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14. ABSTRACT Hypothermia occurs as the core temperature decreases below 35°C. Many patients become hypothermic after severe injury due to environmental exposure during transportation, infusion of cold fluids, and decreased ability to maintain normal core body temperature (37°C). Patients with severe trauma die because of hypothermia, metabolic acidosis, coagulopathy, this phenomenon is known as the lethal triangle. Studies have shown the outcome of trauma patients with hypothermia is far worse than those with either trauma or hypothermia alone. It has been shown resuscitation requirements are increased with trauma patients who become hypothermic. Internal warming has been considered the most effective for rewarming severely hypothermic patients which involves infusion of warm fluids. In combat settings, a fluid warmer with light portability and minimal power requirement capabilities would greatly improve the treatment of injured who are in need of fluid replacement and return core body temperature as quickly as possible to normal and prevent further complications associated with hypothermia. No such process is currently available.					
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FINAL TECHNICAL REPORT

GRANT #: N00014-05-1-0848

PRINCIPAL INVESTIGATORS: G. Tom Shires, MD, John Fildes, MD (email: jfildes@medicine.nevada.edu)

INSTITUTION: University of Nevada, Reno, University of Nevada School of Medicine

GRANT TITLE: High Speed Blood and Fluid Transfusion Equipment

AWARD Period: 1 August 2005 – 30 December 2006

OBJECTIVE:

Hypothermia occurs as the core temperature decreases below 35 °C. Many patients become hypothermic after severe injury due to environmental exposure during transportation, infusion of cold fluids, and decreased ability to maintain normal core body temperature (37 °C). Patients with severe trauma die because of hypothermia, metabolic acidosis and coagulopathy, this phenomenon is known as the lethal triangle. Studies have shown the outcome of trauma patients with hypothermia is far worse than those with either trauma or hypothermia alone. It has also been shown resuscitation requirements are increased with trauma patients who become hypothermic. Internal warming has been considered the most effective for rewarming severely hypothermic patients which involves infusion of warm fluids. In combat settings, a fluid warmer with light portability and minimal power requirement capabilities would greatly improve the treatment of injured who are in need of fluid replacement and return core body temperature as quickly as possible to normal and prevent further complications associated with hypothermia. Detailed study of the effects of hyperthermia on the blood components as well as systemic response of the body to hyperthermia will also be studied in great detail.

APPROACH:

The University of Nevada School of Medicine (UNSOM) and Rocky Research are developing a new temperature conditioning blood and fluid infusion/transfusion technology that can be recharged with electric power, but incorporates high power density thermal battery technology to allow for rapid fluid heating without any electric energy demand. This will allow for fast blood infusion and transfusion during electric power loss periods as well as in battle field locations without access to electrical power and will thereby dramatically increase the response capability of medical personnel in the battlefield. The thermal battery technology is based on a sorption process which can be regenerated in the field with a diversity of energy sources including electricity of any voltage or frequency, as well as thermal energy, if desired. The proposed research and development project employs designs and materials that overcome current fluid handling, temperature conditioning, and fluid administration deficiencies in existing system designs and will include extensive testing for functionality and reliability with animal and

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volunteer patient testing. In addition, the body response to various temperature and flow characteristics of fluid will be measured in vivo and in vitro.

ACCOMPLISHMENTS:

Rocky Research and the University of Nevada School of Medicine Trauma Institute have successfully completed their efforts under Task 1, Task 2, and Task 3 as outlined in the original application (Figure 1).

1. The requirements for the high speed blood and fluid transfusion heater have been defined.
2. The thermal and transport properties for both saline and blood at 37°C have been identified (Table 1).
3. Testing of the Level 1 infuser has been done. In addition, tests have been conducted with two different complex compounds based heat producing absorbents. These sorber sizes tested provide a capacity that is in agreement and allows for a conservative design for this generation component of the high speed blood and fluid transfusion device with both the CC 260-2360 and the CC 180-1580 sorber (Figures 2, 3).
4. Biological testing of the safety of infused fluids at varying rates and temperatures is under study at the present time. Inflammation and elevation of cytokines have been shown in Task 2.
5. Several biological studies are under way studying the various components of blood and tissue and their response to varying infused temperature rate and volume. These include a.) osmotic fragility and plasma free hemoglobin; b.) neutrophils viability; c.) platelet aggregometry.

EXPANDED ACCOMPLISHMENTS:

The requirements for the high speed blood and fluid transfusion heater have been defined based on information provided in technical journal papers, as well as information provided from technical literature for the present infusion warmer used in the field. Additional information was developed at Rocky Research by testing a high speed infusion warmer used in the emergency room at the University Medical Center Hospital in Las Vegas, Nevada. The development of the heater requires a definition of the requirements for fluid infusion rate, allowable temperature and tolerance, fluid delivery temperature, anticipated fluid temperature drop between the heater and the patient and the temperature of fluid before heating. Since the heater will be discharged in the field, a specification for the allowable time for recharge of the heater had to be generated. Based on the need to not cool the patient, the minimum set point temperature for the infused fluid is 37°C. A maximum temperature of 42°C is desired, which would make it 0.3°C higher than the set point for the Level 1 infuser. Since standard tubing will be employed, the fluid temperature drop from the infuser to the patient will be the same as with present technology. However, Rocky will examine the possibility of insulating tubing to minimize this.

The thermal and transport properties for both saline solution and whole blood are important to the design of the blood warmer in terms of heat transfer and pressure drop. Because 0.9% saline is essentially identical to water, values for water are used. Since the warmer should be designed to accommodate both blood and saline solution, the

implications of the differences in these properties must be considered. In terms of heat transfer surface performance and pressure drop, the higher viscosity of blood vs. saline has the greatest impact on design. The dramatic difference between the two fluids in this property drives the requirement towards larger surface areas and larger passage sizes to accommodate whole blood. The blood warmer system will produce heat by an exothermic, but reversible, chemical absorption process. Because of this it will need very little power for operation. The heater system will include a small battery capable of powering the controls and fans for the duration of the infusion period.

The ability of the heat generating component for the infuser, the complex compound sorber, to provide the necessary heat required had to be determined so that the selection of the most suitable complex compound and its sizing could be done. Tests were conducted with two different complex compound based heat producing absorbents. The first of these used the compound CC180-1580 while the second used CC260-1260. The testing of CC180-1580 was previously reported on in the Task 1 report to provide the reader with some perspective on the characteristic performance of a complex compound. These tests are included in this report for completeness. From a thermodynamic performance perspective, what differentiates the two complex compounds are their vapor pressures and heat evolution per mole of ligand absorbed. The vapor pressure of CC260-1260 is lower than CC180-1580, making it more capable of operation at low temperature ambient conditions. It also provides a higher heat of absorption per mole of ligand. However, typically, CC180-1580 sorbers are slightly smaller in size and weight which is advantageous for the blood warmer product. Because of these tradeoffs, tests were conducted using both complex compounds.

One important finding from these test results are that a thermal battery with CC260-1260 has higher heat rates than the CC180-1580 sorber. As shown, the maximum output rates are close to 1000 Watts as compared to about 500 Watts with the complex compound CC180-1580. The direct benefit of this is that a smaller extended heat surface area will be needed to transfer the same amount of energy to the fluid being heated. Also noticed is the capability of this complex compound to provide heating at lower ambient temperatures. It is believed that at an ambient temperature of 0°F this sorber can provide adequate heating. The sorber sizes tested provide a capacity that is in agreement and allows for a conservative design for this heat generation component of the high speed blood and fluid transfusion device.

The purpose of Task 3 was to develop and demonstrate a first prototype of the infusion fluid warmer appliance. Prior tasks focused on internal design of sorbers and demonstrating the ability of ammonia-complex compound absorbers to release sufficient stored energy to quickly warm at least one unit of blood from 4°C to 37°C for infusion into a patient, and to accomplish this without reliance on any outside source of power. The major issue in design of a first prototype was selecting and proving methods of harvesting the heat from the sorption reaction and transferring that heat to an infusion fluid. The device that is actually in contact with the infusion fluid should be single-use to minimize the possibility of contamination. Two methods of harvesting and transferring heat were investigated. One relies on an intermediate pumped loop, while the second

method utilizes a single-use heat exchanger that is clamped directly on the shell of the sorber. The clamp-on method was chosen for use in the first prototype (Figures 4, 5, 6, 7).

There are significant biological factors to consider when it comes to temperature, rate, and volume of transfusions. The potential for things such as thermal and shock injuries must be measured. Blood is composed of various types of cells and proteins each with their own function including clotting and immune response. Each element of the blood has unique properties and in so far as their ability to tolerate different temperatures so as to maintain structural and functional integrity. The studies currently being measured include:

1. Chemiluminescence is now used to measure cytokines.
2. Infusing fluids at the highest temperature safely tolerated by the body will allow for faster resolution of hypothermia. It has been shown that red blood cells may be heated in vitro to 48°C for up to 4 hours without significant hemolysis or increase in osmotic fragility. Platelets and albumin are also very crucial elements of whole blood. Including these constituents in an analysis of temperature effects on whole blood provides further insight into the efficacy of infusing fluids at increased temperatures.
3. Osmotic fragility and plasma free hemoglobin are measured in collected blood that is transported at 37.5°C (Figure 8).
4. Neutrophils are isolated from fresh blood using a method developed by De and Roach.
5. Impedance aggregometry measures that electrical impedance between electrodes immersed in whole blood. The increased impedance that occurs as platelets aggregate onto electrodes is converted into aggregation units by system software and plotted against time. Unlike optical aggregometry, which requires centrifugation and analysis of platelet-rich plasma (PRP), impedance aggregometry involves whole blood and tests platelet function under more physiologic conditions.
6. Suspensions of washed platelets are heated in water baths at temperature from 40-80°C for 10 minutes to 4 hours. The amount of lactate dehydrogenases (LDH) lost from cells into the suspending fluid is measured to estimate the extent of platelet lysis. LDH activity is to be assessed according to Bergmeyer, et al.

WORK PLAN:

Large amounts of blood loss cause hemorrhagic shock, a physiologic state which, if left untreated for up to one hour, results in massive release of chemical cascades producing devastating and irreversible effects on the body. Administering resuscitative fluids such as normal saline (NS) and Ringer's lactate (RL) decreases these events and turns the process of hemorrhagic shock from an irreversible and devastating process into a reversible and recoverable process. Another resuscitation fluid, hypertonic saline (HTS) has been used in the past by both military and civilian medical personnel and continues to be evaluated by research groups. Currently, NS and RL provide the most reliable, cost effective and available source of crystalloid resuscitative fluids in the United States and around the world. Infusing fluids at the highest temperature safely tolerated by the body will allow for faster resolution of hypothermia. It has been shown that red blood cells may be heated in vitro to 48°C for up to 4 hours without significant hemolysis or increase

in osmotic fragility. Osmotic fragility and plasma free hemoglobin are measured. Neutrophils are isolated from fresh blood using a method developed by De and Roach. Impedance aggregometry measures the electrical impedance between electrodes immersed in whole blood. Evidence of cellular injury is being measured through the assessment of cytokines and malondialdehyde as a measure of lipid peroxidation.

Rocky Research will design the prototypes. All components will be designed or fully specified, depending on if they are to be purchased or fabricated parts. A design for the assembled prototype will also be generated, allowing for instrumentation. The prototype will be used for testing of different configurations of certain components, and accordingly the design will allow for change out of select components. Data acquisition will be computerized for real-time data collection at a data collection frequency suitable for the process being measured. Relevant process parameters and environmental temperatures will be measured. Fluid flow and fluid temperatures into and out of the appliance are the ultimate parameters of interest. Fluid temperatures will be logged along with process parameters. Flow will be measured or calculated based on time and weight. Control of these first prototypes will be manual, or if complexity warrants, a programmable microcontroller will be utilized. Rocky Research has successfully designed, built, and used microcontroller on several projects. Prototypes will include fluid transport means and thermal contact between sterile fluid tubing and the heating appliance. Initial tests will be conducted with water to vary flow rates and heating rates. Testing will include a range of supply temperatures and flow rates. In a reiterative process, the laboratory prototype will be revised and refined to reflect operational experience gained and improvements discovered during testing at Rocky Research and UNSOM. This will result in an engineering prototype. A series of two or more prototypes will be built and tested.

PATENT INFORMATION: None

AWARD INFORMTAION: None

REFEREED PUBLICATIONS: None

BOOK CHAPTERS, SUBMISSIONS, ABSTRACTS AND OTHER PUBLICATIONS:
None

High Speed Blood and Fluid Transfusion Equipment

Objective

- Development of a fluid warmer with light portability and minimal power requirements for treatment of the injured.
- Detailed study of the effects of hyperthermia on the blood components as well as systemic response of the body to hyperthermia will also be studied in great detail.

Approach

- Developing a new temperature conditioning blood and fluid infusion/transfusion technology which can be operated with electric power, but incorporates high power density thermal battery technology to allow for rapid fluid heating without any electric energy demand.
- The body response to various temperature and flow characteristics of fluid will be measured in vivo and in vitro.

Accomplishments

- The requirements for the high speed blood and fluid transfusion heater have been defined.
- The thermal and transport properties for both saline and blood at 37°F have been measured.
- Testing of the Level 1 Infuser has been done. In addition, tests have been conducted with two different complex compounds based heat producing absorbents.
- Biological testing of the safety of infused fluids at varying rates and temperatures is under study at the present time. Inflammation and elevation of cytokines have been shown.
- Several biological studies are under way studying the various components of blood and tissue and their response to varying infused temperature rate and volume. These include a.) osmotic fragility and plasma free hemoglobin b.) neutrophils viability c.) Platelet aggregation.

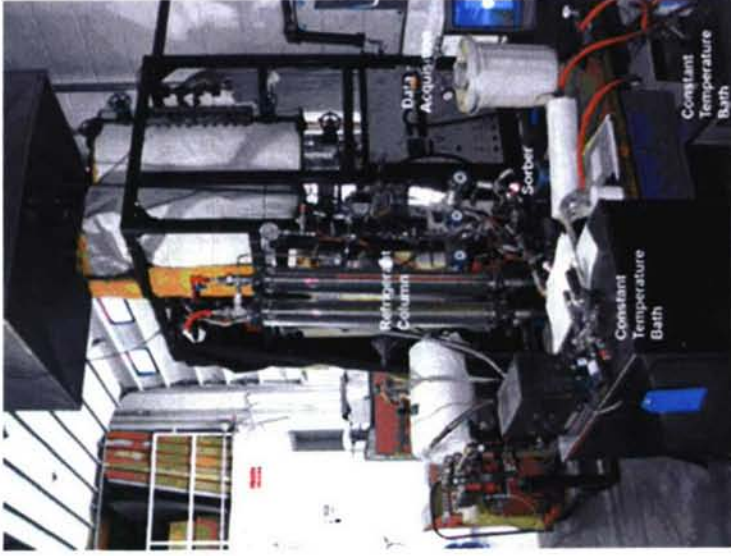


Figure 1. High speed blood and fluid transfusion equipment.

	Density (g/cc)	Viscosity (cP)	Specific heat (kJ/kg°C)	Thermal conductivity (W/m °C)
Normal Saline (or Water)	0.993	0.692	4.182	0.627
Whole Blood	1.056-1.066	2.18 -3.59	3.594	0.492 ± 0.009

Table 1. Physical Properties of Blood and Saline at 37 °C

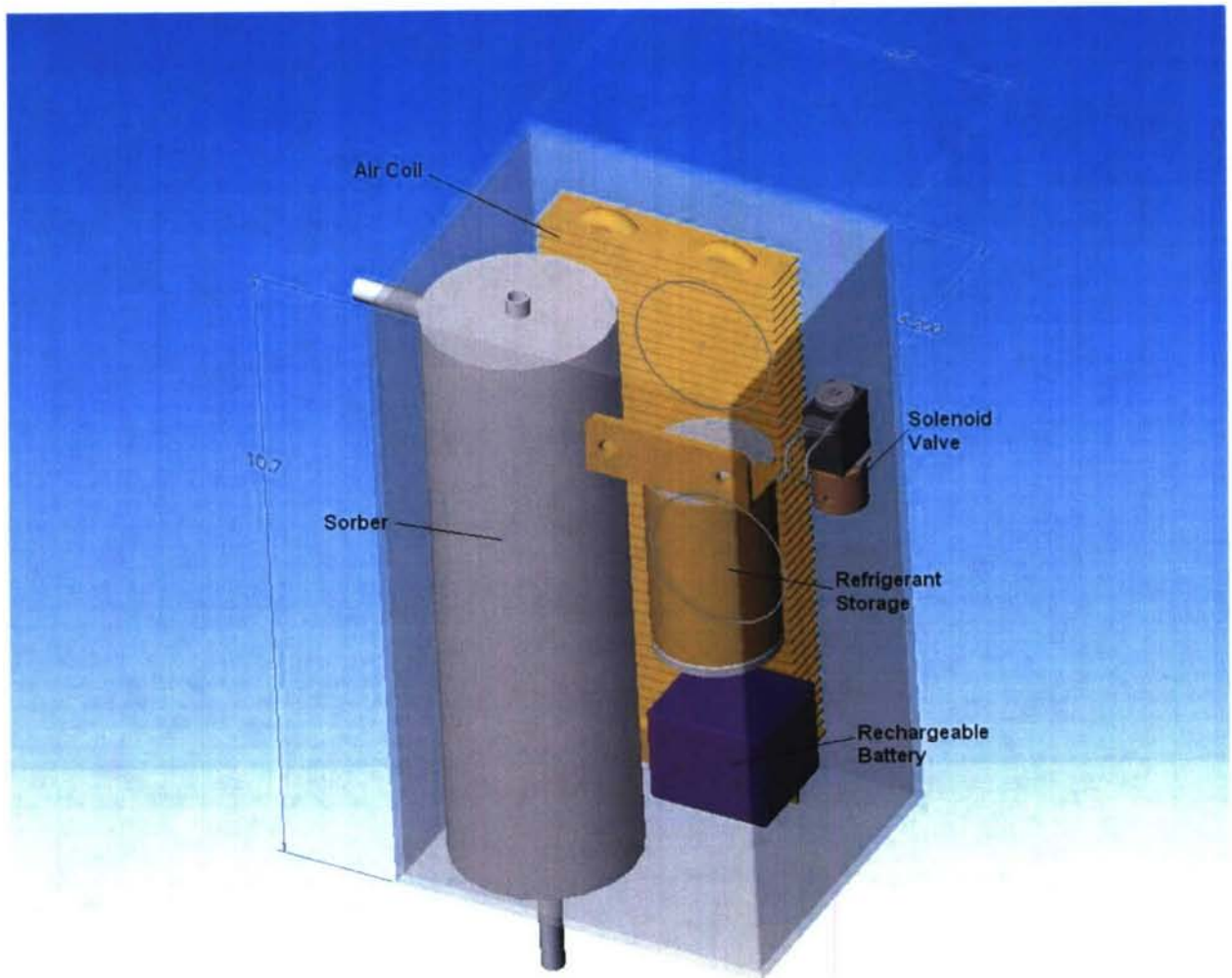


Figure 2. Rotated view of blood warmer components

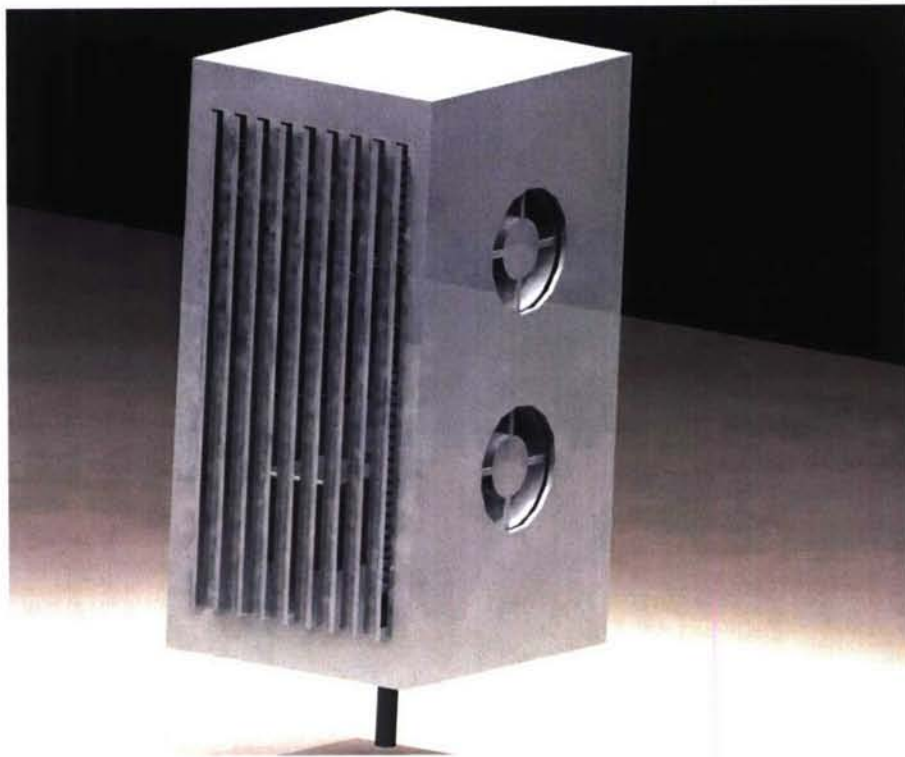
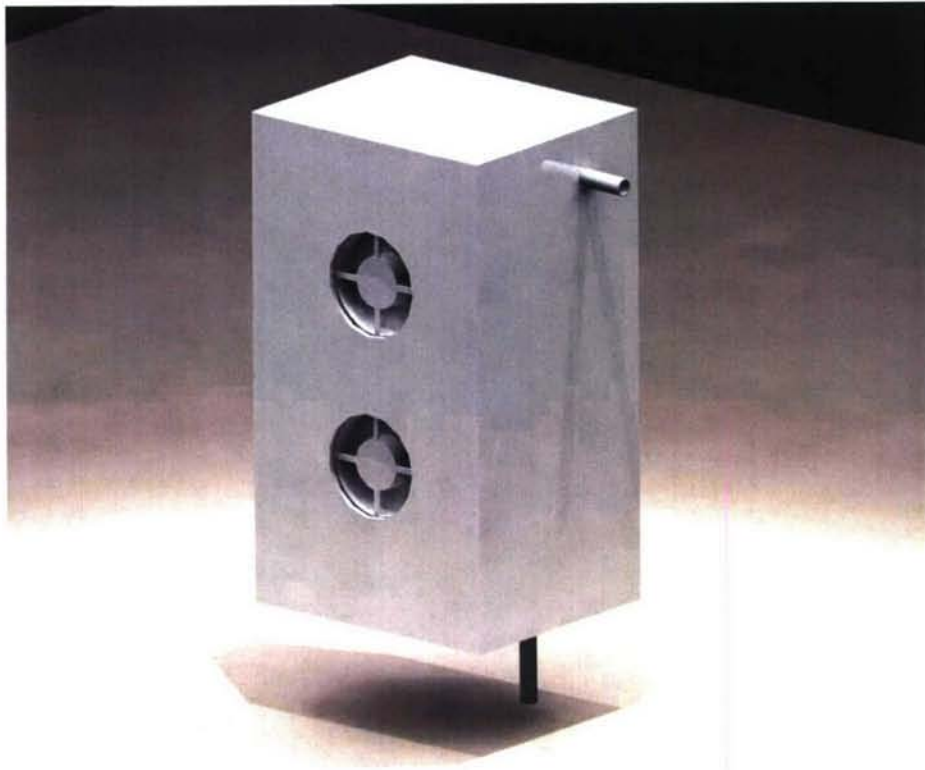


Figure 3. Preliminary rendering of the blood warmer product.

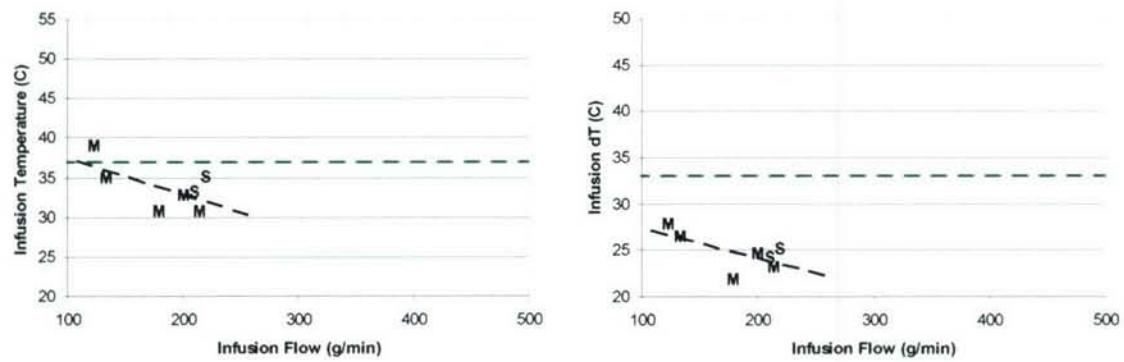


Figure 4. Test results for intermediate loop concept.

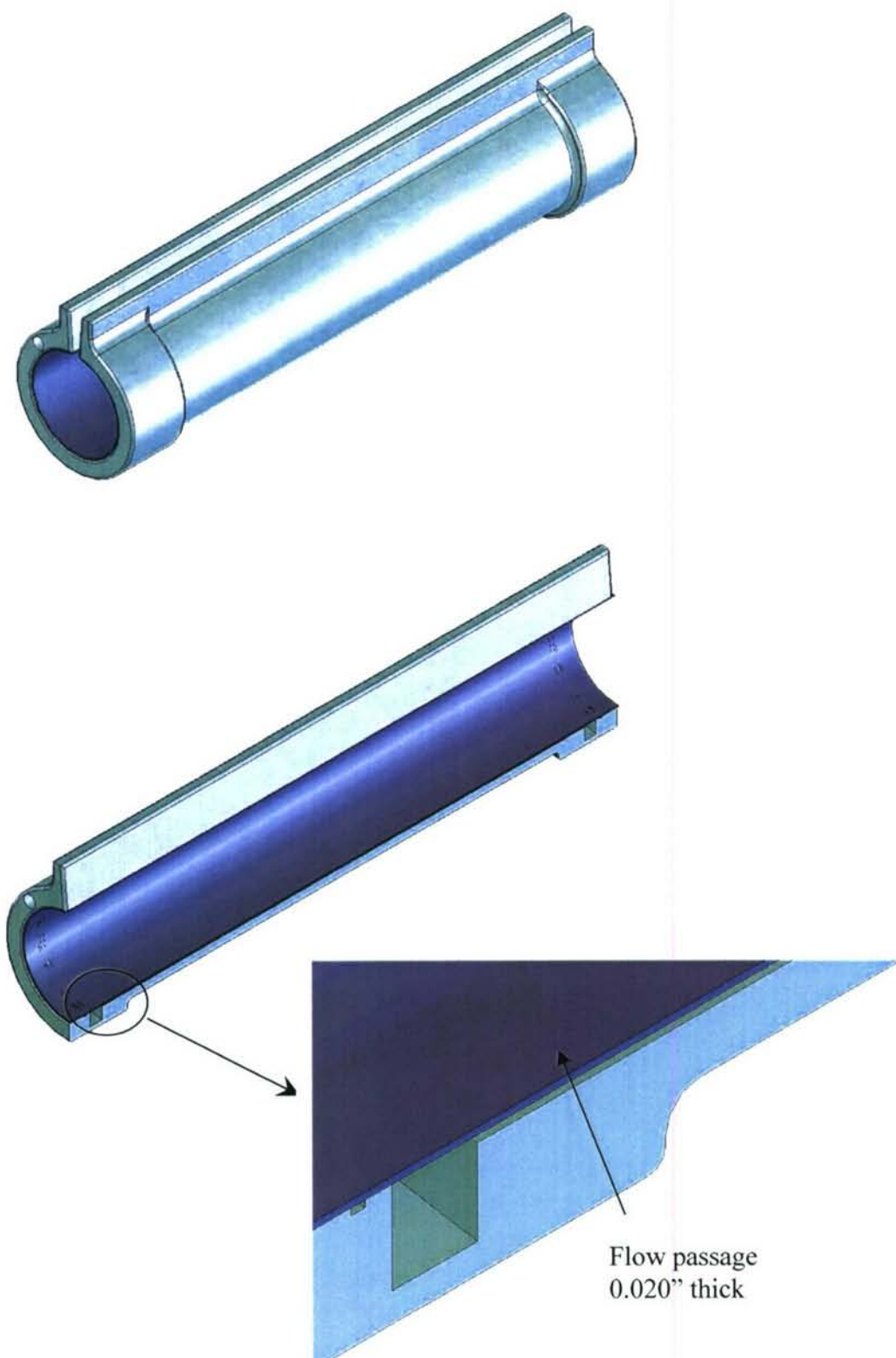


Figure 5. Clamp-on single-use heat exchanger for infusion fluid warmer.



Figure 6. Infusion fluid warmer breadboard with heat exchanger installed.



Figure 7. Prototype fluid infusion warmer in refrigerator for testing.

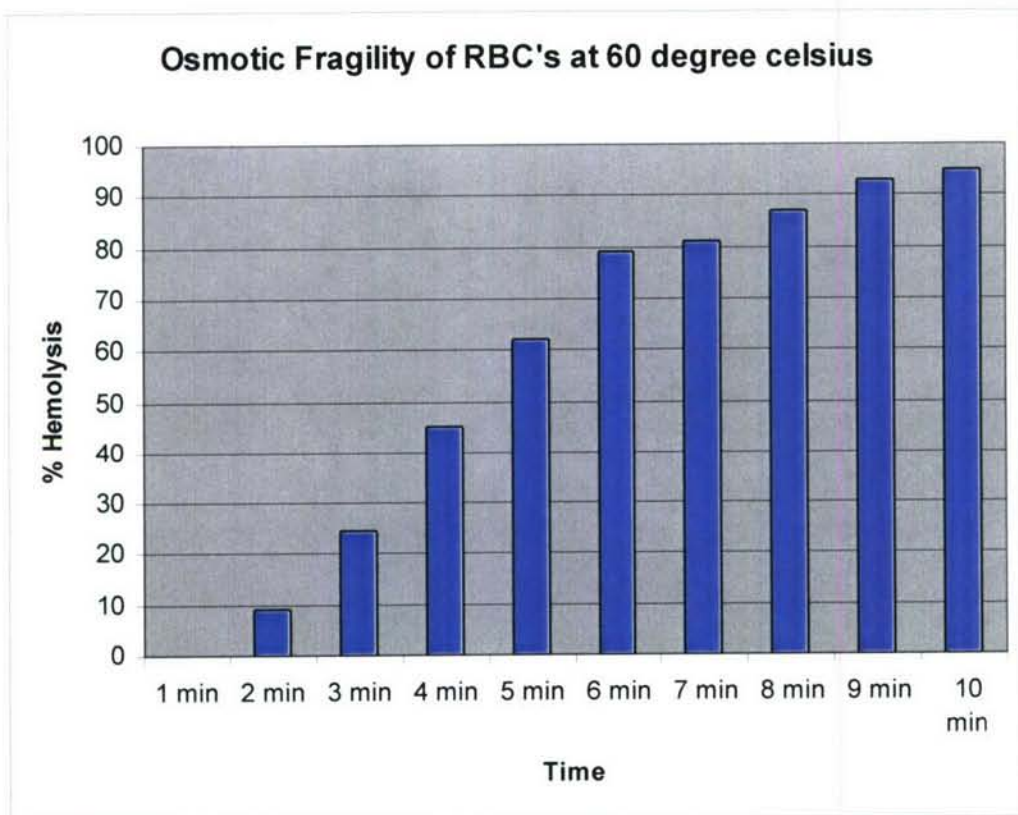


Figure 8. Osmotic fragility of RBC's at 60 degree celsius