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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J. B. Carlisle
Consultant
Department of Anaesthesia,
Torbay Hospital,
Torquay, UK
Email: john.carlisle@nhs.net

References

1. Sliver N. *The signal and the noise*, 1st edn. Random House, UK: Penguin, 2013.
2. Coulson TG, Bailey M, Reid CM, et al. The association between peri-operative acute risk change (ARC) and long-term survival after cardiac surgery. *Anaesthesia* 2017; 1467–75.
3. Billah B, Reid CM, Shardey GC, Smith JA. A preoperative risk prediction model for 30-day mortality following cardiac surgery in an Australian cohort. *European Journal of Cardiothoracic Surgery* 2010; **37**: 1086–92.
4. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619–36.
5. Carlisle J. Commentary: life is a line, not a dot. *Colorectal Disease* 2017; **19**: 64–6.
6. Pandit JJ. Dispassionate indicator or evil curse: are some scoring systems for predicting postoperative mortality lethal? *Anaesthesia* 2017; **72**: 905–8.
7. Papachristofi O, Sharples LD, Mackay JH, Nashef SAM, Fletcher SN, Klein AA. The contribution of the anaesthetist to risk-adjusted mortality after cardiac surgery. *Anaesthesia* 2016; **71**: 138–46.
8. Australian Life Tables 2010-2012. http://www.aga.gov.au/publications/#life_tables (accessed 15/08/2017).
9. Carlisle JB, Danjoux G, Kerr K, Snowden C, Swart M. Validation of long-term survival prediction for scheduled abdominal aortic aneurysm repair with an independent calculator using only pre-operative variables. *Anaesthesia* 2015; **70**: 654–65.

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

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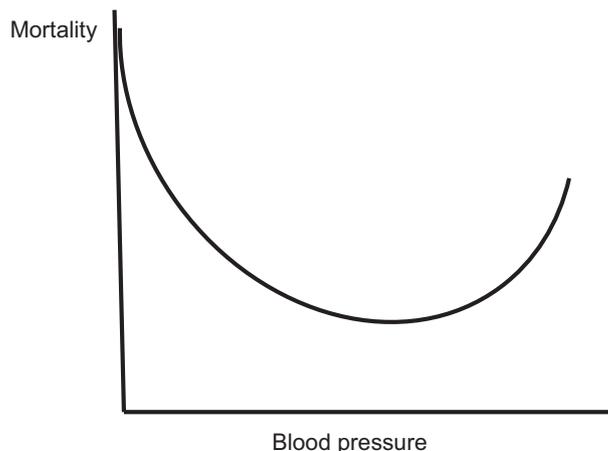
Figure 1 Graphical representation of mortality against blood pressure in early damage control resuscitation during active haemorrhage.
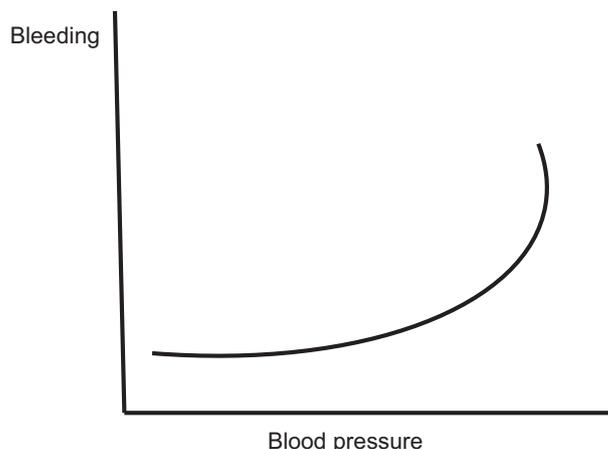

Figure 2 Graphical representation of bleeding against blood pressure in early damage control resuscitation during active haemorrhage.

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

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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D. G. Nevin
Consultant
Department of Anaesthesia and London's Air Ambulance, The Royal London Hospital Major Trauma Centre, Bart's Health NHS Trust, London, UK
Email:
daniel.nevin2@bartshealth.nhs.uk
K. Brohi
Professor
Centre for Trauma Sciences, The Blizard Institute, Queen Mary University of London, London, UK

References

1. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma; fourth edition. *Critical Care* 2016; **12**: 100.
2. World Health Organization. Cause-specific mortality and morbidity. 2009. http://www.who.int/whosis/whostat/EN_WHS09_Table2.pdf (accessed 19/06/2017).
3. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World Journal of Surgery* 2007; **31**: 1507–11.
4. Stanworth SJ, Davenport R, Curry N, et al. Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *British Journal of Surgery* 2016; **103**: 357–65.
5. Glen J, Constanti M, Brohi K, Guideline Development Group. Assessment and initial management of major trauma: summary of NICE guidance. *British Medical Journal* 2016; **22**: 353.
6. Hussmann B, Heuer M, Lefering R, et al. Prehospital volume therapy as an independent risk factor after trauma. *Biomedical Research International* 2015; **2015**: 354367.
7. Geeraedts LM Jr, Pothof LAH, Caldwell E, de Lange-de Klerk ES, D'Amours SK. Prehospital fluid resuscitation in hypotensive trauma patients: do we need a tailored approach? *Injury* 2015; **46**: 4–9.
8. Boffard KD, ed. *Manual of definitive surgical trauma care: incorporating definitive anaesthetic trauma care*, 4th edn. Boca Raton, FL: Taylor and Francis Group, 2016.
9. Holcomb JB. Major scientific lessons learned in the trauma field over the last two decades. *PLoS Medicine* 2017; **14**: e1002339.
10. Edwards S, Smith J. Advances in military resuscitation. *Emergency Nursing* 2016; **24**: 25–9.
11. Quinn D, Frith D. Assessing the damage control resuscitation: development, drivers and direction. *Emergency Medicine Australasia* 2015; **27**: 485–7.
12. Harris T, Thomas GOR, Brohi K. Early fluid resuscitation in severe trauma. *British Medical Journal* 2012; **345**: e5752.
13. Carrick MM, Leonard J, Slone DS, Mains CW, Bar-Or D. Hypotensive resuscitation among trauma patients. *Biomed Research International*. 2016; **2016**: 8901938.
14. Sharrock AE, Midwinter M. Damage control – trauma care in the first hour and beyond: a clinical review of relevant developments in the field of trauma care. *Annals of the Royal College of Surgeons England* 2013; **95**: 177–83.
15. Khan S, Brohi K, Chana M, et al., International Trauma Research Network (INTRN). Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. *Journal of Trauma and Acute Care Surgery* 2014; **76**: 561–7.
16. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive trauma patients with penetrating torso injuries. *New England Journal of Medicine* 1994; **311**: 1105–9.
17. Shaftan GW, Chiu CJ, Dennis C, Harris B. Fundamentals of physiologic control of arterial hemorrhage. *Surgery* 1965; **58**: 851–6.
18. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock* 2006; **26**: 115–21.
19. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active haemhorrage: impact on in-hospital mortality. *Journal of Trauma* 2002; **52**: 1141–6.
20. Hussmann B, Taeger G, Lefering R, et al. Lethality and outcome in multiple injured patients after severe abdominal and pelvic trauma: influence of preclinical volume replacement - an alaysis of 604 patients from the trauma registry of the DGU. *Unfallchirurg* 2011; **114**: 705–12.
21. Haut ER, Kalish BT, Cotton BA, et al. Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a national databank analysis. *Annals of Surgery* 2011; **253**: 371–7.
22. Daniel Y, Habas S, Malan L, Escarment J, David JS, Peyrefitte S. Tactical damage control resuscitation in austere military environments. *Journal of the Royal Army Medical Corps* 2016; **162**: 419–27.
23. Chang R, Eastridge BJ, Holcomb JB. Remote damage control resuscitation in austere environments. *Wilderness Environmental Medicine* 2017; **28**: S124–34.
24. Ravi PR, Puri B. Fluid resuscitation in haemorrhagic shock in combat casualties. *Disaster Military Medicine* 2017; **3**: https://doi.org/10.1186/s40696-017-0030-2.
25. Barnhart G, Cullinan W, Pickett JR. Prolonged field care of a casualty with penetrating chest trauma. *Journal of Special Operations Medicine* 2016; **16**: 99–101.
26. Stein P, Kasere A, Sprengel K, et al. Change of transfusion and treatment paradigm in major trauma patients. *Anaesthesia* 2017; **72**: 1317–26.
27. Schochl H, Voelckel W, Schlimp CJ. Management of trauma haemorrhage - the European perspective. *Anaesthesia* 2015; **70**(Suppl. 1): 102–9.
28. Dutton RP. Management of traumatic haemorrhage – the US perspective. *Anaesthesia* 2015; **70**(Suppl. 1): 108–12.

29. Bridges LC, Waibel BH, Newell MA. Permissive hypotension: potentially harmful in the elderly? A National Trauma Data Bank Analysis. *American Journal of Surgery* 2015; **81**: 770–7.

30. Brunauer A, Koköfer A, Bataar O, Gradwohl-Matis I, Dankl D, Dünser MW. The arterial blood pressure associated with terminal cardiovascular collapse in critically ill patients: a retrospective cohort study. *Critical Care* 2014; **18**: 719.

31. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPRR randomised clinical trial. *Journal of the American Medical Association* 2015; **313**: 471–82.

32. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first six hours of massive transfusion improves outcomes in a large multi centre study. *American Journal of Surgery* 2009; **197**: 565–70.

33. Godier A, Samama C-M, Susan S. Plasma/platelets/red blood cell ratio in the management of the bleeding traumatised patient: does it matter? *Current Opinions in Anaesthesia* 2012; **25**: 242–7.

34. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *Journal of Trauma Injury Infection and Critical Care* 2003; **54**: 1127–30.

35. Cap A, Hunt BJ. The pathogenesis of traumatic coagulopathy. *Anaesthesia* 2015; **70**(Suppl. 1): 96–101.

36. Davenport R, Brohi K. Cause of trauma-induced coagulopathy. *Current Opinions in Anaesthesia* 2016; **29**: 212–9.

37. Gruen RL, Brohi K, Schreiber M, et al. Haemorrhage control in severely injured patients. *Lancet* 2012; **380**: 1099–108.

38. Senthilkumaran S, David SS, Manikam R, Thirumalaikolundusubramanian P. Permissive hypotension in a head-injured multi trauma patient: controversies and contradictions. *Journal of Anaesthesiology and Clinical Pharmacology* 2015; **31**: 428–9.

39. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *Journal of Trauma* 1993; **34**: 216–22.

40. Pigula FA, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. *Journal of Pediatric Surgery* 1993; **28**: 310–6.

41. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; **80**: 6–15.

42. Wiles M. Blood pressure in trauma resuscitation: 'pop the clot' vs. 'drain the brain'? *Anaesthesia* 2017; **72**: 1448–55.

43. Stern SA, Zink BJ, Mertz M, Wang X, Dronen SC. Effect of initially limited resuscitation in a combined model of fluid percussion brain injury and severe uncontrolled haemorrhage shock. *Journal of Neurosurgery* 2000; **93**: 305.

44. Hu Y, Wu Y, Tian K, et al. Identification of ideal resuscitation pressure with concurrent traumatic brain injury in a rat model of haemorrhage shock. *Journal of Surgical Research* 2015; **195**: 284–93.

45. Gunnar W, Jonasson O, Merlotti G, Stone J, Barrett J. Head injury and haemorrhage shock: studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. *Surgery* 1988; **103**: 398.

46. Hariri RJ, Firlick AD, Shepard SR, et al. Traumatic brain injury, haemorrhage shock, and fluid resuscitation: effects on intracranial pressure and brain compliance. *Journal of Neurosurgery* 1993; **79**: 421.

47. Vrettos T, Poimenidi E, Athanasopoulos P, et al. The effect of permissive hypotension in combined traumatic brain injury and blunt abdominal trauma: an experimental study in swines. *European Review for Medical and Pharmacological Sciences* 2016; **20**: 620–30.

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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