Editorial

Blood pressure management in trauma: from feast to famine?

In 2007, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a review of trauma services in England, Wales and Northern Ireland [1]. This demonstrated that almost 60% of major trauma cases received care that was judged to be less than good practice. This led to a review of major trauma care within England by the National Audit Office [2], which subsequently led to the creation of major trauma centres (MTCs). As a result of the advent of MTCs the management of trauma within the UK has changed radically over the past few years, from both organisational and clinical perspectives [3]. This has led to an upsurge in interest amongst medical professionals as to how best to manage trauma cases. The basis of much of UK trauma management over the past 30 years has been derived from teaching from the Advanced Trauma Life Support (ATLS) courses [4]. These guidelines have faced increasing criticism over the past decade, especially regarding their insensitivity to change (with updates typically occurring on a 3–4 year cycle) and applicability to UK practice [5, 6]. Despite these weaknesses, some ATLS concepts have become enshrined into trauma management and teaching, though without much supporting evidence. Examples of

this include the trimodal distribution of death following trauma and the ATLS classification of shock, both of which have been shown to be theoretical concepts rather than useful clinical entities [7–10].

Further challenges to ATLS management recommendations came from the implementation of military trauma strategies. The conflicts in Iraq and Afghanistan led to the development of novel management strategies in both trauma resuscitation and surgery (discussed in detail in a recent supplement in this journal [11]), some of which have been translated back to civilian practice. One area of focus is the concept of permissive hypotension as part of a damage control resuscitation (DCR) strategy in the management of the bleeding trauma patient.

Permissive hypotension (or hypotensive resuscitation) was conceived because of the theoretical risk of excess fluid administration's interfering with the endogenous coagulation process, by inducing a dilutional coagulopathy, by clot disruption from an increase in arterial pressure, or through the abolition of reflex physiological vasoconstriction. This led to the recommendation that fluid administration should be delayed until haemorrhage has been controlled, even though this often would result in a

period of suboptimal end-organ perfusion. Typical systolic blood pressure (SBP) targets in permissive hypotension are 70–90 mmHg although a recent article [12] has suggested that DCR targets should be a SBP and mean arterial pressure (MAP) of 80 and 50 mmHg, respectively. Over the past three years, guidelines from professional bodies (including the ambulance service) and review articles have been published, recommending the use of permissive hypotension in trauma management [13–16], but it is unclear whether there is robust evidence to support this practice, especially for the UK trauma population.

The concept of permissive hypotension was first described by Cannon et al. [17], a group of Captains in the Army Medical Corps, from their experience in the management of injuries received during the First World War. They noted that "*Injection of a fluid that will increase blood pressure has dangers in itself. If the pressure is raised before the surgeon is ready to check the bleeding that may take place, blood that is sorely needed may be lost.*" It is of note, however, that in the same series of articles, one of Cannon's co-authors, Cowell [18], recognised the problems associated with periods of prolonged hypoperfusion, stating "*…the treatment of*

shock must be prompt and directed towards preventing an increase in the unfavorable conditions". The recommendations of Cannon et al. were largely forgotten for much of the 20th century and the majority of fluid resuscitation strategies were derived from experimental animal studies. Wiggers et al.'s animal models of controlled haemorrhage throughout the 1940s [19] led to the recognition of the reversible nature of shock with volume replenishment. Further work in the 1960s [20] demonstrated that balanced crystalloid solutions could be used to replace haemorrhagic losses (leading to the adoption of replacement in a 3:1 crystalloid:blood volume ratio), but more physiological animal models of uncontrolled haemorrhage, developed in the 1980s [21], suggested that large-volume crystalloid resuscitation may be harmful. Subsequently, numerous animal studies confirmed the beneficial effects of permissive hypotension for penetrating trauma [22], which was gradually assimilated into clinical practice despite the lack of human studies. The direct translation of research done in animal models to clinical practice in humans should be undertaken with caution. The Cochrane group undertook a systematic review of fluid resuscitation animal experiments [23] and found marked heterogeneity throughout the studies. Concerns were also expressed regarding the power calculations and randomisation methods employed in the studies, and the authors suggested that a degree of publication bias may exist.

If we are unable to translate the results of animal models of permissive hypotension to trauma patients confidently, then evidence must be sought from trials involving humans. Unfortunately, there are few high-quality trials examining this issue, and those that do exist have focused on patients with penetrating trauma. The landmark study by Bickell et al. [24] is the largest study of its kind. This was a prospective, randomised control trial comparing immediate with delayed fluid resuscitation in 598 hypotensive patients (SBP < 90 mmHg) with penetrating torso trauma. In-hospital survival in the group who only received intravenous crystalloid once they reached the operating theatre was significantly higher than those who received fluid in the pre-hospital environment and emergency department (70% vs 62%, respectively, p = 0.04). This study, however, does have a number of significant limitations. Randomisation was performed using an alternate-day selection method and 22 of the patients in the delayed-fluid resuscitation group actually received some fluid, in breach of protocol. The study's main weakness is the large number of patients (70) who died before reaching the operating theatre. This may have resulted in the study's being prone to a degree of immortal time bias [25]. The cause of death of these patients is not discussed in the paper, and so it is not clear whether they represent the most haemodynamically unstable subjects. The mean SBP in the delayed fluid group improved from 59 to 113 mmHg with minimal intravenous fluid, so the study population may not have been

bleeding significantly. If the survival ratios are recalculated excluding this subset, then there is no statistical difference between the two interventions (28% vs 22%, respectively, p = 0.13) [26].

Bickell et al.'s study [24], however, focused upon patients with penetrating trauma, which is relatively rare in the UK. For example, only 3% of the trauma cases admitted to the East Midlands Trauma Centre in the last year had injuries caused by penetrating trauma, the remainder suffering blunt trauma (CG Moran, personal communication, 20/12/2012). This is of great importance in the context of permissive hypotension, as there has been little research involving humans in this area. A UK trial [27] looked at the pre-hospital administration of intravenous fluids by paramedics to adult trauma patients. Participants were randomly assigned to receive either no intravenous fluid (if the anticipated time to hospital was < 60 min) or immediate fluid resuscitation (if indicated by operating protocols). Of the 1309 patients recruited, over 95% had suffered blunt trauma. Overall, there was no difference in either mortality or serious morbidity between the two groups, but protocol compliance was very poor. Only 31% of the immediate-resuscitation group actually received fluids, whilst 20% of the no-fluid group had fluid administered at some point. In addition, randomisation methods were questionable, with paramedic teams randomised to treatment arms, rather than individual patients. A retrospective matched pairs control study [28],

using data from the Pennsylvania Trauma Registry, examined outcomes in hypotensive (SBP < 90 mmHg) victims of blunt trauma. The study sample was divided into two groups according to the amount of pre-hospital intravenous fluid that had been administered: those who had received > 500 ml; and those who had received no fluid. There was no difference in survival to hospital discharge or length of stay between the two groups, although the group who received fluids had a significantly higher SBP on admission. It is of note that over 20% of the study participants had suffered a head injury. A second study looked at the effect of resuscitation in hypotensive (SBP < 90 mmHg) trauma patients with evidence of active bleeding [29]. A target 'normal' SBP of > 100 mmHg was compared with a hypotensive target of 70 mmHg in 110 patients, of whom around 50% had suffered blunt traumatic injuries. The duration of haemorrhage and survival were not different between the two groups, although the actual difference in average SBP between the groups was statistically, but not clinically, significant (114 vs 100 mmHg, respectively).

In summary, there is a paucity of well conducted randomised control trials comparing hypotensive with normotensive resuscitation strategies. The question remains, therefore, as to what the optimal blood pressure is for the trauma patient who may still be actively bleeding. As a neuroanaesthetist, my greatest concern regarding the widespread adoption of permissive

hypotension is the potential to cause a secondary brain injury through a reduction in the cerebral perfusion pressure. Traumatic brain injury is common in the UK trauma population and is responsible for around half of all trauma deaths [30]. It is widely stated in the literature that traumatic brain injury is a contraindication to permissive hypotension, but in the emergency department it may be very difficult to exclude a significant brain injury confidently before computed tomography scanning. Altered conscious levels are often seen in polytrauma patients due to the presence of major extracranial injuries, the administration of opioid analgesia or the ingestion of alcohol or illicit drugs. Chestnut et al. showed in a retrospective analysis of severely brain-injured patients that a single episode of hypotension (SBP < 90 mmHg) was associated with a doubling of mortality and a parallel increase in morbidity rates amongst survivors [31]. As a result, European guidelines for the management of traumatic brain injury recommend the early maintenance of a MAP > 80 mmHg or SBP > 120 mmHg [32, 33]. A recent retrospective review of over 15 000 moderate to severely head injured trauma patients has suggested that the threshold for hypotension in traumatic brain injury should be redefined as a SBP < 110 mmHg [34]. This is of increasing importance due to the changing nature of the traumatic brain injury population. The median age of patients suffering traumatic brain injury has increased over the past three dec-

ades from 25–29 years [35, 36] in the 1980s, to 38 years [37] in the 1990s, and is now 42–48 years [38, 39] in the most recent studies. This means that clinicians are faced with a trauma population with a greater number of comorbidities (especially hypertension) who may, therefore, be more vulnerable to the effects of hypotension.

Further work using data from the Trauma Audit Research Network database has shown a similar association between hypotension and mortality in trauma patients without brain injury. In blunt trauma, a significant increase in mortality was seen with SBP < 100 mmHg, with mortality rates doubling at < 100 mmHg, tripling at < 90 mmHg and increasing by five- to six-fold at < 70 mmHg, even after correction for other factors such as age and injury severity score [40]. Similar results were seen in patients with penetrating trauma, with mortality doubling with SBP < 110 mmHg and becoming four- to ten-fold higher at < 90 mmHg [41].

This does raise the question as to whether the focus on fluid management and resuscitation in trauma has shifted from one extreme to the other. It is clear that the management of hypotension in trauma using predominately large volume crystalloid infusions has quite correctly been consigned to history, but at present there appears to be little evidence for the widespread adoption of permissive hypotension as an alternative. A middle ground may exist whereby blood pressure can be supported and even optimised through the use of low-volume resuscitation tech-

niques involving hypertonic solutions, or by the early institution of vasopressor therapy. There is little evidence, however, supporting the use of either strategy in the hypotensive trauma patient. A secondary analysis of data from 921 blunt trauma victims suggested that the use of vasopressors (phenylephrine, noradrenaline, dopamine or vasopressin) within 12 h of injury was associated with an 80% higher risk of mortality, whilst aggressive fluid resuscitation resulted in a 40% reduction in mortality [42]. Vasopressin has shown some promise as an effective vasopressor in trauma on the basis of animal studies and case reports [43], and a multicentre randomised controlled trial is underway examining the pre-hospital administration of vasopressin in patients with traumatic haemorrhagic shock (SBP < 90 mmHg) that is refractory to hypertonic saline (VITRIS Study; ClinicalTrials.gov identifier: NCT00379522). At present, however, there is insufficient evidence to recommend the use of any individual vasopressor. Similarly, the potentially beneficial effects of hypertonic solutions, namely the rapid restoration of plasma volume with minimal oedema formation, in conjunction with a reduction in intracranial pressure, have still not been demonstrated in large scale clinical studies [44].

Modern trauma management focuses upon the principles of haemostatic resuscitation by the early replacement of coagulation factors and platelets in conjunction with antifibrinolyic therapy. This strategy, in tandem with the recognition of the need for rapid transfer from the emergency department for definitive haemorrhage control (in the operating theatre or angiography suite), may be the best way to 'protect the clot' in trauma patients rather than by the use of permissive hypotension with its inherent risks. Trauma patients are a complex population, with each individual requiring a unique management strategy tailored to his/her needs – the acceptance of a single global blood pressure target would appear to be the antithesis of this principle. In the context of the trauma seen in the UK, which is predominately blunt in nature with a high rate of associated head injury, permissive hypotension may yet prove to be a valuable tool in the trauma team's armamentarium, but at present should only be used with great caution and in selected cases.

Competing interests

MDW has received honoraria from AstraZeneca for participation in advisory boards.

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Editorial

Who should undertake extracorporeal membrane oxygenation?

Extracorporeal membrane oxygenation (ECMO) describes a process whereby blood is continuously pumped from a patient through a membrane oxygenator that imitates gas exchange, removing carbon dioxide and adding oxygen. Oxygenated blood is then returned to the patient. The equipment required and the circuit itself are not dissimilar to those used for cardiopulmonary bypass (CPB)