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Review

Direct Peritoneal Resuscitation: A review

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HIGHLIGHTS

- DPR instills hypertonic solution into the abdomen in addition to IV resuscitation.
- DPR causes rapid vasodilation and improves visceral organ blood flow after shock.
- DPR reduces edema and allows earlier abdominal closure after damage control surgery.
- DPR reduces serum levels of inflammatory cytokines and other mediators.
- DPR increases the number of organs procured per donor after acute brain death.

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ABSTRACT

Conventional treatment for hemorrhagic shock includes the infusion of intravenous (IV) fluid and blood products in order to restore intravascular volume. However, even after normal heart rate and blood pressure are restored, the visceral organs often remain ischemic. This leads to organ dysfunction and also releases numerous cytokines and inflammatory mediators which activate the body's inflammatory response. The use of Direct Peritoneal Resuscitation (DPR) helps counteract this response. This requires infusion of hypertonic fluid into the abdomen in addition to IV resuscitation. This causes rapid and sustained dilation of the arterioles, especially those in the intestine, which reduces organ ischemia and cellular hypoxia. Studies in animals have demonstrated that use of DPR after hemorrhagic shock can reduce organ edema, improve liver blood flow, and reduce serum levels of inflammatory cytokines. Subsequent human studies have shown that DPR after damage control surgery for hemorrhage or sepsis leads to faster abdominal closure, higher rate of primary fascial closure, and reduced abdominal complications. Peritoneal resuscitation has also shown benefits in the resuscitation after acute brain death, including reduced inflammatory mediators and organ edema. Use of DPR in potential organ donors leads to an increase in the number of organs procured per donor, most frequently by increasing the number of lungs procured.

1. Background

Severe traumatic injury can lead to hemorrhagic shock. The traditional treatment for significant hemorrhage is the administration of intravenous (IV) crystalloid solutions as well as blood products to restore intravascular volume [1]. However, despite resuscitation that restores heart rate and blood pressure to normal, patients can still progress to organ dysfunction. In response to shock the body experiences a profound vasoconstriction of both the pulmonary and systemic circulation. Even after normalization of hemodynamics, this vasoconstriction resolves slowly, possibly due to the intense catecholamine surge and sympathetic response that accompanies trauma and hemorrhage [2]. The visceral organs such as the small intestine and liver are particularly prone to prolonged ischemia as the body shunts blood to more vital organs such as the brain, heart, and kidneys [3,4].

This prolonged hypoperfusion of the intestine can precipitate a severe prolonged inflammatory response due to mobilization of Damage-associated molecular pattern molecules (DAMPs) from ischemic tissue [5]. Additionally, hypovolemic shock has been demonstrated to cause sloughing of the intestinal mucosa and increased intestinal permeability. This is associated with decreased function of tight junctions between endothelial cells [6]. This

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increased permeability of the bowel wall allows bacteria by-products to translocate out of the bowel lumen. It has also been demonstrated that even a short period of intestinal ischemia leads to activation of inflammatory cytokines and other mediators [4]. Efforts to develop antagonists for specific inflammatory mediators have thus far been ineffective in clinical studies, and fail to address the root of the problem of global tissue ischemia and inflammation [7]. Thus, our work attempts to reverse the intestinal hypoperfusion that is the underlying cause of inflammation and organ dysfunction after shock.

2. Initial microcirculatory studies

Peritoneal dialysis (PD) fluid is causes visceral vasodilation. This is thought to be due to the hypertonicity of the fluid, as well as the lactate, glucose, and glucose degradation products contained within the fluid [8]. Our initial microcirculatory studies directly examined the effects of PD fluid application to the terminal ileum, and demonstrated that all levels of visceral arterioles rapidly dilated when exposed to hypertonic fluid (see Fig. 1) but did not respond to isotonic solution [9]. These observations suggested that infusion of a hypertonic solution into the abdomen during periods of low intestinal blood flow, such as during hemorrhagic or septic shock, could help maintain blood flow to the visceral organs. This novel resuscitation was dubbed Direct Peritoneal Resuscitation (DPR).

The hypertonicity of solution appears to reduce transcellular water diffusion through the aquaporin channels of cells following ischemia. This serves to maintain blood flow to the abdominal organs, by reducing endothelial cell swelling and maintaining capillary bed cross sectional area during and after resuscitation, leading to better tissue blood flow and reduced cellular ischemia. Use of adjunctive DPR preserves endothelial cell function when compared to conventional resuscitation [10]. DPR also prevents the significant visceral edema via the same mechanism leading to better cellular function and reduced edema produced cellular dysfunction. Microscopic evidence points toward a preservation of organ and cellular architecture following shock in patients treated with DPR compared to those treated with conventional resuscitation techniques alone [11].

3. Animal model

To better examine the use of DPR *in vivo* we utilized an animal model for hemorrhagic shock, and subsequently for acute brain death. The hemorrhagic shock model used male Sprague–Dawley rats. The animals were anesthetized and then underwent tracheostomy and cannulation of the carotid artery, internal jugular vein, and femoral artery and vein. Hemorrhage was induced with blood withdrawal to mean arterial pressure (MAP) of 40% baseline for 60 min. Rats were resuscitated with blood and saline with or without intraperitoneal injection of Delflex solution. Animals were sacrificed four hours after resuscitation was complete. The acute brain death (ABD) model began similarly, but after the vascular cannulas were inserted a 4F angiocatheter was inserted into the epidural space and inflated to induce intracranial hypertension and ultimately brain death. Animals were then resuscitated with IV saline with or without DPR.

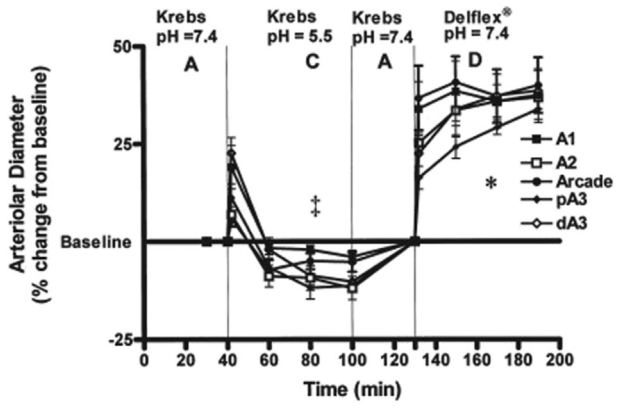

Fig. 1. Percent change in diameter of different levels of arterioles when treated with Delflex solution vs solutions of differing pH.

4. DPR improves organ blood flow

In the hemorrhage model, MAP responded to resuscitation and returned to pre-hemorrhage levels in both conventional resuscitation (CR) and DPR animals [7,10,12]. Similarly, liver blood flow returned to normal in CR and DPR groups after resuscitation. However, in the CR group, liver blood flow begins to fall as soon as resuscitation is complete (Fig. 2). The addition of DPR prevents this decrease [11]. Using colorimetric microspheres we demonstrated that the addition of DPR improves blood flow in jejunum, ileum, spleen, pancreas, lung, and skeletal muscle [12].

In the ABD model, brain death is signaled by a sympathetic surge marked by high blood pressure and heart rate, followed by profound hypotension as sympathetic tone is lost. Ongoing resuscitation is required to maintain blood pressure in these patients. In our ABD experiments use of high levels of IV fluid (IVF) improved heart rate, MAP, and mortality compared to low levels of IVF resuscitation. Use of DPR achieved similar results while requiring much less total IVF. The addition of DPR also significantly increased liver blood flow and correlated with the lower levels of alanine transaminase and alkaline phosphatase [13].

5. DPR reduces organ edema and tissue necrosis

In the hemorrhage model, histologic examination demonstrated that CR animals had significant edema in the liver (see Fig. 3) and sloughing of the villi and loss of intestinal crypts in the ileum. The DPR animals showed significantly reduced tissue damage and better preservation of cellular architecture [11]. In the ABD model the high IVF group was the most like the DPR group in terms of outcome. However, examination of the lung, liver, and ileum demonstrated significantly more edema in all three organs in the IVF only group when compared to the DPR group [13].

6. DPR reduces serum inflammatory cytokines and DAMPs

The fact that effects of DPR extend to organs beyond the abdominal cavity suggests that the mechanism by which DPR improves organ blood flow is not mediated exclusively through direct contact. Examination of serum cytokine levels in sham (no hemorrhage), CR, and DPR animals revealed that inflammatory cytokines such as IL-1α, IL-1β, and IL-6, were increased in CR animals and equivalent to sham animals in the DPR group after hemorrhagic shock. Inflammatory mediator IFN-γ was increased in CR and DPR animals compared to sham, and anti-inflammatory IL-10 was reduced in CR and DPR animals [11]. Similar results were seen in the ABD model, where pro-inflammatory cytokines IL-1α, IL-1β, IL-6, IFN-γ, and IL-18 were reduced in the DPR group compared to the groups which received IVF alone [13].

Tissue damage also leads to the release of damage-associated molecular patterns (DAMPs). This is a diverse group of molecules which act much like external pathogens, activating the same toll-

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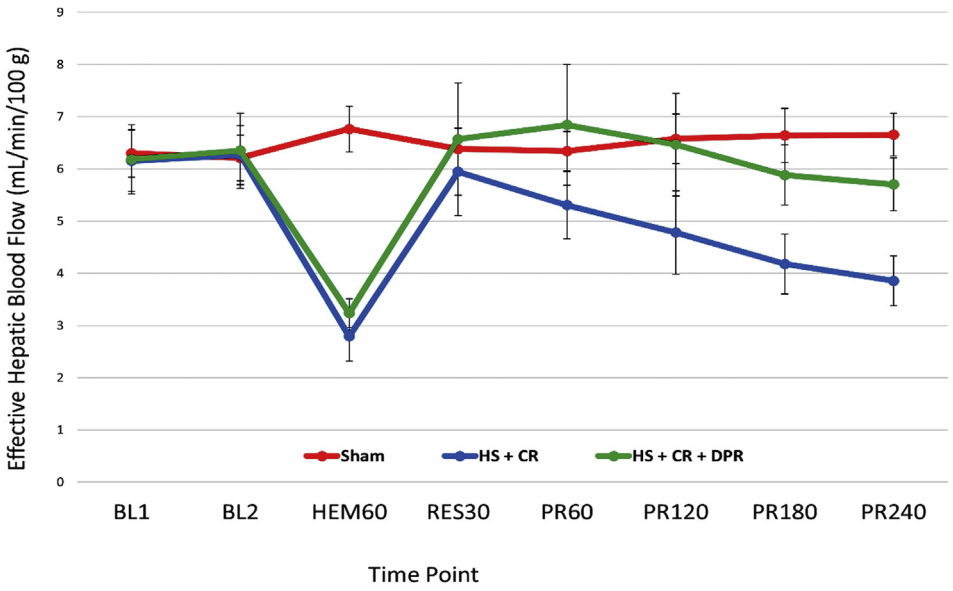

Fig. 2. Use of DPR prevents a reduction in hepatic blood flow compared to CR (BL = baseline, HEM = hemorrhage, PR = post-resuscitation).

like receptors that ramp up the body's inflammatory response [14]. Serum hyaluronic acid and High-Mobility Group Box 1 (HMGB-1) protein levels, which are markers of cellular injury, were elevated in the CR group and become equivalent to shams with the addition of DPR. Hyaluronic acid forms a part of tight junctions. HMGB-1 is normally sequestered in the nucleus due to its paracrine inflammatory properties, and thus finding it in the cytosol is a sign of tissue damage. Immunohistochemistry staining showed that in sham and DPR animals HMBG-1 remained contained in the nucleus, while in CR animals it migrated to the cytosol (Fig. 3). Levels of pro-inflammatory lipopolysaccharide (LPS) were increased in CR compared to both DPR and sham animals [11].

The fact that different cytokines responded differently to the application of DPR suggests that the anti-inflammatory properties of DPR are not global, but in fact act through specific inflammatory pathways. The effects seen on tight junction proteins indicates that not only does DPR reduce the production of inflammatory mediators, but also helps maintain the permeability of the intestine and reduce the release of these inflammatory mediators into the circulation.

7. Application in humans

In humans, we initially applied DPR to patients with an open abdomen after laparotomy for trauma or intra-abdominal sepsis. To perform this, the tubing from a 19F JP drain is inserted through the abdominal wall and the internal end placed around the base of the mesentery. The abdomen is then temporarily closed with a vacuum device. We typically use an improvised vacuum-assisted closure device (Barker type) including an underlay of perforated sterile plastic sheeting, blue towels, two chest tubes, and an adherent dressing such as an Ioban (see Fig. 4). A good seal with the adherent dressing is essential to maintain suction and prevent the fluid from leaking. The chest tubes are connected to each other and to suction using a Y connector. Chest tubes should be at least 28F and the bowel must be protected from the suction ports on the tubes. The PD solution is infused through the JP tubing at 800 cc/hr for the first hour and then continuously lavages the abdomen at 400 cc/hr. The chest tubes are kept to continuous wall suction. We have found the 2.5% glucose-based PD solution to be the most effective, even when compared to more hypertonic solutions, which tended to desiccate the tissue and pull fluid from the intravascular space [9,15]. The DPR solution should be warmed to 37 °C to avoid inducing hypothermia.

In patients without an open abdomen, the access is inserted at the bedside or at the time of operation. A small incision is made below the umbilicus and a commercially-available Diagnostic Peritoneal Lavage catheter is inserted using the open Seldinger technique. One liter of PD fluid is instilled over an hour utilizing either gravity or a bedside IV pump. The fluid is left in the abdomen for an hour, and then allowed to drain via gravity over an hour. This sequence is repeated during acute resuscitation. Higher infusion volumes should be avoided due to the risk of abdominal compartment syndrome in the closed abdomen.

8. Results of human studies

Use of DPR has expanded into human studies and shown numerous benefits. A retrospective study demonstrated that use of DPR after damage-control surgery for hemorrhagic shock decreased the time to definitive abdominal closure, as well as increased the rate of primary fascial closure. Rates of significant complications, such as enterocutaneous fistula and abdominal hernia were also reduced, likely due to the improved fascial closure rate [16]. While resuscitation practices in trauma patients have changed since the publication of that manuscript, these initial efforts produced promising results. Additionally, the use of DPR following abdominal catastrophes has also shown an improvement in time to abdominal closure and primary fascial closure rate, as well as reduced ventilator days and ICU length of stay when compared to propensity-matched controls [17]. Most recently, we have demonstrated that use of DPR in brain dead organ donors improves the organ procurement rate per donor, particularly by increasing lungs procured, likely due to reduced edema and improved blood flow [18].

9. Future directions

Further experiments will continue to explore the potential benefits and applications of DPR. While we have demonstrated reduced levels of inflammatory cytokines, we have not yet shown

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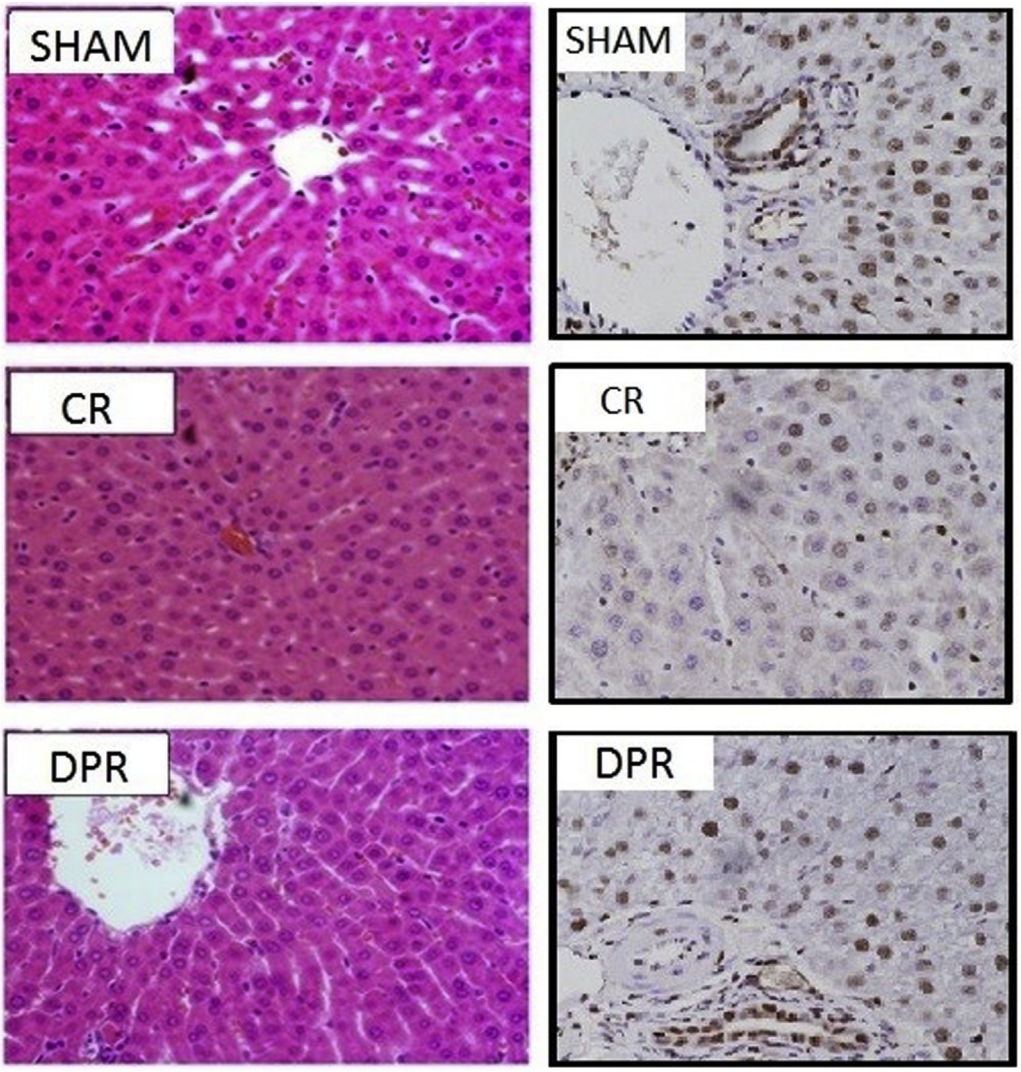

Fig. 3. Left: Hepatic H&E staining showing increased cellular edema with CR and preserved cell architecture with DPR. Right: Immunohistochemistry staining in liver showing migration of HMGB-1 into the cytosol after CR and maintenance of HMGB-1 in the nucleus with DPR.

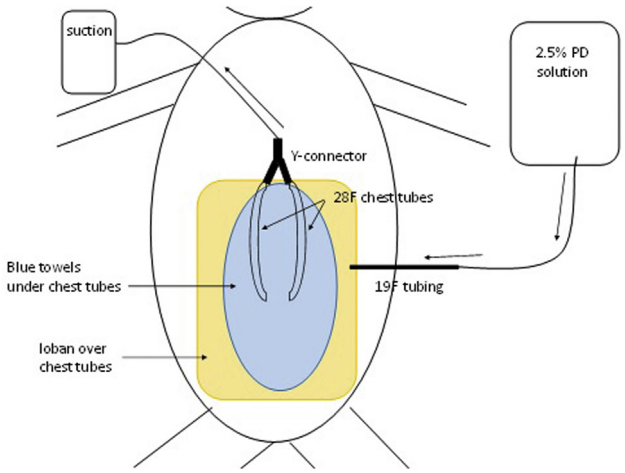

Fig. 4. Set-up for continuous DPR in patients with an open abdomen.

whether this translates to changes in leukocyte activity, especially the infiltration of macrophages and neutrophils into organs. Experiments to explore this relationship are ongoing. Also, we have only used commercially-available hypertonic fluid for DPR, and addition of other compounds to the fluid could cause additional changes to the post-resuscitation physiology seen after shock. Finally, within our organ donor patients, the need for organ outcomes follow-up continues to investigate if DPR improves organ function in organ recipients.

Ethical approval

Not Applicable, study is a review.

Author contribution

JW: wrote manuscript; JS: edited manuscript.

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Conflicts of interest

None.

Guarantor

Jason W Smith MD PhD.

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