the word) and test their truth, or rather the falsehood of the null hypothesis. If you can think of such a testable hypothesis, let me know. Experimentation distils knowledge from information, the signal from the noise.

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Editorial

Permissive hypotension for active haemorrhage in trauma

Uncontrolled bleeding is the leading cause of the vast majority of potentially preventable deaths after major trauma [1–3]. A recent national study showed that the mortality in trauma patients requiring massive transfusion approaches 50% [4]. Half of these deaths occur within the first 24 h, and half of those are exsanguinating deaths within the first 3 h of arrival [1, 5–7]. The foundation of resuscitation of the shocked patient has always focused on restoring perfusion and eliminating oxygen debt. However, in recent years it has become apparent that actively bleeding patients cannot be ‘resuscitated’, cannot have perfusion restored and cannot clear their oxygen debt [8]. Attempts to volume resuscitate these patients not only fail to achieve these targets, but in doing so lead to haemodilution, coagulopathy, tissue oedema, organ dysfunction and death. Contemporary management of these patients has switched goals from restoring perfusion to maintaining haemostatic competence. This ‘damage control resuscitation’ paradigm targets early haemorrhage control and preservation of coagulation [8–11]. Permissive hypotension is a central part of this approach to the management of haemorrhage [12, 13].

Permissive hypotension implies accepting an adequate, not normal, blood pressure. It is employed in the actively bleeding patient until haemostasis is obtained, after which point definitive resuscitation begins. This approach in no way violates the underlying principle that restoration of systemic blood flow and adequate tissue perfusion in critically ill patients should be achieved as quickly as possible. However, volume infusion in the face of continued blood loss results in dilutional coagulopathy and hypothermia, while the transient elevation in blood
pressure contributes to further bleeding from wounds and vessels [6, 7, 12, 14]. This approach may be associated with organ dysfunction, abdominal compartment syndrome and death in major trauma patients [12–15]. Permissive hypotension, therefore, can facilitate an environment that optimises coagulation, albeit at the potential expense of optimal tissue perfusion pressure, until repair restores the integrity of the system [9]. In essence, it may be described as a short-term potentially injurious insult to allow a greater global net result.

What is the evidence?

There is a large body of experimental literature which supports a permissive hypotensive strategy [5]. While complete absence of fluid resuscitation is an inappropriate strategy, as it may leave perfusion pressures dangerously low, aggressive volume resuscitation promotes excessive bleeding by displacement of established clots, and is associated with increased mortality [8, 13, 16–18]. It is likely that the early resuscitation strategies for active bleeding are represented by a U or J shaped curve if plotting mortality or bleeding against blood pressure (Figs. 1 and 2). This is well supported by animal data, though the limitations of extrapolating such data to humans are well recognised [5].

Clinical studies to support the permissive hypotensive approach are difficult to conduct and sparse. The classic study by Bickell looking at penetrating torso trauma compared a restrictive vs. a standard volume resuscitation strategy in the pre-hospital environment. A mortality benefit and lowered complication rate was shown in the restrictive group [16]. Dutton’s subsequent paper compared in-hospital resuscitation in trauma to target blood pressures of either 70 or 100 mmHg. In this study, the mortality was the same in the normotensive and hypotensive groups. Neither benefit nor harm for permissive hypotension was demonstrated [12, 19]. The most striking result from both these studies was that blood pressure targets could not be sustained and the normotensive arms were associated with much higher fluid volume requirements. More recent research has suggested that high-volume fluid therapy is associated with increased mortality, transfusion requirements and coagulopathy in adult and paediatric populations [6, 13, 15, 20]. However, to date, there are no good quality prospective studies [13].

Data from the pre-hospital environment is similar. Hussmann et al. retrospectively reviewed 7600 patients and showed that increasing volumes of fluid administered in a pre-hospital setting were an independent risk factor for mortality (> 2 l prehospital volume OR 2.7, 95%CI 1.6–4.5 vs. ≤ 500 ml) [6]. Other data show that although pre-hospital fluid has been associated with reductions in the shock index at lowered volumes (0.5–1.0 l), higher volumes (1–2 l) are associated with significant increases in the incidence of in-hospital blood transfusion (OR 3.3, 95%CI 2.0–5.3) [7]. Volumes of more than 2 l of crystalloid were independently associated with a nearly 10-fold increase of subsequent blood transfusion in hospital (OR 9.9, 95%CI 4.0–24.6) [7].

A retrospective review of a German trauma registry database (17,200 multiply-injured patients) demonstrated an increasing incidence of coagulopathy with increasing volumes of fluid resuscitation. Coagulopathy was observed in > 40% of patients who received > 2 l fluid; > 50% of patients who received > 3 l fluid; and in > 70% of patients who received > 4 l fluid. Some researchers have concluded that routine use of pre-hospital fluid should be discouraged for all trauma patients [21]. However, critics of such an over-simplified approach argue that this may lead to dangerous under-resuscitation in certain scenarios and could be detrimental [7].

More recently, accumulated data from military conflicts has allowed a large amount of observational research [10, 22]. Management of wounded soldiers has focused on damage control resuscitation principles, including permissive hypotension, administered as a ‘haemorrhage bundle’. Early application of these principles is recommended, with particular emphasis on permissive hypotension [22–25].

Many of these principles have been translated into civilian trauma practice [9, 11, 13, 26]. Despite regional differences in the approach to resuscitation, permissive hypotension appears to be central, with variations only by degrees [27, 28]. This has led to dramatic reductions in observed vs. predicted massive transfusion, and reductions in both blood and blood product...
transfusion in some centers [26]. Although the civilian trauma environment does not necessarily represent a similar epidemiological profile to healthy soldiers, a recent National Trauma Data Bank analysis in the USA found that, despite elderly trauma patients having a higher likelihood of death over younger patients, there was no synergistic effect of age and (lowered admission) blood pressure on mortality. They concluded that permissive hypotension may be a possible management strategy even in elderly patients [29].

Clinical practice

Clearly a balance must be sought, and multiple approaches and consensus opinions have been put forward [5, 7]. This has led to guideline recommendations supporting permissive hypotension [1, 5, 7, 15]. The European guideline on the management of major bleeding and recent National Institute for Health and Care Excellence (NICE) guidelines recommend the following in actively bleeding patients [1, 5]:

1. Application of a restrictive approach to volume resuscitation until early definitive control of bleeding.
2. Titration of pre-hospital volume resuscitation to a palpable central pulse.
3. In-hospital emphasis on rapid haemorrhage control, titrating volume resuscitation to maintain a central circulation.

These recommendations practically aim to titrate fluid resuscitation to maintain systolic blood pressure around 80–90 mmHg, which roughly equates to a central pulse or patient cerebration. This can be achieved with small fluid boluses of 250 ml, titrated to response. This volume is arbitrary, though such boluses should be sufficient to improve blood pressure because, in the setting of major blood loss, the circulation is usually highly constricted, with a small volume of distribution. Only small volumes are required to push patient haemodynamics up the Starling curve and improve cardiac output.

The question of what blood pressure to aim for has still has not been answered. What does seem to be clear is that patients suffering trauma do not necessarily seem to be disadvantaged if short periods of hypotension are permitted [11, 13, 26, 29]. There is some experimental evidence that tissue autoregulatory thresholds may be lower than originally suspected [30]. A study looking at a group of intensive

Figure 1 Graphical representation of mortality against blood pressure in early damage control resuscitation during active haemorrhage.

Figure 2 Graphical representation of bleeding against blood pressure in early damage control resuscitation during active haemorrhage.
care patients, including following trauma, recorded blood pressures at the point of acute deterioration and death. Blood pressure ranges as low as 35–60 mmHg systolic and 20–35 mmHg diastolic were tolerated before death [30]. These values would be considered to be at the lowest end of the spectrum and therefore should never be reached or tolerated. To ensure crucial maintenance of coronary perfusion pressure, a safety limit (for example, one or two standard deviations) above these arterial blood pressure levels should be maintained [30].

Patients with severe injuries need blood product-based resuscitation with appropriate ratios of packed red blood cells to plasma and platelets (such as 1:1:1) [31–33]. Severe bleeding in trauma patients can result in disordered blood clotting [34, 35]. Until recently, this effect was thought to be a late phenomenon, arising primarily from loss of coagulation factors during haemorrhage and dilution from resuscitation fluids. However, it is now recognised that acute traumatic coagulopathy occurs within minutes of injury in roughly 25% of patients, and is associated with a four-fold increase in mortality [34]. The process is multifactorial, but is thought to be, in part, due to an endogenous process occurring as a result of tissue damage in severe shock, with tissue factor release and a widespread inflammatory response [34–37].

**Traumatic brain injury**

The obvious area of contention is the appropriate strategy for the management of an actively-bleeding patient with traumatic brain injury (TBI) [38]. Retrospective observational data for patients with TBI suggest that a reduction in mean arterial pressure is associated with increased mortality [39, 40]. Recent guidelines published by the Brain Trauma Foundation advocate maintaining a systolic blood pressure above 110 mmHg (level 3 evidence), but do not specifically state whether this applies during active haemorrhage [41]. Currently, there is controversy about whether the guidelines for permissive hypotension should be changed in the presence of head injury because there is no human evidence from prospective studies [38, 42].

In experimental data, overly aggressive fluid resuscitation in combined TBI and haemorrhage is detrimental to cerebral perfusion [43, 44]. Higher crystalloid infusion to maintain blood pressure leads to increased fluid extravasation, damaged microvasculature, cerebral oedema and raised intracranial pressure, negating any benefit from raising arterial blood pressure [44–46]. In a swine experimental model with induced haemorrhage and simultaneous TBI, all animals with an aggressive fluid resuscitation strategy died. In the permissive hypotension resuscitation group, the survivors (50%) were able to have their haemodynamic profile and cerebral oximetry parameters restored to pre-injury levels when resuscitated [47].

Guidelines are again based on informal consensus and if a patient has both TBI and severe active bleeding, both the European and the NICE guidelines recommend [1, 5–7]:

1. **Haemorrhagic shock is dominant, continue restrictive volume resuscitation.**
2. **Traumatic brain injury is dominant, use a less restrictive volume resuscitation approach to maintain cerebral perfusion pressure.**

A final point to consider is the duration that permissive hypotension should be tolerated. Particular consideration should be given to the environment where access to surgical care may be delayed [10, 22–25]. Attempts at a so-called ‘hybrid’ resuscitation combining elements of permissive hypotension and normotensive resuscitation are being pioneered. Permissive hypotension is ‘allowed’ for up to 60 min, to ‘encourage’ thrombus formation; this may have a role in mitigating coagulopathy as well as reducing systemic inflammatory response and cytokine burden [24, 26]. Thereafter, gradual restoration of a normotensive haemodynamic profile is instituted to ensure microvascular perfusion and end-organ oxygen delivery [14, 15]. In practice, the duration of permissive hypotension should be as short as possible, and therefore all attempts should be directed at early control of active haemorrhage.

The actively bleeding patient remains a challenge for the trauma team. Tissue perfusion, coagulopathy management and bleeding limitation must be carefully balanced. Permissive hypotension, while potentially physiologically undesirable, is a technique employed on the journey to a greater overall destination. While the strategy may yet require fine
tuning, permissive hypotension is an effective adjunct that has almost certainly contributed to the recent improvements in outcomes for trauma patients with active haemorrhage.

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Editorial

Blood pressure in trauma resuscitation: ‘pop the clot’ vs. ‘drain the brain’?

Introduction

In this issue of Anaesthesia, Nevin and Brohi [1] eloquently discuss the role of permissive hypotension in the management of the actively bleeding trauma patient. Since the advent of major trauma centres in the UK, there has been widespread adoption of permissive hypotension as part of ‘damage control resuscitation’ in the immediate management of haemorrhage secondary to trauma. As the authors themselves note, this is a contentious area with many uncertainties and, as a neuro-anaesthetist, I feel that it is important to consider the potential risks and limited


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