Intra-Arterial Perimortem Resuscitation Using a Micellar Colloid

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ABSTRACT Objective: The following were studied in a perimortem mouse model of rapid blood loss: (a) efficacy of a prototypical micellar colloid, Intralipid 20%, (IL20), compared to albumin (b) comparison of intra-arterial and intravenous resuscitation, (c) efficacy of IL20 at a volume 2 × the volume of blood removed, and (d) efficacy of oxygenated IL20 after clinical death (CD). Methods: CD, the absence of breathing and zero blood pressure (BP), was produced by removing 55% of the blood volume within 3 minutes. After CD, the chest was opened to observe ventricular contraction. IL20, Ringer's lactate (RL), or albumin was infused perimortem. Results: Without resuscitation CD occurred in 2.85 ± 0.40 minutes. Ventricular contraction persisted 20.50 ± 1.11 minutes after CD. RL infused immediately after CD restored breathing if given intra-arterially but not intravenously. IL20 was superior to the prototypical colloid, albumin in maintaining the BP. Increasing the volume of IL20 further increased BP. Delayed RL infusion after CD failed to restore breathing. Delayed resuscitation after CD with oxygenated IL20 restored breathing and BP. Conclusions: Micellar colloid is superior to the prototypical colloid albumin and can possibly be of use when signs of life are no longer present. In extremis, intra-arterial infusion is superior to intravenous infusion.

INTRODUCTION

Exsanguination is the cause of 91% of potentially survivable battlefield deaths.[1] Fifty-one percent of soldiers who die on the battlefield are encountered in cardiorespiratory extremis.[2] Most battlefield deaths occur within 10 minutes of injury (http://www.nhs.uk/Livewell/Militarymedicine/Pages/Survivingbattlefield.aspx). There is an unmet need for effective interventions in the 10 minute perimortem time frame sometimes referred to as "the platinum 10 minutes" as opposed to the "golden hour" (http://www.army.mil/article/55508/Battlefield_medicine_and_the_urgency_to_save_Soldiers/).

To address this, we developed a new mouse model of perimortem state by rapid and massive blood removal, because current animal models are not representative of the soldier who has massive bleeding on the battlefield, which is when most of the losses occur. In current animal models, the animals are intubated to control respiration, and body temperature is controlled. This model is analogous to a wounded soldier in the operating room (OR) where these factors can be controlled. This is not the case on the battlefield. The soldiers who have rapid and large-volume blood loss due to major organ or vessel injury often do not survive to get to the OR. Or the evacuation times are longer because of hostile surroundings, which make slower bleeding critical. For this reason in our experiment, the animals were not intubated. Also neither the animals nor the resuscitation fluids were warmed. These experiments were designed to determine how to salvage soldiers who do not survive with the current technology.

In general, for resuscitation, colloids are favored over crystalloids. This is because colloids raise and maintain blood pressure (BP) with a smaller volume and for a longer time. This enables paramedics to carry less weight as fluid onto the battlefield. For a soldier on the battlefield who has a weak pulse due to blood loss, U.S. Military Tactical Combat Casualty Care guidelines call for the rapid intraosseous or intravenous infusion of 500 mL of a colloid, 6% hetastarch (Hextend; Hospira, Lake Forest, Illinois), when blood products are not available. If there is no improvement in the pulse, an additional 500 mL bolus of Hextend is infused (Military Health System and Defense Health Agency Website: http://www.health.mil/tccc).

However, concerns have been raised about the safety of hetastarch-based (HES) products. A Cochrane review of the effect of hetastarch on renal function concluded that:

> "The current evidence suggests that all HES products increase the risk in AKI (acute kidney injury) and RRT (renal replacement therapy) in all patient populations and a safe volume of any HES solution has yet to be determined. In most clinical situations it is likely that these risks outweigh any benefits, and alternate volume replacement therapies should be used in place of HES products".[3]

Increased mortality,[4,5] and increased bleeding because of dysregulation of clotting factors,[6,7] are the concerns with hetastarches. In order to reduce the possibility of bleeding, the military protocol limits the volume of Hextend administration to 1,000 mL.[7] The validity of this upper dose limit in trauma patients is not established and the limit is possibly

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Portions of this work were presented at the Advanced Technology Applications for Combat Casualty Care (August 13–16, 2012) and the Military Health System Research Symposium (August 18–21, 2014), both held in Ft. Lauderdale, FL.

Animal procedures were approved by The Animal Care and Use Committee of the LSU Health Sciences Center at Shreveport. The authors are officers of the company, Vivacelle Bio, Inc., (VBI). VBI was formed in order to develop products that are based on the findings of this article. These findings were made before the formation of VBI or any other commercialization effort.

doi: 10.7205/MILMED-D-15-00206

even lower given the increased bleeding tendency associated with trauma. The Food and Drug Administration (FDA) has issued a warning against the use of HES products in critically ill patients due to safety concerns.[8]

The 1,000-mL limit also creates a significant logistical challenge, which threatens the military medical mission. Evacuation times in future wars could be much longer than has been the case in recent conflicts. This could require multiple boluses with volumes well beyond 1,000 mL to maintain pulse and mentation.

Therefore, the military has an unmet need for a more flexible and effective resuscitation fluid with broader applications. Stated otherwise, a safer and more effective resuscitation fluid for saving the lives of our military service men and women is urgently needed.

In order to meet this need, we are developing a new class of colloid for resuscitation that consists of components that have been shown to be safe and effective when introduced into the bloodstream. The colloid of this fluid is a micelle that contains highly purified nonallergenic[9] soybean oil. Highly refined soybean oil is not considered allergenic by the FDA.[10] A micelle is comprised of molecules in which one segment is soluble in water and the other segment is soluble in oil. When such molecules are placed into water and mixed they spontaneously form an aggregate known as a micelle as illustrated in Figure 1. The water-soluble part of the molecule (black) faces outward, whereas the oil soluble tail (dark green) faces inward forming a hydrophobic core. When soybean oil (light green) is added to the mixture, it localizes to the oily inner part of the micelle, which is the hydrophobic core.

The properties of this colloid are consistent with a safer and more effective resuscitation fluid. The FDA approved this colloid for intravenous use in total parenteral nutrition in 1972. Examples of these commercially available products are Intralipid (Baxter International, Deerfield, Illinois) and Liposyn (Hospira, Lake Forest, Illinois). Intralipid at a soybean oil concentration of 20 g/100 mL Intralipid 20% (IL20) has also been rapidly infused for local anesthetic toxicity[11] and toxicity associated with overdose of verapamil.[12] This supports the hypothesis that the micelles would be safe in hypotension due to blood loss. In these initial experiments, we did not add balancing electrolytes because as a baseline we wanted to determine the effect of unaltered emulsion. Isotonicity is provided by 2.25% w/v glycerol in Intralipid so that the osmolality of 260 is approximately that of Ringer's lactate (RL). Adding electrolytes would have created a hyperosmolar infusate.

We previously showed in mice that IL20 was superior to RL, the resuscitation fluid recommended by the American College of Surgeons, in raising and maintaining the BP after the removal of 55% of the blood volume in mice. In addition, we showed that there was a linear relationship between the oxygen content of the emulsion and soybean oil concentration. When exposed to 100% oxygen, the oxygen content of Intralipid at 30% soybean oil was equivalent to the oxygen available from blood at a hemoglobin level of 12 g/dL. At 20% soybean oil, the oxygen content was equivalent to that of blood at a hemoglobin level of 7 g/dL. We found that the oxygen was rapidly released from the emulsion. In another study, blood was removed from mice and a mean BP of 30 mm Hg was maintained for 90 minutes. Resuscitation was then carried out using either shed blood or IL20. At 24 hours after resuscitation with IL20, there was no evidence of fat emboli in the lungs (hematoxylin/eosin stain).[13] In these current pilot studies, we proceeded to determine how the micellar colloid would be deployed in the perimortem period.

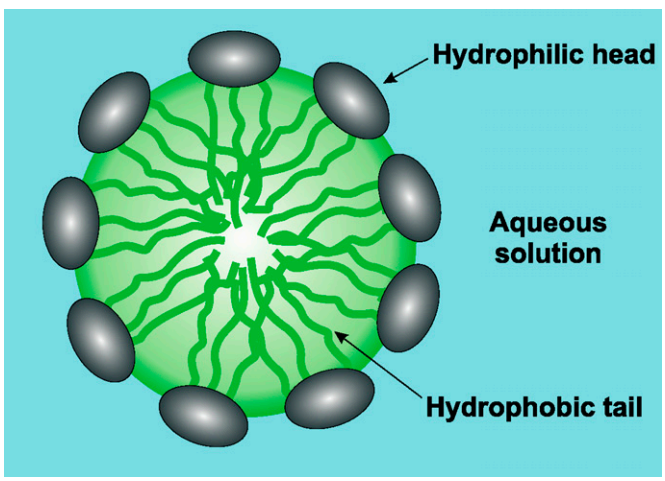

FIGURE 1. Illustration of a soybean oil-containing micelle. The micelle is formed by egg phospholipids shown with black heads and dark green tails. The tails are hydrophobic and therefore point inward in order to avoid the aqueous (blue-green) environment. The heads are hydrophilic and therefore face the aqueous environment. In the hydrophobic core of the micelle formed by the phospholipid tails, there is a droplet of soybean oil kept intact in the hydrophobic environment and separated from the aqueous environment by the phospholipid heads.

METHODS

Animals and Animal Procedures

The Animal Care and Use Committee of the LSU Health Sciences Center at Shreveport, Louisiana, approved the animal procedures. Male and female mice weighing 27 to 47 g were utilized. Mice were anesthetized using ketamine/xylazine administered intraperitoneally. After making sure the mice were well anesthetized, the internal jugular vein and/or the carotid artery were cannulated and 55% of blood volume was removed over 3 minutes. At various time points after blood removal, test fluids in volumes equal to one or two times the volume of blood removed were infused over 2 minutes. BP was measured at the carotid artery using a BP-2 monitor made by Columbus Instruments (Columbus, Ohio), which measures the BP as a voltage. A standard curve was prepared. Measured voltages were converted to BP using the following formula:

$$BP = (\text{Voltage} - 0.1006)/0.0107$$

In order to mimic battlefield conditions, warming measures and respiratory support were not applied to the mice. In spite of the absence of a controlled physiological environment, there was little variability in the effects of severe rapid blood loss and anesthesia. This was evidenced through a study of the pH, PO_2, and PCO_2 after the induction of anesthesia and before the removal of blood. These data were obtained from 50 mice. In these mice, we found mean ± SE values of pH = 7.15 ± 0.01, PO_2 = 115.68 ± 2.49, PCO_2 = 51.86 ± 1.25, and base excess = −9.822 ± 0.4744. In each mouse, we noted the time of clinical death (CD) as defined by loss of respirations and BP. After CD, the chest was opened and the time it took for ventricular contraction to cease was observed. In current animal models, the respirations would be controlled as if in an OR. Our intention in these experiments was to observe cardiac contraction in the uncontrolled environment that exists on or near the battlefield. The effect of intravenous and intra-arterial RL infusion was compared in preliminary experiments. In these experiments, 55% of the blood volume was removed and the mice were observed until breathing ceased. Immediately after the cessation of breathing, the mice were given RL either intravenously or intra-arterially. None of the five mice given RL intravenously resumed respirations. In contrast, six of six mice given RL intra-arterially resumed respirations for various times after infusion. These experiments revealed that in extremis intra-arterial infusion was more effective than intravenous infusion. Therefore, a carotid artery catheter only was placed and infusions were given intra-arterially in all subsequent experiments.

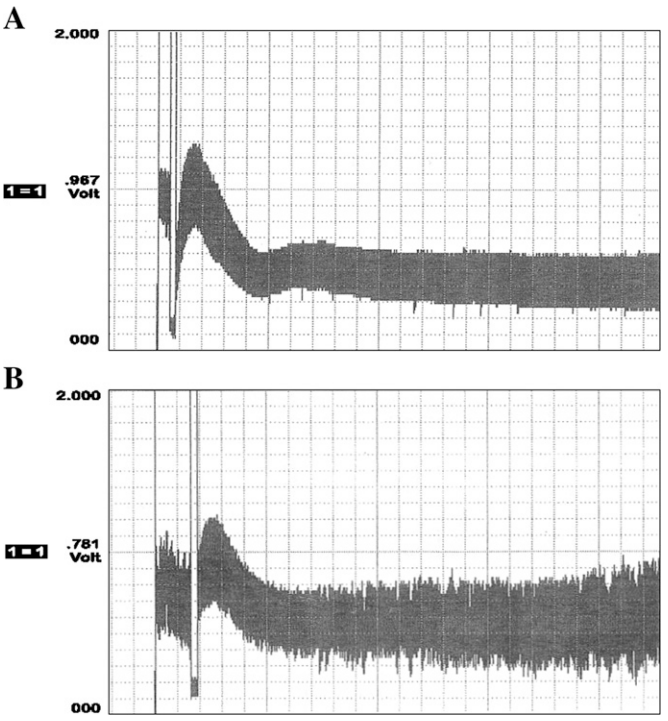

FIGURE 2. (A) Comparison of blood pressure (BP) response after infusion of 5% albumin in normal saline to infusion ofIL20. The graph depicts BP vs. time after infusion of 5% albumin and shows a high initial pressure, and decline to below prehemorrhage pressure. (B) Comparison of BP response after infusion of 5% albumin in normal saline to infusion of IL20. The graph depicts BP vs. time after infusion of IL20 and shows a high initial increase, and decline to pressure within the range of prehemorrhage pressure.

MATERIALS

NaCl, human albumin, and heparin were obtained from SIGMA-Aldrich (St. Louis, Missouri). IL20 was obtained from SIGMA-Aldrich (or Baxter) RL was prepared in the laboratory with the salts obtained from SIGMA-Aldrich. It was comprised of deionized distilled water, 109 mM NaCl, 28 mM, Na (L) lactate, 4 mM KCl, and 1.5 mM $CaCl_2$.

Statistical Analysis

Unpaired two-tailed Student's *t* test was used to compare the difference between two mean BP s. Two-way analysis of variance was used to evaluate differences in BP response curves between two different volumes of IL20. Nonparametric data were analyzed using the Mann–Whitney *U* test. Significance was set at $p < 0.05$.

RESULTS

There was no significant difference in the initial BP achieved after resuscitation with either IL20 or 5% albumin. However, 1 hour after the initial increase, the mean BP of the mice that received 5% albumin was 59.15 ± 2.95% (n = 6) of the prehemorrhage pressure. In contrast, the mean BP of mice 1 hour after the infusion of IL20 was 73.2 ± 2.78% (n = 6) of the prehemorrhage pressure. These mean values were significantly different with p = 0.0060. The difference in pressures may be translatable to the clinical situation in which a mean pressure of 65 mm Hg is considered adequate while a pressure below 60 mm Hg is not. These findings are illustrated in Figure 2.

Figure 2 shows representative changes in BP observed after replacing 55% of the blood volume with either 5% albumin or IL20 immediately after the removal of blood. The volume of replacement fluid was equal to the volume of blood removed.

From left to right, there are three phases. In the first phase, BP is recorded before removal of blood. In the second phase, the result of removing 55% of blood volume over 3 minutes is seen. This resulted in a mean pressure ±SE of 10.488 ± 1.474 in mice that were later given 5% albumin (n = 6) and 9.667 ± 2.450 in mice that were later given IL20 (n = 6). There was no significant difference between these means. In the third phase, infusates were administered over 2 minutes. After the infusion, a rapid increase in mean BP was observed in both groups. After the initial increase, the BP of the mice that received albumin decreased faster than those that were given IL20. This decrease was below the prehemorrhage pressure (Fig. 2A). In contrast, after the initial increase in mice that received IL20 the BP remained within the range of the pre

hemorrhage BP as shown in Figure 2B. The mice that received albumin and the mice that received IL20 were observed for an average of 2.41 ± 0.008 hours and 3.23 ± 0.669 hours after the infusion, respectively. There was no significant difference in these times.

Next, the BP attained after giving IL20 in a volume double the volume of removed blood was determined and compared to the BP obtained after the infusion of a volume of IL20 equal to the removed blood volume. The rationale of this experiment was to determine the effect of giving an excess of the emulsion. Our prediction was that it would raise the BP higher than lesser volumes of the emulsion. However, because there were no previous reports of the emulsion being given after severe and rapid blood loss, we were concerned about the possibility of cardiodepressant effects and decrease in BP such as that observed when perfluorocarbons are rapidly infused.[14,15]

Systolic pressures are shown in Figure 3A and diastolic pressures are shown in Figure 3B. The difference between the curves for 2 × vs. 1 × the removed blood volume was significant to the level of $p < 0.001$. As predicted, the BP increased with the administration of a higher volume of the emulsion.

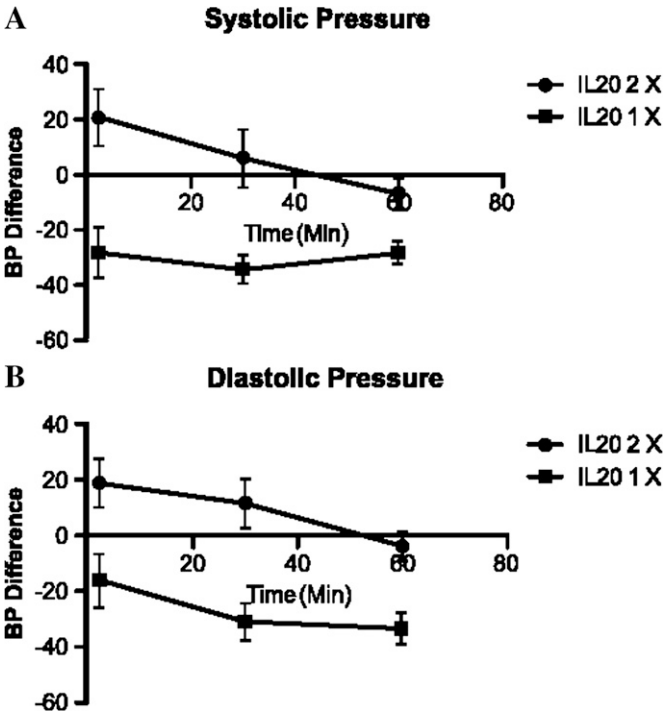

FIGURE 3. (A) Systolic pressures. The top line on the graph shows the result of Intralipid 20%(IL20 infused at a volume 2 × the volume of blood removed. The bottom line of the graph shows the result of IL20 infused at a volume 1 × the volume of blood removed. All of the values are normalized to the prehemorrhage blood pressure (BP), which equals 0 on this graph. ($n = 6$ mice for each curve). (B) Diastolic pressures. The top line of the graph shows the result of IL20 infused at a volume 2 × the volume of blood removed. The bottom line of the graph shows the result of IL20 infused at a volume 1 × the volume of blood removed. All of the values are normalized to the prehemorrhage BP, which equals 0 on this graph. ($n = 6$ mice for each curve).

Infusion After CD

We found that CD, as indicated by the loss of respiration and measurable BP, occurred within 2.85 ± 0.40 minutes ($n = 75$ mice) of removal of blood. After CD, the chest was opened to observe cardiac ventricular contraction. Ventricular contraction persisted for a mean duration of 20.50 ± 1.11 minutes ($n = 93$ mice) after CD. We compared the effect of administering RL intra-arterial or intravenously immediately after CD. The chest was not opened in these experiments. Intra-arterial resuscitation restored breathing in 6 of 6 mice, albeit with a high degree of variability in post resuscitation survival time. In contrast, intravenous resuscitation after CD failed to restore breathing in five of five mice. Using the Man–Whitney U test, the p value was 0.0055 for the difference in the median values. This suggests intra-arterial resuscitation was superior to intravenous resuscitation. Survival times are listed in Table I.

Next, instead of infusing fluid immediately after removal of blood we delayed intra-arterial infusion of RL for 1 ($n = 2$) and 3 minutes ($n = 2$) after CD. RL infusion failed to restore respiration 1 and 3 minutes after CD. However, intra-arterial infusion of oxygenated IL20 5 minutes after CD resulted in the restoration of spontaneous respiration in six of six mice. Oxygenation was achieved by bubbling 100% oxygen through

TABLE I. Length of Breathing Time After Infusion (Minutes)

	Intra-Arterial	Intravenous
	165.00	0
	6.78	0
	4.00	0
	20.00	0
	5.00	0
	3.00	0
Mean ± SE	33.96 ± 26.33	0

TABLE II. Data Showing Results After 55% of Mouse Blood Volume was Removed Over 3 Minutes

Mouse Number	Survival Time After Clinical Death (Minutes)	1st Peak Blood Pressure
1	1.5	58/13
2	77.1	81/69
3	97.8	35/28
4	103.0	88/61
5	111.1	134/83
6	114.8	125/115
Mean ± SE	84.2 ± 17.41	86.83 ± 15.53 (Systolic) 61.50 ± 15.12 (Diastolic)

Mice were observed until they stopped breathing. 5 minutes after the cessation of respiration, oxygenated IL20 was infused over 2 minutes. In six of six trials, mice infused with oxygenated IL20 had restored respiration and BP. Mouse number 1 and 3 survived up to 1.5 and 97.8 minutes, respectively. Mouse numbers 2, 4, 5, and 6 were euthanized at 77.1, 103, 111.1, and 114.8 minutes, respectively. Mouse number 2 was euthanized after awaking completely.

IL20 for 2 minutes. The survival times of the 6 mice are shown below in Table II.

Mouse number 1 and 3 survived up to 1.5 and 97.8 minutes, respectively. Mouse numbers 2, 4, 5, and 6 were euthanized at 77.1, 103, 111.1, and 114.8 minutes, respectively. Mouse number 2 was euthanized after awaking completely.

DISCUSSION

Over the past 2 decades, there have been multiple efforts to develop effective and safe resuscitation fluids and "blood substitutes." The following are the results of those efforts and their associated problems.

- — Hetastarch-based products reported to cause renal failure and increased mortality. FDA warns against use in critically ill patients. Increased bleeding tendency compels the use of no more than 1,000 mL. This number is not established in trauma patients.
- — Perfluorocarbons did not fare well in clinical trials.[14] Produces hypotension and an intense inflammatory response when rapidly infused.[15] These products are not FDA approved.
- — Modified hemoglobin such as Hemopure increased mortality in clinical trials[16]; very expensive to produce. This product is not FDA approved.
- — Plasma requires blood typing. Is a cause of the transfusion-related acute lung injury; increases mortality[17,18] and can transmit disease. Anaphylactic reaction is possible.
- — Whole blood requires blood typing may use O negative initially. Can cause transfusion-related lung injury; can transmit disease. Supply is very limited and blood is expensive. Anaphylactic reaction possible.
- — Hypertonic saline causes kidney failure and increased mortality.[19]
- — Albumin increases bleeding;[20,21] expensive; supply is limited, can transmit disease.

An ideal colloidal resuscitation fluid would be effective and safe; would not promote bleeding and could be given in large volumes. It would maintain a viable BP and mentation in the event of a delay in evacuation without the fear of disease transmission. Also, there would not be any inherent supply limitations. The fluid would be inexpensive and have an extended shelf life. We now report experiments that demonstrate a prototypical micelle preparation, IL20, can be the basis of an effective resuscitation fluid after the loss of blood. Evidence in support of the safety of micellar colloids is found in our previous report in which mice survived 24 hours after resuscitation and there was no evidence of lung injury or fat embolism. In addition, there are numerous reports of rapid infusion of IL20 as an antidote to the overdose of local anesthetics and other medications.[22–26] In contrast to the hetastarch products and albumin that have been shown to enhance bleeding, IL20 has been shown to preserve clotting.[27] Other benefits are that the formulation based on IL20 will not transmit disease, has a long shelf life of $\geq$18 months, is available in unlimited supply and is fairly inexpensive to manufacture. Other properties of IL20 that enhance its attractiveness as the basis of a resuscitation fluid are that it has been shown to inhibit reperfusion injury,[28] activate prosurvival genes[29,30] and can be metabolized to produce energy. These and other properties could reduce the incidence of multiple organ dysfunction syndrome post resuscitation.

The greater potency relative to RL and albumin in raising and/or maintaining the BP suggests that IL20 would be a very effective low-volume resuscitation fluid that would minimize the weight of fluid a paramedic needs to carry onto the battlefield. Higher concentrations of soybean oil in the formulation would potentially have even greater efficacy.

These pilot experiments also provide insight into the transition between life and death.

One of the earliest reports of the advantage of intra-arterial over intravenous resuscitation was that of Seeley[31] in 1951. Dr. Sam F. Seeley was a Brigadier General in the Medical Corps and Chief of Surgery at the Walter Reed Army Hospital. We have shown that after CD with the absence of pulse and respirations, there is a period of 20 minutes during which the heart continues to contract, though these contractions are inadequate to produce a measurable BP. Restoration of breathing and BP with intra-arterial infusion is superior to the intravenous route possibly because arterial delivery produces better perfusion of the coronary and bronchial arteries than venous delivery. This approach could be useful for nontraumatic as well as traumatic cardiac arrest. In Advanced Cardiovascular Life Support, the immediate goal is to improve coronary artery perfusion. The rapid intra-arterial infusion of micellar colloids could markedly improve the attainment of this goal.

Access to the arterial system could be gained via the femoral vessels using the pulse or if there is no pulse using a handheld ultrasound.

IL20 has worked well in these and previous experiments as a prototypical micellar colloid containing soybean oil. Although our results have shown it to be effective, it is not ideal in its present form for use as a resuscitation fluid. One reason is that it lacks electrolytes. Replacement of a significant portion of the blood volume with a fluid that does not contain sodium could result in hyponatremia and related complications. In experiments, now in progress, we have added electrolytes and in addition reduced the diameter of the micelle thereby increasing its stability. "We do not consider our micellar preparation to be a blood substitute. In our view, our emulsion is a resuscitation fluid with many properties that are potentially useful for rescuing patients in shock. Two properties, which we explored in an earlier publication,[13] are the ability of the emulsion to reversibly absorb oxygen and nitric oxide. We found that a 20% soybean oil emulsion can be loaded with sufficient oxygen to support life. Moreover, the reversible absorption of nitric oxide would enable the emulsion to reverse the drop in BP caused by excessive nitric oxide that is released in shock after blood

loss.[32] In this experiment, we established the necessity of the intra-arterial infusion of resuscitation fluid in order for soldiers with extreme blood loss to survive. In addition, we have begun the development of a new resuscitation fluid that is superior to the standard colloid albumin in maintaining the BP and that does not have the adverse effects of albumin and other colloids in use today."

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