Narrative Review Article

Vol. 2, No. 3; 2018; pp 103–110
DOI: 10.26676/jevtm.v2i3.58

Novel Interventions for Non-Compressible Torso Hemorrhage: Secondary Considerations in Consequences of Aortic Occlusion

Alicia M Bonanno MD[1] and James D Ross PhD[2]

[1]*Department of Surgery, Oregon Health and Science University, Portland, Oregon, USA*
[2]*Division of Trauma and Acute Care Surgery, Oregon Health and Science University, Portland, Oregon, USA*

Non-compressible torso hemorrhage in trauma remains a leading cause of death in austere environments. Advancements for treatment include resuscitative endovascular balloon occlusion of the aorta (REBOA), selective aortic arch perfusion (SAAP), and external compression approaches (junctional tourniquets and abdominal aortic tourniquets), which have provided several promising avenues. However, the application of these devices carries the risk of distal ischemia and the consequences associated with reperfusion injury. This review aims to look at these novel interventions and the physiologic burden associated with them. Following a review of these new advents, we will evaluate the possible solutions to reverse the physiologic penalties.

Keywords: *Non-Compressible Torso Hemorrhage; REBOA; Selective Aortic Arch Perfusion; Junctional Tourniquets; Cytosorbants*

Received: 2 May 2018; Accepted: 26 June 2018

INTRODUCTION

Hemorrhage is the leading cause of preventable death in pre-hospital combat casualty care and civilian trauma [1,2]. The majority of potentially survivable deaths involve hemorrhages in the torso, which are difficult to control in the field [3]. There have been several promising advancements in modalities for management, including resuscitation with balanced blood products, aortic occlusion [e.g. resuscitative endovascular balloon occlusion of the aorta (REBOA) and selective aortic arch perfusion (SAAP)], and abdominal aortic/junctional tourniquets. Interventions involving compression or aortic occlusion give a short-term survival advantage by offering continued perfusion to vital organs; however, the associated morbidity of ischemia distal to the occlusion can result in irreversible injury and potentially exacerbate trauma induced systemic inflammatory response syndrome (SIRS) [4–7].

With advancements in endovascular techniques for aortic occlusion in trauma, the physiologic sequelae are still poorly understood. There is both translational evidence and clinical outcomes, which indicate that our focus must shift to the management of these outcomes. Multiple accounts of distal ischemia and secondary reperfusion injury following recirculation have been reported following occlusion [6]. Ischemia-reperfusion injury (IRI) develops through several signaling pathways involving ischemic-induced cell injury, impaired intracellular calcium hemostasis, depletion of ATP, the formation of toxic metabolites and production of free radicals leading to further oxidative damage [8]. It can also cause a subsequent inflammatory response resulting from the induction of multiple cytokines and chemokines

Corresponding author:
James D Ross, Associate Professor of Surgery, Division of Trauma, Critical Care & Acute Care Surgery, Department of Surgery, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road, Portland, Oregon 97239, USA.
Email: rosja@ohsu.edu

Author contributions: Both authors contributed to the review and writing of this manuscript.

Conflicts of interest: None.

Funding: None.

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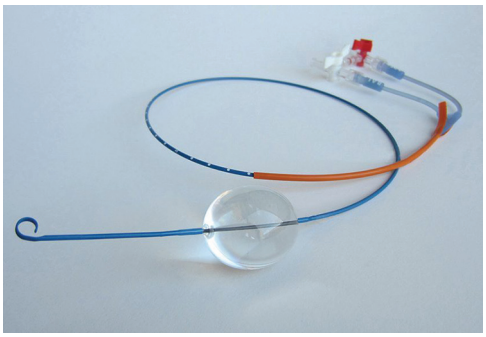

Figure 1 ER-REBOA™ catheter (reprinted with permission from Prytime Medical™).

with worsening of oxidative stress [9]. This, in turn, leads to complications in regulating vascular barrier properties, control of adhesion and extra-vascular trafficking of immune cells, regulation of vascular tone, and control of hemostatic mechanisms [10].

The purpose of this review is to discuss and compare the different modalities of treatment for non-compressible hemorrhage in the context of therapeutic window and technique, physiologic impact, and logistical constraints. In particular, we will discuss the implications of these therapies and the consequences associated with IRI. Finally, we will examine therapeutic targets for managing the physiologic dyshomeostasis or "physiologic penalty" that can be incurred by aortic occlusion during non-compressible hemorrhage control.

REBOA

Despite improvements in resuscitation, non-compressible torso hemorrhage is challenging to manage without control of the bleeding source. Different techniques have been proposed recently including REBOA (Figure 1) [11]. REBOA is an endovascular technique of achieving distal control to treat NCTH that has resulted in near cardiovascular collapse [11,12]. The hopes of this technique are to reduce mortality, along with reperfusion injury, in control of non-compressible torso hemorrhage [13].

Reports of the use of balloon occlusion of the aorta were seen as early as the Korean War [11]. In 1954, Hughes et al. described the use of a novel intra-aortic balloon catheter for the use of moribund patients with uncontrolled hemorrhage (>10 U of blood administered) in the hopes of enhancing perfusion of the coronary arteries [12]. In 1986, Low et al. had demonstrated its use again with a death due to ischemia in one patient and difficulty with placement in others [14]. The application of REBOA over the following years lagged due to technology, lack of skill set for placement, and anticipated ineffectiveness [11,15]. With the recent evolution of technology and endovascular advancements, there has been an increased use and push for further research [11,15].

The current technique of placement is by deploying a balloon occlusion catheter into the aorta via the common femoral artery (CFA) [11]. The CFA is palpated, identified via ultrasound or found under direct vision by cutdown [15]. The artery is then accessed using a sheath which can then be upsized over a wire for use with larger balloon catheters. Following access, the insertion depth can be approximated via external landmarks, x-ray confirmation or under fluoroscopy [11,15,16]. The balloon catheter is then inserted into the pre-determined level and inflated until aortic occlusion is achieved [17].

The aorta is divided into three zones as described by Stannard et al. [11]. Zone 1 is an occlusion site denoted between the left subclavian artery to the celiac artery. Zone 1 is above the xiphoid process. Zone 2 is between the celiac artery and the lowest renal artery and is known as the no-occlusion zone. Zone 3 is designated as the area below the lowest renal artery to the aortic bifurcation and the anatomical landmark for the bifurcation is the umbilicus [11,15,17].

Aortic occlusion and cross clamping in the settings of abdominal exsanguination are usually pursued in the setting of near cardiovascular collapse [15]. The emergent nature of this procedure makes balloon positioning and confirmation more difficult. Given the acuity of the situation, it may not be feasible for positioning confirmation via fluoroscopy, as these may not be available. The majority of Level I trauma centers confirm placement via plain film (52%), followed by blind insertion (26%), and fluoroscopy (13%) [18]. Current techniques for confirmation of placement require imaging that is not readily available in an austere environment, however, promising results of fluoroscopy free deployment of REBOA has been reported by special operations medical forces in recent combat operations [19].

Fluoroscopy free placement of REBOA catheters using anatomical landmarks, however, may be associated with potentially harmful complications ranging from balloon malposition to aortic rupture. Placement proximal to Zone I could theoretically lead to ischemic stroke or dangerously elevated cardiac afterload [20]. Placement in Zone II can lead to occlusion of the celiac trunk, superior mesenteric artery, or inferior mesenteric artery leading to visceral ischemia [20]. Placement distal to Zone III can occur in the iliac artery; injury to which can cause severe pelvic or junctional hemorrhage [20]. Misplacement in a groin access site can cause dissection or ischemia to the lower extremity with the risk of amputation [4]. Scott et al. have reported inadvertent placement in the renal artery in animal studies involving REBOA [21].

While fluoroscopy free deployment represents a technical/mechanical risk factor for REBOA use, there are additional physiological penalties to consider [6,7]. The decision to perform aortic occlusion requires a balance of the need to support pressure and the physiologic consequences of occlusion. Kralovich et al., for example, reported ventricular strain and impaired function

following balloon occlusion in swine [22]. Another study by White et al. demonstrated lactic acidosis and elevated serum lactate levels in swine during aortic occlusion [17]. However, in comparison to resuscitative thoracotomy, lactate levels are decreased and there is less requirement for fluids during resuscitation [17].

Although REBOA appears to have less metabolic acidosis than aortic cross clamping, there are still physiologic consequences associated with placement and duration of occlusion appears to be a factor in the amount of tissue damage [6]. Markov et al. found that in comparison to control animals, REBOA groups had greater increases in serum lactate after balloon deflation subsequent to visceral and lower extremity reperfusion [7]. In another example, Annecke et al. demonstrated remote pulmonary injury following lower body ischemia and reperfusion [25]. Additionally, in retrospective studies, there have been reports of higher hospital mortality with REBOA use in Zone 1 following occlusion times greater than 30 minutes, lower extremity ischemia, and acute kidney injury [4,26].

Markov et al. and several others have demonstrated a negative physiologic effect with increasing periods of occlusion, especially when greater than 40–60 minutes [7,25,26]. Although duration of aortic occlusion resulting in negative physiologic sequelae have not been easily extrapolated from the current literature due to ischemic burden present from hemorrhagic shock, there is a consensus that increases in occlusion time increases adverse effects [28]. Complications that have resulted following prolonged occlusion include irreversible organ injury, supraphysiologic increases in blood pressure causing cardiac failure, worsening traumatic brain injury, and increased mortality [23,24,25]. Lastly, Morrison et al. demonstrated that greater occlusion times were associated with increased release of interleukin (IL)-6, increased acute respiratory distress syndrome (ARDS), and increased lactate burden [6].

Several studies have proposed partial balloon deflation in order to mitigate these physiologic consequences and reperfusion injury associated with increasing occlusion times [27,29,30]. Partial REBOA (P-REBOA) is a continuous, low volume, distal perfusion through partial aortic occlusion [30]. Russo et al. demonstrated that P-REBOA was able to maintain proximal mean arterial pressure (MAP) at normal physiologic levels, avoid hemodynamic extremes, and continue distal perfusion to minimize ischemia and subsequent IRI when compared to complete occlusion [30].

By maintaining even a small amount of perfusion distally, there is the potential to reduce rates of tissue ischemia and rebound hypotension after balloon deflation, which can result in decreased morbidity and mortality [29]. It also has the potential to decrease the effects of supraphysiologic elevations in systolic blood pressure and increased afterload [29]. Not only can partial REBOA be a promising solution to these sequelae, but we can continue to mitigate secondary insults by properly defined strategies in the use of aortic occlusion by limiting overall occlusion times, monitoring responses to ongoing blood transfusions, and prompt hemorrhage control in the operating room. Overcoming the limitations associated with complete aortic occlusion could further impact management of non-compressible torso hemorrhage.

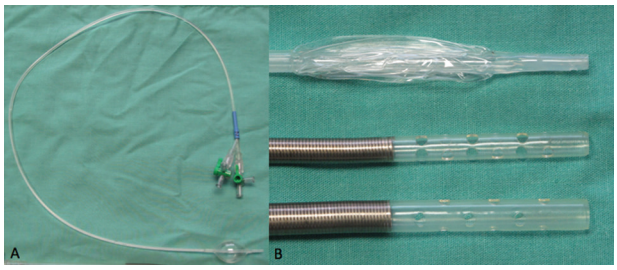

Figure 2 Example of 87 cm selective aortic arch perfusion catheter prototype (**a**) and 11.5 Fr balloon catheter tip compared to extracorporeal membrane oxygenation catheters (**b**).

SAAP

SAAP is a resuscitation technique for medical and traumatic cardiac arrest [32]. SAAP is a catheter that is placed into the descending thoracic aorta that is used to provide perfusion to the heart and brain with an oxygen-carrying perfusate while also limiting further subdiaphragmatic hemorrhage (Figure 2) [33]. Theoretically, this could reverse myocardial ischemia and acidosis, increase myocardial contractility, restore arterial vasomotor tone, and possibly promote the return of spontaneous circulation (ROSC) [32]. The benefit over REBOA would be in those patients with lost intrinsic circulation.

The technique itself is similar to REBOA, in which a large lumen balloon catheter is inserted through the femoral artery into the high thoracic aorta just distal to the left subclavian artery takeoff [32]. The balloon is then inflated preventing distal flow and further hemorrhage. An oxygenated perfusate is then infused into the isolated aortic arch, thus increasing flow to the heart and brain. Different types of perfusate have been tested such as red blood cells (RBCs), fluorocarbon and hemoglobin-based oxygen carriers [34].

As SAAP takes over perfusion to the heart and brain, the blood products transfused through the catheter can cause profound ionized hypocalcemia and ventricular dysrhythmias [34]. Manning et al. demonstrated co-administration of intra-aortic calcium appeared to counteract this complication and allowed for successful ROSC [34]. Blood is presently the only feasible product available for use at this time and would need continuous infusion of calcium during SAAP.

Prior SAAP studies have used other products such as perfluorocarbons and hemoglobin-based oxygen carriers that currently are not approved for use [34]. These perfusates are hypothesized to increase oxygen delivery

to tissues and possibly decrease oxidative stress. This resuscitation fluid would be helpful in the critical management of hypovolemia while simultaneously reducing or preventing end-organ injury due to IRI [33].

Other proposed perfusate additives can include the addition of epinephrine. Limitations are noted on the total infusion volume, rate, and total infusion that can be used [32]. Manning et al. demonstrated that with normal saline in swine studies, despite using substantial flow rates, mid-aortic arch pressures did not reach normal physiologic ranges [32]. With the addition of epinephrine, however, the mid-aortic and coronary perfusion pressures increased well into the normal physiologic range [32].

The temperature of the perfusate, as well, remains unaddressed. A relatively hypothermic solution may be beneficial for facilitating neurologic recovery but may make defibrillation more difficult [32]. Further studies need to be undertaken to establish the best temperature for the perfusate.

Multiple complications have been associated with this technique with some similarities to REBOA. These include pulmonary edema, cerebral edema, aortic dissection, aortic rupture, catheter misplacement, air embolism, femoral artery injury/thrombosis, and wound infection or hematoma [32]. Current research is still ongoing regarding the physiologic consequences of SAAP. These consequences will also need to be compared to those who are revived after cardiac arrest without the use of SAAP, as arrest alone has similar effects on ischemia-reperfusion. At this time, we can only infer that it will have similar complications to REBOA, along with sequelae of distal ischemia and possible reperfusion injury in prolonged occlusion.

External Compression Approaches

Junctional trauma is defined as an injury occurring at the junction of two anatomically distinct zones. Junctional hemorrhage cannot be controlled by standard limb tourniquets, creating an area of uncompressible hemorrhage [35]. To attempt to control this in the field, there have been advancements in specialized tourniquets capable of controlling these areas, including the abdominal aortic and junctional tourniquet (AAJT).

This tourniquet has been suitable in explosive device situations where there is a high level of leg amputation, urogenital, and pelvic injuries [35]. Its clearance has also been expanded for junctional use at the groin level [35]. Application of the tourniquet is aimed at compression of the groin or pelvic area, particularly the iliac vessels. The belt is placed around the lower abdomen and pneumatic bladder is inflated to 300 mmHg. Theoretically, it is able to compress the abdominal wall enough to occlude the underlying abdominal aorta and vena cava [35].

There have been several studies in both human and swine populations demonstrating the effectiveness of AAJT at reducing peripheral blood flow [35,36,37]. Several case reports have also demonstrated its use, including application during an en-route phase of care to control severe hemorrhage in a casualty with traumatic bilateral amputation of the lower extremities [38]. Following application and resuscitation, the patient who was previously in extremis upon arrival, had improvement of end-tidal CO_2, return of a carotid pulse, and survived through surgical intervention following transport [38]. Thus, the AAJT may be a promising intervention in combat trauma during situations of prolonged field care and temporary control of NCTH.

The hemodynamic responses seen with application show a significant increase in blood pressure and a significant reduction in circulatory volume with an increase in peripheral vascular resistance [35]. A notable tachycardia also occurred following application, which may be attributed to the discomfort or pain that is caused by application [35]. This aspect of painful application was also noted on human test subjects [36]. The pressure applied in order to cease blood flow caused moderate pain in the subject, however, pain scores returned to zero upon device deflation [36].

Kheirabadi et al., however, observed several concerning aspects in the application of AAJT including respiratory arrest upon release of the tourniquet, sudden cardiac arrest after reflow, sudden hyperkalemia, elevations in lactate, and metabolic acidosis [35]. Their group also demonstrated marked increases in creatine kinase (CK). Of note, there were no observations of acute renal failure and disseminated intravascular coagulation (DIC), despite a similarity to some of the physiologic changes in crush syndrome. In addition, these complications were not seen in studies where application time was decreased [35].

Given the possible complications associated with AAJT placement, there may be unforeseen and even detrimental consequences during release due to the distal ischemia as seen with other methods of occlusion. Further studies need to be undertaken in swine and human populations in regards to the physiologic effects of AAJT placement and release.

SIRS, IRI, and Future Metabolic Targets

The SIRS response in trauma and burns shares similar features with sepsis but may have mechanisms more intimately tied to tissue oxygenation and perfusion. Severe trauma and sepsis were found to be associated with increased inflammation and also compromised immune systems [39]. Surgery and trauma cause selective suppression of the T helper (Th)-1 lymphocytes with a shift toward Th-2 cytokine patterns for immune suppression, which differs from the immune response associated with sepsis [40]. This increased inflammation is evidenced by elevated IL-6, neutrophilia, increased immature granulocyte counts, anemia, lymphopenia, and tachycardia [41].

Not only do we see an inflammatory response from SIRS in trauma but IRI has the ability to create another induction of inflammation with release of various cytokines, chemokines, and increased oxidative stress [9]. With this cascade of events, there is further microvascular dysfunction in ischemic tissues and organs following reperfusion. IRI produces complications in regulating vascular barrier properties, control of adhesion and extra-vascular trafficking of immune cells, regulation of vascular tone, and control of hemostatic mechanisms [10].

Radical oxygen species (ROS) that are produced after reperfusion following traumatic injury are one of the most potent chemoattractants for polymorphonuclear leukocytes (PMNs) and result in further cell membrane damage by lipid peroxidation [42]. This increase in activated PMNs is the main cause of secondary organ and tissue damage with subsequent development of multi-organ dysfunction (MOD) and ARDS [42]. Several cytokines are also activated, including IL-1, IL-6, thromboxane A2 (TXA2) and tissue necrosis factor (TNF), which provide signals between the responding leucocyte and the vascular endothelial barrier and are believed to be responsible for selective adhesion and transmigration of leukocytes [43].

Aortic occlusion, in particular, has been associated with the greater release of IL-6 and increasing lactate levels with inflammatory sequelae, including increased incidence of ARDS [6]. The increasing lactate reported in multiple studies was associated with a significant ischemia related perfusion injury [6]. There are also significant metabolic derangements seen with the release of tourniquets and deflation of balloon catheters [6,35]. This includes profound hyperkalemia that, as discussed previously, may be similar to a crush injury with the use of AAJT or IRI in aortic occlusion.

Along with IRI and the increasing rates of massive blood transfusion (>100–50 mL/min), we are more commonly seeing severe hyperkalemia and acute kidney injury (AKI). Rates of AKI occurred in 12.5% of the combat population with a 5-fold increased risk of death [44]. Hyperkalemia may occur during massive transfusion secondary to increased concentration in blood with longer durations of storage [45]. This, in turn, has been linked to cardiac arrest in trauma patients and critically ill adults following a massive blood transfusion.

In order to prevent post-transfusion hyperkalemia, a potassium adsorption filter has been developed [46]. This filter aims to function by adsorbing excess potassium ions from red blood cell concentrate. The maximum speed that blood can be transfused through this filter is at a rate of 50 mL/min [46]. Matsurra et al. studied potassium adsorption with rates of transfusion and noted that there is a decreased amount of adsorption with increasing rates of transfusion [46]. Given these results, it may not be feasible for use in massive transfusion protocols, as the rate is not adequate.

More recently, however, newer modifications to potassium filters for use in austere environments have been developed for use as a "bridge to dialysis" concept. The gold standard for renal replacement therapy is difficult in this setting given the logistical footprint of equipment, high volumes of sterile fluid, and the training necessary for operation. There are currently ongoing studies evaluating the feasibility of a simplified hemoperfusion system that can reduce potassium in cases of acute hyperkalemia during pre-hospital combat casualty care.

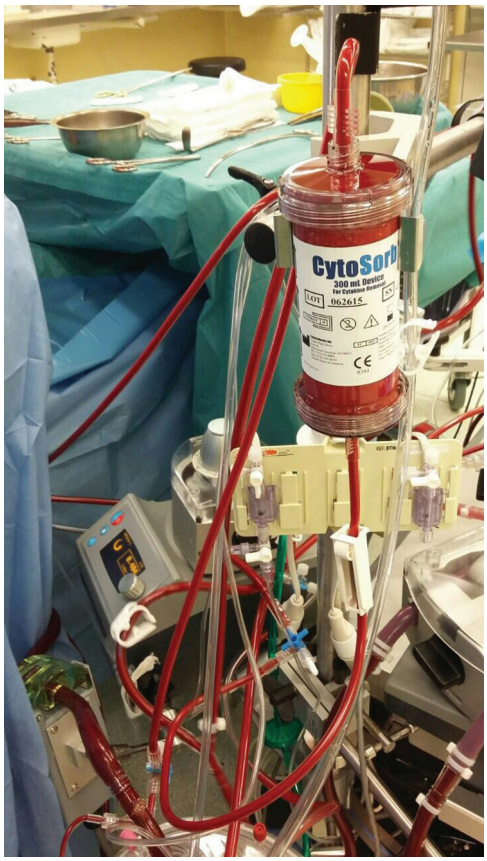

Figure 3 CytoSorb® filter for removal of serum cytokines.

With the complications of IRI and hyperkalemia associated with aortic occlusion, there is also an increase in multiple cytokines that in part create a secondary injury in trauma patients. Removal of these harmful cytokines has been shown to produce an effective result in critically ill patients. Cytokine filtration has been demonstrated in several patient populations including SIRS, sepsis, cardiopulmonary bypass surgery, and even ex vivo lung perfusion [47,48,49]. Given that the cytokines released in IRI are similar to SIRS and sepsis, cytokine filtration may be a promising additional target.

Cytokine adsorber, or Cytosorb (Figure 3), works by non-selectively removing various mediators via hemoadsorption [47]. It contains hemocompatible, porous polymer beads and adsorbs mediators by size exclusion chromatography and hydrophobic interactions [47]. The column is attached to a circuit for filtration such as hemodialysis or continuous renal replacement therapy [47].

Over-abundant cytokines and other proteins can then be removed and a balance of inflammatory mediators is achieved [47].

Cytosorb has been investigated in many different patient populations and utilized in specific case studies. In a small study, patients with ARDS and sepsis underwent filtration with Cytosorb and it was noted that the circulating levels of IL-6 were almost halved vs. the standard of care. However, there has been no research on clinical outcomes to state that this therapy reduces mortality [50].

Another promising avenue for research has been the advent of adenosine deaminase (ADA) inhibitors. Adenosine, in particular, is associated with increased cellular release during SIRS and has functions in vasomotor control, cardiac rhythm, coagulation, and immune function [51]. It is thought to have a protective effect on physiologic responses, including in selective vasodilation, moderate leukocyte activation, and diminish peroxidation of tissues [51].

An inhibitor of ADA, 2′-deoxycoformycin or pentostatin, has been shown to have improved survival in SIRS with a reduction in leukocyte adhesion and vascular damage in the mouse model [51,52]. The elimination half-life is approximately 5–6 hours and the binding to ADA is irreversible, which puts significant variability on the biologic half-life depending on organ/tissue [51,53]. Another study with a mouse model experiencing SIRS from fecal peritonitis also demonstrated significant survivor benefit up to 6 days after insult, with both pretreatment and treatment when clinical signs manifested [51]. Law et al. also demonstrated reduced extravasation of albumin, diminished leukocyte rolling and adhesion and attenuated pro-inflammatory cytokine responses [51].

Following these studies, pentostatin has been evaluated in steroid resistant graft versus host disease, hairy cell leukemia, inflammatory bowel disease, and malignant pleural mesothelioma [54,55,56,57]. It has shown some benefit in leukemia patients, however, further studies are still underway in its use in other populations. The use of pentostatin as a prophylactic agent in SIRS and trauma requires further studies but may have a beneficial effect in reducing the physiologic consequences and rates of mortality.

CONCLUSION

With the advent of several innovative techniques for aortic occlusion in trauma, we must shift our focus to the physiologic penalty associated with distal occlusion. Although these patients benefit in the moment of pre-hospital casualty care, we may be further harming them with a secondary hit of distal ischemia and reperfusion injury. Pentostatin, Cytosorb, and potassium filters are a promising beginning to this avenue of treatment and further studies need to be undertaken to determine feasibility in austere environments.

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