Extracorporeal organ support following trauma: The dawn of a new era in combat casualty critical care

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Death after severe trauma in the civilian and military setting occurs in a trimodal distribution.[1,2] Historically, the majority of injury-related mortality occurs in the prehospital setting owing to hemorrhage. Of patients who survive to hospital admission, another group of deaths occurs in the acute phase owing to devastating head injury or uncontrolled hemorrhage.[2] Among patients who survive these immediate and acute phases of trauma, the last significant phase of mortality occurs in the days and weeks following injury from sepsis and multiple-organ failure (MOF).[2–4]

The immediate care of the severely injured is guided by structured clinical practice guidelines that have been widely adopted for the prehospital and early hospital settings. Early use of tourniquets, hemostatic dressings, and the concepts of damage-control surgery and hemostatic resuscitation have led to more patients surviving the immediate and early phases of severe trauma.[5,6] As advances in prevention and treatment of death from hemorrhage occur, there may be an expected decrease in mortality during the early aspects of the trimodal pattern of mortality. Specifically, improved survivability of the initial phases of injury can be expected to result in a greater number of physiologically compromised patients prone to MOF surviving later into the hospitalization. As such, directing a significant portion of current and future clinical expertise and scientific study to advanced organ support techniques is prudent.

During the past two decades, technologic advances have allowed extracorporeal methods of organ support to be delivered safely and effectively.[7] As a result, application of extracorporeal organ support and extracorporeal blood purification techniques has been increasingly used with more novel approaches.[6–8] Continuous renal replacement therapy (CRRT) for the management of acute kidney injury (AKI) and the resultant severe metabolic derangements has become commonplace in many trauma centers.[8] Recent advances in extracorporeal life support (ECLS) technology have spawned interest in wider application of lung support in trauma critical care for supporting gas exchange.[9] The combination of venoarterial extracorporeal membrane oxygenation (ECMO) and deep hypothermia are under investigation and have the potential to take damage-control surgery to the next level.[10] In addition, better understanding of the innate immune-inflammatory response to severe injury and the severe dysregulation of homeostatic mechanisms that follow is increasingly recognized as a common pathway toward MOF in a variety of critical illnesses.[11–13] These advances have generated interest in the concept of blood purification for the purposes of immune modulation and possible prevention of MOF.[14]

In recent years, it has become increasingly recognized that select numbers of combat casualties who survive initial injury and surgical intervention may benefit from the early application of extracorporeal support technologies.[15] Initially logistic, training and skill maintenance challenges associated with the use of these technologies limited their application in the austere combat environment. However, because of the military's sustained commitment to comprehensive trauma care, many these challenges have been overcome. Although use of extracorporeal support technologies within the combat casualty care arena remains a work in progress, today, these state-of-the-art modalities including ECLS are available to those injured in the wartime setting. The objective of this report is to provide a contemporary overview of extracorporeal organ support modalities and blood purification techniques and their role in the management of severe trauma and thermal injury.

EXTRACORPOREAL LUNG SUPPORT

ECMO

The concept of using a pump and a membrane lung for cardiopulmonary support dates back to the 1930s.[16] However, the actual use of this approach for adult patients in an intensive care unit (ICU) did not occur until 1971.[17] Moreover, interest in ECMO for respiratory failure waned when 2 early trials in adults found that with the existing technology, there was no survival benefit to this approach.[18,19] Recent advances in pump and membrane technology have led to renewed interest ECMO as the adverse consequences of ventilator-associated lung injury and the lack of clear benefit from other rescue interventions have become more widely recognized. Indeed, the multicenter randomized controlled CESAR trial conducted in the United Kingdom demonstrated a significant reduction in death and long-term disability in patients referred for management in an experienced ECMO center.[20] As these results were being disseminated, use of ECMO for H1N1-associated respiratory failure in the 2009 pandemic demonstrated an impressive survival rate of 75% in this profoundly ill patient population.[21]

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With proper team training and a commitment to providing the highest level of critical care support by hospital leadership, adult ECMO can be safely used to support adults with severe respiratory failure.[22] Presently, the indications for initiation and the optimal management of the ventilator and ECMO circuit are being explored in expert centers. At the San Antonio Military Medical Center on Fort Sam Houston (San Antonio), Texas, there is great interest in expanding the historic neonatal and pediatric ECMO capability of Wilford Hall United States Air Force Medical Center to now include adult patients. After 2 years of advanced planning during the integration of Wilford Hall United States Air Force Medical Center and Brooke Army Medical Center, this vision has materialized (Fig. 1). The next step is using this capability in support of the military's combat casualty care mission.

Battlefield Delivery

Early during combat operations in Afghanistan and Iraq, a select number of patients with severe adult respiratory distress syndrome (ARDS) exceeding standard critical care capability began to emerge. Such critically ill patients were unable to be supported by conventional ventilation or exceeded the clinical competence of deployed nonspecialist personnel. Furthermore, standard ventilator and critical care support during long-range aeromedical evacuation precluded safe transfer to specialized centers of care in Germany or the United States. As a result, these patients either slowly improved to meet criteria for safe aeromedical evacuation out of the theater of war or died of severe respiratory failure.

In 2005, a multidisciplinary group of physicians at the receiving facility in Landstuhl, Germany (Landstuhl Regional Medical Center [LRMC]), identified this capability gap.[23,24] A partnership developed between LRMC and an academic regional pulmonary failure specialty center in Southwest Germany. This partnership was instrumental in the early development of second-generation ECMO therapies.[25,26] The LRMC team of medical and surgical intensivists instituted specialized therapies unavailable to both the deployed intensivist and the standard critical care air transport team (CCATT).[27,28] First established as an out of theater asset, this LRMC team was shortly followed by the development of an acute lung rescue transport team that augmented ongoing CCATT missions evacuating the most severely injured out of Afghanistan and Iraq[29] (Fig. 2).

In addition to ARDS rescue adjuncts such as a nitric oxide analog (inhaled epoprostenol) and alternative ventilator modes unavailable to downrange teams (high-frequency percussive ventilation), extracorporeal oxygenation therapies were instituted. Principally through advances in European critical care and the miniaturization of ECMO venovenous and venoarterial ECMO, new possibilities for adult extracorporeal therapies in a transportable unit emerged. The initial clinical experience started in 2005 with a pumpless extracorporeal lung assist (iLA, Novalung).[25,26] The NovaLung interventional lung assist (NovaLung GmbH, Heilbronn, Germany) is a compact gas exchange system powered by the patient's native cardiac output. Through a percutaneous catheter based arteriovenous shunt driven by systemic arterial pressure, the polymethylpentane

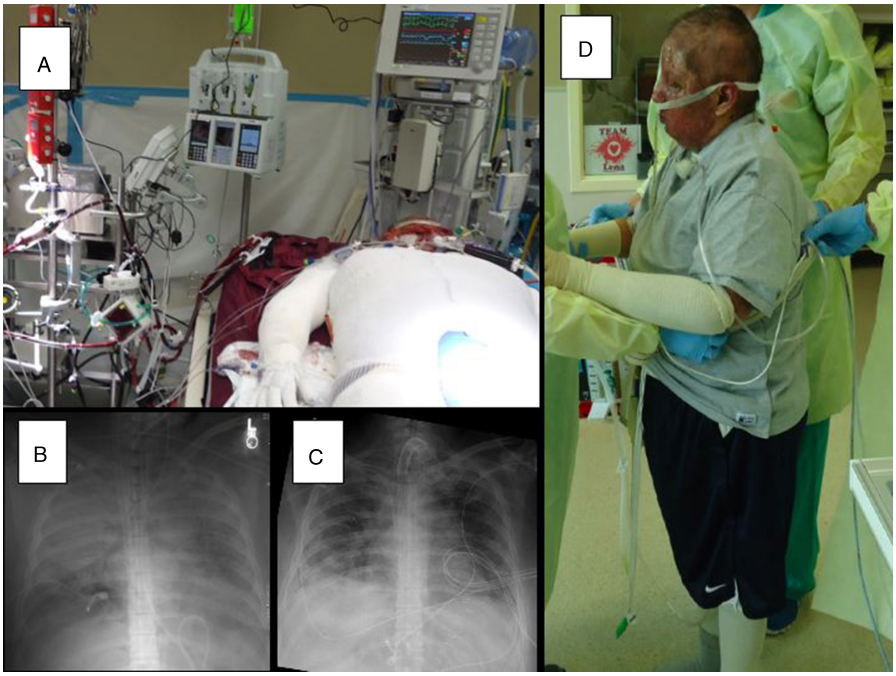

Figure 1. A 37-year-old woman with toxic epidermal necrolysis in our burn center ICU developed severe ARDS and toxic epidermal necrolysis–related pulmonary dysfunction refractory to ventilator optimization and rescue oxygenation therapies (*A*). ECMO was initiated through a dual lumen internal jugular cannula (*B*) and was continued for 23 days (*C*) until her pulmonary dysfunction improved to where she could be managed on minimal ventilator support. ECMO was discontinued, and she was able to participate in active physical therapy by post-ECMO Day 7 (*D*).

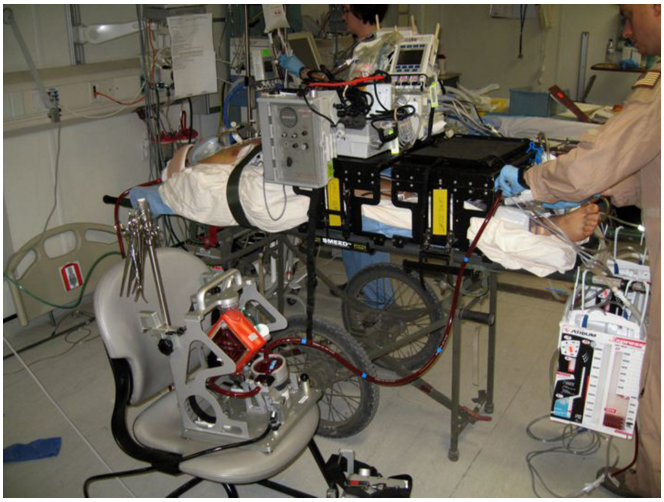

Figure 2. Foreground: ECMO unit in deployed environment (Bagram Air Base).

hollow fiber "lung" membrane resists plasma leakage and separates the arterial blood and gaseous oxygen flow phases. The device produces effective CO_2 extraction and modest improvement to Pa_{O_2} at blood flow rates of 1.0 L/min to 2.5 L/min. With the exception of an oxygen source, the system requires no electrical or other external support, an important advantage for the deployed environment. Because of the properties of extremely efficient CO_2 removal, it was ideal for patients with ARDS-related hypercarbic respiratory failure. However, for those with refractory hypoxic failure, other options were required.

During the last 5 years, the miniaturization and advanced technology of centrifugal pump-driven venoarterial and venovenous lung assistance made it possible to bring such technology to the deployed environment.[22] The ECMO centrifugal drive system (Rotaflow, Maquet Corp, Rastatt, Germany), provided the same efficient CO_2 removal with the advantage of increased oxygenation efficiency through both a venous and arterial configuration. Currently, the Rotaflow system has essentially replaced the pumpless lung assist device. Cannulation is via an ultrasound-guided percutaneous Seldinger technique at either two sites (typically right internal jugular and femoral veins) or single site using a dual-lumen catheter (Avalon Laboratories, Rancho Dominguez, CA) (Fig. 3). The first combat casualty was cannulated in 2010 after sustaining a severe penetrating wound requiring pneumonectomy. Since then, five additional patients have undergone venovenous ECMO cannulation for blast lung–related severe hypoxic failure. A recent series of 10 combat casualties transported out of the combat zone to Europe with follow-on care reported a 90% rate of survival at 1 year after injury.[30] Heparin-induced thrombocytopenia in one patient was the only treatment-related major complication.

In the wake of these successes, there is now great interest in bringing these critically ill patients to the United States while still on ECMO. For more than 25 years, the US Air Force has maintained a team capable of worldwide ECMO transport for pediatric and neonatal patients.[31] More recently, the US Army Burn Flight Team[32] and US Air Force CCATTs[28] have also demonstrated the ability to safely transport critically ill burn and polytrauma patients over long distances. A proposal to integrate these transport capabilities into a hub of adult ECMO operations at San Antonio Military Medical Center is now being put forward for consideration.

Partial Lung Support

The use of ECLS technology for partial lung support dates back to 1972 with observations of persistent hypocapnia during hemodialysis, which were attributed to "loss of CO_2 through the coil."[33] Several years later, pioneering work by Gattinoni et al.[34] suggested that it is possible to achieve partial-to-near total removal of metabolically produced CO_2 by means of arteriovenous decarboxyllation in uninjured conscious lambs. Subsequently, the same group demonstrated that it is feasible to completely uncouple oxygenation from ventilation and use the natural lung for oxygenation alone, with the ventilatory function being performed by artificial lung devices.[35] Using these concepts, Pesenti et al.[36] proposed the concept of "respiratory dialysis" when they modified a CRRT circuit to achieve partial CO_2 removal in an effort to reduce mechanical ventilator support in humans.

"Partial lung support" is a method of assisting lung ventilation and oxygenation to a lesser degree than complete mechanical ventilation and is accomplished by altering blood and gas flow through a polymer gas-exchange filter known as a membrane lung. At lower blood flow rates (<1,000 mL/min), CO_2 removal is possible, although physiologically significant oxygenation is unattainable. Changes in the flow of gas through the membrane lung can regulate the amount of CO_2 removal while maintaining constant blood flow through the circuit. In principle, partial lung support could be achieved during traditional "full" ECMO by "dialing down" support in a situation analogous to reducing pressure support during weaning from mechanical ventilation. Currently, partial lung support can be administered via dedicated partial lung support devices using standard dual lumen catheters, akin to percutaneous hemodialysis catheters. These devices (Hemolung, Alung Inc., Pittsburgh, PA;

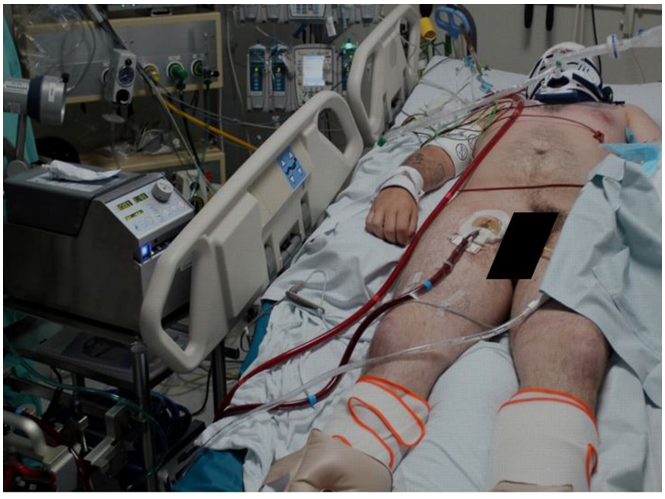

Figure 3. Venovenous ECMO at LRMC.

Decap Smart, Decap, Hemodec, Salerno, Italy; Cardiohelp and the new low-flow device Cardiohelp PALP, Maquet Cardiovascular Inc., Rastatt, Germany; the NovaLung ILA and the recently introduced MiniLung Petite, NovaLung, Heilbronn, Germany) were specifically designed for removal of CO_2 during hypercapnic crises of various etiologies. Because these devices are capable of operating at flows (300–1,000 mL/min), they cause less hemodynamic disturbance than traditional ECMO.[9,37–41]

There are several emerging uses for partial lung support in trauma and combat casualty care. First, partial lung support augments lung protective strategies by allowing for maximal reduction in minute ventilation settings to levels that exceed those recommended by ARDSNet (current targets are tidal volumes of 4 mL/kg and plateau pressures of $\leq$25 cm H_2O). In addition, partial lung support can manage the resulting metabolic consequences of low tidal volume lung protective ventilation by removing CO_2. Experimental evidence supporting these salutary effects of partial lung support is accumulating in the literature. Cardenas et al.[39] were able to remove 75% of metabolically produced CO_2 in healthy mechanically ventilated sheep using a low-flow CO_2 removal device. In a similar study pursuing adjunct use of ECLS and mechanical ventilation in healthy mechanically ventilated swine, the Hemolung device removed 50% of metabolically produced CO_2 while maintaining normocapnea.[7] Zanella et al.[42] demonstrated the feasibility of augmenting the CO_2 removal efficiency of an membrane lung by loading the blood entering the membrane lung with lactic acid. If further developed for long-term use, this approach could lead to removal of 50% to 100% of CO_2 at approximately 250 mL/min. The Decap Smart demonstrated the ability to manage the metabolic consequences of low tidal volume ventilation in ARDS patients while permitting lower than ARDSNet–recommended target plateau pressures providing lung protective ventilation. In addition, levels of inflammatory mediators were lower in the DEcap Smart–treated patients.[43] The versatility of these devices are evidenced by the partial lung support's adjunct role with mechanical ventilation for temporary ex vivo lung perfusion and preservation of donor lungs and showed similar posttransplant outcomes to conventional lung transplantations.[44] Partial lung support also has potential for avoidance of mechanical ventilation.[40,45] As we curiously await clinical data benchmarking the new partial lung support devices, it is clear that we now have a panel of tools available to reduce dependence on mechanical ventilation by means of partial lung support.

RENAL REPLACEMENT THERAPY

The earliest modern description of AKI in the combat setting was published in 1941. In this seminal work, Beall and Bywaters[46] first described the syndrome of rhabdomyolysis in four victims of the London bombings in World War II. Renal replacement therapy (RRT) was first used in combat casualties during the Korean conflict and was later used in Vietnam.[47] The initial description of RRT in the Korean conflict reported a decrease in mortality from 80% to 90% to 68%.[48] In the Vietnam era, one small trial demonstrated a benefit to early initiation of RRT with mortality rates of 36% and 80% in the early and late initiation groups, respectively.[49] In the current conflict, AKI has been associated with increased mortality in US personnel who sustained thermal injury during combat operations.[50] Continuous venovenous hemofiltration (CVVH) has also been demonstrated to improve outcomes in this patient population.[51] The latter study examined the mortality rate of severely burned military casualties before (n = 16) and after (n = 18) the initiation of a CRRT program and found a decrease in both 28-day mortality (22% vs. 75%, $p = 0.002$) and in-hospital mortality (56% vs. 88%, $p = 0.04$). Data from AKI in the civilian trauma population have similarly been associated with an increased risk of multiorgan dysfunction, ICU length of stay, and mortality.[52,53] Additional data suggest that initiating CRRT earlier in the ICU course may confer a survival benefit for trauma patients if started before fulminate renal failure.[54]

During the wars in Afghanistan and Iraq, RRT capability has gradually been deployed in more forward medical treatment facilities. Early in the course of the war in Iraq, the US Navy Ship Comfort was deployed in support of combat operations. This hospital ship was equipped with conventional hemodialysis machines (Fresnius Medical Care, Waltham, MA) and provided RRT for three patients.[55] Medical doctrine at the time assumed that forward deployed RRT would not be required because the treatment priority was rapid stabilization, damage-control resuscitation, and evacuation out of theater to locations where RRT was available. However, as the wars in Afghanistan and Iraq progressed, the occasional need for RRT was identified in both US military personnel and local nationals.[55] In these cases, deployed nephrologists, intensivists, and surgeons displayed remarkable ingenuity in using available materials to provide continuous arteriovenous hemofiltration,[56] CVVH, and peritoneal dialysis.[57] Given these experiences, medical doctrine has evolved to incorporate RRT in select echelon or Level III surgical and critical care facilities in the theater of operations. In 2010, NxStage System One machines (NxStage Medical, Lawrence, MA) were deployed to the Craig Joint Theater Hospital, on Bagram Airfield, Afghanistan.[15] To support delivery of this capability, a concerted effort has been made to have consistent coverage with personnel trained in the initiation and management of RRT in this facility. A recent series of combat causalities with CRRT initiated in a combat zone reported successful evacuation of all nine patients to a regional medical center (LRMC) and highlighted the ability to provide this therapeutic modality in the theater of operations.[58]

The optimal mode of RRT (i.e., CVVH, continuous venovenous hemodialysis [CVVHD], continuous venovenous hemodiafiltration, sustained low-efficiency dialysis, or conventional hemodialysis) in the setting of critical illness is a subject of debate. A recent meta-analysis of this topic highlights the paucity of data with respect to this question and did not demonstrate a difference in outcomes between hemofiltration and other modalities.[59] There is little-to-no evidence for the optimal mode of RRT in the burn and trauma population specifically; however, there is a theoretical advantage to hemofiltration. RRT achieves clearance by one of two methods: diffusion and convection. Techniques that use a dialysate obtain the majority of their clearance through diffusion of molecules across a semipermeable membrane, while hemofiltration uses ultrafiltration with subsequent replacement fluid (convection). As discussed later, the convective clearance obtained through

hemofiltration is superior for middle molecule clearance, which has the potential to modulate immune dysregulation. In the deployed setting, however, one must balance the desire to remove middle molecules with the need to preserve limited resources. CVVHD is slightly more efficient at small molecule clearance than predilution CVVH using the same volume of replacement fluid.[60] Therefore, in the initial management of electrolyte disturbances in war wounded (e.g., hyperkalemia), CVVHD should be considered. It is important to emphasize that this is in the deployed setting. At higher echelons of care in Germany and the United States, where supplies are more readily available, CVVH should be considered, given its potential benefit in terms of cytokine clearance.

Two populations of trauma patients deserve special mention. The first are those with traumatic brain injury. In these patients, the rapid solute clearance obtained from conventional hemodialysis has been suggested to increase intracranial edema and should thus be avoided.[61] The slower clearance associated with a continuous modality (CVVH or CVVHD) is preferable in these patients. Furthermore, there is emerging speculation that nonselective cytokine removal or clearance of detrimental excitatory neurotransmitters (glutamate) by CVVH may have beneficial effects.[8,62–64] If removal of these substances is shown to improve outcomes, the convective clearance of CVVH may be superior to the diffuse clearance of CVVHD for patients with traumatic brain injury.

The second population deserving special mention is patients with rhabdomyolysis. This condition is known to be associated with AKI and higher rates of mortality in patients with burn injury.[65] AKI in this setting is postulated to be caused in part by the toxic effects of myoglobin (oxygen-free radical production and precipitation with the Tamm-Horsfall protein in the tubule).[66] Removal of myoglobin from systemic circulation via CVVH is therefore an attractive therapeutic option. However, as recently reviewed by Cruz and Bagshaw,[67] trials are limited to case reports and small case series. Furthermore, while the molecular weight of myoglobin is 17 kD and thus would theoretically be filtered by conventional hemofiltration membranes, little myoglobin is removed by this method. The authors speculated that this could be caused by myoglobin adsorption in the membrane. Further study is required to determine if different CVVH membranes, frequent filter changes, or alternate extracorporeal techniques for myoglobin removal will improve outcomes.

EXTRACORPOREAL BLOOD PURIFICATION

The systemic inflammatory response to injury is an overexuberant attempt to bolster the host defenses with increases in inflammatory mediators, which leads to deranged physiology in the acute period with cardiovascular collapse, acute lung injury, renal, central nervous system, hepatic, and intestinal failure. This initial hyperinflammatory response of mediators such as interleukin 1 (IL-1), IL-6, IL-8, tumor necrosis factor α may also have immune "priming" effects, such that any subsequent insult, particularly infectious, can lead to fulminant systemic inflammatory response syndrome and death.[68,69]

Expanding indications of existing extracorporeal therapies to attenuate the immune response are occurring in the setting of severe thermal injury and severe sepsis. In addition, a better understanding of the innate immune-inflammatory response to severe injury and the severe dysregulation of proinflammatory and anti-inflammatory cytokines has resulted in the concept of blood purification for the purposes of immune modulation, primarily during sepsis.[14,70–72] This novel concept has gained traction following disappointing results with targeted immunomodulatory therapies using monoclonal antibodies in the setting of hypercytokinemia.[73] Rather than effecting single points in the interconnected inflammatory response pathways, the nonspecific removal of mediators lowers their peak concentration by nonselectively removing them from the blood based on size and charge. This "peak concentration hypothesis" states that by lowering the amounts of these mediators, many of the subsequent biochemical signaling and feedback mechanisms, which intensify the immune response, may be attenuated.[74,75] The two primary methods of cytokine removal are filtration based on molecular size, surface adhesion to materials that capture the inflammatory mediators, or both. While differing in the types of filtering mechanisms used to remove cytokines from circulation, the following blood purification techniques all use existing CRRT platforms with various modifications in the circuit to remove inflammatory mediators (Fig. 4). To date, blood purification has not been widely studied after trauma, and any description of its use has been in the setting of posttrauma sepsis.[70] Currently, there are no reports of blood purification techniques used to control the robust inflammatory response immediately after trauma or thermal injury.

High-Volume Hemofiltration

Perhaps, the blood purification technique that is most readily available is high-volume hemofiltration (HVHF). HVHF is an aggressive mode of CVVH and is characterized by high replacement fluid rates (>50–100 mL/kg/h). Using this high volume and the larger pore sizes of conventional hemofilters to

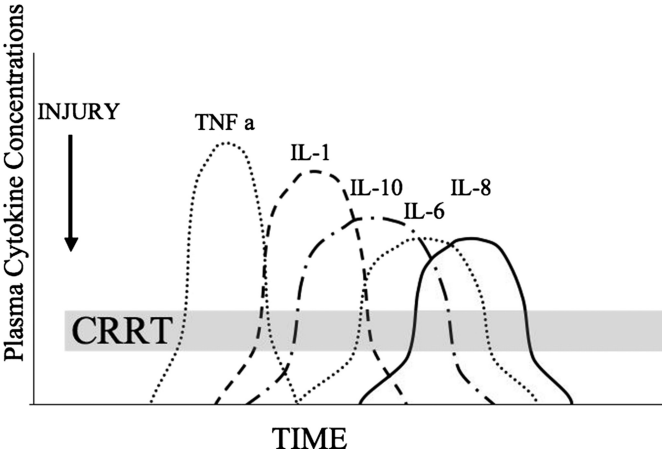

Figure 4. The ''peak concentration hypothesis'' states that the nonspecific removal of inflammatory cytokines lowers their peak concentration and may decrease the overall severity of the inflammatory response following insult.

remove substances results in a nonselective removal of inflammatory cytokines that range from 5 kD to 50 kD in size. Initial interest in this modality as an adjunct for immunomodulation began in the early 1980s.

Several experimental and clinical studies have suggested that hemofiltration at sufficient doses can "clear" inflammatory mediators in various shock states and that this nonspecific cytokine removal is associated with positive physiologic effects including improvement of hemodynamic instability and other important clinical outcomes.[76–81]

Piccinni et al.[82] described improvement in hemodynamics, gas exchange, and 28-day survival compared with historical controls after the institution of early, isovolemic hemofiltration for the treatment of oliguric renal failure patients with septic shock. The 28-day survival of 55% was significantly higher than in the historical control arm (27%, $p < 0.05$). The authors hypothesized that early HVHF may nonspecifically affect mediators (both proinflammatory and anti-inflammatory) and improve outcomes by modulating both the early, multiple-organ dysfunction due to systemic inflammation and later immunoparalysis of sepsis.

In a multicenter prospective randomized trial involving 61 patients with shock after out-of-hospital cardiac arrest, HVHF (200 mL/kg/h) was associated with improved 6-month survival (odds ratio, 4.4; 95% confidence interval, 1.1–16.6) when compared with control.[83]

A large multicenter prospective randomized trial was recently conducted in Europe called the IVOIRE (hIgh VOlume in Intensive caRE) study and compared early HVHF (70 mL/kg/h) versus a standard CVVH (35 mL/kg/h) in patients with septic shock and mild AKI (NCT00241228, clinicaltrials.gov) in a mixed ICU population. At the time of submission of this article, the results of that trial are not yet available. Another multicenter trial is currently underway in burn patients with septic shock and AKI and will shed light on the overall efficacy and safety of this mode of blood purification (NCT01213914, clinicaltrials.gov) after severe thermal injury.

Adsorptive Techniques

With the use of the same circuitry, additional inflammatory mediator clearance can be achieved by modifying the hemofilter so that it absorbs molecules of specific size, charge, or both. The adsorptive filters remove cytokines much more efficiently than does the convective clearance of HVHF. The relative strength of adhesion is influenced by the chemical composition and surface charge of the filter. Polymethylmethacrylate filters and filters constructed with Polymyxin B for the adsorption of endotoxin have also demonstrated effective cytokine clearance in the setting of sepsis and pancreatitis.[84,85] In a recent prospective multicenter randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]), Cruz et al.[86] demonstrated hemodynamic improvement and overall mortality benefit when standard CRRT was combined with two sessions of Polymyxin B hemoperfusion in patients with intra-abdominal sepsis.

Adsorption columns represent the newest innovations in blood purification.[71,87–89] These columns contain large numbers of polymer beads that provide similar adhesive surface properties of the adsorption filters with vastly magnified surface areas. Beads within these columns remove particles of a specific molecular weight from systemic circulation via the principle of size exclusion chromatography. Larger particles (such as red blood cells) flow around the beads, while small solutes (such as sodium) freely flow through pores in the beads. Conversely, cytokines are trapped in these pores and not returned to systemic circulation. This technology has garnered increased interest in the field of blood purification as it obviates the need for the convective hemofiltration process, with its attendant fluid and electrolyte losses. Currently, clinical investigation of the efficacy of adsorption columns has been limited to sepsis, but initial results are promising.

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) was devised in the 1970s as a method of blood purification via the selective removal of blood components based on either weight (centrifugal) or size (membrane filtration) or both. Blood from the patient cycles through the pheresis machine and is separated into plasma and other formed blood products. The plasma is shunted away into a collecting system and banked fresh frozen plasma, and/or 5% albumin is returned to the patient. While this method is effective in removing inflammatory mediators in the plasma, like other blood purification techniques, it is rather nonselective in that both pathogen substances and beneficial proteins, such as coagulation factors, are removed together.[90] In addition, the actual process of TPE is fairly safe, with an overall incidence of death at less than 0.05%. The majority of complications arise not from untoward hemodynamic effects but rather from viral transmission or anaphylaxis from fresh frozen plasma infusion, hypocalcaemia arising from citrate-containing anticoagulants for the circuit, and coagulation abnormalities.

Well-defined guidelines for the appropriate clinical setting and timing of TPE in trauma patients have yet to be determined.[91] To date, the experience with TPE after trauma has been limited to adjuvant resuscitation measures in refractory burn shock. Several studies from the early 1980s did report success with TPE in the setting of burn shock resuscitation failure.[92–94] However, the only prospective, randomized trial performed showed no alteration in the course of burn shock to the seven patients randomized into the treatment group. Moreover, there was no decrease in the amount of intravenous fluid (IVF) needed to achieve resuscitation.[92–94] This same group later reported their experience with TPE's immunomodulatory effects after burn. They discovered that in addition to reversing the course of a failing burn resuscitation, TPE helped decrease serum immunosuppressive activity and was found to bolster postburn lymphocyte function.[95]

To date, there is no clearly defined role for TPE in burn shock salvage. This may be caused by its relative obscurity in the trauma/critical care community, and its lack of clearly demonstrated efficacy in burn resuscitation. Yet, recent experience with TPE demonstrated significant physiologic improvement and cessation of increasing IVF rates in the setting of refractory burn shock. Mean arterial pressure and urine output both greatly increased in response to TPE, while lactate levels and IVF rates both decreased.[96,97]

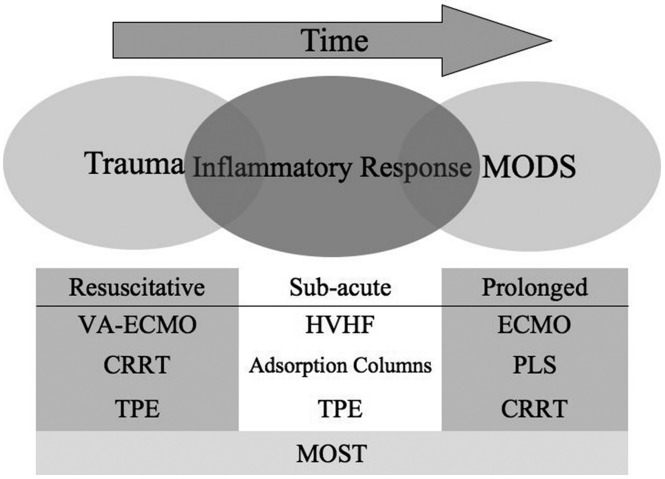

Figure 5. From the time of initial injury, extracorporeal organ support may have utility in the resuscitative, subacute, and prolonged hospitalization phases. The concept of multiorgan support therapy may provide comprehensive organ support as early as the initial resuscitation and extend throughout the entire hospitalization.

Future Directions

Multiorgan Support Therapy

The concepts and technologies of extracorporeal organ support continue to evolve and are rapidly culminating with support of multiple failing organ systems.[98] The ultimate goal of multiorgan support therapy would be to link all of these therapies (RRT, blood purification, as well as lung and cardiovascular support) into one multifaceted intervention and delivery platform. Increases in data management and computing capacity would combine with biosensors and artificial intelligence to recapitulate the interconnectedness between organ systems. Such a capability would maintain homeostasis in the face of physiologic derangement and provide ease of use for practitioners without advanced training in extracorporeal organ support (Fig. 5). Advances in nanotechnology are allowing the creation of complex filters with multiple functions (detoxification and synthesis of proteins) and increased capacity. In addition, refinements in mechanisms and engineering of extracorporeal organ support devices are allowing for decreased size and more accessible user interfaces. Taken together, these novel improvements create exciting and powerful possibilities for the critical care of severely injured military personnel in austere environments where portability, versatility, and ease of use are paramount.

The ideal arrangement is to have a robust research program in place that can practically enable providers in far forward locations to identify capability gaps, while researchers at home investigate solutions to fill them.

CONCLUSION

Advances in trauma care and combat casualty care research have resulted in a decrease in early mortality from hemorrhage. The resulting increase in survivorship is a call for innovative research on as well as development and application of an array of advanced organ support techniques to mitigate the effects of multisystem organ failure. Ongoing and future combat casualty care research should build on recent and landmark progress to refine extracorporeal organ support modalities and blood purification techniques focusing on streamlined delivery platforms for application in austere settings.

AUTHORSHIP

All authors drafted and critically revised the manuscript.

DISCLOSURE

The authors declare no conflicts of interest.

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EDITORIAL CRITIQUE

Extracorporeal therapy in the critical care setting has expanded significantly during the past decades. Total extracorporeal organ support (cardiac, pulmonary, renal, hepatic, or immune) with a modular nonthrombogenic fully automated extracorporeal circuit is on the horizon: the future is now!

Neff et al. have provided an expert/comprehensive/timely review of significant advances in extracorporeal organ support that are available for critically ill/injured patients. It is truly remarkable that these high technology advances have been made available to combat casualties in austere environments by military physicians' commitment and dedication to advanced critical care, with resultant markedly improved trauma patient outcomes in recent military conflicts.

They report increasing veno-venous extracorporeal membrane oxygenation (VV-ECMO) use for severe hypoxemia treatment in combat casualties, with cannulation in the war zone with excellent outcomes. In the civilian setting, we have transitioned to increasing use of "ambulatory VV-ECMO" with percutaneous placement of a single bicaval dual-lumen cannula to avoid deconditioning with early mobility. Intensive care unit nurses provide care, with interval evaluation by ECMO specialists. Prolonged heparin-free VV-ECMO is now possible, allowing increasing use in trauma. A randomized trial (ECMO for Severe ARDS, EOLIA) is currently underway in France.

This review also highlights significant renal replacement therapy advances for acute kidney injury treatment. An additional advance is the selective cytopheretic device (SCD), a synthetic membrane device, which binds/inhibits activated leukocytes along a continuous renal replacement therapy extracorporeal circuit. A prospective trial in acute kidney injury patients confirmed mortality reduction with SCD (22.22% vs. 77.78%, $p = 0.027$). A second study confirmed decreased 60-day mortality (31.4%), significantly lower than that of standard of care. A multicenter randomized trial is ongoing to assess SCD safety/efficacy.

Extracorporeal liver support has undergone significant technological advances. The Food and Drug Administration approved (December 2012) the Molecular Adsorbent Recirculating System (MARS) for the treatment of hepatic

encephalopathy caused by chronic liver disease decompensation. The Extracorporeal Liver Assist Device (ELAD) provides continuous extracorporeal liver support with immortalized human hepatocytes. Two randomized studies documented significant improvement in bridge-to-transplant/recovery and a strong trend toward increased survival. Extracorporeal liver support will be an additional module for multiorgan support therapy.

We are indebted to the military critical care physicians for their superb care of the critically injured patients from the combat setting. Their commitment to advancing the critical care that they provide to these patients, in particular with extracorporeal organ support, is truly remarkable. We trust that ongoing military-civilian collaboration in extracorporeal critical care technologies will continue to improve outcomes in the care of critically ill/injured patients with organ failure for the future.

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