THE PULMONARY AND SYSTEMIC RESPONSE TO TRAUMA

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DECLARATION

This thesis represents research undertaken in the Department of Orthopaedic and Trauma Surgery, University of Edinburgh and has been composed by the author. The work is original, and is my own except where specifically acknowledged at the end of the Thesis. It has not been submitted elsewhere in candidature for any other degree, diploma or qualification.

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ABSTRACT

Introduction. Major trauma initiates a series of events including medullary fat embolism, a neuro-endocrine response, and activation of the inflammatory and coagulation systems. In a proportion of patients, these processes may lead to a syndrome of respiratory insufficiency and multiple organ dysfunction. It is not know exactly how the development of these complications relates to the initial trauma sustained, nor in what order they occur or what the interactions or relative importance of the components of the stress response are.

Hypotheses Severe musculoskeletal injury produces an identifiable early physiological stress response, which has haemodynamic, embolic, inflammatory and coagulation components. The severity and specific anatomical location of this injury are important in determining the level of risk of subsequent post traumatic respiratory compromise. Measurements of the degree of activation of the coagulation and inflammatory systems allow a more accurate assessment of this level of risk.

Studies. Three complementary studies were performed. (1) An epidemiological analysis was carried out to determine whether the severity of injury and the anatomical location of injuries sustained affected the development of Acute Respiratory Distress Syndrome (ARDS) in a consecutive series of 7192 trauma admissions to a single hospital. (2) A clinical study was then performed on a prospective cohort of trauma admissions in order to investigate the activation of the inflammatory and coagulation systems after injury. In this study, three groups were compared: those with isolated tibial and femoral fractures and those with long bone fractures in association with other injuries. The evolution of the stress response from the time of admission, through surgery, and over the first postoperative week was measured in terms of a series of circulating factors and mediators. (3) In the third study, a novel animal model of major trauma was developed in order to investigate these processes in a controlled environment. This model was then used to study the neuro-endocrine, embolic, coagulation and inflammatory components of the stress response to a reproducible bone and soft-tissue severe injury, and to investigate whether the subsequent surgical treatment of the injury affected this response.

Results. Regression analysis of those epidemiological factors associated with the risk of ARDS demonstrated that the Injury Severity Score (ISS), the presence of a femoral fracture, the combination of long bone and abdominal injuries and unstable physiological observations on admission were each independently associated with ARDS. In the prospective cohort study, the serum concentrations of a number of mediators, particularly interleukin-6, was shown to correlate with the severity of injury. However, no marker was found to be a useful indicator of the later development of respiratory insufficiency. In the laboratory study, an immediate depressant response of the cardiovascular system to injury was identified, the components of the stress response were observed to evolve in a reproducible manner and the additional surgical treatment of the injury was not found to make a significant difference to this response.

Conclusion. Several epidemiological, clinical and laboratory factors contributing to the development of the post-traumatic stress response are measurable. A group of patients at increased risk of respiratory insufficiency can be identified by their epidemiological features, but the role of measurements of plasma markers of inflammatory and coagulation activation remains to be defined.

SECTION 1: INTRODUCTION

SECTION ONE

Introduction

1.1. THE CLINICAL PROBLEM

Trauma is the most common cause of death in those under the age of 45 in Scotland, and is the fifth most common cause of death for all age groups together [1]. Mortality following major trauma is commonly understood to follow the trimodal distribution described by Trunkey [2], with death occurring either virtually instantaneously from catastrophic cranial or thoracic injury, or during the initial 'golden' hours after trauma from critical but remediable injuries, or over the subsequent days and weeks from progressive mulitsystem dysfunction. Whilst patients in the first group are by definition unsalvageable, and management of the second group has been addressed by the universal introduction of accepted resuscitation principles, the morbidity and mortality of the third group (that is, amongst those developing multisystem dysfunction) remains high. More recent research suggests that the second peak may not apply to patients in Scotland, and that virtually all potentially preventable deaths occur in the third group [3].

Respiratory insufficiency is common after trauma [4], it is a key determinant of morbidity and mortality, and often precedes the systemic manifestations of multisystem dysfunction [5;6]. The clinical signs of inadequate tissue oxygenation are well recognised: agitated or obtunded sensorium, tachypnoeia, tachycardia and cyanosis. These signs are easily confirmed by measurements of haemoglobin saturation and arterial oxygen tension, which are routinely monitored after major trauma. A discrete underlying cause may be apparent on clinical assessment (Table 1.1) and the most appropriate therapeutic strategy in these cases is thereby evident.

In addition to these discrete causes however, the onset of post-traumatic respiratory insufficiency may be promoted by pathophysiological processes arising from the injury itself. These include pulmonary fat embolism, hypovolaemic shock, the stress response to trauma, disordered blood coagulation and altered pulmonary vascular bed permeability. These entities are themselves interrelated and modified by the injury pattern (Fig 1.1). The resulting hypoxaemic state has been variously termed fat embolus syndrome, shock lung, acute lung injury, Acute Respiratory Distress Syndrome and neurogenic pulmonary oedema [7]. These terms have been applied inconsistently and often interchangeably, and in some instances probably reflect recognition of the same pathological and clinical process by those in disparate branches of medicine. Although many features of the inflammatory pathway are recognised *(vide infra)*, there remain a number of uncertainties regarding the aetiology, pathophysiology and appropriate treatment of refractory post-traumatic respiratory insufficiency.

Table 1.1. Causes of hypoxaemia after trauma

Type 1 Respiratory Failure: inadequate oxygenation
(resulting in hypoxaemia[8;9])

Upper airway obstruction
- Foreign body or misplaced Endotracheal tube

Thoracic injury
- Flail chest, pneumothorax, pulmonary contusion, aspiration pneumonitis

Circulatory failure
- Hypovolaemia, cardiac tamponade, cardiac failure (including fluid overload)

Type II Respiratory Failure: inadequate ventilation
(resulting in hypoxaemia and hypercapnia >6.1 kPa [8;9])

Head Injury

Drug toxicity
- Prescribed or non-prescribed drugs including alcohol taken prior to injury
- Drugs given during resuscitation including analgesics and anaesthetic agents

Table 1.2. Conditions associated with the fat embolism syndrome [10-13]

Mechanical fat embolism
- Bone fracture
- Arthroplasty
- Cardiac massage
- Liposuction
- Sickle-cell crisis
- Bone marrow transplant
- Caisson disease
- Intravenous nutrition

Chemical fat embolism
- Pancreatitis
- Fatty liver of alcohol abuse, pregnancy or steroid therapy
- Systemic lupus erythematosis
- Severe sepsis

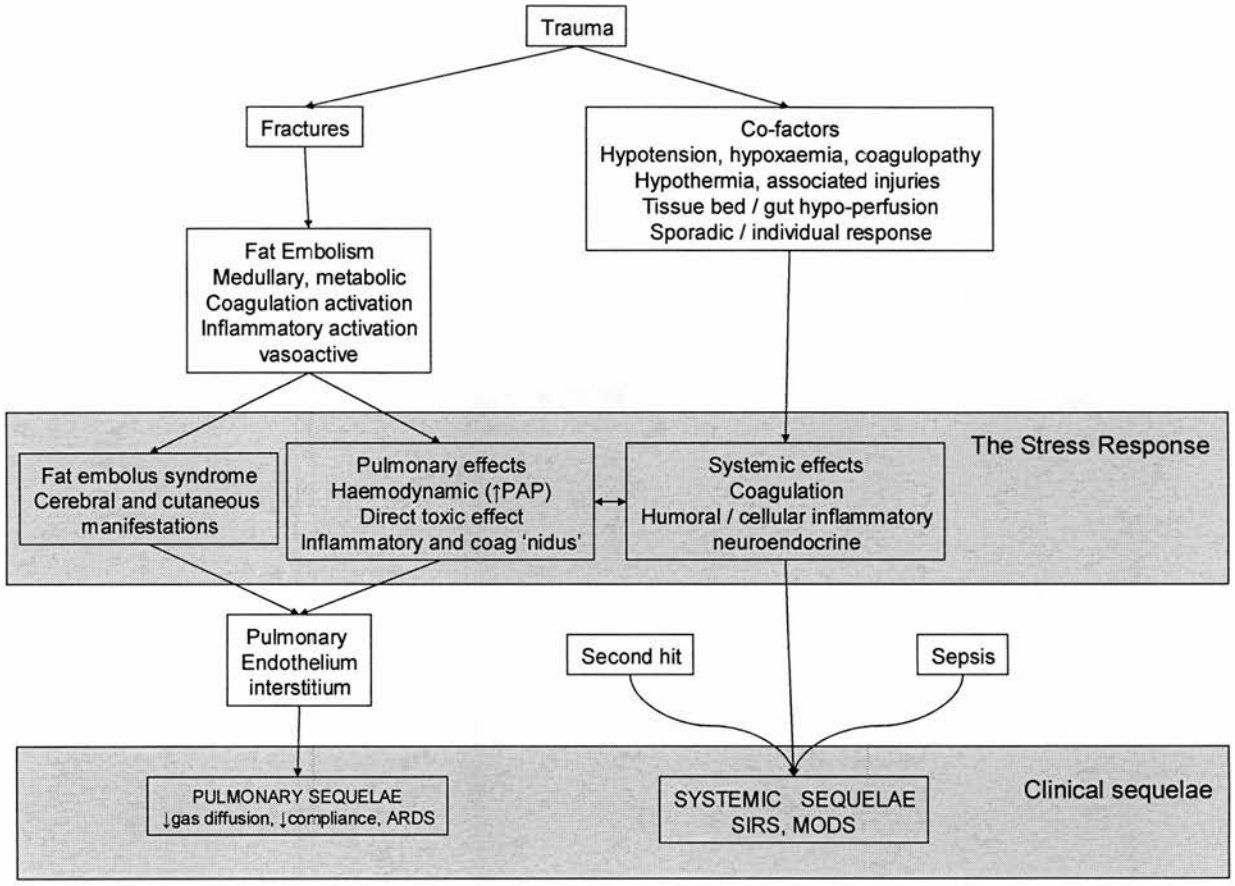


Figure 1.1. Flow chart to show schematic representation of the Stress Response to Trauma

1.2. FAT EMBOLISM

Although Fat Embolus Syndrome (FES) is a rare but distinct clinical diagnosis (*vide infra* Section 1.2.6), the embolisation of fat and marrow particles (fat embolism) *per se* is virtually ubiquitous following bone fracture, and does not in itself necessarily give rise to significant clinical sequelae. Such humoral fat emboli following trauma may be derived from any of three sources: intravasation from the medullary cavity of bone, the destabilisation of serum lipids, and from the formation of fat *de novo* from depot precursors.

1.2.1 Medullary embolic fat.

There are at least 130 mls of medullary fat present in the adult human tibia or femur [14] which is in liquid phase at body temperature. This fat may enter (or 'intravasate' into) the circulation via disruptions of the thin-walled intraosseous venous sinuses when intraosseous pressure exceeds venous pressure. Bone fracture is not necessarily required: several cases of fatal fat embolism are reported after bone contusion [15], or other conditions resulting in increased intramedullary pressure (Table 1.2). However, embolism is more commonly associated with traumatic fracture [16], during which forceful pressure waves are created within the medullary cavity [17], resulting in the intravasation of fat and bone marrow elements. The quantity of embolic fat is related to the energy of the fracture [17], but measurable pulmonary fat embolisation occurs in over 90% of patients with fractures [18;19]. Direct pressurisation of the medullary canal during the instrumentation of fractures [20] or the implantation of joint prostheses unsurprisingly also results in substantial fat intravasation [21;22].

1.2.2 Biochemical sources of embolic fat.

Serum lipids are comprised of triglycerides (rendered soluble by combination with cholesterol and phospholipids to form chylomicrons) and free fatty acids. Chylomicrons may be induced to aggregate and coalesce by physiological stress under the influence of

C-reactive protein, forming emboli of up to 35μm in diameter [13;16]. Free fatty acids represent a smaller proportion of serum lipid but are far more metabolically active, being unbound to albumin. Physiological stress, with activation of the sympatho-adrenal system, results in the release of free fatty acids from lipid depots with a rise in serum levels of up to three times normal [6;23], and where mobilisation exceeds metabolic requirements and the binding capacity of albumin, deposition occurs in systemic tissues and the pulmonary parenchyma [15]. Fat transport mechanisms may be overwhelmed by this excess lipid, resulting in further destabilisation and coalescence of chylomicrons.

These biochemical mechanisms may be of crucial importance in the fat embolism associated with non-traumatic conditions such as pancreatitis, and the 'fatty livers' of pregnancy and steroid therapy (Table 1.2). Indeed, fat embolism has been reported at post-mortem examination in over 30% of patients dying after prolonged illness from non-traumatic conditions [13;16]. The contribution of this 'metabolic' lipid to fat embolus after *trauma* is, however, likely to be secondary to that of medullary fat. Animal experiments investigating the composition of the embolic fat retrieved from the pulmonary circulation after bone trauma confirm that the fatty acid profile is quite unlike that of plasma, but is identical to that of bone marrow [24]. Moreover, labelled serum lipids fail to appear in pulmonary fat emboli after trauma [24]. In contrast, labelled fat from the bone marrow does appear in pulmonary embolic fat, and experimentally this can be prevented by the application of a tourniquet to the limb prior to fracture[16]. It may be concluded therefore that post-traumatic embolic fat derives principally from fractured bone.

1.2.3 Mechanical embolic pulmonary obstruction.

Embolic fat passing through the right-sided cardiac circulation is disrupted to form showers of microemboli [25] which enter the pulmonary vascular bed. The lung is an

efficient filter with a mean capillary diameter of 8μm: only sufficiently large to permit the passage of deformable erythrocytes. These small vessels are occluded by fat emboli. Obstruction is manifest physiologically as raised pulmonary artery pressure, which rises to maintain pulmonary blood flow and can be measured directly with the use of a Swan-Ganz catheter. This increased right heart after-load results in impaired ventricular function (the Starling effect). Were the pulmonary capillary bed to function purely as a simple filter with no compensatory control mechanisms then the theoretical mechanical consequences would be disastrous: just 20 ml of fat, if broken down uniformly, will yield 40 billion microemboli 10 μm in diameter which would be sufficient to block every capillary in the lung [15].

However, fat embolus size and distribution within the capillary bed is not uniform, and capillary diameter may be altered in response to local homeostatic control mechanisms, allowing areas of low perfusion to accommodate increased flow by vasodilatation. Arterio-venous connections (or 'shunts') of up to 500 μm diameter have been described in human lungs [15], and additionally direct trans-cardiac shunting may occur via a patent foramen ovale [26], which is present in 20% of the population. As fat is present in liquid phase, and thus highly deformable, considerable shunting from the pulmonary to the systemic circulation is possible, albeit at the cost of reduced gas exchange [5]. Pulmonary reserve is therefore considerable: over half of the vascular bed must be occluded before pulmonary artery pressure rises [27] and pure mechanical obstruction is unlikely to account for the full spectrum of respiratory consequences of fat embolism[18].

1.2.4 Chemical and vasoactive consequences of fat embolism

Neutral fats such as those present in bone marrow are chemically innocuous to the endothelium and lung parenchyma [28], and clinical symptoms of respiratory insufficiency are often only evident 12 to 72 hours after embolisation. The delay is ascribed to the time taken for local hydrolysis of the neutral fat by lipoprotein lipase to form fatty acids [10;15;16]. Free fatty acids are exceptionally toxic to pulmonary tissue, causing disruption

of the alveolar capillary membrane and the development of haemorrhagic pulmonary oedema accompanied by reduced surfactant activity. Both thromboplastin from damaged tissues and circulating fat emboli activate platelets, initiating activation of the coagulation pathway. The resulting thrombus forms a coating around the fat, resulting in consumption of platelets and erythrocytes [6], and a typical lamellar appearance to the emboli with a thick layer of platelets around a fatty core [29;30]. The activated coagulation system is further stimulated by free fatty acids resulting in prolonged thrombin and prothrombin times, consumption of platelets and fibrin deposition[31]. The fibrinolytic system is activated concurrently, and an increase in fibrin degradation products is seen [32]. Highly vasoactive mediators released by platelets, such as thromboxane, serotonin and histamine cause pulmonary arterial and arteriolar vasoconstriction, further contributing to the increase in pulmonary arterial pressure and shunt [5;14;30].

1.2.5 Histological features and resolution

A characteristic sequence is observed after fat embolism [33]. An inflammatory response is first seen at 24 hours when eosinophils and neutrophils appear, but a more marked, general change occurs at 72 hours when leucocyte infiltration, congestion and atelectasis are most prominent and pulmonary petechiae are first observed. Most fat is presumed to clear by lipase degredation, or trans-capillary shunting [34], however, some is scavenged and fat-laden macrophages are seen in bronchio-alveolar lavage fluid from 63% patients developing fat embolism, compared with only 2% without the condition [35]. Remaining fat, marrow and overlying thrombus are later degraded in situ by histiocytes after endothelialisation and fibrosis [36].

1.2.6 Progression to the Fat Embolus Syndrome

In a minority of trauma patients, however, resolution and recovery do not occur, and instead these patients develop a characteristic series of complications dominated by refractory hypoxaemia. This is termed the Fat Embolus Syndrome (FES) and is distinct from the mere presence of fat embolism. Right to left haemodynamic shunting occurs early in the manifestation of FES [5;6] and is largely responsible for the hypoxaemia, and

also allows fat to enter systemic vascular beds. The local mechanical and chemical effects of the systemic embolic fat cause cerebral sequelae consisting of confusion, agitation and visual scotomata, occurring in 70% patients with FES concurrently with the shunt [5;11]. Cutaneous petechiae (of the axillae, conjunctivae and anterior chest wall) and the development of coagulopathy, thrombocytopaenia, and a falling haemoglobin level occur somewhat later [5]. A fever, and the presence of fat in the plasma and urine are characteristic but not specific. The diagnostic criteria of Gurd and Wilson (Table 1.3) [37] are widely quoted although these are largely empirical, and other criteria have been proposed [5;13;38]. There are no pathognomic features or investigations for FES, and many of its manifestations are common to other acute inflammatory processes. The diagnosis is often made by exclusion on the basis of clinical suspicion. Clinically, most patients spontaneously improve from Fat Embolism Syndrome and return to normal after five days [6], but there is an associated mortality of between 10% [5;39] and 20% [10].

In rare cases, a fulminant form of FES is described, in which massive embolism to the pulmonary tree occurs following major trauma or intramedullary nailing, resulting in rapid right ventricular failure and death [12;25;26;40;41].

It is remarkable that despite the virtual inevitability of pulmonary fat embolism after bone fracture, and the likelihood that at least some of this fat enters the systemic circulation via shunts, FES itself is relatively rare. The actual incidence is dependent upon the definition used, and tends to be higher in prospective studies [5] than in retrospective reviews [42], but is unlikely to be higher than 10% even amongst patients with femoral or pelvic fractures [5]. Less severe, subclinical, forms may be more common [4;6].

It is not clear what precipitates the development of FES in some patients. The incidence of FES is generally higher amongst those with more severe injuries as rated by Injury Severity Score [5], and increases with increasing numbers of long bones fractured [6;12;42], but the progression of fat embolisation to the Fat Embolus Syndrome appears otherwise

sporadic, and can occur unexpectedly following a minor sporting fracture. Predisposing co-factors such as hypovolaemic shock or disseminated intravascular coagulation have been proposed [43] [11;41], but are not sufficiently specific to be of clinical use in predicting the condition [6]. It is likely that factors other than the presence of embolic fat are of importance in determining the development of respiratory insufficiency after trauma, and these many, interrelated factors may be considered together under the term 'the physiological stress response to trauma'

1.3. THE STRESS RESPONSE TO TRAUMA

The response to physiological stresses such as trauma, major surgery, burns and sepsis is triphasic (fig 1.2). Typically, an 'ebb' (shock) phase occurs first, acting to maintain central perfusion at the expense of gut, musculoskeletal and skin oxygenation. Onset is prompt and neurologically mediated[44]. Stimulation of the sympatho-adrenal system and release of catecholamines allows a rapid haemodynamic response to shock, but also serves to initiate a variety of other processes such as proteolysis, glycogenolysis, gluconeogenesis, and the secretion of rennin (and therefore angiotensin and aldosterone) and growth hormone. The ebb phase may be curtailed by resuscitation and is followed by the hyperdynamic 'flow' phase in which reparative processes are initiated.

The flow phase arises not only as a consequence of the preceding neuroendocrine events, but also directly from a response by the injured tissue itself. In addition, hypoxic injury to remote tissue (particularly the gut [45] and skin [46]), occurring during the hypoperfusion of the ebb phase, and subsequent reperfusion, contributes to the stress response. Underlying this response is a complex array of mediators, receptors and cells which is centred upon the interaction of the neutrophil and the endothelium, via protein mediators such as cytokines, and molecules such as nitric oxide.

Under certain conditions the stress response is excessive and the cellular interactions initiated at the time of injury, occurring against the background of the ebb and flow phases, result in the Systemic Inflammatory Response Syndrome (SIRS) in which widespread inflammation occurs. In a proportion of patients this culminates in multiple organ dysfunction (MODS). These complications may follow the initial trauma (Fig 1.2, c) or arise as a result of subsequent additional stimuli (d).

Finally, a recuperative (anabolic) phase occurs, lasting weeks to several months, during which there is metabolic and functional recovery (e).

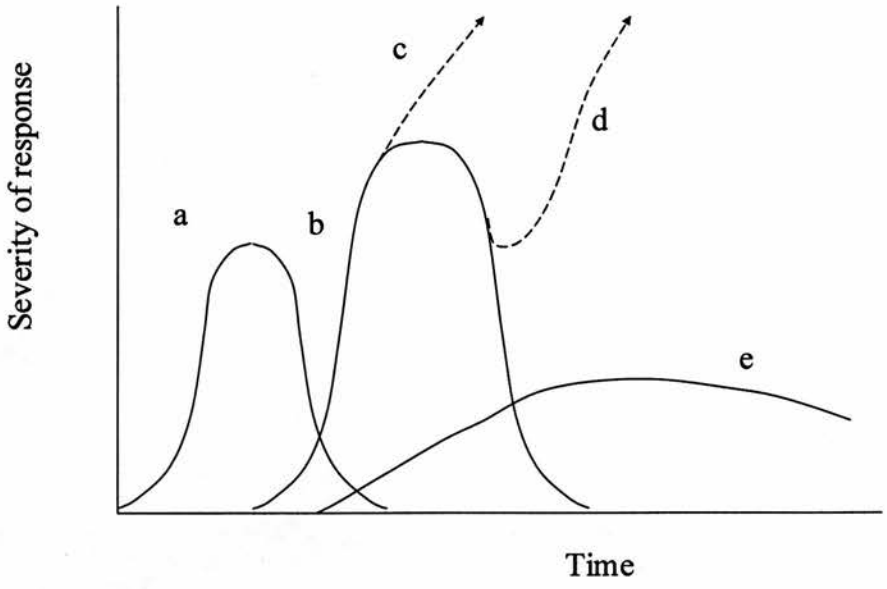


Figure 1.2: Graphic representation of the phases of the Stress Response to Trauma
a: ebb phase, b: flow phase, c: excessive first hit leading to exaggerated stress response, d: second hit resulting in reactivation of the stress response, e: anabolic phase

1.3.1 Cytokines

Cytokines are soluable, low molecular weight proteins, and their production requires active gene transcription and protein synthesis, which may take several minutes or hours following a noxious stimulus. Cytokines are pleiotrophic, and the same cytokine may be produced by a number of different cell types and have a variety of effects on a range of different cells under different circumstances [47]. Different cytokines may have identical effects on any given cell type. Cytokines may be autocrine (influencing the same cell), paracrine (influencing cells in the immediate environment) or endocrine (having effects at distant sites). These effects occur as a result of cytokine binding with specific cell surface receptors, which trigger intracellular pathways which themselves regulate gene transcription. By this mechanism, cytokines not only stimulate the production of other cytokines, but also directly influence target cell proliferation, differentiation and activity. This process of elaboration and amplification of the response results in an 'inflammatory web' of activity that has a profound effect on local and systemic homeostasis[47;48].

Cytokines can be classified as either pro-inflammatory or anti-inflammatory, and indeed certain cytokines such as Il-6 have been shown to display pleiotropism in this regard, displaying either pro-inflammatory or anti-inflammatory effects in varying circumstances. Pro-inflammatory cytokines include tumour necrosis factor - α (TNFα), interleukin - 6 (Il-6), and interleukin – 8 (Il-8) which serve to initiate inflammatory activity and the release of other cytokines, and to stimulate the hepatic acute phase response. Anti-inflammatory cytokines (including Il-4, Il-10 and Il-13) suppress this inflammatory activity. Immunological assay techniques have allowed the *in-vitro* study of these processes and although substantial advances have been made in the analysis of portions of this response, the extreme complexity of the system has so far prevented a comprehensive understanding of it. The main cytokines implicated in the stress response to trauma, and their effects, are summarised in Table 1.5 and section 1.3.5.

Table 1.3. Gurd and Wilson's diagnostic criteria

Major	Respiratory symptoms, signs and radiographic changes Cerebral signs unrelated to head injury or other conditions Petechial rash
Minor	Tachycardia over 110 beats per minute Pyrexia >38.5 °C Retinal changes of fat or petechiae Renal changes Jaundice *(Laboratory):* Acute fall in haemoglobin Sudden thrombocytopaenia High ESR Fat macroglobulinaemia

One major and four minor criteria and fat macroglobulinaemia are required for diagnosis[37]

Table 1.4.
Definitions of terms used to describe pulmonary and systemic complications.

ARDS[49]	$PaO_2:F_iO_2 < 26.7$ Diffuse bilateral pulmonary infiltrates on plain chest radiograph PA wedge pressure < 18 mmHg or no evidence of left atrial hypertension
ALI[49]	$PaO_2:F_iO_2 < 40$ Diffuse bilateral pulmonary infiltrates on plain chest radiograph PA wedge pressure < 18 mmHg or no evidence of left atrial hypertension
SIRS[50]	Systemic Inflammatory Response Syndrome. [a] Two or more of: Temperature >38°C or <36°C HR > 90 beats per minute RR >20 breaths per minute or $PaCO_2$ <4.3 K Pa WCC <4 000 or > 12 000 cells per mm^3
MODS[50]	The presence of altered organ function in an acutely ill patient such that normal homeostatic biological mechanisms cannot be maintained without intervention

Table 1.5. Pro-inflammatory cytokines implicated in the stress response to trauma.

TNF α	Tumour Necrosis Factor - α (Cachexin) When infused into human volunteers or animals causes stress response: fever, SIRS, coagulopathy, haemodynamic abnormalities. Levels of TNF α are significantly increased in human subjects who die, and neutralising antibodies to TNF α improves survival in models of septic shock.[47;51] Produced by neutrophils, lymphocytes, macrophages and endothelial cells Activates neutrophils Up-regulates adhesion molecules – E-selectin, ICAM-1 Increaes capillary permeability Lipolysis and proteolysis and anaerobic glycolysis Induces a coagulopathy Induces Il-1, Il-6, Il-8 and Il-10
Il-1	Inerleukin-1. Two subsets : α and β Infusion into humans and experimental animals causes SIRS response, and levels predict the severity of sepsis[51] Produced by monocytes, macrophages, neutrophils. Activates neutrophils, endothelial cells: upregulation of adhesion molecules Causes fever by stimulation of the hypothalamus. Increases capillary permeability Stimulates production of TNFα, Il-6, Il-8
Il-6	Produced by monocytes, macrophages, neutrophils, endothelial cells. Levels predict outcome in sepsis [51] and trauma[52] Promotes coagulation cascade [53] Induces the hepatic acute phase response Production stimulated by TNFα and Il-1 response. Exact role unclear
Il-8	Belongs to subgroup termed 'chemokines' because of ability to recruit inflammatory cells to site of injury.[54] Implicated in genesis of ARDS [55] Produced by neutrophils, macrophages and endothelial cells. Levels predict outcome in trauma [52] Enhances neutrophil function Stimulates adhesion, chemotaxis, degranulation and respiratory burst Increases endothelial permeability

1.3.2. Tissue inflammation: the neutrophil

The local release of inflammatory cytokines initiates a defined sequence of neutrophil chemotaxis and recruitment which occurs by a process of margination from the central stream of capillary circulation, first with 'pavementing' on the endothelial surface, followed by rolling and adhesion to the endothelium. This process requires the expression of specific adhesion molecules by both the neutrophil (CD11-b) and endothelial cell (inter-cellular adhesion molecules (ICAM), and selectins) and is stimulated by the local secretion of Il-8 [54;56]. Endothelial permeability is increased, and the neutrophil gains access to the interstitial space by diapedesis, and then degranulates with the release of cytokines, reactive oxygen metabolites and proteases [57]. These substances cause local disruption of cell membranes and connective tissue. Fat may also be directly involved in neutrophil activation and adhesion. Oelic acid (a major constituent of bone marrow fat) directly up-regulates neutrophil CD11-b expression, and neutrophil adherence to fibrinogen coated surfaces, thus encouraging neutrophil accumulation [58].

The activation of the inflammatory cascade thus results in an increase in endothelial permeability, with tissue oedema, neutrophil sequestration and degranulation, and the local release of further cytokines and directly cytotoxic substances. Whilst in most tissues these events occur in the post-capillary venules, in the lung the capillary bed itself is the target [59;60].

1.3.3 Coagulation system activation

The coagulation system is also intimately involved in the stress response to trauma. The extrinsic pathway of the coagulation system is activated after injury by the exposure of

fat and subendothelial tissue factor, resulting in thrombin and fibrin formation (Fig 3.1, Section 3.2). This activation is promoted by the inflammatory response in two ways. Circulating TNFα, Il-1 and Il-6 further stimulate the expression of tissue factor and up-regulate fibrinogen production, resulting in a pro-coagulant response. In addition, the same cytokines also stimulate increased levels of plasminogen activator inhibitor (PAI-1), which leads to inhibition of fibrinolysis, resulting in an anti-fibrinolytic response [53;61]. Locally, after injury, this serves to promote haemostasis. However, systemic activation causes a shift in the dynamic equilibrium between the stimulation and suppression of coagulation, and results in a net systemic coagulation response (demonstrated by elevated prothrombin fragment and fibrinogen levels), platelet activation (elvated β-thromboglobulin levels) and fibrinolysis (elevated D-dimers) [62]. Intravascular fibrin micro-thrombi are generated and embolise in distal vascular beds, and the consumption of clotting factors and platelets results in a prolonged prothrombin time or even disseminated intravascular coagulation (DIC) [63]. With trans-endothelial exudation of oedema fluid, coagulation factors and cytokines, fibrin and fibrinogen deposition also occurs in the extravascular space.

In turn, the constituents of the coagulation pathway, particularly thrombin, factor Xa and fibrin further stimulate the inflammatory system in a positive feedback loop, a process termed 'cross-talk' [63].

As a result, platelets levels fall over the 24 hours after injury, whilst fibrinogen levels and prothrombin time rise gradually over the first four days [63]. Such coagulopathy during this period may be directly injurious (promoting haemorrhage) and may also be a useful marker for the severity of the stress response, having been shown to be an independent predictor of mortality after trauma [64].

The procoagulant pathway is modulated by numerous negative feed-back loops. For example, activated protein C (APC) is a potent anticoagulant enzyme that is activated by

thrombin. It is anti-thrombotic in that it inhibits the expression of tissue factor by monocytes and endothelial cells, and inactivates several coagulation factors. APC is also profibrinolytic in that it inhibits PAI, which is a potent inhibitor of tissue plasminogen activator (tPA), a crucial element of the fibrinolytic pathway. APC also has an anti-inflammatory effect by suppressing thrombin formation and by directly reducing neutrophil rolling and sequestration [65]. Reduced peripheral levels of APC are associated with increased mortality in sepsis, and recombinant APC is an effective therapeutic agent in septic patients [65]. Antithrombin III (AT III) has a similar anti-thrombotic effect by inhibiting conversion of prothrombin to thrombin and fibrinogen to fibrin. Its administration in animal models of acute lung injury has been shown to reduce lung injury and hypoxaemia [66] although its clinical role is not established [67].

1.3.4 Platelets, complement, nitric oxide and the endothelium

Platelets may be activated by contact with subendothelial structures or by elements of the inflammatory cascade such as Il-6 [53;68]. The local activation of platelets results in the exposure of a procoagulant surface membrane that catalyses the reaction of coagulant proteins of the clotting cascade. In addition, activation causes the release of serotonin, adenosine diphosphate and platelet activating factor which serve to stimulate neutrophils and increase capillary permeability, and thereby aggravating tissue oedema [61]. This is closely associated with complement activation, which locally assists haemostasis and the clearance of debris [47]. However, activated complement also accelerates the local inflammatory process with the release of histamine and results in increased vascular permeability, in which C3a and C5a are particularly implicated [47].

Nitric oxide (NO), which is normally continuously produced by endothelial cells, regulates vascular tone. Its production is upregulated by pro-inflammatory cytokines resulting in vasodilatation, and this is likely to be a key event in the overspill of inflammation to the systemic circulation [47]. Its metabolites, peroxynitrite and

superoxide, cause endothelial dysfunction and are directly cytotoxic, affecting DNA transcription and cell-level respiration.

The endothelial cell is an active participant in the processes of inflammatory and coagulation activity. In its resting state, it produces NO, tissue-factor pathway inhibitor, PAI-1, and tissue plasminogen activator (t-PA). After activation by TNFα and Il-1 however, it reduces this anticoagulant activity and becomes predominantly pro-coagulant with the production of mediators such as tissue factor and cytokines, including Il-6. Activation crucially increases endothelial permeability, allowing fluid and protein exudation [69]. The glomerular bed has been studied as a marker for generalised hyper-permeability, and significantly raised levels of albumin excretion have been shown in trauma patients subsequently developing ARDS and respiratory insufficiency [70].

1.3.5. The systemic inflammatory response: SIRS, MODS and CARS.

Locally, inflammation produces the clinically recognisable features of rubor, calor, dolor, and tumour, and encourages the removal of damaged and necrotic tissue, and stimulates tissue repair. However, after major trauma, this inflammatory activation extends beyond the local environment into the systemic circulation. This arises from over-production of cytokines with inadequate counter-inflammatory regulation. The trauma patient has been described graphically as a 'stew of pulsating cytokines' [71]. Over-spill is assisted by the vasodilatation arising (for example) by overproduction of nitric oxide and its metabolites [47].

Systemic overspill causes further amplification of the stress response, and results in a number of physiological effects which together are recognised clinically as the Systemic Inflammatory Response Syndrome (SIRS). Pyrexia develops, controlled by the

hypothalamus under the influence of Il-1, and there is increased production, recruitment and activation of neutrophils. This is recognised as part of the normal physiological response to stress [56], but an excessive response has severe consequences and the extent of SIRS at admission after trauma correlates closely with length of stay and mortality [72]. Activated neutrophils become inflexible [73] and express adhesion molecules [74], and this encourages their sequestration within capillary beds where degranulation results in micro-environmental damage to the endothelium and extravascular tissue. This, together with the embolism of microthrombi and vasomotor dysfunction, produces tissue ischaemia, resulting in failure of cell respiration and transcription, and organ dysfunction. The failure of more than two organ systems is recognised clinically as the Multiple Organ Dysfunction Syndrome (MODS) and has a high associated mortality [75]. An overwhelming stress response to the initial injury may be sufficient to precipitate organ dysfunction (Fig 1.2, stress response curves).

The inflammatory response is modulated by a counter regulatory anti-inflammatory response (which, though not clearly defined as such, is often referred to as a syndrome: CARS), mediated by cytokines Il-4, Il-10 and Il-13. In the physiological context of the stress response, this gradually terminates the hyper-dynamic phase and allows return to function [56].

This sequence of events may escape satisfactory control, however, and just as inflammatory hyper-stimulation can cause organ dysfunction, so inflammatory over-suppression (excessive CARS) is also deleterious. Increased Il-10 secretion and decreased expression of HLA-DR antigens by monocytes after trauma is associated with immunosuppression, progressive sepsis and pulmonary shunt [76;77].

1.3.6 Markers of inflammatory activity

Measurements of the circulating components of the inflammatory and coagulation pathway provide an insight into the milieu following trauma (Table 1.5). TNF-α and Il-1 have high levels of circulating receptor antagonists (sTNFr and Il-1ra) and have very short half-lives in vivo, which may protect against their powerful and widespread effects. As a result their circulating levels are low or undetectable even after major trauma [78;79 80] and shed receptors to these cytokines provide a more helpful assay [78].

In contrast, Il-6 and Il-8 are markedly raised in the systemic circulation after trauma (Table 1.5), tending to peak between seven and 24 hours, and usually returning to normal after three to four days [52;75;76]. The degree of elevation of Il-6 is associated with the severity of trauma [52;79]. There is no increase in Il-6 after ankle fracture, compared with normal levels (around 10 pg ml^{-1}), but levels increase to 50 pg ml^{-1} after an isolated femoral fracture and nearly 600 pg ml^{-1} after multiple trauma with femoral fracture [79].

Although Il-6 levels as high as 700 pg ml^{-1} have been reported in patients not suffering complications [79], there is accumulating circumstantial evidence that the degree of elevation of these cytokines after injury correlates with the likelihood of subsequent adverse outcome [75]. Serum levels of Il-6, Il-8, and elastase are significantly higher amongst those developing multiple organ dysfunction, and levels are higher again in those dying of MODS [75]: Nast-Kolb reported that trauma patients developing MODS had a mean Il-6 at admission of over 700 pg ml^{-1}, compared with a mean level of less than 200 pg ml^{-1} at admission for those patients not developing complications [75]. Pape reported that Il-6 concentrations in excess of 500 pg ml^{-1} were associated with the development of MODS [81;82]. However, there is some apparent variation between centres in the levels that are considered to be significant, which has caused some confusion in the literature. In one study, death from ARDS was reported in a patient with femoral fractures with a presenting Il-6 of 272 pg ml^{-1}. Although this level was twice that of the

31 surviving patients, and the Il-6 level was cited as indicating greatly exaggerated inflammatory activation [83], this level is lower than those reported for far less severely affected patients from other centres. There appears to be insufficient experience with these techniques to base judgements or management decisions on reported absolute levels of Il-6.

Markers of neutrophil activation and adhesion are also raised after trauma. ICAM, L-selectin, CD-11 [83;84] and elastase [85] levels are all raised at the time of admission. Markers of coagulation system activation are also raised after trauma, and the degree of elevation is also associated with the development of complications [62;63;69;75]. Patients developing respiratory insufficiency have been shown to have significantly greater perturbations in coagulation times, platelet consumption, and the levels of β-thrombolglobulins, prothrombin fragments and D-dimers [62].

Measurements of cytokines and markers of inflammatory and coagulation activation are attractive as surrogate outcome measurements after trauma, and the identification of a discrete test or tests which would correlate with clinical outcome is a highly desirable goal. However the sensitivity, specificity and relationship with clinical complications remains undefined for analyses of this highly complex system of cascades. These measurements remain research tools at present.

1.3.7. *Neutrophil priming and the second hit.*

The primary insult which initiates the systemic stress response is termed the 'first hit'. In addition to this direct response, the 'first hit' has a further important effect: the priming of neutrophils. Neutrophils become 'primed' by mediators such as Il-6, Il-8 and

PAF to become sequestered in capillary beds. Once primed, a more intense response is generated in reaction to a subsequent stimulus [52;54;57;86;87], termed the 'second hit'. This priming response may persist for over 24 hours after the first hit [87].

Surgery is a potent potential second hit, and has been shown to intensify the inflammatory response [79;83]. The nailing of femoral fractures in particular causes an incremental increase in circulating levels of elastase and Il-6 [83]. The second hit has also been associated with an increased risk of MODS [85]. The magnitude of this secondary response is related to the first hit [79], and thus is more marked in severely injured patients. It is also proportional to the magnitude of the second hit (the type of surgery performed). In comparisons of surgical strategies, immediate intramedullary nailing raised Il-6 levels from 55 to 250 pg ml^{-1}, whilst with primary external fixation resulted in no such increase [80](section 5.3). Il-8 mediated neutrophil migratory capacity is also increased by reaming and nailing of fractured long bones, whereas primary external fixation does not produce this response [88].

Much interest centres on whether there is an association between this second hit response detected using surrogate outcome measurements, and clinical respiratory insufficiency, and whether such complications can be diminished by pharmacological therapy, or by reducing the severity of the second hit.

1.3.8. Variability in response and genetic polymorphisms

Patients with unexceptional injuries have been noted to suffer exaggerated systemic responses to injury, and a genetic basis for such sporadic complications has been proposed [83]. Genetic polymorphisms account for variations in phenotypic traits, and may be substitutions, insertions or deletions of a single DNA nucleotide or haplotypes [61]. They may exist in the promoter or coding regions of a gene and alter the production or

structure of a protein. They may influence the circulating levels of inflammatory or coagulation mediators and therefore may influence the clinical response following trauma. A few polymorphisms have been identified as important after injury. For example, a single base-pair (4G/5G) promoter polymorphism exists for the PAI-1 gene which governs plasma concentrations of PAI-1. In a well-designed study of 61 comparable trauma patients it was shown that the homozygous 4G/4G genotype resulted in increased levels of PAI-1, with a mortality of 51%, whereas the mortality of the heterozygous 4G/5G genotype was only 28% and of the 5G/5G genotype, only 15% [89]. High levels of PAI-1 impair fibrinolysis and result in persistence of fibrin in the circulation and microcirculatory beds. The resulting exaggerated stress response was demonstrated by elevated levels of TNFa and Il-1 in these patients.

Many more genetic polymorphisms have been identified which are procoagulant and antifibrinolytic and may have a relationship with the post-traumatic response. Polymorphisms have been described for fibrinogen, factor V, protein C, protein S and PAI-1 and are associated with an increased risk of myocardial infarction, cerebrovascular thrombosis, deep vein thrombosis and pulmonary thromboembolism [61;90]. Several pro-inflammatory polymorphisms have been identified in relation to auto-immune, inflammatory and neoplastic disease, and these may also have an influence in the post-traumatic state [91-93].

1.4. THE PULMONARY RESPONSE

Respiratory insufficiency arising from trauma has a complex pathophysiology which includes fat embolism, and activation of the inflammatory and coagulation systems. The following is a suggested paradigm for understanding the processes involved.

1.4.1. Initial response to injury

1. The nociceptive stimulus of traumatic injury stimulates a neuro-endocrine response with resulting autonomic changes and the release of catecholamines.
2. Fat from the medullary cavity of fractured long bones is released into the venous circulation and embolises in the pulmonary vascular bed, resulting in local tissue hypoperfusion and hypoxia. Right heart afterload increases, pulmonary arterio-venous connections open up, and shunting of deoxygenated blood (and its embolic contents) occurs into the systemic circulation.
3. Metabolic fat depots are mobilised and may contribute to the volume of circulating (and embolised) fat.
4. Neutral fat embolised in the pulmonary vascular bed is hydrolysed to form free fatty acids, causing alveolar disruption and reduced surfactant activity.
5. Tissue factor and fat at the injury site and in embolising particles directly activate the extrinsic coagulation system and platelets. Thrombus and fibrin coat the circulating emboli, thus decreasing their deformability and increasing their size and propensity to embolise in tissue beds. This combination of fat and thrombus may form an 'inflammatory nidus' promoting activation of the inflammatory cascade, and the combination appears to be important in the development of further clinical sequelae [62]. Once initiated, the systemic activation of the coagulation system becomes self-perpetuating and amplified as tissue factor is subsequently expressed directly by several cell types (epithelium, endothelium, fibroblasts and macrophages). DIC and ARDS coexist in 20% patients [62].

Procoagulant activity is seen in BAL fluid of patients with ALI, and fibrinolytic activity is markedly decreased or absent [68;69].

6. Vasoactive agents such as thromboxane released by platelets promote pulmonary vasoconstriction, further increasing right heart afterload.
7. Locally injured tissue becomes inflamed, and cytokines are released into the systemic circulation where a systemic response is initiated. The severity of the response is related to trauma 'dose', and the severity of the hypoperfusion/ reperfusion insult [45;46], and is modified by genetic predisposition [89].
8. 'Cross-talk' between the inflammatory and coagulation systems stimulates and amplifies both [69]. Fibrin stimulates monocytes and endothelial cells to produce the pro-inflammatory cytokines TNFα, Il-6 and Il-8 [61]. In turn, cytokines induce the expression of tissue factor, which potentiates further extravascular fibrin deposition.
9. Il-8 is produced directly by pulmonary macrophages in response to hypoxia [94] and fat, and appears in BAL fluid within two hours of injury in increased quantities in those who later develop ARDS [95].
10. Neutrophils, primed after injury to respond more readily to Il-8, migrate in response to this local region of increased Il-8 production [54].
11. Neutrophils are attracted, activated, become rigid and are sequestered in the lungs [73;96], and subsequently degranulate with the release of enzymes and active oxygen species. These cause membrane disruption and increase alveolar permeability. Experimental neutrophil depletion reduces lung injury [96].
12. Neutrophils are also directly activated by fat, further encouraging adhesion, accumulation and degranulation [58].
13. Inflammation within the lung vasculature with resulting increased epithelial permeability causes oedema of both parenchyma and alveoli. Fluid and fibrin deposition reduce gas exchange and lung compliance, producing ventilatory deficits and radiographic changes [97-99].

14. Neutrophils crossing the endothelium and epithelium and appear in BAL fluid along with degranulation products such as reactive oxygen species and elastases, and with fat [35]. Hydrogen peroxide can be detected in the exhaled breath [100].
15. ARDS and ALI are clinically recognised according to specific criteria (Table 1.4) when arterial oxygenation falls despite an adequate oxygen supply. 'ARDS is a broad avenue entered by many different side streets that represent the various initiating sources of severe lung injury' [98], and there are no specific features associated with post-traumatic ARDS.
16. ARDS developing within 48 hours of injury ('early ARDS') is associated with severe hypovolaemic shock, gross tissue hypo-perfusion with marked base deficit and severe hypoxaemia [101]. The evolution of ARDS more than 48 hours after admission ('late ARDS') frequently follows the additional development of a lower respiratory tract infection and is associated with death from progressive multiple organ system failure [101].

1.4.2. Multiple injuries and thoracic injury

There is a close association between the severity of injury and the risk of pulmonary complications. In the 1970s the risk of FES was known to increase significantly with the number of long bones fractured [102], and more recently the incidence of ARDS has been shown to be increased with rising Injury Severity Score [103]. It has been suggested that particular injury patterns represent an increased risk [104], but there are numerous confounding factors in this group of patients. The use of massive blood transfusions in particular is associated with respiratory insufficiency [105-107].

Direct thoracic injury, particularly pulmonary contusion, is a potent cause of respiratory failure and results in ARDS in up to 40% cases [108;109]. Meta-analyses suggest that a direct thoracic injury is three time more likely to be associated with respiratory failure

than is a long bone fracture [21], and several authors have confirmed that after a femoral fracture, an additional thoracic injury imparts a greater risk of pulmonary complications [104;110].

Interest has centred on the converse question: whether a patient with thoracic injury is at any additional risk when this injury is accompanied by a concomitant injury to other anatomical sites such as a femoral fracture [104]. Contused, atelectatic or collapsed regions of lung are haemorrhagic and oedematous, and have a reduced capillary bed perfusion. Therefore, in the presence of lung injury, the pulmonary blood flow may be directed to a smaller volume of parenchyma, thus delivering a greater concentration of fat and thrombus, and thus a long bone injury might exacerbate a thoracic injury. However the majority of studies report that the additional femoral fracture is inconsequential in precipitating respiratory insufficiency, and it is the thoracic injury rather than the femoral fracture which determines overall risk [111-117]. This has been substantiated in a recent meta-analysis of all English-language studies examining the effects of thoracic and long bone injury, which has reported that the relative risk of post-traumatic respiratory insufficiency after thoracic injury alone is not significantly different from that after combined thoracic and long bone injury [21].

1.4.3. The second hit.

It has been suggested that early fracture surgery represents an important second hit in the development of respiratory insufficiency, especially in those patients with multiple injuries or with thoracic injury [83]. The concept of a system with limited capacity to withstand inflammatory activation has been proposed, in which the initial trauma has used up much of the reserve. The second hit, if sufficiently severe, outstrips the remaining reserve and results in decompensation and SIRS. The process of transfer to

theatre and performing surgery potentially exposes the patient to physiological instability in the form of pain, movement, hypothermia, hypotension (and thus capillary bed hypoperfusion) and further surgical trauma (with further activation of primed inflammatory and coagulation pathways). The additional fat embolism caused by reamed intramedullary nailing has been particularly implicated in this regard [83]. Although there is little data regarding the duration of this period of increased susceptibility, the interval between two days and four days post injury is generally associated with a particularly high risk of a second hit precipitating a major inflammatory over-response [80;118], particularly when there is evidence of existing inflammatory over-activation [82].

Strategies proposed for minimising the effect of the second hit are discussed in detail in section 1.5.

1.5. MANAGEMENT OF POST-TRAUMATIC RESPIRATORY INSUFFICIENCY

Numerous simultaneous improvements in the management of trauma patients appear to have resulted in a marked fall in the incidence of respiratory insufficiency from up to 22% of trauma admissions in the 1960s and 1970s, when much of the published work on FES was produced [102], to below 5% in recent studies. Many factors are likely to be of importance in this falling incidence, including better pre-hospital care, more rapid and (aggressive) resuscitation protocols, and improved intensive medical supportive therapy. Major advances in fracture management have also occurred over the past four decades, from a conservative approach requiring immobilisation, to an interventional strategy involving operative internal stabilisation and early patient rehabilitation.

1.5.1 Orthopaedic interventions

Orthopaedic fracture management has developed considerably over the past five decades, and four general trauma management strategies are apparent:

1. Conservative Treatment

Until the 1970s the accepted treatment in Britain for long bone fractures was conservative, with the use of plaster of Paris and traction. Prolonged immobilisation was attended by the recognised complications of recumbency: muscular wasting, peptic stress ulceration, decubitus ulceration, infections of the respiratory and urinary tracts and psychological depression [102;119]. In addition, conservative management was associated with a reported incidence of FES of up to 22% [102].

The contemporary explanation for the high incidence of FES was the unrelieved pressure within the fracture haematoma, predisposing to continued fat intravasation [120]. The later reduction in incidence with stabilisation was held to relate to haematoma decompression [11;120]. In fact, direct intraosseous pressure manometry in patients undergoing femoral fracture manipulation has shown that repeated movements at the fracture site itself cause intramedullary pressure to increase to over 150 mmHg [43]. Intra-abdominal sonography of the vena cava in sheep by the same group of researchers has shown that the intraosseous pressure threshold for venous embolism is only 50mmHg [43]. This fat embolism is exacerbated by the formation, disruption and release of thrombus from adjacent tissues [121], which results in transient hypoxia [122] and perpetuates the stimulation of the stress response. In addition, the immobile, supine patient is prone to atelectasis, pneumonia and reduced functional residual capacity which causes shunting and impairs oxygenation. The introduction of internal fixation techniques was accompanied by a marked reduction in incidence of FES to under 5% [102].

2. Delayed stabilisation

Despite the popularisation of internal stabilisation for isolated fractures in the 1970s, initial management of patients with major injuries continued for a period to be largely conservative. FES was known historically to be more common in these patients, and they were considered to be 'too sick to be operated on' acutely, and stabilisation was therefore delayed for several days [102].

3. Early Total Care – and the reaming controversy.

Early and delayed stabilisation were directly compared in several retrospective reviews [103;123-131], and a small prospective study [132], and no increased risk found. Indeed, the risk of ARDS was demonstrated to be five times higher in patients who had stabilisation delayed beyond 24 hours [103]. The influential prospective randomised study by Bone [133]

confirmed a decreased risk of ARDS, FES, pulmonary emboli and pneumonia in those patients with multiple injuries undergoing stabilisation of all long bone fractures within 24 hours of injury. However, this paper has been criticised [134;135] and these impressive results have not been reproduced in any subsequent study. In one review of this subject [135] it was observed that three patients underwent thoracotomy in the late stabilisation group (n=37), compared with no patients requiring thoracotomy the early stabilisation group (n=46), possibly suggesting an increased rate of direct thoracic trauma amongst the late group. However, it is not clear from the paper whether any of these patients undergoing thoracotomy subsequently developed complications. Even if these three patients were assumed to have developed a complication and were to be excluded from the analysis, the numbers of patients developing respiratory insufficiency would have been 16 in the early stabilisation group and 33 in the late group. The concept of Early Total Care (ETC) has now been widely accepted.

There is strong biological support for this concept. Delayed stabilisation of fractures results in prolonged activation of the coagulation and complement responses [136]. Markers rise after injury and rapidly decrease towards normal following surgical stabilisation of fractures. However, prolonged activation of the stress response is demonstrated by persistent elevation of these markers in those patients treated with skeletal traction until delayed stabilisation is performed, after which they return rapidly to normal [136].

A paradox is evident, that although the intramedullary stabilisation of fractures reduces the incidence of post traumatic respiratory insufficiency, nailing also provides the circumstances for the exacerbation of the stress response and lung injury. Refinements in the technique of nailing have in been sought in order to minimise this second hit. Animal and surrogate end-point studies have suggested that the use of unreamed intramedullary nails [83;137], altered reamer design [138], faster reamer revolutions with slower introduction of the reamer [139], and venting of the distal fragment [140] may result in less severe pulmonary injury, but this has not been substantiated by clinical studies.

4. Damage Control Orthopaedics

A small discrete group of multiply injured patients who are physiologically unstable despite initial resuscitation are unsuitable for prolonged or extensive immediate surgery. These patients have reduced reserve, having reached (or exceeded) the limits of physiological compensation. The second hit involved in potentially prolonged procedures such as femoral nailing or articular reconstruction may delay the return of homeostasis, thus compromising outcome. It has been proposed that these patients should undergo a rapid, minimally invasive stabilisation procedure (such as external fixation), followed by a period of resuscitation and physiological stabilisation in the Intensive Therapy Unit [80;135;141;142]. It is suggested that such temporary skeletal stabilisation may offer the advantages inherent in ETC, whilst obviating some of the potential risks [143]. Over a period of time as short as eight hours, such patients may regain their core temperature, circulating volume, coagulation potential and satisfactory oxygenation. Tissue hypoperfusion is thereby reversed, returning lactate and mixed venous oxygen saturation levels to normal [135;143]. Definitive surgical stabilisation is then a safer prospect, and confers the mechanical advantages of intramedullary stabilisation, which are of course especially pertinent to this group of patients. Recently, this widely accepted concept has been formalised as 'Damage Control Orthopaedic (DCO) Surgery' [110;141;143]. It has also been proposed that DCO principles should be applied not only to those patients who are physiologically unstable or *in extremis*, but also to those termed 'borderline' patients [110] (Table 1.6). However, the usefulness of this definition of the 'borderline' patient is uncertain in that it includes those who are haemodynamically shocked or who have acute right heart failure, and would therefore usually be considered clinically to be physiologically unstable.

Table 1.6. Characteristics of the 'Borderline' Trauma Patient [110]

Polytrauma with Injury Severity Score > 40
Polytrauma with Injury Severity Score > 20 *plus* thoracic injury (AIS >3)
Polytrauma *plus* abdominal / pelvic injury *plus* systolic BP < 90 mmHg
Pulmonary artery pressure exceeding 30 mmHg
Pulmonary artery pressure rise exceeding 6 mmHg during nailing of femur

Detailed research-based evidence for the benefits of this approach has not been available, because of the small numbers of patients who sustain this injury pattern, and the multiplicity of factors which influence their outcome. One retrospective analysis of patients sustaining major trauma has suggested an improved outcome over several decades with the increasing use of damage control techniques [141]. This review reported the outcome in 514 admissions to a German trauma centre with blunt polytrauma (with an Injury Severity Score over 18) which included a femoral fracture. The authors identified a fall in the number of cases of ARDS in patients over a period from 1981 to 2000 from 68% in the first nine years to 25% per year over the last eight years, although the diagnostic criteria used were not reported. Over the later period from 1993-2000, the institution had promoted the concept of DCO and had increased the use of external fixation from 17% to 36% cases, and decreased the use of plates from 23% to 7%. The proportion of patients treated by IM nailing remained constant at 58-60%, although the proportion of these nails which were unreamed increased from 14% to 86%. The authors reported a lower rate of ARDS in the last nine years in the externally fixed group (9%) compared with the nailed group (15%) despite a slightly higher injury severity score (ISS 36 compared with 39 respectively). They also reported a reduction in the rate of ARDS amongst patients treated by nailing from 33% in the first 9 years to 15% in the last eight years. They concluded that these improvements might have been due to a lower 'surgical burden' in the external fixator and unreamed nail patients. There are of

course a host of confounding factors which may have influenced these changes in incidence (described above), and there is a possibility of selection bias in such un-randomised retrospective studies, and it is therefore not possible to draw firm conclusions from this report. In particular, a clinical advantage in using unreamed nails has not been demonstrated, and a well designed prospective multi-centre trial of 315 patients (109 of whom were multiply injured with ISS > 18) comparing reamed and unreamed nails failed to show any difference in the incidence of pulmonary complications including ARDS, FES and pneumonia [144]. A power study following this trial concluded that over 2000 patients would be required to determine whether any statistically significant difference exists.

A recent study using cytokine levels as surrogate outcome measures gives support to the concept of minimising the second hit. In a well-designed multicentre European study, multiply injured (ISS>16), but physiologically stable, patients with femoral shaft fractures (n=35) were randomised to intramedullary nailing or external fixation within 24 hours of injury. An elevation of Il-6 was shown peaking at 24 hours after immediate intramedullary nailing, but this elevation did not occur after external fixation, nor after subsequent conversion to definitive nail stabilisation [80]. This lack of response to secondary nailing (performed an average of three days after external fixation in this study) may relate to the post-traumatic CARS phase of anergy (section 2.3.5). This study could be criticised in that physiologically unstable patients in whom DCO is potentially of benefit were excluded, and therefore it is not certain that these results can be directly applied to the 'at risk' population. In addition, no clinically significant respiratory sequelae developed in either group, confirming that surrogate outcome measures such as Il-6 levels may not relate directly to clinical outcome. However, the finding that the biological response to the two surgical strategies is different in magnitude is of great interest.

There are a number of potential *disadvantages* of the DCO approach. For example additional complications might arise from subjecting patients to multiple procedures

rather than a single operation, and there is a potential risk of deep infection after conversion from external fixation to an intramedullary device. However these disadvantages have not been substantiated. The incidence of local complications is minimal, and the conversion to later definitive intramedullary stabilisation is regarded as safe [143;145]. The remaining criticism of this technique is that if no suitable physiological window presents itself in the first few weeks after temporary external fixation, then later conversion to definitive stabilisation may be technically difficult, with an unsatisfactory anatomical and functional outcome.

1.5.2 Medical interventions

Early approaches to the treatment of post-traumatic respiratory insufficiency reflected the limited understanding of the underlying pathophysiology of the condition. Three early randomised trials of methylprednisolone as a 'membrane stabiliser' claimed a reduced incidence of FES in the treatment group [38;146;147], but sepsis proved to be a significant complication [148], and subsequent modern studies have not supported its use [149]. Pre-treatment with heparin in experimental models has been shown to reduce the degree of pulmonary compromise [32] and intravascular coagulation [31], and heparin transiently enjoyed widespread clinical use [15;39], despite the dangers of haemorrhage and rapid lipolysis [15;150]. However, its use has not shown consistent benefits in reducing lung injury and a recent review of anticoagulant therapies concluded that its current role remains to be defined [67]. Ethanol (which decreases lipolysis) and dextrose (which decreases FFA mobilisation) [147;151;152] have also been used empirically.

Recent advances in many fields, particularly the immunology of sepsis, have suggested more focussed possible treatments. Anti-cytokine therapies such as the administration of specific receptor antagonists to Il-1 reduced death from sepsis in experimental models

[153]. Antibodies to adhesion proteins CD 11 and ICAM significantly reduced pulmonary endothelial injury in animal models of sepsis [154], and cyclooxygenase inhibitors, by reducing thromboxane synthesis and neutrophil adherence have been shown to decrease lung injury [155], if given early [156]. Specific blockade of tissue factor and factor VII reduces coagulation activation and prevents lung dysfunction and fibrin deposition in animal models of sepsis [157], and administration of tPA and AT III reduces lung injury in animal models of ARDS [158]. There are numerous significant differences between species in the activity of the inflammatory and coagulation systems [159] however, and studies in humans have so far been less encouraging [67;69].

Activated protein C (APC), in contrast, has been shown to reduce mortality in septic human patients, an effect which may be due to its promotion of fibrinolysis, or its direct inhibition of Il-1, Il-6 and TNF-α expression [69]. Although APC increased the risk of significant haemorrhage (which limits its applicability in trauma), the success of this immunological therapy raises the prospect of more specific drug treatments in the future [67].

1.6. LIMITATIONS OF EXISTING RESEARCH

Research into post-traumatic respiratory insufficiency has historically followed three main paths: epidemiology, animal studies and human patient studies.

1.6.1 Epidemiological studies

Epidemiological research has aimed to define the incidence of respiratory insufficiency after trauma, and to identify markers for its development. Demographic variables such as age and sex have been studied, with younger patients found to be at higher risk [129]. The severity ('dose') and anatomical location of injury has also been associated with the likelihood of complications [160], with multiply injured patients and especially those with injuries to the femora or thorax held to be at risk. Pre-existing morbidities and genetic predisposition [89] to inflammatory or coagulation activation (or suppression) may place injured patients at higher risk of complications.

A number of studies have investigated the epidemiology of respiratory insufficiency amongst ITU patients, or amongst highly selected groups of multiply injured patients. No data is available regarding the overall incidence of respiratory insufficiency after trauma, or the importance of injury pattern or severity. In particular, the precise importance of a thoracic injury remains controversial. Previous studies have used variable definitions of respiratory insufficiency, preventing meaningful comparisons, although internationally accepted classifications are now available [49].

1.6.2 Clinical (patient–based) studies

Three problems beset clinical studies.

(i) Statistical power.

The number of patients presenting to any one institution with injuries sufficiently severe to fall into a putative 'high risk' group is small, and within this group, only a small proportion of patients are likely to go on to develop respiratory insufficiency. Thus it would be very difficult to perform randomised trials of potential interventions with sufficient power in a single centre. Several studies have increased numbers by using surrogate outcome measures such as systemic cytokine levels, which reduces the immediate clinical relevance of the results obtained. Multicentre studies have many advantages and the European Polytrauma Study on the management of Femoral Fractures (EPOFF) collaboration [80] produced the interesting data discussed above (Damage Control Orthopaedics).

Retrospective studies have larger numbers and can look at clinical outcomes. The outcomes from major trauma have generally improved over the past three decades, and a number of simultaneous improvements in care may be important, including faster rescue, improved initial resuscitation, better invasive haemodynamic monitoring, advances in ventilator design and use, antibiotic therapy and nutritional support. The effect of changes in orthopaedic practice in retrospective studies is difficult to dissect out from this background of confounding factors.

(ii) Location.

Major traumatic injuries generally occur outwith the hospital setting, and therefore those patients who are most likely to suffer respiratory insufficiency are not available for study during the first several minutes or even hours after injury. Comparison with a 'baseline' pre-injury state is not possible, and investigation of the earliest phases of the stress response is clearly restricted.

(iii) Pathophysiology.

The basic pathophysiology of the stress response is poorly understood, particularly at the earliest stages of its evolution. There are a number of 'candidate molecules' from various locations within the inflammatory and coagulation pathways of potential interest which could be assayed, promoted or antagonised in order to manipulate the stress response.

However, the origin, target, action, mechanism of action, and interactions of each of these candidates in the individual trauma patient remains to some extent conjecture and in practical terms the researcher faced with this list must make a limited selection which will inevitably provide a restricted picture of the overall biological response.

A considerable body of work already exists regarding *sepsis-related* respiratory insufficiency, and much of this may be applicable as a guide to the post-traumatic situation. However, the major limitation of existing clinical studies of medical therapies in sepsis is that they are generally administered in the ITU setting, following the diagnosis of SIRS, ARDS or sepsis. It is clear that the inflammatory and coagulation pathways are already highly activated and elaborate at this stage and may be resistant to effective control.

An understanding of the early stress response pathway is highly desirable as the ability to commence an effective medical therapy at the time of admission (or even at the scene of injury) targeted at a key stage of the stress response pathway would potentially allow the stress response to be attenuated or avoided.

1.6.3 Animal Studies

Animal studies offer a number of attractive potential benefits: the number of animals and severity of injuries can be standardised, and adjusted to allow meaningful statistics, and the immediate response to injury can be studied. Animal studies may provide an opportunity to determine the early temporal sequence involved in the highly complex stress response and correlate this with later outcome. However, there are a number of limitations which have hampered animal studies.

(i) Technical limitations of existing animal models

Previous animal research in this field has centred on the effect of fracture stabilisation in a variety of canine, porcine, ovine and simian models. The variables studied have been the severity of injury (for example the presence or absence of lung contusion), the effects of different techniques (such as plating and nailing), and the effects of different reamer or nail design.

The Toronto model reported by Schemitsch and colleagues [161-164] uses skeletally mature mongrel dogs. Fat embolism is produced by retrograde reaming of the intact femur and anterograde reaming of the intact tibia. The canal is then pressurised by the injection of cement and insertion of a Steinmann pin. In one series of experiments, in addition to this pressurisation, a transverse osteotomy of the contralateral femur was performed through an open dissection using a saw to create a notch, and a low-energy three-point bend to complete the crack. Study groups were then compared, with the fracture stabilised using a plate or nail. This group have also studied the effects of a pulmonary contusion produced using a piezoelectric force transducer and C-clamp via a thoracotomy.

The Hannover model reported by Pape and colleagues [138;165;166] uses merino sheep. In this model, severe physiological perturbation is produced by venesection and the creation of hypovolaemic shock for two hours followed by resuscitation. In one study,

lung contusions were created by directly squeezing the lung with pliers via a thoracotomy. In two studies, a lymph fistula was prepared by cannulating a mediastinal lymph node via a thoracotomy. In each study, the sheep were allowed to recover for forty-eight hours before further procedures were performed on day three. The group report the effects of reaming the intact femora, of variations in the reamer design, and have compared the effects of nails and plates.

The Vienna model, reported by Wozasek and colleagues, is also ovine and uses mountain sheep [20;167;168]. In one study a similar protocol to that of the Hannover group was used, with the initial creation of a lymph fistula [167], and subsequent reaming and nailing of the intact femur and tibia on day three. In the two other studies reported by this group, a thoracotomy was produced to allow an echo probe to be placed directly upon the beating heart. They describe the effects of reaming and nailing both femora and tibiae, which were intact in one study and with creation of an incomplete femoral wedge osteotomy through a surgical incision in the other.

Several other groups have reported single studies using ovine, porcine, canine and other models. These experiments are summarised in Tables 1.7 and 1.8.

Each of these studies have used a model which is based upon the instrumentation of intact bones, or following surgical osteotomy. There are several technical concerns regarding this approach. The pathophysiological milieu of an uninjured, skeletally stable model is likely to be very different from that existing after traumatic injury. For example, severe blunt injury to the skin and soft tissues is not encountered in 'trauma' models which incorporate an intact or surgically osteotomised bone, but skin is an important reservoir of pre-formed cytokines [169;170] and the soft tissue injury itself produces an important stress response which may materially influence outcome [158;171]. The immediate biological effect of surgical osteotomy itself, based on surgical experience, could not be compared to that from a traumatic fracture.

The effect of the first hit has therefore not been studied. Only one study, published by Reikeras in 1987, provides an exception and gives a tantalising glimpse of the neuroendocrine response to a surgical nociceptive stimulus [172]. The author reports that during retrograde reaming of the intact canine femur mean aortic and pulmonary artery pressure fell significantly, but returned to normal within five minutes. No other positive findings are presented, and the author concludes that a 'neurogenic reflex mechanism' may have been responsible.

This lack of a true biological 'first hit' in existing models may compromise those studies claiming to test the effect of the second hit.

There are also methodological concerns regarding the suitability of models without fractures for studying the physical effects of fat embolism. Mechanically, the effect of intramedullary instrumentation of an intact long bone is different from that observed in the presence of a fracture which permits a venting effect on the pressurised intramedullary contents.

Some authors have attempted to allow for this venting effect by creating a surgical osteotomy in the diaphysis. However, this does not appear to be effective. Those studies in which a surgical osteotomy has been created do not show any less marked intraosseous pressure rise or embolus release [139;167;173] than those in which the femur has been left intact [20]. The direct physiological effects of osteotomy also appear to be minimal: intravascular echocardiography during complete surgical osteotomy reveals only 'a few small embolic particles' [173] in comparison with the prolonged release of larger quantities of embolus seen on high-energy fracture or reaming and nailing [25].

The risk of respiratory insufficiency developing may be increased in the presence of additional injury 'co-factors' [11] and a number of reported studies have increased the level of physiological stress in the model used by inducing concomitant injuries other than that to the limb. Haemorrhagic shock has been created by venesection

[138;139;165;168;174]. Lung contusion has been described using direct crushing of lung tissue via a thoracotomy [138;161;165] or direct external blows [167;173-175]. An 'ARDS-like state' has been described by administering an intravenous infusion of perilla ketone [176]. In several studies, additional data has been obtained regarding pulmonary lymph flow using the lymph collection technique of Staub [165;168;177] and whilst not intended as an additional injury, this technique is known to cause pulmonary microvascular damage and dysfunction [138].

There are a number of concerns regarding each of these models. The model used by Pape [138;165;166] requires the creation of haemorrhagic shock, lung contusion and in some cases a lymph fistula two days before intact femoral reaming and nailing is performed, with an intervening conscious recovery period. This is entirely unlike the trauma situation where a limb injury occurs concurrently with its associated fat embolism and shock. The reported acute *mortality* from the venesection process alone is 33% in this model [165], even before lung contusion and surgery, suggesting that this is an extreme instance of physiological stress. Isolated haemorrhage, such as that produced by the venesection used in the model of Pape and others, produces a cardiovascular redistributive response quite unlike that that produced by haemorrhage in the presence of a somatic injury. It has been shown that an injury providing afferent stimulation results in inhibition of the barroreceptor reflex with redistribution of the cardiac output to skeletal muscle and reduced perfusion of tissues with low ischaemic tolerance such as the gut, and is associated with an increased mortality [178].

Perilla ketone is the toxic constituent of purple mint which is known to cause fatal interstitial oedema in grazing animals [179]. The direct infusion of perilla ketone causes an increase in lung microvascular permeability, with increased pulmonary oedema and reduced oxygen diffusion, without altering pulmonary haemodynamics [180]. However, in models where this chemical was administered one hour before femoral reaming [176], several deviations from injury physiology are evident. In such models respiratory

insufficiency precedes injury rather than following it. At the biological level, there are important differences in the development of pulmonary insufficiency, in that perilla ketone does not increase local levels of neutrophils or arachadonic acid metabolites [180], and therefore does not replicate the neutrophil 'priming' effect of a first hit injury.

Those models that incorporate the creation of a thoracotomy in order to conduct echocardiological examination [20;167] or cause injuries to the lung [138;161;165] are also potentially compromised as the uncontrolled effects of the surgical approach, altered lung ventilation and the presence of a chest drain may alter thoracic compliance and venous return to the heart.

No group has reported a model which creates reproducible high energy injuries to bone and the surrounding soft tissues which replicates the clinical situation of trauma. This may circumvent crucial steps in injury physiology, and osteosynthetic biomechanics, which may invalidate many of the conclusions reached by these studies.

(ii) Methodological problems

The components of the inflammatory and coagulation pathways produce their effects by offering unique surface ligands, and recognition of these sites is the basis for research assays. However, there are structural differences in these ligands between species and there is limited cross-reactivity between enzyme-linked immunoassays (ELISAs) for human components of these pathways, and those for animal components. Although ovine Il-6 assays have recently been reported [181] and have been offered commercially, other assays commonly used in research upon human patients are not widely available for animal research.

Animal studies also require the use of anaesthesia for humane reasons, and this introduces a potential confounding factor in that most anaesthetic agents are cardiovascular and endocrine depressants, an effect which may be dose and time dependent. The effect of such depression on the stress response to trauma is not known.

Further practical problems may inhibit animal research including difficulties in obtaining equipment of a size appropriate to the study animal, difficulties in reproducing injuries accurately, the expense of maintaining the animals, and the process involved in obtaining licences.

Table 1.7. Studies of embolism in sheep

Ref	Author Year	Fracture?	Technique studied	Embolus measurement?	Haemodynamics?	Inflam. / coag	Notes
7	Wozasek 1994	No	Reamed nailing	No	Variable effect on PAP	No	Additional effect from haemorrhagic shock and endotoxia
8	Wozasek 1994	No	Reamed nailing	Echo via thoracotomy	No	No	Association between intraosseous pressure, instrumentation and embolus
10	Duwelius 1997	Osteotomy	UIMN vs RIMN Two reamer types	Intravascular echo Histology	SBP, PAP, CO	No	No significant difference comparing reaming, nailing and pulmonary injury
21	Mousavi 2002	Osteotomy	RIMN Two types, speeds	TOE and Gurd test	SBP, CVP related to driving speed		Hypovolaemia IMP compared
25	Pape 1994	No	Reamers: 3 types	No	Immediate, transient increase in PAP	Neutrophils	No change in neutrophil activity Pulmonary permeability increases
34	Pape 1992	No	RIMN vs UIMN	No	Transient increase in PAP during reaming	Neutrophils	Neutrophil activity variable Pulmonary permeability increases
26	Wenda 1993	No	Direct injection of air, marrow and saline	Echo of vena cava Histology	No	No	
30	Neudeck 1996	Osteotomy (wedge)	RIMN vs UIMN vs plate	Echo via thoracotomy	PAP not significantly affected	No	
38	Wolinsky 1998	Osteotomy	RIMN assessing effect of Chemical lung injury.	No	Not reported		Osteotomy 'clamped closed' before reaming.
[182]	Wolinsky 1996	Osteotomy	RIMN	Echo via thoracotomy	No significant effect on SBP, CVP, PAP	No	

RIMN: reamed intramedullary nail, UIMN: unreamed intramedullary nail, TOE: transoesophageal echocardiography, SBP: systemic blood pressure, PAP: pulmonary artery pressure, CVP: central venous pressure, CO: cardiac output, IMP: intramedullary pressure.

Table 1.8. Studies of embolism in other animals

Ref	Author Year	Fracture?	Technique studied	Embolus measurement?	Haemodynamics?	Inflammation / coagulation	Notes
Pigs							
24	Buttaro 2002	No	RIMN vs URIMN	Histology	Non-significant change in PAP	No	
42	Rautanen 1996	No	Direct injection bone marrow suspension via PA catheter	N/A	SBP, CVP and PAP increased		
Dogs							
4	Kerstel 1971	Both femora – pipe tongs	Nil	No	No	No	Source of fat
	Jacobs 1973	Blows with steel bar	Nil	Lung histology	No	No	Description of lung pathology
32	Manning 1983	Three point bending fracture	Reaming	Fat from femoral veins quantified	No	No	See text
39	Schemitsch 1998	No	Ream plus pressurized cement	Histology	PAP increased after cement	Histology – no inflammation	After 72 hours
36	Elmaraghy 1999	No	Chest injury vs fat embolism	Histology	PAP increased after reaming and cement	Histology – no inflammation	
40	Elmaraghy 1998	No	Cement / lavage	Femoral vein triglycerides	PAP increased with reaming and cement	Histology – no inflammation	
41	Schemitsch 1997	Osteotomy and bend	Plate vs RIMN vs UIMN	Histology	PAP increased with reaming and cement	Histology – no inflammation	After 24 hours
88	Liska 2003	No	Canine THR	TOE detected emboli	No	No	
Others							
23	Kropfl 1999 (Baboons)	Osteotomy	RIMN vs UIMN	Gurd test on blood from IVC	No	No	IMP
35	Heim 1995 (Rabbits)	No	RIMN vs UIMN	Histology	No	No	

1.7. AIMS OF STUDIES, RESEARCH QUESTIONS AND HYPOTHESIS.

Three studies were performed in order to address the epidemiology of ARDS, the nature of the post traumatic stress response in human patients, and the nature of the immediate stress response in an ovine model.

Study 1. Epidemiology of ARDS.

Aim: to review the prospectively collected data on a large cohort of general trauma admissions in order to investigate the epidemiology of ARDS.

Research Questions:

1. What is the incidence of ARDS in our general trauma population?
2. What features of the injury or injury patterns predispose to the development of ARDS?
3. Is thoracic injury important in determining incidence?

Study 2. Post-traumatic activation of the coagulation and inflammation systems.

Aims of study:

1. To study the degree of inflammatory and coagulation activation present in a prospective cohort of patients with tibial and femoral fractures, with and without additional thoracic trauma, for the first week after injury, beginning at the time of admission, and
2. To identify whether any factors at the time of admission and in the perioperative period correlate with the later development of respiratory insufficiency.

Research questions:

1. What is the degree of activation of the coagulation and inflammatory systems at the time of admission to the Accident and Emergency Department, and does this vary with the severity of injury?
2. How does this activation profile evolve perioperatively and over the subsequent week postoperatively?
3. What features at the time of admission correlate with the development of respiratory insufficiency in the perioperative and postoperative periods?

Study 3. Immediate response to trauma.

Aim: to study the immediate response to high energy extremity injury in a controlled manner, in an ovine model of major trauma, and to compare the haemodynamic, embolic and coagulation responses following this injury alone with those following surgical stabilisation of these fractures.

Research Questions:

1. What is the initial haemodynamic, embolic and coagulation response to a high energy fracture of the femur and tibia in the ovine model?
2. How is this response modified by intramedullary reaming and nailing?

1.8. THESIS HYPOTHESES

Severe musculoskeletal injury produces an identifiable early physiological stress response, which has haemodynamic, embolic, inflammatory and coagulation components. The severity and specific anatomical location of this injury are important in determining the level of risk of subsequent post traumatic respiratory compromise. Measurements of the degree of activation of the coagulation and inflammatory systems allow a more accurate assessment of this level of risk.

1.9 GENERAL STATISTICAL OVERVIEW

Parametric and non-parametric statistical methods were used as required, with the assistance of the SPSS software package version 11.5.0. A difference was taken as significant when the p value reached 0.05 or less. The specific tests employed for each analysis are detailed in each chapter. Professional statistical advice and supervision was obtained from Dr Richard Smith, of the Scottish Trauma Audit Group for the statistics in Chapter Two and from Dr Robert Elton, Medical Statistician, for the statistics reported in Chapters Three and Four.

SECTION TWO

The epidemiology of ARDS

2.1 INTRODUCTION

Adult Respiratory Distress Syndrome is a rare but important complication of trauma, with a mortality of around 50%, and considerable morbidity amongst survivors[183]. The etiology and pathophysiology of the condition are poorly understood[184] and the early clinical signs are subtle and easily missed[185], which often results in delays in diagnosis. An understanding of the epidemiology of Adult Respiratory Distress Syndrome is therefore important in identifying those patients who are potentially at risk.

A number of risk factors for the development of Adult Respiratory Distress Syndrome following trauma have been proposed, including long bone fracture, pelvic fracture, head injury, direct chest injury, tissue hypoxia and massive blood transfusion[186-188]. However, the relative importance of each of these insults, either in isolation or in combination, has not previously been characterized in a prospective cohort study.

The principal aims of this prospective study were to determine the incidence and demographics of Adult Respiratory Distress Syndrome in a large cohort of patients requiring admission to hospital following trauma, and to describe the relative importance of injuries to the extremities, thorax, head and abdomen to the risk of development of this condition using modern, validated, generic and injury-specific scoring systems. From this, we aimed to construct a series of criteria which would allow identification of patients at risk for this complication, who might benefit from early vigilant monitoring

in a high-dependency setting, to facilitate earlier clinical detection and allow supportive therapy to be instituted at an earlier stage in those who develop this complication.

2.2 PATIENTS AND METHODS

Study design

Between January 1993 and December 2000 a prospective cohort study of all trauma admissions to the Royal Infirmary of Edinburgh was conducted by the Scottish Trauma Audit Group. All patients admitted to hospital following trauma aged thirteen years or over were included in the study. Patients aged over 65 years who had sustained fractures of the neck of femur or pelvic rami, those patients discharged within 72 hours, and pre-hospital deaths were excluded in order to conform with the Major Trauma Outcome Study[189]. These patients with hip or pelvic rami fractures, or those discharged within 72 hours were considered to be at low risk of developing Adult Respiratory Distress Syndrome. This was verified by a subsequent review in which no patient was found to have been re-admitted with respiratory complications after initial discharge from the Emergency Department. Patients who died within two days of admission were also excluded from analysis because these patients were also likely to have died from their injuries before developing Adult Respiratory Distress Syndrome.

Demographic details, medical history, mechanism of injury, anatomical location, severity of injury and physiological observations were recorded at the time of admission by dedicated and specially trained Research Workers who were not involved in any subsequent data analysis. In addition, validated scoring systems, including the Abbreviated Injury Score[190], the Revised Trauma Score (Table 2.1)[191], the Injury Severity Score[192] and the Glasgow Coma Scale were used to grade the severity of injury. All patients underwent daily review by the Research Workers until death or discharge, and the development of any respiratory complications noted.

Table 2.1: The Revised Trauma Score

Variable	Range	Score
Respiratory Rate	10-29	4
	Over 29	3
	6-9	2
	1-5	1
	0	0
Systolic Blood Pressure	Over 89	4
	76 – 89	3
	50 – 75	2
	1 – 49	1
	0	0
Glasgow Coma Scale	13- 15	4
	9 – 12	3
	6 – 8	2
	4 – 5	1
	3	0

The score for each of the three variables above is multiplied by a weight (derived from regression analysis); the Revised Trauma Score is the sum of the three weighted scores. Patients who do not score 4 in all three categories are defined as physiologically compromised.

Patient management

The Royal Infirmary of Edinburgh is a major University Teaching Hospital providing all trauma services to a stable population of 600,000. The majority of serious injuries result from road traffic accidents and falls, and there are relatively few penetrating or gunshot injuries. There is a helicopter service for some tertiary referrals but not for routine transportation of trauma victims. A pre-hospital care land ambulance (Medic 1) staffed by Senior Accident and Emergency Physicians is used to provide on-site resuscitation where prolonged extrication of trauma patients is anticipated, and is available over a radius of 50 miles, attending 75 trauma calls per annum. The Accident and Emergency department physicians carry out initial resuscitation and physiological stabilization. Definitive management is multidisciplinary and is conducted according to trauma protocols. Hemodynamically unstable patients with unstable pelvic fractures initially undergo pelvic external fixation in the operating theatre immediately prior to laparotomy or thoracotomy by general abdominal surgeons and cardiothoracic surgeons where this is required. Interventional radiology facilities for iliac arterial embolisation are available onsite for those pelvic fractures remaining hemodynamically unstable. Facilities for immediate CT scanning exist and, where required, neurosurgery or monitoring on a dedicated neurological intensive care unit using invasive intracranial pressure monitoring is available. Unstable patients are managed in the intensive care unit and further definitive surgery is generally avoided during the 'flow' phase of the stress response between two and five days post injury.

The policy of the Orthopaedic Trauma Unit for the management of polytraumatised patients is to stabilize all fractures, using internal or external fixation where possible, as soon as the patient's physiological condition permits. For stable patients, isolated injuries are stabilized on their merits within twenty-four hours. All long bone lower limb diaphyseal fractures in adults are treated with reamed, locked intramedullary nailing.

Patient demographics

7192 consecutive trauma admissions were studied. The median age was 49 years (interquartile range 30-68) and 3968 (55%) patients were male. Blunt trauma was responsible for injury in 6987 cases (97%).

Extremity, thoracic, abdominal and head injury group characteristics

The median age of those patients with extremity injury was 51 (interquartile range 30-69), which was higher than for patients with abdominal injury (median age 31 years, interquartile range 23.5-43), thoracic injury (median 43 years, interquartile range 28-61), and head injury (median 42 years, interquartile range 26-63). Sex distribution was equal in the extremity group (3116 of 6067 patients (51%) male), but was markedly skewed in the abdominal injury group (275 of 345 patients, 80% male), the thoracic injury group (612 of 878 patients, 70% male) and the head injury group (859 of 1190 patients, 72% male).

The most common mechanism of injury for extremity trauma was a fall from a height of less than two metres (3236 patients, 53%). The most common mechanism for the remaining three groups was a road traffic accident (429 (49%) of those patients with thoracic injuries, 164 (48%) with abdominal injuries and 488 (41%) patients with head injuries).

Outcome measures

The primary outcome measure was the development of Adult Respiratory Distress Syndrome during the index admission, as defined by the American-European Consensus Conference (Table 2.2)[193]. We retrospectively reviewed all audit records. In those patients in whom respiratory insufficiency had been suspected, the original medical

notes were examined in order to ensure the diagnosis complied with the consensus diagnostic criteria.

Table 2.2: Criteria stipulated by the American–European Consensus Document for the diagnosis of Adult Respiratory Distress Syndrome [49;193]

PaO_2/FiO_2	< 26.7 kPa
Radiology	Bilateral infiltrates on frontal chest radiograph
PAWP	<18mmHg or no clinical evidence of left atrial hypertension

Statistical methods

The relationship between the incidence of Adult Respiratory Distress Syndrome in the cohort and each potential explanatory variable was first described and examined using Mann-Whitney U tests (continuous variables), Fisher Exact tests (2-category variables) and chi-square tests (variables with 3 or more categories). Full data was available for all patients, except for social deprivation category (data available from 1996, N=3317) and pre-existing medical conditions (data for cardiovascular, respiratory, central nervous system and renal conditions and diabetes available from 1996, N=3963; for known malignancies, alcoholism, psychiatric problems and substance abuse from 1998, N=2147). We then conducted a multiple logistic regression analysis to identify those variables that were independently predictive for the subsequent development of Adult Respiratory Distress Syndrome. All data analysis was conducted using SPSS software (Version 10, SPSS Inc, Chicago, Illinois).

2.3 RESULTS

Demographic and Admission Data

Incidence and demographics of Adult Respiratory Distress Syndrome

Thirty-six (0.5%) of 7192 trauma patients developed Adult Respiratory Distress Syndrome, giving an annual incidence of 0.8 per 100 000 population per year due to trauma. The incidence was highest amongst younger patients (aged under 40 years, Table 2.3), and the median age of those patients developing Adult Respiratory Distress Syndrome was twenty-nine years, which was significantly younger than those who did not (median age fifty years, $p=0.001$). There was no significant difference in sex distribution (20 males and 16 females) or between different social classes (based on postcode of residence). The presence of co-morbidities (including respiratory disease, cardiovascular disease, diabetes mellitus, renal disease, known malignancy, alcohol abuse, drug abuse and psychiatric illness) was not shown to be significantly associated with the incidence of Adult Respiratory Distress Syndrome, amongst those at risk for the condition (Table 2.3).

Mechanism of Injury

30 (83%) patients developing Adult Respiratory Distress Syndrome did so following high-energy transfer injuries (Table 2.3) and all cases occurred following blunt trauma. In one case the mechanism of injury was unknown, the patient being found unconscious in the street with a head injury. The risk of developing Adult Respiratory Distress Syndrome was significantly higher after high-energy injury (a road traffic accident or a fall from a height of over two meters) than a low energy injury (remaining mechanisms of injury, $p<0.001$) with a relative risk of 5.1 (95% confidence intervals 4.8-27.8). The

median age of patients involved in high-energy injuries was 35 years, significantly younger than that for low-energy injuries (median age of 56 years, $p<0.001$).

Table 2.3: Incidence of Adult Respiratory Distress Syndrome by Mechanism of Injury and Patient Demographics

		Incidence of ARDS*	% Incidence	P
Type of Injury	Blunt	36/6987	0.5%	0.63
	Penetrating	0/205	0.0%	
Mechanism of Injury	Road Traffic Accident	25/1560	1.6%	<0.001
	Assault	0/459	0.0%	
	Fall (> 2m)	5/675	0.7%	
	Fall (< 2m)	4/3640	0.1%	
	Sport	1/550	0.2%	
	Other	1/308	0.3%	
Age	13-39	24/2736	0.9%	0.002
	40-59	4/1806	0.2%	
	60+	8/2650	0.3%	
Sex	Male	20/3968	0.5%	1.00
	Female	16/3224	0.5%	
Social status	Affluent	4/733	0.5%	0.35
	Average	13/1551	0.8%	
	Deprived	4/1033	0.4%	
Pre-existing Medical Conditions	Cardio-Vascular	0/704	0.0%	0.02
	Respiratory	5/459	1.1%	0.18
	Central Nervous System	0/183	0.0%	0.62
	Diabetes	0/115	0.0%	1.00
	Renal	0/4	0.0%	1.00
	Known Malignancy	0/26	0.0%	1.00
	Alcoholism	1/171	0.6%	0.60
	Psychiatric	2/136	1.5%	0.15
	Substance Abuse	1/47	2.1%	0.22

Significance tested using Fisher Exact tests for 2 category variables, chi-square tests for variables with three or more categories. Data incomplete for deprivation group and pre-existing medical conditions as not collected in earlier years of study (see Methods).
** Amongst those patients who were at risk of the condition, see statistical methods.*

Admission observations and initial management

The incidence of Adult Respiratory Distress Syndrome was significantly higher amongst patients with a Glasgow Coma Scale below 8 (Table 2.4, $p<0.001$, relative risk 5.8 versus remainder, 95% confidence intervals 4.0-8.3), patients with a systolic blood pressure below 90 mmHg ($p=0.002$, relative risk 5.4, 95% confidence intervals 2.7-10.6), and patients with either a respiratory rate below ten or above thirty breaths per minute ($p<0.001$, relative risk 6.0 versus remainder, 95% confidence intervals 2.4-15.3). Patients whose initial surgical intervention was a laparotomy had a significantly higher incidence of Adult Respiratory Distress Syndrome compared with those requiring an initial orthopedic procedure or not requiring any surgical intervention. This represented a relative risk of 5.3 (95% confidence intervals 1.8-15.4) and 3.9 (95% confidence intervals 1.3-12.0) respectively. None of the twenty-eight patients requiring an initial thoracotomy, and only one of 159 patients requiring initial neurosurgical intervention (0.6%) developed this complication.

Injury Severity and Anatomical Location

Injury Scores

The incidence of Adult Respiratory Distress Syndrome increased significantly with increasing Injury Severity Score ($p<0.001$, Table 2.4). No patient with a score of nine or lower developed the condition, whilst the incidence was 3.7% amongst those with a score of over twenty-five. Compromised admission physiological observations (Table 2.1) were also associated with a significantly increased incidence of Adult Respiratory Distress Syndrome ($p<0.001$, Table 2.4)

Specific Injuries by anatomical location

For patients with head, chest or extremity injuries the incidence of ARDS increased significantly with the maximum severity of injury in those body regions ($p= 0.02$ to $p= 0.001$, Table 2.5).

Table 2.4. Incidence of Adult Respiratory Distress Syndrome by Admission Observations, Initial Management and Overall Injury Severity Score.

		Incidence of ARDS	% Incidence	P
GCS	3-8	13/259	5.0%	<0.001
	9-12	3/162	1.9%	
	13-15	20/6771	0.3%	
Systolic BP (mm Hg)	0	2/19	10.5%	<0.001
	50-75	0/25	0.0%	
	76-89	3/56	5.4%	
	90+	31/7092	0.4%	
Respiratory rate (breaths/minute)	0	1/9	11.1%	<0.001
	1-9	1/11	9.1%	
	10-29	29/6986	0.4%	
	30+	5/186	2.7%	
RTS	Normal	15/6556	0.2%	<0.001
	Compromised	21/636	3.3%	
Type of Operation	Orthopedic	20/4765	0.4%	0.002
	Laparotomy	4/151	2.6%	
	Other	2/296	0.7%	
	None	10/1980	0.5%	
Injury Severity Score	ISS 1-8	0/1993	0.0%	<0.001
	ISS 9-15	10/4385	0.2%	
	ISS 16-24	12/436	2.8%	
	ISS 25-75	14/378	3.7%	

Significance tested using Fisher Exact tests for 2 category variables, chi-square tests for variables with three or more categories. Compromised RTS defined as in Table 2.1.

Table 2.5. Incidence of Adult Respiratory Distress Syndrome for each Anatomical Region by Abbreviated Injury Score

Maximum Abbreviated Injury Score (AIS)	Head		Thorax		Abdomen		Extremity	
	Incidence	*%*	*Incidence*	*%*	*Incidence*	*%*	*Incidence*	*%*
0 (No injury)	19/6002	0.3%	17/6314	0.3%	22/6847	0.3%	6/1125	0.5%
1 (Minor)	3/418	0.7%	0/182	0.0%	4/128	3.1%	0/407	0.0%
2 (Moderate)	0/65	0.0%	2/143	1.4%	5/92	5.4%	6/1673	0.4%
3 (Serious)	4/288	1.4%	8/369	2.2%	2/81	2.5%	22/3968	0.6%
4 (Severe)	2/221	0.9%	6/162	3.7%	1/23	4.3%	2/16	12.5%
5 (Critical)	8/198	4.0%	3/22	13.6%	2/21	9.5%	0/3	0.0%
p value*	**0.01**		**0.001**		**0.54**		**0.02**	

**** Mann Whitney U-test (excluding patients with no injury in the tested body region)***

Table 2.6. Incidence of Adult Respiratory Distress Syndrome for Specific Injury types

		Incidence of ARDS*	% Incidence	p value
Head Injuries	Skull fracture	7/563	1.2%	0.02
	Intracerebral hemorrhage	7/426	1.6%	0.005
Thoracic Injuries	Pneumothorax or hemothorax	11/336	3.3%	<0.001
	> 3 rib fractures	7/160	4.4%	<0.001
Extremity Injuries	Tibial fracture	8/1039	0.8%	0.23
	Femoral fracture	12/525	2.3%	<0.001
	Pelvic fracture	13/382	3.4%	<0.001

Significance tested using Fisher Exact test for specific injuries

** amongst those patients with the injury specified.*

The incidence associated with specific injuries in each region is shown in Table 2.6. The incidence was greater than 2% (i.e. more than four times more frequent than in the study population as a whole) amongst patients with pneumothorax or haemothorax, more than three fractured ribs, femoral fractures and unstable pelvic ring fractures.

Injury Combinations

The incidence of Adult Respiratory Distress Syndrome after an isolated injury to any body region was less than 1% (Table 2.7). Most combinations of two injuries together resulted in a similarly low incidence. However, the combination of abdomen and extremity injuries together resulted in an incidence of 2.9%. Injuries to three anatomical sites in combination resulted in an increased incidence of between 2.5% and 10.2%, with

the highest incidence observed when injuries to the extremities, thorax and abdomen were sustained in combination. Injuries to all four regions together resulted in an incidence of 6.4%, not significantly higher than that for three injuries in combination (p value not significant).

Fractures of the tibial or femoral diaphysis, and unstable fractures of the pelvic ring, had a higher incidence of Adult Respiratory Distress Syndrome when these injuries were accompanied by concomitant head, thoracic or abdominal injuries (Table 2.8).

Multivariate analysis of ARDS occurrence

On univarate testing, some variables or variable combinations were associated with a high incidence of Adult Respiratory Distress Syndrome (for example, a GCS of 3 to 8 (5%), chest injuries with Abbreviated Injury Score of 4 or more (4.9%), and tibial, femoral or pelvic fractures combined with abdominal injuries (10-15%), but only identified between 3 and 13 of the 36 affected patients. Other variables identified more affected patients but referred to higher numbers of patients at risk (e.g. 25 Adult Respiratory Distress Syndrome patients amongst 1560 individuals involved in Road Traffic Accidents (1.6%), 21 affected patients amongst 636 patients with compromised presentation physiology (3.3%), and 26 affected patients amongst 814 patients with Injury Severity Score 16-75 (3.2%). Given that so many variables were associated with the occurrence of this condition, but that many of the variables were themselves related (for example the mechanism of injury was associated with Injury Severity Score, and the Abbreviated Injury Score was associated with total Injury Severity Score) we tested their combined affects using logistic regression analysis (Table 2.9).

Injury Severity Score was the first variable to enter the forward stepwise logistic regression model, explaining 18.5% of the variation in the incidence of Adult Respiratory Distress Syndrome. Femoral fractures explained a further 3.8% of variation

in incidence, and addition of the occurrence of a combined extremity and abdominal injury in the same patient and the Revised Trauma Score explained a total of 27.3% of the variance.

Table 2.7. Incidence of ARDS for isolated and combined injuries

	Abdomen	Extremity	Thorax	Head	N	% ARDS	Relative Risk (95% CI) compared with extremity injury alone	
Isolated injury:								
	▲				0/79	0.0%	-	-
		▲			6/4981	0.1%	-	-
			▲		1/228	0.4%	3.6	(0.4 – 30)
				▲	4/431	0.9%	7.6	(2.2 – 27)
Two injured body regions:								
			▲	▲	0/48	0.0%	-	-
	▲			▲	0/9	0.0%	-	-
	▲		▲		0/39	0.0%	-	-
		▲		▲	3/453	0.7%	5.4	(1.4 – 22)
		▲	▲		4/278	1.4%	11.8	(3.3 – 41)
	▲	▲			2/68	2.9%	23.8	(4.9 – 115)
Three injured body regions:								
		▲	▲	▲	4/158	2.5%	20.5	(5.8 – 72)
	▲		▲	▲	1/21	4.8%	37.8	(4.7 – 301)
	▲	▲		▲	2/23	8.7%	66.5	(14.1 – 313)
	▲	▲	▲		6/59	10.2%	76.7	(25.4 – 231)
Four injured body regions:								
	▲	▲	▲	▲	3/47	6.4%	49.9	(12.8 – 193)

Table 2.8. Incidence of Adult Respiratory Distress Syndrome after Fractures of the Tibia, Femur and Pelvis with and without Concomitant Head, Thoracic and Abdominal Injury.

	Without head injury		With head injury		p value
	N	% ARDS	N	% ARDS	
Tibial fracture	5/941	0.5%	3/98	3.1%	0.03
Femoral fracture	8/465	1.7%	4/60	6.7%	0.04
Pelvic fracture	9/276	3.3%	4/106	3.8%	0.76
	Without thoracic injury		**With thoracic injury**		**p value**
	N	**% ARDS**	**N**	**% ARDS**	
Tibial fracture	4/987	0.4%	4/52	7.7%	<0.001
Femoral fracture	8/473	1.7%	4/52	7.7%	0.02
Pelvic fracture	3/276	1.1%	10/106	9.4%	<0.001
	Without abdominal injury		**With abdominal injury**		**p value**
	N	**% ARDS**	**N**	**% ARDS**	
Tibial fracture	5/1010	0.5%	3/29	10.3%	0.001
Femoral fracture	8/498	1.6%	4/27	14.8%	0.002
Pelvic fracture	6/319	1.9%	7/63	11.1%	0.002

Table 2.9: Multivariate analysis of factors affecting incidence of ARDS

Explanatory variables	Category	Odds Ratio (Exp *B*)	95% CI for Exp *B*	P
ISS Group	**ISS 9-15**			<0.001
	ISS 1-8	**0.00**	0.00-10[11]	
	ISS 16-24	**8.13**	3.27-20.3	
	ISS 25-75	**4.83**	1.63-14.3	
Femoral fracture	**No**			<0.001
	Yes	**3.91**	1.83-8.34	
Combined Extremity & Abdomen Injuries	**No**			<0.001
	Yes	**5.01**	2.20-11.4	
RTS		**0.72**	0.59-0.89	0.01
	Constant, b=-4.66	**0.009**		

Variables are listed in the order in which they entered the calculation (a forward stepwise selection process, taking the variable with the greatest significance on univarate testing first). For all variables except RTS, Exp B is the factor by which the odds of developing ARDS change when the category is compared with the base category (the category entering the calculation first, ISS), and values of Exp B above one indicate a higher risk of developing ARDS compared to the base category.

RTS is a continuous variable in which, unusually, a lower scor represents a more severely injured patient. For RTS, Exp B is the change in odds of contracting ARDS associated with a one unit increase in RTS, and the values below one indicate the odds decrease as the RTS increases.

*Model-building was terminated when a P-to-enter value of 0.01 was reached. Other variables tested during the model building process (but not included in the final model) were age, sex, GCS, respiratory rate and Systolic BP on presentation, type of injury (blunt/penetrating), presence and AIS of head, chest, extremity, abdominal or other injuries (5 variables each) and all 2-way interactions between these injury combinations (e.g. extremity*head, extremity*chest, chest*abdomen, etc), and tibial, femoral and pelvic fractures and extremity fractures in combination with head, chest or abdominal injuries. ISS= Injury Severity Score, RTS = Revised Trauma Score, AIS = Abbreviated Injury Score*

Active monitoring of the 814 patients with Injury Severity Score 16-75 (i.e. those likely to have been admitted to the intensive care or high dependency units)h would have identified 26 out of 36 patients with Adult Respiratory Distress Syndrome. Monitoring the 525 patients with a femoral fracture would have identified 12 affected patients, monitoring the 197 with combined extremity and abdominal injuries would have identified 13 patients, and monitoring the 636 with compromised physiology on presentation would have identified 21 patients. Many patients fell into more than one of these categories, and criteria for monitoring were therefore developed which would have allowed identification of the maximum number of those patients who later developed Adult Respiratory Distress Syndrome.

If all patients with an Injury Severity Score of 16-75 had been monitored, only ten patients would have remained undetected. These remaining ten patients who were not ISS 16-75 all fell in the ISS 9-15 group (range ISS 9-14). Amongst the 4385 patients in this ISS group, 455 had a femoral fracture of whom six developed Adult Respiratory Distress Syndrome. Of the four ISS 9-15 patients with Adult Respiratory Distress Syndrome who did not have a femoral fracture, two more would have been identified by monitoring a further 55 patients with combined extremity and abdominal injuries, and a further one by monitoring another 192 patients who had compromised admission physiological observations.

Altogether 35 of the 36 (97%) Adult Respiratory Distress Syndrome cases would have been identified by active monitoring of all patients with an Injury Severity Score over 16, a femoral fracture, a combined extremity and abdominal injury, and/or compromised admission physiological observations. Given that no cases of Adult Respiratory Distress Syndrome were recorded in the 1993 patients with minor injuries (ISS 1-8), this high rate of identification of future ARDS patients could have been achieved by monitoring 1516 (21%) of the study population of 7192 patients. If resources for monitoring were an issue, only one of these 35 patients would be missed by removing the compromised Revised Trauma Score criteria. In this case 34 out of 36 (94%) patients with Adult

Respiratory Distress Syndrome would have been detected by monitoring 1324 (18%) of the 7192 patients in the study population. The one ARDS patient who was not identified by any of these criteria was a twenty-five year old sports-injured patient with isolated comminuted fractures of the shafts of the right tibia and fibula.

2.4 DISCUSSION

Previous estimates of incidence

Previous studies have attempted to examine the incidence of Adult Respiratory Distress Syndrome. The first estimate of the 'all causes' incidence was produced by the National Institutes of Health in 1972 at 75 per 100,000 general population per year [194]. Although widely quoted, this figure is an order of magnitude greater than most recent intensive care based epidemiological studies which have reported figures of between 1.5 to 13.5 per 100,000 per year[186;187;194-196]. Although the incidence of Adult Respiratory Distress Syndrome amongst trauma admissions has not previously been reported, the population incidence due to trauma alone can be estimated from those presented in four previous studies[186-188;195] (Table 2.10). These show an incidence of between 0.4 and 2.0 per 100,000 population per year, which is similar to the figure calculated in this study of 0.8 per 100,000 per year.

Direct comparison of these results with previous studies is not possible, however, due to the varying definitions for Adult Respiratory Distress Syndrome which have been used, and the differing case-mix. Some published data from Germany, for example, are derived from trauma registries with large numbers of severely injured patients, allowing powerful statistical analysis of a relatively discrete group of polytraumatised patients [197]. The nomenclature for pulmonary injury has been inconsistent in previous studies, with variable use of terms such as shock-lung, fat embolus syndrome and neurogenic pulmonary oedema. Over half of published reports have failed to provide a definition for the condition [183]. The diagnostic criteria proposed by the American-European Consensus Conference in 1994[193] have more recently allowed comparisons to be made between studies, despite some criticism of the measurements used[198]. However, previous studies have either been entirely intensive care-based, with the features of a different patient population with a wide variety of precipitating aetiologies, or have investigated a highly-

selected subgroup of polytraumatised patients[199-201]. No previous study has identified the incidence of Adult Respiratory Distress Syndrome using modern criteria amongst general trauma admissions, nor have any studied the importance of detailed injury pattern and combination in contributing to this risk.

Univariate analysis

It has been shown that Adult Respiratory Distress Syndrome is rare after blunt trauma: the overall incidence was 0.5% in this cohort. However, high-energy injury, young age, compromised admission physiologic observations, specific injuries such as skull fracture or pleural injury, and long bone and pelvic fractures were all associated with an increased incidence. An increased incidence was also seen amongst those patients scoring highly on each of the generic and injury-specific scoring systems studied (Glasgow Coma Score, Injury Severity Score, Revised Trauma Score and Abbreviated Injury Score).

Patients with injuries to only one anatomical region had a low incidence of Adult Respiratory Distress Syndrome (of less than 1%). Although the absolute numbers of patients developing this complication were small, the incidence increased in patients who had injuries to more than one anatomical region in combination. Patients with two injuries had incidences up to 2.9%, whilst those with three injuries in combination had incidences up to 10.2%. A significantly greater incidence was also seen in patients with lower extremity injuries when those injuries were accompanied by concomitant injuries to the head, thorax or abdomen.

Multivariate analysis of risk factors

Multivariate regression analysis was performed in order to stratify these individually significant factors, many of which were themselves linked. The best combination of

variables predicting risk were the Injury Severity Score, the presence of a femoral fracture, the combination of an extremity and an abdominal injury, and compromised physiological observations at presentation.

The Injury Severity Score, providing a crude estimate of 'dose of injury', was the most important of these factors (explaining 18.5% variation in incidence). No patient with an Injury Severity Score of less than nine in this series developed Adult Respiratory Distress Syndrome, suggesting that there may be a threshold level for the 'dose' of trauma required for its development.

The presence of a femoral fracture was the second independent variable entering the model (Table 2.9). The importance of this injury as a cause of respiratory insufficiency has long been recognized [184], and the advantages of early skeletal stabilization of such fractures has been well established in a number of studies and meta-analyses [21;102;128;129;131;133]. As the policy of the Orthopaedic Trauma Unit is to stabilize all long bone fractures definitively as early as the patients' condition allows, we have not been able to study the effect of the timing of surgery.

Combined injuries to the extremities and abdomen was the next variable entered. Abdominal injury represents a heterogeneous group, potentially combining a number of pathologies which may contribute to the development of respiratory complications. Visceral injury results in hemorrhage, hypovolaemic shock and tissue hypoperfusion, leading to the release of cytokines and activation of the coagulation and inflammatory cascades. Abdominal pain and swelling result in diaphragmatic splinting, hypoventilation and atelectasis [2] which may exacerbate hypoxaemia. Patients with combined abdominal and extremity injury may require a prolonged period of recumbency which may also increase the risk of pulmonary complications.

Combined injuries to the femur and thorax, and Damage Control Orthopedics

The patient with combined thoracic trauma and a long bone injury has been particularly implicated as being at increased risk, and suitable for a 'damage control' approach (see introduction, section 1.5.1). However, because only a small number of patients are affected by this combination of injuries, and only a small proportion of these go on to develop Adult Respiratory Distress Syndrome, it would be difficult to prove the efficacy of a change in the timing and type of orthopedic intervention in this group of patients in a randomized trial. Indeed, based on the findings in this cohort, a power study suggests that in order to have an 80% chance of detecting a 50% reduction in the incidence of Adult Respiratory Distress Syndrome from a modified surgical strategy, a study recruiting 1,154 patients with combined femoral and thoracic injuries would be required. A study of 8,600 such patients would be required to show a 20% reduction in incidence.

Although in the present study the additional presence of a thoracic injury increased the incidence of Adult Respiratory Distress Syndrome after femoral fracture from 1.7% to 7.7%, this combination was not independently predictive of ARDS and did not enter the final regression model. This is in agreement with a recent review of the available literature, which concluded that in patients with both thoracic and long bone injuries, it is the presence of a thoracic injury which determines the likelihood of Adult Respiratory Distress Syndrome and that the additional presence of a long bone injury (however treated) does not influence this likelihood [184]. The results of this study suggest that it is likely that the total 'dose' of injury as measured by the Injury Severity Score is the more important factor in the development of Adult Respiratory Distress Syndrome than this particular combination of injuries *per se*.

Limitations of this study

Not all cases of Adult Respiratory Distress Syndrome in this study were explained by the presence of severe trauma or other such risk factors, and a proportion remain apparently sporadic or idiosyncratic. The otherwise unaccountable development of Adult Respiratory Distress Syndrome in the individual in this series with an isolated tibial fracture after sport illustrates this. Phenotypic variations in the expression of components of both the inflammatory and coagulation systems have been established in association with other hyperstimulatory conditions, and may be important in individuals who develop the condition unexpectedly[202-205]. Such genetic predisposition clearly cannot be predicted by this type of epidemiological study.

There are numerous other insults which have a possible association with the stress response and respiratory dysfunction and may have had an additional influence on the development of Adult Respiratory Distress Syndrome. These include transient hypotension or hypoxemia, capillary bed hypoperfusion, hypothermia, gastric aspiration, sepsis and massive blood transfusion[2]. It was not possible to identify with confidence the numbers of patients affected by these putative insults and it was not possible to analyze their contribution.

Some patients with more subtle respiratory compromise may not have been included in this analysis. Sub-clinical forms of hypoxemia are known to occur after trauma in up to one third of patients which resolve completely with supportive treatment [185]. These were not detected by the methods employed in this study.

Although the incidence of Adult Respiratory Distress Syndrome arising from trauma has been clarified, the selection of the inclusion criteria for the study population was inevitably subjective. The entire population of patients presenting to the Accident and Emergency Department following trauma as out-patients was not studied nor those who

were discharged within forty-eight hours, who were believed to be at low risk of respiratory complications. This assumption was confirmed, as no patient was readmitted with respiratory compromise after early discharge during the period of the study. The data is based on a population suffering mainly blunt trauma, presenting to a single European centre, and caution may be required when extrapolating these figures to other populations such as those from North American urban populations where the proportion of penetrating injuries is higher[206,207].

The demographic distribution of patients with extremity injury was different from those with head, abdominal and thoracic injuries. Extremity injury affected a higher proportion of older females with more lower-energy injuries. The contemporary pattern of trauma is changing and these results reflect the increasingly common problem of low energy osteopaenic fractures in the elderly[208]. These patients are at lower risk of Adult Respiratory Distress Syndrome and this therefore may have skewed the results of the extremity group, when compared to the other anatomical regions.

Table 2.10. Summary of Studies Addressing the Epidemiology of Adult Respiratory Distress Syndrome.

Author	Population studied	Time period studied	Consensus criteria used?	Overall population incidence per 100,000	Number trauma patients with ARDS	Trauma incidence per 100,000
Villar[209]	1,997 ITU admissions from 700,000 population Canary Islands	3 years (1983 – 85)	No	3.5	6	0.6[(a)]
Webster[210]	5,636 ITU admissions from 3.6 million population from Yorkshire, UK	1 year (1985)	No	4.5	Unknown	Unknown
Thomsen[211]	Unknown number of ITU admissions from 1.72 million population in Utah	1 year (1989/90)	No	4.8 – 8.3	Unknown	Unknown
Hoyt et al[212]	3,289 Level 1 trauma admissions, San Diego, USA	3 years (1989-91)	No	Unknown	40	Unknown
Lewandowski[105]	Unknown number of ITU admissions from 3.44 million population in Berlin	2 months (1991)	No	3.0[(a)]	3[(b)]	0.4[(a)]
Luhr[106]	13,346 ITU admissions from 11.7 million population of Sweden, Demark and Iceland	8 weeks (1997)	Yes	13.5	18	1.1[(a)]
Bersten[107]	1,977 ITU admissions from 2.9 million population in Australia	2 months (1999)	Yes	28	19	2.0[(c)]
This study	7,192 trauma admissions from 600 000 population	8 years (1993 – 2000)	Yes	Not studied	36	0.5

(a) calculated, and (b) estimated from data presented, (c) if patients with pulmonary contusion included but those due to barotrauma excluded

SECTION 3

Post-traumatic activation of the coagulation and inflammation systems

3.1 INTRODUCTION

Patients at risk of developing respiratory insufficiency are at present most satisfactorily identified by their injury profile [213]. However, while this approach has reasonable sensitivity, it has poor positive predictive value and cannot identify those cases of respiratory insufficiency which are sporadic, occurring after apparently innocuous trauma [83]. Analysis of the interleukin-8 concentrations within bronchioalveolar lavage fluid taken at the time of presentation has been shown to be indicative of the risk of the later development of ARDS but is invasive and requires additional expertise in the Emergency department [95]. Urinary albumin excretion rate eight hours after admission following trauma has been shown to offer a high positive and negative predictive value for the later development of ARDS and respiratory insufficiency, but is not so discriminatory at the time of admission [70;214]. It has been proposed that laboratory measurements of humoral inflammatory and coagulation markers at the time of admission may allow more convenient and precise identification of patients at increased risk [62;215].

3.2 PATIENTS AND METHODS

The study was approved by the local Regional Ethics Committee. Thirty-nine patients were enrolled at the time of admission to the Accident and Emergency department into a prospective cohort study. Inclusion criteria were age between sixteen and eighty years old and a closed fracture of the tibial or femoral diaphysis, with or without a concomitant thoracic injury. Patients were excluded if they had a known pre-existing coagulation abnormality or were receiving drugs known to affect coagulation, or refused consent. Patients unable to give consent as a consequence of unconsciousness were recruited in line with ethical committee guidance, and retrospective consent obtained once the patient's condition permitted. Physiological observations and a description of injuries according to the Abbreviated Injury Scale (AIS)[24], the Injury Severity Score (ISS)[189] and Thoracic Trauma Severity Score (TTSS)[109] were made at the time of admission.

Fourteen patients had suffered isolated fractures of the tibia (Group 1), seventeen patients had suffered isolated fractures of the femur (Group 2), and eight patients had suffered tibial or femoral fractures in association with thoracic injury (Group 3). The demographic distribution within these groups was not significantly different (ANOVA (ages) $p=0.2$, χ^2 (sex) $p=1$, χ^2 (mechanism of injury) $p=0.7$, Table 3.2).

Table 3.1. The Thoracic Injury Severity Score [109]

	P:F (mmHg)	Rib fractures	Contusion	Pleura	Age	Points
O	>400	Nil	Nil	None	<30	0
I	300-400	1-3	1 lobe	PT	30-41	1
II	200-300	3-6	2 lobes 1 lobe bilat	HT/ HPT	42-54	2
III	150-200	Bilateral	< 2 lobes bilat	HT / HPT bilat	55-70	3
IV	<150	flail	> 2 lobes bilat	TPT	>70	5

The points for each component are added to give the total score. P:F- ratio between the arterial partial pressure of oxygen and the inspiratory fraction of oxygen. PT – pneumothorax. HT – haemothorax. HPT – haemopneumothorax, TPT – tension pneumothorax.

Table 3.2: Demographics

Group		1	2	3
Description		Tibia only	Femur Only	Tibia/Femur plus thorax
Number of patients		14	17	8
Age, median (range)		33 (22 to 48)	26 (16 to 61)	28 (19 to 43)
Male : Female		9:5	13:4	6:2
MOI	Fall	6	4	
	Crush	1	2	
	RTA: in vehicle	2	9	7
	RTA: Pedestrian	5	2	1

All tibial and femoral fractures were stabilised within twenty-four hours of injury by reamed intramedullary nailing. A radial arterial cannula was inserted preoperatively after the induction of general anaesthesia (and clinical testing for collateral circulation), and was removed before reversal of anaesthesia in those patients not requiring this monitoring for therapeutic reasons. Arterial blood samples were taken from this cannula where available, or otherwise from direct aspiration from the radial artery, for blood gas analysis. In addition 15 ml blood was obtained either from the arterial line or from a peripheral venous cannula for the measurement of the humoral mediators described below. Each sample was taken at the following time points: on admission, immediately prior to intramedullary nailing, immediately after surgery, twenty-four hours after surgery (three days after injury), five days after injury and at seven days after injury. Samples were collected in citrated tubes and placed immediately on ice, and then centrifuged at 2,500 rpm at 4 ° C. The supernatant plasma was collected and frozen at -40°C for later analysis in batches. The cell pellet was stored for DNA analysis.

Enzyme-linked immuno assay (ELISA) techniques were used to measure the plasma concentrations of components of the coagulation, fibrinolysis and inflammatory pathways (Figure 3.1). Tissue plasminogen activator (tPA, which converts plasminogen to plasmin), β thromboglobulin (βTG, liberated by activated platelets), prothrombin fragments (PF_{1+2}, by-products of prothrombin cleavage to thrombin) soluble tissue factor (sTF, which is exposed on injured endothelium and directly activates the extrinsic pathway by activating factors VII), plasminogen activation inhibitor (PAI, an inhibitor of fibrinolysis), D-dimers (DD, a fibrin degradation product reflecting lysis of stable cross-linked fibrin), soluble Intercellular Adhesion Molecule-1 (sICAM, which mediates the binding of leukocytes to endothelial cells and is used as a marker of leukocyte activation) and interleukin-6 (Il-6) were measured at each time period. Inherited procoagulant predispositions were sought by testing for genetic polymorphisms for Factor V Leiden and prothrombin 20210 G to A. Patients who are either homozygous or heterozygous for either gene are at increased risk of venous thrombosis.

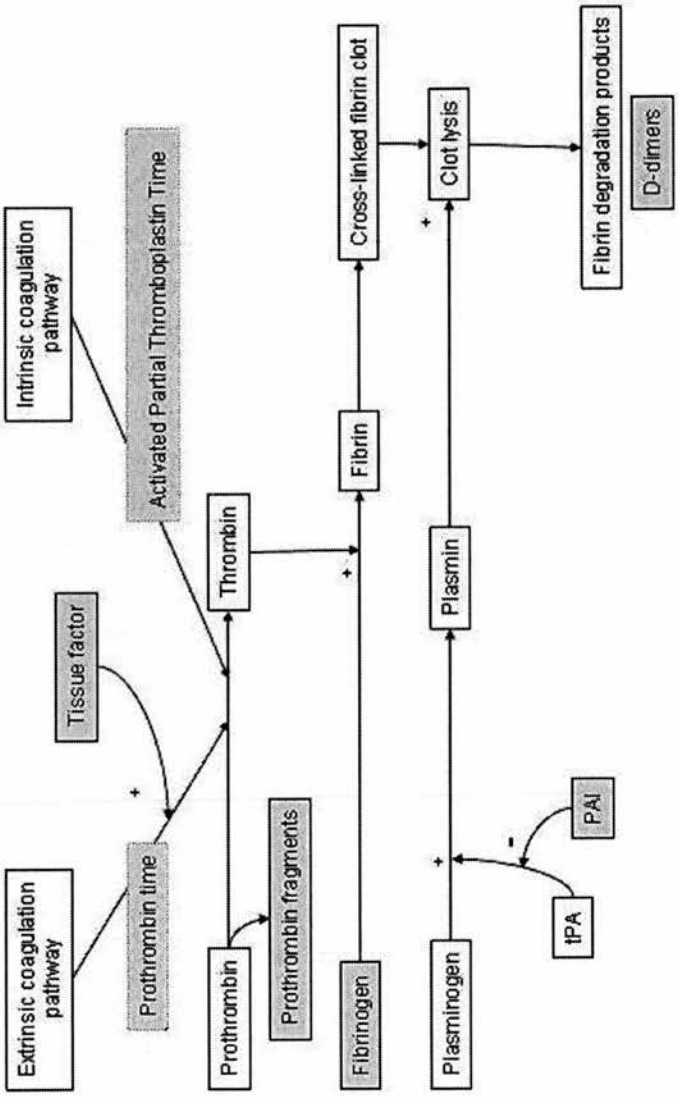


Figure 3.1. The Coagulation and Fibrinolysis Pathways

Illustrating components used in this study

Outcome measures

All patients were reviewed daily for clinical evidence of the development of respiratory insufficiency or fat embolism. The primary outcome measure was the development of Acute Lung Injury or Adult Respiratory Distress Syndrome as defined by the American-European Consensus Conference criteria [49], or Fat Embolus Syndrome as defined by Gurd and Wilson [37]. Surrogate outcome measures were lesser degrees of impairment of gas exchange, and humoral measurements of inflammatory and coagulation mediators. The severity of gas exchange impairment was assessed according to the ratio between the arterial partial pressure of oxygen (in kPa) and the inspired fraction of oxygen (P:F ratio). A ratio of less than 26.7 is one of the criteria used to support a diagnosis of ARDS and a ratio below 40 supports a diagnosis of ALI. In the absence of the other features required to make either diagnosis, these levels were taken as surrogate indicators of severe and moderate respiratory impairment respectively.

Statistical analysis

The Mann-Whitney test was used to compare groups at each time period and the Wilcoxon signed ranks test used to assess the significance of changes within groups. The Spearman test was used to assess the significance of correlations between variables.

3.3 RESULTS

Respiratory insufficiency

On admission, five patients had moderate respiratory insufficiency with a P:F ratio below 40. By the time of surgery, seven had developed a P:F ratio below 40, of whom two (in Group 3) had severe respiratory insufficiency with a ratio below 26.7. Over the twenty-four hour period postoperatively, ten patients out of thirty eight (26%) had a P:F ratio below 40 of whom eight were below 26.7. Half of the combined injury group (Group 3) had a P:F ratio below 26.7 in the first twenty-four hours postoperatively. One patient with an isolated femoral fracture developed FES and ARDS. The results for this patient are presented separately from the remainder of Group 2. All patients recovered with supportive therapy.

Although there was no significant difference between groups in P:F ratios at the time of admission, P:F ratios were significantly lower in Group 3 compared with the other two groups preoperatively and at each time point thereafter until day 3 ($p<0.05$, Fig 3.1). Although there was no statistically significant change in the P:F ratio between the preoperative and postoperative measurements in any of the groups studied, there was a significant decrease over this period when all 39 patients were analysed together ($p=0.06$).

Correlations with postoperative respiratory insufficiency

The level of each measured humoral marker at admission, and each injury scoring system, was tested for correlation with the development of respiratory insufficiency (as measured by P:F ratio) on day 3. The strongest correlations were found for admission P:F value ($p<0.0001$), injury group ($p<0.0001$), injury severity score ($p=0.015$) and prothrombin fragments 1 and 2 level ($p=0.04$). Neither the TTSS, the level of Il-6, nor any other marker measured had a significant correlation.

The inflammatory markers: Interleukin-6 and s-ICAM

All patients had elevated levels of Il-6 at presentation (Fig. 3.2), and only three had levels that had returned to normal seven days later. Il-6 levels at each time point correlated closely with the ISS ($p<0.01$) and were significantly higher in the combined injury group (Group 3) than either of the isolated injury groups at presentation ($p<0.005$). This difference remained significant until day four postoperatively (Fig 3.3). Although there was no significant rise from preoperative to postoperative levels, there was a continued rise over the subsequent twenty-four hours which reached statistical significance when all 39 patients were studied together (preoperative level vs. day 3 level, $p=0.045$). Levels subsequently fell for the remainder of the week in all patients.

Median s-ICAM levels were normal on admission in all groups (Fig. 3.4). There was a gradual increase in levels over the week following injury in all patients, with median levels above normal on day 7 for Groups 2 and 3. There was no significant difference in the degree of elevation between groups, and surgery did not result in a significant further increase.

The coagulation markers

The prothrombin time (PT) was significantly longer in Group 3 at admission compared with Group 1 ($p=0.006$), although both groups remained within the normal range. Although PT was slightly above normal in Group 3 at the preoperative and postoperative time points, there were no significant trends over time or differences between groups (Fig 3.5).

Median activated partial thromboplastin times were within the normal range for all groups at each time point (Fig 3.6). There were no significant differences either between time points within a group or between groups, throughout the study period.

Fibrinogen levels gradually rose throughout the study period in all groups, although this rise was not significant in any group (3.7). Although at admission, the levels were significantly higher in Group 1 than in Group 2, there were no other significant differences either between time points within a group or between groups, throughout the study period.

Median platelet counts were below normal for Group 3 throughout the study period until day 7. The median levels for the other two groups were normal throughout the study period. The counts were lower in Group 3 than Group 1 at admission and lower in Group 3 than in Group 2 on day 3, but otherwise there was no significant difference between these median levels at any time point (Fig 3.8).

D-dimers, PF_{1+2} and βTG levels were each significantly raised at admission in all groups (Figs 3.9, 3.10 and 3.12), with higher levels tending to be found in those with more severe injuries (significance relationships shown in figures). In each case, the degree of activation was seen to diminish over the course of the week after injury. PAI levels at admission were elevated only in Group 3, with significantly higher levels observed compared with the other two groups at admission and preoperatively (Fig 3.11). These returned to normal by day 5. Median PAI levels in Groups 1 and 2 were within the normal range throughout the study period.

Although median levels of tissue factor were significantly lower in Group 3 than in the other two groups on admission, there was no other significant difference either between groups or within each group for the remainder of the week following.

The median levels of tPA were depressed in all patients (Fig 3.13). There was no other significant difference either between groups or with time over the period studied.

DNA

Only one patient was identified as having a genetic procoagulant trait, being heterozygous for the factor V (Leiden) gene. This 24 year old male patient sustained an isolated fracture of his tibia in a road traffic accident in which he was the driver of a car. He underwent an uncomplicated stabilisation of his tibia with an intramedullary nail, and made a rapid and uneventful postoperative recovery. Neither his coagulation nor his inflammatory marker levels were significantly different from the remainder of his group.

Thoracic trauma severity score

The TTSS was applicable to the eight patients with thoracic trauma. On patient scored nine points, five seven points and one patient scored three points. None of these patients developed ARDS or FES.

ARDS patient

A twenty-three year old female patient with an uncomplicated, isolated, closed femoral fracture sustained whilst playing football was admitted to the orthopaedic ward for traction and analgesia in preparation for intramedullary stabilisation the following day. At admission her oxygenation was normal, with a PaO_2 of 16 kPa on room air, giving a P:F ratio of 76 kPa. Sixteen hours after admission she became progressively hypoxaemic and then transiently became unresponsive. She responded rapidly to face mask oxygenation, but in view of a persisting hypoxaemia, tachycardia and tachypneoa she was transferred to the intensive care unit for observation. Eighteen hours later, once her condition had been stabilised, she underwent intramedullary nailing of the femoral fracture. Postoperatively, she developed a petechial rash and diffuse pulmonary infiltrates on her chest radiograph with no evidence of cardiac failure. Although remaining self-ventilating she required the application of continuous positive airway pressure and an inspired fraction of oxygen of 0.6, resulting in PaO_2 of 8.3 kPa (P:F ratio 13.8 kPa). She therefore fulfilled the diagnostic criteria for both ARDS and FES. This patient's hypoxaemia was intractable and her P:F ratios over the study period are shown

in Fig 3.2. She developed a superadded methicillin sensitive *staphylococcus aureus* and *haemophilus influenza* nosocomial pneumonia on day 3 requiring antibiotic therapy and a subsequent *clostridium difficile* colitis on day 10. She made a satisfactory recovery from each of these complications and was transferred to the orthopaedic ward after fifteen days and was discharged from hospital 10 days later. Her laboratory results are shown in Figures 3.2 to 3.12.

This patient's Il-6 level at admission was below the median value for the remaining patients with isolated femoral fractures, and was not seen to be elevated prior to the onset of clinical symptoms of respiratory distress. However, by the time of transfer to theatre eighteen hours later the level was markedly higher than those of the remainder of the group (Fig 3.3), and remained higher for the duration of the study period. The maximum level achieved was 285 pg ml^{-1} on day five.

This patient's levels of soluble ICAM were higher than those of any other patient at the time of admission, but fell over the perioperative period to lie within the interquartile range of the remaining patients. These levels rose again at day 5, becoming higher than those of the remaining patients, and remaining so at day seven. The most severely injured patients (Group 3) had lower sICAM levels at admission than did the less severely injured patients (Group 1).

This patient's prothrombin time and APPT also fell outwith the interquartile ranges of the remaining patients (Figs 3.5 and 3.6) at the time of admission. However, the levels of fibrinogen, prothrombin fragment, PAI and tissue factor were all within the interquartile range at this time point (Figs 3.7, 3.10, 3.11 and 3.13).

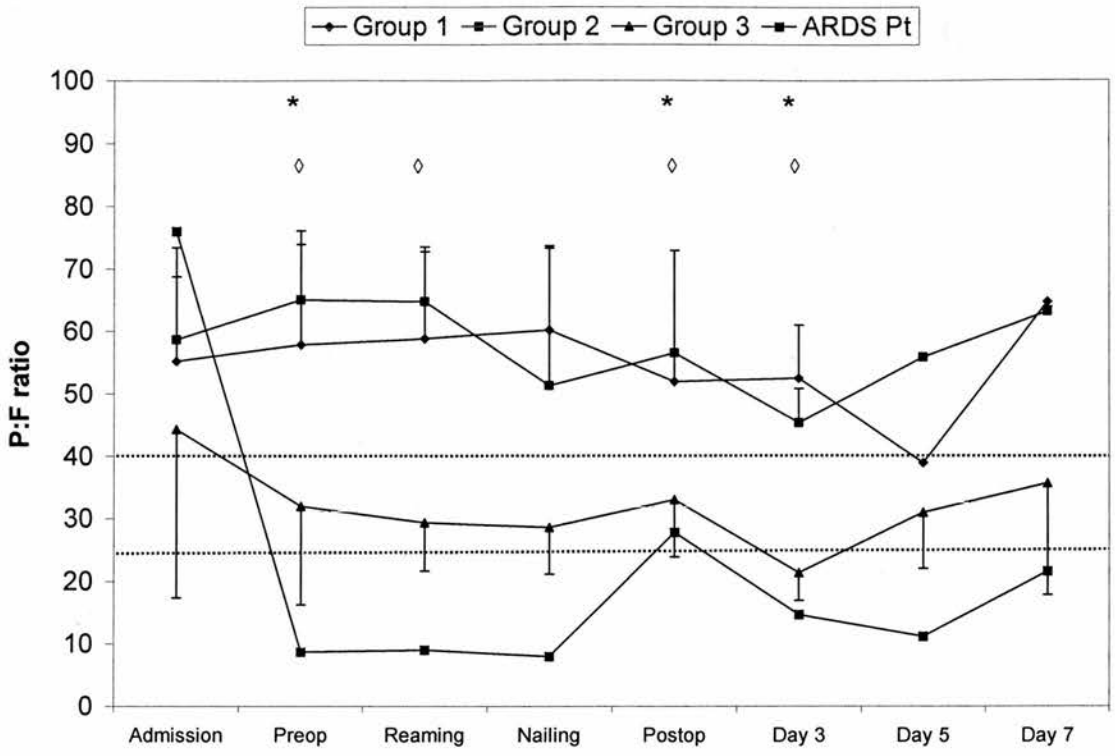


Figure 3.2. P:F ratio. Median P:F ratios over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines indicate the ratios cited in the criteria for the diagnosis of ALI (40 kPa) and ARDS (26.7 kPa) [49].

* significantly lower P:F ratio in Group 3 compared with Group 1.

◊ significantly lower P:F ratio in Group 3 compared with Group 2.

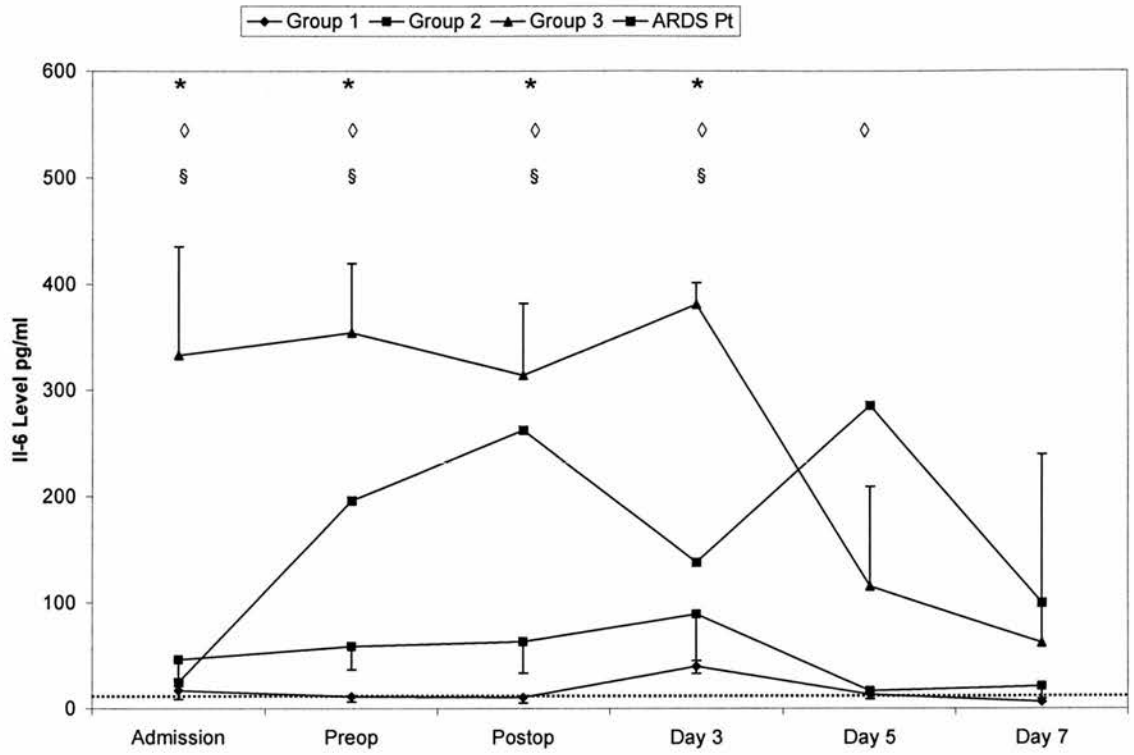


Fig 3.3. Il-6 levels. Median Il-6 levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal level (<11.5 pg ml^{-1}).

* significantly higher IL-6 level in Group 3 compared with Group 1.

◊ significantly higher IL-6 level in Group 3 compared with Group 2.

§ significantly higher IL-6 level in Group 2 compared with Group 1.

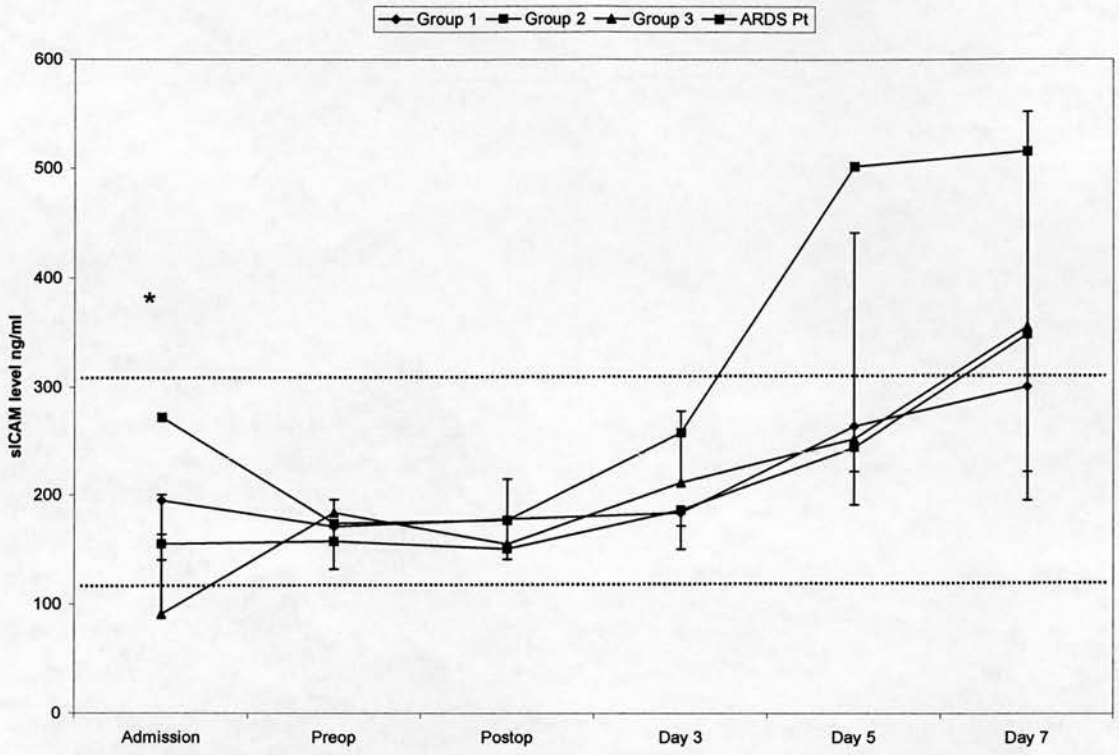


Fig 3.4. sICAM level. Median sICAM levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (115-306 ng/ml).

* significantly higher sICAM level in Group 1 compared with Group 3.

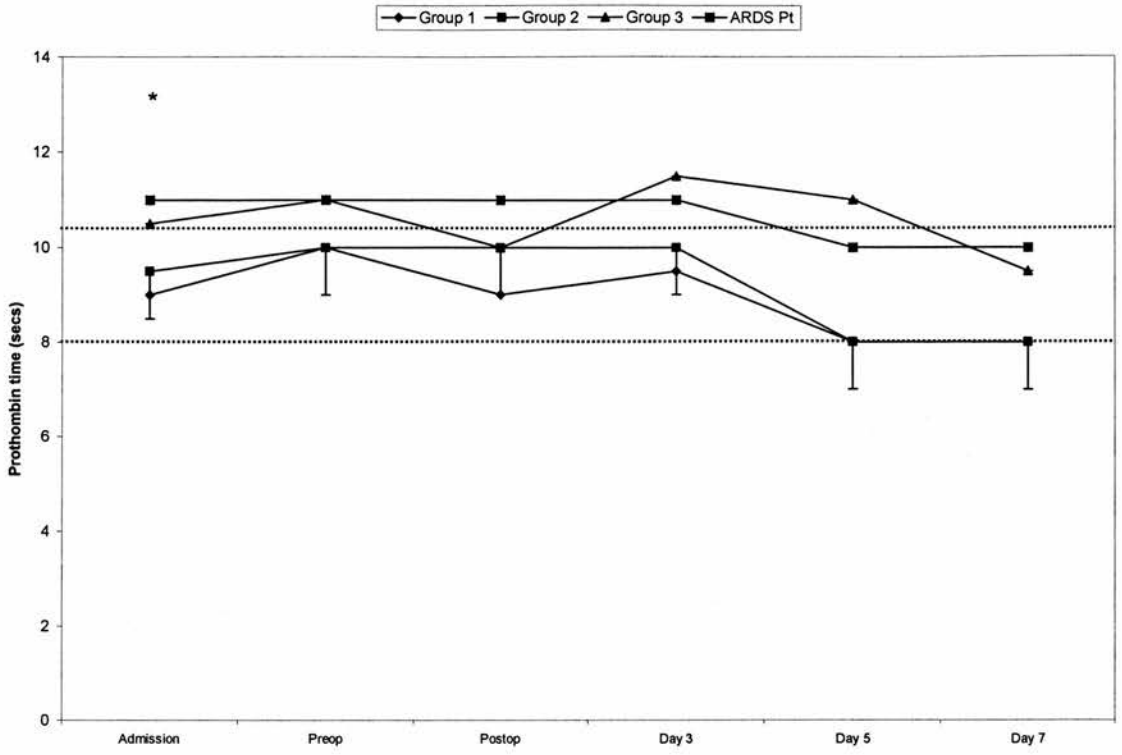


Fig 3.5. Prothrombin time. Median prothrombin time over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (8-10.5 seconds)

* significantly prolonged PT in Group 3 compared with Group 1.

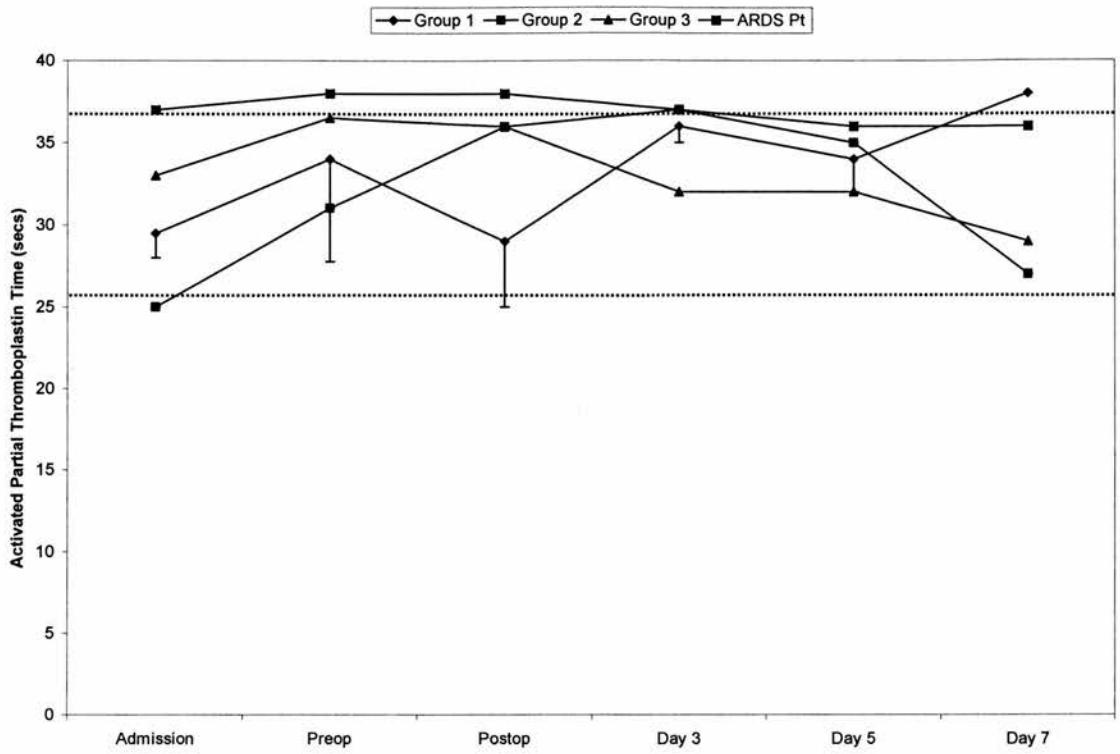


Fig 3.6. Activated partial thromboplastin time. Median prothrombin time over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (26 – 37 seconds). No significant differences between groups at any time point.

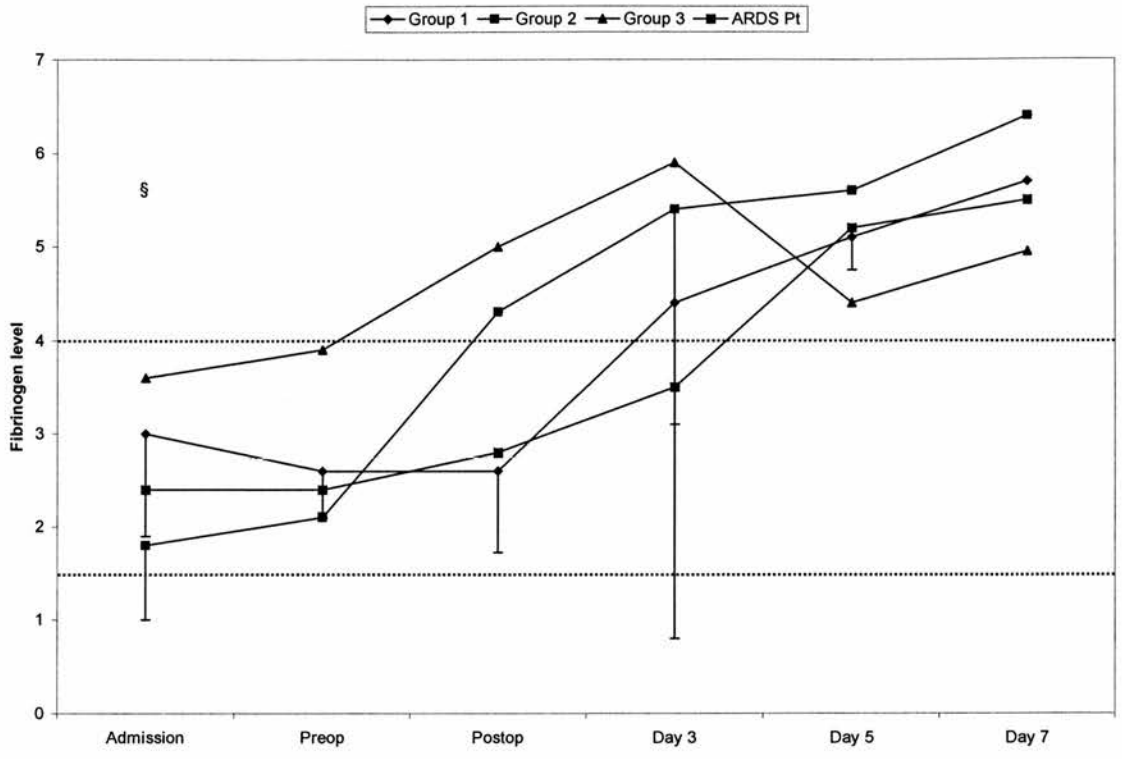


Fig 3.7. Fibrinogen level . Median fibrinogen levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (1.5 – 4 g/L).

§ significantly higher fibrinogen level in Group 1 compared with Group 2.

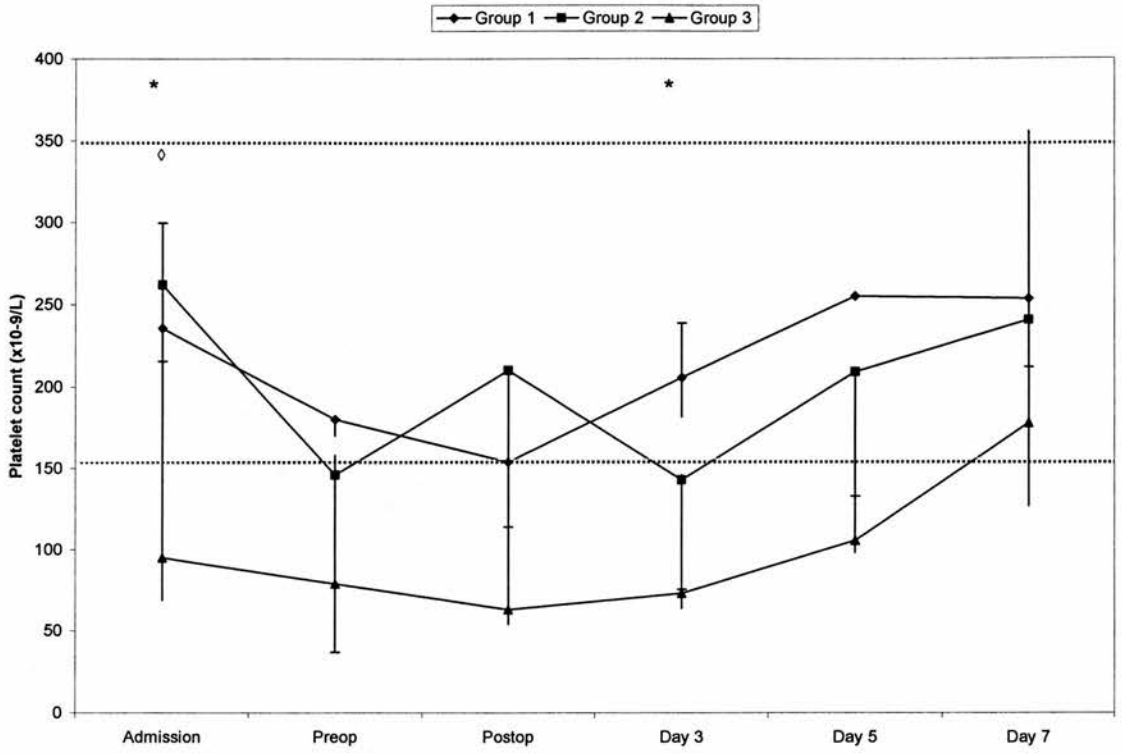


Fig 3.8. Platelet count Median fibrinogen levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (150 – 350 $x10^9$/L).

* significantly lower platelet count in Group 3 compared with Group 1.

◊ significantly lower platelet count in Group 3 compared with Group 2.

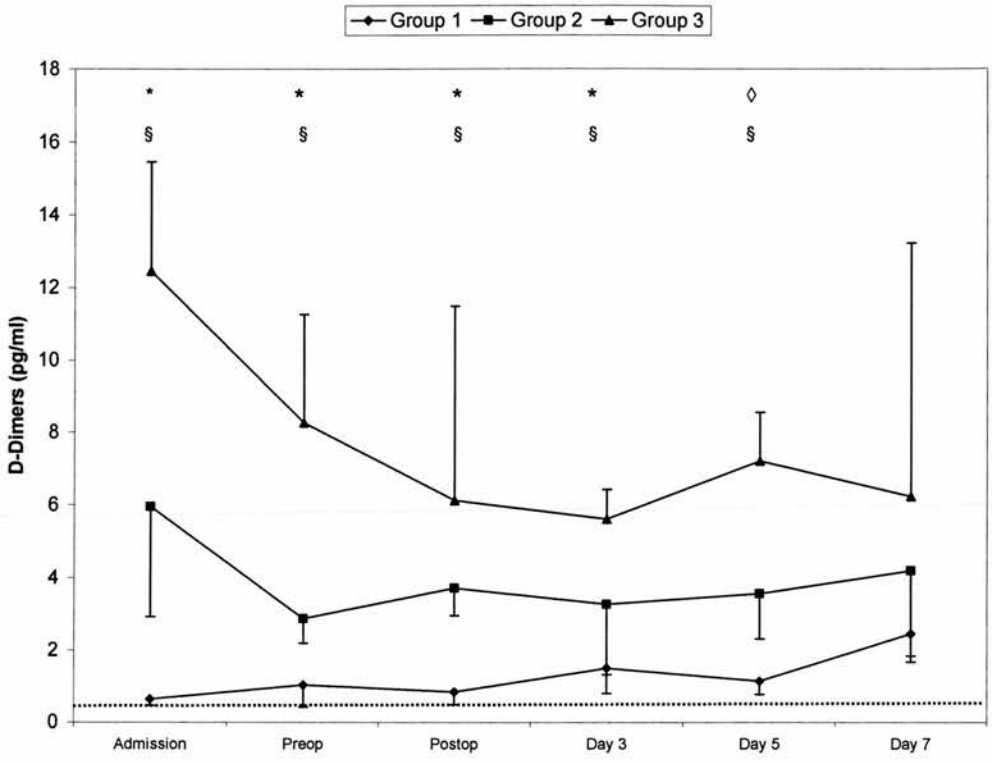


Fig 3.9. D-dimers. Median D-dimers levels over the week following injury for the three study groups. Bars indicate interquartile ranges, and interrupted lines show the normal level (<500 ng/ml).

* significantly higher D-dimers level in Group 3 compared with Group 1.

◊ significantly higher D-dimers in Group 3 compared with Group 2.

§ significantly higher D-dimers in Group 2 compared with Group 1.

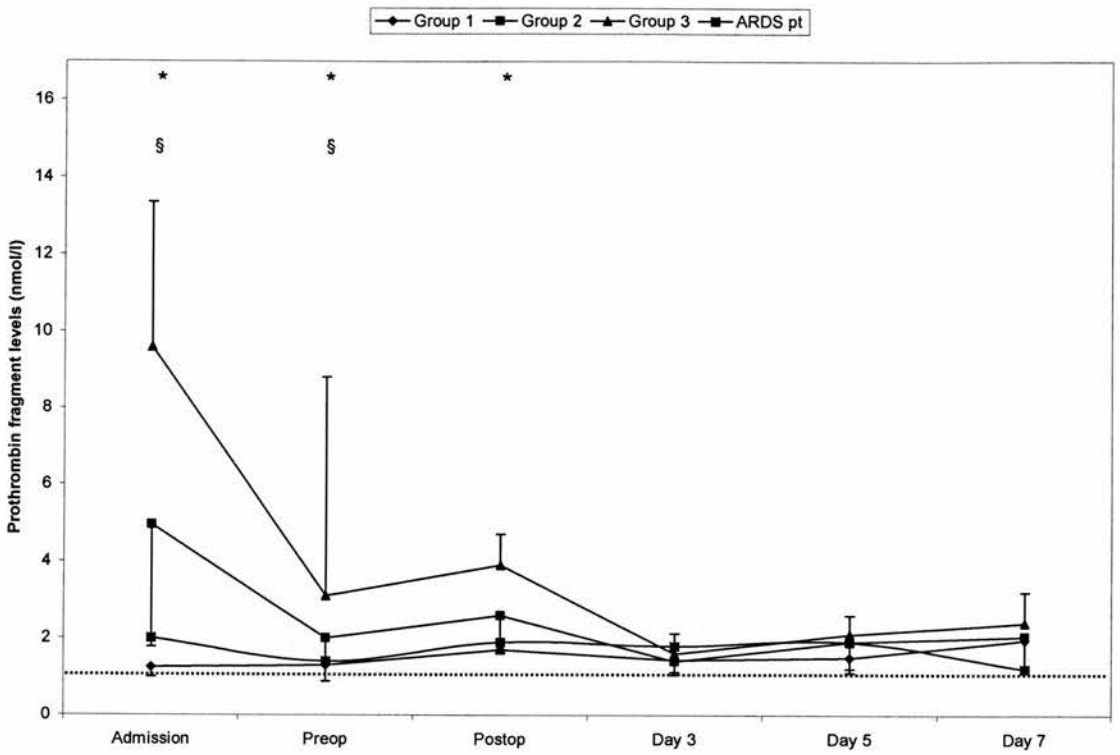


Fig 3.10. Prothrombin Fragments $_{1+2}$. Median prothrombin fragment levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (0.4 – 1.1 nmol/l).

* significantly higher PF $_{1+2}$ level in Group 3 compared with Group 1.

§ significantly higher PF $_{1+2}$ levelin Group 2 compared with Group 1.

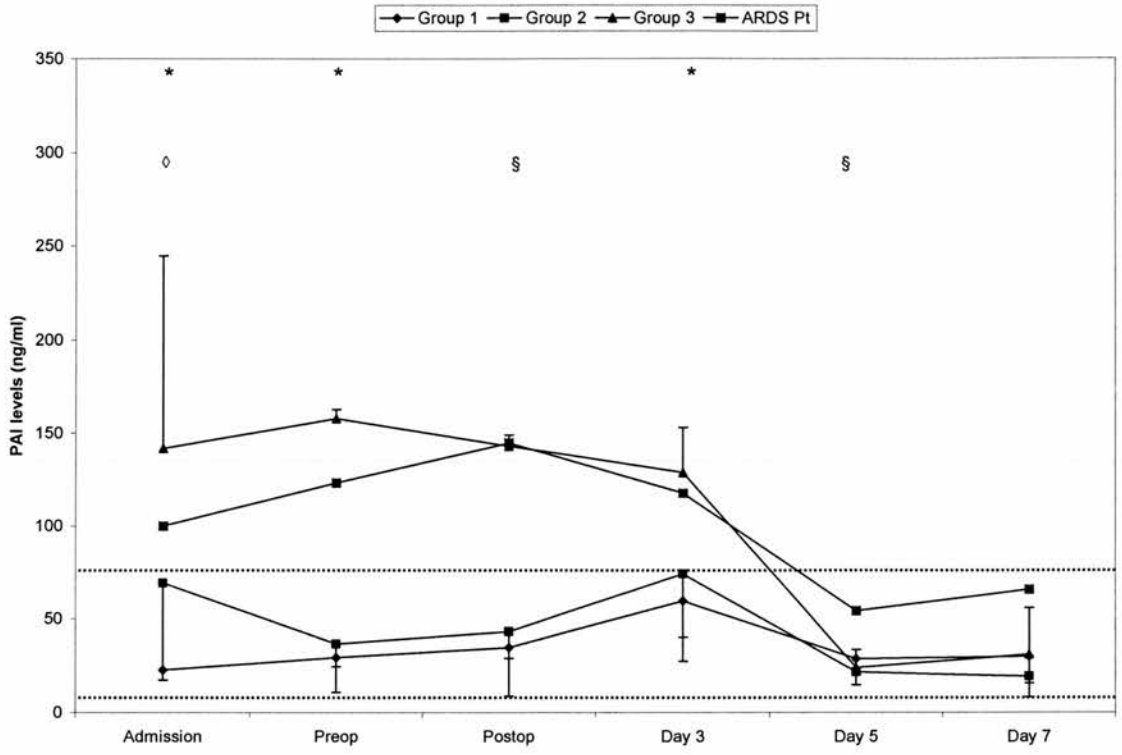


Fig 3.11: PAI level. Median PAI levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (11-69 ng/ml).

* significantly higher PAI level in Group 3 compared with Group 1.

◊ significantly higher PAI level in Group 3 compared with Group 2.

§ significantly higher PAI level in Group 2 compared with Group 1.

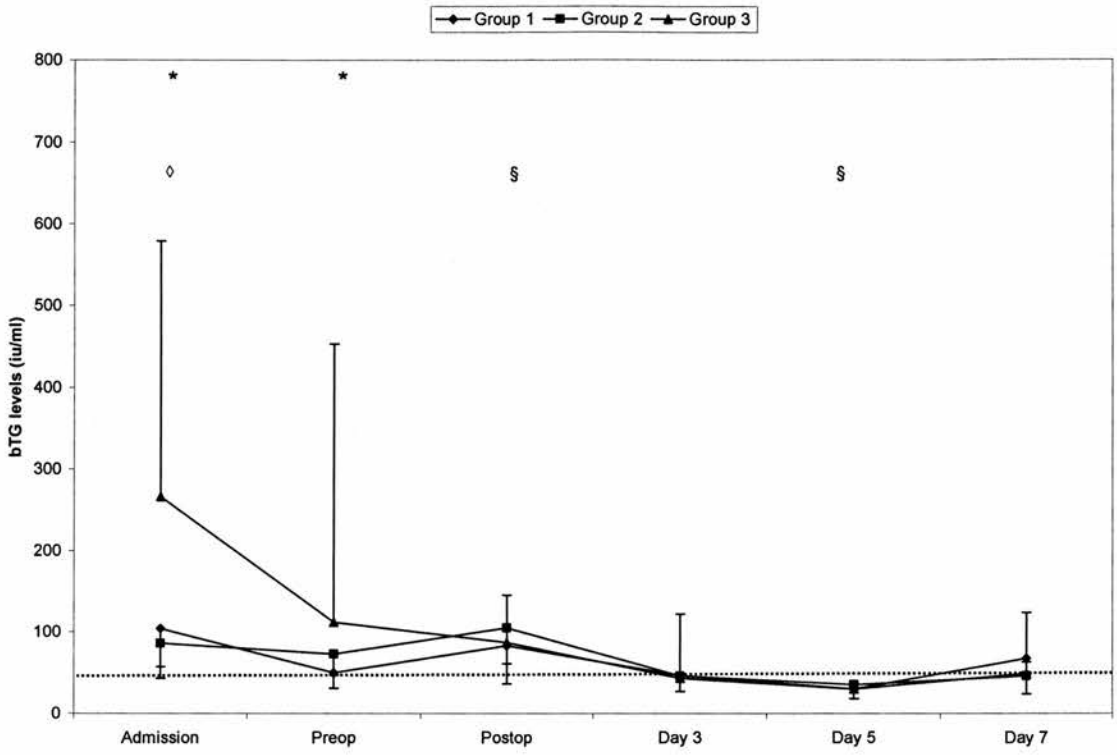


Fig 3.12: βTG level. Median βTG levels over the week following injury for the three study groups. Bars indicate interquartile ranges, and interrupted lines show the normal range (10-40 iu/ml).

* significantly higher βTG level in Group 3 compared with Group 1.

◊ significantly higher βTG level in Group 3 compared with Group 2.

§ significantly higher βTG level in Group 2 compared with Group 1.

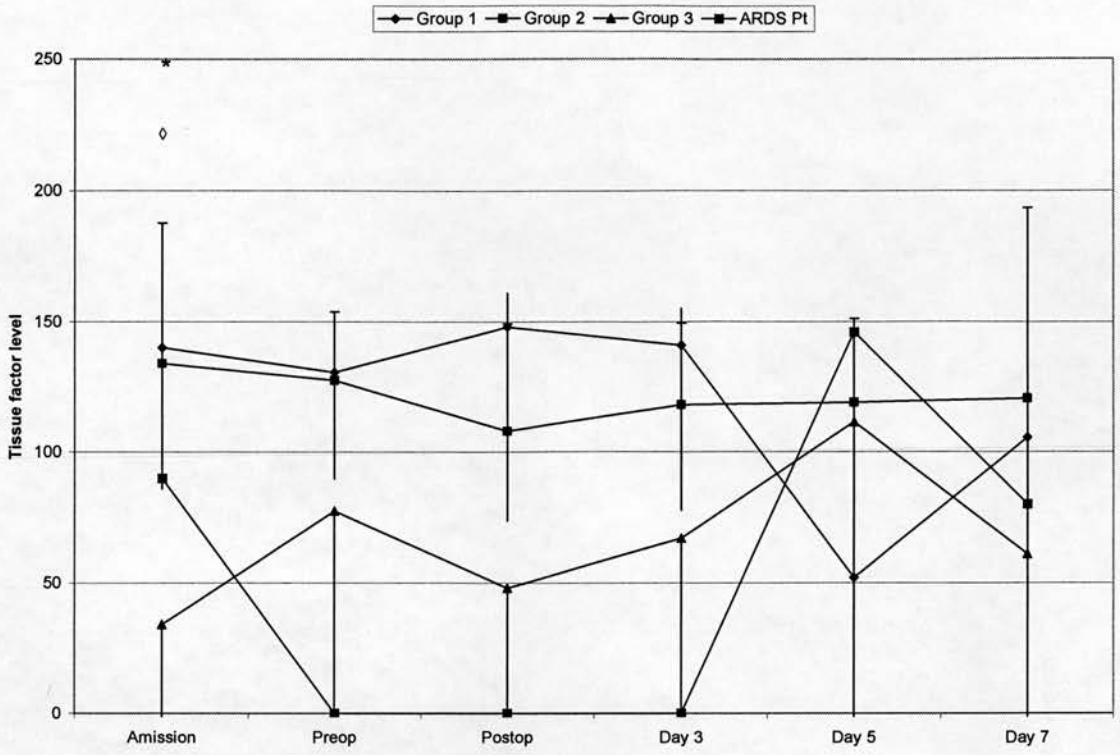


Fig 3.13: Tissue Factor. Median tissue factor levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges.

* significantly higher TF level in Group 3 compared with Group 1.

◊ significantly higher TF level in Group 3 compared with Group 2.

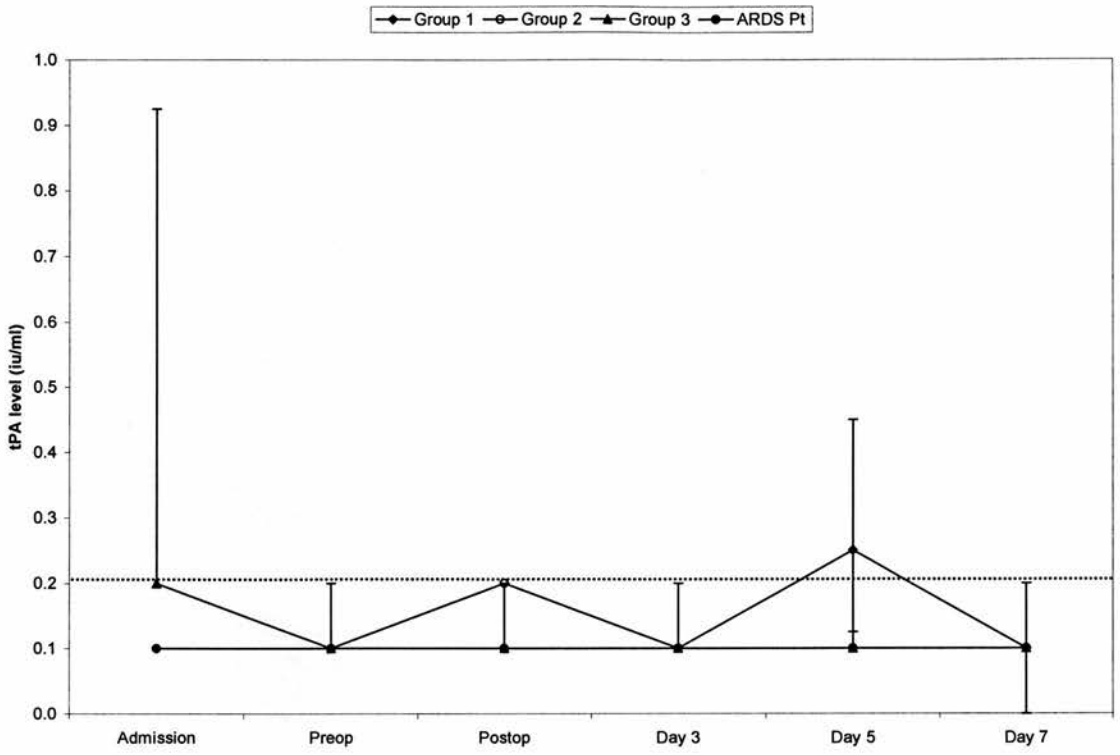


Fig 3.14: Tissue Plasminogen Activator. Median tissue plasminogen activator levels over the week following injury for the three study groups and the patient who developed ARDS. Bars indicate interquartile ranges, and interrupted lines show the normal range (0.2 – 2 iu/ml).

No significant differences between groups at any time point.

3.4 DISCUSSION

The pattern of activation of a number of components of the coagulation and inflammatory systems over the week following long bone injury in a prospective cohort of patients has been described, and this has been compared these with a patient who developed unexpected post-traumatic ARDS. The features correlating most closely with postoperative respiratory insufficiency were admission respiratory insufficiency, injury severity score and the presence of a thoracic injury. Il-6 levels correlated closely with the level of injury (as assessed by both ISS and patient group, $p<0.01$ in each case) and rose further in the twenty-four hours after surgery, but there was no correlation between these levels at admission and the later development of respiratory insufficiency or change in P:F ratio. Although the levels of Il-6, fibrinogen, D-dimers, prothrombin fragments 1 and 2, plasminogen activation inhibitor and β thromboglobulins were significantly elevated in the more severely injured patients (Group 3) at the time of presentation, we were not able to show s-ICAM nor tissue plasminogen activator to be satisfactory discriminators between patients with different degrees of injury, or to correlate with injury or postoperative course. In a patient who developed unexpected post-traumatic ARDS after a seemingly innocuous injury, only the level of sICAM at the time of admission was substantially different from those of the remaining patients with the same injury. No correlation has been shown between the activation of the inflammatory, coagulation or thrombolytic cascades at the time of admission, and outcome given the number of patients studied.

Gross coagulation abnormalities increase the likelihood of death after trauma by several orders of magnitude [64], however, perturbations of this severity are unusual and suggest coagulation factor consumption after haemorrhage rather than a physiological stress reaction. One previous study has shown that perioperative elevation of sensitive markers of coagulation activation correlated with the risk of ALI and ARDS after reamed nailing, in a mixed cohort of pathological and traumatic fractures [62]. In this

previous report, a novel scoring system which combined the results of seven different assays of coagulation activation was independently significantly associated with the development of ALI or ARDS in the postoperative period on multivariate regression analysis [62]. We have been unable to confirm this finding in the present study. This may be a reflection of the population mix: the previous study included patients undergoing intramedullary nailing for pathological fractures and patients who had surgery delayed for over 24 hours. These factors are associated with greater coagulation activation and an increased risk of pulmonary complications [133], and may have resulted in greater numbers of patients with respiratory insufficiency than would otherwise have been the case.

Unexpected development of ARDS

None of the measured indices of inflammatory or coagulation activation at admission were able to discriminate between the patient who unexpectedly developed ARDS and the remaining patients with isolated femoral fractures, with the exception of her sICAM level. Her admission Il-6 level was below the suggested 'threshold' level of 500 pg ml^{-1} [82]. The Il-6 level was elevated immediately preoperatively beyond the level of the other patients with the same injury, but this was *after* clinical signs of respiratory insufficiency had developed. Her maximum Il-6 level of 285 pg ml^{-1} was reached at 5 days after injury, reflecting her clinical course as at this time point she had developed ARDS and a superadded lower respiratory tract infection. It is not clear why respiratory insufficiency developed in this patient prior to surgery: there was no identifiable 'second hit', and she did not have a either of the two pro-coagulant genetic polymorphisms we tested for. A similar situation was encountered by Giannoudis et al who reported the unexpected development of ARDS and early death in a patient with bilateral femoral fractures treated by intramedullary stabilisation [83]. Although this patient did have a higher Il-6 level at presentation (270 pg ml^{-1}) than the remainder of the patients reported in his study, this was no higher than that of many of the patients in the current cohort who did

not experience complications. The use of a specific 'threshold' level of Il-6 therefore appears at present to offer neither sensitivity nor specificity.

In the patient reported here, sICAM levels were transiently higher than those of the remaining study patients at admission, although remaining within the normal range. However, these promptly fell by the following day. This single result is interesting but of uncertain importance, particularly given the significantly lower sICAM levels in the most severely injured patients (Group 3) compared with the least severely injured (Group 1). sICAM levels later rose towards the end of the week, and were again higher in the patient suffering ARDS than in the remaining patients. However, by this stage she had developed ARDS. The levels of sICAM were not detailed for the patient reported by Giannoudis. None of the coagulation markers measured distinguished the patient reported in this study from the remaining patients at any time point. Neither Il-6 nor any other of the markers measured therefore appears to be useful for identifying patients at high risk of ARDS who would not otherwise be suspected as a consequence of their severe injuries.

Limitations of this study

More robust conclusions might be drawn from a larger number of patients developing ARDS following trauma: only one of the patients in the present series developed this complication. There is a relatively low prevalence of ARDS amongst trauma patients (0.4 % after tibial fracture, 1.7 % after femoral fracture and 7.7 % after combined long bone and thoracic injury) [213], and a very much larger study would be required in order to establish the absence of a correlation with this clinical outcome measure. However, using P:F ratios as a surrogate outcome measure, we found that several patients developed marked respiratory insufficiency after injury, and that this correlated most strongly with admission respiratory insufficiency and injury severity score, rather than with the markers studied, which were not able to identify the patient who did

unexpectedly develop ARDS. We do not feel that the paucity of ARDS cases detracts from the interest of these findings.

We calculated the TTSS for all patients suffering thoracic trauma. In recognition of the fact that evidence of respiratory insufficiency may only become evident gradually, this scoring system uses information collected over the first twenty-four hours after admission and was not proposed as a tool for initial assessment at admission. In our cohort we have not found the TTSS to correlate with the development of postoperative respiratory insufficiency.

SECTION FOUR

The early response to major trauma and intramedullary nailing

4.1 INTRODUCTION

Investigation of the physiological events occurring at the time of injury has not been possible because these occur outwith hospital. Existing animal models do not incorporate high energy incident forces and do not therefore adequately replicate injury physiology. In addition, a number of existing models of fracture stabilisation deviate from normal osteosynthetic biomechanics, and therefore do not adequately reproduce the series of events precipitating the pathophysiological stress response.

A new ovine model was developed in which reproducible high energy injuries to bone and the surrounding soft tissues replicated the physiological sequelae of trauma.

4.2 ANIMALS AND METHODS

Home Office Personal and Project Licenses under the Animals (Scientific Procedures) Act 1986 were obtained (numbers PIL 60/9064 and PPL 60/3007), and the experimental protocol was reviewed and approved by the University of Edinburgh Ethical Review Committee (number PL94).

Twenty one Scottish Blackface neutered male sheep of one year of age and weighing 35 - 50 kg were studied in three groups of seven animals. The entire study was performed under general anaesthesia. Group 1 (the control group) underwent placement of monitoring cannulae and a femoral stabilising cable but received no further intervention. Group 2 (the 'fracture' group) underwent fracture of both femora and tibiae. Group 3 (the 'fracture and nailing' group) underwent the same fractures and subsequent stabilisation by reamed intramedullary nailing.

The animals were acclimatized to laboratory housing for at least two weeks before the experiment. Food but not water, was withheld for twelve hours before anaesthesia. General anaesthesia was induced with intravenous (IV) etomidate (Hypnomidate; Janssen-Cilag, Saunderton, Buckinghamshire UK; 0.5 mg kg^{-1}) and midazolam (Hypnovel; Roche, Welwyn Garden City; UK) 0.5 mg kg^{-1}. After endotracheal intubation with a cuffed endotracheal tube, intermittent positive pressure ventilation was instituted using a mechanical ventilator (Manley Pulmovent MPP; Harlow, Essex, UK). Minute volume was set initially at 12 ml kg^{-1} with a 1:2 oxygen : nitrous oxide mixture. Gas flows and ventilator settings were later adjusted to achieve end-tidal CO_2 concentrations ($FE'CO_2$) of 5.3 kPa. The inspired and expired fractions of oxygen and carbon dioxide were monitored using a multi-channel patient monitor (Datex-Engstrom C/S3 Compact). Anaesthesia was maintained with halothane (Rhodia Organique, Bristol) delivered from a Fluotec Mark 3 vaporizer (Cyprane, Keighley, Yorkshire, UK). End-tidal concentrations of 1.1% halothane were maintained throughout the procedure and monitored using a Lamtec Anaesthetic Monitor which had been pre-calibrated with a proprietary standard (BOC, UK). Neuromuscular blockade was established where required using IV rocuronium (88μg per kg; Esmeron, Organon-Teknika, Netherlands). Supplemental doses of 20 μg kg^{-1} were given when the train of four count in the carpal flexor muscles was in excess of two.

Throughout anaesthesia, heart rate and cardiac rhythm were continuously monitored using a three lead precordial electrocardiogram trace. A central venous percutaneous sheath introducer (Arrow, PA, USA) was placed in the left internal jugular vein using a Seldinger technique, and flushed with normal saline. A pulmonary artery catheter (Swan-Ganz CCOmboV, Edwards Lifesciences, CA, USA) was passed via the sheath into the cranial vena cava, and its balloon inflated. Waveform analysis from the tip lumen allowed the catheter to be advanced into the pulmonary artery. The catheter allowed continuous cardiac output (QT) measurement using a heating coil by thermodilution principles. The QT value displayed was a calculated mean of five sequential accepted measurements with outlier rejection. The catheter employed fibre-optic reflectance spectrophotometry to measure SvO_2, and both QT and SvO_2 were recorded at baseline, immediately before each intervention, and at the end of the experiment. In addition the catheter allowed measurement of central venous pressure (CVP) and pulmonary artery pressure (PAP) and these values were recorded at five second intervals.

A 3 French kink-resistant arterial cannula (Cook, Indianna, USA) was introduced into the right auricular artery for continuous monitoring of systolic, diastolic and calculated mean arterial pressures. On five occasions, this vessel was found to be too small to cannulate and therefore the carotid artery was used employing a Seldinger technique. Arterial blood gas samples were taken from this line at predetermined intervals. A second venous cannula was placed in the right jugular vein for the administration of drugs, maintenance intravenous fluids (0.9% saline at room temperature infused at a constant 10 ml kg^{-1} $hour^{-1}$) and for obtaining venous blood samples. At predetermined intervals, six ml aliquots were withdrawn into citrate collecting tubes and centrifuged at 3000 rpm for 30 minutes. The supernatant was aspirated and stored at -80 °C. The prothrombin and activated partial prothrombin times (PT and APPT) were later measured in batches. Plasma levels of fibrinogen and antithrombin III (AT III) were later assayed using ELISA techniques. Temperature was monitored continuously using a nasopharyngeal thermistor probe (Helliga Servomed, Germany) and normothermia

maintained using several techniques. All haemodynamic and respiratory data were collected and saved at five second intervals via an RS232 connection from the Datex monitor by dedicated software (Datex-Ohmeda S/5 Collect, Version 4) installed upon a laptop computer. This was later converted to ASCII format for subsequent statistical analysis (Photograph of monitoring apparatus, Fig 4.1).

A trans-oesophageal echocardiography (TOE) omniplanar probe was placed in the oesophagus in order to obtain screen images of the pulmonary artery (Hewitt Packard Sonus 2000 scanner, Philips Medical Systems). Trans-cardiac embolism was recorded using the integral VHS video recorder for thirty seconds before each fracture or stabilisation procedure, and the exact timing of the event was noted by entering a suitable screen annotation. Recording was continued for at least two minutes or until all embolism had ceased. TOE embolic sequences were graded from VHS recordings by two observers and the mean score taken. A modified Mayo scoring system was used, based on the amount of echogenic filling of the region of interest, duration of embolism, and size of embolic particles (Table 4.1).

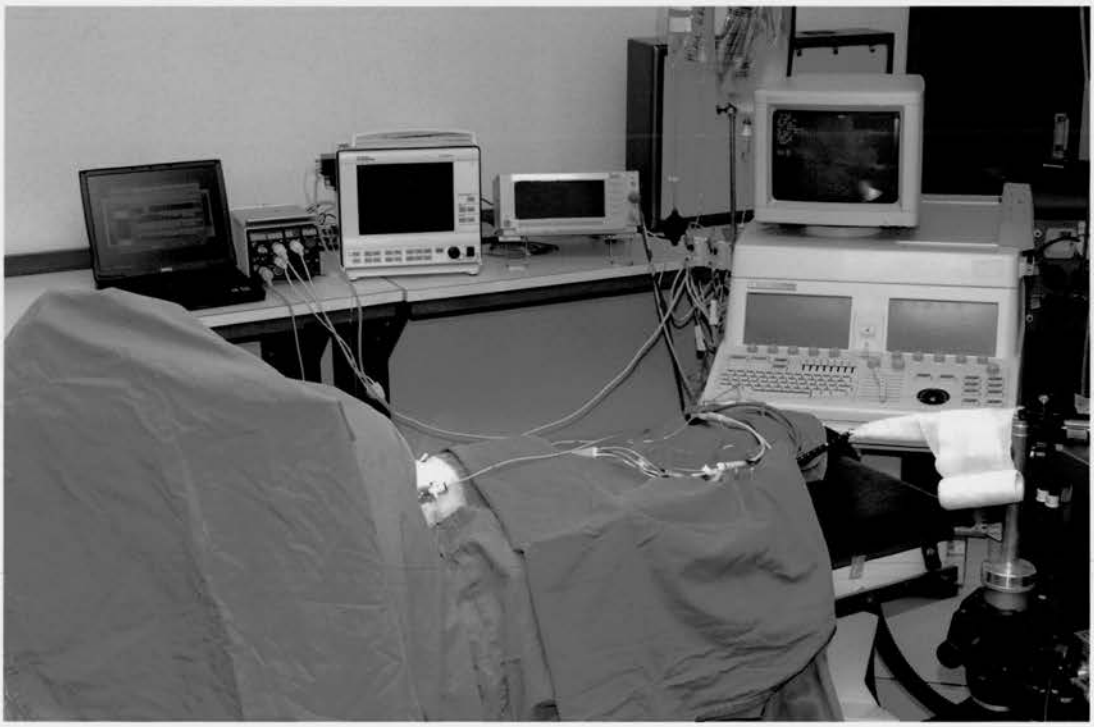
Table 4.1. Modified Mayo Scoring of Embolism.

Score	Amount	Duration	Size
0	None	None	None
1	Sporadic embolic signals	< 1 minute	< 2 mm
2	Small embolic shower	1 – 3 minutes	> 2 mm
3	Pronounced shower	> 3 minutes	> 5 mm

The final score is the sum of the scores for each of the three components: amount of embolic material seen, the duration of the embolic sequence, and the size of the largest echogenic particle seen during the sequence.

Figure 4.1. Monitoring apparatus

Experiment in progress. From top left, clockwise, the data collection computer, the Datex monitor, the cardiac output monitor, the intravenous fluid sets and pressure transducers, the trans-oesophageal echocardiogram (TOE) monitor, the TOE probe, and the Swan-Ganz catheter entering the introducer sheath are seen.



Surgery was performed at least sixty minutes after the induction of anaesthesia and after fifteen minutes of stable haemodynamic conditions, with the sheep placed in dorsal recumbency. A stabilising cable (Dall-Miles, 2.0mm, Stryker Howmedica Osteonics) was placed around the femur in the subtrochanteric region through a 4 cm incision using blunt dissection through muscle in all animals including controls. Rigid immobilization of the limbs of those animals in the fracture and nailing groups was produced with contoured block clamps at the knee and the subtrochanteric cables, secured to a steel box frame housing a pneumatic actuator (100 mm bore ram, PRA/182000, Norgren Pneumatics, Staffordshire, UK) (Fig 4.2 a to d). This was fired at 1.1 MPa (11bar), generating a thrust force of 8600 N which was directed via a cylindrically contoured head against the intact limb at the mid diaphyseal level, creating high energy comminuted fractures with overlying soft tissue trauma. Four fractures were produced in sequence, the femoral fractures occurring first. A delay of fifteen minutes was required between fractures to allow repositioning of the apparatus.

In Group 3 (the 'nailing' group), stabilisation of all four fractures was performed one hour after the last fracture through a midline stifle (knee) arthrotomy. The entry point was breached with an awl, before introducing a guide wire across the fracture. Canal preparation was performed using sequential AO pneumatic reamers in 0.5 mm increments to allow the introduction of a 10 mm Grosse-Kempf tibial nail in to the femur, and an 8mm Seidel humeral nail into the tibia.

At the conclusion of each experiment the sheep was killed whilst remaining anaesthetised using intravenous pentobarbital (60 mg kg^{-1}).

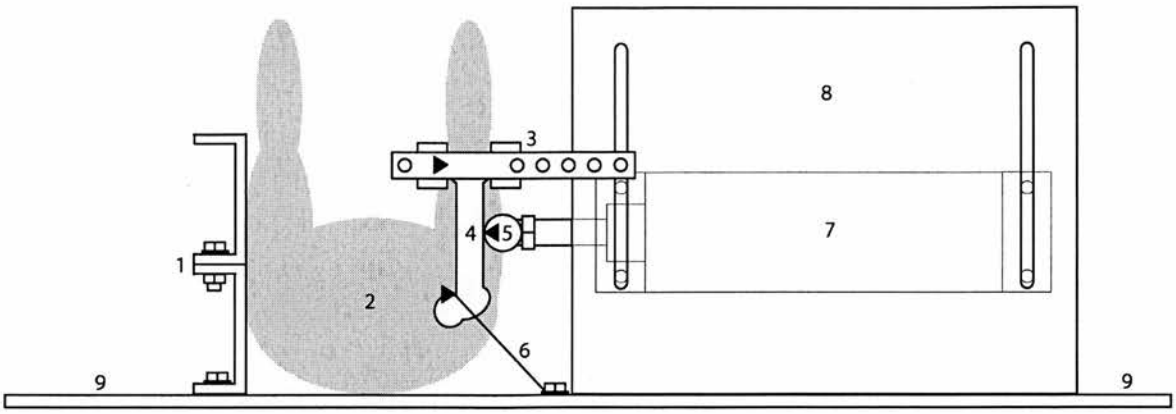
The heart and lungs were removed for *post mortem* analysis. The lungs were inflated with 10% buffered formalin at a pressure of 60 cm water and subsequently immersed in formalin. The right kidney was removed, sectioned coronally and immersed in formalin. At twenty-four hours, both specimens were removed from formalin and drained. The

lungs were separated, and trimmed to 8mm sections. Six standard, uniform tissue blocks were taken for histology, two from each of the central, apical and ventral (peripheral) aspects of each lung. Two blocks were taken from the right kidney.

Blocks were prepared for paraffin and frozen sections. Paraffin blocks were processed in a vacuum impregnating tissue processor overnight, and embedded in paraffin wax. Sections were cut on a microtome at 4 microns for H&E and MSB stains. Blocks for frozen section were frozen in OCT, and cryostat sections were cut at 6 microns for the Oil Red O stains. Histological analysis was performed under light magnification. The numbers of regions containing embolic fat and bone marrow, or thrombus were counted in each of the standardised sections.

Radiographs of the legs were taken to confirm the presence and type of fractures obtained.

Figure 4.2 (a) The experimental apparatus –configured for femoral fracture



1. Bracing wall
2. Sheep
3. Tibio-femoral joint (Knee) clamp
4. Femur
5. Impact head
6. Proximal femur wire
7. Pneumatic actuator
8. Actuator housing
9. Base plate

Figure 4.2 (b).

Photograph of experimental apparatus configured for femoral fracture

Clockwise, from top right, the knee clamp, housing, impact head and femoral wire are demonstrated.

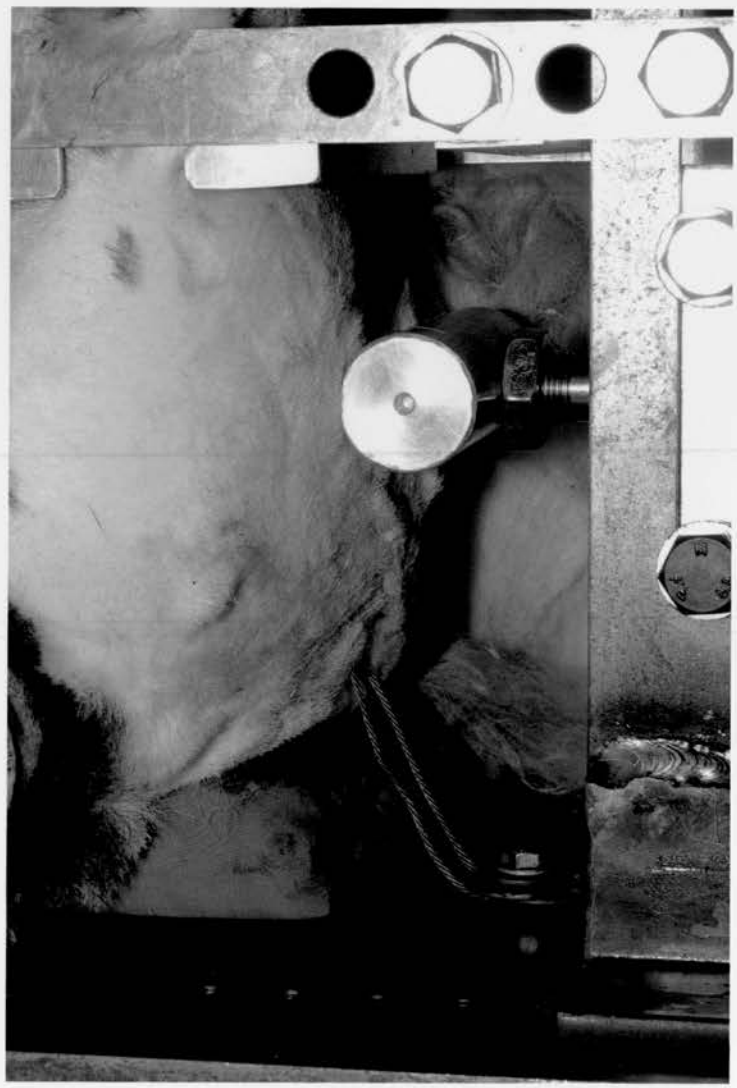
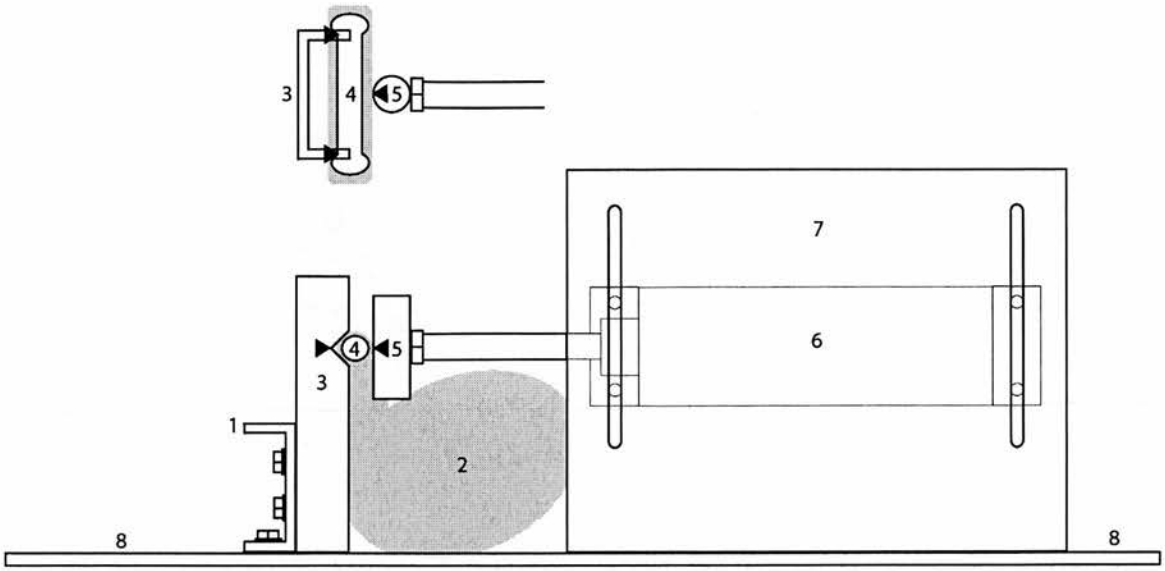
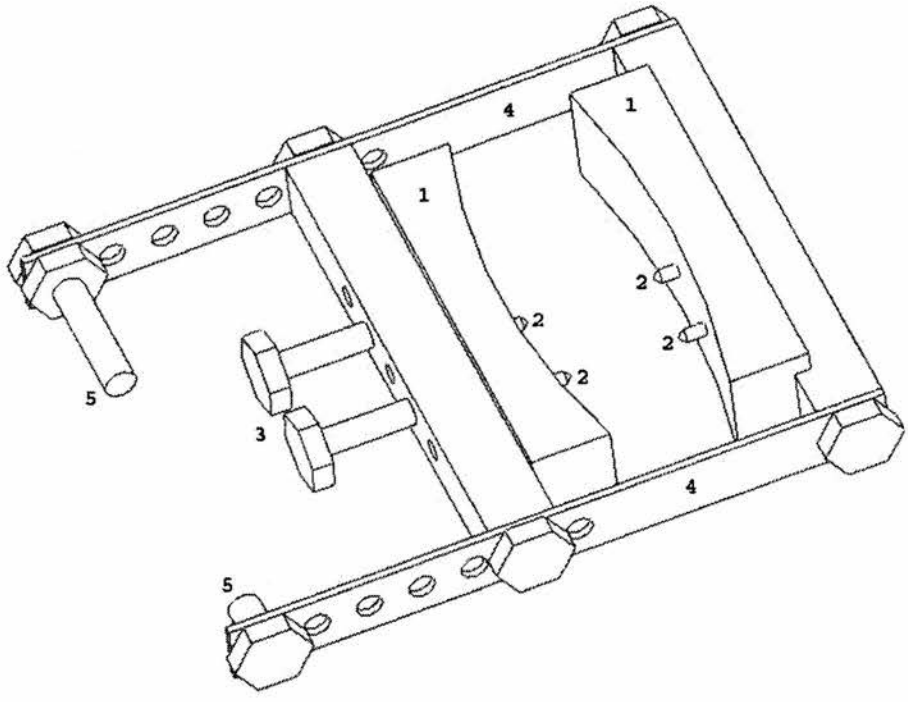


Figure 4.2(c) The experimental apparatus – configured for tibial fracture



1. Mounting for U- section with V- notch
2. Sheep
3. U- section with V- notch
4. Tibia
5. Impact head
6. Pneumatic actuator
7. Actuator housing
8. Base plate

Figure 4.2(d) The experimental apparatus – femoral clamp



1. Contoured clamping blocks
2. Protruding periosteal pins
3. Adjustment bolts
4. Adjustable steel bars
5. Bolts for attachment to actuator housing

Statistical analysis

Heart rate and blood pressure readings were recorded at five second intervals and for the purposes of analysis were averaged over the following time periods, determined in time in seconds from time of fracture: pre-fracture (-60 to -5), 30 seconds (25 to 35), 1 minute (50 to 70), 2 minutes 110 to 130), 5 minutes (290 to 310), 10 minutes (590 to 610) and 15 minutes (890 to 910). In addition, the single 5-second and 10-second readings were used for summary statistics.

To reduce multiple testing in the statistical analyses, these values were further averaged to give a short term (5 seconds to 1 minute) and long term (2 to 15 minutes) outcome figure, each of which was compared to the pre-fracture levels in intervention sheep only using paired *t*-tests. A similar analysis was used to test the effects of reaming and nailing.

In the control sheep, the time corresponding to the time of fracture in the intervention groups was identified and summary results for the previous minute and the subsequent 15 minutes were calculated as for the intervention sheep. Changes in pre-fracture levels from the first to subsequent fractures were then compared between the intervention and control groups by two-sample *t*-tests.

The mean combined embolus scores for the fractures were compared with the mean combined scores for the reaming ands nailing procedures using a paired t-test.

Flow data were analysed separately. The mean change from pre-fracture levels for each group were calculated at each time point, and these means compared at each point using two-sample *t*-tests.

4.3 RESULTS

Immediate Haemodynamic Response to Fracture

Heart rate and systolic blood pressure fell immediately in response to both the first and second fractures, and this response was maintained for at least 15 minutes (Table 4.2 and Fig 4.3(a)). Central venous pressure and pulmonary artery pressure also fell in response to a fracture, and this response reached greatest significance between 2 and 15 minutes after injury (Fig 4.3(b)). The effect of these depressions was incremental, in that the depressed pressures after fracture had not recovered before the depressant effect of the subsequent fracture was seen at 15 minutes (Fig 4.3 (a) and (b)). No significant additional haemodynamic response was seen following nailing and reaming in Group 3 (Table 4.3: effect of reaming and nailing).

Table 4.2. The haemodynamic response to fracture.

Time	HR	Systemic Blood Pressure			Central Venous Pressure	Pulmonary Arterial Pressure		
		Systolic	Diastolic	Mean	Mean	Systolic	Diastolic	Mean
				Immediate response: 0-1 minute				
F1	**	***	***	***			**	
F2	***	***	***	***				
F3								
F4	**						*	
				Early response: 2 – 15 minutes				
F1	**	***	***	***	***	***	***	***
F2		***	***	***	***	***	***	***
F3								
F4		*	*					

The table shows the statistical significance of the fall in each variable from the pre-fracture level, over the immediate phase (first minute) and early phase (2-5 minutes) following the first fracture (F1), second fracture (F2) etc.

* $p<0.05$, ** $p < 0.01$, *** $p<0.001$.

Table 4.3: The haemodynamic response to reaming and nailing

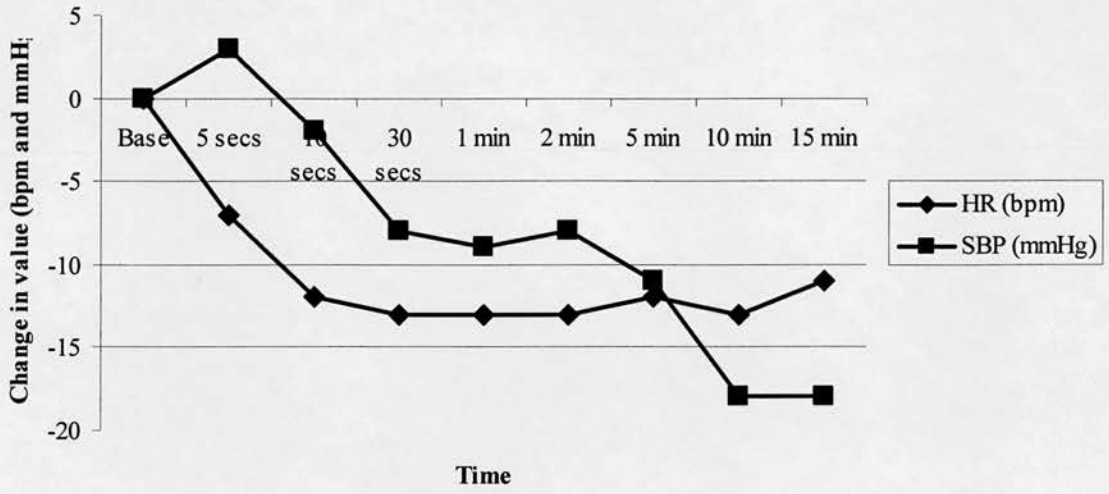
Time	HR	Systemic Blood Pressure			Central Venous Pressure	Pulmonary Arterial Pressure		
		Systolic	Diastolic	Mean	Mean	Systolic	Diastolic	Mean
				Early response: 0-1 minute				
R1								
N1								
R2								
N2		*						
R3								
N3								
R4						*	*	
N4		*	*	*	*	*	*	
				Late response: 2 – 15 minutes				
R1								
N1								
R2								
N2								
R3						*	*	*
N3						*		
R4								
N4								

The table shows the statistical significance of the fall in each variable from the pre-fracture level, over the immediate phase (first minute) and early phase (2-5 minutes) following the first reaming (R1) and nailing (N1) procedures, second reaming (R2) and nailing (N2) procedures etc.

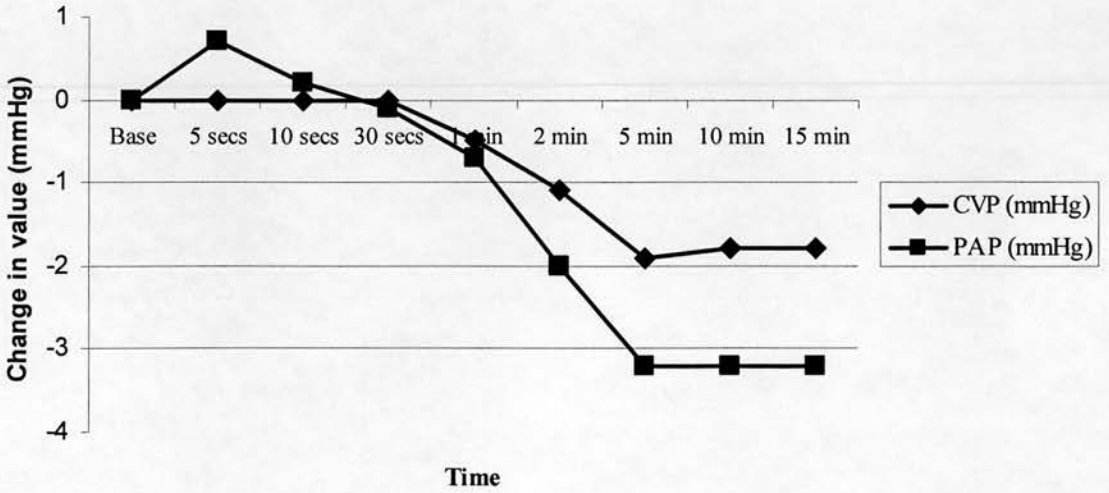
* $p<0.05$, ** $p < 0.01$, *** $p<0.001$.

Figure 4.3. The immediate haemodynamic response to fracture:
Fall in (a) HR and SBP and (b) CVP and PAP. Value shown is a mean for all animals undergoing the first fracture (Groups 2 and 3 combined).

(a)



(b)



Haemodynamic Changes during the course of sequential fractures and nailing

Whilst heart rate fell during the sequence of fractures, it did not change statistically significantly over the experimental period (Fig 4.4 (a)). Mean arterial pressure fell significantly by a mean of 35 mmHg during the train of four fractures (Fig 4.4 (b), $p<0.03$). No further decrease occurred as a result of the process of reaming and nailing these fractures. The central venous pressure in Group 1 (the control group) rose slightly during the course of the experiment, whilst that of Groups 2 and 3 fell by an average of approximately 3 mmHg during the train of four fractures and then remained stable (Fig 4.4 (c), NS). No evidence of spontaneous recovery from this fall in CVP was seen.

Fig 4.4. Haemodynamic changes over the course of the experiment

Change in each variable shown at each time point. Each of four fractures is shown separately (#1 *et seq*), as is each nailing procedure (N1 *et seq*). Group 1: Controls, Group 2: Fractures only, Group 3: fractures stabilised by reamed intramedullary nailing.

(a) Heart Rate: change from baseline (beats per minute)

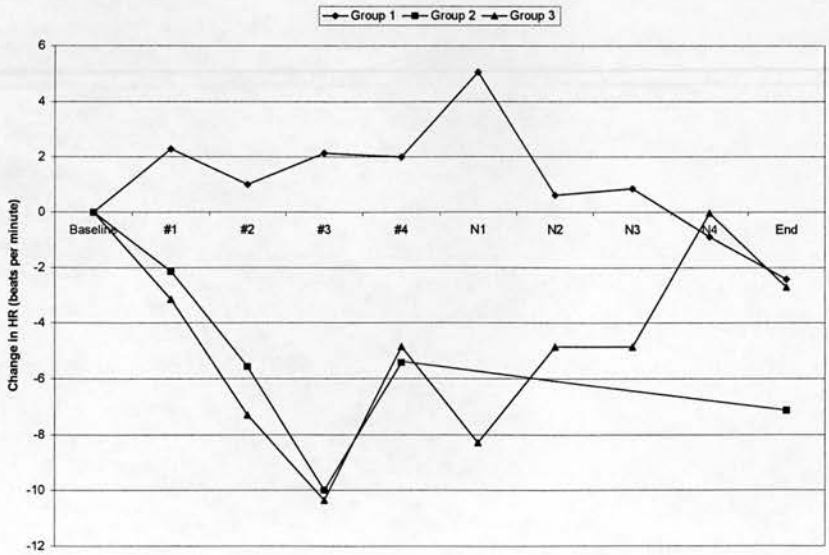
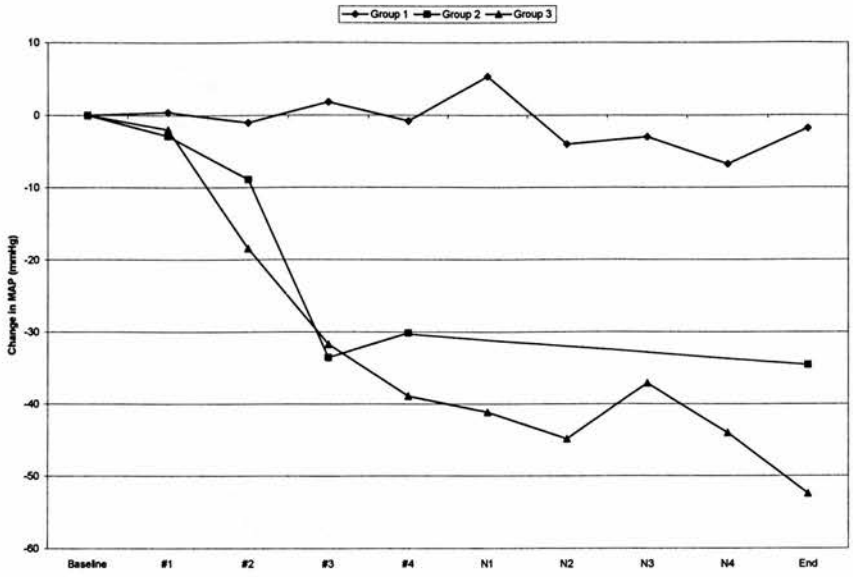


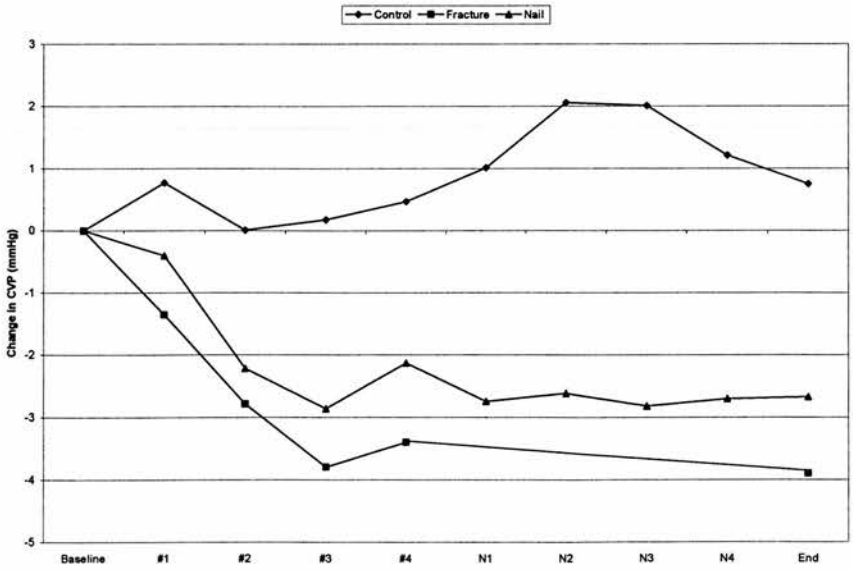
Fig 4.4. Haemodynamic changes over the course of the experiment (cont.)

Change in each variable shown

(b) Mean Arterial Pressure: change from baseline (mmHg)



(c) Central Venous Pressure change from baseline (mmHg)

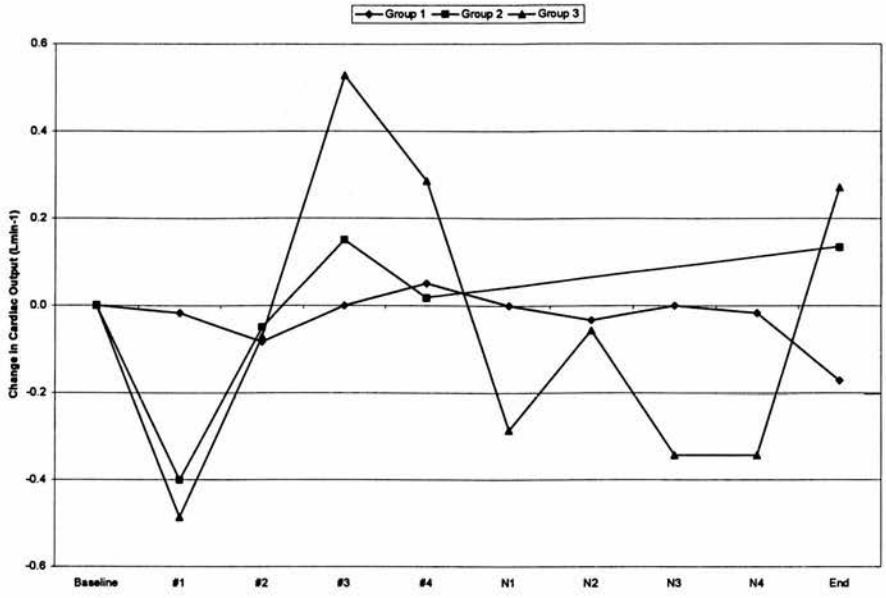


Flow data

Cardiac output, mixed venous oxygen concentration, stroke volume and systemic vascular resistance did not change significantly from baseline during the experimental period (Figs 4.5 (a) to (d), p=NS). However, some trends were evident. The mixed venous oxygen concentration gradually increased in the Group 1, in contrast to Groups 2 and 3 where an initial reduction during the fractures was followed by a period of recovery (Fig 4.5(b)). Systemic vascular resistance gradually declined over the experimental period, and this again was more marked in Groups 2 and 3. Oxygenation was calculated as a ratio of the arterial oxygen tension to the inspired fraction of oxygen. This ratio did not vary significantly over the course of the experimental period (Fig 4.6, p=NS).

Figure 4.5. Change in flow variables

(a) Change in Cardiac Output ($Lmin^{-1}$)



(b) Change in Mixed Venous Oxygen Concentration (%)

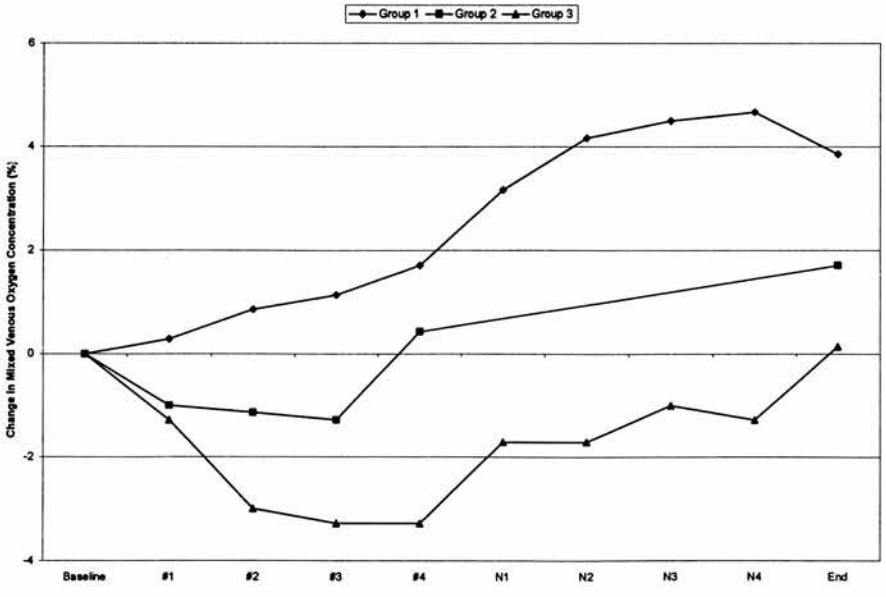
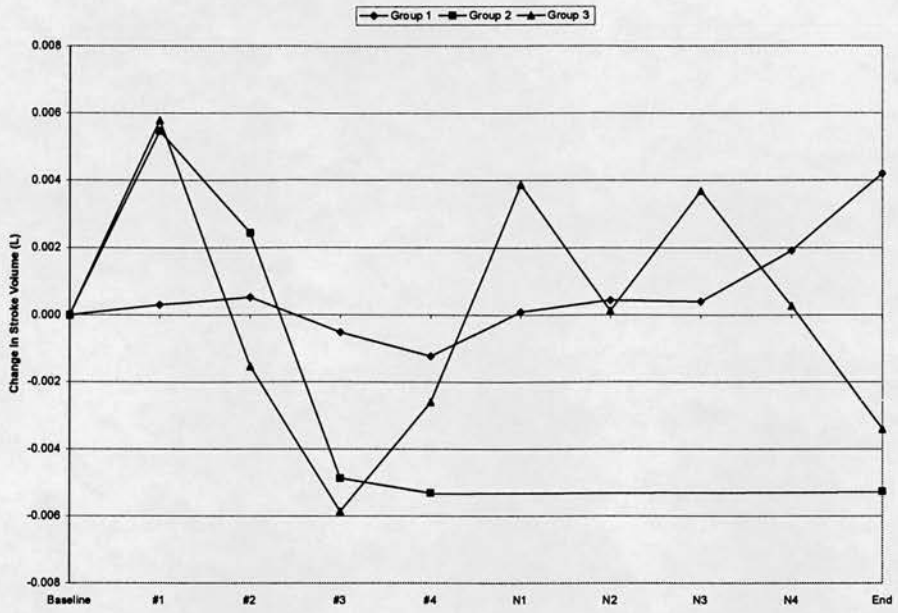


Figure 4.5. Change in flow variables (cont)

(c) Change in Stroke Volume (L)



(d) Change in Systemic Vascular Resistance

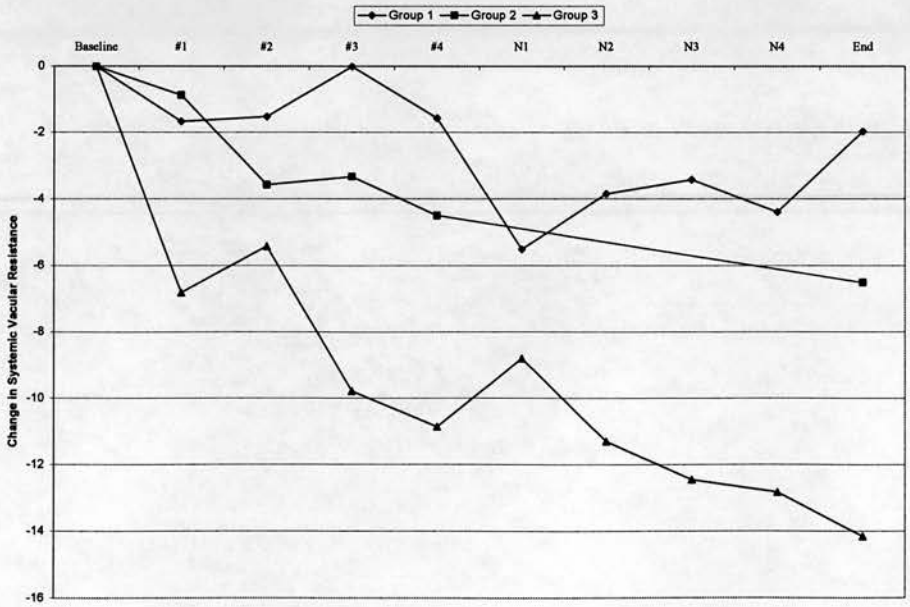
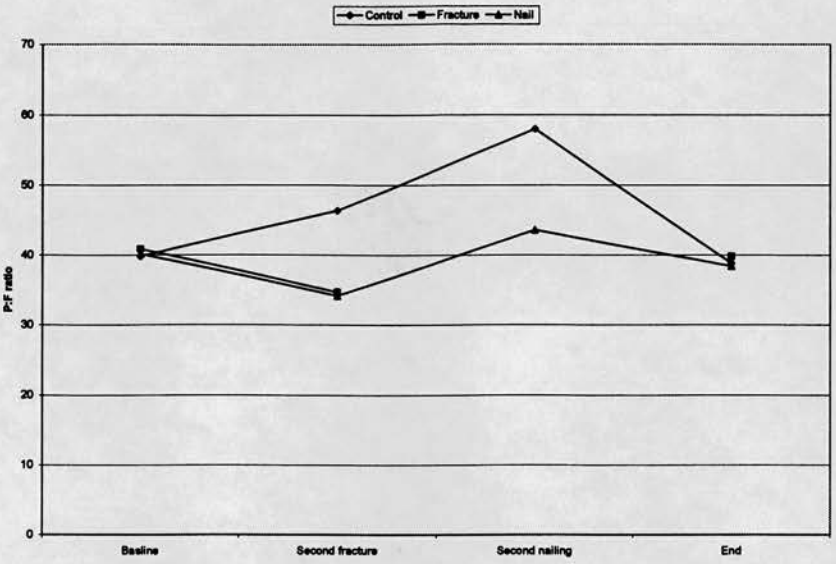


Figure 4.6: Changes in ratio of inspired oxygen fraction to arterial oxygen pressure



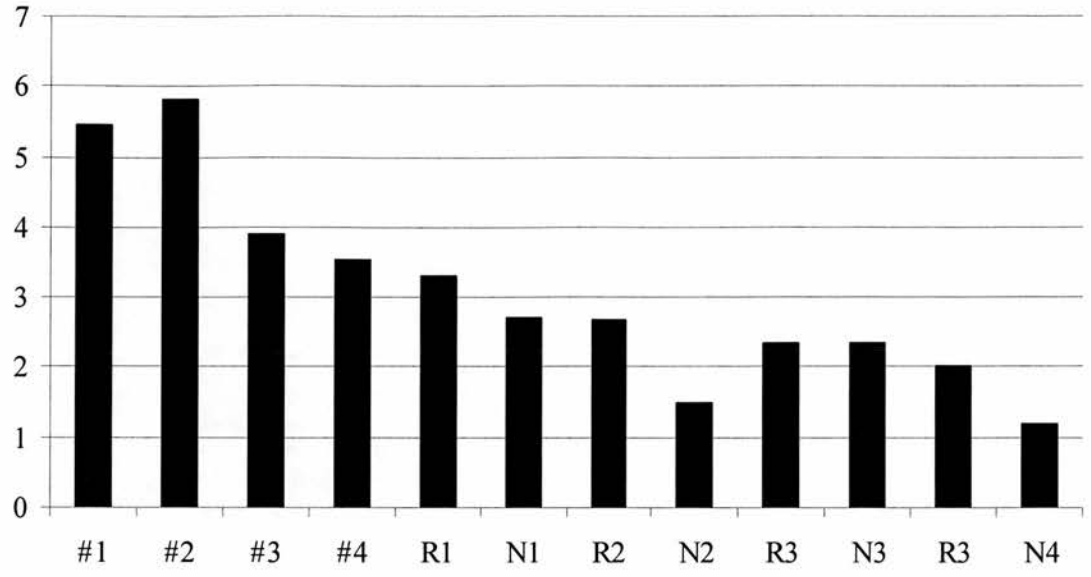
Embolism

No emboli were seen before injury. Mean embolic scores were calculated for each of the four fractures, for each reaming sequence and for each nailing procedure (Fig 4.7). Pronounced and sustained embolic showers were detected following each femoral fracture. Smaller showers were detected after tibial fracture. The embolic scores during the reaming and nailing sequences were of significantly ($p< 0.01$) lesser magnitude than those following fracture (Fig 4.7), with only sporadic, short-lived embolic events observed.

Maximal embolism occurring at the time of reaming tended to coincide with the passage of the first reamer, but insufficient embolism was detected to allow accurate calculation separate scores for each phase of the reaming sequence. Particle size tended to increase with time: only small particles were seen at the time of the first femoral fracture, but larger embolic particles were seen during subsequent injury or stabilisation. Minor, short-lived embolic events were observed occasionally during the movement of the sheep required to alter the actuator position or to prepare for stabilisation.

Bone marrow and thrombus emboli were confirmed histologically in the majority of lung tissue blocks studied (Figs 4.8 – 4.10). Insufficient material was detected for meaningful quantitative analysis: five areas of thromboembolism were detected Group 2 and a further six in Group 3. Pure fat emboli without associated thrombus were detected in one sample from each of the Groups 2 and 3. No emboli were detected in the control animals and no systemic embolism was detected in any renal tissue block. No patent foramen ovale was found in any heart.

Figure 4.7. Mean embolic scores following fracture, reaming and nailing
Modified Mayo score, see Table 4.1.



Bar chart shows mean score after first and second (femoral) fractures (#1 and #2), third and fourth (tibial) fractures (#3 and #4), and after each reaming procedure (R1 et seq) and nailing procedure (N1 et seq)

Figure 4.8. Photomicrograph showing embolised fat.

Haematoxylin and Eosin stained section of ovine lung parenchyma under light microscopy, showing bone marrow embolism within a pulmonary artery.

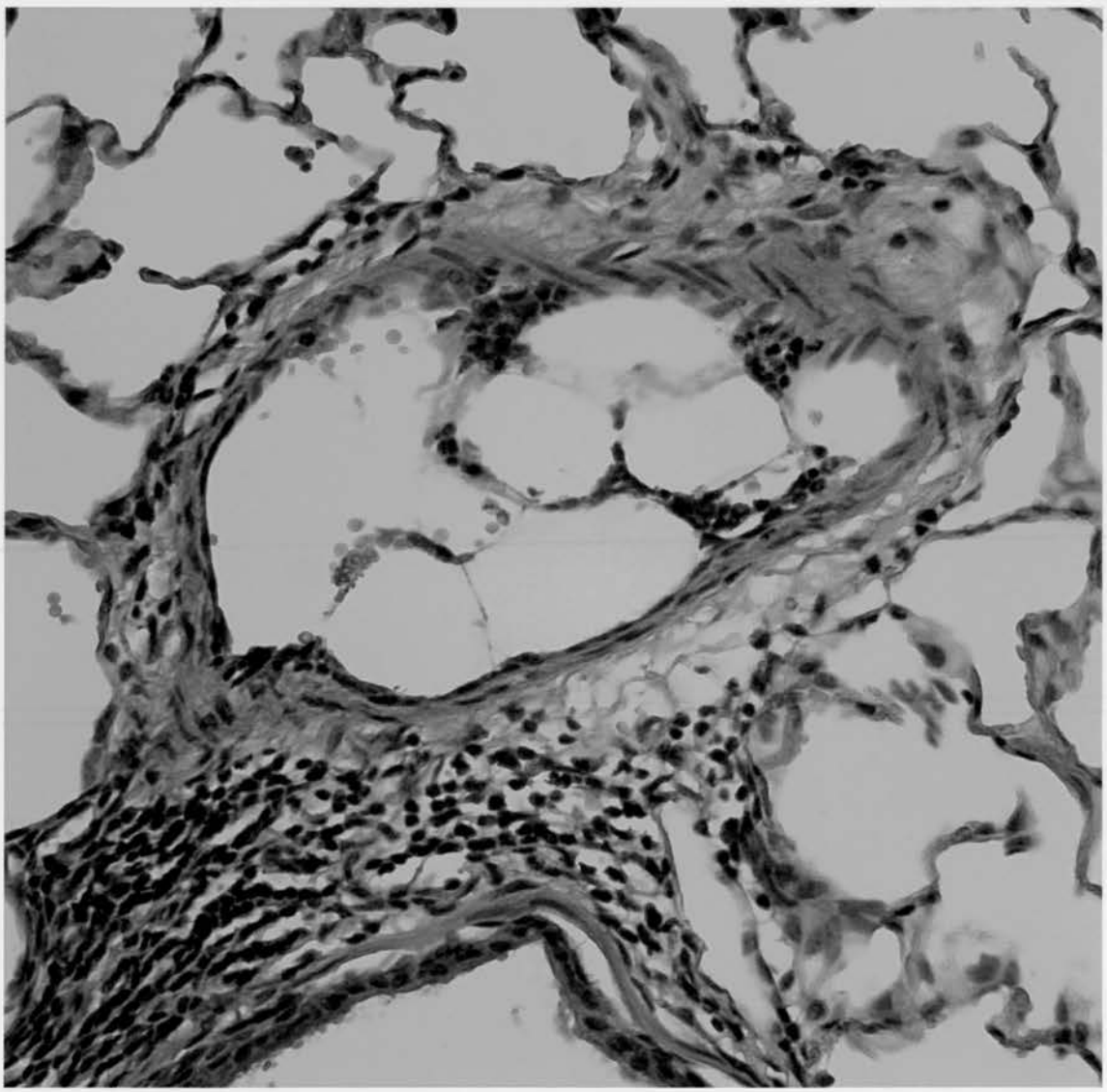


Figure 4.9. Photomicrograph showing embolised thrombus.

Haematoxylin and Eosin stained section of ovine lung parenchyma under light microscopy, showing a pulmonary artery containing by *ante-mortem* thrombus.

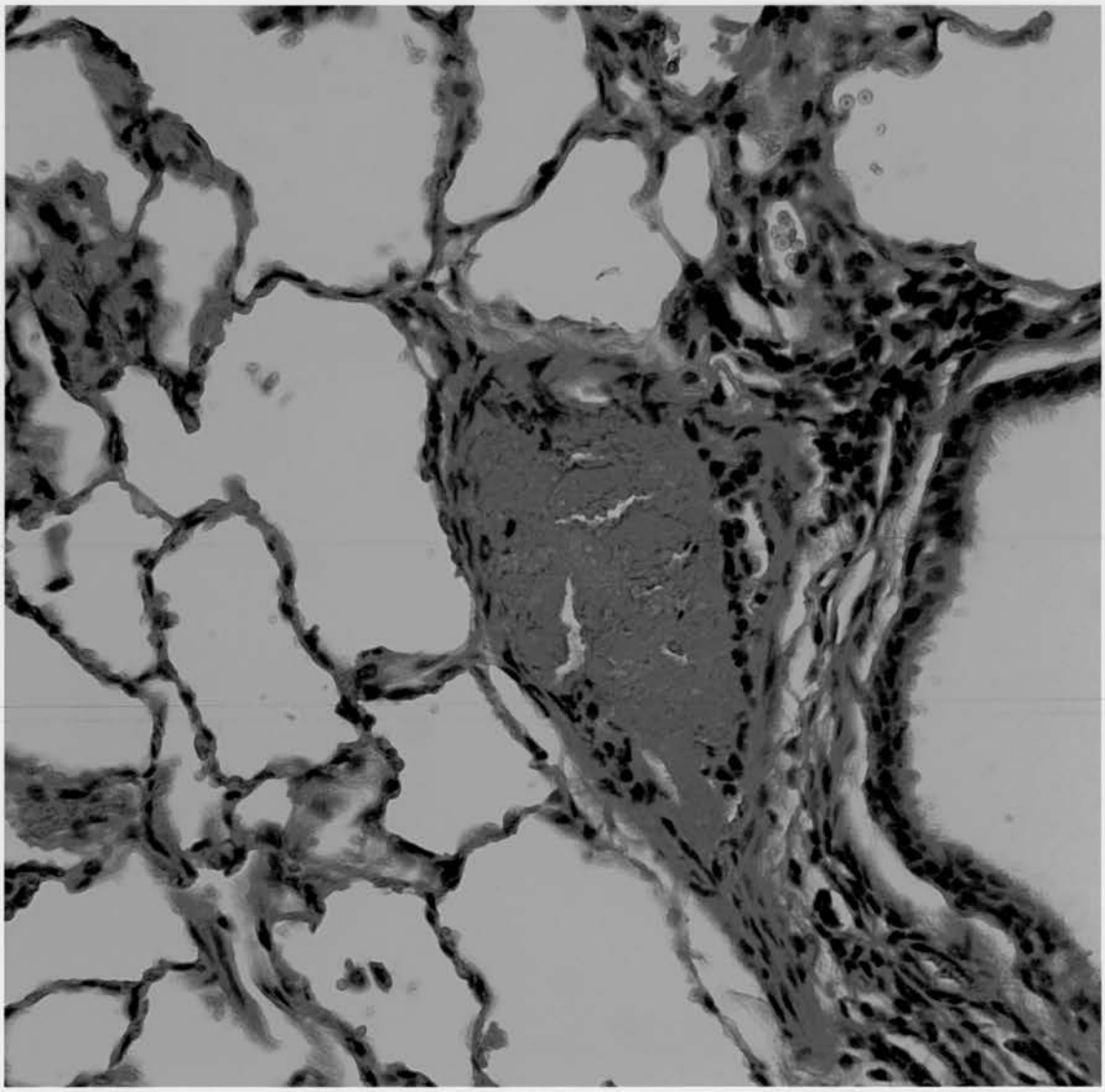
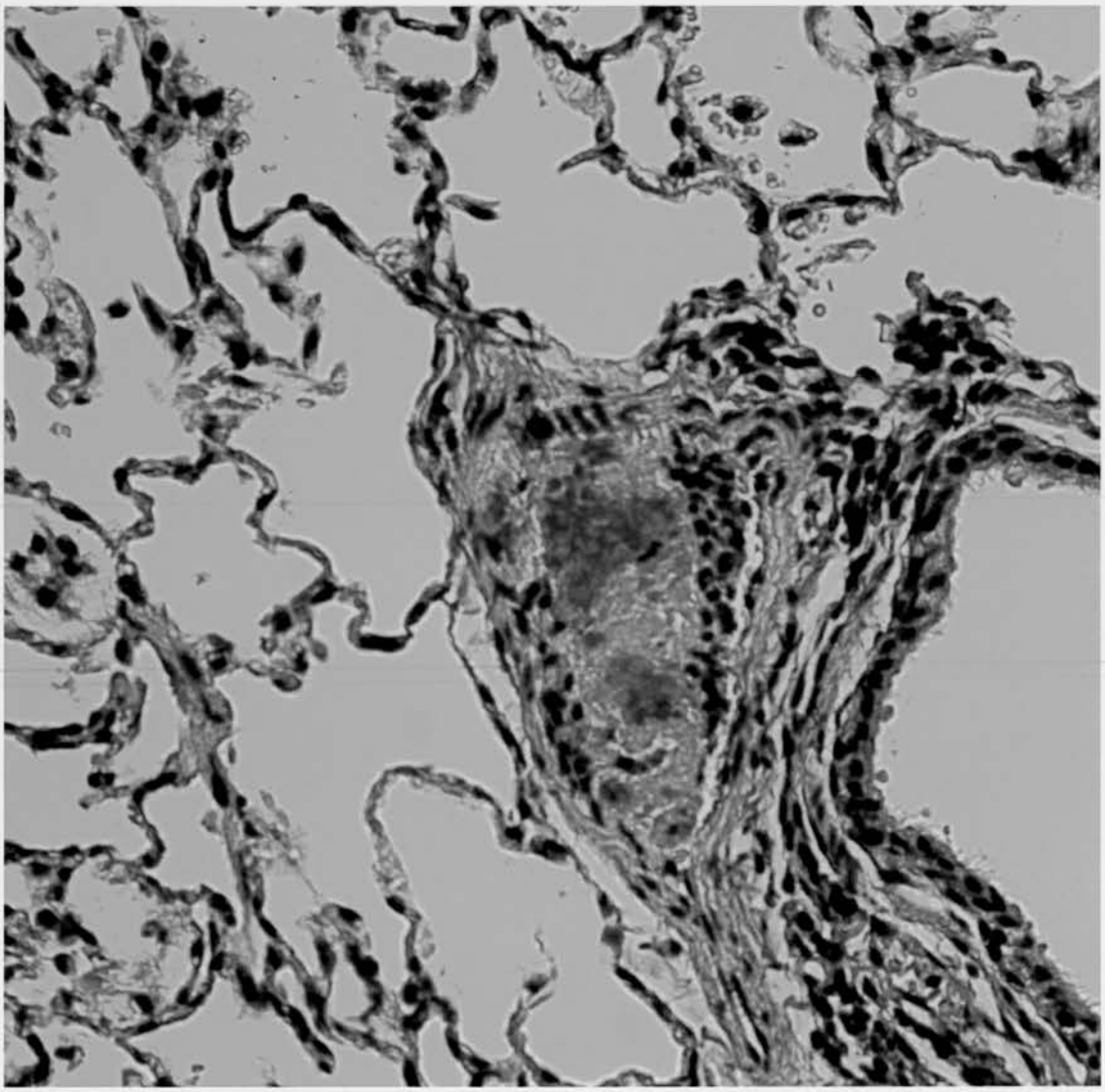


Figure 4.10. Photomicrograph showing embolised marrow contents.
Serial section of ovine lung parenchyma block (stained with H&E in Fig 4.9), stained with Martius Scarlet / Blue, under light microscopy, showing fibrin (red stain) confirming *ante-mortem* thrombus within a pulmonary artery.



Coagulation

Prothrombin time increased over the duration of the experiment in all animals, but there was no significant difference between groups (Fig 4.11). Activated partial prothrombin time did not significantly vary either with time or between groups (Fig 4.12). Both fibrinogen and antithrombin III however, demonstrated a progressive decrease in levels over time (Figs 4.13 and 4.14). This decrease was significantly greater in Groups 2 and 3 than in Group 1 ($p < 0.01$ and $p < 0.001$ respectively). There was not, however, a significant difference between Groups 2 and 3 in the levels of either factor.

Fig 4.11: Change in Prothrombin time

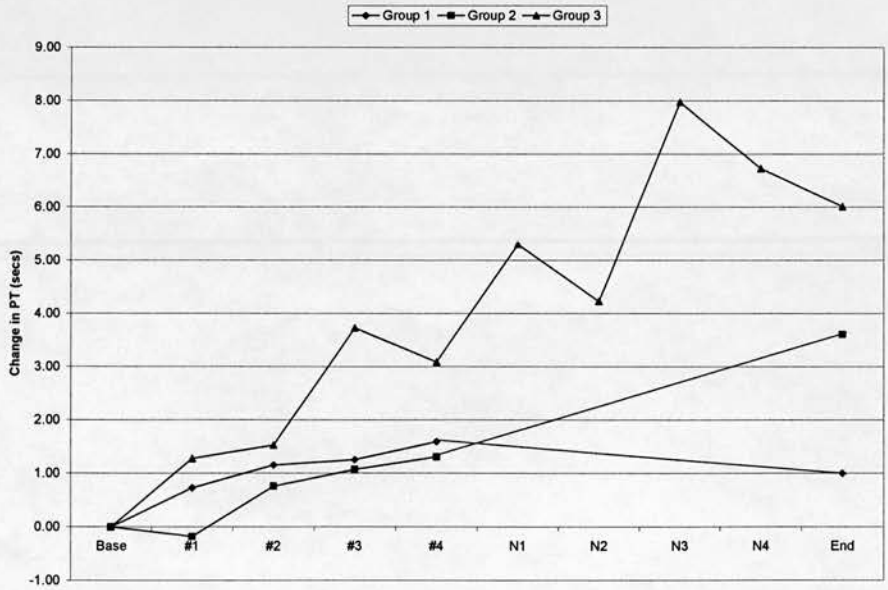


Fig 4.12: Change in APPT

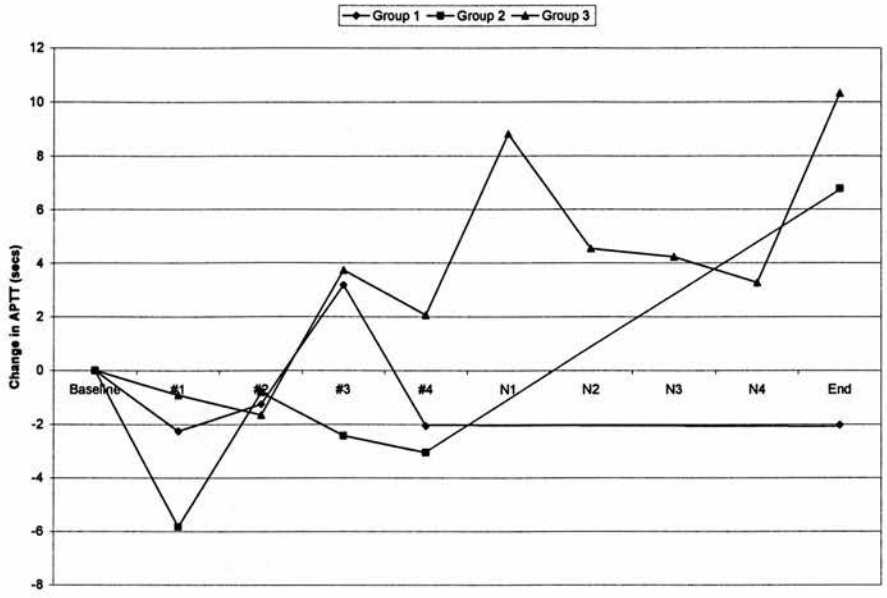


Figure 4.13 : Change in fibrinogen level

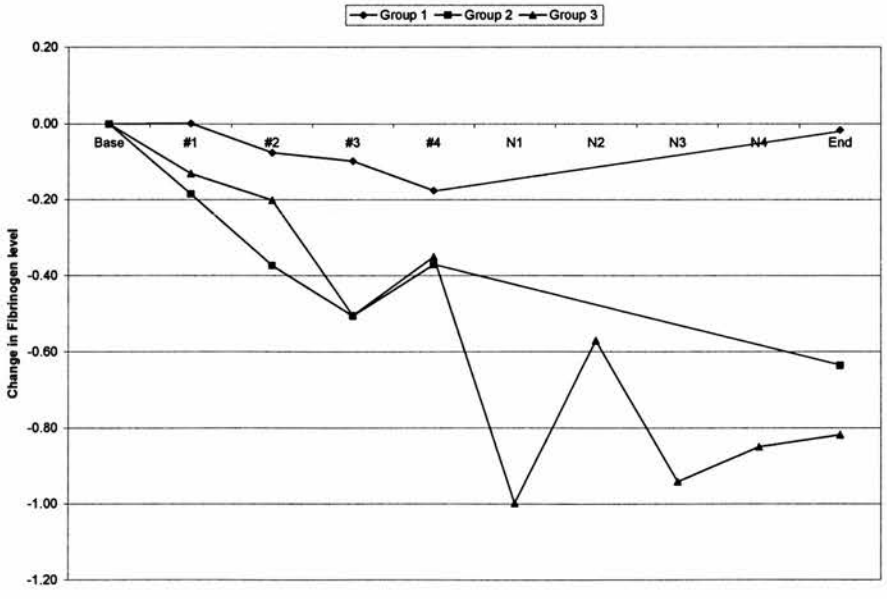
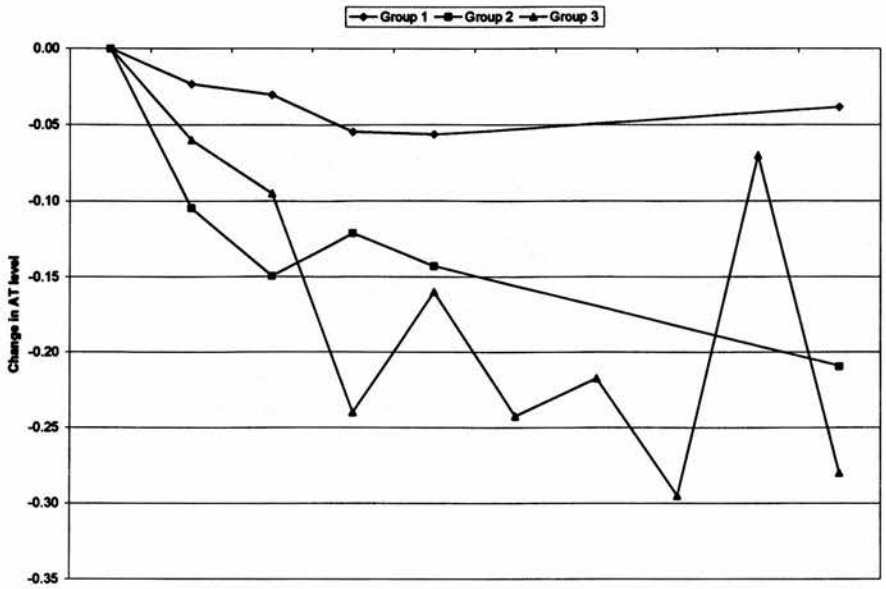


Figure 4.14 : Change in Antithrombin III levels



4.4 DISCUSSION

Overview

Following major traumatic injury in an ovine model, there was an immediate haemodynamic depressant response that was significant and prolonged. This was followed after approximately twenty seconds by demonstrable trans-cardiac embolus. Significant activation of the coagulation system subsequently developed as demonstrated by the consumption of fibrinogen and antithrombin III. These responses were not seen in control animals which underwent general anaesthesia but were not injured. The response was no greater in those animals undergoing injury followed by fracture stabilisation with reamed intramedullary nails, than in those animals exposed to injury alone.

Immediate Haemodynamic Response to Fracture

The immediate haemodynamic response to trauma was depression of both heart rate and blood pressure. This is of interest as nociceptive stimuli are classically associated with sympathetic 'fight or flight' ('alerting' or 'ergotropic') responses mediated by the sympathetic nervous system [216;217].

There are a number of possible physiological mechanisms which may have contributed to this reaction. These include the arterial chemoreceptor reflex, which may in certain circumstances result in bradycardia and hypotension. However, we were not able to demonstrate a fall in arterial oxygenation prior to the observed cardiovascular response, making this unlikely. An alternative explanation would be cardiovascular depression from the anaesthetic agent. However, this is unlikely to be important when considering the rapid fall in heart rate and pressures immediately after fracture encountered in this study. Furthermore, no significant depressant effect of halothane anaesthesia on the control animals was detected (Figs 4.4 (a) to (c) and Fig 4.5 (a) and (c)).

An alternative possible mechanism is the cardiac C-fibre afferent reflex. Although it is unclear what may have stimulated this response in the present study, the sudden movements of the thorax during femoral fracture may have been sufficient to initiate a response. This phenomenon is also termed the von Bezold-Jarisch reflex [218;219] and this label has been expanded to include responses seen in association with shoulder arthroscopy [220], fracture manipulation [221], or even emotion [222;223], and experimental initiation by afferent nerve stimulation and peripheral tissue damage has been described[224-226]. However, each of these reports describes a modification of the cardiovascular response occurring after the generation of haemorrhagic shock and during resuscitation, not an immediate cardiovascular response to injury itself. In this study there was a gradual trend towards reduction in systemic vascular resistance suggesting a reduction in peripheral vascular tone (Fig 4.5 (d)), however this did not reach statistical significance. The lack of statistical significance in the flow data may be a result of small group size or of variation between animals within each group.

This paradoxical tropotropic or withdrawal response effect has also been described occurring in a number of equivalent situations in animals. The Virginian Opossum provides the most dramatic example, exhibiting marked bradycardia, bradypnoea, hypotension, viscid mucus and collapse when confronted by an overwhelmingly threatening or nociceptive stimulus, thus 'playing possum' and escaping predation [227;228]. Similar responses are seen in the animal husbandry of sheep, cattle and deer, where the animal initially resists handling (for example hoof paring) and then suddenly collapses. A single short report exists of a response similar to that reported in the present study, consisting of a reduction in heart rate and both systemic and pulmonary arterial pressures in response to experimental reaming of the femoral canal in dogs [172]. Unfortunately no other details were given in the paper, although the author speculated that a vagal response was operating.

It appears that under certain circumstances an overwhelmingly noxious stimulus invokes a physiological response characterised by sympathetic withdrawal and increased

parasympathetic outflow [222] . It is unclear whether this injury response is identical in humans, but patients presenting with hypotension after trauma may not be purely hypovolaemic, particularly when this response is seen in association with bradycardia, but may be experiencing autonomically-mediated cardiovascular depression. If this could be substantiated clinically, then modulation of this response (for example with anticholinergics) may prove a more effective method of resuscitating these patients than rapid infusion of large volumes of fluid as recommended by the ATLS doctrine [229], and might avoid the fluid overload sequelae that later attend over-infusion.

Comparison with other animal models

Previous animal research in this field has centred on the effect of fracture stabilisation [164;165;167;230-232], in a variety of canine, porcine, ovine and simian models. These models have been directed towards the study of massive fat embolisation during surgery and have centred on the instrumentation and pressurisation of *intact* bones, or following surgical osteotomy. The variables studied have been the effects of different stabilisation techniques (such as plating and nailing), the effects of different reamer or nail design, and the importance of concurrent lung contusion.

The applicability of these models to the investigation of the stress response following traumatic injury may be limited. For example, severe blunt injury to the skin and soft tissues is not encountered in existing models, but skin itself is an important reservoir of pre-formed cytokines [169;170] and the soft tissue injury produces an important stress response which may materially influence outcome [158;171;233]. This severe injury to bone and soft tissue is considered to comprise a physiological 'first hit' stress response with neutrophil activation. A subsequent stimulus such as surgery [52;57;86;87] represents a 'second hit', resulting in a more intense inflammatory response [52;57;86;87]. In order to recreate an element of the first hit, some models have incorporated the creation of haemorrhagic shock by venesection, and with thoracotomy and lymph duct cannulation, following which the animal is allowed to recover consciousness, before canal reaming is

performed forty-eight hours later [138;165;166]. However, the cardiovascular response to haemorrhage alone is markedly different in nature to that following haemorrhage in the presence of tissue injury [178;225]. These techniques in isolation, and the delay between their infliction and bone instrumentation with fat embolism do not appear to replicate closely the clinical situation which pertains to the severely injured patient with traumatic fractures.

The use of intact or osteotomised bones in the study of intramedullary instrumentation produces an artificially extensive fat embolism. This is amplified in some models by the additional application of pressurisation using cement [161-164]. Some authors have attempted incorporate the pressure venting effect of the fracture by creating a surgical osteotomy in the diaphysis [164;232]. However, the experimental effects of osteotomy are unlike those of a fracture: intravascular echocardiography during complete surgical osteotomy reveals only 'a few small embolic particles' [173] in comparison with the prolonged release of larger quantities of embolus seen on high-energy fracture or reaming and nailing [25]. Osteotomy also appears to be ineffective in replicating the effect of traumatic venting: those studies in which an osteotomy has been created do not show any less marked intraosseous pressure rise or embolus release [139;167;173] than those in which the femur has been left intact [20].

Thus existing animal models are not ideally suited to the study of the stress response because they do not recreate the milieu of the first hit, and because they artificially increase the extent of the embolic component of the second hit.

Coagulation activation

Coagulation activation has previously been shown to occur after bone injury in rabbits [231] and sheep [166] as well as human patients [62]. Reamed nailing of the intact femur causes a reduction in fibrinogen [166;231]and antithrombin III [166] levels in both rabbits and sheep. In contrast, unreamed femoral nailing has been shown not to cause a significant decrease

in these levels below baseline [166], and it has been proposed that the degree of reduction is associated with the degree of injury sustained. We have found a significant decrease in both fibrinogen and antithrombin III after fracture alone, suggesting further that models incorporating instrumentation of intact bones may not be entirely appropriate.

Limitations of this study

The sheep was chosen as the most appropriate large animal model for several reasons. The sheep has been used in a number of previous studies (Table 1.6 and 1.7 in Section One, Introduction) providing the basis for comparison. In addition, catheters, transoesophageal probes, reamers and implants designed for human patients are suitable for use in sheep. However, there is a discrepancy in the size of the sheep femur, which is smaller both absolutely and proportionally in comparison with the human femur, and it has been suggested that this may reduce the amount of medullary fat available for embolism[138]. The femur of animals of similar size, such as the pig, is even shorter and is better protected under muscle than the sheep. This would have presented great difficulties in obtaining and stabilising the fractures.

The short duration of the study period (five hours) prevented the study of the later stages of the inflammatory response, and other more direct measures of lung injury.

Grading of the embolic response is necessarily subjective, and previous reports in this field have tended to use simple, all-encompassing, intuitive scales from 0 – 3 [20;139]. The more detailed scoring system used by Ereth and co-workers in their study from the Mayo Clinic[22] allows more in-depth analysis of the nature and extent of the embolism seen and is to be preferred. The embolic events observed in their study of human patients undergoing hip arthroplasty differ from those seen in the current study as they tended to be of greater intensity but shorter duration. This scale was therefore modified to reflect this and provide greater discriminative ability (Table 4.1). Comparison with

previous studies is difficult because of the subjectivity inherent in embolus grading. However, high energy fracture in sheep appears to cause embolism that is of lower initial intensity but of longer duration than that from canal pressurisation during arthroplasty in human patients[22] or animals[234], or that from experimental models of embolus using instrumentation of intact or osteotomised femora[20;43;167;173].

SECTION FIVE

DISCUSSION

The pulmonary and systemic response to trauma involves a number of interlinked physical and chemical processes, and this response is progressively amplified as the activation of each pathway is elaborated, resulting in the development of systemic inflammation and multiple organ failure in a proportion of patients. An understanding of the early phases of the stress response pathway, and the ability to identify patients at high risk of developing complications either from their epidemiological profile, initial observations or from a simple investigation, would potentially allow this response to be attenuated or avoided, thereby reducing the morbidity and mortality from trauma. Possible interventions might include a medical therapy targeted at a key stage of the stress response pathway, given at the scene of injury or at the time of admission, or an alteration in surgical technique in those patients who are at risk of these complications. Three studies were performed in order to address these areas of interest.

Epidemiological study

Several general indicators of the risk of mortality or of developing ARDS after injury have been proposed. While such features as the history of a high energy injury, the presence of multiple injuries, and the clinical findings of physiological instability are well recognised as conferring an increased risk of complications and death, such epidemiological features have not been formally analysed in order to confirm and stratify their significance as predictors of ARDS.

In the epidemiological study described in Section Two, patients with an Injury Severity Score of over 16, patients with a femoral fracture, with combined injuries to the extremities and abdomen and those with compromised physiological observations at admission were each independently found to be at a statistically significantly increased risk of ARDS compared with the remaining patients. This finding confirms that although the overall 'dose' of trauma is the primary feature determining outcome, the presence of a major long bone fracture is a major independent factor in the development of ARDS, and suggests that processes unique to this injury such as medullary fat embolism may represent important components of the stress response (Fig 1.1). As a result, this group of 'at risk' patients was chosen as the study group for the clinical study reported in Section Three. The nature of the fat embolism occurring at the time of fracture was then studied in further detail in the study reported in Section Four.

The significance of abnormal physiological observations on admission in predicting ARDS confirmed in this study emphasises the importance of the 'first hit' response occurring in the period immediately following injury and before medical intervention, where physiological homeostatic mechanisms may rapidly be overwhelmed to the point of decompensation. This response was further investigated in the laboratory study reported in Section Four.

If patients with any of the group of high-risk injuries identified in this study were to have been intensively monitored, over 97% of ARDS cases would have been detected, with the only case not identified by these criteria being a patient with a tibial fracture sustained playing football. Although this demonstrates a very satisfactory sensitivity (97%) and a reasonable specificity (79%), this represents a positive predictive value of only 2.3%. Thus while epidemiological data will assist in identifying patients at increased risk, the use of these criteria has two weaknesses: it erroneously identifies as 'at risk' a large number of patients who do not subsequently develop ARDS, and it fails to identify those cases occurring apparently sporadically following relatively minor

trauma. A more discrete and accurate marker for risk is therefore required if susceptible patients are to be identified accurately at the time of admission, which is the time point of greatest interest, since it is the earliest feasible moment when the patient's clinical and biochemical status can be assessed, and the earliest moment when an intervention could be applied. A second, clinical, study was therefore designed to assess the importance of admission respiratory function and humoral markers of inflammation and coagulation in identifying patients at risk of the later development of complications.

Clinical study

In the clinical study described in Section Three, pulmonary gas exchange and a series of inflammatory and coagulation indices were measured at the time of admission to the Emergency department after trauma, and over the subsequent week. The levels of these markers were tested for correlation with the subsequent development of respiratory complications. In common with the findings of the epidemiological study in Section Two, the severity of injury (as graded by ISS) correlated with the later development of respiratory insufficiency. Unsurprisingly, the presence of respiratory insufficiency at the time of admission also correlated with later respiratory insufficiency. However, none of the measured humoral indices demonstrated a statistically significant correlation with the development of this complication. Only one patient developed ARDS, manifesting with the features of Fat Embolus Syndrome, following a relatively innocuous injury. With the exception of a correlation with soluble intercellular adhesion molecule (sICAM) levels at admission, none of the measured indices were able to identify this patient as being different from the remaining patients with the same injury. The significance of this isolated result is uncertain as sICAM levels in this patient fell to lie within the interquartile range of the remaining patients by the next day. Furthermore, sICAM levels were lowest in the most severely injured patient group who were at the greatest risk of later respiratory insufficiency, and highest in the least severely injured patient group, who had the lowest risk of complications. There has been recent

substantial interest in the role of measurements of other inflammatory markers, and the application of Il-6 measurements in particular has been investigated extensively: Il-6 has been shown to be present in elevated concentrations at the time of presentation after trauma [74;82;83] and to rise further after reamed femoral nailing [80;83]. Although Il-6 levels have not been shown specifically to correlate with the risk of respiratory complications, the combination of excessively elevated Il-6 after trauma and early surgery during the flow phase of the stress response (between days 2 – 4) has been shown to be associated with the development of Multiple Organ Dysfunction Syndrome (MODS) [82], and an increased likelihood of death [81]. A level of 500 pg ml^{-1} has previously been suggested as a 'threshold' level, above which 'damage control' surgery might be advantageous [82]. However, although over a quarter of the patients in the present study suffered impairment of gas exchange postoperatively, none of the patients had levels as high as 500 pg ml^{-1} at any point, and the one patient who did develop ARDS had a much lower level than this (25 pg ml^{-1}) at admission.

On the basis of these results, it has not been possible to propose any additional role for the routine monitoring of inflammatory or coagulation markers for use in the clinical prediction of post-traumatic complications.

The clinical study demonstrated that a measurable stress response with considerable activation of both the inflammatory and coagulation systems is present at the time of admission after trauma, and that this activation increases in a number of cases over the perioperative period. However, because injury to human patients inevitably occurs in an uncontrolled manner outwith the research environment, it was not possible to collect baseline data or make early observations of the development of this response. Moreover, it was not possible to study the impact of the 'second hit' arising from surgical fracture stabilisation in this observational study. A novel animal model was therefore developed to allow the study of the early stress response, and the effect on this response of early long bone reaming and nailing.

Animal study

Major injury resulted in a marked immediate depressant haemodynamic response, consisting of a bradycardia and a fall in pulmonary and systemic blood pressures. This has not previously been described in this context and has a resemblance to other similar reflexes both in animals (such as the 'possum' response) and humans (such as the von Bezold-Jarisch reflex).

Abnormal physiological observations including hypotension on admission were found to be an important predictor of ARDS in the epidemiological study reported in Section Two. If this response is preserved between sheep and humans, and a neurologically-mediated cardiovascular depression is contributory to these impaired parameters, it is possible that this early stimulation of the stress response (as opposed to haemorrhage alone) may be an important factor in the later development of respiratory insufficiency. This may have implications for the resuscitation of patients presenting with hypotension after trauma, particularly where this occurs in association with bradycardia, when sympatomimetic drugs or parasympathetic blockade may be more appropriate therapy than volume replacement alone.

Following the depressant haemodynamic response, a shower of trans-cardiac embolus was seen. This was similar to that seen in clinical studies of humans undergoing long bone intramedullary nailing [25;62], but was of shorter duration. However, the total quantity of the embolus seen after fracture was statistically significantly greater than that seen after the intramedullary stabilisation of these fractures in this model, suggesting that any pulmonary injury precipitated by embolisation may be substantially determined at the time of injury rather than by the subsequent stabilisation of a fracture. The severity of the physiological stress response, in terms of the haemodynamic response, pulmonary gas exchange and systemic coagulation activation detected in the group of animals undergoing fracture stabilisation was indistinguishable from that seen in the

group of animals with injury alone. This is of note when the recent interest in 'Damage Control Orthopaedics' is considered, where the concept of the 'second hit' has in some centres led to a move away from primary intramedullary stabilisation of long bone fractures towards an 'elective' orthopaedic trauma practice based on initial temporary external fixation followed by delayed intramedullary nailing.

5.1 CONCLUSION

The hypothesis (Section 1.8, page 54) has been confirmed in part.

Severe musculoskeletal injury ***does*** produce an identifiable early physiological stress response, which ***does*** have haemodynamic, embolic, inflammatory and coagulation components. The severity and specific anatomical location of this injury ***are*** important in determining the level of risk of subsequent post traumatic respiratory compromise. ***However,*** measurements of the degree of activation of the coagulation and inflammatory components of the stress response at the time of admission ***have not been shown*** to add to the assessment of this level of risk.

SECTION SIX

Future Work

Overview

The ultimate goal of this line of research is to have sufficient understanding of the stress response to trauma, its molecular interactions and pathways, and its genetic basis, to be able to identify patients who are destined to experience important complications after trauma and to be able to intervene in order to attenuate or avoid such complications. This could include therapeutic strategies aimed at reducing the first hit response or at minimising the surgical second hit.

The successful use of recombinant activated protein C (Section 1.5.2) in attenuating the coagulative and inflammatory response to sepsis provides encouragement that a range of similar biological agents can be identified that can be applied to the injured patient. It is not currently possible to speculate as to which component or components would be most applicable to this approach. Interleukin-6 is currently the focus of most attention in this field, but there is some speculation that it may represent a counter-inflammatory cytokine, and it is likely that future attention will be directed elsewhere.

Clinical Research

The interesting clinical course of the patient who unexpectedly developed ARDS in the study reported in Section Three has stimulated interest in the systemic sequelae of Fat Embolus Syndrome. This patient, despite being a highly trained laboratory scientist, and apparently making a full recovery from her complications, has been found to have severe subtle congnitive defects, and her scores for some problem solving functions have

been found to be within the bottom 3% of the population. Another orthopaedic surgeon (Mr Andy Gray MRCS), who has continued this line of work, has investigated this phenomenon in a prospective series of trauma and elective arthroplasty patients, using a trans-cranial Doppler (TCD) scanner to record the quantity of cerebral embolism occurring during surgery, and cognitive testing tools and chemical markers of brain injury to assess the consequence of this embolism. This research will be presented by Mr Gray within a further thesis in the future.

Animal Laboratory Research

(i) Improvements to the model

The model reported in Section Four was effectively a prototype and for practical reasons experiments were limited to five hours in duration. Some physiological processes of interest take longer than this to evolve, and we have therefore addressed this limitation by extending a subsequent series of experiments to twenty-four hours. In addition, the effects of resuscitation from shock have also been addressed in this series of experiments, by allowing the animals to become haemodynamically and biochemically shocked following injury, and then resuscitating them from this state.

We plan to improve the nature of the model by increasing the number of actuators such that bilateral femoral fractures can be caused simultaneously rather than sequentially. We also plan to use TCD to assess transcranial embolism, allowing this to be correlated with *post-mortem* histology.

As bronchio-alveolar lavage has been shown to be helpful in predicting human ARDS [95], we have adopted this technique as a surrogate outcome measure.

We have identified a source of ovine Il-6 enzyme-linked immuno-assays which we have purchased, and by analysing plasma and BAL fluid this will allow us to assess the inflammatory response to injury.

(ii) Further Lines of enquiry

In our subsequent series of extended experiments, (for which the principal investigator was again Mr A Gray), we have investigated the effects of 'damage control orthopaedic surgery' techniques by comparing the effects of intramedullary nailing to the effects of external fixation of the fractures. Our outcome measures were (a) the haemodynamic response, (b) the coagulation response and (c) BAL fluid analysis. The results of these experiments are due to be presented by us in the near future.

We now plan (and have secured funding for) a third series of experiments in which we will trial a new reaming device which aims to reduce the 'second hit' embolic load by aspirating medullary contents into a waste collector, so reducing fat intravasation.

SECTION SEVEN

Publications, prizes and research grants arising from this research

Publications

TO White, Jenkins PJ, Smith RD, Cartlidge CW, Robinson CM.
The epidemiology of posttraumatic adult respiratory distress syndrome.
Journal of Bone & Joint Surgery (Am). 2004 Nov ; 86-A(11):2366-76.

Submitted

T.O. White, R.E. Cluttton, D. Salter, D. Swann, J. Christie, C.M. Robinson
The early response to major trauma and intramedullary nailing.

T.O. White, H. Hannah, C.A. Ludlam, J. Christie, C.M. Robinson
Post-traumatic activation of the coagulation and inflammation systems

Prizes

2004 Michael Turner Prize (Scottish Orthopaedic Meeting paper, First Prize)

2003 Surgeon-in-Training Gold Medal, Royal College of Surgeons, Edinburgh

2003 Roy Petrie Memorial Prize (for research, First Prize)

2003 SE Scotland Research Forum (First Prize, Registrars papers)

Research Grants

2004	£25 000	AO Foundation (awarded to R Clayton and Mr CM Robinson)
2003	£25 000	AO Foundation (awarded to Mr A Gray and Mr CM Robinson)
2003	£ 6 000	Royal College of Surgeons of Edinburgh
2003		Scottish Orthopaedic Research Trust (SORT-IT) Fellowship
2001	£40 000	Wishbone Trust

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Professor AHRW Simpson, who provided advice and reviewed the manuscript.

Section 2.

Dr Richard Smith, Medical Statistician, Scottish Trauma Audit Group, performed and advised on the preparation of the statistical results.
Dr Paul Jenkins, SHO in Accident and Emergency Medicine, collected much of the data and initially conducted the project.

Section 3.

Professor CA Ludlam MD, FRCP, advised and collaborated on the project.
Pam Dawson performed the assays.
Dr Jim Ross, Reader in Surgery at the University of Edinburgh, who provided bench space for processing the blood samples taken.
Miss Hayley Hannah, MRCS, Research Fellow, who assisted in obtaining blood samples
Dr Rob Elton, Medical Statistician, advised on the preparation of the statistical results
The Scottish Orthopaedic Research Trust into Trauma (SORT-IT) provided salary funding.
The Wishbone Trust funded the consumables used in the study.

Section 4.

Dr Rob Elton, Medical Statistician, advised on the preparation of the statistical results.
Dr Alistair Lee, Consultant Anaesthetist and Intensivist, Royal Infirmary of Edinburgh, and Mr Paul Dark, Clinical Lecturer and Honorary Consultant Intensivist, University of Manchester, provided advice on physiology and reviewed the manuscript.
Dr Donald Salter, Reader in Pathology, advised on and reviewed the tissue specimens processed by his department.
Mrs Joan Docherty, provided animal welfare advice and sheep husbandry.
Mr Brendan Hawes BEng, built the 'comminuter' and assisted in running the experiments.
Philips Medical Systems provided the transoesophageal echo probe and scanner.
Edwards Lifesciences provided the continuous cardiac output monitor.
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REFERENCES

1. Gener al Register Office for Scotland. GROS - Causes of death 2000 Annual Report. General Register Office for Scotland . 2003.

2. Bake r CC, Oppenheimer L, Stephens B, Lewis FR, Trunkey DD. Epidemiology of trauma deaths. *Am.J Surg* 1980;**140**:144-50.

3. W yatt JP, Beard D, Gray A, Busuttil A, Robertson CE. Rate, causes and prevention of deaths from injuries in south-east Scotland. *Injury* 1996;**27**:337-40.

4. Moed BR, Bo yd DW, Andring RE. Clinically inapparent hypoxemia after skeletal injury. The use of the pulse oximeter as a screening method. *Clin Orthop* 1993;269-73.

5. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome: prospective evaluation in 92 fracture patients. *Crit Care Med* 1990;**18**:42-6.

6. Riseborough EJ,.Herndo n JH. Alterations in pulmonary function, coagulation and fat metabolism in patients with fractures of the lower limbs. *Clin Orthop* 1976;248-67.

7. Rogers FB, Shackford SR, Trevisani GT, Davis JW, Mackersie RC, Hoyt DB. Neurogenic pulmonary edema in fatal and nonfatal head injuries. *J Trauma* 1995;**39**:860-6.

8. Yentis S, Hirsch N, S mith G. Anaesthesia and Intensive Care A-Z, an encyclopaedia of principles and practice. Oxford: Butterworth Heineman, 2000.

9. L umb A. Nunn's Applied Respiratory Physiology. Oxford: Butterworth Heinemann, 2000.

10. Fabian TC. Un ravelling the fat embolism syndrome. *N.Engl.J Med* 1993;**329**:961-3.

11. L evy D. The fat embolism syndrome. A review. *Clin Orthop* 1990;281-6.

12. ten Duis HJ, Nijsten M W, Klasen HJ, Binnendijk B. Fat embolism in patients with an isolated fracture of the femoral shaft. *J Trauma* 1988;**28**:383-90.

13. Hulman G. Pathog enesis of non-traumatic fat embolism. *Lancet* 1988;**1**:1366-7.

14. Peltier LF. Fat embolism. An appraisal of the problem. *Clin Orthop* 1984;3-17.

15. Beck J,.Collins J. Theoretical and clinical aspects of posttraumatic fat embolism syndrome. *American Academy of Orthopedic Surgeons: Instructional Course Lectures* 1973;38-87.

16. Hulman G. The patho genesis of fat embolism. *J Pathol.* 1995;**176**:3-9.

17. Sauter AJ,.Klopper PJ. Fat embolism after static a nd dynamic load. An experimental investigation. *Acta Orthop Scand.* 1983;**54**:94-100.

18. Gitin TA, Seidel T, Cera PJ, Glidewell OJ, Smith JL. Pulmonary microvascular fat: the significance? *Crit Care Med* 1993;**21**:673-7.

19. Sevitt S. Fat Embolism. I n Clar, C, Badger F, Sevitt S, eds. *Modern Trends in Accident Surgery and Medicine*, pp 214-27. London: Butterworth & CoF, 1959.

20. Wozasek GE, Simon P, Redl H, Schlag G. Intramedullary pressure changes and fat intravasation during intramedullary nailing: an experimental study in sheep. *J Trauma* 1994;**36**:202-7.

21. Robinson CM. Current concepts of respi ratory insufficiency syndromes after fracture. *J Bone Joint Surg Am* 2001;**83-B**:781-91.

22. Ereth MH, Weber JG, A bel MD, Lennon RL, Lewallen DG, Ilstrup DM *et al.* Cemented versus noncemented total hip arthroplasty--embolism, hemodynamics, and intrapulmonary shunting. *Mayo Clin Proc.* 1992;**67**:1066-74.

23. Bake r PL, Pazell JA, Peltier LF. Free fatty acids, catecholamines, and arterial hypoxia in patients with fat embolism. *J Trauma* 1971;**11**:1026-30.

24. Kerstell J. Pathogenesis of post-traumatic fat embolism. *Am.J Surg* 1971;**121**:712-5.

25. Pell AC, Christie J, Keating JF, Sutherland GR. The detection of fat embolism by transoesophageal echocardiography during reamed intramedullary nailing. A study of 24 patients with femoral and tibial fractures. *J Bone Joint Surg Br* 1993;**75**:921-5.

26. Pell AC, Hughes D, Keating J, Christie J, Busuttil A, Sutherland GR. Brief report: fulminating fat embolism syndrome caused by paradoxical embolism through a patent foramen ovale. *N.Engl.J Med* 1993;**329**:926-9.

27. Malik AB. Pulmonar y microembolism. *Physiol Rev.* 1983;**63**:1114-207.

28. Jones JG, Minty BD, Beeley JM, Royston D, Crow J, Grossman RF. Pulmonary epithelial permeability is immediately increased after embolisation with oleic acid but not with neutral fat. *Thorax* 1982;**37**:169-74.

29. Christie J. The coagulati ve effects of fat embolisation during intramedullary manipulative procedures. *Techniques in Orthopaedics* 1996;**11**:14-7.

30. Pape HC, G iannoudis PV, Grimme K, van Griensven M, Krettek C. Effects of intramedullary femoral fracture fixation: what is the impact of experimental studies in regards to the clinical knowledge? *Shock* 2002;**18**:291-300.

31. Saldeen T. Intravascular coagulation in the lungs in experimental fat embolism. *Acta Chir Scand.* 1969;**135**:653-62.

32. Saldeen T. The importan ce of intravascular coagulation and inhibition of the fibrinolytic system in experimental fat embolism. *J Trauma* 1970;**10**:287-98.

33. Solowa y HB, Robinson EF, Sleeman HK, Huyser KL, Hufnagel HV. Resolution of experimental fat embolism. *Arch.Pathol.* 1970;**90**:230-4.

34. Weisz G. Fat Embolism. *Current Problems in Surgery* 1974;1-54.

35. Chastre J, Fagon JY, Soler P, Fich elle A, Dombret MC, Huten D *et al.* Bronchoalveolar lavage for rapid diagnosis of the fat embolism syndrome in trauma patients. *Ann.Intern.Med* 1990;**113**:583-8.

36. Schinella RA. Bone ma rrow emboli. Their fate in the vasculature of the human lung. *Arch.Pathol.* 1973;**95**:386-91.

37. Gurd AR,.Wi lson RI. The fat embolism syndrome. *J Bone Joint Surg Br* 1974;**56B**:408-16.

38. L indeque BG, Schoeman HS, Dommisse GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. *J Bone Joint Surg Br* 1987;**69**:128-31.

39. Rokkanen P, Lahdensuu M, Kataja J, Julkunen H. The syndrome of fat embolism: analysis of thirty consecutive cases compared to trauma patients with similar injuries. *J Trauma* 1970;**10**:299-306.

40. ten Duis HJ. The fat embolism s yndrome. *Injury* 1997;**28**:77-85.

41. Ha gley SR. The fulminant fat embolism syndrome. *Anaesth.Intensive Care* 1983;**11**:162-6.

42. Robert JH, Hoffme yer P, Broquet PE, Cerutti P, Vasey H. Fat embolism syndrome. *Orthop Rev.* 1993;**22**:567-71.

43. Wenda K, Runkel M, De greif J, Ritter G. Pathogenesis and clinical relevance of bone marrow embolism in medullary nailing--demonstrated by intraoperative echocardiography. *Injury* 1993;**24 Suppl 3**:S73-S81.

44. Scientific Foundations o f Trauma. 2005.

45. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. *J.Trauma* 1994;**37**:881-7.

46. Catania RA, Schwach a MG, Cioffi WG, Bland KI, Chaudry IH. Does uninjured skin release proinflammatory cytokines following trauma and hemorrhage? *Arch.Surg.* 1999;**134**:368-73.

47. Kim PK,.Deutschman CS. Inflammatory responses and mediators. *Surg Clin North Am.* 2000;**80**:885-94.

48. Pallister I. The effects of surgical fracture fixation on the systemic inflammatory response to major trauma. *Journal of the American Academy of Orthopaedic Surgeons* 2005;**13**:93-100.

49. Bern ard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L *et al.* Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. *J Crit Care* 1994;**9**:72-81.

50. Bone RC, B alk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;**101**:1644-55.

51. Boontham P, Chandran P , Rowlands B, Eremin O. Surgical Sepsis: dysregulation of immune function and therapeutic implications. *The Surgeon: Journal of the Royal College of Surgeons of Edinburgh* 2003;**1**:187-206.

52. Partrick DA, Moor e FA, Moore EE, Biffl WL, Sauaia A, Barnett CC, Jr. Jack A. Barney Resident Research Award winner. The inflammatory profile of interleukin-6, interleukin-8, and soluble intercellular adhesion molecule-1 in postinjury multiple organ failure. *Am.J Surg* 1996;**172**:425-9.

53. Kerr R, Stirling D, Ludlam CA. Interleukin 6 and haemostasis. *Br.J.Haematol.* 2001;**115**:3-12.

54. Pallister I, Dent C, Topley N. Increased neutrophil migratory activity after major trauma: a factor in the etiology of acute respiratory distress syndrome? *Crit Care Med.* 2002;**30**:1717-21.

55. Cho llet-Martin S, Montravers P, Gibert C, Elbim C, Desmonts JM, Fagon JY *et al*. High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. *Infect.Immun.* 1993;**61**:4553-9.

56. Giannoudis, P . V., Perry, S, and Smith, R. M. Systemic response to trauma. Current Orthopaedics 15, 176-183. 2001.

57. Botha AJ, Moore FA , Moore EE, Sauaia A, Banerjee A, Peterson VM. Early neutrophil sequestration after injury: a pathogenic mechanism for multiple organ failure. *J.Trauma* 1995;**39**:411-7.

58. Mastran gelo AM, Jeitner TM, Eaton JW. Oleic acid increases cell surface expression and activity of CD11b on human neutrophils. *J.Immunol.* 1998;**161**:4268-75.

59. Wagner JG,.Roth RA. Neutrophil migration mech anisms, with an emphasis on the pulmonary vasculature. *Pharmacol.Rev.* 2000;**52**:349-74.

60. Doerschuk CM, Tas aka S, Wang Q. CD11/CD18-dependent and -independent neutrophil emigration in the lungs: how do neutrophils know which route to take? *Am.J.Respir.Cell Mol.Biol.* 2000;**23**:133-6.

61. Russell JA. Genetics of coagulation factors in acute lung injury. *Crit Care Med.* 2003;**31**:S243-S247.

62. Robinson CM, Ludlam C A, Ray DC, Swann DG, Christie J. The coagulative and cardiorespiratory responses to reamed intramedullary nailing of isolated fractures. *J.Bone Joint Surg.Br.* 2001;**83**:963-73.

63. Gando S. Disseminated intravascula r coagulation in trauma patients. *Semin.Thromb.Hemost.* 2001;**27**:585-92.

64. Mac Leod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J.Trauma* 2003;**55**:39-44.

65. Bern ard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N.Engl.J Med* 2001;**344**:699-709.

66. Uchiba M, Okajima K, Murakami K. Effects of various doses of antithrombin III on endotoxin-induced endothelial cell injury and coagulation abnormalities in rats. *Thromb.Res.* 1998;**89**:233-41.

67. L aterre PF, Wittebole X, Dhainaut JF. Anticoagulant therapy in acute lung injury. *Crit Care Med.* 2003;**31**:S329-S336.

68. Seeg er W, Hubel J, Klapettek K, Pison U, Obertacke U, Joka T *et al.* Procoagulant activity in bronchoalveolar lavage of severely traumatized patients--relation to the development of acute respiratory distress. *Thromb.Res.* 1991;**61**:53-64.

69. I dell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. *Crit Care Med.* 2003;**31**:S213-S220.

70. Pallister I, Gosling P, Alpar K, Bradley S. Prediction of posttraumatic adult respiratory distress syndrome by albumin excretion rate eight hours after admission. *J.Trauma* 1997;**42**:1056-61.

71. Giannoudis PV. Current concepts of the infl ammatory response after major trauma: an update. *Injury* 2003;**34**:397-404.

72. Napolitano LM, Ferrer T, McCarter RJ, Jr., Scalea TM. Systemic inflammatory response syndrome score at admission independently predicts mortality and length of stay in trauma patients. *J Trauma* 2000;**49**:647-52.

73. Giannoudis PV, Pape HC, Cohen AP, Krettek C, Smith RM . Review: systemic effects of femoral nailing: from Kuntscher to the immune reactivity era. *Clin.Orthop.* 2002;378-86.

74. Giannoudis PV, Smith R M, Banks RE, Windsor AC, Dickson RA, Guillou PJ. Stimulation of inflammatory markers after blunt trauma. *Br J Surg* 1998;**85**:986-90.

75. Nast -Kolb D, Waydhas C, Gippner-Steppert C, Schneider I, Trupka A, Ruchholtz S *et al.* Indicators of the posttraumatic inflammatory response correlate with organ failure in patients with multiple injuries. *J.Trauma* 1997;**42**:446-54.

76. Giannoudis PV, Smith R M, Windsor AC, Bellamy MC, Guillou PJ. Monocyte human leukocyte antigen-DR expression correlates with intrapulmonary shunting after major trauma. *Am.J Surg* 1999;**177**:454-9.

77. Smith RM, Giannoudis PV, Bellamy MC, Perry SL, Dickson RA, Guillou PJ. Interleukin-10 release and monocyte human leukocyte antigen-DR expression during femoral nailing. *Clin Orthop* 2000;233-40.

78. Tan LR, Waxman K, Scannell G, Ioli G, Granger GA. Trauma causes early release of soluble receptors for tumor necrosis factor. *J Trauma* 1993;**34**:634-8.

79. Pape HC, Schmidt RE, R ice J, van Griensven M, das GR, Krettek C *et al.* Biochemical changes after trauma and skeletal surgery of the lower extremity: quantification of the operative burden. *Crit Care Med.* 2000;**28**:3441-8.

80. Pape HC, Grimme K, va n Griensven M, Sott AH, Giannoudis P, Morley J *et al.* Impact of intramedullary instrumentation versus damage control for femoral fractures on immunoinflammatory parameters: prospective randomized analysis by the EPOFF Study Group. *J.Trauma* 2003;**55**:7-13.

81. Pape HC, Remmers D, G rotz M, Schedel I, von Glinski S, Oberbeck R *et al.* Levels of antibodies to endotoxin and cytokine release in patients with severe trauma: does posttraumatic dysergy contribute to organ failure? *J.Trauma* 1999;**46**:907-13.

82. Pape HC, van Griensv en M, Rice J, Gansslen A, Hildebrand F, Zech S *et al.* Major secondary surgery in blunt trauma patients and perioperative cytokine liberation: determination of the clinical relevance of biochemical markers. *J.Trauma* 2001;**50**:989-1000.

83. Giannoudis PV, Smith R M, Bellamy MC, Morrison JF, Dickson RA, Guillou PJ. Stimulation of the inflammatory system by reamed and unreamed nailing of femoral fractures. An analysis of the second hit. *J.Bone Joint Surg.Br.* 1999;**81**:356-61.

84. Maekaw a K, Futami S, Nishida M, Terada T, Inagawa H, Suzuki S *et al.* Effects of trauma and sepsis on soluble L-selectin and cell surface expression of L-selectin and CD11b. *J Trauma* 1998;**44**:460-8.

85. Wa ydhas C, Nast-Kolb D, Trupka A, Zettl R, Kick M, Wiesholler J *et al.* Posttraumatic inflammatory response, secondary operations, and late multiple organ failure. *J Trauma* 1996;**40**:624-30.

86. Zallen G, Moore EE, Johnson JL, Tamura DY, Aiboshi J, Biffl WL *et al.* Circulating postinjury neutrophils are primed for the release of proinflammatory cytokines. *J Trauma* 1999;**46**:42-8.

87. Botha AJ, Moore FA , Moore EE, Kim FJ, Banerjee A, Peterson VM. Postinjury neutrophil priming and activation: an early vulnerable window. *Surgery* 1995;**118**:358-64.

88. Bahtia, R, Pallister, I., Dent, C, Jones, SA, and Topley, N. Modulation of Interleukin-8 mediated neutrophil migration following major lower limb fracture and operative stabilisation. European Journal of Trauma . 2005.

89. Meng es T, Hermans PW, Little SG, Langefeld T, Boning O, Engel J *et al.* Plasminogen-activator-inhibitor-1 4G/5G promoter polymorphism and prognosis of severely injured patients. *Lancet* 2001;**357**:1096-7.

90. Seligsohn U,. Lubetsky A. Genetic susceptibility to venous thrombosis. *N.Engl.J.Med.* 2001;**344**:1222-31.

91. Rasmussen TE, Hallett J W, Jr., Metzger RL, Richardson DM, Harmsen WS, Goronzy JJ *et al.* Genetic risk factors in inflammatory abdominal aortic aneurysms: polymorphic residue 70 in the HLA-DR B1 gene as a key genetic element. *J.Vasc.Surg.* 1997;**25**:356-64.

92. Woo P. C ytokine polymorphisms and inflammation. *Clin.Exp.Rheumatol.* 2000;**18**:767-71.

93. Skoog T, van 't Hooft FM, Kallin B, Jovinge S, Boquist S, Nilsson J *et al.* A common functional polymorphism (C-->A substitution at position -863) in the promoter region of the tumour necrosis factor-alpha (TNF-alpha) gene associated with reduced circulating levels of TNF-alpha. *Hum.Mol.Genet.* 1999;**8**:1443-9.

94. Hirani N, Antonicelli F, Strieter RM, Wiesener MS, Ratcliffe PJ, Haslett C *et al.* The regulation of interleukin-8 by hypoxia in human macrophages--a potential role in the pathogenesis of the acute respiratory distress syndrome (ARDS). *Mol.Med.* 2001;**7**:685-97.

95. Donnell y SC, Strieter RM, Kunkel SL, Walz A, Robertson CR, Carter DC *et al.* Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. *Lancet* 1993;**341**:643-7.

96. Orell SR. Lung pathology in respiratory distress following shock in the adult. *Acta Pathol.Microbiol.Scand.[A]* 1971;**79**:65-76.

97. Goodman PC. Radiograp hic findings in patients with acute respiratory distress syndrome. *Clin Chest Med* 2000;**21**:419-33, vii.

98. Tomashefski JF, Jr. Pulm onary pathology of acute respiratory distress syndrome. *Clin Chest Med* 2000;**21**:435-66.

99. Steinberg KP,.Hudson LD. Acute lung injury and acute respiratory distress syndrome. The clinical syndrome. *Clin Chest Med* 2000;**21**:401-17, vii.

100. Baldwin SR, Simon RH, Grum CM, Ketai LH, Boxer LA, Devall LJ. Oxidant activity in expired breath of patients with adult respiratory distress syndrome. *Lancet* 1986;**1**:11-4.

101. Croce MA, Fabian TC, Davis KA, Gavin TJ. Early and late acute respiratory distress syndrome: two distinct clinical entities. *J Trauma* 1999;**46**:361-6.

102. Riska EB, von Bonsdorff H, Hakkinen S, Jaroma H, Kiviluoto O, Paavilainen T. Prevention of fat embolism by early internal fixation of fractures in patients with multiple injuries. *Injury* 1976;**8**:110-6.

103. Johnson KD, Cadambi A, Seibert GB. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma* 1985;**25**:375-84.

104. Pape HC, Auf 'm'Kolk M, Paffrath T, Regel G, Sturm JA, Tscherne H. Primary intramedullary femur fixation in multiple trauma patients with associated lung contusion--a cause of posttraumatic ARDS? *J Trauma* 1993;**34**:540-7.

105. L ewandowski K, Metz J, Deutschmann C, Preiss H, Kuhlen R, Artigas A *et al.* Incidence, severity and mortality of acute respiratory distress failure in Berlin. *American Journal of Respiratory Critical Care Medicine* 1995;**151**:1121-5.

106. L uhr OR, Antonsen K, Karlsson M, Aardal S, Thornsteinsson A, Frostell CG *et al.* Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweeden, Denmark and Iceland. *American Journal of Respiratory Critical Care Medicine* 1999;**159**:1849-61.

107. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *American Journal of Respiratory Critical Care Medicine* 2002;**165**:443-8.

108. Cohn SM. Pul monary contusion: review of the clinical entity. *J.Trauma* 1997;**42**:973-9.

109. Pape HC, Remmers D, R ice J, Ebisch M, Krettk C, Tscherne H. Appraisal of early evaluation of blunt chest trauma; Development of a standardised scoring system for initial decision making. *Journal of Trauma - Injury, Infection and Critical Care* 2000;**49**:496-504.

110. Pape HC, Giannoudis P, Krettek C. The timing of fracture treatment in polytrauma patients: relevance of damage control orthopedic surgery. *Am.J.Surg.* 2002;**183**:622-9.

111. Bone LB, Babikian G, Stegemann PM. Femoral canal reaming in the polytrauma patient with chest injury. A clinical perspective. *Clin Orthop* 1995;91-4.

112. Bone LB, Anders MJ, Rohrbacher BJ. Treatment of femoral fractures in the multiply injured patient with thoracic injury. *Clin Orthop* 1998;57-61.

113. Bosse MJ, MacKenzie E J, Riemer BL, Brumback RJ, McCarthy ML, Burgess AR *et al.* Adult respiratory distress syndrome, pneumonia, and mortality following thoracic injury and a femoral fracture treated either with intramedullary nailing with reaming or with a plate. A comparative study. *J Bone Joint Surg Am.* 1997;**79**:799-809.

114. van Os JP, Roumen RM, Schoots FJ, Heystraten FM, Goris RJ. Is early osteosynthesis safe in multiple trauma patients with severe thoracic trauma and pulmonary contusion? *J Trauma* 1994;**36**:495-8.

115. Carlson DW, Rodman GH, Jr., Kaehr D, H age J, Misinski M. Femur fractures in chest-injured patients: is reaming contraindicated? *J Orthop Trauma* 1998;**12**:164-8.

116. van der Mad e WJ, Smit EJ, van Luyt PA, van Vugt AB. Intramedullary femoral osteosynthesis: an additional cause of ARDS in multiply injured patients? *Injury* 1996;**27**:391-3.

117. Boulan ger BR, Stephen D, Brenneman FD. Thoracic trauma and early intramedullary nailing of femur fractures: are we doing harm? *J Trauma* 1997;**43**:24-8.

118. Re ynolds MA, Richardson JD, Spain DA, Seligson D, Wilson MA, Miller FB. Is the timing of fracture fixation important for the patient with multiple trauma? *Ann.Surg* 1995;**222**:470-8.

119. Riska EB, von Bonsdo rff H, Hakkinen S, Jaroma H, Kiviluoto O, Paavilainen T. Primary operative fixation of long bone fractures in patients with multiple injuries. *J Trauma* 1977;**17**:111-21.

120. Editorial Comment. *J.Trauma* 1982;**22**:894.

121. Winquist RA. 2003. Personal Communication

122. Tachak ra SS,.Sevitt S. Hypoxaemia after fractures. *J.Bone Joint Surg.Br.* 1975;**57**:197-203.

123. Behrm an SW, Fabian TC, Kudsk KA, Taylor JC. Improved outcome with femur fractures: early vs. delayed fixation. *J Trauma* 1990;**30**:792-7.

124. Svenningsen S, Ness e O, Finsen V, Hole A, Benum P. Prevention of fat embolism syndrome in patients with femoral fractures--immediate or delayed operative fixation? *Ann.Chir Gynaecol.* 1987;**76**:163-6.

125. Rogers FB, Shackford SR, Vane DW, Kaups KL, Harris F. Prompt fixation of isolated femur fractures in a rural trauma center: a study examining the timing of fixation and resource allocation. *J Trauma* 1994;**36**:774-7.

126. Seibel R, LaDuca J, Hassett JM, Babikian G, Mills B, Border DO *et al.* Blunt multiple trauma (ISS 36), femur traction, and the pulmonary failure-septic state. *Ann.Surg* 1985;**202**:283-95.

1 27. Bone LB, McNamara K, Shine B, Border J. Mortality in multiple trauma patients with fractures. *J Trauma* 1994;**37**:262-4.

128. Charash WE, Fabian TC, Croce MA. Delayed surgical fixation of femur fractures is a risk factor for pulmonary failure independent of thoracic trauma. *J Trauma* 1994;**37**:667-72.

129. Pinne y SJ, Keating JF, Meek RN. Fat embolism syndrome in isolated femoral fractures: does timing of nailing influence incidence? *Injury* 1998;**29**:131-3.

130. Talucci RC, Manning J, L ampard S, Bach A, Carrico CJ. Early intramedullary nailing of femoral shaft fractures: a cause of fat embolism syndrome. *Am.J Surg* 1983;**146**:107-11.

131. Meek RN, Vivoda EE, Pi rani S. Comparison of mortality of patients with multiple injuries according to type of fracture treatment--a retrospective age- and injury-matched series. *Injury* 1986;**17**:2-4.

132. L ozman J, Deno DC, Feustel PJ, Newell JC, Stratton HH, Sedransk N *et al.* Pulmonary and cardiovascular consequences of immediate fixation or conservative management of long-bone fractures. *Arch.Surg* 1986;**121**:992-9.

133. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am.* 1989;**71**:336-40.

134. Olson SA. Earl y versus delayed stabilization of femoral fractures. *J.Bone Joint Surg.Am.* 2003;**85-A**:1394.

135. Phillips TF,.Contreras DM. Timing of oper ative treatment of fractures in patients who have multiple injuries. *J Bone Joint Surg Am.* 1990;**72**:784-8.

136. Schoffel U, Bonnaire F, van Specht BU, Kuner EH. Monitoring the response to injury. *Injury* 1991;**22**:377-82.

137. Pape HC, Reg el G, Dwenger A, Krumm K, Schweitzer G, Krettek C *et al.* Influences of different methods of intramedullary femoral nailing on lung function in patients with multiple trauma. *J Trauma* 1993;**35**:709-16.

138. Pape HC, Dwen ger A, Grotz M, Kaever V, Negatsch R, Kleemann W *et al.* Does the reamer type influence the degree of lung dysfunction after femoral nailing following severe trauma? An animal study. *J Orthop Trauma* 1994;**8**:300-9.

139. Mousavi M, David R, Schwendenw ein I, Schaden E, Marlovits S, Kolonja A *et al.* Influence of controlled reaming on fat intravasation after femoral osteotomy in sheep. *Clin Orthop* 2002;263-70.

140. Martin R, Leighton RK, Petrie D, Ikejiani C, Smyth B. Effect of proximal and distal venting during intramedullary nailing. *Clin Orthop* 1996;80-9.

141. Pape HC, Hildebrand F, Pertschy S, Zelle B, Garapati R, Grimme K *et al.* Changes in the management of femoral shaft fractures in polytrauma patients: from early total care to damage control orthopedic surgery. *J.Trauma* 2002;**53**:452-61.

142. Bur gess, A. R. 2003. Personal Communication

143. Scalea TM, Boswell SA, Scott JD, Mitchell KA, Kramer ME, Pollak AN. External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: damage control orthopedics. *J.Trauma* 2000;**48**:613-21.

144. Powell, JN. A prospective, randomised trial comp aring reamed and unreamed intrmedullary nailing: an analysis of pulmonary complications. Pocs American Orthopedic Trauma Association Meeting, San Antonio , 90-91. 2000.

145. Nowotarski PJ, Turen CH, Brumba ck RJ, Scarboro JM. Conversion of external fixation to intramedullary nailing for fractures of the shaft of the femur in multiply injured patients. *J.Bone Joint Surg.Am.* 2000;**82**:781-8.

146. Alho A. Fat embolism s yndrome: etiology, pathogenesis and treatment. *Acta Chir Scand.Suppl* 1980;**499**:75-85.

147. Stoltenberg JJ,.Gusti lo RB. The use of methylprednisolone and hypertonic glucose in the prophylaxis of fat embolism syndrome. *Clin Orthop* 1979;211-21.

148. Mellor A,.Soni N. Fat e mbolism. *Anaesthesia* 2001;**56**:145-54.

149. Bern ard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ *et al.* High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N.Engl.J.Med.* 1987;**317**:1565-70.

150. Burhop KE, Seli g WM, Beeler DA, Malik AB. Effect of heparin on increased pulmonary microvascular permeability after bone marrow embolism in awake sheep. *Am.Rev.Respir.Dis.* 1987;**136**:134-41.

151. Goris RJ, Gimbrere JS, v an Niekerk JL, Schoots FJ, Booy LH. Early osteosynthesis and prophylactic mechanical ventilation in the multitrauma patient. *J Trauma* 1982;**22**:895-903.

152. Shier MR, Wilson RF, James RE, Riddle J, Mammen EF, Pedersen HE. Fat embolism prophylaxis: a study of four treatment modalities. *J Trauma* 1977;**17**:621-9.

153. Ohlsson K, Bjork P, B ergenfeldt M, Hageman R, Thompson RC. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. *Nature* 1990;**348**:550-2.

154. Walsh C J, Carey PD, Cook DJ, Bechard DE, Fowler AA, Sugerman HJ. Anti-CD18 antibody attenuates neutropenia and alveolar capillary-membrane injury during gram-negative sepsis. *Surgery* 1991;**110**:205-11.

155. Care y PD, Leeper-Woodford SK, Walsh CJ, Byrne K, Fowler AA, Sugerman HJ. Delayed cyclo-oxygenase blockade reduces the neutrophil respiratory burst and plasma tumor necrosis factor levels in sepsis-induced acute lung injury. *J.Trauma* 1991;**31**:733-40.

156. Balk RA, Jacobs RF, Tr yka AF, Townsend JW, Walls RC, Bone RC. Effects of ibuprofen on neutrophil function and acute lung injury in canine endotoxin shock. *Crit Care Med* 1988;**16**:1121-7.

157. Welt y-Wolf KE, Carraway MS, Miller DL, Ortel TL, Ezban M, Ghio AJ *et al.* Coagulation blockade prevents sepsis-induced respiratory and renal failure in baboons. *Am.J.Respir.Crit Care Med.* 2001;**164**:1988-96.

158. Harda way RM, Williams CH, Marvasti M, Farias M, Tseng A, Pinon I *et al.* Prevention of adult respiratory distress syndrome with plasminogen activator in pigs. *Crit Care Med.* 1990;**18**:1413-8.

159. Parsons PE. Mediators a nd mechanisms of acute lung injury. *Clin Chest Med* 2000;**21**:467-76.

160. Siegel JH, Rivkind A I, Dalal S, Goodarzi S. Early physiologic predictors of injury severity and death in blunt multiple trauma. *Arch.Surg.* 1990;**125**:498-508.

161. Elmara ghy AW, Aksenov S, Byrick RJ, Richards RR, Schemitsch EH. Pathophysiological effect of fat embolism in a canine model of pulmonary contusion. *J Bone Joint Surg Am.* 1999;**81**:1155-64.

162. Elmara ghy AW, Humeniuk B, Anderson GI, Schemitsch EH, Richards RR. The role of methylmethacrylate monomer in the formation and haemodynamic outcome of pulmonary fat emboli. *J Bone Joint Surg Br* 1998;**80**:156-61.

163. Schemits ch EH, Turchin DC, Anderson GI, Byrick RJ, Mullen JB, Richards RR. Pulmonary and systemic fat embolization after medullary canal pressurization: a hemodynamic and histologic investigation in the dog. *J Trauma* 1998;**45**:738-42.

164. Schemitsch EH, Jain R, Turchin DC, Mullen JB, Byrick RJ, Anderson GI *et al.* Pulmonary effects of fixation of a fracture with a plate compared with intramedullary nailing. A canine model of fat embolism and fracture fixation. *J Bone Joint Surg Am.* 1997;**79**:984-96.

165. Pape HC, D wenger A, Regel G, Schweitzer G, Jonas M, Remmers D *et al.* Pulmonary damage after intramedullary femoral nailing in traumatized sheep--is there an effect from different nailing methods? *J Trauma* 1992;**33**:574-81.

166. Pape HC, Ba rtels M, Pohlemann T, Werner T, von Glinski S, Baur H *et al.* Coagulatory response after femoral instrumentation after severe trauma in sheep. *J.Trauma* 1998;**45**:720-8.

167. Neudeck F, Wozasek GE, Obertacke U, Thurnher M, Schlag G. Nailing versus plating in thoracic trauma: an experimental study in sheep. *J Trauma* 1996;**40**:980-4.

168. Wozasek GE, Thurnher M, Redl H, Schlag G. Pulmonary reaction during intramedullary fracture management in traumatic shock: an experimental study. *J Trauma* 1994;**37**:249-54.

169. Kupper TS. Immune and inflammatory processes in cutaneous tissues. Mechanisms and speculations. *J.Clin.Invest* 1990;**86**:1783-9.

170. Kupper TS, Deitch E A, Baker CC, Wong WC. The human burn wound as a primary source of interleukin-1 activity. *Surgery* 1986;**100**:409-15.

171. Pape H C. Pulmonary and systemic fat embolization after medullary canal pressurization: a hemodynamic and histologic investigation in the dog. *J Trauma* 1999;**47**:190.

172. Reikeras O. Ca rdiovascular reactions to intramedullary reaming of long bones in dogs. *Acta Anaesthesiol.Scand.* 1987;**31**:48-51.

173. Duwelius PJ, Huckfeldt R, Mullins R J, Shiota T, Woll TS, Lindsey KH *et al.* The effects of femoral intramedullary reaming on pulmonary function in a sheep lung model. *J Bone Joint Surg Am.* 1997;**79**:194-202.

174. Co hn SM,.Zieg PM. Experimental pulmonary contusion: review of the literature and description of a new porcine model. *J Trauma* 1996;**41**:565-71.

175. Nichols RT, Pearce HJ, Greenfield LJ. Effects of experimental pulmonary contusion on respiratory exchange and lung mechanics. *Arch.Surg* 1968;**96**:723-30.

176. Wolinsk y PR, Banit D, Parker RE, Shyr Y, Snapper JR, Rutherford EJ *et al.* Reamed intramedullary femoral nailing after induction of an "ARDS-like" state in sheep: effect on clinically applicable markers of pulmonary function. *J Orthop Trauma* 1998;**12**:169-75.

177. Staub NC, Bland RD, B righam KL, Demling R, Erdmann AJ, III, Woolverton WC. Preparation of chronic lung lymph fistulas in sheep. *J.Surg.Res.* 1975;**19**:315-20.

178. Mackwa y-Jones K, Foex BA, Kirkman E, Little RA. Modification of the cardiovascular response to hemorrhage by somatic afferent nerve stimulation with special reference to gut and skeletal muscle blood flow. *J.Trauma* 1999;**47**:481-5.

179. Kerr LA, Johnson BJ, Burrows GE. Intoxication of cattle by Perilla frutescens (purple mint). *Vet.Hum.Toxicol.* 1986;**28**:412-6.

180. Cog geshall JW, Lefferts PL, Butterfield MJ, Bernard GR, Carroll FE, Pou NA *et al.* Perilla ketone: a model of increased pulmonary microvascular permeability pulmonary edema in sheep. *Am.Rev.Respir.Dis.* 1987;**136**:1453-8.

181. McWaters P, Hurst L, Chaplin PJ, Collins RA, Wood PR, Scheerlinck JP. Characterisation of monoclonal antibodies to ovine interleukin-6 and the development of a sensitive capture ELISA. *Vet.Immunol.Immunopathol.* 2000;**73**:155-65.

182. Wolinsk y PR, Sciadini MF, Parker RE, Plitman JD, Snapper JR, Rutherford EJ *et al.* Effects on pulmonary physiology of reamed femoral intramedullary nailing in an open-chest sheep model. *J Orthop Trauma* 1996;**10**:75-80.

183. Garbe r BG, Hebert PC, Yelle JD, Hodder RV, McGowan J. Adult respiratory distress syndrome; a systematic overview of incidence and risk factors. *Critical Care Medicine* 1996;**24**:687-95.

184. Robinson CM. Current concepts of respiratory insufficiency syndromes after fracture. *J Bone Joint Surg Am* 2001;**83-B**:781-91.

185. Moed BR,.Bo yd DW. Clinically inapparent hypoxemia after skeletal injury; The use of the pulse oximeter as a screening method. *Clin Orthop* 1993;**293**:269-73.

1 86. L ewandowski K, Metz J, Deutschmann C, Preiss H, Kuhlen R, Artigas A *et al.* Incidence, severity and mortality of acute respiratory distress failure in Berlin. *American Journal of Respiratory Critical Care Medicine* 1995;**151**:1121-5.

187. L uhr OR, Antonsen K, Karlsson M, Aardal S, Thornsteinsson A, Frostell CG *et al.* Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweeden, Denmark and Iceland. *American Journal of Respiratory Critical Care Medicine* 1999;**159**:1849-61.

188. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *American Journal of Respiratory Critical Care Medicine* 2002;**165**:443-8.

189. Cha mpion HR, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Bain LW, Jr. *et al.* The Major Trauma Outcome Study: establishing national norms for trauma care. *J.Trauma* 1990;**30**:1356-65.

190. Abbreviated Injury Score (Updated). *Association for Advanced Automotive Medicine, Des Plaines, Illinois 60018, USA* 1998.

191. Bo yd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma* 1987;**27**:370-8.

192. Yeats D. Scorin g Sytems for Trauma. *British Medical Journal* 1990;**301**:1090-4.

193. Bern ard GR, Artigas A, Brigham KL. The American - European Consensus Conference on ARDS; definitions, mechanisms, relevant outcomes and clinical trial coordination. *American Journal of Respiratory Critical Care Medicine* 1994;**149**:818-24.

194. Hudson LD,.Steinberg KP. Epidemiology of Acute Lung Injury and ARDS. *Chest* 1999;**116**:74S-82S.

195. Villar J,.Slu tsky A. The Incidence of Adult Respiratory Distress Syndrome. *American Review of Respiratory Disease* 1989;**140**:814-6.

196. T homsen GE,.Morris AH. Incidence of the adult respiratory distress syndrome in the State of Utah. *American Journal of Respiratory Critical Care Medicine* 1995;**152**:965-71.

197. Regel G, Lobenhoffer P, Grotz M, Pape HC, Lehmann U, Tscherne H. Treatment results of patients with multiple trauma: an analysis of 3406 cases treated between 1972 and 1991 at a German Level I Trauma Center. *J.Trauma* 1995;**38**:70-8.

198. Villar J, Perez -Mendez L, Kacmarek RM. Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999;**25(9)**:930-5.

199. Johnson KD, Cadambi A, Seibert GB. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma* 1985;**25**:375-84.

200. Zir an BH, Le T, Zhou H, Fallon W, Wilber JH. The impact of the quantity of skeletal injury on mortality and pulmonary morbidity. *J Trauma* 1997;**43**:916-21.

201. Ho yt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T *et al.* A risk analysis of pulmonary complications following major trauma. *J Trauma* 1993;**35**:524-31.

202. Rasmussen TE, Hallett J W, Jr., Metzger RL, Richardson DM, Harmsen WS, Goronzy JJ *et al.* Genetic risk factors in inflammatory abdominal aortic aneurysms: polymorphic residue 70 in the HLA-DR B1 gene as a key genetic element. *J Vasc.Surg* 1997;**25**:356-64.

203. Woo P. C ytokine polymorphisms and inflammation. *Clin Exp.Rheumatol.* 2000;**18**:767-71.

204. Skoog T, van 't Hooft FM, Kallin B, Jovinge S, Boquist S, Nilsson J *et al.* A common functional polymorphism (C-->A substitution at position -863) in the promoter region of the tumour necrosis factor-alpha (TNF-alpha) gene associated with reduced circulating levels of TNF-alpha. *Hum.Mol.Genet.* 1999;**8**:1443-9.

205. I acoviello L, Di Castelnuovo A, De Knijff P, D'Orazio A, Amore C, Arboretti R *et al.* Polymorphisms in the coagulation factor VII gene and the risk of myocardial infarction. *N.Engl.J Med* 1998;**338**:79-85.

206. Ho yt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T *et al.* A risk analysis of pulmonary complications following major trauma. *J Trauma* 1993;**35**:524-31.

207. Engelh ardt S, Hoyt D, Coimbra R, Fortlage D, Holbrook T. The 15-year evolution of an urban trauma center: what does the future hold for the trauma surgeon? *J Trauma* 2001;**51**:633-7.

208. Kannus P, Palvanen M, Parkkari J, Vuori I. Osteoporotic fractures in elderly Finnish persons; sharp increase in 1970-1988 and alarming projections for the new millennium. *Acta Orthopaedica Scandinavica* 2000;**71**:465-70.

209. Villar J,.Slu tsky A. The Incidence of Adult Respiratory Distress Syndrome. *American Review of Respiratory Disease* 1989;**140**:814-6.

210. Webste r NR, Cohen AT, Nunn JF. Adult respiratory distress syndrome - how many cases in the UK? *Anaesthesia* 1988;**43**:923-6.

211. Thomsen GE,.Morris AH . Incidence of the adult respiratory distress syndrome in the State of Utah. *American Journal of Respiratory Critical Care Medicine* 1995;**152**:965-71.

212. Ho yt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T *et al.* A risk analysis of pulmonary complications following major trauma. *J Trauma* 1993;**35**:524-31.

213. White TO, Jenkins PJ, Smith RD, Cartlidge CW, Robinson CM. The epidemiology of posttraumatic adult respiratory distress syndrome. *J.Bone Joint Surg.Am.* 2004;**86-A**:2366-76.

214. Pallister I, Dent C, Wise CC, Alpar EK, Gosling P. Early post-traumatic acute respiratory distress syndrome and albumin excretion rate: a prospective evaluation of a 'point-of care' predictive test. *Injury* 2001;**32**:177-81.

215. Giannoudis PV, Hildebra nd F, Pape HC. Inflammatory serum markers in patients with multiple trauma. Can they predict outcome? *J.Bone Joint Surg.Br.* 2004;**86**:313-23.

216. Alam M,.Smirk F. Obser vations in man upon a pulse accelerating reflex from the voluntary muscles of the legs. *J.Physiol* 1938;**92**:167-77.

217. Alam M,.Smirk F. Obser vations in man upon blood pressure raising reflex arising from the voluntary muscles. *J.Physiol.* 1937;**89**:372-83.

218. von Bezold A,.Hirt L. Uber die physiologischen Wirkungen des essigsauren veratrins. *Untersuchungen aus dem physilogischen laboratorium* 1867;75-156.

219. Jarisch A,.Richter H. Die afferenten Bahnan des Veratrineffektes in den Herznerven. *Naunyn-Schmiedebergs Archiv fur experimentelle Pathologie und Pharmakologie* 1939;**193**:355-71.

220. D'Al essio JG, Weller RS, Rosenblum M. Activation of the Bezold-Jarisch reflex in the sitting position for shoulder arthroscopy using interscalene block. *Anesth.Analg.* 1995;**80**:1158-62.

221. Marco CA,.Ma rco AP. Profound bradycardia related to long bone fracture manipulation. *J.Emerg.Med.* 1996;**14**:305-8.

222. Engel G L. Psychologic stress, vasodepressor (vasovagal) syncope, and sudden death. *Ann.Intern.Med* 1978;**89**:403-12.

223. Kinsella SM,.Tucke y JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br J Anaesth.* 2001;**86**:859-68.

224. Rad y MY, Kirkman E, Cranley J, Little RA. A comparison of the effects of skeletal muscle injury and somatic afferent nerve stimulation on the response to hemorrhage in anesthetized pigs. *J.Trauma* 1993;**35**:756-61.

225. Rad y MY, Kirkman E, Cranley J, Little RA. Nociceptive somatic nerve stimulation and skeletal muscle injury modify systemic hemodynamics and oxygen transport and utilization after resuscitation from hemorrhage. *Crit Care Med.* 1996;**24**:623-30.

226. Foex BA, Kirkman E, Little RA. Injury (nociceptive afferent nerve stimulation) modifies the hemodynamic and metabolic responses to hemorrhage in immature swine. *Crit Care Med.* 2004;**32**:740-6.

227. Gabrielsen GW,.Smith EN. Ph ysiological responses associated with feigned death in the American opossum. *Acta Physiol Scand.* 1985;**123**:393-8.

228. Norton A, B eran A, Misrahy G. Encephalograph during 'feigned' sleep in the opossum. *Nature* 1964;**204**:162-3.

229. Advanced T rauma Life Support Course Manual. p 121. American College of Surgeons, 1989.

230. Buttaro M, Moc etti E, Alfie V, Paniego G, Pineiro L. Fat embolism and related effects during reamed and unreamed intramedullary nailing in a pig model. *J Orthop Trauma* 2002;**16**:239-44.

231. Heim D, Re gazzoni P, Tsakiris DA, Aebi T, Schlegel U, Marbet GA *et al.* Intramedullary nailing and pulmonary embolism: does unreamed nailing prevent embolization? An in vivo study in rabbits. *J Trauma* 1995;**38**:899-906.

232. Kropfl A, Davi es J, Berger U, Hertz H, Schlag G. Intramedullary pressure and bone marrow fat extravasation in reamed and unreamed femoral nailing. *J Orthop Res.* 1999;**17**:261-8.

233. Egdahl R. Pituitar y-adrenal response following trauma to the isolated leg. *Surgery* 1959;**46** :9-21.

234. L iska WD,.Poteet BA. Pulmonary embolism associated with canine total hip replacement. *Vet.Surg* 2003;**32**:178-86.

THE EPIDEMIOLOGY OF POSTTRAUMATIC ADULT RESPIRATORY DISTRESS SYNDROME

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Background: Although adult respiratory distress syndrome is an important early complication of blunt trauma, the epidemiology and risk factors for its development remain poorly defined. The aims of this study were to determine the prevalence and demographics of this complication in a prospective cohort series of patients admitted to the hospital following injury. We also assessed the contribution of the severity and pattern of the injury to the risk of this complication developing. By identifying factors associated with the highest risk of the development of adult respiratory distress syndrome, we aimed to produce guidelines to facilitate earlier detection.

Methods: We prospectively studied 7192 patients admitted to a single university hospital, over an eight-year period, for treatment of a traumatic injury. With the exception of patients who had sustained a hip fracture or who had been discharged within seventy-two hours after admission, all patients who required hospital admission following trauma, were older than thirteen years of age, and were a resident within the catchment area were included in the analysis. The prevalence and demographics of posttraumatic adult respiratory distress syndrome were identified for patients who had sustained musculoskeletal, thoracic, abdominal, and head injuries, either in isolation or in combination. The relative risks of this condition developing were calculated according to the injury pattern. Multiple logistic regression analysis was performed to identify the most highly significant predictors of the development of adult respiratory distress syndrome.

Results: Adult respiratory distress syndrome developed in thirty-six (0.5%) of the patients. The prevalence was significantly higher among younger patients ($p = 0.002$), and 83% of the cases followed high-energy trauma. The prevalence of adult respiratory distress syndrome after isolated thoracic, head, abdominal, or extremity injury was <1%. Patients with injuries to two anatomical regions had a higher prevalence (up to 2.9%), and those with injuries to three anatomical regions had an even higher prevalence (up to 10.2%). Multiple logistic regression analysis showed the Injury Severity Score, the presence of a femoral fracture, the combination of abdominal and extremity injuries, and observations of compromised physiological function on admission each to be an independent predictor of the later development of adult respiratory distress syndrome.

Conclusions: The prevalence of adult respiratory distress syndrome increases with injury severity and combinations of injuries to more than one anatomical region. We have been able to quantify the importance and relative risks associated with these injuries. The implications of our findings with regard to facilitating early detection of this complication are discussed.

Level of Evidence: Prognostic study, Level I-1 (prospective study). See Instructions to Authors for a complete description of levels of evidence.

Adult respiratory distress syndrome is a rare but serious complication of trauma, associated with a mortality rate of approximately 50% and with considerable morbidity among survivors[1]. The etiology and pathophysiology of the condition are poorly understood[2] and the early clinical signs are subtle and easily missed[3], which often results in delays in diagnosis. An understanding of the epidemiology of adult respiratory distress syndrome is therefore important for identifying patients who are potentially at risk.

A number of risk factors for the development of adult respiratory distress syndrome following trauma have been proposed, including long-bone fracture, pelvic fracture, head injury, direct chest injury, tissue hypoxia, and massive blood transfusion[4-6]. The relative importance of each of these insults, either in isolation or in combination, has not been previously characterized in a prospective cohort study, to our knowledge.

TABLE I The Revised Trauma Score

Variable*	Score
Respiratory rate	
10-29 bpm	4
>29 bpm	3
6-9 bpm	2
1-5 bpm	1
0 bpm	0
Systolic blood pressure	
>89 mm Hg	4
76-89 mm Hg	3
50-75 mm Hg	2
1-49 mm Hg	1
0 mm Hg	0
Glasgow Coma Scale score	
13-15	4
9-12	3
6-8	2
4-5	1
3	0

*The score for each of the three variables is multiplied by a weight (derived from regression analysis); the Revised Trauma Score is the sum of the three weighted scores. Patients who do not receive a score of 4 in all three categories are considered to be physiologically compromised.

The principal aims of this prospective study were to determine the prevalence and demographics of adult respiratory distress syndrome in a large cohort of patients who had been admitted to the hospital following trauma as well as to describe the relative importance of injuries to the extremities, thorax, head, and abdomen to the risk of development of this condition with use of validated generic and injury-specific scoring systems. On the basis of these findings, we tried to identify a series of criteria that would allow identification of patients who were at risk for this complication and thus who might benefit from early vigilant monitoring and therapy.

Materials and Methods

Study Design

Between January 1993 and December 2000, a prospective cohort study of all patients, thirteen years of age or older, who were admitted to our institution following trauma, was conducted by the Scottish Trauma Audit Group. Patients over sixty-five years of age who had sustained a fracture of the femoral neck or pelvic ramus, those discharged within seventy-two hours after admission, and those who died before admission to the hospital were excluded in order to conform with the Major Trauma Outcome Study[7]. Such patients were considered to be at low risk for the development of adult respiratory distress syndrome, and that hypothesis was verified by a subsequent review in which no patient in the excluded group was found to have been readmitted to the hospital with respiratory complications after initial discharge from the emergency department. Patients who died within two days after admission were also excluded from our analysis because they were likely to have died from their injuries before adult respiratory distress syndrome could develop.

The demographic details, medical history, mechanism of injury, anatomical location, severity of injury, and physiological observations were recorded at the time of admission by specially trained research workers who were not involved in any subsequent data analysis. In addition, validated scoring systems, including the Abbreviated Injury Score[8], the Revised Trauma Score (Table I)[9], the Injury Severity Score[10], and the Glasgow Coma Scale[11] were used to grade the severity of injury. All patients' cases were reviewed daily by research workers until death or discharge, and the development of any respiratory complications was noted.

Patient Management

Our institution is a major university teaching hospital providing all trauma services to a stable population of 600,000. The majority of serious injuries result from road traffic accidents and falls, and there are relatively few penetrating or gunshot injuries. There is a helicopter service for some tertiary referrals but not for routine transportation of trauma victims. A prehospital-care land-ambulance staffed by senior accident and emergency physicians is used to provide on-site resuscitation when prolonged extrication of trauma patients is anticipated; it is available over a radius of 50 mi (80.5 km), and it attends an average of seventy-five trauma calls per annum. The accident and emergency department physicians carry out initial resuscitation and physiological stabilization. Definitive management is multidisciplinary and is conducted according to trauma protocols. Hemodynamically unstable patients with unstable pelvic fracture initially undergo pelvic external fixation in the operating theater immediately prior to laparotomy or thoracotomy by general abdominal surgeons and cardiothoracic sur-

TABLE II American-European Consensus Diagnostic Criteria for Adult Respiratory Distress Syndrome[12]

Variable	Criteria
PaO_2/FiO_2*	<26.7 kPa
Radiographic findings	Bilateral infiltrates on frontal chest radiograph
Pulmonary artery wedge pressure	<18 mm Hg or no clinical evidence of left atrial hypertension

*Arterial oxygen tension/fraction of inspired oxygen.

geons when this is required. Interventional radiology facilities for iliac arterial embolization are available on site for pelvic fractures remaining hemodynamically unstable. There are facilities for immediate computerized tomographic scanning, and invasive intracranial pressure monitoring on a dedicated neurological intensive-care unit is available. Unstable patients are managed in the intensive-care unit, and additional definitive surgery is generally avoided during the "flow" phase of the stress response, between two and five days after the injury.

Our policy for the management of patients who have sustained trauma is to stabilize all fractures, with use of internal or external fixation when possible, as soon as the patient's physiological condition permits. In physiologically stable patients, isolated injuries are stabilized on their merits within twenty-four hours. All long-bone diaphyseal fractures in the lower limbs of adults are treated with reamed, locked intramedullary nailing.

Patient Demographics

The study included 7192 consecutive trauma admissions. The median age of the patients was forty-nine years (interquartile range, thirty to sixty-eight years), and 3968 (55%) of the patients were male. Blunt trauma was responsible for the injury in 6987 patients (97%).

Characteristics of the Extremity, Thoracic, Abdominal, and Head-Injury Groups

The median age of the patients with an extremity injury was fifty-one years (interquartile range, thirty to sixty-nine years), which was higher than that of the patients with an abdominal injury (median age, thirty-one years; interquartile range, 23.5 to forty-three years), a thoracic injury (median age, forty-three years; interquartile range, twenty-eight to sixty-one years), or a head injury (median age, forty-two years; interquartile range, twenty-six to sixty-three years). The sex distribution was equal in the extremity-injury group (3116 [51%] of the 6067 patients were male), but it was markedly skewed in the abdominal-injury group (275 [80%] of the 345 patients were male), the thoracic-injury group (612 [70%] of the 878 patients were male), and the head-injury group (859 [72%] of the 1190 patients were male).

TABLE III Prevalence of Adult Respiratory Distress Syndrome According to Mechanism of Injury and Patient Demographics

	Cases of Adult Respiratory Distress Syndrome*		
	No./Total	Percent	P Value*
Type of injury			0.63
Blunt	36/6987	0.5%	
Penetrating	0/205	0.0%	
Mechanism of injury			<0.001
Road traffic accident	25/1560	1.6%	
Assault	0/459	0.0%	
Fall (>2 m)	5/675	0.7%	
Fall (<2 m)	4/3640	0.1%	
Sport	1/550	0.2%	
Unknown	1/308	0.3%	
Age			0.002
13-39 yr	24/2736	0.9%	
40-59 yr	4/1806	0.2%	
≥60 yr	8/2650	0.3%	
Sex			
Male	20/3968	0.5%	1.00
Female	16/3224	0.5%	
Socioeconomic status†			
Affluent	4/733	0.5%	0.35
Average	13/1551	0.8%	
Deprived	4/1033	0.4%	
Pre-existing medical conditions†			
Cardiovascular	0/704	0.0%	0.02
Respiratory	5/459	1.1%	0.18
Central nervous system	0/183	0.0%	0.62
Diabetes	0/115	0.0%	1.00
Renal	0/4	0.0%	1.00
Known malignant tumor	0/26	0.0%	1.00
Alcoholism	1/171	0.6%	0.60
Psychiatric	2/136	1.5%	0.15
Substance abuse	1/47	2.1%	0.22

*Significance was tested with use of the Fisher exact test for two-category variables and with the chi-square test for variables with three or more categories. †The data are incomplete for socioeconomic status and for pre-existing medical conditions, as data for those variables were not collected in the earlier years of the study (see text).

The most common mechanism of injuries to the extremities was a fall from a height of <2 m (3236 patients, 53%). The most common mechanism in the remaining three groups was a road traffic accident (429 [49%] of the patients with a thoracic injury, 164 [48%] of those with an abdominal injury, and 488 [41%] of those with a head injury).

Outcome Measures

The primary outcome measure was the development of adult respiratory distress syndrome, as defined by the American-European Consensus Conference (Table II)[12], during the index admission. The original medical notes on the patients in

TABLE IV Prevalence of Adult Respiratory Distress Syndrome According to Observations on Admission, Initial Management, and Overall Injury Severity Score

	Cases of Adult Respiratory Distress Syndrome		
	No./Total	Percent	P Value*
Glasgow Coma Scale score			<0.001
3-8	13/259	5.0%	
9-12	3/162	1.9%	
13-15	20/6771	0.3%	
Systolic blood pressure			<0.001
0-49 mm Hg	2/19	10.5%	
50-75 mm Hg	0/25	0.0%	
76-89 mm Hg	3/56	5.4%	
≥90 mm Hg	31/7092	0.4%	
Respiratory rate			<0.001
0 bpm	1/9	11.1%	
1-9 bpm	1/11	9.1%	
10-29 bpm	29/6986	0.4%	
≥30 bpm	5/186	2.7%	
Revised Trauma Score†			<0.001
Normal	15/6556	0.2%	
Compromised	21/636	3.3%	
Type of operation			0.002
Orthopaedic	20/4765	0.4%	
Laparotomy	4/151	2.6%	
Other	2/296	0.7%	
None	10/1980	0.5%	
Injury Severity Score			<0.001
1-8	0/1993	0.0%	
9-15	10/4385	0.2%	
16-24	12/436	2.8%	
25-75	14/378	3.7%	

*Significance was tested with use of the Fisher exact test for two-category variables and with the chi-square test for variables with three or more categories. †A compromised Revised Trauma Score is defined in Table I.

whom respiratory insufficiency had been suspected were examined in order to ensure that the diagnosis complied with the consensus diagnostic criteria.

Statistical Methods

The relationship between the prevalence of adult respiratory distress syndrome in the cohort and each potential explanatory variable was first described and examined with use of Mann-Whitney U tests (continuous variables), Fisher exact tests (two-category variables), and chi-square tests (variables with three or more categories). Complete data were available for all patients, except in the socioeconomic status category (data in this category were available for 3317 patients seen between 1996 and 2000) and pre-existing medical conditions category (data on cardiovascular, respiratory, central nervous system, renal, and diabetic conditions were available for 3963 patients seen from 1996 to 2000 and data on known malignant tumors, alcoholism, psychiatric problems, and substance abuse were available for 2147 patients seen from 1998 to 2000). We then conducted a multiple logistic regression analysis to identify variables that were independently predictive of the subsequent development of adult respiratory distress syndrome. All data analysis was conducted with use of SPSS software (version 10; SPSS, Chicago, Illinois).

Results

Demographic and Admission Data

Prevalence and Demographics of Adult Respiratory Distress Syndrome

Adult respiratory distress syndrome developed in thirty-six (0.5%) of the 7192 trauma patients, an annual incidence of 0.8 per 100,000 population per year. The prevalence was highest among younger patients (less than forty years of age; Table III), and the median age of the patients in whom adult respiratory distress syndrome developed was twenty-nine years, which was significantly younger than the median age (fifty years) of those in whom the syndrome did not develop ($p = 0.001$). There was no significant difference in sex distribution (twenty male patients and sixteen female patients) or between different socioeconomic groups (based on postal code of residence). The presence of comorbidities (including respiratory disease, cardiovascular disease, diabetes mellitus, renal disease, known malignant tumors, alcohol abuse, drug abuse, and psychiatric illness) was not found to be significantly associated with the prevalence of adult respiratory distress syndrome among those for whom such data were available (Table III).

Mechanism of Injury

Thirty (83%) of the cases of adult respiratory distress syndrome developed following high-energy injuries (a road traffic accident or a fall from a height of >2 m) (Table III), and all cases occurred following blunt trauma. In one case, the mechanism of injury was unknown, as the patient had been found unconscious, with a head injury, in the street. The risk of adult respiratory distress syndrome developing was significantly higher after high-energy injury than it was after low-energy injury (the remaining mechanisms of injury) ($p < 0.001$), with a relative risk of 5.1 (95%

TABLE V Prevalence of Adult Respiratory Distress Syndrome for Each Anatomical Region According to the Abbreviated Injury Score

Maximum Abbreviated Injury Score	Cases of Adult Respiratory Distress Syndrome							
	Head Injury		Thoracic Injury		Abdominal Injury		Extremity Injury	
	No./Total	Percent	No./Total	Percent	No./Total	Percent	No./Total	Percent
0 (No injury)	19/6002	0.3%	17/6314	0.3%	22/6847	0.3%	6/1125	0.5%
1 (Minor)	3/418	0.7%	0/182	0.0%	4/128	3.1%	0/407	0.0%
2 (Moderate)	0/65	0.0%	2/143	1.4%	5/92	5.4%	6/1673	0.4%
3 (Serious)	4/288	1.4%	8/369	2.2%	2/81	2.5%	22/3968	0.6%
4 (Severe)	2/221	0.9%	6/162	3.7%	1/23	4.3%	2/16	12.5%
5 (Critical)	8/198	4.0%	3/22	13.6%	2/21	9.5%	0/3	0.0%
P value*	0.01		0.001		0.54		0.02	

*Significance was tested with use of the Mann-Whitney U test (with exclusion of patients with no injury in the tested body region).

confidence interval, 4.8 to 27.8). The median age of the patients who sustained high-energy injuries was thirty-five years, which was significantly younger than the median age (fifty-six years) of those who sustained low-energy injuries ($p < 0.001$).

Observations on Admission and Initial Management

The prevalence of adult respiratory distress syndrome was significantly higher among the patients with a score on the Glasgow Coma Scale of <8 ($p < 0.001$; relative risk, 5.8 compared with the remainder; 95% confidence interval, 4.0 to 8.3), the patients with a systolic blood pressure of <90 mm Hg on admission ($p < 0.001$; relative risk, 5.4; 95% confidence interval, 2.7 to 10.6), and the patients with either a respiratory rate of less than ten or more than thirty breaths per minute ($p < 0.001$; relative risk, 6.0; 95% confidence interval, 2.4 to 15.3) (Table IV). Patients in whom a laparotomy was the initial surgical intervention had a significantly higher prevalence of adult respiratory distress syndrome than did those requiring an initial orthopaedic procedure (relative risk, 5.3; 95% confidence interval, 1.8 to 15.4) or not requiring any surgical intervention (relative risk, 3.9; 95% confidence interval, 1.3 to 12.0). Adult respiratory distress syndrome developed in none of the twenty-eight patients requiring an initial thoracotomy and in only one (0.6%) of the 159 patients requiring initial neurosurgical intervention.

Severity and Anatomical Location of Injury

Injury Scores

The prevalence of adult respiratory distress syndrome increased significantly with an increasing Injury Severity Score ($p < 0.001$; Table IV). The condition did not develop in any patient with a score of <9, whereas the prevalence was 3.7% among those with a score of ≥25. Observations of compromised physiological function on admission (Table I) were also associated with a significantly increased prevalence of adult respiratory distress syndrome ($p < 0.001$; Table IV).

Anatomical Location of the Injury

The prevalence of adult respiratory distress syndrome increased significantly with increases in the maximum injury severity in the patients with head, chest, and extremity injuries ($p = 0.02$ to $p = 0.001$; Table V).

The prevalence of adult respiratory distress syndrome associated with specific injuries in each region is shown in Table VI. The prevalence was >2% (i.e., more than four times more frequent than in the study population as a whole) among patients with a pneumothorax or hemothorax, more than three fractured ribs, a femoral fracture, or an unstable pelvic ring fracture.

TABLE VI Prevalence of Adult Respiratory Distress Syndrome According to Specific Type of Injury

	Cases of Adult Respiratory Distress Syndrome		
	No./Total	Percent	P Value*
Head injuries			
Skull fracture	7/563	1.2%	0.02
Intracerebral hemorrhage	7/426	1.6%	0.005
Thoracic injuries			
Pneumothorax or hemothorax	11/336	3.3%	<0.001
>3 rib fractures	7/160	4.4%	<0.001
Extremity injuries			
Tibial fracture	8/1039	0.8%	0.23
Femoral fracture	12/525	2.3%	<0.001
Pelvic fracture	13/382	3.4%	<0.001

*Significance was tested with use of the Fisher exact test.

TABLE VII Prevalence of Adult Respiratory Distress Syndrome Associated with Isolated and Combined Injuries

	Abdominal Injury	Extremity Injury	Thoracic Injury	Head Injury	Cases of Adult Respiratory Distress Syndrome		Relative Risk (95% Confidence Interval) Compared with Extremity Injury Alone
					No./Total	Percent	
Isolated injury							
	▲				0/79	0.0%	—
		▲			6/4981	0.1%	—
			▲		1/228	0.4%	3.6 (0.4-30)
				▲	4/431	0.9%	7.6 (2.2-27)
Two injured body regions							
			▲	▲	0/48	0.0%	—
	▲			▲	0/9	0.0%	—
	▲		▲		0/39	0.0%	—
		▲		▲	3/453	0.7%	5.4 (1.4-22)
		▲	▲		4/278	1.4%	11.8 (3.3-41)
	▲	▲			2/68	2.9%	23.8 (4.9-115)
Three injured body regions							
		▲	▲	▲	4/158	2.5%	20.5 (5.8-72)
	▲		▲	▲	1/21	4.8%	37.8 (4.7-301)
	▲	▲		▲	2/23	8.7%	66.5 (14.1-313)
	▲	▲	▲		6/59	10.2%	76.7 (25.4-231)
Four injured body regions	▲	▲	▲	▲	3/47	6.4%	49.9 (12.8-193)

Injury Combinations

The prevalence of adult respiratory distress syndrome after an isolated injury to any body region was <1% (Table VII). Most combinations of two injuries were associated with a similarly low prevalence; however, the combination of abdominal and extremity injuries resulted in a prevalence of 2.9%. Injuries to three anatomical sites resulted in an increased prevalence of between 2.5% and 10.2%, with the highest prevalence observed when injuries to the extremities, thorax, and abdomen had been sustained in combination. Injuries to all four regions resulted in a prevalence of 6.4%, which was not significantly higher than that associated with a combination of three injuries.

Fractures of the tibial or femoral diaphysis and unstable fractures of the pelvic ring were associated with a higher prevalence of adult respiratory distress syndrome when they were accompanied by a concomitant head, thoracic, or abdominal injury (Tables VIII, IX, and X).

Multivariate Analysis of Occurrence of Adult Respiratory Distress Syndrome

On univariate testing, some variables or variable combinations were found to be associated with a high prevalence of adult respiratory distress syndrome. For example, a Glasgow Coma Scale score of 3 to 8 was associated with a 5% prevalance; chest injuries with an Abbreviated Injury Score of ≥4, with a 4.9% prevalence; and a tibial, femoral, or pelvic fracture combined with an abdominal injury, with a 10% to 15% prevalence. However, these variables were identified in only three to thirteen of the thirty-six patients affected by adult respiratory distress syndrome. Other variables identified more affected patients but referred to higher numbers of patients at

TABLE VIII Prevalence of Adult Respiratory Distress Syndrome After Fractures of the Tibia, Femur, and Pelvis with and without Concomitant Head Injury

	Cases of Adult Respiratory Distress Syndrome				
	Without Head Injury		With Head Injury		
	No./Total	Percent	No./Total	Percent	P Value
Tibial fracture	5/941	0.5%	3/98	3.1%	0.03
Femoral fracture	8/465	1.7%	4/60	6.7%	0.04
Pelvic fracture	9/276	3.3%	4/106	3.8%	0.76

TABLE IX Prevalence of Adult Respiratory Distress Syndrome After Fractures of the Tibia, Femur, and Pelvis with and without Concomitant Thoracic Injury

	Cases of Adult Respiratory Distress Syndrome				
	Without Thoracic Injury		With Thoracic Injury		
	No./Total	Percent	No./Total	Percent	P Value
Tibial fracture	4/987	0.4%	4/52	7.7%	<0.001
Femoral fracture	8/473	1.7%	4/52	7.7%	0.02
Pelvic fracture	3/276	1.1%	10/106	9.4%	<0.001

risk. For example, adult respiratory distress syndrome developed in twenty-five (1.6%) of the 1560 individuals involved in a road traffic accident, twenty-one (3.3%) of the 636 patients with compromised physiological function on presentation, and twenty-six (3.2%) of the 814 patients with an Injury Severity Score of 16 to 75. Given that so many variables were associated with the occurrence of this condition and yet were related to other variables (for example, the mechanism of injury was associated with the Injury Severity Score, and the Abbreviated Injury Score was associated with the total Injury Severity Score), we tested their combined effects with logistic regression analysis (Table XI).

The Injury Severity Score was the first variable to be entered into the forward stepwise logistic regression model; it explained 18.5% of the variation in the prevalence of adult respiratory distress syndrome. A femoral fracture explained an additional 3.8% of the variation in the prevalence, and the addition of a combined extremity and abdominal injury in the same patient and the Revised Trauma Score explained a total of 27.3% of the variance.

Proactive monitoring of the 814 patients with an Injury Severity Score of 16 to 75 would have identified twenty-six of the thirty-six patients with adult respiratory distress syndrome. Monitoring of the 525 patients with a femoral fracture would have identified twelve affected patients, monitoring of the 197 with combined extremity and abdominal injuries would have identified thirteen, and monitoring of the 636 with compromised physiological function on presentation would have identified twenty-one. Many patients fell into more than one of these categories, and we therefore developed criteria for monitoring that would have allowed identification of the maximum number of patients in whom adult respiratory distress syndrome later developed.

Altogether, thirty-five (97%) of the thirty-six cases of adult respiratory distress syndrome would have been identified by active monitoring of all patients with an Injury Severity Score of ≥16, a femoral fracture, a combination of extremity and abdominal injuries, and/or observations of compromised physiological function on admission. Given that no cases of adult respiratory distress syndrome were recorded in the 1993 patients with minor injuries (Injury Severity Score between 1 and 8), this high rate of identification of patients in whom adult respiratory distress syndrome would develop could have been achieved by monitoring 1516 (21%) of the study population of 7192 patients. If resources for monitoring were an issue, the low Revised Trauma Score could be removed as a criterion with the result of missing only one of the thirty-five patients. If that had been done, thirty-four (94%) of the thirty-six patients with adult respiratory distress syndrome would have been detected by monitoring 1324 (18%) of the 7192 patients in the study population. The one patient with adult respiratory distress syndrome who was not identified by any of these criteria was a twenty-five-year-old patient who had sustained isolated comminuted fractures of the shafts of the right tibia and fibula in a sports injury.

Discussion

Previous investigators have examined the incidence of adult respiratory distress syndrome. The first estimate of the "all-causes" incidence was reported by the National Institutes of Health, in 1972, to be 75 per 100,000 general population per year[13]. Although widely quoted, this figure is an order of magnitude greater than the incidences reported in most recent intensive-care-based epidemiological studies, which

TABLE X Prevalence of Adult Respiratory Distress Syndrome After Fractures of the Tibia, Femur, and Pelvis with and without Concomitant Abdominal Injury

	Cases of Adult Respiratory Distress Syndrome				
	Without Abdominal Injury		With Abdominal Injury		
	No./Total	Percent	No./Total	Percent	P Value
Tibial fracture	5/1010	0.5%	3/29	10.3%	0.001
Femoral fracture	8/498	1.6%	4/27	14.8%	0.002
Pelvic fracture	6/319	1.9%	7/63	11.1%	0.002

TABLE XI Multivariate Analysis of Factors Affecting Prevalence of Adult Respiratory Distress Syndrome*

Explanatory Variables	Odds Ratio (Exp B)	95% Confidence Interval for Exp B	P Value
Injury Severity Score			
9-15			<0.001
1-8	0.00		
16-24	8.13	3.27-20.3	
25-75	4.83	1.63-14.3	
Femoral fracture			
No			<0.001
Yes	3.91	1.83-8.34	
Combined extremity and abdominal injuries			
No			<0.001
Yes	5.01	2.20-11.4	
Revised Trauma Score			
	0.72	0.59-0.89	0.01
Constant, b = –4.66	0.009		

*Variables are listed in the order in which they were entered into the forward stepwise selection process. For all variables except the Revised Trauma Score, Exp B is the factor by which the odds of adult respiratory distress syndrome developing change when the category is compared with the base (first-listed) category. The Revised Trauma Score is a continuous variable for which Exp B is the change in the odds of adult respiratory distress syndrome developing associated with a one-unit increase in the Revised Trauma Score. Values of Exp B of more than one indicate a higher risk of adult respiratory distress syndrome developing compared with that associated with the base category. Values of less than one indicate that the odds decrease as the explanatory variable increases. Model-building was terminated when a P-to-enter value of 0.01 was reached. Other variables tested during the model-building process (but not included in the final model) were age; sex; Glasgow Coma Scale score; respiratory rate and systolic blood pressure on presentation; type of injury (blunt or penetrating); presence and Abbreviated Injury Score of head, chest, extremity, abdominal, or other injuries (five variables each); and all two-way interactions between these injury combinations (e.g., extremity*head, extremity*chest, chest*abdomen, and so on), and tibial, femoral, and pelvic fractures and extremity fractures in combination with head, chest, or abdominal injuries.

have ranged between 1.5 and 13.5 per 100,000 per year[4,5,13-15]. Although the incidence of adult respiratory distress syndrome following trauma admissions has not previously been reported, to our knowledge, the population incidence due to trauma alone can be estimated from the incidences presented in four previous studies[4-6,14] (see Appendix). These incidences ranged between 0.4 and 2.0 per 100,000 population per year, which is similar to our finding of 0.8 per 100,000 per year.

Direct comparison of the results of our work with those of previous studies is not possible because of variations in the definitions of adult respiratory distress syndrome and differing case-mix. The nomenclature for pulmonary injury has been inconsistent in previous studies, with variable use of terms such as *shock-lung, fat embolus syndrome,* and *neurogenic pulmonary edema.* More than half of the published reports did not provide a definition of the condition[1]. More recently, the diagnostic criteria proposed by the American-European Consensus Conference in 1994[12] have allowed comparisons between studies, despite some criticism of the measurements used[16]. However, previous studies either have been based entirely on intensive-care data, with the features of a different patient population and a wide variety of precipitating etiologies, or have investigated a highly selected subgroup of patients with polytrauma[17-19]. To our knowledge, no previous report has described the incidence of adult respiratory distress syndrome, as described with use of modern criteria, among general trauma admissions or has addressed the importance of the injury pattern and the combination of injuries with regard to contributing to the risk of the development of the syndrome.

We have shown that adult respiratory distress syndrome is rare after blunt trauma: the overall prevalence was 0.5% in our cohort. High-energy injury, young age, compromised physiological function on admission, specific injuries such as skull fracture or pleural injury, and long-bone and pelvic fractures were all associated with an increased prevalence. An increased prevalence was also seen among patients who were given high scores with each of the generic and injury-specific assessment systems used in the study.

Patients with an injury in only one anatomical region had a low prevalence of adult respiratory distress syndrome (<1%). Although the complication developed in only a small number of patients, the prevalence increased in patients who had injuries to more than one anatomical region. Patients with two injuries had a prevalence as high as 2.9%, whereas those with three injuries had a prevalence as high as 10.2%. In addition, patients with a lower-extremity injury had a significantly greater prevalence when they also had a concomitant injury to the head, thorax, or abdomen.

Multivariate regression analysis was performed in order to stratify these individually significant factors, many of which

were linked with each other. The best combination of variables for predicting the risk of adult respiratory distress syndrome was the Injury Severity Score, the presence of a femoral fracture, the combination of an extremity and an abdominal injury, and observations of compromised physiological function at presentation.

The Injury Severity Score, which provides a crude estimate of the "dose of injury," was the most important factor, explaining 18.5% of the variation in the prevalence of adult respiratory distress syndrome. The complication did not develop in any patient with an Injury Severity Score of <9, suggesting that there may be a threshold level for the "dose" of trauma required for its development.

The presence of a femoral fracture was the second independent variable entered into the model (Table XI). The importance of this injury as a cause of respiratory insufficiency has long been recognized[2]. The term *fat embolus syndrome* has been used in this context, as the pathophysiology has been assumed to center on the release and intravasation of medullary fat after the fracture and its embolization to the cerebral and cutaneous circulations as well as the pulmonary vascular bed[20]. Although, historically, affected patients were considered to be too sick to be operated on, the advantages of early skeletal stabilization of such fractures have been established in a number of studies and meta-analyses[21-25]. The influential randomized controlled trial reported by Bone et al., for example, demonstrated that multiply injured patients had a higher prevalence of respiratory insufficiency and a longer stay in the intensive-care unit when femoral stabilization had been delayed[26]. As our policy is to stabilize all long-bone fractures definitively as early as the patient's condition allows, we have not been able to study the effect of the timing of surgery.

Combined injuries to the extremities and abdomen was the next variable entered into the model. Abdominal injury represents a heterogeneous group, potentially combining a number of pathological entities that contribute to the development of respiratory complications. Visceral injury results in hemorrhage, hypovolemic shock, and tissue hypoperfusion, leading to the release of cytokines and activation of the coagulation and inflammatory cascades. Abdominal pain and swelling result in diaphragmatic splinting, hypoventilation, and atelectasis[2], which may exacerbate hypoxemia. Patients with combined injuries to the abdomen and extremities may require a prolonged period of recumbency, which may also increase the risk of pulmonary complications.

Combined Injuries to the Femur and Thorax, and Damage-Control Orthopaedics

Although intramedullary stabilization of long-bone fractures reduces morbidity and mortality after injury, a paradox is evident in that the process of reaming and nailing causes increased fat embolism[27] and possibly an incremental activation of the stress response[28]. A number of animal studies in which surrogate outcome measures were used have suggested modifications to surgical technique that might reduce fat embolism, including the use of intramedullary nails without reaming[29,30], alterations in the design of reamers[31], faster reamer revolutions with slower introduction of the reamer[32], and venting of the distal fragment[33], but the advantages of these strategies have not been substantiated by clinical studies. In a subgroup of severely injured patients who are physiologically unstable, with hypovolemic shock, hypothermia, or coagulopathy, immediate definitive fracture stabilization by nailing may be detrimental and a rapid, minimally invasive procedure (such as the application of an external fixator) to provide skeletal stability followed by a period of physiological stabilization in the intensive-care unit is beneficial. This concept has recently been formalized as damage-control orthopaedic surgery[34,35]. The patient with combined thoracic and long-bone injuries has been particularly implicated as being at increased risk and suitable for the "damage-control" approach. Because only a small number of patients are affected by this combination of injuries, and adult respiratory distress syndrome develops in only a small proportion of them, it would be difficult to prove the efficacy of a change in the timing and type of orthopaedic intervention in this group of patients in a randomized trial. On the basis of our findings in this cohort, a power calculation suggests that in order to have an 80% chance of detecting a 50% reduction in the prevalence of adult respiratory distress syndrome as a result of a modified surgical strategy, a study recruiting 1154 patients with combined femoral and thoracic injuries would be required. A study of 8600 such patients would be required to show a 20% reduction in prevalence.

Although, in the present study, the additional presence of a thoracic injury increased the prevalence of adult respiratory distress syndrome after femoral fracture from 1.7% to 7.7%, this combination was not independently predictive of adult respiratory distress syndrome and did not enter the final regression model. This finding is in agreement with that of a recent review of the available literature, in which the authors concluded that, in patients with both thoracic and long-bone injuries, it is the thoracic injury that determines the likelihood of adult respiratory distress syndrome and the additional presence of a long-bone injury (however treated) does not influence that likelihood[2]. Our data suggest that it is likely that the total "dose" of injury, as measured by the Injury Severity Score, is more important in the development of adult respiratory distress syndrome than is this particular combination of injuries *per se*.

Limitations of This Study

Not all cases of adult respiratory distress syndrome in our study were explained by the presence of severe trauma or other such risk factors; a proportion remain apparently sporadic or idiosyncratic. This is illustrated by the otherwise unaccountable development of adult respiratory distress syndrome in an individual in our series who sustained an isolated tibial fracture in a sports injury. Phenotypic variations in the expression of components of both the inflammatory and the coagulation system have been identified in association with other hyper-

stimulatory conditions and may be important in individuals in whom adult respiratory distress syndrome develops unexpectedly[36-39]. Such genetic predisposition clearly cannot be predicted by this type of epidemiological study.

There are numerous other insults that have a possible association with the stress response and respiratory dysfunction and that may have had an additional influence on the development of adult respiratory distress syndrome. These include transient hypotension or hypoxemia, capillary bed hypoperfusion, hypothermia, gastric aspiration, sepsis, and massive blood transfusion[2]. We were unable to identify with confidence the number of patients affected by those putative insults and were unable to analyze their contribution.

Some patients with more subtle respiratory compromise may not have been included in our analysis. Subclinical forms of hypoxemia are known to occur after trauma in up to one-third of patients and to resolve completely with supportive treatment[3]. These were not detected by the methods employed in this study.

Although we have presented the prevalence of adult respiratory distress syndrome following trauma, the inclusion criteria used for our study population were inevitably subjective. We did not include the entire population of patients presenting to the accident and emergency department following trauma or those who were discharged within forty-eight hours, as we believed them to be at low risk for the development of respiratory complications. This assumption was confirmed, as no patient was readmitted with respiratory compromise after early discharge during the period of the study. Our data are based on a population who sustained mainly blunt trauma and presented to a single European center, and caution is required when extrapolating our results to other populations such as North American urban populations, in whom the proportion of penetrating injuries is higher[40,41].

The demographic distribution of the patients with extremity injuries was different from that of the patients with head, abdominal, and thoracic injuries. Extremity injuries affected a higher proportion of older women, and more of them were low-energy injuries. The contemporary pattern of trauma is changing, and our results reflect the increasingly common problem of low-energy osteopenic fractures in the elderly[42]. These patients are at lower risk for adult respiratory distress syndrome, and this fact may have skewed the results in the extremity-injury group when compared with the groups with injuries in other anatomical regions.

Recommendations

We identified and stratified a number of demographic, physiological, and injury-related risk factors for the development of adult respiratory distress syndrome. The mortality associated with this condition remains high, partly as a consequence of our incomplete understanding of its pathogenesis, the lack of specific therapeutic treatments, and the failure to recognize the subtle early signs of impending respiratory compromise. Prompt identification of patients who are at increased risk is therefore important for improving management.

We suggest that, while clinical suspicion and observation remain central to the diagnosis of adult respiratory distress syndrome, patients with an Injury Severity Score of ≥16, those with a femoral fracture, those with combined injuries to the extremities and abdomen, and those with observations of compromised physiological function on admission would benefit from close physiological monitoring in a high-dependency setting, in order to facilitate early detection and allow appropriate intervention to be instituted for patients in whom adult respiratory distress syndrome develops.

Appendix

(eA) A table summarizing previous studies on adult respiratory distress syndrome is available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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References

1. **Garber BG, Hebert PC, Yelle JD, Hodder RV, McGowan J.** Adult respiratory distress syndrome: a systematic overview of incidence and risk factors. *Crit Care Med.* 1996;24:687-95.
2. **Robinson CM.** Current concepts of respiratory insufficiency syndromes after fracture. *J Bone Joint Surg Br.* 2001;83:781-91.
3. **Moed BR, Boyd DW, Andring RE.** Clinically inapparent hypoxemia after skeletal injury. The use of the pulse oximeter as a screening method. *Clin Orthop.* 1993;293:269-73.
4. **Lewandowski K, Metz J, Deutschmann C, Preiss H, Kuhlen R, Artigas A, Falke KJ.** Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. *Am J Respir Crit Care Med.* 1995;151:1121-5.
5. **Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell CG, Bonde J.** Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. *Am J Respir Crit Care Med.* 1999;159:1849-61.
6. **Bersten AD, Edibam C, Hunt T, Moran J; Australian and New Zealand Intensive Care Society Clinical Trials Group.** Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States.

Am J Respir Crit Care Med. 2002;165:443-8.

7. **Champion HR, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Bain LW Jr, Flanagan ME, Frey CF.** The Major Trauma Outcome Study: establishing national norms for trauma care. *J Trauma.* 1990;30:1356-65.
8. *Abbreviated injury score (updated).* Des Plaines, IL: Association for Advanced Automotive Medicine; 1998.
9. **Boyd CR, Tolson MA, Copes WS.** Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma.* 1987;27:370-8.
10. **Yates DW.** ABC of major trauma. Scoring systems for trauma. *BMJ.* 1990; 301:1090-4.
11. **Teasdale G, Jennett B.** Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1994;2:81-4.
12. **Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R.** The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149(3 Pt 1):818-24.
13. **Hudson LD, Steinberg KP.** Epidemiology of acute lung injury and ARDS. *Chest.* 1999;116(1 Suppl):74S-82S.
14. **Villar J, Slutsky AS.** The incidence of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1989;140:814-6.
15. **Thomsen GE, Morris AH.** Incidence of the adult respiratory distress syndrome in the state of Utah. *Am J Respir Crit Care Med.* 1995;152:965-71.
16. **Villar J, Perez-Mendez L, Kacmarek RM.** Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med.* 1999;25:930-5.
17. **Johnson KD, Cadambi A, Seibert GB.** Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma.* 1985;25:375-84.
18. **Ziran BH, Le T, Zhou H, Fallon W, Wilber JH.** The impact of the quantity of skeletal injury on mortality and pulmonary morbidity. *J Trauma.* 1997;43:916-21.
19. **Hoyt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T, Fortlage D.** A risk analysis of pulmonary complications following major trauma. *J Trauma.* 1993;35:524-31.
20. **Gurd AR, Wilson RI.** The fat embolism syndrome. *J Bone Joint Surg Br.* 1974; 56:408-16.
21. **Riska EB, von Bonsdorff H, Hakkinen S, Jaroma H, Kiviluoto O, Paavilainen T.** Prevention of fat embolism by early internal fixation of fractures in patients with multiple injuries. *Injury.* 1976;8:110-6.
22. **Robinson CM.** Current concepts of respiratory insufficiency syndromes after fracture. *J Bone Joint Surg Br.* 2001;83:781-91.
23. **Charash WE, Fabian TC, Croce MA.** Delayed surgical fixation of femur fractures is a risk factor for pulmonary failure independent of thoracic trauma. *J Trauma.* 1994;37:667-72.
24. **Pinney SJ, Keating JF, Meek RN.** Fat embolism syndrome in isolated femoral fractures: does timing of nailing influence incidence? *Injury.* 1998;29:131-3.
25. **Meek RN, Vivoda EE, Pirani S.** Comparison of mortality of patients with multiple injuries according to type of fracture treatment—a retrospective age- and injury-matched series. *Injury.* 1986;17:2-4.
26. **Bone LB, Johnson KD, Weigelt J, Scheinberg R.** Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am.* 1989;71:336-40.
27. **Pell AC, Christie J, Keating JF, Sutherland GR.** The detection of fat embolism by transoesophageal echocardiography during reamed intramedullary nailing. A study of 24 patients with femoral and tibial fractures. *J Bone Joint Surg Br.* 1993;75:921-5.
28. **Pape HC, Grimme K, van Griensven M, Sott AH, Giannoudis P, Morley J, Rolse O, Ellingsen E, Hildebrand F, Wiese B, Krettek C; EPOFF Study Group.** Impact of intramedullary instrumentation versus damage control for femoral fractures on immunoinflammatory parameters: prospective randomized analysis by the EPOFF Study Group. *J Trauma.* 2003;55:7-13.
29. **Pape HC, Regel G, Dwenger A, Krumm K, Schweitzer G, Krettek C, Sturm JA, Tscherne H.** Influences of different methods of intramedullary femoral nailing on lung function in patients with multiple trauma. *J Trauma.* 1993;35:709-16.
30. **Giannoudis PV, Smith RM, Bellamy MC, Morrison JF, Dickson RA, Guillou PJ.** Stimulation of the inflammatory system by reamed and unreamed nailing of femoral fractures. An analysis of the second hit. *J Bone Joint Surg Br.* 1999;81:356-61.
31. **Pape HC, Dwenger A, Grotz M, Kaever V, Negatsch R, Kleemann W, Regel G, Sturm JA, Tscherne H.** Does the reamer type influence the degree of lung dysfunction after femoral nailing following severe trauma? An animal study. *J Orthop Trauma.* 1994;8:300-9.
32. **Champion H, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Bain LW Jr, Flanagan ME, Frey CF.** The Major Trauma Outcome Study: establishing national norms for trauma care. *J Trauma.* 1990;30:1356-65.
33. **Martin R, Leighton RK, Petrie D, Ikejiani C, Smyth B.** Effect of proximal and distal venting during intramedullary nailing. *Clin Orthop.* 1996;332:80-9.
34. **Pape HC, Hildebrand F, Pertschy S, Zelle B, Garapati R, Grimme K, Krettek C, Reed RL 2nd.** Changes in the management of femoral shaft fractures in polytrauma patients: from early total care to damage control orthopedic surgery. *J Trauma.* 2002;53:452-61.
35. **Scalea TM, Boswell SA, Scott JD, Mitchell KA, Kramer ME, Pollak AN.** External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: damage control orthopedics. *J Trauma.* 2000;48:613-21.
36. **Rasmussen TE, Hallett JW Jr, Metzger RL, Richardson DM, Harmsen WS, Goronzy JJ, Weyand CM.** Genetic risk factors in inflammatory abdominal aortic aneurysms: polymorphic residue 70 in the HLA-DR B1 gene as a key genetic element. *J Vasc Surg.* 1997;25:356-64.
37. **Woo P.** Cytokine polymorphisms and inflammation. *Clin Exp Rheumatol.* 2000;18:767-71.
38. **Skoog T, van't Hooft FM, Kallin B, Jovinge S, Boquist S, Nilsson J, Eriksson P, Hamsten A.** A common functional polymorphism (C—>A substitution at position -863) in the promoter region of the tumour necrosis factor-alpha (TNF-alpha) gene associated with reduced circulating levels of TNF-alpha. *Hum Mol Genet.* 1999;8:1443-9.
39. **Iacoviello L, Di Castelnuovo A, De Knijff P, D'Orazio A, Amore C, Arboretti R, Kluft C, Benedetta Donati M.** Polymorphisms in the coagulation factor VII gene and the risk of myocardial infarction. *N Engl J Med.* 1998;338: 79-85.
40. **Hoyt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T, Fortlage D.** A risk analysis of pulmonary complications following major trauma. *J Trauma.* 1993;35:524-31.
41. **Engelhardt S, Hoyt D, Colmbra R, Fortlage D, Holbrook T.** The 15-year evolution of an urban trauma center: what does the future hold for the trauma surgeon? *J Trauma.* 2001;51:633-7.
42. **Kannus P, Palvanen M, Niemi S, Parkkari J, Jarvinen M, Vuori I.** Osteoporotic fractures of the proximal humerus in elderly Finnish persons: sharp increase in 1970-1998 and alarming projections for the new millennium. *Acta Orthop Scand.* 2000;71:465-70.
43. **Webster NR, Cohen AT, Nunn JF.** Adult respiratory distress syndrome—how many cases in the UK? *Anaesthesia.* 1988;43:923-6.