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Haemodynamic changes in trauma

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Editor's key points

- With increasing blood loss the systemic arterial pressure (SAP) is at first maintained and then decreases.
- The SAP response to haemorrhage may be altered by musculoskeletal and blast injury.
- Protracted hypotensive resuscitation may be associated with the development of severe acidosis.
- Morphine modifies the response to haemorrhage in some species and this is currently being investigated in man.

Trauma is the leading cause of death during the first four decades of life in the developed countries. Its haemodynamic response underpins the patient's initial ability to survive, and the response to treatment and subsequent morbidity and resolution. Trauma causes a number of insults including haemorrhage, tissue injury (nociception) and, predominantly, in military casualties, blast from explosions. This article discusses aspects of the haemodynamic responses to these insults and subsequent treatment. 'Simple' haemorrhage (blood loss without significant volume of tissue damage) causes a biphasic response: mean arterial blood pressure (MBP) is initially maintained by the baroreflex (tachycardia and increased vascular resistance, Phase 1), followed by a sudden decrease in MAP initiated by a second reflex (decrease in vascular resistance and bradycardia, Phase 2). Phase 2 may be protective. The response to tissue injury attenuates Phase 2 and may cause a deleterious haemodynamic redistribution that compromises blood flow to some vital organs. In contrast, thoracic blast exposure augments Phase 2 of the response to haemorrhage. However, hypoxaemia from lung injury limits the effectiveness of hypotensive resuscitation by augmenting the attendant shock state. An alternative strategy ('hybrid resuscitation') whereby tissue perfusion is increased after the first hour of hypotensive resuscitation by adopting a revised normotensive target may ameliorate these problems. Finally, morphine also attenuates Phase 2 of the response to haemorrhage in some, but not all, species and this is associated with poor outcome. The impact on human patients is currently unknown and is the subject of a current physiological investigation.

Keywords: haemodynamics; wounds and injuries

Trauma is the leading cause of death in the first four decades of life in the developed countries.[1][2] Haemorrhage is the leading cause of trauma-related death in the military setting[3] and is the second leading cause of death (after traumatic brain injury) in the civilian setting.[4] In military battlefield casualties, explosions are currently the primary mechanism of trauma,[5] while in civilian practice non-blast blunt and penetrating injuries account for most trauma. A trauma casualty therefore suffers a number of insults that often include severe blood loss (and haemorrhagic shock), tissue injury and, in the case of military casualties, blast injuries. All of these insults lead to specific haemodynamic responses, components of which interact to provide physiological challenges for the casualty and impact on responses to treatment such as resuscitation. The aim of this article is to discuss aspects of the haemodynamic responses to haemorrhage and injury, and their impact on the response to resuscitation.

Response to haemorrhage

Cardiovascular response to haemorrhage alone

Haemorrhage in the absence of major amounts of tissue damage is defined as 'simple haemorrhage'. Although it is uncommon in trauma, it is seen clinically in other circumstances (e.g. obstetric bleeding or the result of ruptured oesophageal varices).[6][7] Examining the response to simple haemorrhage provides a convenient starting point before progressing to a discussion of how it is altered by concomitant insults such as nociception in trauma and the effects of drug treatment on the response.

The initiating event is a reduction in venous return because of blood loss, which leads to reduced cardiac filling and a decrease in cardiac stroke volume that in turn causes a decrease in arterial pulse pressure. This reduction in pulse pressure effectively unloads the arterial baroreceptors, which at normal or reduced pressures are sensitive to the rate of change of blood pressure within a pulse and also the absolute level of pressure.[8] The pattern of physiological responses to progressive simple haemorrhage is biphasic.[9] The baroreceptor unloading leads to an initial reflex tachycardia (as a result of vagal inhibition and an activation of sympathetic efferent activity), increase in peripheral vascular resistance and hence maintenance of blood pressure.[6][10] However, as haemorrhage progresses, and blood loss exceeds 20–30% of total blood volume, a depressor phase becomes apparent. This involves a vagally mediated bradycardia [inhibited by atropine,[10] a

reduction in peripheral vascular resistance[9 11 12] and a marked decrease in arterial blood pressure (Fig. 1)]. This second phase is not because of a failure of the baroreflex, because the latter's sensitivity is increased at this stage,[13] nor is it a pre-terminal event,[7 14] but rather it is because of the activation of additional reflexes. The identity of the afferent limbs of these reflexes is uncertain,[15 16] although the cardiac afferent C-fibres may be involved.[17] The end result in a conscious patient is pre-syncope followed by syncope. It is now thought that this second phase of the response to haemorrhage confers some degree of protection because the bradycardia increases diastolic filling time resulting in a small increase in stroke volume and improved coronary perfusion which principally occurs during diastole, although urgent action to restore venous return to some degree is needed for these casualties as they are nearing the end of their ability to compensate. Indeed, some studies have advocated boosting venous return by increasing the effects of the 'respiratory pump' using an inspiratory impedance device as a short-term measure to limit the decrease in cardiac output during haemorrhage.[18]
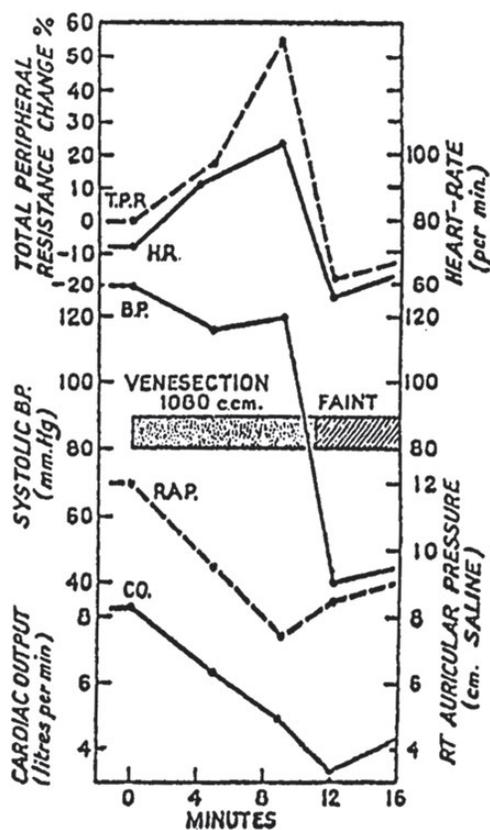

Fig 1 Effects of a progressive 'simple' haemorrhage in a male volunteer showing a biphasic response. Blood was withdrawn by venesection until the subject fainted. TPR, total peripheral resistance; HR, heart rate; BP, arterial blood pressure; RAP, right atrial (auricular) pressure (central venous pressure); CO, cardiac output. Reproduced from Barcroft and colleagues, with permission from Elsevier.[9]

Simulated blood loss in volunteers

Progressive application of lower body negative pressure (LBNP) is a well-established technique used to simulate haemorrhage[19–21] and also a range of other conditions including syncope associated with orthostasis.[22 23] Its use as a model of haemorrhage has recently been confirmed in a study comparing directly the responses with LBNP and actual haemorrhage, concluding that the haemodynamic responses to LBNP and haemorrhage are similar.[24] In the LNBP technique a subject is asked to lie supine with the lower portion of the body (from the waist down) sealed in a chamber. The pressure within the chamber is reduced to sub-atmospheric levels (application of LBNP), which results in blood pooling in the veins of the legs and pelvis. As the LBNP is gradually increased (made more negative with respect to atmospheric), progressively greater amounts of blood are trapped in the lower body and there is a corresponding decrease in venous return to the heart, simulating the effects of haemorrhage. Using this technique it is possible to elicit both the initial compensatory response to haemorrhage (tachycardia while blood pressure is maintained) and the later depressor phase (reflex bradycardia and hypotension) leading to pre-syncope and then syncope.[22 23]

It has long since been recognized by physiologists, anaesthetists, and intensivists that decreases in mean arterial blood pressure (onset of hypotension) are a poor measure of the degree of haemorrhage, principally because the baroreflex maintains blood pressure until blood loss is severe. The situation is further complicated by the interaction of additional reflexes and responses when various forms of injury are superimposed on the blood loss (see below). Several groups have postulated that measures of global blood flow (such as stroke volume or cardiac output),[25] tissue perfusion, or oxygenation[26–30] may give a more timely warning of hidden haemorrhage, because the former are part of the initial effect of haemorrhage while the latter change in response to the physiological alterations (see above) that delay the overt decreases in arterial blood pressure. An interesting suggestion, particularly relevant to the subject of this article, is that alterations in arterial blood pressure waveforms and beat-to-beat pressure variability might also be informative during progressive hypovolaemia. Many anaesthetists and intensivists would empirically view an increasing variability in arterial pressure waveform as a potential indicator of an 'empty' circulation in the absence of any other obvious cause. This principle has been developed further in studies utilizing LBNP to derive a 'compensatory reserve index' (CRI), which has been shown to be of value in predicting when a subject nears the point of decompensation (Phase 2 of the response to simulated blood loss).[31 32] It will be interesting to see how this index performs when the response to haemorrhage is complicated by other responses seen in trauma. If CRI continues to be successful, then it may provide an important method of assessing ongoing haemorrhage in casualties.

Early systemic response to musculoskeletal injury

The neural nociceptive barrage initiated by musculoskeletal injury causes profound changes in cardiovascular control

resulting in alterations in arterial blood pressure, regional oxygen delivery, and the response to any concomitant haemorrhage, all of which have important implications for morbidity and mortality.

Blood pressure, heart rate, and underlying neural mechanisms

Tissue injury or ischaemia produces an increase in arterial blood pressure accompanied by a tachycardia.[33] The increase in arterial blood pressure that accompanies injury is largely mediated by an increase in sympathetic outflow to the vasculature and a consequent increase in total peripheral resistance. This intense sympathetically mediated vasoconstriction induced by injury could lead to a reduction in blood flow to vital organs such as the gut and kidney and possibly lead to ischaemic damage of these organs,[34] hence contributing to the pathophysiology of the response to injury and its sequelae such as multiple organ failure.

Oxygen transport

The injury-induced diversion of blood supply away from vital organs has important implications for whole body utilization of the available oxygen delivery (DO_2) and a concept known as 'critical oxygen delivery'. When cardiac output, and hence whole body DO_2, is progressively reduced (e.g. because of haemorrhage), the body as a whole responds by extracting more oxygen from the available blood flow to maintain oxygen consumption (VO_2). However, this process cannot be extended indefinitely and there comes a point when VO_2 starts to decrease as DO_2 is reduced further. This point at which VO_2 becomes dependent on DO_2 is called the 'critical oxygen delivery' (DO_2Crit) and represents the point at which organs in the body start to suffer physiological damage because of an inadequate DO_2. There is evidence that activation of a neural nociceptive barrage elevates DO_2Crit and reduces a patient's ability to extract oxygen from the available blood supply.[35] This increases a patient's susceptibility to problems of reduced oxygen delivery.

Modulation of the response to haemorrhage by the response to musculoskeletal injury

The cardiovascular changes elicited by a progressive 'simple' haemorrhage are markedly attenuated by the presence of concomitant tissue injury.[10] The initial increase in heart rate after a loss of 10–15% blood volume is reduced, and the vagal bradycardia after greater losses prevented. The attenuation of the heart rate changes normally associated with blood loss seems to offer some degree of protection against the hypotensive effects of a severe haemorrhage.[10] However, this protection may be more apparent than real, as a lower survival rate has been demonstrated in animals subjected to haemorrhage and concomitant electrical stimulation of the sciatic nerve (to simulate injury) compared with animals subjected to haemorrhage alone.[34] It is possible that the better maintenance of blood pressure is achieved at the expense of intense peripheral vasoconstriction leading to ischaemic organ damage that will

exacerbate the severity of injury. It is tempting to speculate that the splanchnic circulation may be selectively vulnerable to such ischaemic damage. There is evidence that, when haemorrhage is superimposed on a background of somatic afferent stimulation (to mimic injury), there is a relative redistribution of blood flow from the gut towards skeletal muscle (in contrast to the pattern seen with simple haemorrhage).[36 37] This diversion of blood flow (oxygen delivery) away from metabolically active organs towards relatively inactive resting skeletal muscle may explain the increase in critical oxygen delivery elicited by somatic afferent nerve stimulation[35] because it effectively 'wastes' a proportion of the cardiac output. Ischaemic damage to the intestinal mucosa may lead to an increased inflammatory response,[38 39] and possibly even increased intestinal permeability and enhanced translocation of endotoxin.[40–42] Therefore, the impairment in cardiac function and tissue oxygen delivery associated with blood loss is greater if the haemorrhage is superimposed on nociceptive nerve stimulation compared with haemorrhage alone.[43] If the haemorrhage is superimposed on real rather than simulated tissue injury, the tolerance to blood loss is reduced even further.[44]

Injuries from explosions (blast injuries)

Injuries from explosions are complex and usually consist of several parts that are defined according to the component of the explosion that caused them.[45] To understand these injuries, we must therefore consider the component parts of an explosion and how they interact with the body. When an explosive detonates it generates an extremely rapid increase in pressure in the immediate vicinity of the explosion: this increase in pressure is almost instantaneous with a rise time of a few microseconds and lasts for a few milliseconds with conventional explosives. The wave of pressure (called the 'peak overpressure') travels outwards at supersonic velocities as a wave of pressure. This is called the 'shock wave'. However, the magnitude of the peak overpressure declines as it travels away from the site of the explosion, initially by an inverse cube relation in which a doubling of the distance reduces the pressure to one-eighth.

As the shock wave is a very brief event with conventional explosives, it does not cause the casualty to move any great distance; this is not the part of the explosion that 'throws things around'. The shock wave can, however, cause serious injury that is defined as 'primary blast injuries', which are almost (but not completely) unique to injuries caused by explosions. Gas containing organs are particularly susceptible and 'blast lung', characterized by pulmonary contusion and rapid development of pulmonary oedema with a consequent reduction in pulmonary gas transfer is an example of primary blast injury.[46 47]

Blast lung is a primary blast injury. The shock wave causes an immediate lung injury which is characterized by rupture of alveolar capillaries, the influx of blood, and extravasation of oedema fluid into lung tissue,[48 49] giving rise to haemorrhagic foci that can be substantial depending on the level of blast loading. The intrapulmonary haemorrhage and oedema

contribute to the initial respiratory compromise in blast lung.[50] The problem is exacerbated because free haemoglobin (Hb) and extravasated blood have been shown to induce free radical reactions which cause oxidative damage[50] and initiates/augments a pro-inflammatory response.[51] Free Hb also causes an accumulation of inflammatory mediators and chemotactic attractants,[52] thereby amplifying the problem.

Fragments of the munition casing and pre-formed fragments contained within the device, and surrounding debris energized by the explosion, are propelled outwards and can collide with the casualty. Injuries from these fragments and debris are defined as 'secondary blast injury' which essentially are conventional blunt and penetrating injuries resulting in tissue damage and haemorrhage.

In addition, the explosion gives rise to a very large volume of hot gas. This literally pushes air and debris outwards, causing more projectile hazards, and acts over a sufficiently long time course to physically throw casualties against other objects, causing blunt injuries classified as 'tertiary blast injuries'. This movement of air is called the 'blast wind'. The shock wave and the blast wind are sometimes collectively called the 'blast wave'.

Other injuries which include burns, responses to toxic chemicals associated with the blast and exaggerated inflammatory responses fall into quaternary and quinary categories,[45] [53] but these are beyond the scope of this article.

A victim of explosive injury is therefore likely to suffer a mixture of these blast-related injuries. Secondary blast injuries account for the majority of blast injuries in survivors, particularly when the explosion has occurred in an open space, although about 11% of the seriously injured also exhibit blast lung.[54] [55] When the explosion occurs in a confined space, the proportion of seriously injured survivors exhibiting blast lung increases dramatically[56] [57] because the shock wave can be amplified and reflected near solid structures, thereby increasing the degree to which a casualty is exposed to the shock wave. We are therefore faced with a casualty who is likely to have extensive tissue damage and severe blood loss, and in a clinically significant minority, also have blast lung resulting in hypoxaemia.

Cardiorespiratory response to primary blast injury to the thorax (blast lung)

A number of experimental studies and clinical reports indicated that primary blast injury to the thorax produces a characteristic triad comprising bradycardia, prolonged hypotension and apnoea followed by rapid shallow breathing[47] (Fig. 2). This response is thought to be an autonomic reflex. More recent studies have shown that the response also includes a reduction in vascular resistance, at least in skeletal muscle (Fig. 2).

The bradycardia and apnoea seen after blast are both mediated by a vagal reflex.[58] [59] The aetiology of the hypotension seen after primary blast injury is complex. The decrease in blood pressure appears to be because of a decrease in peripheral resistance and cardiac output, the latter because of a myocardial impairment which can last many hours after

blast injury.[60] Although the autonomic nervous system plays some part in the hypotension, it is not solely responsible. Recent findings have suggested that primary blast injury causes a rapid release of the potent vasodilator nitric oxide (NO) from the pulmonary circulation,[61–63] which could in theory lead to a systemic response that includes vasodilatation (J.L. Atkins, WRAIR, personal communication, 2008).

Blast lung is therefore a progressive condition characterized by the development of pulmonary inflammation and oedema after initial intrapulmonary haemorrhage as a consequence of damage by the blast shock wave. The combined influence of pulmonary haemorrhage and oedema is to reduce pulmonary gas transfer and lead initially to hypoxaemia and, with worsening blast lung, hypercarbia. Thoracic, but not abdominal,[64] blast produces a triad of bradycardia, hypotension, and apnoea. The bradycardia and apnoea are mediated entirely by a vagal reflex, the most likely candidate being the pulmonary afferent C-fibre reflex. The effects of the hypoxia and altered cardiovascular reflexes can have profound effects on the ability of the casualty to respond to concomitant or further events such as haemorrhage and resuscitation.[65]

Effects of blast injury on the response to haemorrhage and resuscitation

Interaction between the responses to thoracic blast and haemorrhage

Thoracic blast has been shown to augment the bradycardic, hypotensive response to haemorrhage.[66] Furthermore, the effect of blast on the response to haemorrhage can be attenuated by morphine.[66] However, the mechanism whereby the depressor response to severe haemorrhage is augmented by the response to blast is unknown. In experimental studies, enhanced blood loss can be discounted as the underlying cause because there was no post-mortem evidence of additional blood loss into the body cavities. It is therefore possible that the reflex initiated by exposure to blast modifies one of the reflexes mediating the response to haemorrhage.

Two possibilities are immediately obvious. Either the response to blast inhibits the baroreflex (responsible for the compensatory Phase 1 of the response to blood loss) or it augments the depressor reflex (responsible for the hypotensive Phase 2 of the response to haemorrhage). Of these two possibilities, the latter appears the most attractive because treatment with morphine (known to block the depressor reflex after simple haemorrhage) also attenuates the bradycardic, hypotensive response to blood loss after blast and uncovers a tachycardic response in its place.[66]

Effects of blast injury on the response to resuscitation

Once catastrophic haemorrhage has been arrested,[67] fluid resuscitation is often needed to sustain life until the casualty is evacuated to surgical care. Military evacuation timelines can differ significantly from those normally found in civilian settings. Although evacuation times in mature military operations are predominantly short, as are now being seen in Afghanistan, timelines in less mature settings (as we have seen recently)[68] [69]
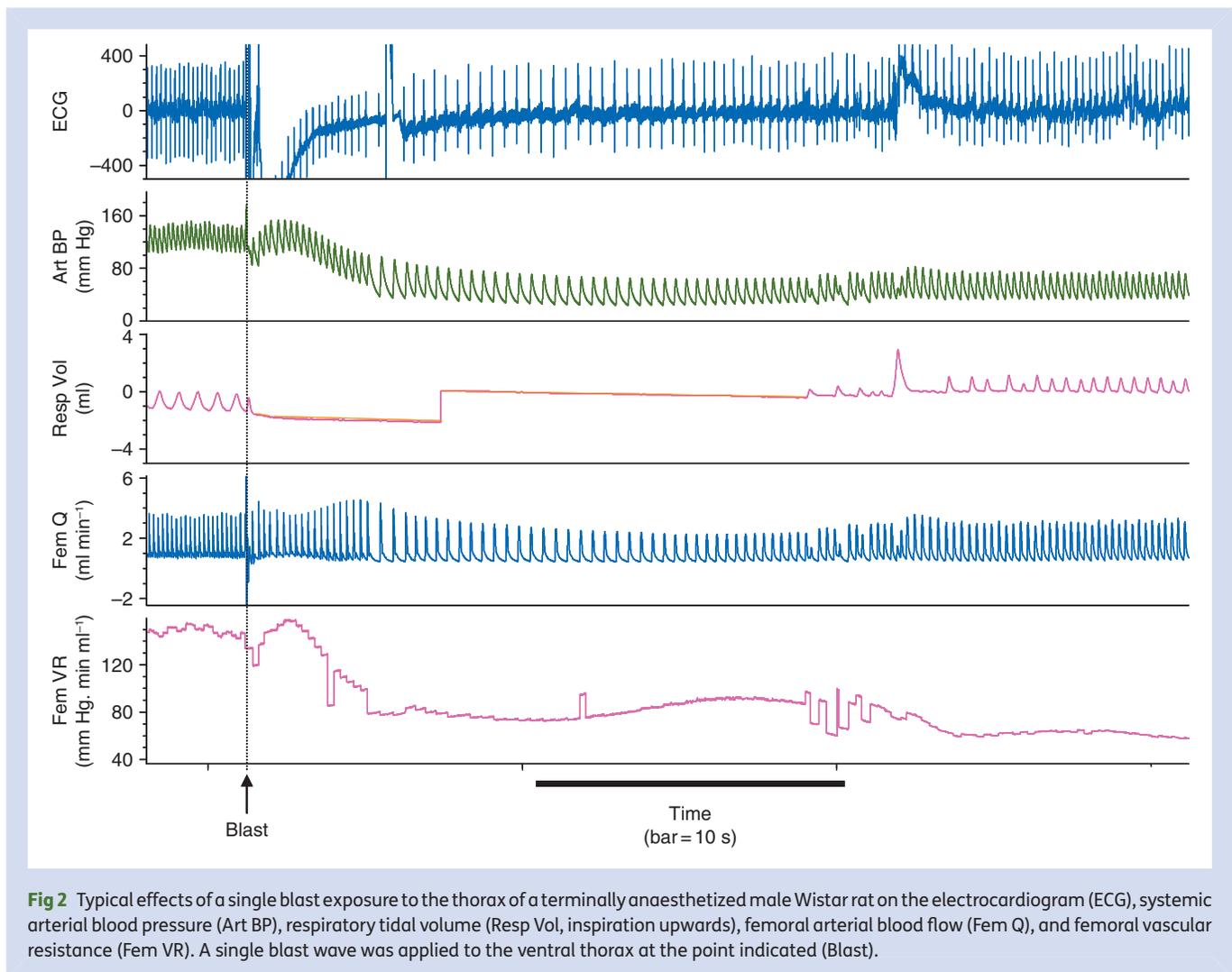
Fig 2 Typical effects of a single blast exposure to the thorax of a terminally anaesthetized male Wistar rat on the electrocardiogram (ECG), systemic arterial blood pressure (Art BP), respiratory tidal volume (Resp Vol, inspiration upwards), femoral arterial blood flow (Fem Q), and femoral vascular resistance (Fem VR). A single blast wave was applied to the ventral thorax at the point indicated (Blast).

can be considerably longer. These concepts may also be applicable to civilian settings (e.g. after terrorist bombings where there is often disruption to infrastructure and security issues relating to secondary devices resulting in delayed evacuation).

A key feature of pre-hospital resuscitation of hypovolaemic casualties is the maintenance of an acceptable oxygen delivery to sustain life, and if possible to limit physiological deterioration while minimizing the risk of disrupting nascent blood clots, causing re-bleeding as the casualty is evacuated to surgical care. A number of authorities therefore advocate the use of 'hypotensive' resuscitation where fluid is limited or withheld to deliberately allow blood pressure to remain below normal levels to minimize the risk of iatrogenic re-bleeding.[70] [71] The evidence base underpinning this relates predominantly to short 'pre-hospital' resuscitation periods in normoxic casualties,[72–74] therefore the situation may develop differently when evacuation becomes prolonged or is complicated by, for example, blast lung and the resultant hypoxaemia.

A preliminary study in terminally anaesthetized pigs was designed to investigate the physiological impact of prolonged simulated evacuation times on the efficacy of hypotensive resuscitation in the presence and absence of whole body blast exposure (resulting in blast lung and hypoxaemia). The overall finding was that prolonged hypotensive resuscitation led to the development of a profound shock state and metabolic acidosis. Whilst this was acceptable for the first hour of resuscitation, it thereafter became overwhelming when performed on a background of hypovolaemia and blast injury, leading to rapidly increasing mortality.[75] As the response to hypotensive resuscitation was acceptable for the first hour, a new paradigm was proposed 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'.

The novel hybrid resuscitation strategy was evaluated in a model of military trauma and extended evacuation times in terminally anaesthetized pigs.[65] The model included an uncompressed Grade IV liver injury to assess whether the new resuscitation strategy would initiate re-bleeding.

Animals were randomly allocated to one of the four groups in a 2×2 design based on the type of injury and treatment strategy:

Injury: all had severe haemorrhagic shock (loss of 30% total estimated blood volume and uncompressed Grade IV liver injury), two groups were also subjected to blast injury while two were not.

Resuscitation strategy: two groups were resuscitated according to NICE and original military guidelines involving hypotensive resuscitation to a simulated palpable radial pulse (target systolic blood pressure of 80 mm Hg, hypotensive) while the other two groups received 'novel hybrid resuscitation' comprising initial hypotensive resuscitation for 60 min followed by a revised normotensive target (systolic pressure of 110 mm Hg, hybrid) thereafter. All resuscitation was performed using normal saline to simulate far-forward pre-hospital conditions.

The primary endpoint was survival over an 8-h period simulating prolonged evacuation. Secondary outcome variables included physiological indices of deterioration such as metabolic acidosis and inflammatory state.

Novel hybrid resuscitation was associated with a significantly increased survival time compared with prolonged hypotensive resuscitation in blast-injured groups (Fig. 3). In contrast, there was no significant difference in survival time between novel hybrid and hypotensive resuscitation in the absence of blast injury (Fig. 3). A statistically and clinically significant metabolic acidosis developed in all groups during the hypotensive phase of resuscitation, characterized by a significant decrease in arterial base excess (Fig. 4). In animals given novel hybrid resuscitation the metabolic acidosis was reversed after the onset of the normotensive phase of resuscitation. In contrast, animals given prolonged hypotensive resuscitation after blast injury and haemorrhage showed a continued decrease in arterial base excess until the animals succumbed. Continued hypotensive resuscitation after haemorrhage in the absence of blast injury resulted in a severe, sustained, metabolic acidosis. A detailed analysis of oxygen transport suggested that the improvement seen with the hybrid resuscitation strategy was associated with enhanced tissue oxygen delivery because animals given hypotensive resuscitation maintained maximal oxygen extraction in an attempt to sustain delivery, while those given hybrid resuscitation were able to decrease below the ceiling in the normotensive phase while the metabolic acidosis was reversed.[65] This physiological effect on oxygen transport and shock was seen in both injury strands.[65] Therefore, hybrid resuscitation conferred physiological advantage even in the absence of blast injury. Further analysis failed to find any evidence of re-bleeding associated with hybrid resuscitation from the uncompressed Grade IV liver injury,[65] but did find that hybrid resuscitation was associated with an attenuated systemic inflammatory response[65] and reduced acute coagulopathy.[76]

Hybrid resuscitation, in this experimental study, was therefore found to be superior to hypotensive resuscitation for extended evacuation times (up to 8 h) in a model of survivable battlefield injury. This should not be viewed as a simple challenge to hypotensive resuscitation but rather sets boundaries to its application when timelines of evacuation are extended, especially if there is concomitant lung injury that reduces oxygenation. Clinical decisions are often based on a compromise representing a balance of risk, and resuscitation is no exception. The evaluation of the casualty should be made on a case-by-case basis. Wherever possible the decision making will include the potential risk of re-bleeding and factors predisposing to physiological compromise (e.g. lung injury) based on nature of injury, together with the imminence of evacuation. More recent studies are focusing on potential additional
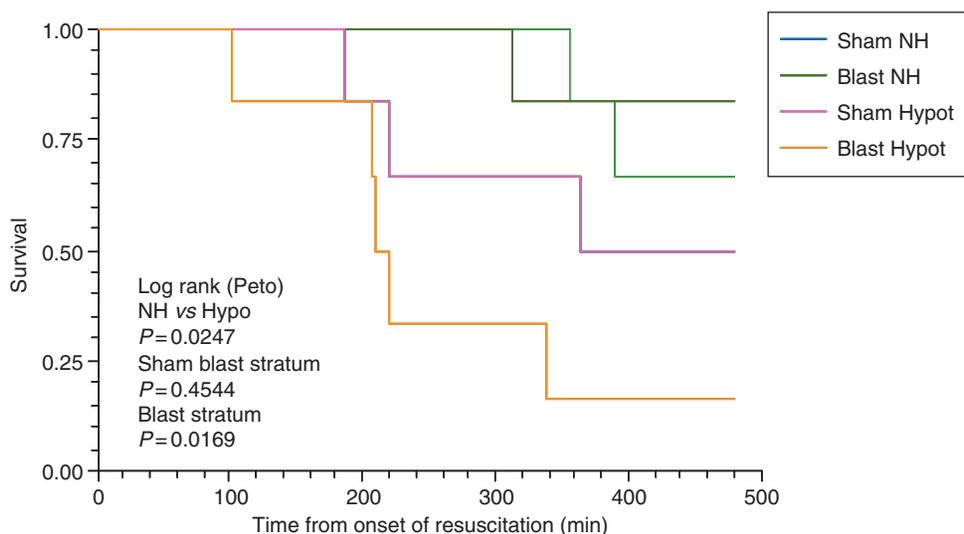
Fig 3 Kaplan–Meier survival plots for four groups of terminally anaesthetized animals subjected to either sham blast (Sham) or blast (Blast), haemorrhagic shock and novel hybrid (NH) or hypotensive (Hypot) resuscitation with 0.9% saline (NS).
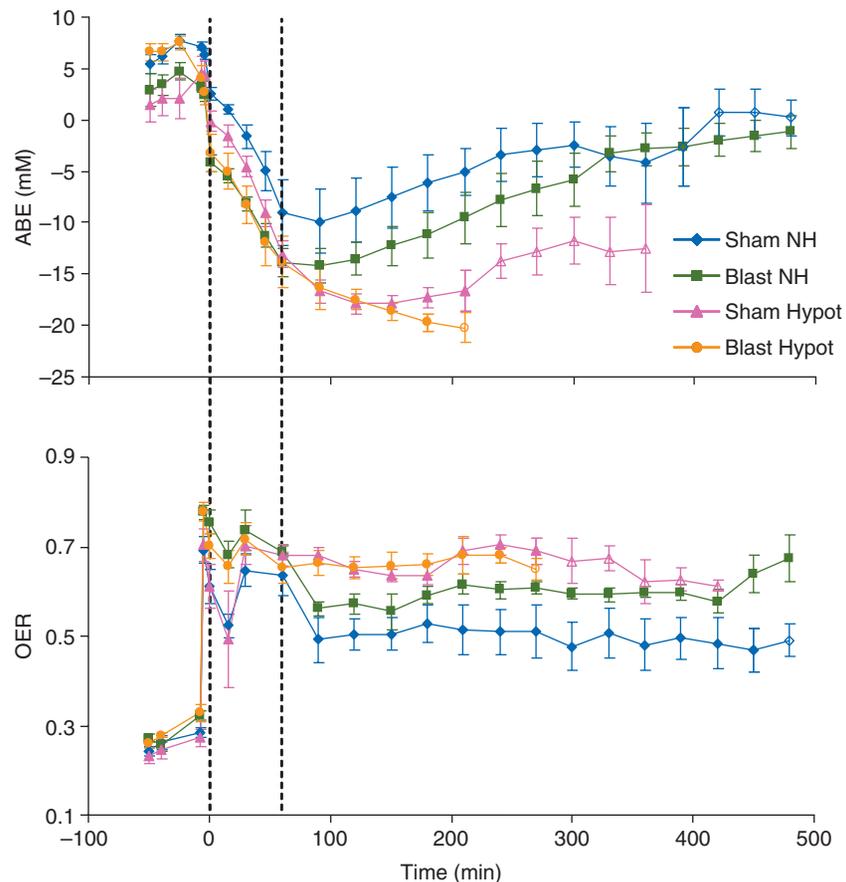
Fig 4 Arterial base excess (ABE) and oxygen extraction ratio (OER) in four groups of terminally anaesthetized animals subjected to either sham blast (Sham) or blast (Blast), haemorrhagic shock, and resuscitation. The first dotted line represents the onset of resuscitation (hypotensive in all groups). The second dotted line indicates the onset of normotensive resuscitation in NH groups and continued hypotensive resuscitation in the Hypot groups.

benefits associated with using blood products (combined packed red blood cells and fresh frozen plasma, PRBC:FFP, 1:1 ratio) in a simulated pre-hospital setting. Preliminary results suggest a possible benefit associated with pre-hospital administration of PRBC:FFP, at least in injury strands without blast, although it should be stressed that these studies are ongoing and no definitive results are available yet.[77]

Effects of opioid analgesic agents on the response to haemorrhage and resuscitation

Morphine is the current standard for analgesia in severe injury in military battlefield casualties.[70] Morphine can also be used for a number of civilian casualties. However, there is evidence that some analgesic agents including the opioids can have profound effects on the response to haemorrhage. Unfortunately, there are important differences between the responses reported using a range of models, and there is a lack of data to allow clear comparison with conscious humans.

In anaesthetized rats and conscious and anaesthetized rabbits pre-treatment with morphine delays or attenuates the second phase of the response to 'simple' haemorrhage (i.e. the bradycardia is blocked and the decrease in blood pressure is delayed until a larger reduction in blood volume has occurred).[78–81] Furthermore, when morphine is administered during active arterial haemorrhage in anaesthetized rats, the decrease in blood pressure is temporarily reversed and the bradycardia is blocked.[78] In contrast, morphine augments the second phase of the response to haemorrhage in sheep.[82] There are no systematic reports of the effects of morphine on the response to blood loss in humans, although some (unreferenced) textbooks suggest that morphine is contraindicated in hypovolaemia as it may exacerbate shock.

When morphine is given during an established shock phase in a model of combined blood loss and tissue injury in anaesthetized rats, it has little effect on blood pressure, but attenuates the response to subsequent resuscitation.[83] Despite a number of differences in the effects of morphine on the pattern of response to blood loss in various animal studies, it is agreed that the effect of morphine is deleterious and leads to increased mortality during prolonged haemorrhagic hypovolaemia in rats.[83–85] It should be stressed that this increased

mortality occurs during prolonged (many hours) haemorrhagic shock, which can occur when evacuation to surgical care is delayed (e.g. for some military battlefield casualties or more rarely in civilian trauma victims). Although the mechanism of the deleterious effect is unknown, it may relate to reduced tissue oxygen delivery because of the haemodynamic response to morphine whereby blood pressure is better maintained at the expense of blood flow to vital organs as a result of increased peripheral resistance.

Unfortunately, the cardiovascular effect of opioids after haemorrhage in humans is unknown—to put it simply, whether there is a problem regarding the cardiovascular effects of analgesic agents in human patients may depend on whether Man is a rat or a sheep, or neither. Ongoing studies are now examining the effects of morphine on the response to brief simulated haemorrhage using LBNP in human volunteers. It must be stressed that the deleterious effects reported in rats is not a risk in the volunteer study because the deleterious effect represents the consequence of several hours of un-resuscitated or minimally resuscitated haemorrhagic shock. The human volunteer study simply examines the effects of morphine on the short-term (minutes) reflex effects that would underpin a longer standing deleterious effect. It should also be stressed that these deleterious effects, if they exist in humans, are in the context of a side-effect of morphine being used as an analgesic during pre-hospital evacuation. The situation may be very different when opioid agents (e.g. fentanyl) are used as a planned adjunct during resuscitation. The whole area relating to the role of endogenous and exogenous opioids in the response to haemorrhage and resuscitation is likely to provide important insight into the way reflex pathways responsible for the responses to trauma are organized, and their implication for the treatment of trauma casualties.

Conclusions

A trauma casualty commonly suffers a number of insults concurrently, each of which gives characteristic haemodynamic responses that often interact with each other, and in turn can impact on the response to treatment. An understanding of these reflexes can help guide the development of new treatment strategies and the limitations of current strategies.

Authors' contributions

E.K. and S.W. made equal contribution to the writing of this review article. E.K. wrote the first draft, S.W. reviewed it, and both authors made revisions. Both authors agree on the content.

Declaration of interest

None declared.

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