Forensic and Legal Medicine

Clinical and Pathological Aspects

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Physiological Responses to Ballistic and Blast Injuries
Alexander Stoll, Sarah Watts, Henrietta Poon and Emrys Kirkman

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INTRODUCTION

Forces that injure

When an explosive detonates, it generates an extremely rapid (effectively instantaneous) increase in pressure in the immediate vicinity of the explosion (1). This has a "knock on" effect on the surrounding air or water, transferring the high pressure as a wave outward faster than the speed of sound from the site of the explosion. The high pressure (called the peak overpressure) usually lasts only for thousandths of a second at any one point. The peak overpressure is followed by a rapid fall in pressure, often to sub-atmospheric levels, before returning to approximately normal. This is called the "shock wave". The magnitude of the peak overpressure falls as it travels away from the site of the explosion (1), initially by an inverse cube relation (doubling the distance reduces the pressure to one-eighth). Because the shock wave is a very brief event when using conventional explosives it does not cause an object or person to move any great distance (i.e. this is not the part of the explosion that "throws things around"). The shock wave can, however, cause serious injury.

Fragments (of the munition casing and pre-formed fragments contained within the device) and surrounding debris energized by an explosion are propelled outward and can collide with objects and people. In addition, the explosion usually gives rise to a very large volume of hot gas. This literally pushes air and debris outward and acts over a sufficiently long time course to throw people against other objects. This is called the "blast wind". The shock wave and the blast wind are sometimes collectively called the "blast wave". Finally, for those close to the explosion, there is also a large amount of heat, which can also cause injury.

Classification of blast injuries

Blast injuries are classified according to the forces causing the injury. There are five main categories (2,3). The original three categories were primary, secondary, and tertiary. Miscellaneous additional injuries from the explosive device give rise to quaternary and post-detonation environmental contaminants creating quinary categories, respectively (4).

1. Primary blast injuries result from the interaction of a shock wave with the body. Injury is largely confined to the air-containing organs, such as the lungs, bowel and ears, often without external signs of injury (5), although primary blast may also cause brain injury.
2. Secondary blast injury results from the impact of fragments and larger missiles accelerated by the blast (ballistic injuries). Injuries caused by these fragments can be penetrating or non-penetrating. This group accounts for the majority of explosion-related injuries.
3. Tertiary blast injury results from the acceleration of the whole body or parts of the body by the blast wave causing translational impacts of the body with the ground or other fixed objects, and/or traumatic amputation of body parts and stripping of tissue.
4. Quaternary blast injury represent a further group of miscellaneous injuries from exposure to an explosion, it includes flash burns, caused by radiant and convective heat, burns caused by combustion of the environment, crush syndrome, and the effects of noxious gaseous products (especially carbon monoxide) liberated in enclosed spaces.
5. Quinary blast injuries are the clinical consequences of "post detonation environmental contaminants" including bacteria (deliberate and commensal, with or without sepsis), radiation ("dirty" bombs) and tissue reactions to fuel and metals.

Altering factors

External factors, the nature of the environment where the victim is exposed to the explosion, as well as the

type of explosive/device, influence the balance of injuries received (6,7). If the explosion occurs within or near structures with surfaces that can reflect the shock wave, then the incidence of primary blast injury is likely to be higher than with an "open field" exposure. For example, the incidence of blast lung (primary blast injury) was high among the severely injured in the Madrid train bombings where the device was detonated within the train (8,9). Casualty analysis from Israel compared injuries among victims where both casualties and the explosive device were within buses, versus the situation where both were adjacent to buses (10). The study showed that the relative proportion of blast lung was higher in the "within-bus" group. The injuries within buses encompassed a spread of body regions including limbs and torso, with relatively few spinal injuries.

A different pattern of injury is present where the casualties are occupants of a structure and the explosion occurs outside, for example, when military vehicles are targets of an external explosion. Physical studies suggest that an external blast wave may diffract around a well-armored military vehicle, and reflect off the structure of the vehicle, rather than enter into the vehicle to cause primary blast injury. The rapid displacement of the vehicle, however, is likely to cause serious tertiary injuries to the occupants (11). This is confirmed in casualty analyses, which report extensive skeletal injuries, particularly to the limbs, spine and head in the most severely injured or fatalities (12,13). Primary blast injury such as blast lung is uncommon (13). This is referred to as "Underbody Blast" (UBB) where an explosive charge detonates underneath an armoured vehicle, with high accelerations over a short distance (14) accompanied by vertical loading to the occupants. It is thought that there are two main routes of transmission of the vertical load to the seated occupants of the vehicle (14); 1) through the feet and up the legs, and 2) through the pelvis and up the spine. This can cause extensive fractures in the foot, ankle and legs (15). The level and nature of the spinal fractures are in turn dependant on the initial rate of acceleration (16). The paucity of primary blast injuries described in these settings relate to explosions outside vehicles designed to protect the occupants from the primary and secondary blast injury (14). If the vehicles are only partially enclosed (or the hulls are breached) then blast lung injuries are also seen (17).

Internal (within the victim's body) altering factors include the physiological state and activity of the individual at the time of injury, tissues injured, degree and duration of hemorrhage, clinical interventions, quaternary injuries and, if present, the effects and responses to quinary blast injuries. Internal factors are complicated further by coagulopathies and inflammatory responses associated with trauma (including those directly associated with brain injury), the interaction between hemorrhage and tissue injury, and modification of these responses in response to primary blast.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Although ballistic and/or explosive injuries will be specific to the incident and the individual(s) involved, the broad principles of injury and the physiological responses to these can be outlined.

The transfer of energy to tissues from a shock wave, shearing forces, penetrating wounds, including those associated with primary to tertiary blast injuries and ballistic injuries, can all damage vasculature. The degree of hemorrhage will be determined, in part, by the magnitude of forces, tissues involved, and the track of projectiles in the body.

"Simple" hemorrhage; the cardiovascular response

Hemorrhage is a leading cause of death in traumatic injury. Simple hemorrhage refers to bleeding where there is no accompanying major tissue damage. The loss of blood during hemorrhage results in reduced venous return, leading to reduced cardiac filling and thus reduced cardiac stroke volume. This causes a fall in arterial pulse pressure, which is detected by arterial baroreceptors, sensitive to changes in both the absolute pressure and rate of change of blood pressure, that is, pulse pressure (18).

In progressive simple hemorrhage, there is a biphasic physiological response to blood loss [19]). In Phase I, vagal inhibition and sympathetic efferent activity leads to reflex tachycardia, increased peripheral vascular resistance and thus maintenance of blood pressure (20,21). As hemorrhage progresses, however, and blood loss exceeds 20 to 30 percent of total blood volume, a depressor phase (Phase II) becomes apparent. This involves a vagally mediated bradycardia, a reduction in peripheral vascular resistance (19,22,23) and a marked fall in arterial blood pressure (Figure 62.1).

The compensatory Phase I is due to baroreceptor unloading. The decompensatory Phase II is not due to a failure of the baroreflex, since the latter's sensitivity is increased at this stage (24), nor is it a pre-terminal event (25,26), but rather it is due to the activation of additional reflex(es). The identity of the afferent limbs of these reflexes is uncertain (27,28), although the cardiac afferent C-fibers may be involved (*see* [29]). The end result in a conscious patient is pre-syncope followed by syncope. It is thought that this second phase of the response to hemorrhage confers some degree of protection since 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 is needed for these casualties as they will quickly de-compensate.

Hemorrhage into cavities or tissues can also interfere with organ function. This type of bleeding can give rise to signs and symptoms associated specifically with the affected organ(s).
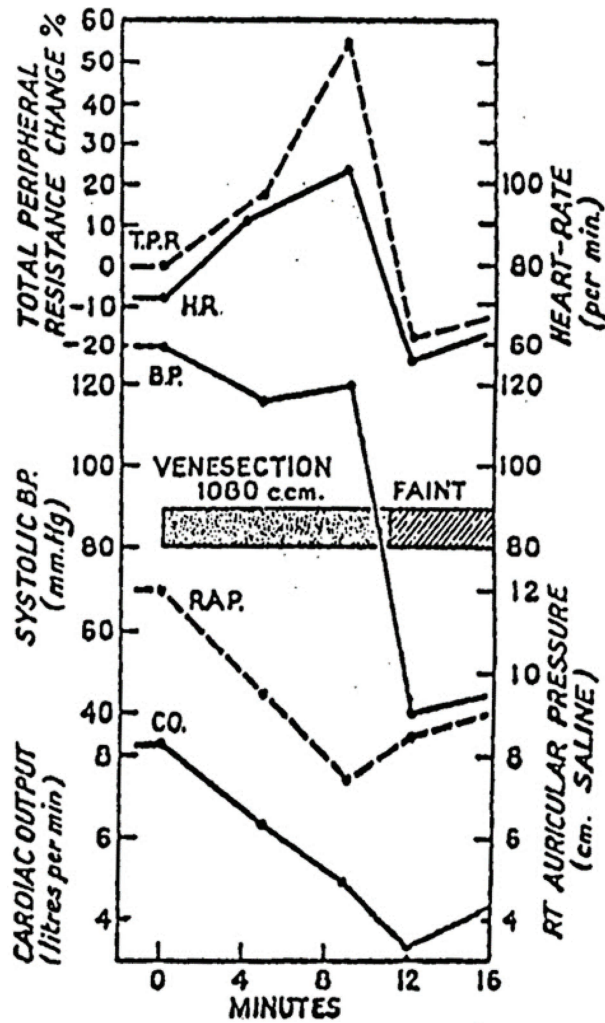
62.1 Effects of a progressive "simple" hemorrhage in a male volunteer showing a biphasic response. Blood was withdrawn by venesection until the subject fainted. TPR, total peripheral resistance; Syst BP, systolic arterial blood pressure; CO, cardiac output; Rt auric p; right atrial pressure (central venous pressure). (From Barcroft *et al.* (19).)

Shock

Shock is defined as the inability of oxygen delivery to meet tissue metabolic demand (30). At the whole body or organ level, oxygen delivery is the product of blood flow and arterial oxygen content, which in turn are influenced by vascular resistance, oxygen saturation and oxygen carrying capacity (hemoglobin concentration). At a microvascular level, shock can also be produced by a failure of local regulation of blood flow and consequently a mismatch of delivery and consumption in specific regions of an organ or tissue. Shock can also result from an increase in diffusion distance between the vasculature and the cells requiring oxygen (diffusion limited shock). This occurs in the case of edema resulting from either a severe inflammatory response or iatrogenic loading of tissues with fluid; for example over-resuscitation with crystalloid. All of these factors can contribute to shock in trauma.

Organs respond to reduced blood flow (e.g. due to hemorrhage) by extracting more oxygen from the available blood flow to maintain oxygen consumption. When this process can no longer compensate for reduced oxygen delivery by the blood, oxygen consumption starts to fall, and the organ is in "shock". The threshold at which oxygen consumption becomes dependent on oxygen delivery is the "critical oxygen delivery" and represents the point at which organs in the body start to suffer ischemic damage. There is evidence that activation of a neural nociceptive barrage normally associated with tissue damage elevates the whole-body critical oxygen delivery threshold and reduces a patient's overall ability to extract oxygen from the available cardiac output (31). This hastens the onset of shock and increases a patient's susceptibility to the metabolic effects of reduced oxygen delivery.

Tissue injury; the inflammatory response

Tissue injuries caused by an explosion and/or projectile(s) are also determined by the magnitude of the forces transferred to tissues, the tissues involved, volume of tissue affected and the wound track(s).

There is a growing interest in the immunologic response to traumatic injury, as this not only forms part of a defensive response to trauma but can also cause secondary problems and injuries for the patient. Skelton and Purcell have reviewed pre-clinical animal models, including references to the investigation of specific mediators (32).

Inflammation, due to the initial tissue damage at the time of injury, affects the progression of the response to injury. This is further confounded by hypoperfusion-induced ischemia, subsequent reperfusion injuries and immune dysfunction in critically ill patients. In summary, the inflammatory response to tissue injury and hemorrhage is initiated by the release of damage-associated molecular patterns (DAMPs) or alarmins, which lead to the activation of immune cells, the complement system, and cytokine release (Figure 62.2). The complex interaction between many pathways may, in severe injury, lead to the concurrent activation of systemic pro- and anti-inflammatory syndromes (systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS), respectively), which can pre-dispose to sepsis and multiple organ dysfunction syndrome (MODS) (32,33).

Initiated by DAMPs, but part of a milieu of catecholamines and reactive oxygen species, the pro-inflammatory actions are on 1) leukocytes (cause cytokine and reactive oxygen species production, proliferation and chemotaxis); 2) induction of the acute phase response, and 3) activation of endothelia (adhesion molecule expression, cytokine release, increased vascular permeability, and glycocalyx shedding). These actions initiate and propagate a pro-inflammatory state, including further tissue damage (32,34).
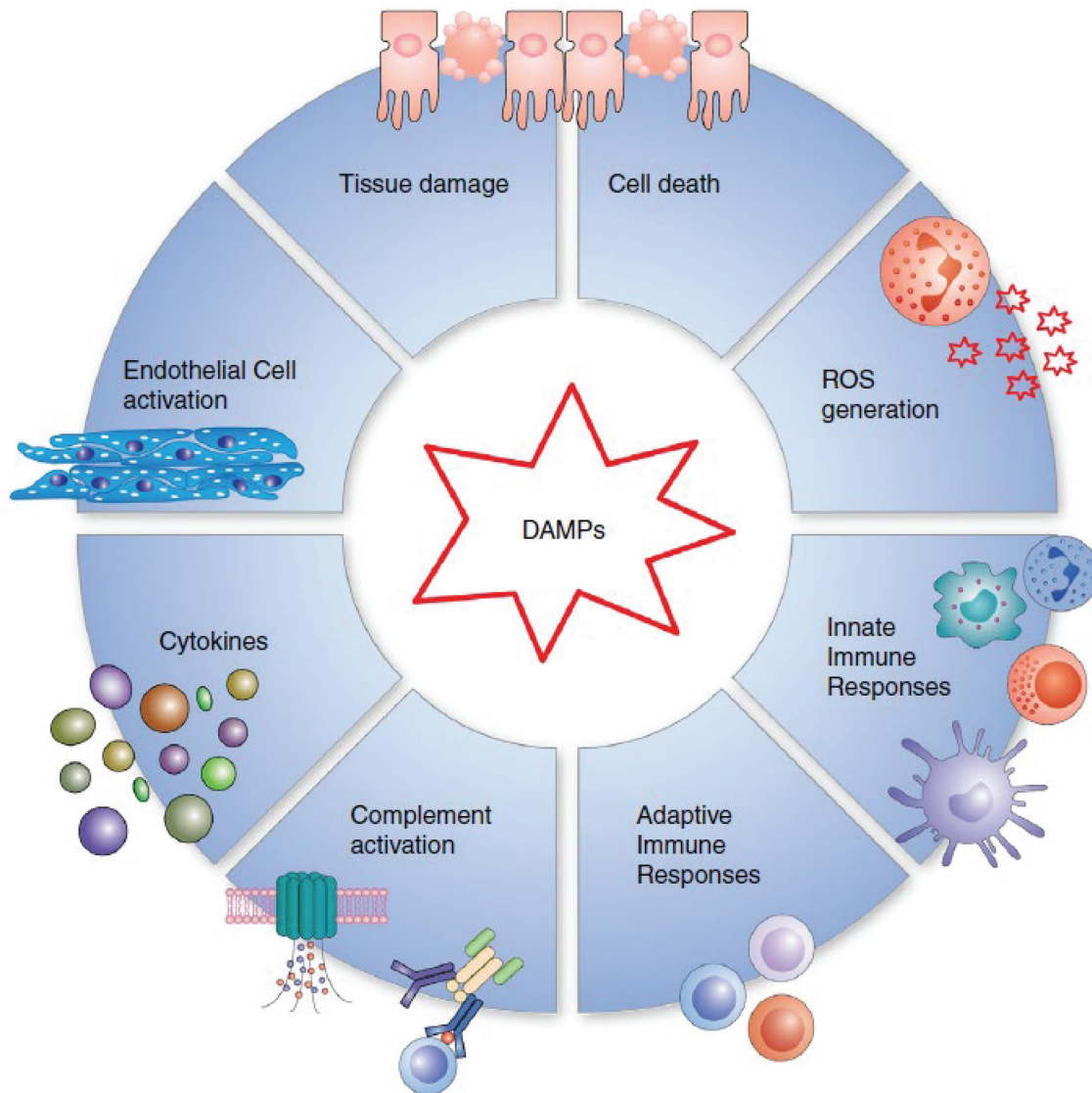
62.2 Damage associated molecular patterns (DAMPs) result in the activation of multiple inflammatory pathways. ROS: reactive oxygen species. (From Skelton and Purcell (32).)

Concomitantly, anti-inflammatory mediators are released, leading to states of immunosuppression. The neutrophil is an example of a leukocyte receiving and transmitting conflicting messages in the complex immune response to trauma. Pro-inflammatory signals result in the increased circulation, margination, extravasation and recruitment of neutrophils to injured tissue. Neutrophil degranulation, extracellular trap and cytokine release, and the generation of reactive oxygen species contribute to local tissue damage, clearance of debris, and propagation of inflammation. Meanwhile, release of juvenile neutrophils, and an altered neutrophil phenotype observed in trauma patients and *ex vivo* studies, exhibit changes in efficacy of these functions. A subset of neutrophils which suppress T-cell proliferation and function is also recognized. Further, lymphocytes are observed to become active and increase in number immediately following trauma, but this is followed by a lymphopenia.

Together, these changes are thought to contribute to the increased risk of infection in trauma patients (32).

Tissue injury with haemorrhage; the cardiovascular response

When considering severe hemorrhage, there is often significant tissue injury. The resulting barrage of nociceptive signals from damaged musculoskeletal tissue elicit a profound change in the cardiovascular response that can have implications for shock, morbidity and mortality.

The biphasic cardiovascular changes elicited by a progressive "simple" hemorrhage are markedly attenuated by the presence of concomitant tissue injury (21). The initial increase in heart rate following a loss of 10 to 15 percent blood volume is reduced, and the vagal bradycardia following greater losses prevented. The attenuation of the heart rate changes normally associated with
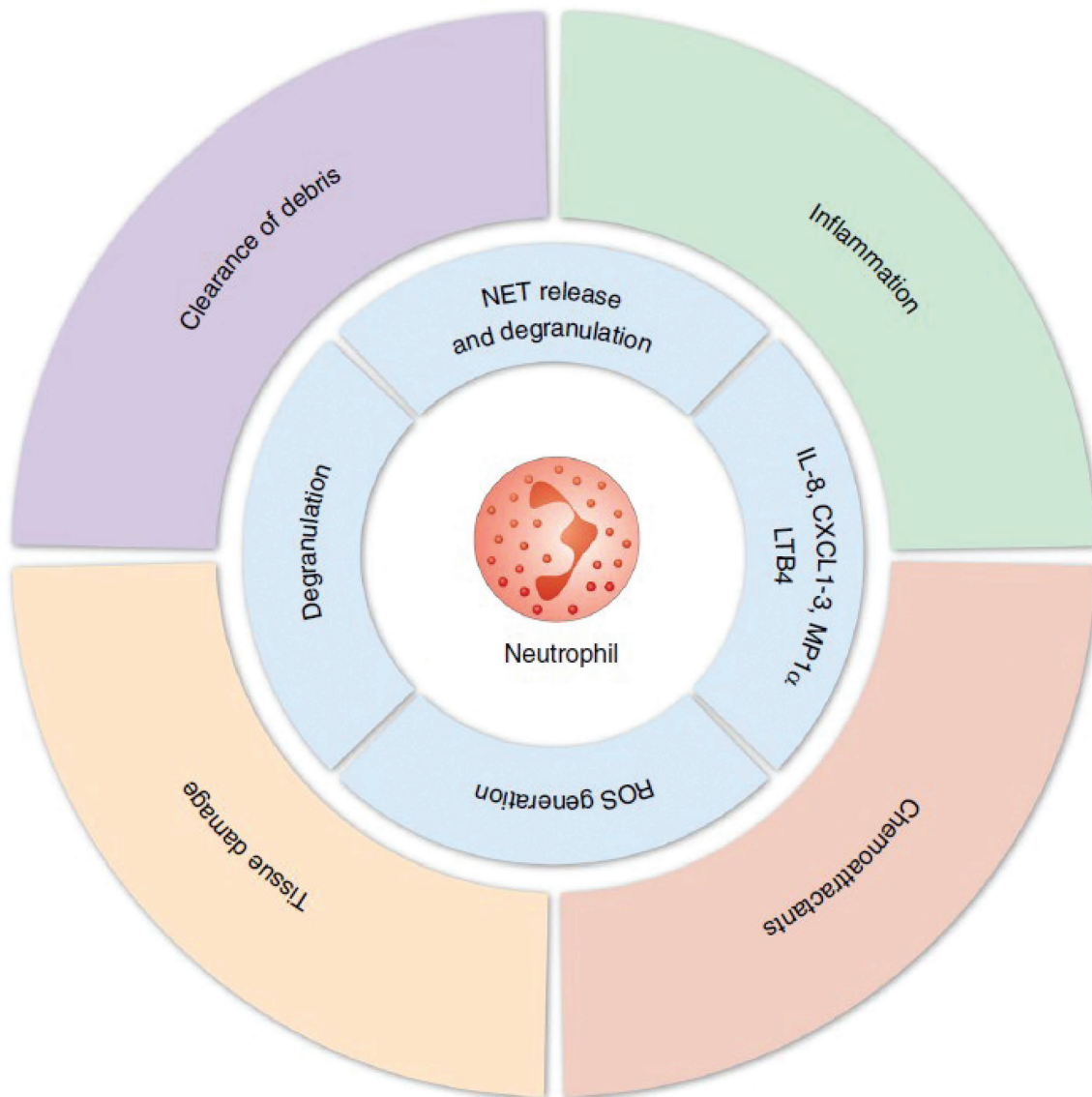
62.3 The diverse role of neutrophils in trauma can contribute to injury and repair. Abbreviations, clockwise from top: NET, neutrophil extracellular trap; IL-8, interleukin 8; CXCL1–3, chemokine C-X-C motif ligands 1–3; MP1α, monocyte chemoattractant protein 1α; LTB4, leukotriene B4; ROS, reactive oxygen species. (From Skelton and Purcell (32).)

blood loss seems to limit the hypotensive effects of a severe hemorrhage (21). However, a lower survival rate has been demonstrated in animals subjected to hemorrhage and concomitant electrical stimulation of the sciatic nerve (to simulate injury) compared to animals subjected to hemorrhage alone (35). It is possible that the better maintenance of blood pressure is achieved at the expense of intense peripheral vasoconstriction that further reduces blood flow, thus exacerbating shock and the severity of secondary (ischemic) injury.

It is possible that the splanchnic circulation may be selectively vulnerable to such ischemic damage. There is evidence that when hemorrhage 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 hemorrhage) (36,37). This diversion of blood flow (oxygen delivery) away from metabolically active organs toward relatively inactive resting skeletal muscle may explain the increase in critical oxygen delivery elicited by somatic afferent nerve stimulation (31) since it effectively "wastes" a proportion of the cardiac output. Ischemic 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), which represent some of the pathophysiological consequences of shock.

Impairment in cardiac function and tissue oxygen delivery (shock) associated with blood loss is greater if the hemorrhage is superimposed on nociceptive nerve stimulation compared to hemorrhage alone (43). If the hemorrhage is superimposed on real rather than simulated tissue injury the tolerance to blood loss is further reduced (44).

Secondary tissue injury due to shock

Tissue injury/ischemia produces an increase in arterial blood pressure accompanied by a tachycardia (45). 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. There is a hierarchy of vascular beds affected by the increased resistance. In "simple hemorrhage" the hierarchy is thought to be skeletal muscle > vital organs (e.g. gut and kidney) >> brain, while in hemorrhage superimposed on musculoskeletal tissue injury (or the resulting nociceptive barrage) there is some evidence that the hierarchy may be vital organs > skeletal muscle >> brain (31,46). Therefore during hemorrhage, blood flow to the brain is initially protected at the expense of peripheral tissue, which suffers early ischemia to varying degrees depending on the circumstances. The fall in blood flow in most vascular beds (especially the periphery) contributes to shock and can lead to ischemic damage of these organs (35) and inflammation. The resulting spill-over of inflammation, especially from the periphery can contribute to the pathophysiology of shock and its sequelae such as multiple organ failure. Secondary tissue injury to individual organs include pathologic changes to the heart, lungs, gut, liver and kidneys, with cardiac, pulmonary and enteric pathophysiological consequences outlined below.

Heart

Cardiac dysfunction secondary to systemic inflammation is associated with DAMPs, complement activation, cytological structural alteration, and altered neuroendocrine function and cardiac metabolism associated with trauma (47). This is complicated further by pharmacological interventions and cardiac dysfunction associated with direct trauma to the heart, and the entanglement of the pathophysiology and pathogenesis of cardiomyopathies and cardiac dysfunction associated with injuries to the brain, burns, bone fractures, abdominal injuries, sepsis, and other acute physical or psychological stressors (47–51). Any functional disturbance to the heart could contribute to shock, morbidity and mortality, either acutely or in the period following initial survival of the insult and could compromise the response to resuscitation.

Lungs

The lung in shock has long been recognized ("wet lung" described in casualties of World War II) and its "grouping" with other acute lung injury/acute respiratory distress syndromes (ALI/ARDS) has been debated (*see* [52] and [53]). This is a syndrome wherein the lungs exhibit morphologic and functional derangement (hypoxemia, edema, reduced compliance, decreased functional residual capacity) as sequelae to indirect injury and including sepsis, shock, burns and mass transfusions (53). Secondary to systemic inflammation, the lungs receive mediators of inflammation hematogenously, resulting in changes centered on the alveolar capillaries (in contrast to direct injury which involves both the capillaries and alveolar septae/spaces) (54). Early morphological changes include leukostasis, endothelial swelling, interstitial edema and sometimes fat emboli. The consequence of these changes is the development of edema spilling over into the alveolar spaces as a result of compromise to the endothelial barrier (endothelial activation from inflammatory mediators and mediated by activated leukocytes) (54). The principal cause of hypoxemia in patients with acute respiratory distress syndromes is this loss of ventilation to fluid filled (and later fibrin lined) alveoli resulting in shunted blood flow (55).

Candidates for the mediation of indirect lung injury include (alone or together) neutrophils (and their dysregulation, causing bystander damage and release of inflammatory, including vasoactive, mediators), lymphocytes and dendritic cells (which have roles in regulation and resolution of the immune response), injury to epithelial cells (forming part of the barrier against fluid influx and mechanism of fluid efflux), injury to endothelial cells, and dysregulation of coagulation and fibrinolysis (53,56). The limited therapeutic approaches relate, in part, to the need for clarification of the mechanisms that eventually converge on the common syndrome of ALI/ARDS (53,57), and the need to tailor therapeutic interventions to the individual and the stage of pulmonary injury progression (58).

The issues are even more complex when other direct and indirect factors are considered which impact the lungs in trauma patients, including direct thoracic injuries, traumatic brain injury (*see* [59,60]), septic shock, substances toxic to the lungs (e.g. gastric content, exogenous chemicals and toxic gases), thermal injury (hot gases), and lung injury associated with mechanical ventilation (56,61–63).

Gut

The intense peripheral vasoconstriction has serious repercussions on splanchnic perfusion, resulting in ischemic morphological changes in the enteric mucosa and liver. An early morphological change is detachment and loss of villus epithelium at the villus tip which then descends down the length of the villus. The exposed "core" (lamina propria) of the villus may then disintegrate and the injury may then extend to reach the level of the villus crypts. The lacteals have a discontinuous lining to facilitate assimilation of larger substances into the lymph, but also means that the villus interstitial fluid equilibrates with the lacteal content, hence the efflux of protein-rich fluid observed in the enteric lumen when there is breakdown of the enteric barrier. Loss of protein-rich fluid into the lumen can also impact upon colloid oncotic pressure, contributing to edema formation locally and systemically, which can also worsen shock (64–66).

Recent work suggests that the inflammation associated with the mucosal injury (including microbial ingress across the damaged gut lining), releases DAMPs which reach the systemic circulation by means of the mesenteric lymphatics and contribute to the systemic inflammatory response by priming neutrophils and

activating and injuring endothelial cells, including lung injury, and the systemic inflammatory response (67,68). The specific factors and DAMPs involved are an area of active research (68), for example, serine proteases (blocking of which reduced secondary lung injury in a rat model) (67), and mucin-2 (which may affect clotting) (69). Assimakopoulous and colleagues illustrate two "vicious cycles": the first involves compromised barrier integrity allowing bacterial translocation into submucosal tissue resulting in a local inflammatory response, further compromising barrier integrity. The second is the gut as a pro-inflammatory organ releasing DAMPs into the mesenteric lymph, damaging the lungs, releasing further DAMPs into the systemic circulation, resulting in SIRS, progressing to MODS and causing further intestinal barrier injury (68). The role of glycocalyx breakdown (69) and the microbiome (70) are being explored.

These factors may be confounded by therapeutic intervention, reperfusion injury, sepsis and MOF. Kidney (71–74) and liver (75,76) function are also impaired by hemorrhagic shock and may have a profound effect on outcome.

Tissue injury in response to resuscitation; ischemia-reperfusion

Local and systemic ischemia-reperfusion injury occurs in trauma patients and is a feature of the response to resuscitation. In addition to the reactive oxygen species, produced from activated neutrophils, tissue damage in ischemia-reperfusion injury generates further reactive oxygen species contributing to endothelial dysfunction. The generation of hypoxanthine during cellular hypoxia (reduced perfusion) depletes cellular second messenger cyclic adenosine monophosphate (cAMP) and subsequently reduces adenosine triphosphate (ATP) (77). This ATP deficiency leads to a series of events resulting in cellular membrane disintegration and DNA damage (77). Apoptosis and necrosis occur in prolonged hypoxic conditions, leading to irreversible tissue damage and the further release of DAMPs to activate the inflammatory response.

During reperfusion of ischemic tissue, the re-introduced oxygen reacts with hypoxanthine (accumulated during ischemia) to produce superoxide anion, which leads to the release of reactive oxygen species (hydroxyl ions) that further exacerbates cellular disturbance and the production of inflammatory mediators (77). Oxidative stress generated from ischemia-reperfusion induces an increased TLR4 surface expression, amplifying the inflammatory response and subsequent organ injury (78).

Coagulopathy in trauma

Trauma induced coagulopathy is now recognized as a serious secondary consequence of injury and the patient's (patho)physiological response to trauma (79–81). Trauma induced coagulopathy has an evolving pathology in the patient, often starting with the consequences of tissue hypoperfusion and developing through phases that can include the consequences of shock-driven acidosis, hypothermia, iatrogenic (and autogenic) hemodilution and factor consumption (79,81). Some authors also suggest an element akin to diffuse intravascular coagulation (DIC), without necessarily having tissue hypoperfusion (82). The initial phase of trauma-related coagulopathy is referred to as acute trauma coagulopathy (ATC), which manifests as attenuated coagulation early after injury.

The first phase of ATC, referred to by some authors, is thought to result from tissue hypoperfusion and is associated with the development of shock and increasing base deficit in the patient (81,83–88). However, it is not the acidosis associated with this shock *per se* that causes ATC, but rather an alteration in the endothelium leading to expression of thrombomodulin. The thrombomodulin interacts with thrombin to activate protein C, resulting in in simultaneous anticoagulation and fibrinolysis (79,83). Some have questioned the detail of this mechanism based on the kinetics of the changes (81). An additional concurrent or alternative mechanism involves damage to the glycocalyx, again driven by hypoperfusion and the sympatho-adrenal activation (89,90) that is an inherent part of the physiological response to hemorrhage and injury (19,31,37,46). The resulting release of a host of substances representing glycocalyx breakdown, including syndecan-1, soluble thrombomodulin and heparin-like substances, lead to autoheparinization (80) and an increase in aPTT (89). Irrespective of the precise mechanism, most authors agree that tissue hypoperfusion is a significant driver (79,81,86). The potential importance of early tissue hypoperfusion and burden of injury has been emphasized by the successful development of a pre-hospital predictive score (Trauma Induced Coagulopathy Clinical Score, TICCS) (91) which uses hypotension as a proxy for tissue hypoperfusion.

The second phase of ATC is related to resuscitation (81). Hemodilution, which is initiated by the physiological mobilization of interstitial fluid into the vascular space, is augmented by any asanguineous fluid given to the casualty with resultant dilution of clotting factors. The fall in hematocrit can also contribute to an alteration in clotting as a consequence of altered blood rheology (92,93). Finally, the acidosis that can be associated with shock and prolonged hypotensive resuscitation (most relevant when evacuation is delayed [94]) can also contribute to the coagulopathy by potentiating the effect of other mechanisms (95).

There is a complex interaction between the coagulation and inflammatory systems, with many common mediators. At present, our understanding of the interactions and interdependencies between the two systems are too rudimentary to allow anything but the most speculative of suggestions.

Another cause of coagulopathy is that caused by traumatic brain injury, affecting clinical outcome (96). Although the pathogenesis needs further investigation, it is considered to be associated with the release of brain-derived factors into the systemic circulation (97).

Predisposition to injury

The respiratory and gastrointestinal tracts are the principal internal organ systems with a direct interface between the internal and external environments, due to their common endodermal origin (98) and exchange functions. They are both predisposed to explosive injury as discussed below, and also result in clinical complications if there are breaches in their barrier function, in explosive or ballistic injury. The auditory tube and tympanic membrane also arise from the endoderm (98) and are predisposed to explosive injury as a result of the gas interface.

Respiratory pathology and pathophysiology

Ventilation and perfusion are carefully balanced in the healthy lung to optimize gas exchange across a very thin barrier (55). Explosive and ballistic injuries can alter the ventilation, perfusion and gas exchange by multiple mechanisms, including those listed in Table 62.1.

Primary blast injury to the lungs

Primary blast injury to the lungs is often referred to as "blast lung" and refers to pulmonary barotrauma (106). This is characterized by pulmonary contusion, rapid development of pulmonary edema and reduction in pulmonary gas transfer (94,107). A shock wave causes rupture of alveolar capillaries, and thus extravasation of blood and edema fluid into lung tissue (108,109), causing hemorrhagic foci, which can be substantial

depending on the level of blast loading (110). Intrapulmonary hemorrhage and edema contribute to the initial respiratory compromise in blast lung (111) that is exacerbated by free hemoglobin and extravasated blood, which induce free-radical reactions and hence oxidative damage (111) and a pro-inflammatory response (112). Free hemoglobin can also potentiate an accumulation of inflammatory mediators and chemotactic attractants (113), together with DAMPs from the injured lung tissue (114), thereby amplifying the primary pathology.

A victim of explosive injury is likely to suffer a mixture of 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 percent of the seriously injured also exhibit blast lung (115,116). When the explosion occurs in a confined space, the proportion of seriously injured survivors exhibiting blast lung increases dramatically (8,9) because the shock wave can be amplified and reflected near solid structures. A casualty is likely to have extensive tissue damage and severe blood loss, and in a clinically significant minority, also have blast lung resulting in hypoxemia. Death may be immediate (excluding cases of body destruction close to the blast) due to air emboli, bone marrow (fat) emboli, and/or massive pulmonary contusion and hemorrhage (110,117).

Blast injury; the cardiorespiratory response

On thoracic exposure to a shock wave from an explosion, there is a cardiorespiratory response thought to be due to an autonomic (vagal) reflex, the afferent arm considered to include pulmonary C-fibers (118). This response

TABLE 62.1 Causes and mechanisms of altered ventilation, perfusion and/or gas exchange in ballistic and/or explosive injury (*see* (99–105) for detail on injuries).

Mechanism compromised	Potential causes in explosive and/or ballistic injury
Ventilation	Positional asphyxia or crushing
	Obstruction of conducting airways by debris or direct damage
	Thoracic wall injury e.g. flail chest
	Respiratory depression (*see* "Cardiovascular and respiratory responses to blast")
	Pneumo- and/or haemothorax
	Acquired atelectasis (collapse of parenchyma) and/or contusion
Perfusion	Shock
	Emboli (e.g. fat, bone marrow, gas)
	Cardiodepression (*see* "Cardiovascular and respiratory responses to blast")
Gas exchange	Hemorrhage within, or aspiration of blood into, airways
	Pulmonary edema
	Low oxygen atmosphere (e.g. smoke, carbon monoxide)
	Damage to respiratory tissues by hot and/or toxic gases from combustion
	Alveolar damage by primary blast injury and/or projectiles

is characterized by bradycardia, prolonged hypotension, and a short apnea (in survivors), which is followed by rapid shallow breathing (94). While the vagal reflex might explain the bradycardia and apnea (118,119), hypotension is likely to result from the interaction between reduced peripheral resistance and reduced cardiac output. It is postulated that the reduced peripheral resistance results from nitric oxide (a potent vasodilator and inflammatory mediator) released in the lung tissue (120–122), possibly having systemic reach (117). Meanwhile, reduced cardiac output is likely a result of reduced cardiac function (123), together with hypoxemia associated with the primary blast lung injury. These events (and other complicating factors) can modify the cardiovascular responses to hemorrhage and resuscitation (117).

Blast injury with hemorrhage; the cardiovascular response

The physiological response to blast with hemorrhage is complex. In experimental models, there appears to be either an inhibition of the baroreflex or an augmentation of the depressor reflex. Morphine can block the depressor (bradycardia and hypotension) reflex in "simple" hemorrhage, and also attenuates the effects of blast on the response to hemorrhage (resulting in a tachycardic response instead). This lends support to the theory that blast augments the depressor reflex (117,124).

Blast injury with hemorrhage; the response to resuscitation

Following arrest of massive bleeding, hypotensive resuscitation is advocated in pre-hospital resuscitation for the short-term support of casualties. This approach is a compromise to 1) maintain oxygen delivery and reduce the risk of physiological deterioration, but 2) minimize the risk of causing further bleeding by deliberately allowing blood pressure to remain below normal levels (117,125–129). Porcine experimental models have demonstrated, however, that this approach, in the presence of blast lung, increased mortality if extended beyond one hour. A switch from hypotensive to normotensive resuscitation at one hour was assessed, and improved outcomes significantly (117,130,131). This gave rise to a concept called "hybrid resuscitation" strategy which improved physiological outcomes in both pigs exposed to blast, tissue injury and hemorrhage and those with tissue injury and hemorrhage only, as a result of enhanced tissue oxygen delivery (117,131,132). In some circumstances, however, the hybrid approach may not be suitable, where there is a very high risk of re-bleeding when the resuscitation blood pressure target is elevated after an hour. An alternative approach in this circumstance is the provision of an elevated inspiratory oxygen fraction (FiO$_2$) (131). However, supplementary oxygen was not as effective in reversing shock as the hybrid resuscitation strategy, again emphasizing the impact and importance of the reduced blood flow in the cardiovascular response to blood loss.

Primary blast injury to the intestinal tract

The intestine is vulnerable to the effects of the blast wave because of the gas-tissue interface present. Primary blast injury to the gut has been categorized in different ways (7,133). A blast wave, particularly with immersed explosions, can result in intestinal injuries including perforation and hemorrhages (7,134,135). At the interface between different densities, stress waves cause direct tissue disruption. Cripps *et al.* also demonstrated that small bowel injury could be attenuated by decoupling the stress wave, while large bowel injury was not attenuated, suggesting the role of shear waves too (possibly because of restricted movement of the large bowel within the peritoneum compared to the small bowel) (135). The terminal ileum and cecum are areas of the gut most commonly affected by primary blast injury (7).

Immediate perforations of the intestinal wall can occur and associated hemoperitoneum and/or peritonitis (135), which can introduce an additional hemodynamic and inflammatory complication to the physiological response. Later perforation may also occur (133,135).

The inflammatory (including enteric nervous system) sequelae to these pathological changes have been suspected as contributory to the response since the early identification of primary blast injury to the intestine (see case reports and discussion by Webster et al. [134]).

Burn injuries associated with explosions

Burn injuries from explosions fall into the quaternary and the quinary injury classes. The heat of the explosion causes the former, while secondary fires resulting from the explosion cause the latter. Most explosions will generate a considerable amount of heat close to its origin. Burns can be caused by radiant heat and by hot gases. Cases with burns are likely to have been close to the origin of the explosion and have other serious injuries and a high fatality rate (136).

Approximately 10 percent of military casualties injured by explosion from a range of conflicts since the Second World War suffered burn injury (137,138). A 6-year retrospective study from a major burns unit in the UK considered blast-burn injury as being a relatively rare occurrence in civilian practice and consisted mostly of minor burns (139). Some incidents can have a disproportionate number of burn injuries, however. The incidence of burns from "homemade" explosives may be higher, with approximately 23 percent of casualties with heat and chemical burns being reported in a small series by the US Centers for Disease Control and Prevention (140). "Homemade" explosives are likely to be less reliable than commercial/military high explosives, and more likely to deflagrate (causing more heat and less explosion), while accidental explosion from powders can be associated with high incidences of burn injury that are often severe (approximately 40% of casualties in one report [141]).

TABLE 62.2 A suggested classification system for burn injuries from explosions adapted from Chukwu-Lobelu et al. (142).

Classification	Description
Primary (also considered a quaternary blast injury)	Burns from the thermal energy of the fireball. Associated with other serious injuries (occurs in the immediate vicinity of the explosion).
	Burns from radiant energy outside the range of the fireball. Flash burns of varying severity and may be associated with inhalation injury.
Secondary (also considered a quinary blast injury)	Burns associated with conflagration

A detailed analysis of the 7/7 terrorist bombings in the UK identified two main groups of victims with burn injuries (142). In survivors, the majority of burns were superficial and caused by radiant heat (flash burns), affecting exposed parts of the body (face, arms and legs) usually healing within 10 days. A wider range of burn injury was seen in non-survivors, encompassing the range of full thickness, partial thickness and flash burns. In a number of these casualties, there were also signs of inhalational injury, including singed nasal hair. Combining their evaluation of the 7/7 bombings with data from other events led the authors to suggest two classes of burn injuries from explosions as shown in Table 62.2.

Those closest to the origin of an explosion are more likely to suffer severe burn injury, and are also more likely to be non-survivors, often with other fatal injuries in addition to the burns (136).

Severe burn injuries elicit a profound pathophysiological response that includes massive and progressive loss of circulatory fluid volume, which in part is due to local and systemic inflammatory responses as well as direct damage to blood vessels (143,144). There is clear evidence of endothelial damage and shedding of syndecan-1 in burns patients, which is primarily associated with shock and inhalational injury (145). The endothelial damage and inflammation, in turn, contribute to a disruption of Starling forces and consequent extravasation of fluid from the microcirculation into the interstitial tissue, and development of edema (144). Recent developments in our understanding of blood and blood products as resuscitation fluids have led to the suggestion, via a potential effect on the endothelium, that they may provide a more effective resuscitation than crystalloids in burns patients (144). It has also been noted that burn patients with inhalation injuries generally require more resuscitation fluids than those without inhalation injury (146).

The inflammatory response in burn patients is particularly severe, distinguishing it from other trauma (143). The impact of the inflammatory response is wide-ranging, not only underpinning widespread edema, but also contributing to secondary damage in other organ systems, for example, secondary disruption of gut barrier function which occurs within hours of severe burn injury (147). The inflammatory response may also compromise cardiac function, leading to reduced contractility and to a degree of apoptosis in cardiac tissue (143), which can impair the response to resuscitation.

Combined blast and burn injury has been shown to result in more severe lung injury than that caused by blast, or burn, injury alone (148,149).

The central nervous system

The response of the central nervous system (CNS) to blast exposure has received an enormous amount of attention because it is unclear which of the forces associated with an explosion cause some of the more subtle injuries, or the route via which they are transmitted. In addition, we have no certainty which of the biological responses observed in models of blast injury are a specific consequence of blast exposure in human victims, or which ones are of pathological significance. The picture is further complicated in a multiply injured casualty, because the responses to, and consequences of, the other trauma can modify the CNS response to an insult (150–152).

Examples of candidate physical mechanisms, by which blast exposure could cause injury to the CNS, include direct coupling of the shock wave via the skull, rapid (but brief) acceleration and rotational forces and slower pressure changes, and "waves of pressure" transmitted to the CNS via the vasculature and cerebrospinal fluid (CSF) (150). A more controversial possibility includes cavitation and formation/collapse of nanobubbles in the CSF and brain tissue (153). Secondary mechanisms include the consequences of an increase in blood–brain barrier permeability (154), and inflammatory responses that originate elsewhere in the body (e.g. the lungs) impinging on the CNS (155), possibly facilitated by an altered blood–brain barrier.

An important driver for the research in this area is the concern that even mild blast exposure, particularly if repeated, may in some individuals have a long-lasting effect, or an effect that becomes apparent later in life. These include damage to white matter tracts (156,157) and accumulation of hyperphosphorylated tau into neurofibrillary tangles, leading ultimately (years later) to chronic traumatic encephalopathy (158). The early part of the tau pathology has been replicated in an animal model, where the tau phosphorylation is thought to be mediated by a mechanism involving substance P (159). Administration of a NK1 receptor antagonist after blast exposure in this murine model has been shown to attenuate the tau phosphorylation and early

neurologic deficits (159), giving the possibility of a future treatment. However, we currently do not know the magnitude or the scope of the problem in individuals exposed to blast, or the relative numbers who suffer headaches that resolve after a few days (160) compared to those that go on to develop more serious, long lasting, consequences.

CONCLUSION

The physiological response to simple hemorrhage is biphasic. Phase I: tachycardia, increased peripheral vascular resistance and maintenance of arterial blood pressure. Phase II: following loss of 20 to 30 percent blood volume, bradycardia, reduced peripheral vascular resistance and reduced arterial blood pressure. Shock is the inability of oxygen delivery to meet tissue metabolic demand. In trauma, shock can be due to inadequate blood flow and/or oxygen content at the systemic or organ level, or at the microvascular level due to mismatches in delivery and consumption, and/or diffusion limited (edema).

Hemorrhage with accompanying tissue injury is typical in trauma. Inflammation is associated with traumatic tissue injury and secondary injury due to ischemia, and reperfusion. The resulting barrage of nociceptive signals can affect the cardiovascular response that can have implications for shock, morbidity and mortality. There is also a complex interaction between inflammatory responses and coagulopathy in trauma (ATC), complicated by therapeutic interventions.

Blast injuries are classified according to the forces causing injury: primary (interaction of the shock wave with the body), secondary (impact from material accelerated by the blast), tertiary (acceleration of the body or body parts), quaternary (other injuries caused by the explosive device), and quinary (consequences of post detonation environmental contaminants). The cardiovascular response to hemorrhage with blast injury is complex, further complicated by the profound effects of burns (if present) and the response to clinical intervention (resuscitation). The response of the CNS to blast exposure has received a lot of attention, and various putative mechanisms are subject to ongoing investigation. CNS injury can be associated with altered responses to haemorrhage, coagulopathy and inflammatory responses.

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