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Review

Direct Peritoneal Resuscitation: A review

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HIGHLIGHTS

- Direct Peritoneal Resuscitation (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. DPR involves 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 unsuccessful 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 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.

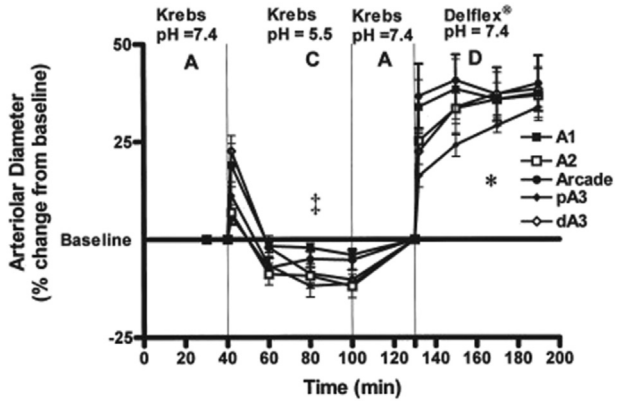

Fig. 1. Percent change in diameter of different levels of arterioles when treated with Delflex solution vs solutions of differing pH.

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 was complete (Fig. 2). The addition of DPR prevented this decrease [11]. Using colorimetric microspheres we demonstrated that the addition of DPR improves blood flow to the 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-