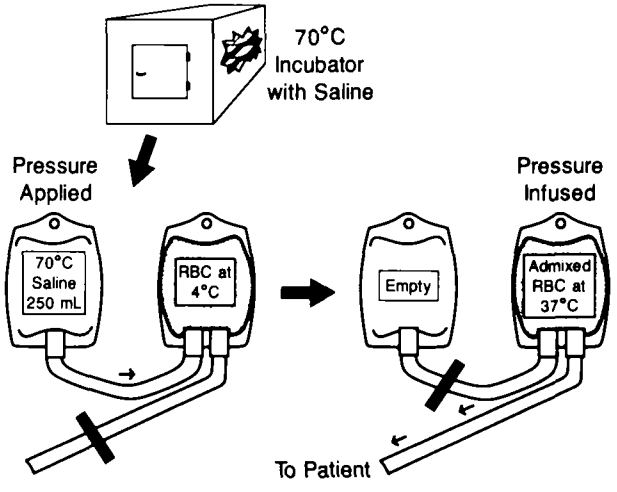

FIG. 2. Rapid admixture blood-warming technique.

Table 1. *Manufacturer's data on blood warmers*

Manufacturer	Model	Heat exchange type	Size (cm)	Weight (kg)	Power (Watts)	On/off switch	Primary temperature control	High-temperature cutoff (°C)	High-temperature alarm	
									Audible	Visible
Datachem Indianapolis, IN	Flo Tem IIe	Dry	20×15×5	27	300	Yes	Electronic	42	Yes	No
Fenwal/Baxter Deerfield, IL	4R4305	Dry	40×20×15	6	700	Yes	Electronic	40	Yes	No
Futurmed Deer Park, NY	Animec AM-125	Dry	17.5×6.3×3.5	0.55	27	No	Electronic	40	No	No
Baxter/Pharmaseal Valencia, CA	DW-1000/A/1220	Dry	10×20×26	3.2	360	Yes	Electronic, thermostat	41.4	Yes	Yes
Baxter/Pharmaseal	DW-1000D	Dry	10×20×25	3.2	360	Yes	Thermostat	39.5	Yes	Yes
Stihler Electronics Stuttgart, Germany	Astotherm IFT 200	Dry	20×17.5×24	2	200	Yes	Electronic, thermostat	41-42 (el.) 42-44 (th.)	Yes	Yes
Stihler Electronics	Astotherm IFT 220	Dry	20×17.5×24	2.5	300	Yes	Electronic, thermostat	41-42 (el.) 42-44 (th.)	Yes	Yes
Dupaco Oceanside, CA	Hemokinetitherm	Water	23×12×17.5	6.8	300	No	Electronic	39	Yes	No
Raymond Jensen El Segundo, CA	709100-1A	Water	22.5×15×10	1.8	170	No	Thermostat	40.5	Yes	No
Level 1 Technology Marshfield, MA	H-250	Counter current	133×38×38	21.4	600	Yes	Electronic, thermostat	41	Yes	Yes
Level 1 Technology	H-500	Counter current	153×45×45	34	1000	Yes	Electronic, thermostat	41	Yes	Yes
Haemonetics Braintree, MA	Rapid Infuser	Counter current	125×48×50	118	1600	Yes	Electronic	41	Yes	Yes
C.R. Bard Tewksbury, MA	Infuser 37	Counter current	59×26×40	21.4	1000	Yes	Electronic	42	Yes	Yes
NA	NA	Rapid admixture sysem	75×75×75§§	13.6§	▓	Yes§§	‖‖	Adjustable	‖‖	‖‖

* Per patient.
† Liquid crystal display.
‡ Optional.
§ When warming from 4-8°C to 30-36°C.
‖ Light-emitting diode.
¶ Not applicable.

caps shielded both ends of the blood bag to prevent overheating of the small amounts of blood trapped within the bag or ports. When the bag reached the desired temperature, a sensor control light signal went out and heating stopped. If heating continued more than 80 seconds, a timing circuit override stopped the heating.[84] The Infusotherm 407 produced pulsed high-frequency waves and continuously rotated the blood bag. The blood temperature was registered from the bag's surface, and warming was stopped at 32°C.[86]

If used correctly, the microwave units do not increase RBC fragility, plasma hemoglobin, or potassium or affect other measurements of RBC injury.[88-90] The volume of blood in the container is important, because overheating and hemolysis can occur if the sensing probe did not properly contact the side of the blood unit or if improper placement caused the unit not to rotate during heating.[91,92] Local overheating could cause hemolysis of smaller WB units or those with a hematocrit above 0.70 when they were warmed to about 36°C.[93]

All these warmers have the disadvantage of being designed primarily to warm WB units. Adaptation to RBC containers, with their smaller size, less-well-defined shape, and higher hematocrits, seems to have been difficult or impossible in most cases. Compounding this problem, they appeared at a time coincident with the gradual disappearance of WB as a transfusion modality and its replacement with RBCs. Scattered reports of malfunction leading to overheating, hemolysis, and transfusion reactions did little to bolster the confidence of the medical world in these devices.[94] None is commercially available in the US today.

Occasionally, commercial culinary microwave units have also been used to warm saline and blood.[95,96] These units have not been subjected to the testing required of medical units, and the potential for RBC damage is great.

Admixture. A method that is commonly used to warm blood is the admixture of warmed isotonic saline with the unit of cold RBCs before rapid transfusion. There were few investigations into this method before the late

Table 1. *Manufacturer's data on blood warmers (cont'd)*

Alarm test	Displays			Disposable parts*	Free-standing	IV pole attachment	Maximum flow (mL/min)	Warranty	Cost ($)	
	Type	Range, C	Incr., C						Unit	Disposable parts*
Yes	LCD†	0–99.9	0.1	IV tubing‡	Yes	Yes	60§	2-yr	950	3
Yes	LED‖	−4 to 40	0.1	Bag	Yes	Yes	150§	1-yr	1,150	8.69
NA¶	Analog	30-36	contin.	NA	No	Yes	9§	1-yr	585	NA
No	Analog	18-49	1.0	Bag (cuff)	No	Yes	200**	1-yr	971	25
Yes	LCD	0-99.9	0.1	Bag (cuff)	No	Yes	200**	1-yr	1,255	25
Yes	LED	15-49	0.1	Tubing	Yes	Yes	66§	1-yr	1,950	2.50
Yes	LED	15-49	0.1	Tubing	Yes	Yes	133§	1-yr	2,270	2.50
No	Analog	0-50	0.5	Coil	Yes	Optional	60§	1-yr	1,010	11
No	Calibration meter	37-40.5	1.0	Coil	Yes	Yes	120§	90-days	695	11
Yes	LCD	38-40	0.1	Tubing, heat exchanger, air filter	Yes	Part of unit	250††	1-yr	2,500	25
Yes	LCD	38-40	0.1	Tubing, heat exchanger, air filter	Yes	Part of unit	750††	1-yr	4,950	85
No	LED	9-45	1.0	Tubing, filter, exchanger, sensor	Yes	No	1500††‡‡	1-yr	51,700	590
No	LED	0-50	0.5	Exchanger	No	Part of unit	300††	1-yr	4,015	329
‖	‖	‖	‖	IV tubing	Yes§§	No	800††	‖	750‖	NA

** When warming from 18 to 30°C.
†† When warming from 4 to 37°C.
‡‡ Maximum flow requires two lines to patient; RBCs diluted with plasma or albumin.
§§ Applies to warming oven.
‖ Dependent on oven model and added alarm system.

1980s. Saline can safely be added to RBCs at 45, 50, and 60°C in a 1:1 dilution to effect rapid warming (Fig. 2).[72,97] We later showed[73,75] that the addition of saline warmed to 70°C to an equal volume of cold (4°C) RBCs resulted in a diluted unit at 37°C and had no adverse effect on osmotic fragility, plasma hemoglobin, plasma potassium, or RBC survival in vivo. An even simpler system adds a standard 250-mL quantity of warm saline to RBC units of all sizes.

The bags of saline do not deteriorate significantly when kept for 2 weeks or less in a warming oven at 70°C. But "standard" units of RBCs (mean ± SD, 305 ± 32 mL) vary substantially. Using the standard 250 mL of warm saline, the smallest units (<0.1% are as small as 220 mL) reach a transient maximum temperature below 44°C. These small units had plasma hemoglobin and plasma potassium levels lower than those in 1:1 diluted, non-heated controls or the normal values for 35-day-old RBCs. Osmotic fragility curves remain the same. The largest units (<0.1% are as big as 410 mL) equilibrate at 30°C. An average-sized unit (305 mL) equilibrates at 36 to 38°C less than 30 seconds after the beginning of admixture.[76] To conform to current standards—that is, not to exceed a final temperature of 38°C—the admixed saline would have to be kept at 65°C or even 60°C. But a lower saline temperature also lessens the clinical efficacy of the system by not allowing the achievement of body temperature when the saline is admixed with the normal-sized or larger units of RBCs. Because even the transient maximum of 44°C has no demonstrable adverse effects, we prefer to keep the saline at 70°C. Quality control of the system is primarily limited to the checking of temperature alarms on the saline-warming oven and to rotation and replacement of warmed saline units.[14,76]

Once blood is warmed to 37°C, it deteriorates rapidly. After 24 hours, as little as 30 percent of the cells is viable.[98] However, the rapid admixture blood-warming method is intended only for rapid transfusion. If not used promptly, the warmed blood must be returned to the blood bank to be discarded.

Polyvinylchloride, used in blood and crystalloid storage bags and tubing, contains plasticizers, with those of most concern being the phthalates. Di(2-ethylhexyl)phthalate (DEHP) and its metabolite, mono-ethyl-

hexylphthalate (MEHP), leach into blood during storage.[99] Warming a bag of saline increases the amount of DEHP leached from the bag during storage (Fratantoni J, oral communication, March, 1990). The plasticizer is taken up by the RBC membrane, where its effects are to diminish the rate of degradation of the RBCs and to enhance resistance to hypotonic lysis.[100-103] More than one-half the DEHP infused during WB transfusions is eliminated within 8 hours. DEHP is only mildly toxic in animals and, when administered in blood, seems not to produce any adverse effects in man.[104] Newer bags for some blood components are made without DEHP.[105]

In-line warming

In-line warming, in which the blood is warmed during transfusion, is the most common method now used in the US and Canada (Table 1). All blood warmers commercially available in the US operate on variations of this technique. In-line blood warmers can generally be divided into those in which IV tubing is immersed in water baths, with or without a countercurrent modification, and those in which the tubing passes through dry heaters.

The transfer of heat from the warmer to the blood is crucial to the effectiveness of any unit. The temperature of the blood being transfused to the patient is inversely related to the flow rate and directly related to both the temperature of the warmer and the initial temperature of the blood.[106]

One drawback of all in-line warming systems is that they can be used for only one patient at a time and, except for one (Haemonetics Rapid Infuser System, Haemonetics Corp., Braintree, MA), for only one IV line at a time. If a blood-warming system is needed for more than one patient or at more than one IV site at a time, the costs multiply rapidly. This is a contrast with pretransfusion warming systems that can serve several patients at once in the same general area (emergency department, operating room, or intensive care unit).

Some advantages of in-line systems are: 1) that they can generally be used as well with RBCs as with WB units, although flow rates may be slower with RBCs; 2) that, once the warmer is set up, new units can be started at once; and 3) that entry ports must be punctured before warming, so warmed blood cannot be mistakenly returned to the blood bank for issue to other patients.

Water bath. Most in-line warmers operate by heat exchange with a water bath. The temperature of the blood at the outlet of the warmer depends on both the temperature of the heat source and the flow rate of the blood. Because of the inefficiency of early systems, especially in rapid transfusions, Chalmers and Russell[59] suggested that the thermostat of the blood warmer be set so that the optimal output temperature is achieved at high flows. The long tubing necessary for heat exchange slows potential maximal transfusion rates, limiting the usefulness of such warmers in situations requiring rapid transfusion.[86] All standard water bath warmers monitor only the temperature of the water bath itself. Alarms on the units are activated by power failure or, in some instances, by the overheating of the water bath. Some countercurrent warmers (see following section) also measure the temperature of the blood or solution leaving the warmer.

Warm-water baths with coils of IV tubing passing through them were the first clinically used blood warmers. These systems ranged from the simple—dropping IV tubing into warm water[107,108]—to more elaborate glass or plastic coils inserted into homemade water baths.[8,12,109-112] Most were designed for large-volume transfusions, but one early system was specifically intended for infants.[109] In the late 1960s, commercial blood-warming units began to be sold.[113,114] Yet reports still appeared of general laboratory water baths being used as blood warmers.[115]

Once commercial water bath blood warmers were accepted, attention turned to the coils used in the warmers. Factors assessed included maximal flow rates, flow volume, efficiency of heat transfer, and convenience.[116] Competition for the standard coiled tubing took the form of thinner-walled tubing with greater heat transfer capabilities and a flattened coil or warming bag.[117,118] The latter design now primarily serves dry-heat in-line warmers. Even with the advent of heat-exchange coils designed specifically for use in blood warming, alternative techniques using standard IV tubing continued to be advocated.[119]

With rapidly widespread use, the hazards associated with water bath blood warmers soon began to appear. Warming coils leaked if not used properly, or they occasionally had blockages due to manufacturing errors.[120,121] The anticipated problem of gas bubble formation during the warming process, resulting in an air embolism, was remedied, and no clinical cases were ever reported.[122,123] Much more serious potential problems were the risk of infection and the overheating of blood. Casewell et al.[124] reported a fatal case of *Pseudomonas aeruginosa* septicemia in a patient given fresh-frozen plasma thawed in a contaminated water bath warmer. Subsequently, water bath warmers were found often to be contaminated with a variety of bacteria.[125,126] Those two factors led some, even without subsequent reports of patient infection from water bath warmers, to suggest the abandoning of water bath warmers in favor of dry-heat warmers.[125] That step seems extreme in light of the availability of disposable, closed-transfusion systems. As a safety measure, however, IV injection ports and tubing connections are routinely kept out of the warming bath.[126] Total hemolysis of blood can result from the blood's overheating in a water bath, although

present-day warmers, with their safety cutoff features, are less likely to cause overheating.[127]

Ungrounded warmers (water bath and dry-heat) can leak current through the fluid path.[128] The grounding of all such equipment should be standard practice in the operating room.

Countercurrent warmers. A relatively new and unique type of water bath warmer is the countercurrent heat exchanger. Designed primarily to warm blood rapidly for transfusion to patients in hemorrhagic shock, the systems use a countercurrent flow of heated water around or interdigitated with the IV blood tubing circuit (Fig. 3).[15,129-131] With the newest models, up to 750 mL per minute can be delivered with blood warmed from about 10 to 35°C. The primary limitation of these systems is the flow capacity of the IV catheter: because the IV catheter is the flow-limiting part of the transfusion system, the use of either a 12-gauge or a No. 8 French catheter is necessary to achieve the maximal flow rates that the fastest units are capable of delivering. Countercurrent warmers are more expensive than other in-line warmers, set-up times are longer, and more time is needed for training.

Dry-heat warmers. Unlike water bath warmers, in dry-heat warmers, the coiled tubing or bag passes around or through an aluminum heating element (Table 1). The earliest model, developed in the late 1960s, could heat blood from 4 to 36°C at a flow rate of 50 mL per minute.[132] The earliest models of commercial systems could heat blood from 10 to 30°C at flow rates of 150 mL per minute without damage to the cells,[70,133,134] and later models could heat from 4 to 37°C at that flow rate.[135] Unfortunately, not all models had that warming capacity.[136-138] Moreover, leakage of current was reported with some units.[139,140] In one case, a malfunction in the temperature control allowed current to leak through the IV tubing, causing second-degree burns of the patient's forearm and subsequent chest pain and hematuria.[141] In another case, malfunction of the temperature monitor caused overheating and hemolysis of the transfused blood.[142] As with all blood warmers, though, reports of complications are infrequent.

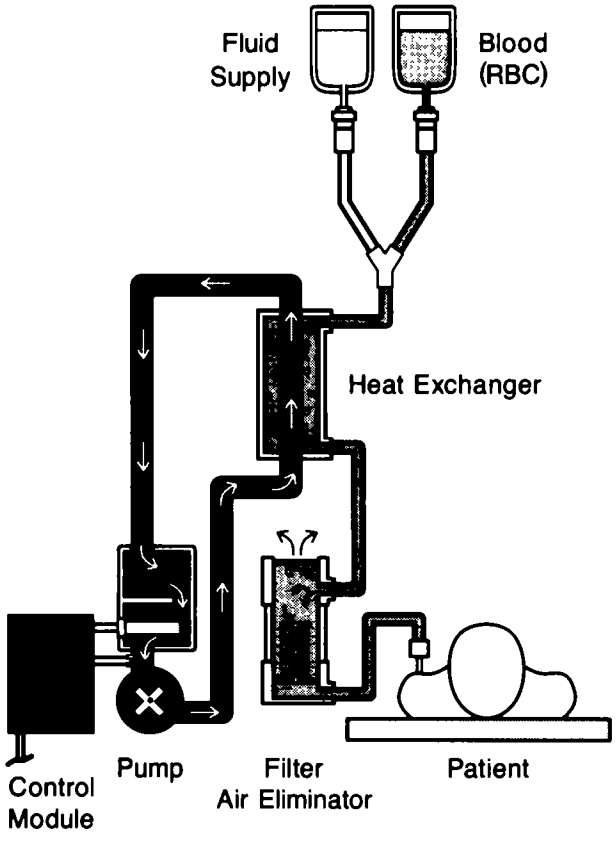

FIG. 3. Countercurrent blood-warming heat exchanger.

Other in-line warmers. One experimental method mixes warmed saline with cold blood in a manifold. The system, an in-line variant of warming with admixed warm saline, has the disadvantage that both the ratio of saline to blood and the resultant temperature are more difficult to control than in systems with pretransfusion mixing.[143,144]

Another method, which has had only animal tests, employs microwave warming of blood during extracorporeal circulation for cardiac surgery.[145] It may be possible to adapt this method for clinical blood warming. If designed correctly, it might not have the complications reported to have afflicted microwave pretransfusion warming of blood.

Direct comparisons of the performance of various blood warmers are rare in the medical literature.[106,116] Further, interpretation of such comparisons may be difficult because of frequent design changes that result from perceived needs, new standards, and reported complications.

Recommendations

One should have a specific purpose in mind before purchasing a blood warmer, remembering that rapid transfusion is not necessary for most elective transfusions, whereas cost, safety, and basic effectiveness are the primary considerations. The potential for high flow rates is important during unexpected, rapid blood loss. The system must be able to warm RBC as well as WB units. In general, 150 mL per minute is the minimum acceptable flow rate.

Table 1 compares the blood warmers now available commercially as well as the rapid saline admixture system, although the latter is not available commercially as such. The costs are approximate and are based on information available during the summer of 1990. Using the table, the reader can see, for example, that of those warmers that do not use countercurrent or rapid admix-

ture warming, only the 4R4305 and the DW-1000 series warmers have a maximum flow rate of at least 150 mL per minute. These rates, though, do not reflect warming from 4 to 37°C.

For rapid blood warming, the saline admixture system has many advantages. It requires only a monitored warming oven, can be used for multiple patients simultaneously, has no disposables other than normal IV supplies, requires little operator training, is the least costly system, and has a blood flow limited only by the capacity of the IV system attached to the patient. Drawbacks include the absence of in-line monitors and some minor unit-to-unit inconsistency in the resulting blood temperatures because of variations in the unit size.

For a commercially available system that has an adequate flow rate for rapid transfusions and has multiple monitoring systems, the least costly is the H-500 (Level 1 Technologies). The major drawback of this system is the cost of the disposable supplies, at $85 per patient. As with most other in-line warmers, only one IV line at a time can be serviced by this system.

Summary

Active blood warming is a recent practice and arises out of conflicting needs. On the one hand, the safety and preservation of blood require refrigerated storage and delivery up to the moment of transfusion. On the other hand, modern methods of very rapid transfusion in resuscitation would cause clinically dangerous hypothermia if unmodified, ice-cold blood were to be so transfused. These needs must be reconciled in the interest of adequate patient care—hence the need for blood warming. Nevertheless, blood warming creates risks of its own and should not be used without justifying clinical indications.

Within limits that extend somewhat above normal body temperature, the application of heat does no harm to stored RBC, a fact that is not reflected in current standards for blood warmers. Bearing in mind the human tendency to "stretch" standards and the fallibility of mechanical devices, caution is always wise. But perhaps the time has come for reconsideration of the present upper limit of 38°C.

Many varieties of blood warmers are available in the US, but none at this time is based on electromagnetic activity. The most common systems now in use are in-line warmers, most of which are not adequate for the type of rapid-transfusion systems currently available. Countercurrent in-line blood warmers and the method of rapid warm saline admixture can both be used successfully for rapid, massive transfusions. Blood warming is seldom necessary or desirable for elective transfusions at conventional rates, even for patients with cold autoagglutinins.

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