Hypotensive Resuscitation in Patients with Ruptured Abdominal Aortic Aneurysm

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Background. The technique of hypotensive resuscitation in haemorrhagic shock involves resuscitation to below normotensive blood pressures achieving the minimum perfusion pressure that will adequately perfuse vital organs until definitive arrest of haemorrhage.

Aim. To summarise the evidence for the use of hypotensive resuscitation in patients with uncontrolled haemorrhagic shock and ruptured abdominal aortic aneurysm (AAA).

Methods. A MEDLINE (1966–2004) and Cochrane library search for articles relating to hypotensive resuscitation was undertaken; see text for further details.

Results. Several animal studies exist using an abdominal aortotomy model of ruptured AAA. These have demonstrated improved tissue perfusion, decreased blood loss and improved survival associated with hypotensive resuscitation compared with aggressive resuscitation. There are several human studies advocating delayed rather than immediate resuscitation in trauma patients but careful review of the literature reveals no prospective studies of hypotensive resuscitation in patients with ruptured AAA.

Conclusions. Animal studies demonstrate superiority of hypotensive resuscitation over aggressive resuscitation but further research is required to assess its efficacy in patients with ruptured AAA.

Keywords: Hypotensive resuscitation; Ruptured aortic aneurysm.

Introduction

Aggressive fluid resuscitation has long been considered the cornerstone in the management of haemorrhagic shock and is widely taught at a basic level.1 The evidence for this approach originated from a canine model of haemorrhagic shock,2 where hypotension was maintained for several hours by controlled haemorrhage and arterial pressure was restored by the infusion of shed blood. Subsequent research demonstrated that crystalloid infusion equivalent to 2–3 times that of the volume of blood lost could adequately restore blood pressure3–5 and many pre-hospital and hospital professionals have employed this technique in the resuscitation of patients with ruptured abdominal aortic aneurysm (AAA).6 However, unlike the animal models, haemorrhage is not controlled before surgery in patients with ruptured AAA and there is considerable evidence that vigorous fluid replacement may exacerbate bleeding7–15 by causing dilutional and hypothermic coagulopathy associated with infusing large volumes of cold fluids; and secondary clot disruption from increased blood flow, increased perfusion pressure and decreased blood viscosity.

In 1918 Cannon16 introduced the concept of deliberate hypotension in the treatment of wounds to the torso with the intent of minimising internal bleeding.

‘Injection of a fluid that will increase blood pressure has dangers in itself. Haemorrhage in a case of shock may not have occurred to a marked degree because blood pressure has been too low and the flow too scant to overcome the obstacle offered by
the clot. 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’.

Recent data have challenged the rationale for aggressive fluid replacement in uncontrolled haemorrhagic shock. Increased survival and decreased blood loss have been demonstrated when patients are resuscitated to below normotensive blood pressures achieving the minimum perfusion pressure that will adequately perfuse vital organs until prompt and definitive arrest of haemorrhage (so-called, hypotensive resuscitation). This article reviews the evidence for the use of hypotensive resuscitation in patients presenting with ruptured AAA.

Methods

A MEDLINE (1966–2004) and Cochrane library search looking for articles relating to hypotensive resuscitation was performed. The terms resuscitation, hypotensive resuscitation, permissive hypotension, aortic aneurysm and uncontrolled haemorrhage were amongst those included. Further articles were identified by following MEDLINE links, by cross-referencing from the reference lists of major articles and by following citations for these studies.

Results

Animal models of hypotensive resuscitation (Table 1)

Several animal studies have been performed using an abdominal aortic tear or aortotomy as a model of ruptured AAA. Owens et al. randomised 20 swine to receive ‘pre-hospital’ Ringers lactate to restore cardiac index (CI) to 100% of base line (standard resuscitation) or 60% (limited pre-hospital resuscitation) for 20 min with a third group receiving no fluid resuscitation during this period. The animals underwent surgical repair of an abdominal aortic tear following which Ringers lactate was infused to maintain mean arterial pressure (MAP) at 80% of baseline. The volumes of pre-hospital and post-operative fluid resuscitation,

| Table 1. Summary of animal trials of hypotensive vs. normotensive resuscitation |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Author/animal model             | Mechanism of injury             | Resuscitation target            | Groups and endpoint of resuscitation | Results                        |
| Bickell/pig                     | Aortotomy                       | Fluid resuscitation or no fluid following haemorrhage | SR—80 ml/kg Ringers, HR—no fluid | 100% mortality (SR), no deaths (HR) |
| Kowalenko/pig                   | Preliminary bleed, aortotomy, bled to MAP 5 mmHg | Fluid resuscitation to achieve MAP for 60 min | SR—MAP 80 mmHg, HR—MAP 40 mmHg, C—nil | One hour mortality—62.5% (SR), 12.5% (HR), 87.5% (C); blood loss—39.9 ml/kg (SR), 8.2 ml/kg (HR), 6.7 ml/kg (C) |
| Owens/pig                       | Preliminary bleed, aortotomy      | Fluid resuscitation to achieve % pre-event CI, 20 min later surgery | SR—CI 100%, HR—CI 60%, C—no fluid | Increased blood loss and fluid requirement (SR); one death (SR and C), no deaths (HR) |
| Stern/pig                       | Preliminary bleed, aortotomy, bled to MAP 5 mmHg | Fluid resuscitation to achieve MAP; compare two models of HR | SR—MAP 80 mmHg, HR1—MAP 60 mmHg, HR2—MAP 40 mmHg | Mortality—78% (SR), 16% (HR1), 11% (HR2); reduced blood loss, Hb, oxygen carriage (SR vs. HR1, HR2); increased oxygen delivery (HR1 vs. HR2); reduced metabolic acidosis (HR1 vs. HR2, SR) |
| Capone/rat                      | Preliminary bleed and tail amputation | Resuscitation for 90 min followed by surgery | C—no fluid/surgery, NR—no preim fluid, HR—MAP 40 mmHg, SR—MAP 80 mmHg | C—all dead within hours, NR—five survive to surgery, HR—all survive to surgery, SR—two survive to surgery |
| Riddez/pig                      | Aortotomy                       | Fluid resuscitation at ratio to blood loss | HR1 1:1, HR2 2:1, SR 3:1, C 0:1 | 50% mortality (SR and C), 25% mortality (HR1 and HR2); rebleeding is cause of death in HR1; hypovolaemic shock is cause of death in HR1 |
| Varela/pig                      | Liver laceration                 | Resuscitation followed by surgery | C—no fluid, HR—MAP 60 mmHg, SR—MAP 75 mmHg | No deaths; increased blood loss and fluid requirement in SR; increased splancnic perfusion and oxygen delivery in HR |

C, control, NR, no resuscitation; HR, hypotensive resuscitation; SR, ‘standard’ resuscitation; MAP, mean arterial pressure; CI, cardiac index.
volume of intraperitoneal blood loss and haemoglobin loss were higher in the standard resuscitation group. Bickell\textsuperscript{10} studied 16 swine who were alternately assigned to receive no fluid or 80 ml/kg Ringers solution following an aortic tear. The volume of intraperitoneal blood was higher in the resuscitated group, all of whom died compared to none of the untreated group. Several of these studies\textsuperscript{10,18,19} were criticised for the lack of mortality in the untreated group, the inference being that these were not life-threatening models of uncontrolled haemorrhage. Kowalenko\textsuperscript{20} created a porcine model with high mortality in the untreated group. Prior to creating an aortotomy, animals were exsanguinated from a femoral artery catheter to achieve MAP of 30 mmHg. Following the aortic tear, animals were bled to MAP of 5 mmHg. Group 1 was resuscitated to 40 mmHg with saline, group 2 to 80 mmHg with saline and group 3 received no treatment. The 1-h survival was higher (87.5\% vs. group II: 37.5\%) and intraperitoneal blood loss was lower (8.2 ml/kg vs. group II: 39.9 ml/kg) in group I. Moderate resuscitation to purposely maintain a hypotensive state was associated with less blood loss and improved survival compared with conventional resuscitation or no treatment.

In the same porcine model, Stern \textit{et al.}\textsuperscript{21} examined the effects of limited fluid replacement in 54 swine bled to a pulse pressure of 5 mmHg followed by resuscitation to achieve MAP of 40, 60 or 80 mmHg. The mortality in the group resuscitated to 80 mmHg was significantly higher, intraperitoneal blood volume was higher and oxygen carrying capacity was lower compared with the other groups. Acidosis was lower and cardiac index higher in the group resuscitated to 60 mmHg compared to those resuscitated to 40 mmHg. Riddez \textit{et al.}\textsuperscript{22} randomised 32 swine to receive no fluid or Ringers lactate at a ratio to blood loss of 1:1, 2:1 or 3:1 commencing 10 min after aortotomy. Mortality was lower in the groups receiving 1:1 and 2:1 fluid (25\%) compared with no fluid or 3:1 fluid (50\%).

In a rat model of haemorrhagic shock and extremity trauma, Capone \textit{et al.}\textsuperscript{12} demonstrated improved survival at 3 days in the group who were immediately resuscitated to 40 mmHg compared to groups who were resuscitated to 80 mmHg or who received delayed treatment (60 vs. 0 vs. 10\%, respectively). Varela \textit{et al.}\textsuperscript{23} randomised 18 swine to receive either delayed resuscitation (no fluid), hypotensive resuscitation (to achieve MAP of 60 mmHg) or ‘aggressive’ resuscitation (to achieve MAP >75 mmHg) for 15 min following a liver laceration resulting in a fall in MAP to 40 mmHg. After this time the liver laceration was repaired and all animals received fluid to achieve a normal MAP of 75 mmHg. Volume of fluid resuscitation and blood loss were lower, and intestinal perfusion was higher in the delayed and hypotensive resuscitation groups.

A recent systematic review of animal trials comparing hypotensive and normotensive resuscitation demonstrated a relative risk of death associated with hypotensive resuscitation of 0.37 (95\% CI, 0.27–0.50).\textsuperscript{24}

\textit{Human studies in trauma victims}

Bickell \textit{et al.}\textsuperscript{25,26} performed randomised controlled trials in a single trauma centre between 1989 and 1992. A total of 598 patients with penetrating torso injury and a systolic BP of less than 90 mmHg at presentation were randomised to immediate fluid resuscitation (IR) (\textit{n}=309) or delayed resuscitation (DR) (\textit{n}=289) where fluid replacement was not commenced before arrival in the operating theatre. The average volume of fluid replacement was 2478 ml in the IR group (870 ml pre-hospital and 1608 ml in the emergency department) and 375 ml in the DR group (92 ml pre-hospital and 283 ml in the emergency department). In the IR group, systolic BP was significantly higher on arrival at the trauma centre (79 vs. 72 mmHg in the DR group; \textit{p}=0.02), haemoglobin concentration and platelet count were lower, and clotting times were prolonged compared with the DR group. The haemodynamic improvement in the IR group was not sustained to arrival in operating theatre and there was no significant difference in transfusion requirements at operation between the groups. Survival was significantly greater (70 vs. 62\% in the IR group; \textit{p}=0.04) and in-hospital stay for survivors was significantly shorter in the DR group. Sampalis \textit{et al.}\textsuperscript{27} further demonstrated that trauma patients who received pre-hospital fluid resuscitation were 2.3 (95\% CI, 1.02–5.3) times more likely to die compared to matched controls who did not receive pre-hospital fluid resuscitation. Hambly and Dutton\textsuperscript{28} demonstrated that trauma patients who received rapid fluid resuscitation were 4.8 times (95\% CI, 2.4–7.1) more likely to die compared to matched controls who were resuscitated with the same fluid volume but at a slower rate of infusion. In patients receiving more than 6 L of rapidly infused fluid the difference between actual and expected survival was striking (37 vs. 57\%; \textit{p}<0.0001). Dutton \textit{et al.}\textsuperscript{29} randomised 110 trauma victims with haemorrhagic shock to be resuscitated to a target systolic BP >100 or

\textsuperscript{Eur J Vasc Endovasc Surg Vol 31, April 2006}
70 mmHg. There was no effect on patient mortality and the authors concluded that systolic BP may be a poor marker of tissue oxygen delivery.

**Human studies in ruptured AAA**

There is a dearth of studies examining hypotensive resuscitation in patients with ruptured AAA. Lawler first speculated that pre-operative fluid resuscitation may lead to increased blood pressure and subsequent exsanguination in patients with ruptured AAA. Stanley Crawford compared his experience of 87 patients with ruptured AAA with 180 patients treated at a level 1 emergency centre in the USA. Both groups had comparable numbers of haemodynamically unstable patients but the 90-day survival rate in Crawford’s experience was 77% compared with a 30-day survival rate of 30% at the level 1 emergency centre. The 30-day survival rate amongst Crawford’s haemodynamically unstable patients was 58%. The level 1 emergency centre advocated aggressive fluid management with the infusion of more than 2 L of colloid pre-operatively. Crawford suggested that improved outcome in his experience was a consequence of hypotensive resuscitation with a target systolic BP of 50–70 mmHg, and withholding fluids to allow clot formation and avoidance of iatrogenic coagulopathy.

In a review of risk factors associated with death following surgical repair of ruptured AAA Hardman et al. correlated hypotension at presentation with mortality. The infusion of more than 3.5 L of fluid prior to surgery was associated with an increased relative risk of death by a factor of 3.54 (95% CI 1.39–8.98; \( p = 0.008 \)). No data were presented on the association between hypotension, the volume of infused fluid and subsequent mortality. However, as the relative risk of death associated with BP (per 10 mmHg) was 0.91 (95% CI 0.82–1.00; \( p = 0.044 \)), it can be inferred that the volume of infused fluid has a more significant impact on the risk of death than systolic BP.

In patients undergoing emergency endovascular stent-grafting for suspected ruptured AAA, there is likely to be a delay in obtaining adequate pre-operative imaging to confirm the diagnosis and assess aneurysm suitability for the endovascular technique. Consequently, hypotensive resuscitation to a target systolic BP of 50 mmHg has been advocated until the patient is in the operating room and a guidewire has been placed in the supracoeliac aorta to allow subsequent inflation of an aortic occlusion balloon should the patient become haemodynamically unstable. Endovascular repair of ruptured AAA has been shown to be associated with a significant reduction in morbidity and mortality compared with open repair in selected patients. Hypotensive resuscitation techniques may contribute to some of the improvement in outcome associated with the endovascular approach.

**Discussion**

Early animal studies demonstrated improved survival and decreased blood loss associated with no fluid resuscitation compared with fluid resuscitation aimed at restoring a near normal MAP. Subsequent animal studies of more severe injury demonstrated improved tissue perfusion and improved survival associated with limited fluid resuscitation aiming at a MAP of 50 and 75% of pre-procedure MAP. These well controlled animal models produce consistent data supporting the use of hypotensive resuscitation in young, healthy animals with no co-morbidity, a group dissimilar to the patients presenting with a ruptured AAA who are elderly and frequently have significant cardiovascular and pulmonary co-morbidity. Small patient numbers and heterogenous groups of patients, protocol violations and the retrospective nature of some studies have a negative impact on the conclusions regarding efficacy in humans. While several human studies have advocated delayed rather than immediate resuscitation in trauma patients, careful review of the literature reveals no prospective studies of the technique of hypotensive resuscitation in patients with ruptured AAA. While it is intuitive to the vascular surgeon that hypotensive resuscitation may have an important role in the management of patients with ruptured AAA, the lack of data suggests that further research is required to assess the efficacy of this technique in this and other groups of critically ill patients.

The ideal trigger to fluid resuscitation in ruptured AAA remains to be identified. Crawford’s target was a systolic BP of 50–70 mmHg while current practice in trauma victims aims at maintaining a systolic BP of 80 mmHg. In practice, the ideal pressure is likely to vary between subjects and depending on co-morbidity. Patients with ruptured AAA are elderly with atherosclerosis and will require higher coronary, cerebrovascular and renal perfusion pressures to avoid ischaemia compared with younger trauma patients without atherosclerotic disease. The lowest
systolic pressure that maintains adequate tissue perfusion is the aim of therapy and clinicians must, therefore, achieve a balance between inadequate fluid replacement which will result in end-organ ischaemia and excess replacement which will lead to rebleeding.22 Clinical markers of ischaemia such as deterioration in conscious level and ST segment depression on electrocardiography may be more valuable as a guide to the need for fluid replacement than a pre-determined parameter such as systolic blood pressure.29 These have previously been identified as independent risk factors for mortality following repair of ruptured AAA.32

One would anticipate that hypotensive resuscitation will have an effect on ischaemia-reperfusion injury (IRI). Stern et al.15 demonstrated a beneficial effect on oxygen delivery and tissue ischaemia in animals resuscitated to a target MAP of 60 mmHg compared with those animals resuscitated to MAP of 40 or 80 mmHg. Similarly, Capone et al.12 demonstrated increased tissue ischaemia in animals who received standard resuscitation to 80 mmHg or delayed resuscitation compared with those animals resuscitated to 40 mmHg. Although large volumes of fluid replacement may maximise perfusion pressure, the subsequent haemodilution effect may have a negative impact on oxygen carriage and delivery. One can speculate that limited fluid replacement may exert a beneficial effect by minimising haemodilution, thereby maintaining oxygen delivery and attenuating subsequent IRI.

There is considerable evidence from animal studies to demonstrate superiority of hypotensive resuscitation over aggressive resuscitation but further research is required to assess the efficacy of this technique in patients with ruptured AAA. The effects of hypotensive resuscitation on oxygen delivery and IRI in hypotensive patients with ruptured AAA is unknown and merits investigation.

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