

Reperfusion strategies in the management of extremity vascular injury with ischaemia

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Background: Extremity injury with ischaemia is the most common pattern of vascular trauma and is a challenge for surgeons who must make decisions about the timing and mechanism of limb reperfusion. In modern military conflicts, effective use of limb tourniquets and rapid transport of the injured have increased the number of casualties who reach a medical service with potentially survivable vascular trauma. This report provides a review of extremity ischaemia and reperfusion following vascular trauma.

Methods: A review was undertaken of extremity vascular injury with ischaemia, including a focus on adjuncts aimed at reducing reperfusion injury and improving neuromuscular recovery and limb salvage.

Results: Findings from basic and clinical research support the need to restore perfusion to an ischaemic limb as soon as possible in order to achieve optimal neuromuscular recovery. Large-animal studies demonstrate that haemorrhagic shock worsens the impact of ischaemia on the neuromuscular structures of the limb and reduces the ischaemic threshold to as little as 1 h. Surgical adjuncts such as vascular shunts, fasciotomy, regional limb cooling and ischaemic conditioning may reduce the severity of ischaemic injury. Medical therapies have also been described including hypertonic saline, statins and ethyl pyruvate, which reduce the inflammatory response following limb reperfusion.

Conclusion: Contemporary translational research refutes a casual approach to extremity vascular injury with ischaemia, instead emphasizing expedited reperfusion. Surgical and medical adjuncts exist to expedite reperfusion and mitigate reperfusion injury. Additional research and development of these adjuncts is necessary to improve quality or functional limb salvage after vascular trauma.

Paper accepted 29 September 2011

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.7790

Introduction

The rate of vascular injury in the wars in Iraq and Afghanistan is higher than previously reported in combat, with injury to extremity vessels being most common^{1–3} (Fig. 1). The burden of this injury pattern has resulted in a reappraisal of operative strategies with a focus on improving functional or working limb salvage. Methods to preserve nerve, muscle and bone in the setting of extremity ischaemia should be considered in two categories: surgical techniques and medical therapies. Surgical techniques are designed to decrease the duration of ischaemia, limit its consequences, or condition tissues to tolerate ischaemia better. Medical therapies are used during vascular repair to mitigate or neutralize the toxicity of reperfusion. This report provides a review of extremity

ischaemia–reperfusion in the context of vascular trauma, emphasizing the surgical approach (Table 1).

Ischaemia and reperfusion injury

Historical context

The importance of limiting the duration of ischaemia in the setting of extremity vascular injury is well recognized, but dogma has focused on restoring perfusion within 6 h. Although correct in intent, the 6-h interval was proposed and adopted based on a limited number of, now dated, studies^{12–14}. Much of the research did not account for concomitant factors likely to influence the neuromuscular ischaemic threshold in the setting of extremity trauma; for example, few studies examined the effect of complex

Report Documentation Page

*Form Approved
OMB No. 0704-0188*

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1. REPORT DATE 01 JAN 2015	2. REPORT TYPE N/A	3. DATES COVERED -		
4. TITLE AND SUBTITLE Reperfusion strategies in the management of extremity vascular injury with ischaemia		5a. CONTRACT NUMBER		
		5b. GRANT NUMBER		
		5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Percival T. J., Rasmussen T. E.,		5d. PROJECT NUMBER		
		5e. TASK NUMBER		
		5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX		8. PERFORMING ORGANIZATION REPORT NUMBER		
		9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		
		10. SPONSOR/MONITOR'S ACRONYM(S)		
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT				
15. SUBJECT TERMS				
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	
a REPORT unclassified	b ABSTRACT unclassified	c THIS PAGE unclassified	UU	18. NUMBER OF PAGES 9
				19a. NAME OF RESPONSIBLE PERSON

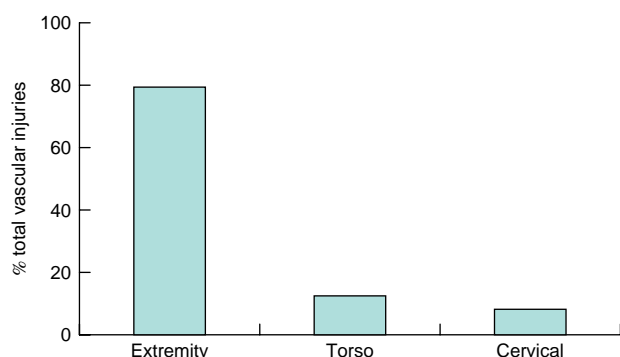


Fig. 1 Distribution of vascular injury from the wars in Iraq and Afghanistan as a percentage of total vascular injuries ($n = 1570$)¹

soft tissue wounds, long bone fractures or haemorrhagic shock. Finally, tolerance of a 6-h ischaemic window was based roughly on clinical studies that categorized limb salvage in a dichotomous manner – amputation or no amputation – labelling any outcome that avoided amputation as favourable. Only recently has the focus on extremity vascular injury centred on improving functional salvage, emphasizing that not all cases of limb salvage are necessarily desirable. In this report contemporary studies are highlighted that demonstrate the need to restore perfusion more quickly to optimize neuromuscular recovery of the injured limb.

Microcirculation

Skeletal muscle is the most important tissue to consider in the setting of extremity ischaemia because it comprises the bulk of the limb. Peripheral nerve cells are known to be more sensitive to ischaemia; however, muscle contains the majority of the extremity circulation including large axial vessels and their tributaries, as well as the microcirculation. Therefore, ischaemic injury to muscle can lead to both life- and limb-threatening consequences in the acute injury

phase (myonecrosis, oedema and compartment syndrome). Although bone and nerve are important elements to consider, restoration of perfusion and achievement of quality limb salvage begins with consideration of skeletal muscle.

Multiple factors influence muscle necrosis, including temperature, muscle fibre type, muscle location and residual blood flow^{15,16}. The earliest effects of limb ischaemia can be seen in the endothelial cells of arterioles and capillaries of muscle tissue. The microcirculation within muscle undergoes change after only minutes of ischaemia, resulting in non-uniform swelling of endothelial cells and endothelial cell dysjunction. This phenomenon is followed by congestion of red blood cells within the lumen of the capillaries and eventual cessation of blood flow to the affected area. Within 3–4 h of ischaemia, thrombosis of the microcirculation ensues and infiltration of leucocytes occurs¹⁷. The effect of this cascade within the muscle microcirculation is decreased oxygen, leading to anaerobic metabolism. With continued oxygen deprivation, the metabolic demand of muscle outpaces anaerobic metabolism, and the cells undergo necrosis and release of inflammatory mediators^{17,18}.

Restoration of blood flow during this cascade does not automatically reverse ischaemia or improve the viability of skeletal muscle cells. On the contrary, reperfusion often has an immediate paradoxical effect, worsening the damage caused by the initial ischaemia. One factor contributing to reperfusion injury is the no-reflow phenomenon¹⁰. The mechanisms of this are not fully characterized, but relate to vascular congestion in the arterioles and capillaries caused by haemoconcentration, thrombosis and swelling of the endothelium. These steps, in turn, result in plugging of capillaries by leucocytes and increased extravascular pressure from interstitial oedema. The no-reflow phenomenon propagates the ischaemic insult by impeding flow from collateral circulation, or through the repaired axial vessel^{18,19}. Microcirculatory thrombosis may

Table 1 Strategies to reduce extremity ischaemia–reperfusion injury

Adjunct	Mechanism	Selected reference
Surgical		
Restoration of perfusion	Reduction of ischaemia time	Hancock <i>et al.</i> ⁴
Vascular shunts	Reduction of ischaemia time	Gifford <i>et al.</i> ⁵
Fasciotomy	Reduction of pressure injury	Ritenour <i>et al.</i> ⁶
Limb cooling	Reduction of reactive oxygen species	Mowlavi <i>et al.</i> ⁷
Conditioning	Reduction of reactive oxygen species	Anderson <i>et al.</i> ⁸
Medical		
Hypertonic saline	Reduction of inflammatory response	Dillon <i>et al.</i> ⁹
Statin medications	Reduction of inflammatory response	Cowled <i>et al.</i> ¹⁰
Ethyl pyruvate	Reduction of inflammatory response	Crawford <i>et al.</i> ¹¹

increase resistance and decrease outflow following vascular repair, and contribute to early failure of the reconstruction (thrombosis). From a practical standpoint the use of local, regional or even systemic anticoagulation, such as heparin sulphate, at the time of vessel repair may be an important adjunct to limit the no-reflow phenomenon, although use of heparin may not be feasible in the setting of severe concomitant injury.

Molecular mechanisms

Reactive oxygen species formed after repair of extremity vascular injury and reperfusion also play an important role in cellular death and tissue injury^{17,19,20}. These molecules are produced as natural byproducts of the metabolism of oxygen, and under normal conditions play a role in cell signalling and homeostasis. Reactive oxygen species such as oxygen anions and peroxides come from activated neutrophils, but can also be produced by the vascular endothelium. These molecules are highly reactive owing to the presence of unpaired valence shell electrons. Under prolonged ischaemic conditions, xanthine oxidase reacts with the breakdown products of adenosine 5'-triphosphate (ATP) and oxygen to generate reactive oxygen species. These molecules cause damage including injury to DNA, oxidation of fatty acids and lipids, and oxidation of proteins and co-factors necessary for enzymatic function^{20,21}. The reactive oxygen species cascade is perpetuated by activation of the cyclo-oxygenase and lipo-oxygenase pathways, which cause further neutrophil activation. From a practical standpoint, to minimize accumulation of reactive oxygen species in the limb in the setting of vessel injury, efforts should be aimed at reducing the duration of ischaemia.

Nitric oxide is another molecule to be considered as part of extremity vascular injury and ischaemia–reperfusion²². The effect of nitric oxide on local tissues varies depending upon the timing and origin of its release following restoration of perfusion. Under normal circumstances, nitric oxide is produced by endothelial cells as a signal transmitter with vasodilatory effects. Under ischaemic conditions, the precursor for nitric oxide, L-arginine, becomes depleted and nitric oxide synthase can produce harmful reactive oxygen species^{20–22}. Nitric oxide can also contribute to reperfusion injury, when excessive amounts produced during reperfusion react with superoxide to produce the damaging oxidant peroxynitrite. In general, endothelial nitric oxide synthase (eNOS) has a protective role in the setting of reperfusion as it decreases platelet aggregation and has an anti-inflammatory effect. In contrast, inducible nitric oxide synthase (iNOS) is more prone to harmful effects owing to the potential

overproduction of nitric oxide, which can be converted to peroxynitrite²².

Anatomical considerations

Skeletal muscle and peripheral nerve are enclosed in compartments of the limb surrounded by bone and fascia. These compartments have a fixed space and are prone to the adverse sequelae of reperfusion injury, namely cellular oedema and tissue swelling. Compartments within the distal extremity (forearm and leg) are especially limited in their ability to accommodate tissue oedema and are therefore more prone to increased compartment pressures following reperfusion. If significant, increased pressure can add a physical component of injury to nerve, muscle and microcirculation already damaged as part of the ischaemic insult^{23,24}. Pressure in the capillaries of the extremities ranges from 10 to 20 mmHg; once this is exceeded venous outflow is obstructed, perpetuating a cycle of raised compartment pressure. Although damage to nerve and muscle is likely to occur at a lower pressure, pressure of 30 mmHg or higher in a fascial compartment constitutes a compartment syndrome requiring fasciotomy. Another definition of compartment syndrome has been described as a pressure within 30 mmHg of the patient's diastolic blood pressure^{23,24}.

Systemic considerations

Extremity reperfusion injury should be considered as having systemic effects as well^{20–22}. Specifically, reperfusion of ischaemic tissues of the limb results in release of intracellular molecules including myoglobin, and of electrolytes such as potassium, that can be harmful to remote organs including the kidneys, heart and lungs. Release of these and other factors results in a systemic inflammatory response causing increased levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and serum creatinine. Another proposed mechanism of systemic injury is activation of xanthine oxidase, an important source of endothelial cell-derived reactive oxygen species.

Surgical strategies to improve functional limb salvage

Restoration of flow

Expedited restoration of blood flow to the ischaemic limb is the most important manoeuvre to improve tissue survival and thus functional limb salvage following extremity vascular injury. This premise was recognized in World War II, when a relationship between medical evacuation

time and amputation rate was observed. Debaquey and Simeone²⁵ reported an increase in the early amputation rate following vascular injury, from 37 per cent when casualties were treated within 10 h to 63 per cent when treatment was delayed beyond 10 h. Despite this observation and similar reports from Hughes in Korea²⁶ and Rich and colleagues in Vietnam²⁷, only recently was attention focused on limiting the duration of ischaemia following extremity vascular injury. In contrast to previous conflicts, the time from injury to surgical care in Iraq and Afghanistan has averaged less than 60 min²⁸. This advance has led to a higher percentage of patients with vascular injuries presenting to surgical facilities where decisions must be made regarding priority of restoration of perfusion and vascular repair. A recent epidemiological study demonstrated that nearly 50 per cent of vascular injuries encountered in Iraq and Afghanistan were amenable to some method of vascular reconstruction¹. These advances have given surgeons and scientists reason to reappraise techniques used to manage extremity vascular injury, including consideration of methods to improve the quality of limb salvage.

A contemporary series of studies has characterized the basic neuromuscular ischaemic threshold of an extremity. Gifford and co-workers²⁹ showed in porcine limb ischaemia that restoration of blood flow within 3 h resulted in a profile of circulating markers of injury similar to that in which flow was restored after 1 h. In contrast, delay of reperfusion until 6 h resulted in a worse circulating marker profile, as well as reduced flow distal to the injury, possibly attributable to microthrombosis of the outflow circulation (no-reflow)²⁹. This model was the first modern study that led to the recommendation of earlier restoration of flow in the setting of extremity vascular injury, challenging the previous 6-h rule. Burkhardt *et al.*^{30,31} employed a 14-day survival model that combined electromyographic and gate strength testing as a physiological measure of recovery to assess function following increasing intervals of hind limb ischaemia. This study demonstrated the neuromuscular ischaemic threshold of the limb to be less than 5 h, and similarly recommended restoration of flow within 3 h of injury for optimal functional recovery.

Using the same model, Hancock and colleagues⁴ demonstrated the impact of haemorrhagic shock on neuromuscular recovery of the limb following vascular injury (*Fig. 2*). These experiments were among the first to demonstrate that concomitant haemorrhagic shock exacerbates the negative impact of extremity ischaemia, reducing the ischaemic threshold of the limb to less than 3 h. The authors went as far as to conclude that, under these conditions, restoration of perfusion within 1 h is necessary to achieve neuromuscular recovery. These studies provided

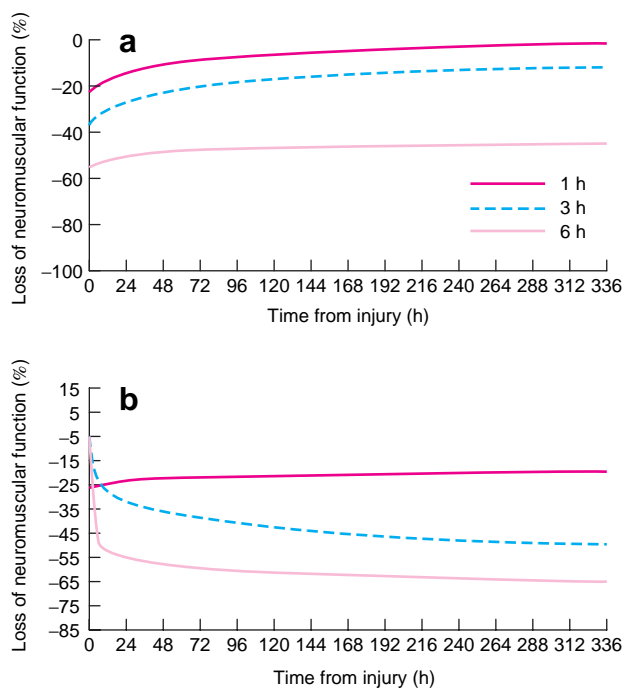


Fig. 2 Extent of neuromuscular recovery following 1, 3 and 6 h of hind limb ischaemia in a porcine model (14-day survival) with and without haemorrhagic shock. **a** In the absence of shock, neuromuscular recovery was near complete at 14 days following both 1 and 3 h of ischaemia. **b** In contrast in the presence of haemorrhagic shock, neuromuscular recovery following 3 h of ischaemia was similar to that following 6 hours. In the presence of haemorrhagic shock, only the 1-h ischaemia group demonstrates an upward inflection of recovery after 14 days.

useful information to surgical teams managing patients with ischaemic extremity vascular injury. Together, they argue against a casual approach, instead emphasizing the importance of expedited restoration of perfusion in order to improve the quality of limb salvage.

Temporary vascular shunt

Temporary vascular shunts represent an important adjunct to allow expedited restoration of flow in certain patterns of extremity vascular injury^{32,33}. In this scenario, a shunt is a flexible hollow tube that can be placed quickly to allow perfusion through, and distal to, the vascular injury site. It is left briefly (usually 2–6 h), after which it is removed and formal vessel repair undertaken. Eger and co-workers³⁴ were among the earliest to publish on the use of a temporary vascular shunt; the technique has increased in popularity in both civilian and military settings. Several reports have described the efficacy of a shunt as an effective adjunct,

including a report by Dawson *et al.*³⁵, which demonstrated that shunts can remain patent for up to 24 h, even in the absence of systemic anticoagulation. Additionally, Gifford *et al.*²⁹ used shunts to restore limb perfusion following increasing ischaemic intervals, confirming high patency rates without the use of heparin.

During the wars in Iraq and Afghanistan, the use of vascular shunts has been extensive, reported in up to one-third of proximal extremity vascular injuries^{32,36}. Taller and colleagues³⁷ demonstrated the unique value of the technique in a series of patients with a mean Injury Severity Score of 25 and Mangled Extremity Severity Score of 8. Temporary shunts were placed as a damage control measure to restore extremity perfusion while other life-threatening injuries were managed. The shunt remained in place while the patient was transferred to a higher level of care, where it was removed and definitive vascular repair performed. Using this adjunct and sequence of care, Taller *et al.*³⁷ reported an early (30 day) limb salvage rate of 100 per cent. Glass and co-workers³⁸ recently published a review of extremity injuries with both a vascular and an orthopaedic component, which showed favourable limb salvage rates with the use of a shunt as an initial adjunct to restore perfusion followed by fracture fixation. This study proposed an algorithm giving priority to the vascular component of the injury, advocating shunt placement followed by fracture fixation and then shunt removal with definitive vascular repair³⁸. Another study by Gifford *et al.*⁵ defined amputation-free survival at nearly 36 months following wartime vascular injury. The use of a shunt had no long-term adverse effects, but appeared to offer a limb salvage advantage in the most severely injured limbs. The majority of recent studies have supported the use of shunts as an adjunct to restore perfusion, and extend the window of opportunity for actual and functional limb salvage.

Fasciotomy

Raised pressure within the compartments of an injured extremity following reperfusion can cause mechanical injury to muscle and nerve, exacerbating the initial ischaemic insult³⁹. This can be avoided by ready application of prophylactic fasciotomy in high-risk limbs. Fasciotomy has been shown to be effective at preserving muscle contraction in a canine model, in a study that also examined the value of therapeutic reperfusion with mannitol and superoxide dismutase⁴⁰. The rate, effectiveness and timing of fasciotomy have been studied during the wars in Iraq and Afghanistan. Ritenour and colleagues⁶ emphasized the importance of prophylactic or early fasciotomy done at the time of the initial operation: delayed fasciotomy,

or fasciotomy that required revision after aeromedical evacuation, led to higher amputation and even mortality rates. This study also demonstrated that the anterior and posterior deep compartments of the leg were the most commonly omitted or missed during an incomplete initial fasciotomy. This finding is especially troubling given that these compartments contain the main neurovascular bundles of the leg.

Kragh and co-workers⁴¹ reported that fasciotomy rates increased significantly after tourniquets were issued with instructions for use to soldiers in 2005, a finding that may reflect increased survivorship of those with extremity vascular injury. In their study, the authors demonstrated that fasciotomy was more likely to be performed in soldiers with greater injury severity. This observation suggested adherence to practice guidelines and application of sound operative principles⁴¹. Although fasciotomy does have risks, it is an important surgical adjunct to improve neuromuscular recovery following vascular injury and reperfusion, supported by research and clinical observation.

Limb hypothermia

Induction of hypothermia has been successful in mitigating ischaemia–reperfusion injury in cardiac surgery. The mechanisms by which induced hypothermia protects against reperfusion injury have not been fully characterized; however, the benefit probably centres on the slowed metabolic rate and production of reactive oxygen species during and immediately after the ischaemia. Animal studies of regional limb cooling have demonstrated favourable effects on pH and lactate, and improved modulation of ATP^{42–44}. Functional outcomes of hypothermia in a rat model demonstrated that limbs cooled to 22° and 30°C (but not 35°C) during ischaemia had improved return of function compared with those that remained normothermic⁴⁵. Mowlavi *et al.*⁷ demonstrated in a rat model that cooling did not necessarily need to take place throughout the entire period of ischaemia; cooling during reperfusion alone was also beneficial. Cooling only during reperfusion resulted in increased muscle viability, less oedema and decreased expression of CD11b (a neutrophil marker). A separate but similar report in hamsters demonstrated benefits of regional limb cooling after inducing hypothermia throughout both the ischaemic and the reperfusion interval, resulting in inhibited leucocyte adherence in striated muscles⁴⁶. To date, regional limb hypothermia has not been viewed as translatable to injured patients who may have associated injuries, including coagulopathy, which could be made worse by cooling. The value of induced hypothermia as an adjunct to limit

reperfusion injury in cardiac surgery is well established and the technique should not be overlooked as an area of future research.

Ischaemic conditioning

Conditioning is based on the concept of optimizing the response of the extremity to ischaemia, and limiting the accumulation and release of reactive oxygen radical species at the time of reperfusion. It can be either preconditioning or postconditioning, depending on whether the manoeuvre takes place before or after the onset of ischaemia. Preconditioning consists of making the tissue ischaemic for short intervals before an expected ischaemic insult. Although there has been much research on preconditioning, this adjunct is less applicable to extremity injury because of the unpredictable nature of trauma. Although preconditioning methods are not intuitively applicable to vascular trauma, Zhao and co-workers^{47,48} determined in an animal model of coronary occlusion that the beneficial effects of preconditioning were similar to those of postconditioning.

Postconditioning can be accomplished by slow or limited reperfusion through the main inflow vessel before full or complete reperfusion, or by repeated episodes of partial reperfusion. Although the mechanisms of postconditioning have not been fully characterized, it has been shown to afford tissue protection through decreased reactive oxygen species and inflammatory markers^{8,49}. Postconditioning also downregulates tissue factor production, delays the washout of adenosine, and stimulates the formation of endogenous opioids and nitric oxide^{50,51}.

Anderson and colleagues⁸ and Wright and co-workers⁴⁹, in separate studies, showed the benefit of limiting the rate of reperfusion at the time of restoration of blood flow following ischaemia. Specifically, temporary or limited reperfusion resulted in less skeletal muscle injury and postreperfusion oedema than immediate, full restoration of flow. In a different small-animal hind limb model, postconditioning resulted in a reduction of inflammatory markers and reactive oxygen species⁵⁰. Postconditioning also preserves the myocardium in patients undergoing percutaneous coronary intervention⁵¹. In this study, postconditioning resulted in a reduction in creatinine kinase levels, increased myocardial perfusion and decreased infarct size.

Conditioning manoeuvres have shown promise in limiting the adverse consequences of reperfusion in the laboratory and in clinical settings. Furthermore, the techniques themselves (limited, partial reperfusion, or episodic bursts of reperfusion) are fairly easily applied following repair of an extremity vascular injury. As such,

these strategies hold promise in improving neuromuscular recovery after extremity vascular injury and should remain a focus of translational research effort.

Medical therapies

Hypertonic saline

Hypertonic saline is a safe fluid for prehospital resuscitation and in some cases decreases the incidence of acute respiratory distress syndrome, renal failure and coagulopathy⁵². Hypertonic saline solutions have a number of properties that make them attractive candidates as therapeutic reperfusion fluids. Specifically, they blunt the production of leucocyte endothelial adhesion molecules and increase the diameter of vessels in the microcirculation⁵³. In separate studies on patients with haemorrhagic shock, Bulger *et al.*⁵⁴ and Rizoli *et al.*⁵⁵ showed that resuscitation with hypertonic saline modulated the inflammatory response favourably.

Translational animal research has also shown favourable effects of hypertonic saline on the inflammatory response. Corso and colleagues⁵⁶ used a shock model in rats to demonstrate that hypertonic saline reduced leucocyte accumulation in the liver. Attuwaybi *et al.*⁵⁷ showed that the use of hypertonic saline prevented inflammation and injury, and impaired gut transit after intestinal ischaemia and reperfusion by inducing the enzyme haem oxygenase 1. In an experimental model of limb ischaemia–reperfusion, rats treated with hypertonic saline before tourniquet release had a significant decrease in myeloperoxidase content, less skeletal muscle oedema and an improvement in the functional properties of the skeletal muscle⁹. These and other studies demonstrate that hypertonic saline has the potential to reduce the adverse effects of reperfusion following extremity vascular injury with ischaemia. A protocol consisting of hypertonic saline administration with slow reperfusion following vascular repair is warranted.

Statins

Pretreatment with 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA reductase inhibitors, or statins) has been shown in the cardiac literature to decrease myocardial infarct size through downstream effects of increasing adenosine and activation of eNOS and the reperfusion injury signalling kinase pathway^{58–60}. Animal studies have also evaluated the use of statins for mitigating limb ischaemia–reperfusion injury. Most of this work focused on oral statins given before an ischaemic limb injury, although statins have also been given by the intra-arterial route at

the time of vascular repair and reperfusion (therapeutic reperfusion).

Cowled *et al.*¹⁰ demonstrated that pretreatment of animals with simvastatin decreased neutrophil sequestration and skeletal muscle inflammation in a rat model of hind limb ischaemia–reperfusion. In a separate study, Dillon and colleagues⁶¹ demonstrated that pretreatment with pravastatin attenuated tourniquet-induced ischaemic skeletal muscle damage in rats, as measured by oedema, leucocyte sequestration and electrical properties⁶¹. The physical properties of the statin medications make them difficult to formulate for intra-arterial administration at the time of vascular repair; however, preliminary studies using this method suggest that statins offer a protective effect on skeletal muscle and peripheral nerves (unpublished data).

The unpredictable nature of extremity vascular injury with ischaemia diminishes the ability to translate many of the studies showing the effectiveness of pre-dosing with statins. People likely to suffer an extremity vascular injury are not likely to be taking statins, because they are usually younger. In order to exploit their beneficial effects in the setting of extremity ischaemia–reperfusion, additional research on formulations of statins for intra-arterial or intramuscular administration is necessary.

Ethyl pyruvate

Ethyl pyruvate has been studied as a modality to mitigate ischaemia–reperfusion injury. It is a derivative of pyruvate, the endproduct of glycolysis and the starting point for the tricarboxylic acid cycle⁶². Ethyl pyruvate has the properties of an endogenous antioxidant and anti-inflammatory agent, including decreasing the activity of iNOS, tumour necrosis factor, cyclo-oxygenase 2 and interleukin 6⁶². Ethyl pyruvate has been shown to mitigate the damaging effects of ischaemia–reperfusion in animal models, including those of myocardial ischaemia–reperfusion. In separate studies, Jang and colleagues⁶³ and Woo *et al.*⁶⁴ showed in rats that pretreatment with ethyl pyruvate resulted in decreased inflammatory markers of ischaemia as well as a decrease in infarct size and improved cardiac function.

Dong and co-workers⁶⁵ recently reported that, in a swine model of shock, inclusion of ethyl pyruvate during resuscitation resulted in decreased circulating markers of inflammation and less organ damage. A recent study from Crawford *et al.*¹¹ reported that in a murine model of limb ischaemia ethyl pyruvate pretreatment resulted in a lower percentage of injured muscle fibres. It also decreased inflammatory markers and reduced tissue thrombosis⁶⁵. Ethyl pyruvate is a promising medication that appears to modulate the effects of ischaemia–reperfusion injury.

Conclusion

Extremity vascular injury with ischaemia is an increasingly common pattern of injury. Decisions related to treatment priorities and methods of reperfusion should take into consideration recent translational research showing evidence for specific surgical and medical adjuncts aimed at improving neuromuscular recovery.

Acknowledgements

The viewpoints expressed in this manuscript are those of the authors and do not reflect the official position of the United States Air Force or Department of Defense.

Disclosure: The authors declare no conflict of interest.

References

- White JM, Stannard A, Burkhardt GE, Eastridge BJ, Blackburne LH, Rasmussen TE. The epidemiology of vascular injury in the wars in Iraq and Afghanistan. *Ann Surg* 2011; **253**: 1184–1189.
- Clouse WD, Rasmussen TE, Peck MA, Eliason JL, Cox MW, Bowser AN *et al.* In-theater management of vascular injury: 2 years of the Balad Vascular Registry. *J Am Coll Surg* 2007; **204**: 625–632.
- Stannard A, Brown K, Benson C, Clasper J, Midwinter M, Tai NR. Outcome after vascular trauma in a deployed military trauma system. *Br J Surg* 2011; **98**: 228–234.
- Hancock HM, Stannard A, Burkhardt GE, Williams K, Dixon P, Cowart J *et al.* Hemorrhagic shock worsens neuromuscular recovery in a porcine model of hind limb vascular injury and ischemia/reperfusion. *J Vasc Surg* 2011; **53**: 1052–1062.
- Gifford SM, Aidinian G, Clouse WD, Fox CJ, Porras CA, Jones WT *et al.* Effect of temporary vascular shunting on extremity vascular injury: an outcome analysis from the Global War on Terror vascular injury initiative. *J Vasc Surg* 2009; **50**: 549–555.
- Ritenour AE, Dorlac WC, Fang R, Woods T, Jenkins DH, Flaherty SF *et al.* Complications after fasciotomy revision and delayed compartment release in combat patients. *J Trauma* 2008; **64**: S153–S161.
- Mowlavi A, Neumeister MW, Wilhelmi BJ, Song YH, Suchy H, Russell RC. Local hypothermia during early reperfusion protects skeletal muscle from ischemia–reperfusion injury. *Plast Reconstr Surg* 2003; **111**: 242–250.
- Anderson RJ, Cambria R, Kerr J, Hobson RW II. Sustained benefit of temporary limited reperfusion in skeletal muscle following ischemia. *J Surg Res* 1990; **49**: 271–275.
- Dillon JP, Laing AJ, Chandler JR, Shields CJ, Wang JH, McGuinness A *et al.* Hypertonic saline reduces skeletal muscle injury and associated remote organ injury following ischemia reperfusion injury. *Acta Orthop* 2008; **79**: 703–707.

- 10 Cowled PA, Khanna A, Laws PE, Field JB, Varelias A, Fitridge RA. Statins inhibit neutrophil infiltration in skeletal muscle reperfusion injury. *J Surg Res* 2007; **14**: 267–276.
- 11 Crawford RS, Albadawi H, Atkins MD, Jones JJ, Conrad MF, Austen WG Jr *et al*. Postischemic treatment with ethyl pyruvate prevents adenosine triphosphate depletion, ameliorates inflammation, and decreases thrombosis in a murine model of hind-limb ischemia and reperfusion. *J Trauma* 2011; **70**: 103–110.
- 12 Malan E, Tattoni G. Physio- and anatomic-pathology of acute ischemia of the extremities. *J Cardiovasc Surg (Torino)* 1963; **4**: 212–225.
- 13 Labbe R, Lindsay T, Walker PM. The extent and distribution of skeletal muscle necrosis after graded periods of complete ischemia. *J Vasc Surg* 1987; **6**: 152–157.
- 14 Scully RE, Hughes CW. The pathology of ischemia of skeletal muscle in man; a description of early changes in muscles of the extremities following damage to major peripheral arteries on the battlefield. *Am J Pathol* 1956; **32**: 805–829.
- 15 Petrusek PF, Homer-Vanniasinkam S, Walker PM. Determinants of ischemic injury to skeletal muscle. *J Vasc Surg* 1994; **19**: 623–631.
- 16 Chan RK, Austen WG Jr, Ibrahim S, Ding GY, Verna N, Hechtman HB *et al*. Reperfusion injury to skeletal muscle affects primarily type II muscle fibers. *J Surg Res* 2004; **122**: 54–60.
- 17 Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovasc Surg* 2002; **10**: 620–630.
- 18 Menger MD, R cker M, Vollmar B. Capillary dysfunction in striated muscle ischemia/reperfusion: on the mechanisms of capillary ‘no-reflow’. *Shock* 1997; **8**: 2–7.
- 19 Gillani S, Cao J, Suzuki T, Hak DJ. The effect of ischemia reperfusion injury on skeletal muscle. *Injury* 2011; [Epub ahead of print].
- 20 Yassin MM, Harkin DW, Barros D’Sa AA, Halliday MI, Rowlands BJ. Lower limb ischemia–reperfusion injury triggers a systemic inflammatory response and multiple organ dysfunction. *World J Surg* 2002; **26**: 115–121.
- 21 Carden DL, Granger DN. Pathophysiology of ischaemia–reperfusion injury. *J Pathol* 2000; **190**: 255–266.
- 22 Khanna A, Cowled PA, Fitridge RA. Nitric oxide and skeletal muscle reperfusion injury: current controversies (research review). *J Surg Res* 2005; **128**: 98–107.
- 23 Hargens AR, Schmidt DA, Evans KL, Gonsalves MR, Cologne JB, Garfin SR *et al*. Quantitation of skeletal-muscle necrosis in a model compartment syndrome. *J Bone Joint Surg Am* 1981; **63**: 631–636.
- 24 Kosir R, Moore FA, Selby JH, Cocanour CS, Kozar RA, Gonzalez EA *et al*. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *J Trauma* 2007; **63**: 268–275.
- 25 Debakey ME, Simeone FA. Battle injuries of the arteries in World War II: an analysis of 2471 cases. *Ann Surg* 1946; **123**: 534–579.
- 26 Hughes CW. Arterial repair during the Korean War. *Ann Surg* 1958; **147**: 555–561.
- 27 Rich NM, Baugh JH, Hughes CW. Acute arterial injuries in Vietnam: 1000 cases. *J Trauma* 1970; **10**: 359–369.
- 28 Rasmussen TE, Clouse WD, Jenkins DH, Peck MA, Eliason JL, Smith DL. Echelons of care and the management of wartime vascular injury: a report from the 332nd EMDG/Air Force Theater Hospital, Balad Air Base, Iraq. *Perspect Vasc Surg Endovasc Ther* 2006; **18**: 91–99.
- 29 Gifford SM, Eliason JL, Clouse WD, Spencer JR, Burkhardt GE, Propper BW *et al*. Early *versus* delayed restoration of flow with temporary vascular shunt reduces circulating markers of injury in a porcine model. *J Trauma* 2009; **67**: 259–265.
- 30 Burkhardt GE, Gifford SM, Propper BW, Spencer JR, Rasmussen TE. A large animal survival model (*Sus scrofa*) of extremity ischemia/reperfusion and neuromuscular outcomes assessment: a pilot study. *J Trauma* 2010; **69**: S146–153.
- 31 Burkhardt GE, Gifford SM, Propper BW, Spencer JR, Williams K, Jones L *et al*. The impact of ischaemic interval on neuromuscular recovery in a porcine (*Sus scrofa*) survival model of extremity vascular injury. *J Vasc Surg* 2011; **53**: 165–173.
- 32 Rasmussen TE, Clouse WD, Jenkins DH, Peck MA, Eliason JL, Smith DL. The use of temporary vascular shunts as a damage control adjunct in the management of wartime vascular injury. *J Trauma* 2006; **61**: 15–21.
- 33 Hancock HM, Rasmussen TE, Walker AJ, Rich NM. History of temporary intra-vascular shunts in the management of vascular injury. *J Vasc Surg* 2010; **52**: 1405–1409.
- 34 Eger M, Golcman L, Goldstein A, Hirsch M. The use of a temporary shunt in the management of arterial vascular injuries. *Surg Gynecol Obstet* 1971; **132**: 67–70.
- 35 Dawson DL, Putnam AT, Light JT, Ihnat DM, Kissinger DP, Rasmussen TE *et al*. Temporary arterial shunts to maintain limb perfusion after arterial injury: an animal study. *J Trauma* 1999; **47**: 64–71.
- 36 Woodward EB, Clouse WD, Eliason JE, Peck MA, Bowser AN, Cox MW *et al*. Penetrating femoropopliteal injury during modern warfare: experience of the Balad Vascular Registry. *J Vasc Surg* 2008; **47**: 1259–1265.
- 37 Taller J, Kamdar JP, Greene JA, Morgan RA, Blankenship CL, Dabrowski P *et al*. Temporary vascular shunts as initial treatment of proximal extremity vascular injuries during combat operations: the new standard of care at Echelon II facilities? *J Trauma* 2008; **65**: 595–603.
- 38 Glass GE, Pearse MF, Nanchahal J. Improving lower limb salvage following fractures with vascular injury: a systematic review and new management algorithm. *J Plast Reconstr Aesthet Surg* 2009; **62**: 571–579.
- 39 Percival TJ, White JM, Ricci MA. [Trauma Issue] Compartment syndrome in the setting of vascular injury. *Perspect Vasc Surg Endovasc Ther* 2011; **23**: 119–124.
- 40 Ricci MA, Graham AM, Corbisiero R, Baffour R, Mohamed F, Symes JF. Are free radical scavengers beneficial

- in the treatment of compartment syndrome after acute arterial ischemia? *J Vasc Surg* 1989; **9**: 244–250.
- 41 Kragh JF Jr, Wade CE, Baer DG, Jones JA, Walters TJ, Hsu JR *et al.* Fasciotomy rates in operations Enduring Freedom and Iraqi Freedom: association with injury severity and tourniquet use. *J Orthop Trauma* 2011; **25**: 134–139.
- 42 Irving GA, Noakes TD. The protective role of local hypothermia in tourniquet-induced ischaemia of muscle. *J Bone Joint Surg Br* 1985; **67**: 297–301.
- 43 Osterman AL, Heppenstall RB, Sapega AA, Katz M, Chance B, Sokolow D. Muscle ischemia and hypothermia: a bioenergetic study using ³¹phosphorus nuclear magnetic resonance spectroscopy. *J Trauma* 1984; **24**: 811–817.
- 44 Wright JG, Kerr JC, Valeri CR, Hobson RW. Regional hypothermia protects against ischemia–reperfusion injury in isolated canine gracilis muscle. *J Trauma* 1988; **28**: 1026–1031.
- 45 Gürke L, Marx A, Sutter PM, Stierli P, Harder F, Heberer M. Function of fast- and slow-twitch rat skeletal muscle following ischemia and reperfusion at different intramuscular temperatures. *Eur Surg Res* 2000; **32**: 135–141.
- 46 Thorlacius H, Vollmar B, Westermann S, Törkvist L, Menger MD. Effects of local cooling on microvascular hemodynamics and leukocyte adhesion in the striated muscle of hamsters. *J Trauma* 1998; **45**: 715–719.
- 47 Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA *et al.* Inhibition of myocardial injury by ischemic preconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 2003; **285**: H579–H588.
- 48 Zhao ZQ, Vinten-Johansen J. Postconditioning: reduction of reperfusion-induced injury. *Cardiovasc Res* 2006; **70**: 200–211.
- 49 Wright JG, Fox D, Kerr JC, Valeri CR, Hobson RW II. Rate of reperfusion blood flow modulates reperfusion injury in skeletal muscle. *J Surg Res* 1988; **44**: 754–763.
- 50 Gyurkovics E, Aranyi P, Stangl R, Onody P, Ferreira G, Lotz G *et al.* Postconditioning of the lower limb–protection against the reperfusion syndrome. *J Surg Res* 2011; **169**: 139–147.
- 51 Xue F, Yang X, Zhang B, Zhao C, Song J, Jiang T *et al.* Postconditioning the human heart in percutaneous coronary intervention. *Clin Cardiol* 2010; **33**: 439–444.
- 52 Mattox KL, Maningas PA, Moore EE, Mateer JR, Marx JA, Aprahamian C *et al.* Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The USA Multicenter Trial. *Ann Surg* 1991; **213**: 482–491.
- 53 Pascual JL, Khwaja KA, Chaudhury P, Christou NV. Hypertonic saline and the microcirculation. *J Trauma* 2003; **54**(Suppl): S133–S140.
- 54 Bulger EM, Cuschieri J, Warner K, Maier RV. Hypertonic resuscitation modulates the inflammatory response in patients with traumatic hemorrhagic shock. *Ann Surg* 2007; **245**: 635–641.
- 55 Rizoli SB, Rhind SG, Shek PN, Inaba K, Filips D, Tien H *et al.* The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. *Ann Surg* 2006; **243**: 47–57.
- 56 Corso CO, Okamoto S, Rüttinger D, Messmer K. Hypertonic saline dextran attenuates leukocyte accumulation in the liver after hemorrhagic shock and resuscitation. *J Trauma* 1999; **46**: 417–423.
- 57 Attuwaybi B, Kozar RA, Gates KS, Moore-Olufemi S, Sato N, Weisbrodt NW *et al.* Hypertonic saline prevents inflammation, injury, and impaired intestinal transit after gut ischemia/reperfusion by inducing heme oxygenase 1 enzyme. *J Trauma* 2004; **56**: 749–758.
- 58 Ye Y, Perez-Polo JR, Birnbaum Y. Protecting against ischemia–reperfusion injury: antiplatelet drugs, statins, and their potential interactions. *Ann N Y Acad Sci* 2010; **1207**: 76–82.
- 59 Vilahur G, Casaní L, Peña E, Duran X, Juan-Babot O, Badimon L. Induction of RISK by HMG-CoA reductase inhibition affords cardioprotection after myocardial infarction. *Atherosclerosis* 2009; **206**: 95–101.
- 60 Lardizabal JA, Deedwania PC. The anti-ischemic and anti-anginal properties of statins. *Curr Atheroscler Rep* 2011; **13**: 43–50.
- 61 Dillon JP, Laing AJ, Chandler JR, Wang JH, McGuinness A, Redmond HP. Pravastatin attenuates tourniquet-induced skeletal muscle ischemia reperfusion injury. *Acta Orthop* 2006; **77**: 27–32.
- 62 Fink MP. Ethyl pyruvate: a novel anti-inflammatory agent. *J Intern Med* 2007; **261**: 349–362.
- 63 Jang IS, Park MY, Shin IW, Sohn JT, Lee HK, Chung YK. Ethyl pyruvate has anti-inflammatory and delayed myocardial protective effects after regional ischemia/reperfusion injury. *Yonsei Med J* 2010; **51**: 838–844.
- 64 Woo YJ, Taylor MD, Cohen JE, Jayasankar V, Bish LT, Burdick J *et al.* Ethyl pyruvate preserves cardiac function and attenuates oxidative injury after prolonged myocardial ischemia. *J Thorac Cardiovasc Surg* 2004; **127**: 1262–1269.
- 65 Dong W, Cai B, Peña G, Pisarenko V, Vida G, Doucet D *et al.* Ethyl pyruvate prevents inflammatory responses and organ damage during resuscitation in porcine hemorrhage. *Shock* 2010; **34**: 205–213.