TRAUMA HEMOSTASIS AND OXYGENATION RESEARCH (THOR) NETWORK POSITION PAPER ON THE ROLE OF HYPOTENSIVE RESUSCITATION AS PART OF REMOTE DAMAGE CONTROL RESUSCITATION

In a casualty with life-threatening hemorrhage, shock should be reversed as soon as possible using a blood-based hemostatic resuscitation fluid. Whole blood is preferred to blood components. As a part of this hemostatic resuscitation, the initial systolic blood pressure (SBP) target should be 100 mm Hg. Remote Damage Control Resuscitation (RDCR) has previously been defined as the prehospital application of damage control resuscitation. In RDCR, it is vital for higher echelon care providers to receive a casualty with sufficient physiologic reserve to survive definitive surgical hemostasis and aggressive resuscitation. The combined use of blood-based resuscitation and limiting SBP is believed to be effective in promoting hemostasis and reversing shock

Shock is a state of oxygen delivery that is inadequate to meet vital organ metabolic demands. The depth and magnitude of shock is referred to as the oxygen debt. Rapid accumulation of critical levels of oxygen debt, coupled with a failure to resolve the debt, results in coagulopathy and organ dysfunction or failure that make ongoing resuscitation increasingly more difficult and eventually impossible. The assessment of shock includes evaluating a combination of vital signs and physical examination findings (mentation, pulse rate and quality, respiration rate, temperature, systolic blood pressure, shock index), together with the measurement of metabolic acidosis (base deficit and/or lactate) when available. Upon admission to advanced levels of care, a SBP of 100 or high has been associated with improved survival. As a result, it is our position that resuscitation of patients at risk of

traumatic hemorrhagic shock aim for a SBP of 100 mmHg, recognizing that a range of 90 mmHg to 110 mmHg may be more practical.

Situational Guidance:

1. With a SBP reading below 100 mmHg, start or continue steady infusion of blood products.
2. With a SBP reading between 100-110 mmHg, slowly reduce infusion rate to aim for an SBP of 100 mmHg.
3. With a SBP reading greater than 110 mmHg reduce infusion to keep venous access patent.

Points:

- This recommendation reflects the OPINION of the THOR Network and is based on the interpretation of existing evidence applied to physiologic principles, and based on clinical experience and expertise. It is not a replacement for clinical judgement in the management of individual patients.
- This opinion relates specifically to prehospital resuscitation of patients without rapid access to hospital and/ or surgical care.
- This recommendation is applicable to the titration of blood product administration only, related to signs of shock, including systolic blood pressure. It is NOT a holistic overview of the treatment of hemorrhagic shock. Specifically, fluid replacement does not detract from hemorrhage control as a clinical priority.
- Blood products are optimal for the resuscitation of hemorrhagic shock. The overuse of clear fluids (crystalloids and colloids) for patients with hemorrhagic shock may worsen outcome. (See section 3, 9.1)

- Evidence suggests that a SBP below 100 mmHg is associated with poor outcomes and an increase in oxygen debt (see section 6).
- An induced SBP over 110 mmHg should be avoided as this may initially worsen hemorrhage. (See section 4).
- Blood should be administered at a steady rate and not pressure infused, in order to avoid a rapid and uncontrolled rise in SBP. (See section 3.3 and 9.3).
- The resuscitation of casualties suffering hemorrhagic shock should begin immediately as soon as blood products and appropriately trained personnel are available. Ideally, resuscitation should not be delayed for more than 30min from the time of injury, regardless of the fluid available. (see section 8).
- In a casualty with a severe traumatic brain injury the goal SBP is 110 mmHg.
- In a casualty with a severe brain injury and hemorrhagic shock, the hemorrhage should be treated as a priority over the brain injury.

1. Introduction

Hypotensive resuscitation for patients suffering from traumatic hemorrhagic shock is a resuscitation strategy within the paradigm of *Damage Control Resuscitation (DCR),*[1] in which fluid administration is restricted until the source of the bleeding has been controlled . The perceived advantage of this strategy is that it limits bleeding from the injury site, and avoids high blood pressures dislodging any clot formed at the injury. On the other hand, an under-resuscitated patient who has ongoing traumatic bleeding will suffer from increasing shock, caused by hypoperfusion, resulting in a deadly spiral that includes endotheliopathy, coagulopathy, acidosis, and hypothermia, eventually leading to "blood failure"[2] and multiple organ dysfunction.

Current DCR principles aim to balance these competing concepts and prevent this deadly spiral by advocating early compressible hemorrhage control, coupled with hypotensive resuscitation until it is possible to obtain surgical control of bleeding; avoidance of the overuse of crystalloids and colloids; correction of acidosis, hypothermia, and hypocalcemia; and hemostatic resuscitation (HR).[3] HR involves early and aggressive use of blood products for the management of traumatic hemorrhagic shock to prevent the deleterious effects of primary and secondary coagulopathy. The degree to which the tension between reducing the risk of re-bleeding and adequate resuscitation of shock is successfully managed in DCR requires careful re-assessment and sound judgment.

The application of damage control resuscitation principles in the prehospital setting, when access to hospital is slow or delayed (>60 minutes from point of injury), is termed *Remote Damage Control Resuscitation (RDCR).*[3] *The concept of RDCR has been proposed by the Trauma Hemostasis Oxygenation Research Network (THOR). The THOR Network is a multidisciplinary group of clinical, translational, and basic science investigators with a common interest in improving outcomes and safety in patients with severe traumatic injury.*[3]. *The network's mission is to reduce the morbidity and mortality from traumatic hemorrhagic shock, in the prehospital phase of resuscitation through education, training, and research.*

Like many guidelines that are applied to acute situations such as trauma, the evidence for or against any particular intervention is incomplete. Often, the evidence that does exist is then extrapolated far beyond the boundaries of its validity. This is particularly the case when applying in-hospital evidence to prehospital guidelines, especially when clinical timelines are prolonged.[3] Therefore, expert opinion and consensus often form the basis of such guidelines.

This review aims to challenge the current concept of hypotensive resuscitation when applied to RDCR in either a civilian or military situation, to suggest targets for resuscitation in this situation, and to act as a call for research into specific questions. Since the evidence is unclear, recommendations made in this review should be interpreted as expert opinion that is open to challenge and interpretation. These opinions should be examined scientifically by future, specific research and altered according to emerging evidence.

2. **Evolution of the hypotensive philosophy**

Post-injury hemorrhagic shock remains the major cause of morbidity and mortality in patients suffering major trauma.[4,5] It has long been advocated that management of these patients should include hemorrhage control when bleeding is ongoing, combined with intravascular fluid volume replacement to restore organ perfusion. Once organ perfusion falls below a critical level, aerobic metabolism cannot be supported, despite oxygen extraction from the blood being maximized, and tissues convert to anaerobic metabolism. If this oxygen deficit persists then an 'oxygen debt' develops.[6] Oxygen debt is a function of the severity of shock and the time spent in shock. To prevent organ injury at the cellular level, this oxygen debt must eventually be repaid, by restoring or increasing the oxygen delivery to the tissues.

Early restoration of near-normal blood pressures was advocated for many years to minimize the oxygen debt.[7] However, as long as one hundred years ago, it was suggested that the elevation of blood pressure to near normal levels by fluid administration may disrupt the formation of nascent clots at bleeding vessels and risks worsening bleeding.[8] Despite these concerns, advances in the understanding of the relationships between traumatic hemorrhage, hypovolemic shock and renal failure led to an increase in emphasis on restoration of circulating volume, leading to a more liberal fluid resuscitation strategy dominating practice until the start of the 21st century.[9,10]

Although the use of liberal fluid resuscitation strategies for patients in hypovolemic shock had become widely accepted by the late 20th century, the evidence to support their use was not strong. Aggressive crystalloid resuscitation of casualties in the Vietnam War, while believed to have saved many lives and reduced the incidence of renal failure, was also recognized to have caused many cases of Acute Respiratory Distress Syndrome (ARDS) or "Da Nang lung" which carried a significant morbidity and mortality. Other syndromes

associated with excess crystalloid use, such as abdominal compartment syndrome, became increasingly recognized.[11] Evidence began to emerge in the 1980s and 1990s that fluid resuscitation with clear fluids, using lower volumes and targeting lower arterial blood pressures, was associated with improved outcomes in patients with hypovolemic shock.

In the 1990's and early 2000's the concept of using a lower-than-normal blood pressure was investigated and a strategy of hypotensive resuscitation for bleeding trauma patients was widely adopted, especially in military situations.[12] Damage control surgery was a concept that evolved into damage control resuscitation (DCR) during the early part of the 2000's.[1,13] Hypotensive resuscitation has been a core principle of DCR.

2.1. DCR vs RDCR

It is important to highlight differences in the strategies of patient management inherent in prehospital and in in-hospital phases of care. Very different monitoring capabilities and treatment options exist, including the availability of anesthesia and immediate surgery. Consequently, a difference in the approach to hypotensive resuscitation is required. DCR principles are applied mainly to hospitalized patients under general anesthesia, while RDCR, in most parts of the world, is applied to pre-hospital patients who are awake and spontaneously breathing, resulting in a significant difference in systemic vascular resistance.

Anesthetized patients are vasodilated by anesthetic drugs and opioids, and often have advanced hemodynamic monitoring, a multidisciplinary team caring for them and ongoing surgery (if required). This allows the in-hospital provider to maintain a higher cardiac output while keeping SVR and pressure targets low, thus maximizing oxygen delivery to the tissues. This approach is nearly impossible to achieve in the pre-hospital setting.

3. Strategies to deliver hypotensive resuscitation

Hypotensive resuscitation aims to target lower-than-normal SBP (typically 80 to 90 mmHg) during the fluid resuscitation of patients with hypovolemia. In order to deliver hypotensive resuscitation a combination of three approaches is typically adopted:

- Late use of fluids
- Restrictive volume administration
- Hypotensive targets

3.1. Late vs early fluid resuscitation

In a large randomized controlled trial, Bickell et al.[14] found that in 598 shocked patients suffering penetrating trauma, the relative risk of death was 1.26 (95% CI 1.00-1.58) higher in the group that received early (pre-hospital and pre OR) rather than delayed (in-hospital) crystalloid infusions. However, the increased mortality was only shown in the subgroup with pericardial tamponade. Schreiber et al.[15] conducted a prospective randomized pilot to test the feasibility and safety of a controlled resuscitation strategy (CR) (250ml bolus of normal saline if SBP (70mmHg) or standard resuscitation (SR) (2000ml bolus of normal saline if BP <90 mmHg) initiated in a prehospital setting. There was no difference in admission mortality (adjusted odds ratio 0.39 [95% CI 0.12, 1.26]) or SBP (105mmHg vs. 98.7mmHg, difference 6.3 mmHg (95% CI -3.3, 15.9)). Total pre-hospital time was 41 and 42.7 mins respectively.

While these two studies might initially appear to support a delay in fluid resuscitation for hemorrhagic shock, they can only be generalized to mature trauma systems with very short prehospital times (< 60 minutes in Bickell's study, < 45 minutes in Schreiber's study) and

access to rapid hospital treatment that included surgery. Furthermore, both trials relied on a crystalloid based resuscitation, rather than blood product based resuscitation.

Until recently, volume replacement was undertaken utilizing crystalloid or colloid solutions. Over recent years the use of blood products has been adopted as part of the hemostatic resuscitation (HR) principle in DCR and RDCR.[10] Although a clear benefit in outcomes attributable to pre-hospital transfusion alone is currently difficult to prove,[16] it has been argued that this development has been instrumental in improving patient outcomes and reducing trauma-related coagulopathy.[17] Historical data and opinion from WWI and WWII conclude that blood is the preferred resuscitation fluid.[18,19] This is discussed further in section 9.1.

3.2. Restrictive vs liberal volume resuscitation

While doubt was cast on the benefits of early administration of fluid in hemorrhagic shock, at around the same time evidence began to emerge that a lower overall volume of fluid used in the resuscitation phase may confer survival benefits. Dunham et al. [20] studied 36 hypotensive trauma patients and demonstrated a relative risk of death of 0.8 (95% CI 0.28-2.29) in those receiving a restrictive fluid regime. More recently, Duke et al.[21] retrospectively studied 307 patients with penetrating torso trauma who received restrictive (<150mls) or standard (>150mls) crystalloid fluid before arrival at hospital. The restrictive fluid group demonstrated lower odds of death (OR 0.69 (95% CI 0.37-0.91)). These retrospective studies should be interpreted with caution, due to the lack of adjustment of confounding factors on mortality.

3.3. Hypotensive vs. normotensive resuscitation

Other studies have examined the effect of targeting lower arterial pressures when resuscitating trauma patients with fluid. A number of animal studies have examined this question using ovine,[22] porcine [23] and rodent [24-26] models, demonstrating that hypotension reduces blood loss and mortality. It should be noted, however, that the models of hemorrhage often employed in animal studies were the ones most sensitive to re-bleeding, e.g. a lesion in a major artery and/or large volumes of crystalloid/colloid given immediately after the vascular lesion, and/or short experimental durations. Additionally, these animal models were conducted under anesthesia with the consequential differences in vascular resistance and regional blood flow associated with anesthetic-induced vasodilatation. Furthermore, animals are generally hypercoagulable when compared to humans. Despite these limitations, collectively these studies do provide compelling evidence that very aggressive and very early resuscitation, principally with clear fluids, is detrimental. As such, they are a very useful starting point. However, in order to follow experimental protocol, these studies often required large volumes to be transfused at rapid rates. The effect of this in one landmark study was that re-bleeding correlated best with pulse pressure, not systolic blood pressure.[27] Moreover, not all animals experienced re-bleeding after volume loading. Some required infusion of norepinephrine to reach systolic blood pressures well above 120mmHg in order to trigger re-bleeding. The volumes, doses and rates required to achieve the protocol were not commensurate with clinical practice at the time, and certainly not now. The conclusions from these animal studies should not be extended beyond the limits of the evidence e.g. to support recommendations that are not time-bound or do not take into account recent developments in resuscitation practice such as early use of blood products.

Clinical studies have initially found it more challenging to demonstrate clear benefits of hypotensive resuscitation. Dutton et al.[28] published a study of 110 hypotensive trauma

patients with presumed hemorrhagic shock who, following arrival in hospital, were randomized to receive fluid resuscitation to a 'hypotensive', or a more conventional blood pressure. No difference in mortality could be demonstrated between the two groups, although the mean systolic blood pressures of the two groups were calculated as 100mmHg and 114mmHg respectively (rather than the intended 70mmHg and >100mmHg). More recently, Morrison et al.[29] published the preliminary findings of a prospective randomized control trial of in-hospital trauma patients with hemorrhagic shock. This examined the initial 90 trauma patients with hemorrhagic shock recruited in a study and randomized to receive intra-operative resuscitation targeting mean arterial blood pressures of 50mmHg or 65mmHg. The hypotensive group had reduced blood loss and a tendency towards lower mortality. While the mean values for mean arterial pressure in the two groups were not statistically different, the *intent* to achieve a certain clinical endpoint is what matters to clinicians. The study was terminated early due to insufficient clinical equipoise and futility.[30]

No large-scale randomized control trial has shown any benefit from hypotensive resuscitation in trauma. A recent Cochrane systematic review highlighted this uncertainty.[31] It also remains unclear whether the restrictive fluid therapy approach might be beneficial due to less crystalloid use or due to hypotension itself. There is also published evidence drawing attention to some of the potential risks attached to hypotensive resuscitation with regards to hypoperfusion and end organ damage[32] although some animal data disputes whether this is significant.[33]

Overall, no strong evidence exists that any of these three strategies can be applied universally to bleeding trauma patients, and no human data exist to guide the duration of a hypotensive strategy. Despite the lack of a strong evidence base, presumably due to the intuitive appeal of

potentially not worsening hemorrhage (while ignoring the potential adverse effects of prolonged hypo-perfusion), the concept of early hypotensive resuscitation for bleeding patients has been adopted in many national trauma guidelines and has entered widespread practice as a result.[34,35] Hypotensive resuscitation guidelines may be applicable to mature trauma systems with short prehospital times, rapid access to surgery and when only crystalloids are used as a prehospital resuscitation fluid. This is not the case in many parts of the world, including large parts of rural Europe, North America, Australasia, and particularly in a military context.

4. Defining an appropriate blood pressure target for resuscitation

When defining a blood pressure target, clinicians must consider a lower and an upper limit. Defining a lower limit has even less evidence that defining an upper limit, especially in a nonanesthetized patient.

As long ago as 1945 Emerson et al.[36] studied 112 battle casualties presenting to a field hospital. Fifty-seven had additional blood volume measurements made. They found that mortality in those arriving in severe shock (SBP<85 mmHg, n= 57) was 35%, whereas those arriving with a SBP >85 mmHg (n=55) was 11%. Of those who died and had additional blood volume measurements (n=13) some assessment of the factors leading to death were made. Two of these cases had extremity injuries, one from a through-and-through gunshot wound to the thigh, and one open bilateral lower limb fractures. Both of these cases should have been amenable to external hemorrhage control. The striking feature of both of these patients was the extended pre-hospital time lines (7 hours and 6 hours from the time of injury) with admission systolic pressures of 50mmHg and 60 mmHg respectively. Despite "adequate" volume resuscitation with blood, they never recovered from shock.

The conclusions from these two cases was *"These patients failed to respond to adequate shock treatment, although in neither case could this failure be attributed to lack of adequate transfusion therapy or to the presence of infection. The sequence of events suggests that failure of shock therapy in these cases is related to irreversible changes in the cardiovascular system resulting from prolonged tissue anoxia."*

This observation would suggest that 85mmHg would be too low to be the lower limit for a prolonged period. In the absence of any evidence, it is the authors opinion that the absolute lower limit of resuscitation should be the currently-accepted level of 80-90 mmHg, although this in itself may well be too low and a higher target of 100 mmHg is more appropriate in order to ensure that 90mm Hg is never breached.

Little more evidence is available to support the definition of an upper limit. In 2007 Eastridge et al.[37] analyzed 871 000 patients from the U.S. national trauma data bank. Severe TBI was excluded. These authors correlated mortality and admission base deficit with admission SBP. Baseline mortality was <2.5%. However, the slope of the graph changed at 110mm Hg such that below 110 mmHg there was a 4.8% increase in mortality for every 10 mmHg drop in SBP. A similar inflection point for base deficit appeared at 118mm Hg. Their conclusions were that "a SBP ≤110 mmHg is a more clinically relevant definition of hypotension and shock than is 90 mmHg." A similar finding was made in a paper from the UK by Hasler et al.,[38] who examined 48 000 patients from the UK trauma registry suffering from blunt trauma. These authors found that the odds of dying increased below a SBP of 110 mmHg, and had doubled below a SBP of 100 mmHg.

These two studies, albeit in mature trauma systems with unknown prehospital times (but unlikely to be 'prolonged'), and not necessarily in patients with ongoing bleeding indicate that a SBP on admission of <110 mmHg is associated with worsening outcomes. Thus, an SBP of 110 mmHg may indicate a 'lower limit of normal' and perhaps the upper bound of a pressure range target for resuscitation.

5. **Hemorrhagic shock and Traumatic Brain Injury**

The evidence for an optimal blood pressure for traumatic head injury management is poor. The 2016, 4th edition Brain Trauma Foundation guidelines[39] relating to in-hospital management of traumatic head injury are:

"*Maintaining SBP at ≥100 mmHg for patients 50 to 69 years old or at ≥110 mmHg or above for patients 15 to 49 or over 70 years old may be considered to decrease mortality and improve outcomes. "*

However, this remains level III evidence. Spaite et al[40] have tried to correlate mortality and blood pressure in the pre-hospital setting. They identified two important features:

i. There is no obvious "inflection point" between an SBP of 40mmHg and 119 mmHg to suggest a clear target BP.
ii. There is a linear relationship between increasing systolic blood pressure and decreasing mortality.

In the absence of any meaningful prehospital data, pre-hospital guidelines should follow the Brain Trauma Foundation guidelines despite the fact that they relate to in-hospital management.

6. Prolonged hypoperfusion

Logically there must come a point at which prolonged hypoperfusion will worsen clinical outcomes. Animal models provide evidence that this is the case. For example, Li et al. [41] studied the effect of permissive hypotension of 60, 90 and 120 minutes duration in rats with uncontrolled hemorrhage, finding that survival rates, survival times and organ function were nearly identical for those in the 60 and 90 minute groups, but in those with hypotensive periods more than 90 minutes, outcomes were significantly worse. Similarly, in a study of 24 pigs[42] with controlled hemorrhage, those treated with severe hypotensive resuscitation (systolic BP 65 mmHg) for eight hours had persistently worse base excess and tissue oxygen saturation, and significantly higher mortality, than animals resuscitated to either systolic BP 90 mmHg or 80 mmHg. Identifying the point at which a hypotensive goal becomes detrimental and responding appropriately, either as a general rule or in an individual patient, is not yet addressed in any international consensus guideline. The best approach may depend on the nature of the traumatic insult and the initial response of the patient.

7. Response to shock after trauma

Simple hemorrhage without concomitant injury follows a well described pattern.[43] A reduction in venous return due to blood loss, leads to reduced cardiac filling and a fall in cardiac stroke volume, which in turn causes a fall in arterial pulse pressure. This reduction in pulse pressure effectively unloads the arterial baroreceptors, leading to an initial reflex

tachycardia and increase in peripheral vascular resistance that helps maintain arterial blood pressure.[44,45]

The increased vascular resistance is not uniform across systemic vascular beds. Some, such as skeletal muscle, splanchnic and renal beds experience profound vasoconstriction, while others, such as cerebral circulation, experience much less (if any) vasoconstriction. The result is twofold:

a) ***For the casualty*** the result is preservation of cerebral blood flow and oxygen delivery at the expense of oxygen delivery to the gut and kidney due to the increased vascular resistance, which is essential for the immediate preservation of life. However the penalty is a slowly developing shock state in many organs[46] and systemic inflammation. The resulting spillover of inflammation can contribute to the pathophysiology of shock and its sequelae such as multiple organ dysfunction.
b) ***For the clinician*** who is monitoring the casualty in the field by measuring pressure and level of consciousness, this response hides the development of the shock and the deterioration of the patient. Only once there is advanced shock does the blood pressure fall, and level of consciousness deteriorate

Rarely does a trauma casualty follow a simple model of hemorrhage. A trauma casualty suffers several insults that often include severe blood loss leading to hemorrhagic shock, tissue injury and pain, and, in the case of military casualties and terrorist incidents, blast. All of these insults lead to specific hemodynamic responses, components of which interact to cause and accentuate shock and provide physiological challenges for the casualty, with consequences for optimal treatment including fluid resuscitation.

7.1. Early systemic response to musculoskeletal injury

In experimental studies, there is evidence that when hemorrhage is superimposed on a background of somatic afferent nociceptive stimulation (to mimic injury) there is a further redistribution of blood flow from metabolically-active gut towards less active skeletal muscle[47,48], which effectively 'wastes' a proportion of the cardiac output. Ischemic damage to the intestinal mucosa may lead to an increased inflammatory response[49,50] and possibly increased intestinal permeability and enhanced translocation of endotoxin.[51-53] Therefore the impairment in cardiac function and tissue oxygen delivery (shock) associated with blood loss is greater if the hemorrhage is superimposed on nociceptive nerve stimulation compared to hemorrhage alone.[54] If the hemorrhage is superimposed on real rather than simulated tissue injury the tolerance to blood loss is reduced even further.[55]

7.2. Impact of alterations in arterial oxygenation: blast injuries

Injuries caused by explosions are complex and usually consist of several parts that are defined according to the component of the explosion that caused them.[56] Blast injuries normally include hemorrhage from penetrating injuries caused by fragments and debris (secondary blast injuries) and tissue damage due to physical acceleration of the casualty (tertiary blast injury) and consequent collision with solid objects. A small proportion of surviving casualties will also suffer injuries due to the shock wave caused by the explosion (primary blast injury). This particularly affects gas-containing organs and can cause significant damage in the lungs, evident as widespread intrapulmonary hemorrhage deep in lung tissue, with a consequent impairment of pulmonary gas transfer and arterial oxygenation.[57,58] The proportion of surviving casualties suffering blast lung varies enormously depending on the nature and positioning of the explosive device in relation to the

environment and the casualty, and any protective equipment worn by the casualty. Recently, in Afghanistan, approximately 11% of severely injured casualties surviving to hospital suffered blast lung,[59,60] while in a terrorist attack on civilians in the confines of train carriages in Madrid, a much higher proportion (63%) of the severely injured suffered blast lung.[61,62] We are therefore faced with casualties who are likely to have extensive tissue damage and severe blood loss, and in a clinically significant minority, also have blast lung resulting in hypoxemia. Overly aggressive fluid resuscitation can worsen hypoxemia, leading to conflicting priorities.

8. Hybrid resuscitation

Experimental studies, in anesthetized pigs, have investigated the development of shock during hypotensive resuscitation and the impact of blast injury on the time-course of the response. During the first hours the degree of shock increased, as measured by base excess. As time went on so did the degree of shock became overwhelming especially when performed on a background of hypovolemia and blast injury, leading to rapidly increasing mortality.[63] Since the response to hypotensive resuscitation was acceptable for the first hour a new paradigm was evaluated which involved initial hypotensive resuscitation (for 60 min) followed by a revised, normotensive, resuscitation target in an attempt to improve tissue perfusion and oxygen delivery to limit or even reverse the shock state. This new paradigm was called 'novel hybrid resuscitation', and was found to improve survival significantly together with a reversal of the shock state in a model of military trauma that incorporated blast injury and extended evacuation times in terminally anesthetized pigs.[64,65] In 2006 the UK military adopted novel hybrid resuscitation as part of clinical guidelines for the prehospital care of traumatic hemorrhage.

9. Applying 'hybrid resuscitation' to prolonged pre-surgical care

During prolonged evacuation (especially if there is pulmonary compromise) the balance of risks evolves in a casualty. Initially, the greater risk might be to disrupt a fragile nascent clot, hence, it might be appropriate to severely restrict fluid administration, and allow blood pressure to remain low. However, clot strength increases with time, so the risk of clot disruption diminishes. Concurrently, the shock state gradually develops over time, to reach levels that can cause significant morbidity and threaten survival. In the animal trials mentioned above, the approach was to reverse shock by raising the BP target at 60 mins simply by using saline and addressing the fact that the therapeutic priority has shifted towards shock.

Using crystalloids did help; however, overuse of crystalloids goes against RDCR principles.[3] Is it possible to have the best of both worlds? Can we limit volume (crystalloid) resuscitation whilst at the same time maximizing oxygen delivery? There are two additional considerations:

- Blood products vs. crystalloids as resuscitation fluids
- Increasing arterial oxygen content

9.1. **Blood products vs. crystalloids**

A recent experimental study examined the effects of early (simulating 'pre-hospital') resuscitation with blood products versus standard of care (crystalloid) in a model of trauma where the lungs were normal.[66] Hypotensive resuscitation (80 mmHg) was compared in three groups given saline, combined packed red cells and fresh frozen plasma (PRBC:FFP) or PRBC alone in a pig model that included tissue injury and hemorrhagic shock. Arterial oxygen content was increased in the blood product groups, most of all in the PRBC alone

group, and reduced in the saline group. The use of blood products (compared to crystalloid) very clearly attenuated the acute traumatic coagulopathy, and had a modest effect in attenuating shock (base excess and lactate). Interestingly, the treatment group that showed the greatest effect on arterial base excess and lactate was that given PRBC:FFP rather than PRBC alone. One possibility is that factors contained in plasma might improve the microvasculature, perhaps through a beneficial effect on the endothelium and possibly attenuating the microvascular component of the shock state.[67-69] The contribution of plasma albumin to buffering of acidosis was also likely of great significance.

In a more recent report utilizing a model that included tissue injury, blast and hemorrhage, the benefit of PRBC:FFP over crystalloid in attenuating shock was more modest, and failed to achieve statistical significance. However, utilization of a hemoglobin-based oxygen carrier (HBOC, MP4Ox, Sangart) led to a further improvement that was significantly better than crystalloid.[70]

Brown at al[71] looked at 240 civilian patients that received prehospital blood transfusion matched to 480 who did not. Patients had short prehospital times (23 mins in both groups) and prehospital hypotension (84 (66-106mmHg) and 88 (73-109 mmHg). The transfusion group received 1300 mls crystalloid and 300 (100- 500) mls pRBC compared to the non transfused group who received 1400 mls of crystalloid. The transfused group had improved 24-hour survival (adjusted odds ratio (95%CI) 4.91(1.51-16.04), p=0.01) and less shock (lower base deficit and lactate) (0.28 (0.09 – 0.85) p=0.03) on admission. Shackleford et al.[72] published a retrospective look at US combat casualties in Afghanistan who received blood transfusion. Those with prehospital blood transfusion were more badly injured, with more traumatic amputations, and therefore had a higher level of pre-hospital care sent to retrieve

them. This included the ability to transfuse blood products. Mortality in the transfused group at 24 hours (5% vs. 19%, p=0.01) and 30 days (11% vs. 23%, p=0.04) was significantly better. Rehn et al [73] have also recently looked at pre-hospital transfusion in a civilian setting in London. The patient group who received blood products pre-hospital used less blood products and less platelets overall compared to the non pre-hospital transfused group. The study was not powered to look at coagulopathy or shock.

Holcomb et al[17] looked at patients that were retrieved by a helicopter system that had pRBC and thawed plasma available, vs helicopter and ground ambulance systems that did not. Those that had received blood products had a better acid base status on arrival

Finally a study of the hemostatic potential of various resuscitative products[74] (whole blood or "reconstituted" whole blood as 1:1:1 or 2:1:1 pRBC:FFP:Plts) showed that the hemostatic potential of whole blood was superior to component therapy and that 1:1:1 was superior to 2:1:1. This showed that, for hemostatic potential at least, blood products are preferred to crystalloid solutions.

Therefore, choice of resuscitation fluid can have an impact on the degree of 'pre-hospital' physiological deterioration. For these reasons, hemostatic resuscitation is increasingly being deployed into military and civilian pre-hospital environments,[75,76] using blood products rather than crystalloids. However pre-hospital blood product use is still only available in a few countries and crystalloid fluids remain the predominant prehospital fluid worldwide.

9.2. Reversing hemorrhagic shock by increasing arterial oxygen content?

Several experimental models of trauma have found that improvements can also be made by increasing arterial oxygen content during hypotensive resuscitation. These improvements are modest compared to those attained by improving flow (see above), suggesting that reduced blood flow is the primary limitation.[77] Supplementary oxygen (increased FiO2) has the greatest likelihood of impact when arterial oxygen saturation is reduced (e.g. as a consequence of blast lung). Further evidence is available from an experimental model of controlled hemorrhagic shock using a fixed hypotensive resuscitation period of two hours in which recovery of oxygen debt and later organ failure was proportional to the degree of increased cardiac index induced by the initial fluid resuscitation.[78] Collectively, the clear but relatively modest gains achieved by utilizing supplementary oxygen and blood products, compared to the effects of later (post 60 min of resuscitation) elevation in the resuscitation blood pressure target (to improve tissue blood flow) suggests that the principal limitation during hypotensive resuscitation is blood flow rather than oxygen content.

The obvious drawback of emphasizing an increase of blood flow and pressure is the potential for increased bleeding from non-compressible wounds and the development of coagulopathy. The rate of bleeding from large arterial wounds in experimental models is positively associated with both mean arterial blood pressure, pulse pressure, and more so with cardiac output.[79] Therefore, the potential for increased blood loss should be carefully weighed against the potential benefit of organ protection during early fluid resuscitation. The considerations of timing, volume, and intensity of initial fluid resuscitation are likely situational, after considering potential trade-offs that include under-resuscitation and ongoing bleeding. Fluid resuscitation may be safely limited or delayed in a situation where rapid and definitive surgical hemostasis is possible, whereas more generous early fluid and blood product resuscitation may be indicated in situations where definitive hemostasis is expected to be delayed and/or blood products are plentiful.

9.3. Delivery rates of fluids

There are no clear guidelines for how fast to deliver resuscitation fluids during active, in hospital resuscitation, let alone in prehospital resuscitation. In hospital, it is common to see clinicians squeezing bags of fluid, or to use rapid infusion devices. It is unclear what the effect of rapidly increasing blood volume with have on the patient, either due to the rapid increase in volume, or due to increasing washout re-perfused vascular beds. There is some limited animal evidence that rapid rates of crystalloids may be bad for hepatocellular function[80], or pro-inflammatory markers[81,82]. However, both these studies use crystalloid, and under-resuscitate the "rapid" infusion groups.

In the absence of any strong evidence a more pragmatic approach needs to be taken. It is difficult, or impossible to use rapid infusion devices in RDCR, meaning that to rapidly infuse fluids, pressure bags or squeezing bags must be utilized, which for a sole or limited number of providers, is logistically challenging. One feature of shocked pre-hospital patients is that they are vasoconstricted with limited vascular compliance, as opposed to vasodilated, anesthetized patients. It is possible that rapid infusions of volume may be detrimental in a vasoconstricted patient, although there is only anecdotal evidence to suggest this.

It is therefore the opinion of the authors that in pre-hospital resuscitation, steady, gravity fed infusions are the ideal, accepting that many situations occur that may require squeezing, or pressure driven infusions, such as the use of intraosseous access, or indeed in moribund patients where rapid resuscitation is needed.

10. Assessing shock states during resuscitation: implications for targets

It has long been recognized by physiologists and anesthetists/intensivists that monitoring mean arterial blood pressure is a poor measure of the degree of hemorrhage and developing shock,[83] principally because reflex increases in vascular resistance (to maintain or elevate pressure) cause a reduction in tissue blood flow that is underestimated or even hidden when blood pressure is the primary assessment. Several groups have postulated that measures of global blood flow (such as stroke volume or cardiac output)[84-88] or tissue perfusion or oxygenation (such as lactate or base excess) [89,90] may give a more timely warning of hidden hemorrhage since the former are part of the initial effect of hemorrhage while the latter change in response to the physiological alterations that delay the overt falls in arterial blood pressure. An interesting suggestion is that alterations in arterial blood pressure waveforms and beat-to-beat pressure variability might also be informative during progressive hypovolemia. This has been viewed empirically as an increasing variability in arterial pressure waveform reflecting an "empty" circulation in the absence of any other obvious cause, which can be used as a marker of developing shock. This principle has been developed further to derive a "Compensatory Reserve Index" (CRI)[91] which might be of utility as a proxy marker of shock.

Falls in arterial base excess (increasing base deficit) and elevations in plasma lactate are long-established indices of shock. This is a good index of shock in quasi-stable patients and an excellent retrospective marker of severity in experimental studies. However, it takes time (tens of minutes) for the acidosis to develop.[91] Consequently, significant falls in base excess (or elevations in lactate) phase-lags an event that causes a rapid change in tissue oxygen delivery (such as hemorrhage or resuscitation) by approximately 30 minutes. Other indices of tissue oxygenation may have better utility under these circumstances. Choice of vascular bed (or organ type) is paramount here because of the hierarchical response to the cardiovascular

reflexes that underpin the response to hypovolemia. The cerebral circulation is well maintained (spared the baroreflex vasoconstriction), so in the absence of brain injury change in level of consciousness is a poor indicator of developing shock. By contrast skeletal muscle and vital organs (e.g. gut and kidney) experience vasoconstriction and reduced flow. Depending on the skills and equipment available it may be possible to use devices aimed at measuring tissue oxygenation such as muscle near infra-red spectroscopy (NIRS), or surrogate markers of organ flow, such as urine output. Other clinical parameters such as skin temperature or capillary refill may also provide useful "flow based" end points of resuscitation.

At present, there is no single machine or measurement that gives a rapid, accurate answer to the degree of shock and response to fluid resuscitation. All of the above indices have merit, but to date no empirical test has shown the outcome superiority of one over another. Even the most responsive and representative marker of shock and resuscitation responsiveness will not provide a balanced picture of whether hemorrhage is being worsened by the (presumably transiently) improved hemodynamic state. In the absence of prospective effectiveness trials, pre-hospital clinicians will continue to need to collect, digest and interpret all the information, overlaid by experience, in order to maximize the chance of a bleeding patient surviving.

11. The practical difficulties in delivering pre-hospital care.

Senior policymakers should carefully take into account the environment, monitoring equipment available, and skills of the pre-hospital care providers when implementing guidelines for RDCR. Without question, it is extremely difficult to maintain a systolic blood pressure at a certain target in patients with ongoing non-compressible bleeding. Even in the

OR, with intra-arterial monitoring, central venous pressure and other advanced hemodynamic monitoring equipment, senior doctors fail to achieve this. To demand this from junior medics in the field sets them up for failure. However, for the majority of prehospital care providers, especially in experienced ones, there needs to be protocols and guidelines that can be adhered to and audited. Therefore, a SBP will remain, for the time being, as an endpoint for most prehospital protocols, augmented be the ability to tailor individual care based on other clinical findings. A more sensible approach may be to allow the medics to base their resuscitation strategies on more simple findings such as the mechanism of injury, trends in vital signs, mentation and other readily available clinical parameters rather than a fixed blood pressure.

12. Conclusions

Hypotensive resuscitation guidelines developed due to concerns that early, large volumes of un-warmed crystalloid solutions were detrimental for patients in an environment where there was rapid access to hospital and surgical treatment. These guidelines are universally applied to trauma patients regardless of the source of bleeding, and whether the patient is at increased risk of bleeding with resuscitation, or at risk of shock due to under resuscitation. The guidelines do not consider the effect of prolonged times to hospital or surgical treatment nor do they consider the effect of blood product resuscitation or indeed better endpoints of resuscitation such as flow based parameters. There remains a paucity of evidence for resuscitation guidelines for prehospital patients although that is slowly changing. There some emerging evidence suggesting that mortality is worse if the SBP is less than 110 mmHg on admission therefore it is reasonable to aim for higher blood pressure target than the current level of 80 – 90 mmHg for prehospital providers.

In summary, the following recommendations are made for the resuscitation of patients who exhibit signs of hemorrhagic shock;

1. Fluid resuscitation should be blood-based where possible
2. If it is feasible to measure blood pressure, a target SBP of 100 mmHg should be used and the pressure should NEVER fall below 90 mm Hg. An upper limit for active resuscitation should be 110 mm Hg
3. Additional resuscitation endpoints should target flow-based measurements, lactate, base excess, or clinical parameters rather than simply the blood pressure. Trends over time are the most useful indicators for the efficacy of resuscitation.

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