Trauma Associated Cardiac Injury & Dysfunction

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Abstract

The existence of a trauma induced secondary cardiac injury (TISCI) remains in doubt. The risk factors and pathological processes that lead to its development are not known, whilst the effects of TISCI on injured patient outcome are uncertain. Concurrently, the incidence of coronary heart disease (CHD) in a trauma population and its influence on mortality are inconclusive. The aim of this research project was to address these specific areas of uncertainty.

Critically injured patients (n=135) were retrospectively investigated for the incidence and nature of adverse cardiac events (ACEs), and levels of the cardiac specific biomarkers Troponin I, B-type Natriuretic Peptide and Heart-type Fatty Acid Binding Protein were measured. Biomarkers and cardiac events were evaluated against outcome. Thereafter, the relationship of pro-inflammatory cytokines with TISCI was explored. A prospective cohort study of 199 trauma patients followed, to confirm the existence of TISCI and describe its clinical features, risk factors and outcomes. Finally, coronary artery calcium, as a marker of CHD, was evaluated on 432 CT scans of the chest of trauma patients aged 45 years or over, and its association with survival after injury was established.

ACEs and early biomarker rises occurred in trauma patients and both were unrelated to the severity of chest injury. Each was associated with higher mortality, and confirmed the existence of TISCI. Risk factors for the development of the condition included increasing age, worsening tissue injury and shock. A relationship with cytokines was demonstrated, and implicated acute inflammation in the pathogenesis of TISCI. Calcification on CT scans revealed the incidence of CHD in an injured cohort approached 70%, although its presence did not impact survival.

There exists a trauma induced secondary cardiac injury which was related to poorer outcome. The condition was associated with inflammation. CHD was widespread in older trauma patients but was not associated with increased in-hospital mortality.

Declaration

I hereby certify that the work described in this thesis is the result of my own independent investigation, except where otherwise stated. Any assistance received has been acknowledged in the text.

Publications and Presentations

Publications

De'Ath HD, Manson J, Davenport R, et al**.** Trauma Induced Secondary Cardiac Injury is Associated with Hyperacute Elevations in Inflammatory Cytokines. Shock. 2013 May; 39(5):415-420

De'Ath HD, Rourke C, Davenport R, et al. Clinical and Biomarker Profile of Trauma-Induced Secondary Cardiac Injury. British Journal of Surgery. 2012; 99(6): 789–797

De'Ath HD, Vulliamy P, Davies C, Uppal R. A Large Ventricular Septal Defect Complicating Resuscitation After Blunt Trauma. Journal of Emergencies, Trauma, and Shock. 2012;5: 350-2

Presentations (*Abstract*)

De'Ath HD, Oakland K, Davies C, Brohi K. Coronary Artery Calcium Scores on Admission Trauma CT Scans and Their Association with In-hospital Survival. ICNC 11, Nuclear Cardiology and Cardiac CT (ESC). Berlin, Germany – May 2013.

De'Ath HD, Manson J, Rourke C, et al. Trauma Induced Secondary Cardiac Injury is Associated with Acute Inflammation. European Shock Society (ESS) - Taormina, Italy – September 2011. (*Shock 2011; 36(S1):12)*

De'Ath HD, Rourke C, Manson J, et al. Trauma Induced Secondary Cardiac Injury. European Society of Cardiology Congress (ESC) - Paris, France -August 2011. (*European Heart Journal 2011; 32:726*)

De'Ath HD, Rourke C, Davenport R, et al. Cardiac Dysfunction after Trauma: A Real and Present Danger. Society of Academic and Research Surgery (SARS) - Dublin, Ireland - January 2011. (*British Journal of Surgery. 2011; 98 (S2):7*)

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Coronary Artery Calcium and Trauma

List of Abbreviations

AA	Atrial Arrhythmias
ACE	Adverse Cardiac Event
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AIS	Abbreviated Injury Score
BNP	B-Type Natriuretic Peptide
BCI	Blunt Cardiac Injury
CAC	Coronary Artery Calcium
CHD	Coronary Heart Disease
CI	Confidence Intervals
CT	Computerised Tomography
Cx	Circumflex (Coronary Artery)
CAC	Coronary Artery Calcium
CACS	Coronary Artery Calcium Score
ECG	Electrocardiogram
ED	Emergency Department
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
fmol	Fentomole
GCS	Glasgow Coma Scale
H-FABP	Heart-type Fatty Acid Binding Protein
hr(s)	Hour(s)
ICU	Intensive Care Unit
IL-1β	Interleukin 1 Beta
IFNγ	Interferon Gamma
IL-6	Interleukin 6
IL-8	Interleukin 8

IL-10	Interleukin 10
IL-12	Interleukin 12
IQR	Interquartile Range
ISS	Injury Severity Score
L	Litre
LAD	Left Anterior Descending (Coronary Artery)
mEq/L	Milliequivalents per Litre
MI	Myocardial Infarction
mins	Minutes
ml	Millilitre
mmol	Millimoles
MODS	Multiple Organ Dysfunction Syndrome
n	Number
n/a	Not Applicable
ng	Nanogram
nm	Nanometre
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
OR	Odds Ratio
Pg	Picogram
RCA	Right Coronary Artery
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
secs	Seconds
SIRS	Systemic Inflammatory Response Syndrome
TISCI	Trauma Induced Secondary Cardiac Injury
TNFα	Tumour Necrosis Factor Alpha
µl	Microlitre
vs	Versus

CHAPTER ONE

Introduction

1.1 The Significance of Trauma

1.1.1 The Health Impact

Trauma may be defined as injury resulting from penetrating or blunt physical force such as stabbings, falls or road traffic accidents (RTAs). It is a leading cause of death throughout the world. Internationally, trauma leads to nearly six million fatalities per year (WHO, 2009). In the United Kingdom (UK), 16,000 people die annually as a result of injury (Office for National Statistics, 2005). It typically affects a younger, active population, and it is the predominant cause of death in people between the ages of one and forty-four years (CDC, 2010).

Trauma is also the cause of significant morbidity worldwide. It is estimated that for every death due to injury, there are two patients left with permanent serious disabilities (TARN, 2006). In 2004, according to the World Health Organization, the average global burden of disease was 237 DALYs (Disability Adjusted Life Years) per 1000 population (WHO, 2004). RTAs alone were the ninth leading cause, accounting for 2.7% of the total. Comparatively, the principal source of disease burden was lower respiratory tract infections, which constituted only a slightly higher 6.2% of all DALYs.

Following trauma, patients may not only be affected with physical impairments but may also suffer from psychological disorders. Injured individuals may experience dramatic changes in their social circumstances, with an inability to return to work, thereby incurring financial difficulties. Others may have problems integrating back into society.

The detrimental aftermaths of injury are not solely limited to the trauma patient. Family and friends may become permanent carers for those with disabilities and may have to dramatically alter their own lifestyles.

Patients may experience behavioural and mood changes and pose risks to themselves or others, which in turn can result in breakdown of relationships and family.

1.1.2 The Financial Burden of Trauma

The management of trauma is very expensive and represents a serious fiscal strain to healthcare providers, individuals concerned and society alike. Studies have estimated that in the National Health Service (NHS), the mean hospital cost of a blunt trauma patient is £9,530 (Christensen et al., 2008b), whilst that of an individual with penetrating injury is £7,983 (Christensen et al., 2008a). National Audit Office (NAO) figures place estimated NHS expenditure of complex trauma management around £0.3-0.4 billion annually (NAO, 2010). Although harder to calculate, the NAO further states that the loss of economic output caused by major trauma could be up to £3.7 billion.

According to data describing the financial burden of trauma in the United States (US), for example, the cost of 50 million injuries in the year 2000 alone was $406 billion (Finkelstein et al., 2006). In terms of productive years lost, therefore, trauma in the US now surpasses any other disease and represents the most expensive category of medical treatment.

1.1.3 Trauma and Research

In spite of the global impact of trauma, it remains a field characterised by a lack of evidence-based practice. This is fundamentally due to a relative paucity of research.

Both the Rand report in the UK (Morgan Jones et al., 2011) and the National Trauma Institute in the US have recently highlighted that trauma remains a poorly recognised public health problem with disproportionately low investments into research. The Rand report concluded that less than one percent of the total UK public expenditure on health research is allotted to trauma. Whilst in the US, in terms of potential life years lost (defined by the millions of dollars per years of potential life lost per 100,000 population), the National Institutes of Health (NIH) support ratio for trauma is only 10 cents, contrasted with US $3.51 for HIV and US $1.65 for cancer. Indeed the total 2008 NIH budget allocation for traumatic injury research was $308 million, compared to a

cancer research allowance of $5.6 billion and an HIV/Aids provision of $2.9 billion (National Trauma Institute, 2010).

In addition to poor funding, trauma remains a challenging field in which to undertake clinical research given that there are difficulties in enrolling patients who may present in physiological extremis, and outside traditional working hours. This is further compounded by the problems associated in obtaining consent in patients who may be unconscious, distressed or lacking capacity.

Consequently, not only is the overall volume of research in trauma limited, but the specific clinical fields investigated within the specialty are narrow.

1.1.4 Trauma Associated Cardiac Injury and Dysfunction

The heart is one of the body's vital organs, yet there exists little evidence on the relationship between it and trauma. To date, most of the literature on the interaction between trauma and the heart has been limited to studies of direct cardiac injury (*Section 1.3*). Much of this evidence is restricted to individual clinical reports or case series.

Indirect, secondary cardiac injury remains a relatively unexplored clinical phenomenon (*Section 1.5*), despite the fact that it has been reported in the non-trauma literature, and demonstrated in experimental studies of trauma-haemorrhage (*Section 1.4*). A trauma induced secondary cardiac injury (TISCI) has neither been specifically identified, nor fully characterised even though it may have important clinical implications in injured patients and their outcomes.

There also remains inconclusive evidence on both the overall incidence of pre-morbid cardiac disease in trauma together with its influence of on outcome, and particularly survival (*Section 1.8*).

The overall aim of this project, therefore, was to provide further evidence and clarification on the relationship between trauma and the heart; a neglected, important and novel area for research.

1.2 Characteristics of Trauma

In civilian trauma, young males are most often affected and a blunt mechanism of injury predominates. In the UK, falls are the commonest cause of trauma (*Figure 1.1*). Naturally, specific characteristics vary between each country.

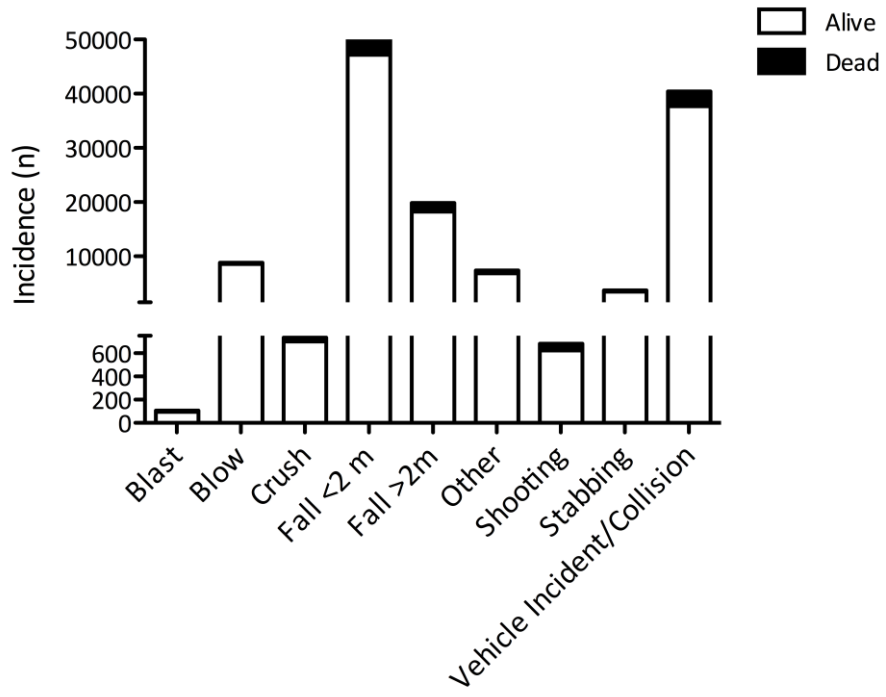


Figure 1.1. A summary of trauma in England and Wales from 2002 to 2011

Blow includes blunt assaults, Others relate to injuries sustained following industrial and farming accidents, for example. (Data courtesy of the Trauma Audit & Research Network).

1.2.1 Measuring Injury Severity

The extent of overall injury is classified by the injury severity score (ISS), an anatomical scoring system. The body is divided into six regions (head and neck, face, chest, abdomen, extremity and external) and each area is ascribed an abbreviated injury score, the AIS, from 0 to 6 (*Table 1.1*).

Table 1.1. AIS Scores Illustrated with Examples of Chest Injury

AIS	Severity of Injury	Examples
0	None	Not applicable
1	Minor	Rib fractures at any location (unilateral/bilateral) with no flail segment
2	Moderate	Sternal fracture
3	Serious	Unilateral lung contusion or haemothorax
4	Severe	Haemothorax with >20% circulating volume loss
5	Critical	Tension pneumothorax or laryngeal/tracheal separation
6	Unsurvivable	Heart avulsion

1.2.2 The Epidemiology of Death in Trauma

The majority of deaths in trauma occur early, either in the pre-hospital phase or in the acute period following arrival to hospital (Evans et al., 2009, Cothren et al., 2007). Most of these fatalities are the result of central nervous system injury. Thereafter, exsanguination is the second leading cause (Chalkley et al., 2011, Søreide et al., 2007). In patients admitted to hospital, multiple organ dysfunction syndrome (MODS) is the major cause of late death, especially amongst those in critical care (Sauaia et al., 1995, Ciesla et al., 2005). Currently, however, neither the extent nor the clinical relevance of cardiac dysfunction in post-traumatic MODS is known.

Following discharge, trauma patients' risk of death is approximately twice as high as age and sex matched uninjured cohorts for up to ten years post injury (Cameron et al., 2005, Davidson et al., 2011). Cardiovascular disease may account for nearly 25% of these deaths (Probst et al., 2009), and is also more common in patients suffering from post-traumatic stress disorder (Bedi et al., 2007). This suggests that trauma could be linked to secondary cardiac dysfunction associated with poorer long-term survival.

However, the relationship between injury and the heart is poorly understood at present. There is a need, therefore, for research on the theme of trauma associated cardiac injury and dysfunction.

1.3 Direct Cardiac Injury

Direct cardiac injury is primary cardiac damage. It is the result of either penetrating or blunt physical trauma directly to the thorax and heart.

1.3.1 Penetrating Cardiac Injury

Penetrating cardiac injuries are associated with very high mortality rates, and are usually the result of stab or gun shot wounds (Tang et al., 2011). The heart chamber most commonly affected is the right ventricle, followed by the left ventricle (Asensio et al., 1998). Combinations of injuries may occur, and the treatment of penetrating cardiac trauma is usually surgical.

1.3.2 Blunt Cardiac Injury

Blunt cardiac injury (BCI) is a term used to encompass a range of pathologies. These include myocardial contusions, atrial and ventricular septal defects (*Figure 1.2 A&B*), valve and coronary artery damage and cardiac rupture. They are often accompanied by trauma to additional areas, including other thoracic structures, the head, abdomen, spine and the extremities.

The leading cause of BCI is an RTA, followed by falls from height. The right side of the heart is most frequently damaged (Turan et al., 2010).

There are several mechanisms implicated in leading to BCI. These include direct praecordial impact with subsequent transmission of kinetic energy to the heart, and sudden deceleration leading to cardiac disruption. In addition, crush injury from compression of the organ between the spine and sternum, and sudden rises in intra-thoracic pressure due to compression of the abdomen or lower extremities have all been implicated (Schultz et al., 2004).

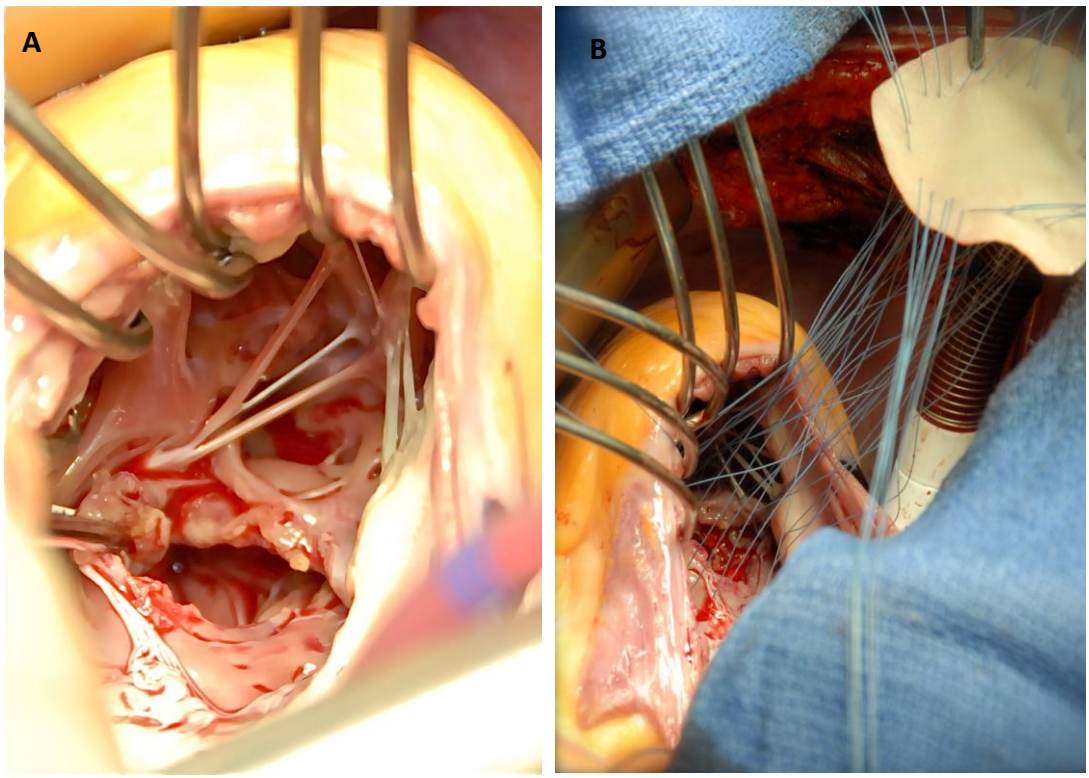


Figure 1.2. A&B. Traumatic ventricular septal resulting from blunt thoracic injury

A: View of the defect. **B:** Photograph of bovine patch parachuted into place to seal the defect (images taken during open cardiothoracic repair).

The commonest BCIs are myocardial contusions. Their precise incidence is unknown, however, as there exists no standard global consensus on their diagnostic criteria. In addition, because the clinical significance of contusions remains contentious, some clinicians may not always actively seek to detect their presence.

The presentation of BCI is variable, and dependent both on the nature and location of the injuries (Shorr et al., 1987). Myocardial contusions may present silently, or alternatively may lead to arrhythmias (Guan et al., 2007, Riezzo et al., 2008). Cardiac ruptures are usually fatal and diagnosed during postmortem examination.

Other manifestations of BCI include evidence of cardiac ischaemia or dysfunction, including arrhythmias (Ismailov et al., 2007), heart failure and cardiogenic shock.

The presentation of BCI may be delayed (Sakka et al., 2000) and lead to chronic health problems.

Limited evidence from a handful of patients has suggested that myocardial injury may lead to potentially fatal arrhythmias even up to a year after the initial traumatic event (Amino et al., 2009). Indeed, there is research to suggest that BCI associated with valvular insufficiency could be a potential risk factor for congestive heart failure in the long-term (Ismailov et al., 2005).

The basis for diagnosis of BCI is the subject of ongoing debate. Electrocardiographic (ECG) findings are both variable and non-specific, and may include sinus tachycardia, conduction defects, bundle branch blocks or evidence of global ischaemia (Babu et al., 2009). Cardiac biomarkers are helpful, particularly in the diagnosis of contusion, and the evidence currently favours the use of Troponin (primarily T and I) (Peter et al., 2006, Sybrandy et al., 2003).

Echocardiography may facilitate the diagnosis of BCI, and is useful in assessing cardiac function. A transoesophageal approach may be of value when transthoracic images are suboptimal (Karalis et al., 1994). More recently, there is mounting evidence that cardiac magnetic resonance imaging (MRI) may provide the most detailed assessments of cardiac function and morphology following blunt chest trauma (Dellegrottaglie et al., 2008).

The treatment of BCI is predominantly based on direct management of the complications that may arise, such as arrhythmias or heart failure.

1.4 Indirect, Secondary Cardiac Injury – The Experimental Evidence

Post-traumatic secondary cardiac injury is the development of cardiac injury or dysfunction in the absence of direct trauma to the heart.

1.4.1 Experimental Evidence of Post-traumatic Secondary Cardiac Injury

The majority of evidence to suggest that trauma can lead to secondary cardiac injury and dysfunction has been presented in animal studies of experimental trauma-haemorrhage. Most of the published literature has focused on research in rodents.

One unit that has been notably active in this field is the centre led by Dr I H Chaudry, at the University of Alabama in the US. The group have not only sought to determine the pathogenic processes that lead to post-traumatic secondary cardiac injury, but also to identify mechanisms that may mitigate such damage to the heart.

To replicate the clinical scenario of soft tissue trauma with blood loss and associated hypotension, both this unit and others have based their research on variations of the following methodology. A laparotomy incision is combined with controlled haemorrhage (through cannulated femoral arteries) until a mean arterial pressure (MAP) of 35 +/- 5 mmHg is achieved. When the animals can no longer maintain this pressure, Ringer's lactate is given until 40% of the volume bled out is returned. Thereafter, animals are resuscitated with shed blood, and eventually euthanised at varying time points following the experiments.

Using this methodology, studies have demonstrated that cardiac dysfunction occurs within two hours (hrs) of trauma-haemorrhage, and may remain 24 hrs thereafter. Cardiac output, stroke volume and positive and negative dP/dt (an index of ventricular performance) are all diminished following soft tissue injury and haemorrhage, whilst total peripheral resistance is amplified (Yang et al., 2007).

Interleukin 6 (IL-6) is an inflammatory cytokine produced by several cells including monocytes, T and B lymphocytes, fibroblasts, endothelial cells, neutrophils, macrophages and cardiomyocytes. Secondary cardiac dysfunction following trauma-haemorrhage may be associated with increases in both plasma and cardiac IL-6 (Yang et al., 2004), as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), intercellular adhesion molecule 1 (ICAM-1), myeloperoxidase (MPO) activity, and cytokine-induced neutrophil chemoattractant (CINC) 1 and 3 amongst others (Yang et al., 2006). CINC 1 and 3 belong to the interleukin 8 (IL-8) family, which are in turn produced by a variety of cells including monocytes, T lymphocytes and macrophages. These proteins are all potent chemotactic factors for neutrophils.

Blockade of IL-6 with antagonists leads to diminished levels and activities of the molecules described above, implicating inflammation, and IL-6 in particular, in secondary cardiac dysfunction induced by trauma-haemorrhage.

Non-lethal mechanical trauma has also been shown to induce the production of tumour necrosis factor alpha (TNFα), an inflammatory cytokine produced primarily by macrophages. When normal cardiomyocytes are exposed to TNFα in the plasma from animals subject to such injury, increased activation of caspase-3 (a marker of apoptosis) was seen (Li et al., 2007). In association, amplification of inducible nitric oxide synthase (iNOS) expression with nitric oxide (NO) and superoxide production occurs. Decreased adiponectin (an anti-inflammatory adipokine) concentrations are also observed (Liu et al., 2011). In these models, cardiomyocyte apoptosis is related to cardiac dysfunction, and this may be reversed when apoptosis is blocked (Tao et al., 2005).

The inhibition of TNFα may lead to reduction of this cellular apoptosis and further limit the expression of iNOS, the overproduction of NO and superoxide and the excessive protein nitration in the heart (Li et al., 2007). Additionally, adiponectin levels may be restored with subsequent attenuation of cardiac ischaemia-reperfusion injury.

Haemorrhagic shock alone may lead to an increase in cardiac TNFα in mice within an hour of resuscitation, and this is associated with left ventricular dysfunction within six hours (Vallejo et al., 2004). Importantly, the failure to restore cardiac systolic function, including blood pressure, may be a major determinant of mortality (Chatpun et al., 2011). Following haemorrhage, the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) in the heart is also associated with increased TNFα messenger RNA expression. The activation of p38 MAPK is in turn linked to subsequent ventricular arrhythmias, and microscopic inflammatory damage to the heart, including neutrophil accumulation (Sato et al., 2007).

When haemorrhagic shock and ventricular fibrillation (VF) are induced in pigs, and followed by resuscitation, female animals manifest lower evidence of cardiac injury (lower Troponin I levels) and higher survival rates compared to males (Semenas et al., 2010). Although demonstrated in this study of sexually immature piglets with similar hormone levels across the sexes, there is a bulk of convincing evidence that the female gender confers protection to the heart against post-traumatic secondary injury (Yang et al., 2006, Wang et al., 2005).

Research suggests a principal mechanism is the attenuation of the inflammatory response by oestrogen. The administration of 17β-oestradiol after trauma-haemorrhage has been shown to restore cardiac function and reduce injury to the heart. 17β-oestradiol is believed to mediate its cardioprotective effects mainly through cardiac ER-β receptors (Ba et al., 2008), and the specific pathways through which its effects are exerted are the subject of multiple studies (Yu et al., 2007).

One such mechanism suggested is the upregulation of p38 MAPK activation, together with increased endothelial NOS expression in the heart (Kan et al., 2008). Other studies have also shown the administration of 17β-oestradiol prevents increases in plasma IL-6, TNFα, CINC-1 and ICAM-1, and improved cardiac performance results (Mizushima et al., 2000a).

Another proposed mechanism for the cardioprotective role of oestrogen is via the hypoxia-inducible factor (HIF) 1α pathway. HIF-1 α is a protein complex which is expressed in response to hypoxia and cellular stress and it is found in higher levels in the heart following trauma-haemorrhage. It increases vascularisation of hypoxic areas and upregulates expression of IL-6.

Administration of both oestrogen and HIF-1α inhibitors has been shown to reduce cardiac levels of molecules implicated in cardiac damage. These include IL-6, HIF-1α and NF-κB (Nickel et al., 2009).

The administration of 17β-oestradiol has been shown to improve cardiac performance and normalise cardiac and systemic levels of IL-6 and TNFα, together with several cardiac chemokines including MPO, ICAM-1, CINC-1. This action may also be the result of the upregulation of heme oxygenase 1, a heat shock protein (Hsu et al., 2009). Heat shock proteins (hsp) provide cellular protection against exogenous stress and the upregulation of others including hsp 32, 60, 70, and 90 has also been shown following 17β-oestradiol administration, with a subsequent cardioprotective effect (Yu et al., 2006). Similarly, cellular stress prior to trauma-haemorrhage leads to the induction of hsp 70, and diminished plasma TNFα levels and improved cardiac function may result (Mizushima et al., 2000b, Meng et al., 2002).

A small number of further studies have examined the roles of additional hormones such as Flutamide (Hsieh et al., 2005a, Hsieh et al., 2005b) and others (Shimizu et al., 2006) in trauma-haemorrhage models. All have repeatedly demonstrated secondary cardiac injury and dysfunction following soft tissue injury and haemorrhage, and have also implicated inflammation in the process.

Additional mechanisms in post-traumatic secondary cardiac injury and dysfunction have also been proposed. These include gut-induced cardiac dysfunction in association with abnormalities of calcium handling (Sambol et al., 2008, Lee et al., 2008).

Furthermore, the importance of mitochondria has been highlighted (Jian et al., 2011), and both the upregulation and improvement of their function are suggested to be cardioprotective following trauma-haemorrhage (Hsieh et al., 2006, Jian et al., 2012).

Similarly, increased tissue levels of O-linked N-acetylglucosamine (O-GlcNAc) may improve cardiac function and diminish TNFα and IL-6 mRNA levels, NF-κB and NF-κB DNA binding and ICAM-1, and MPO activity in the heart (Zou et al., 2007, Zou et al., 2008).

In general, the experimental evidence establishes the existence of an acquired secondary cardiac injury and dysfunction in animal models of trauma and haemorrhage. The studies demonstrate that cytokines and inflammation lead to functional rather than structural changes in the heart. These result in decreased contractility and myocardial depression mediated by endogenously produced pro-inflammatory factors. They also generate cardiomyocyte injury and apoptosis through oxidative and nitrative stresses. This in turn may further compound cardiac dysfunction.

Inhibition of inflammation and pro-inflammatory factors may normalise cardiac function and reduce the extent of injury to the heart. Indeed, there is evidence that anti-inflammatory resuscitation may confer a survival benefit, but whether this is due to an improvement in cardiac function has not been proven (Cai et al., 2009).

1.4.2 Limitations and Applicability of the Experimental Evidence

The experimental literature presents convincing evidence that tissue injury and haemorrhage may lead to secondary cardiac injury and dysfunction.

The studies have combined histological analysis of heart tissue complete with assessments of cardiac function to provide confirmation of indirect injury to the heart resulting from trauma and blood loss. They demonstrate that acquired myocardial dysfunction occurs in the absence of pre-existing, intrinsic cardiac disease.

There are, however, restrictions to the experimental studies which limit both their applicability and their relevance to the clinical setting.

Trials are designed to create damage to the heart, leading to artificial and prescribed scenarios that are not reflective of the true clinical context in which trauma patients are observed and managed. Secondary cardiac injury and dysfunction are observed because they are the actively desired product of the research methodology.

In these studies, the animals are severely traumatised and shocked artificially, usually with an identical mechanism of injury and the same degree of physiological shock. Consequently, it is difficult to draw conclusions from the experimental evidence and apply them to whole trauma populations, who present with a very wide variety of injuries and a broad spectrum of physiological derangement.

Furthermore, physiological traits are not comprehensively reported and ISS is not measured in animal tests. As such, these studies fail to identify or even to suggest those patients at risk of secondary cardiac injury outside of those who are severely injured and shocked.

Moreover, all creatures are euthanised after the experiments at designated time points. Clinical outcomes of secondary cardiac injury and dysfunction can therefore seldom be identified, especially if these include aspects commonly reported in the clinical literature such as length of stay or in-hospital mortality. In addition, the experiments themselves are limited to small numbers of animals, which potentially undermine the statistical power of their findings.

One centre has dominated the literature, so evidence lacks validation from multiple units reporting additional varied experiments in this field.

Finally, the experimental literature is not directly translational to clinical practice. The animals are not exposed to the same degree and nature of interventions as trauma patients are, including medication, procedures, multiple operations and superimposed factors such as infection. The effects these have on the human heart are therefore inevitably neglected.

Most of the studies are performed in rodents, which make results poorly comparable to humans. Animals are young and healthy, and do not suffer co-morbidity or poor background physiology (e.g. due to age, smoking, alcohol excess or obesity). This further limits the applicability of the experimental evidence to the clinical context.

Clinical evidence is required, therefore, to substantiate the findings of the animal model experiments.

1.5 Indirect, Secondary Cardiac Injury – The Clinical Evidence

There are few clinical studies investigating the relationship between trauma and secondary cardiac injury and dysfunction. Those in existence can be divided broadly into two categories. The first are studies that have demonstrated cardiac damage through clinical manifestations (such as adverse cardiac events or histological evidence, *Section 1.5.1*). The second are those that have demonstrated injury to the heart using cardiac biomarkers (*Section 1.5.2*).

1.5.1 Post-Traumatic Secondary Cardiac Injury and Clinical Manifestations

Perhaps the earliest published evidence to suggest that the heart is susceptible to post-traumatic secondary cardiac injury was presented as far back as 1922. Cardiac rupture was described in an individual who sustained a crush injury to the abdomen, in spite of the absence of trauma to the thorax (Stephens, 1922). In 1933, postmortem descriptions of heart rupture without chest wall injury were presented, and a mechanism of increased intravascular hydrostatic pressure due to compression of the legs and abdomen was proposed (Beck et al., 1933). Subsequently, an isolated study of traumatic heart disease found no relationship between the severity of thoracic trauma with the incidence of cardiac injury (Arenberg, 1943).

Thereafter followed a relative hiatus of research in this field, and only a handful of studies have since investigated the specific relationship between trauma and indirect, secondary cardiac injury and dysfunction.

Amongst the first was a postmortem survey which revealed secondary myocardial lesions in the victims of homicide (Cebelin et al., 1980). In the analysis, coroners' records of 15 patients were examined whereby death followed assault, but no trauma to the brain, the viscera or any significant bone fractures were present.

Microscopic examination of the hearts revealed the majority of individuals had myofibrillar degeneration, namely scattered clusters of myocytes with homogeneous eosinophilic transverse bands alternating with areas of fine granulation. Moreover contraction bands were observed, a process whereby hypercontraction (secondary to catecholamine surges) of the cardiac muscle leads to structureless masses of contractile protein. Accordingly, the data presented provided good evidence of post-traumatic secondary cardiac injury, and suggested that such heart damage was the result of the cardiotoxic effect of catecholamines.

Nonetheless, this study was prone to weaknesses including its retrospective nature and small study population. By virtue of postmortem data, these findings could not be translated to living patients, and microscopic evidence of cardiac injury is of uncertain clinical significance. Because neither the degree of injury severity nor physiological derangement prior to death was detailed, those at risk of secondary cardiac injury could not be deduced from this work.

Finally, 53% (n=8/15) of the study subjects had pre-existing heart disease. To accommodate for this a control group was created and included patients who died pre-hospital with atherosclerotic disease. These individuals demonstrated no such changes in their myocardium. They did not receive resuscitation in hospital, however. Hence they neither were directly comparable, nor excluded the possibility that pre-morbid heart disease was the underlying cause of the post-traumatic secondary cardiac injury observed.

In spite of these limitations, the findings of this study were reinforced by later work in pathology, which demonstrated similar myocardial lesions induced by trauma and its subsequent treatment (Yoshida et al., 1992). In addition to contraction bands, varying concentrations of calmodulin (a marker of early cardiac ischaemia) were present in the hearts of dead patients who had been subject to severe injury followed by attempts at resuscitation.

This marker was observed despite in many cases an absence of macroscopic cardiac damage. In this particular analysis, however, chest injury and cardiac damage were not identified independently.

An earlier cohort study of some 2,820 individuals revealed that critical illness was associated with an increase in cardiac arrhythmias (Artucio et al., 1990).

Severely injured patients accounted for four percent of the population, and nearly half of these had a cardiac arrhythmia (44%). Atrial tachyarrhythmias were the most common, and occurred in ten percent of the trauma patients. Of these, atrial fibrillation (AF) was the most frequent diagnosis. In addition, ventricular arrhythmias, nodal rhythms, atrial bradyarrhythmias and conduction defects were also observed. More than half the trauma patients with cardiac arrhythmias died, but rhythm disturbances were not significantly associated with death.

This study was among the earliest to describe cardiac arrhythmias in a trauma population, and revealed that the incidence of such disorders was high. Nonetheless, the analysis was retrospective, and because the research was not solely dedicated to trauma, the actual injured population included was relatively small (107 patients).

Furthermore, in the absence of detail on patient characteristics such as the ISS and the extent of thoracic injury, no conclusions could be drawn on whether these arrhythmias were manifestations of secondary cardiac injury and dysfunction. Finally, although the study revealed that cardiac arrhythmias were not associated with a higher risk of death, the authors themselves acknowledge that the study was not designed to establish the outcomes associated with such rhythm disturbances.

A decade later, the link between trauma and myocardial infarction (MI) was investigated in a single centre, retrospective database analysis (Moosikasuwan et al., 2000). Of the 11,866 injured patients identified over a period of nearly ten years, nineteen (0.16%) were diagnosed with an MI.

In five (0.04%) of these individuals, the MI occurred definitively post-injury.

This led the authors to conclude that trauma may predispose patients to an increase in adverse cardiac events (ACEs).

The study was nonetheless subject to a number of limitations. In the first instance, the research investigated only one diagnosis, namely MI, and did not establish the incidence of a wider range of ACEs, such as arrhythmias or bundle branch blocks for example. Because of its retrospective nature and the use of a database to ascertain events, it is likely that the authors also underestimated the true incidence of MI following trauma. Only 0.16% of the study population had an MI despite the fact that the national incidence of MI in the US is around 2.7% (Roger et al., 2012). All the patients in whom an MI was diagnosed were older, and each had risk factors for developing cardiovascular events, including pre-existing heart disease. Two (40%) of the patients also sustained significant chest injuries.

The number of individuals reported was very small, with insufficient detail about injury and physiology characteristics. Accordingly, the study suggested more that injury predisposes to cardiac events in older frailer patients with pre-existing heart disease, and rather less that trauma may lead to secondary cardiac injury.

A small case-control study published in 2003 investigated the incidence of cardiac events following burns. Trauma patients, matched for age, sex and length of hospital stay were used as the control group (Meyers et al., 2003). Although the authors found that burns patient were at an increased predisposition to cardiac events, trauma patients, in contrast, were not. In 56 injured individuals, there were no cases of MI, and only one of ventricular tachycardia. Three instances of premature ventricular beats and 12 cases of sinus tachycardia (ST) were also recorded. Accordingly, the study provided no supporting evidence for the existence of trauma induced secondary cardiac injury or dysfunction.

Little detail, however, is provided about these injured patients thereby making it difficult to interpret the paper's findings in the wider trauma context.

Being retrospective in nature, the authors acknowledge they may have underestimated the incidence of cardiac events, and in particular brief spells of arrhythmia. The research was also further limited by its relatively small study population.

In contrast, a link between trauma and secondary cardiac injury and dysfunction was presented in an American retrospective review of a million injured patients (Ismailov et al., 2005). Data from 19 states were examined to identify the nature of injuries associated with the risk of developing an acute MI, based on the International Classification of Diseases - Ninth Revision-Clinical Modification (ICD-9-CM) discharge diagnosis codes.

Of some 1,051,081 injury discharges, 32,616 (3.10%) acute MIs were diagnosed. The study revealed blunt chest trauma was associated with an increased risk of MI. More significantly, the authors demonstrated that abdominal or pelvic trauma led to a 65% (Odds Ratio [OR] 1.65, 95% Confidence Intervals [95% CI] 1.26-2.16) increase in the risk of acute MI in patients below the age of 46 years, regardless of confounders or coronary artery status.

In patients over the age of 46 years, abdominal or pelvic trauma alone nearly doubled the risk of acute MI (OR 1.93, 95% CI 1.42-2.62). When the diagnosis was confirmed by coronary angiography, the risk of MI was six times greater (OR 6.33, 95% CI 4.00-9.99).

This landmark study was the first large-scale analysis to demonstrate that trauma could be a non-atherosclerotic mechanism that could lead to MI. It provided good evidence that trauma may be associated with secondary cardiac damage, independent of the severity of thoracic injury. It also implied that previous investigations of cardiac events in trauma

(Moosikasuwan et al., 2000) had significantly underestimated the incidence of MI in injured populations.

Conversely, this study was limited to analysing discharge codes for diagnoses, and was essentially retrospective in nature.

It too was therefore subject to potential under-reporting of cardiac events and data inaccuracies. Such methodology also meant that neither individual patient characteristics nor specific risk factors for post-traumatic MI were identified.

It is also worth noting that when the diagnosis of MI was confirmed by coronary angiography in patients under the ages of 46 years, abdominal and pelvic trauma was no longer a significant risk factor when adjusted for using logistic regression (OR 0.88, 95% CI 0.21-3.76). The study only investigated the dependent variable of MI, but did not look at the nature and features of other ACEs. It was also not clear whether skull fractures, intracranial injuries, and extremity trauma were excluded, thus restricting the applicability of the findings to a specific subset of injured patients only. The final limitation of the study is that the authors did not examine and compare the outcomes of trauma patients with and without MI, and so whilst they demonstrated the possible existence of post-traumatic secondary cardiac injury, they did not reveal the clinical significance of it.

A later French paper reported the incidence and risk factors associated with AF in injured patients on a surgical intensive care unit (ICU) (Seguin et al., 2006). Over an 18 month period, 293 patients were prospectively recruited, of which 16 (5.5%) developed AF.

Risk factors for AF were identified using logistic regression analysis and included age over 40 years (OR 6.3, 95% CI 1.4-28.7), three or more body regions injured (OR 6.2, 95% CI 1.8-21.4), catecholamine use (OR 5.7, 95% CI 1.7-19.1), the presence of systemic inflammatory response syndrome (SIRS) (OR 4.4, 95% CI 1.2-16.1) and finally the degree of physiological derangement using the Simplified Acute Physiology Score II (OR 11.6, 95% CI 1.3-10.3).

Although AF was associated with twice the death rate, this was not found to be statistically significant. ICU length of stay was longer in the AF cohort.

This study was not only the first to investigate AF specifically in trauma patients, but also to be undertaken prospectively. As such, it provided data on risk factors for AF, and described the outcomes associated with this cardiac event. This was also the first clinical paper to hint indirectly at a relationship between a post-traumatic secondary cardiac event and inflammation, through the association of AF with factors known to cause or result from inflammation.

In contrast to their previous research (Seguin et al., 2004), this analysis demonstrated that AF was not associated with thoracic injury, and hence provided further evidence that trauma may cause secondary damage to the heart. These conflicting results might be explained by the fact that the authors' previous investigation in 2004 examined AF in a heterogeneous population of patients on ITU. It was thus not specific to trauma patients (who accounted for 34% of the study with only 1% developing AF). Moreover, in their prior analysis blunt thoracic trauma was the only variable measured.

Nonetheless, there were limitations to the more recent dedicated trauma study of 2006. Again only one ACE was investigated despite previous evidence that trauma may also lead to MI. The research was conducted in a specific cohort of patients, namely the critically injured, and thus the overall incidence and risk factors associated with secondary cardiac injury in all types of trauma populations was not identified. Finally, given the wide confidence intervals produced by the logistic regression model, it may be that this study was underpowered and included too few numbers of patients. This may have led to inaccurate results.

Atrial arrhythmias (AA) were the subject of a retrospective study of 3,499 critically injured patients on an American ICU (Hadjizacharia et al., 2011). AA were present in roughly six percent of their population (n=210).

In this analysis the only independent risk factor for developing an arrhythmia was age over 55 years (OR 4.61, 95% CI 3.44-6.17). AA were associated with poorer outcomes, including higher mortality (OR 2.24, 95% CI 1.50-3.33), longer lengths of hospital and ITU stay, and more days spent on a ventilator. Patients with AA on beta-blockers had lower mortality (OR 0.41, 95% CI: 0.17-0.91).

Again this study suggested the existence of trauma associated cardiac dysfunction and in this instance, its association with worse outcomes. No relationship was found between AA and chest trauma, although the authors did not state that this was clearly adjusted for in a regression model. The study was also weakened by its retrospective nature, the investigation of solely one category of ACE (AA) and once again restricting the analysis to critically injured patients only.

Remarkably, all of the studies described above are also limited by the fact that none have attempted to substantiate further the presence of secondary cardiac dysfunction with biochemical evidence of heart injury.

The use of cardiac specific biomarkers is common both in clinical practice and research in predominantly medical specialties. In trauma, cardiac biomarkers have primarily been investigated in the context of BCI, and only a handful of studies have investigated their applicability in determining the secondary effects of trauma on the heart.

1.5.2 Post-Traumatic Secondary Cardiac Injury and Cardiac Biomarkers

1.5.2.1 Brain-type Natriuretic Peptide

BNP is a cardiac neurohormone synthesised and secreted by the ventricles of the heart. It is released as the precursor molecule pre-prohormone BNP, and is subsequently cleaved by proteolysis into proBNP (108 amino acids) and a signal peptide (26 amino acids). Thereafter, proBNP is split into BNP (32 amino acids) and the inactive N-terminal fragment prohormone BNP peptide (NT-proBNP, 76 amino acids).

BNP is released in response to excessive stretching of cardiomyocytes. It causes a decrease in peripheral vascular resistance leading to a reduction in blood pressure (*Figure 1.3*). BNP suppresses the renin-angiotensin-aldosterone axis and leads to natriuresis (Levin et al., 1998).

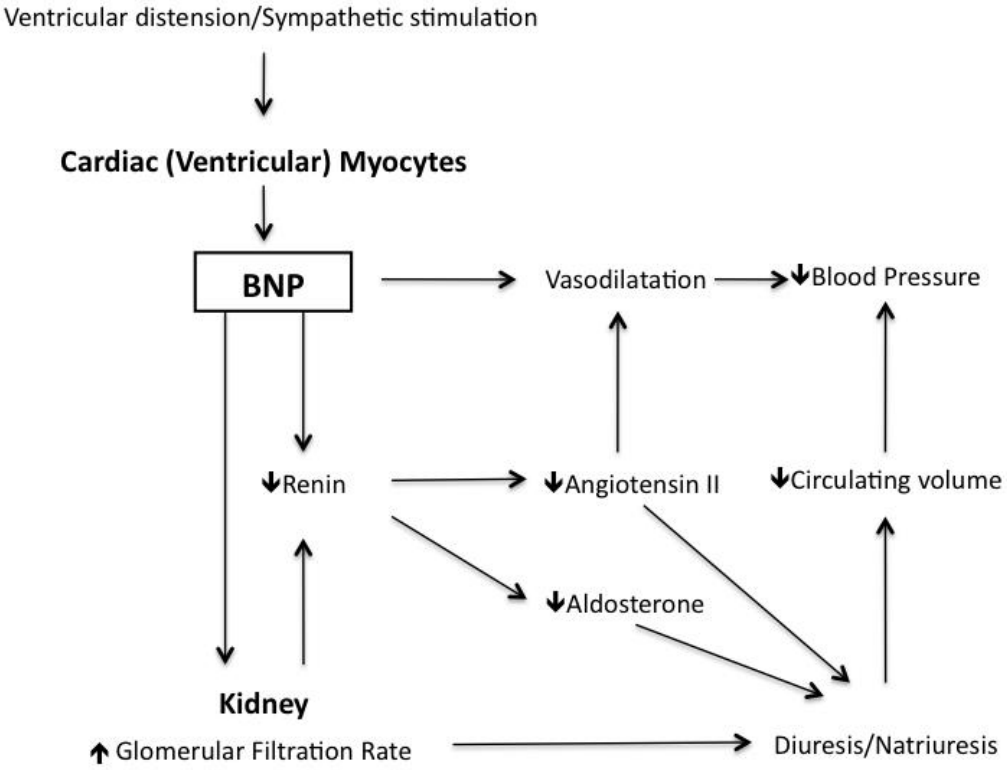


Figure 1.3. The action of BNP

Traditionally, BNP has been used as marker of cardiac failure. Increasingly, however, it is being recognised as an indicator of myocardial dysfunction and injury in a variety of disease states. Evidence has demonstrated its prognostic value in terms of predicting both ACEs and survival in non-traumatic conditions (Post et al., 2008, Meyer et al., 2007, Choi et al., 2009, Charpentier et al., 2004, Kistorp et al., 2005).

In trauma patients, BNP been shown to be elevated in the absence of echocardiographic evidence of congestive heart failure, with release unrelated to head injury (Stewart et al., 2007). Less convincing data has also suggested a relationship between increasing BNP levels and volume overload (Friese et al., 2007).

Indeed a very weak pattern of association between lower biomarker values and blood loss has been proposed (Kia et al., 2006).

In a prospective study of 26 multiply injured patients, an inverse relationship was established between NT-proBNP and cardiac index (Kirchhoff et al., 2008).

The biomarker was measured at six time points between admission and 72 hrs. All the patients had rises in NT-proBNP, and levels were significantly correlated with MODS. This data suggested that NT-proBNP may be valuable in evaluations of cardiac impairment, and might indicate the severity and prognosis of MODS in the trauma setting.

Nonetheless, the findings were from a very small pilot study of critically injured patients. Individuals with head injuries and pre-existing heart disease were excluded. Consequently, the findings of this research were not directly translational to whole trauma populations given that these are by definition very heterogeneous in nature.

1.5.2.2 Troponin I

Troponin is found in skeletal and cardiac muscle and is made up of three subunits, Troponin C, Troponin T and Troponin I.

Troponin C binds with calcium to produce changes in Troponin I. Troponin T and I are cardiac regulatory proteins that control the interactions between actin and myosin (Sharma et al., 2004). Troponin I inhibits the formation of bridges between actin and myosin in the resting state, and is highly specific to the heart (*Figure 1.4*).

Plasma elevations of Troponin I reflect damage to the heart but do not indicate the mechanism (Babuin et al., 2005). Raised levels have demonstrated cardiac injury in a number of disease states (Adams et al., 1993, Lim et al., 2006).

Troponin I has also been shown to be of prognostic value, predicting both future ACEs and death in a variety of clinical settings (Wu et al., 2004, Quenot et al., 2005, King et al., 2005, Kim et al., 2002, Chong et al., 2008).

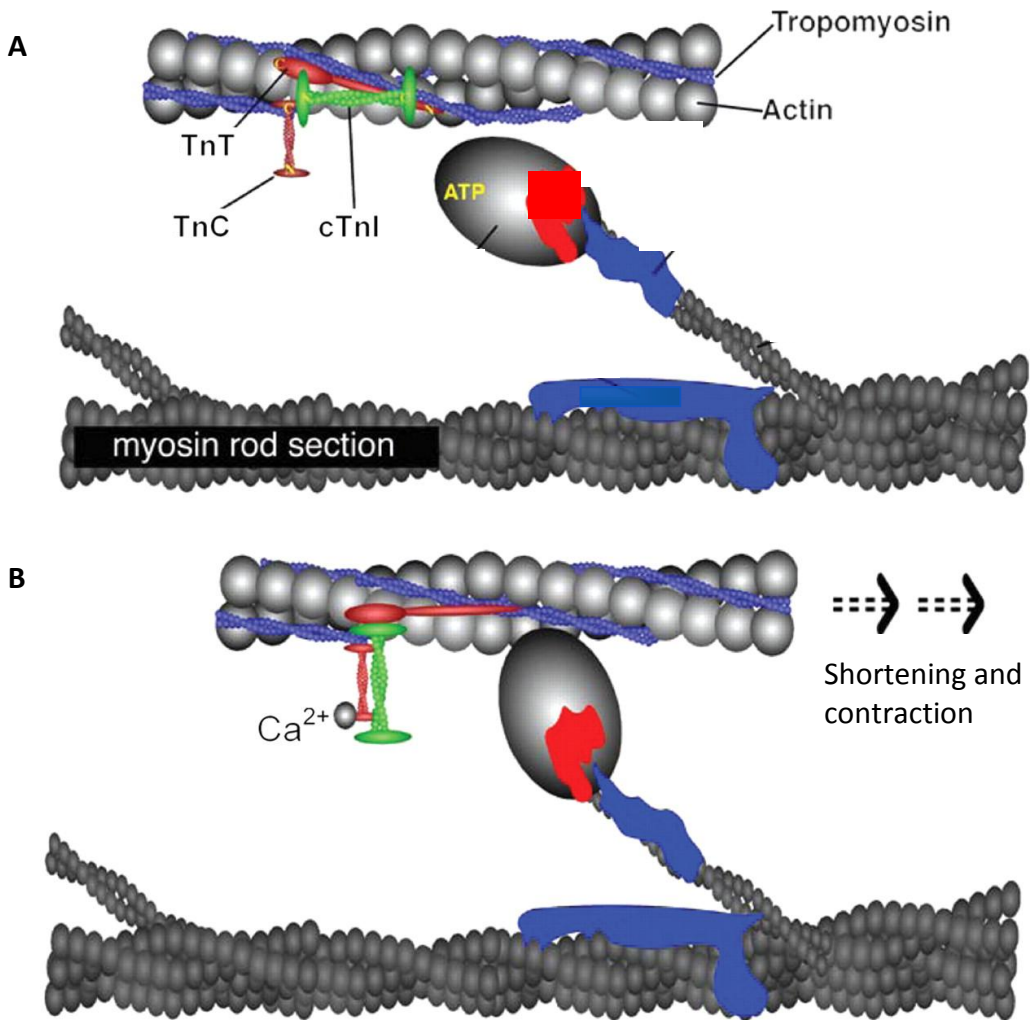


Figure 1.4. The cardiac sarcomere during diastole and systole

A. Troponin I inhibits the binding of myosin to actin in the relaxed state (diastole). **B**. When Troponin C binds with calcium, this inhibition is cancelled and Tropomyosin settles between two grooves of actin to enable myosin binding, leading to shortening of the sarcomere and contraction of muscle (systole), TnT=Troponin T, TnC=Troponin C, TnI=Troponin I (Modified from Hamdani et al., 2008, with permission).

The first study to investigate secondary cardiac injury in trauma using Troponin I was a prospective analysis on a French ICU of young critically injured individuals (Edouard et al., 1998). Patients with a history of pre-existing cardiovascular disease were excluded. Six (35%) of the cohort demonstrated a rise in Troponin I, which occurred in the absence of echocardiographic evidence of myocardial contusion, thereby suggesting

secondary cardiac injury. In addition, biomarker rises were associated with hypotension and MODS.

These findings should nonetheless be interpreted in the context of a very small and selective study of critically injured patients, and could not be applied to the general trauma population at large. Furthermore, Edouard published a much larger analysis of 728 patients six years later and suggested that Troponin I release was in fact fundamentally the result of direct cardiac injury (Edouard et al., 2004). In this later study, elevations in Troponin I occurred in 86 (12%) individuals, seven of whom had "medical ischaemia". Of the 54 early survivors in this group, 35 (65%) had a chest injury and 23 (43%) a myocardial contusion based on ECG changes.

Throughout the whole population, ECG changes were noted in 35 (4.8%) patients and included ST segment depression and elevation, bundle branch blocks and arrhythmias.

The 17 patients with significant and sustained release of Troponin I included seven (41%) patients diagnosed with coronary artery injury and nine (53%) with echocardiographic abnormalities. Troponin I release was not prognostic of late mortality (OR 1.32, 95% CI 0.61–2.85).

Although a much larger study, the power of this analysis remained potentially low given the relatively small number of patients with a Troponin I rise. Accordingly, the prognostic significance of this biomarker was not conclusively determined by this research. While many of the patients with Troponin I rises had chest injuries, certain diagnoses of myocardial contusion were based on ECG abnormalities.

Contusions may present with a wide and non-specific spectrum of ECG changes and there is no global consensus on their diagnostic criteria. It should not have been assumed, therefore, that patients had myocardial contusions unless there was echocardiographic confirmation.

As with previous research, this analysis also limited itself to a critically injured cohort, and hence the findings might not be applicable to all trauma patients.

Lastly, timings of the biomarker samples were poorly described. Troponin I were reported as measured on admission to ICU, at six and 12 hrs thereafter and continued until levels normalised. In the first instance, the time to admission to ITU following injury is variable. Some patients may be admitted rapidly and directly to a unit, whilst others may be delayed by the need for imaging or emergent intervention first. Second, the authors gave no indication as to the point at which Troponin I levels normalised. Consequently, the paper provided no detail on the relationship of cardiac injury with time.

Perhaps the most significant study of Troponin I as a marker for secondary cardiac injury in trauma was published in 2005.

Critically injured patients admitted to an ICU with two sequential Troponin I measurements were included (M. Martin et al., 2005). Over a thousand individuals were recruited and just under a third of the cohort (29%) had a rise in Troponin I. When adjusted for, only the severity of injury, base excess and degree of physiological derangement were predictors of Troponin I increase.

Neither the presence nor severity of thoracic injury, however, was associated with Troponin I suggesting again that trauma might cause secondary cardiac injury.

Elevated Troponin I levels were also a significant predictor of mortality (OR 2.1, 95% CI 1.4–3.1). Fifty patients (4.6%) had an ACE of some description and these were associated with increases in Troponin I. The precise nature of such cardiac events was not reported. The analysis also demonstrated that beta-blockers were linked to survival, and a 50% decrease in mortality was seen in patients with Troponin I increases on these medications.

This study was limited, however, by its retrospective nature and once again, the findings remained pertinent to critically injured patients only. The authors failed to describe their exclusion criteria, and provided no significant details on the features and diagnoses of patient ACEs. The analysis was based on the peak Troponin I concentration of each patient, and the timing of sampling in this study was also vague. Consequently, deductions on the significance of chronology, and the patterns of release of this biomarker after trauma could not be made.

Troponin I was measured in another European study of 106 patients presenting after mild trauma (Lagi et al., 2008). Only individuals who presented without evidence of acute cardiac events were included.

Biomarker levels were measured during the first 24 hrs (at six hourly intervals) and individuals were followed up for six months after discharge for either death or cardiac morbidity. Seventeen patients (16%) had a rise in Troponin I, of which eight (47%) had an ACE during follow up.

ACEs included two cases of acute MI, two of cardiac syncope and three instances of cardiac death. The results implicated that cardiac injury and dysfunction may follow even mild trauma. Importantly, this was also the first study to suggest the prognostic significance of Troponin I in non-critically ill trauma patients, and further the biomarker's predictive value of future, longer term cardiac events.

Nevertheless, the lack of detailed methodology made the study difficult to interpret. Injury severity was not measured using an ISS score, but instead an arbitrary scale scantily explained. As such the authors' definition of mild trauma was vague. Injury and patient characteristics were not given, and associations between cardiac events and Troponin I not adjusted for. The relationship between chest injury and Troponin I rise or ACEs was not provided and as such the study provided no evidence either to support or negate the existence of post-traumatic secondary cardiac injury.

In paediatric trauma patients, Troponin I has also been shown to rise (Sangha et al., 2012). In 59 patients aged between 1-17 years, 16 (27%) had a rise in the biomarker.

Four (25%) of these individuals had an abnormal echocardiogram, although the anomalies were trivial in nature. All patients had normal ECGs but 15 had chest injuries. Troponin I rises were associated with worsening injury severity, greater fluid requirements and higher rates of intubation. Three children (5%) died from catastrophic brain injury, all with a rise in Troponin I.

This study demonstrated that children may also develop Troponin I rises which could not be due to pre-existing cardiac disease given such individuals were excluded. Although an increase in Troponin I was associated with chest injury, only four patients actually had any evidence of BCI on their echocardiogram. Accordingly, it is possible that some of these patients were in fact manifesting secondary cardiac damage.

Although perhaps the first dedicated study of Troponin I in paediatric trauma patients, the research was nonetheless limited to a relatively small sample size, and failed to adjust for any of its variables.

The relationship between cardiac injury (defined by a rise in Troponin I) and infection was most recently investigated in a review of 1752 patients on a trauma ICU (Monaghan et al., 2012). Individuals were retrospectively reviewed for demographics, the presence of co-morbidity and injury characteristics. Laboratory records identified patients in whom a Troponin I was ordered and the value thereof, while microbiology data revealed those diagnosed with urinary tract infections (UTI) or ventilator-associated pneumonia (VAP).

Cardiac injury (Troponin I >0.15ng/mL) was present in 160 (9%) critically injured individuals, whilst severe cardiac injury (Troponin I >1.0ng/mL) was found in 63 (4%). Age, chronic obstructive pulmonary disease, UTI, VAP and ISS were all predictors of cardiac injury.

Conversely the presence of pre-morbid congestive heart failure (CHF) was not associated with a Troponin I rise. Only age and diabetes were significant risk factors for severe cardiac injury.

These findings led the authors to conclude that there exists an association between infection with an increased risk of cardiac injury, and that this could be due to "infection-related, inflammatory mediated cardiac dysfunction".

Age, CHF and increasing ISS were predictors of mortality, and hypertension appeared protective. Although severe cardiac injury alone did not meet significance ($p<0.063$), the interaction between severe cardiac injury and age was associated with death.

The study was well powered. It attempted to investigate a potentially important yet previously unreported cause of late death in trauma, namely the association between infection and cardiac injury.

Nonetheless, it was subject to multiple limitations. Suspicion of cardiac injury was based on including any patient in whom a Troponin I was ordered, in spite of a wide spectrum of clinical indications, and the likely variability between one clinician and another's motivation for seeking the test. Testing bias was therefore not adjusted for. The analysis did not reveal the relationship of Troponin I to chest trauma, and no other markers of cardiac dysfunction were examined. Accordingly, the study did not demonstrate whether Troponin I rises were the result of BCI or secondary cardiac injury. Furthermore, the analysis calculated threshold levels for the biomarker despite variations in normal values, thus rendering the findings poorly translational to other trauma populations. Being retrospective in nature, results were dependent on accuracy of documentation and data recollection, which may have led to an under-estimation of effect sizes. Moreover, given the relatively small frequencies of co-morbidities, the statistical tests may have been underpowered.

The study provided little further insight, therefore, into post-traumatic secondary cardiac injury, its pathogenesis and associated clinical outcomes.

1.5.2.3 Heart-type Fatty Acid Binding Protein

Heart-type Fatty Acid Binding Protein (H-FABP) is a small cytoplasmic protein (12-15 kilodaltons, KDa) found abundantly in the heart. It transports insoluble fatty acids from the cell membrane to mitochondria for lipid oxidation, to enable the production of energy (Alhadi et al., 2004). It is normally present at low levels in the plasma, but appears in the circulation more rapidly than the Troponins following damage to heart cells. It is a reliable marker of myocardial cell damage, and may be the earliest, most sensitive biomarker to rise following cardiac injury (McMahon et al., 2012).

H-FABP is also a significant predictor of poor outcomes, and raised levels have been associated with mortality and risk of future adverse events in various disease states (Viswanathan et al., 2010, Jo et al., 2012).

In trauma, H-FABP has only been assessed in an experimental setting of myocardial injury, and was found to be a good early marker of cardiac damage (Clements et al., 2010).

Yet despite evidence supporting its value as an early and highly sensitive cardiac biomarker with good prognostic capabilities, it remains one that has never been described in the clinical setting of trauma. It therefore represents an appropriate original target for investigation in injured patients.

1.6 Trauma, Inflammation and the Heart

Of the studies described previously in Section 1.5, few have attempted to determine the underlying mechanisms that may have led to post-traumatic secondary cardiac injury and dysfunction. Amongst those that have, links to inflammation, and conditions such as SIRS and MODS have most often been implicated.

1.6.1 SIRS and MODS

Trauma induces an inflammatory response in injured patients which may lead to SIRS. The degree of SIRS is dependent both on endogenous (e.g. hypoxia and metabolic acidosis) and exogenous factors such as the extent of tissue injury and shock (Keel at al., 2005). Mild to moderate SIRS is an appropriate response to trauma and is designed to facilitate the body's stress response to injury. Exaggerated SIRS, however, leads to MODS, a syndrome defined by the failure of two or more organ systems (Hassoun et al., 2001).

Both the SIRS score on admission (Napolitano et al., 2000) and the degree of post-traumatic secondary organ dysfunction are critical factors in determining the outcomes of injured patients, including their length of stay, survival and, ultimately, longer-term quality of life (Dewar et al., 2009).

In trauma, SIRS and MODS are the result of the immune response. Following sterile tissue injury, alarmins are released into the circulation (such as high-mobility group box protein 1 [HMGB1] and mitochondrial DNA) and recognised by receptors present both on the surface and on the inside of cells.

This triggers the innate immunity and results in cytokine production and inflammation (Manson et al., 2011). This may also lead directly to ischaemia–reperfusion injury to the heart (Andrassy et al., 2008).

In injured patients, cytokine levels may predict the severity of illness, the development of MODS and survival (Hranjec et al., 2010).

In the clinical trauma literature on cytokines, TNFα, IL-6 and IL-8 have been the principal focus of research.

TNFα exerts multiple effects throughout the body, including the heart, where it causes cardiac muscle cell (cardiomyocyte) injury and dysfunction (Horton et al., 2000). IL-6 is a cytokine with numerous biological functions, and is a potent inducer of the acute phase response (Van Snick, 1990). IL-8 exhibits chemotactic properties and performs multiple functions such as the induction of lysosomal enzyme release from neutrophils (Harada et al., 1994). The production of IL-8 occurs in response to inflammatory stimuli, including the presence of TNFα.

1.6.2 Cytokines, Inflammation and the Heart

Cytokines, and in particular TNFα, IL-6 and IL-8 have been shown to rise acutely after trauma and production may be correlated to the ISS (Jiang et al., 1997). The three cytokines demonstrate different timings of release following injury, and levels may not only discriminate those at risk of MODS (Jastrow et al., 2009), but also might identify which organs are likely to become dysfunctional (Maier et al., 2007).

In non-trauma literature, cytokines and inflammation have been associated with both acute and chronic cardiac disease and heart failure (Hohensinner et al., 2011, Prabhu et al., 2004, Chen et al., 2008).

TNFα leads to cardiomyocyte apoptosis through caspase activation and subsequent deoxyribonucleic acid (DNA) fragmentation. TNFα has negative inotropic effects, and also initiates the cytokine cascade leading to the production of IL-6 and Il-8 amongst others. This results in greater inflammation and worsening injury to the heart (Prabhu, 2004). IL-6 leads directly to cardiac dysfunction, through iNOS mediated depressions of myocardial contractility, in combination with disorders of cellular calcium homeostasis (Saini et al., 2005). IL-8 may lead to granule enzyme release and oxidative burst in neutrophils which damage the heart, particularly in the context of ischaemia reperfusion injury (Stangl et al., 2002).

In trauma, the cardiovascular impairment associated with SIRS appears mainly the product of decreases in afterload and myocardial contractility (R. S. Martin et al., 2005).

In a model of early post-traumatic MODS (i.e. occurring by day three of admission), the heart was shown to be the predominant organ of dysfunction (Moore et al., 1996). However, this study graded the extent of cardiac failure according to the level of inotropic support, despite the fact that these medications are used in multiple clinical scenarios and do not necessarily reflect abnormalities of myocardial function.

Although damage to heart tissue and function is recognised in post-traumatic SIRS and MODS, the specific association of the heart with cytokines and inflammation after trauma has been the subject of very little investigation.

Merely one clinical study of 17 severely injured patients has attempted to describe the relationship between rises in TNFα, IL-6 and IL-8 with secondary cardiac injury (Jiang et al., 1997). Although suggestive, the analysis was limited by its small population, and most notably by the use of creatine phosphokinase (CPK) as the indicator of heart damage. Because CPK is not specific to heart tissue and is released following skeletal muscle trauma, the evidence no longer favours its utility as a cardiac biomarker. Given the patients in the study were severely injured, CPK will have been raised regardless of the presence of cardiac injury. Furthermore, the presence or extent of chest trauma was not described, and hence the study did not reveal whether cardiac injury was the result of direct cardiac damage or was secondary in nature.

Consequently, the association between cytokines, inflammation and secondary cardiac injury and dysfunction in trauma remains a novel and necessary area of research.

1.7 Head Trauma and Secondary Cardiac Injury

Damage to the brain can to lead to indirect injury to the heart. Studies have reported Troponin I rises, ECG abnormalities and histological changes in the myocardium secondary to intracranial bleeding, primarily following subarachnoid haemorrhage (Tanabe et al., 2008, Andreoli et al., 1987, Elrifai et al., 1996).

In trauma, the secondary effects of head injury on the heart have also been investigated. Small studies have revealed ECG abnormalities in patients with head trauma (Mcleod et al., 1982), allied with histological evidence of cardiac injury. Others have reported myocardial dysfunction and neurogenic pulmonary oedema in patients with isolated head injury. These were associated with high mortality rates, and further pathological confirmation of myocardial damage was presented (Bahloul et al., 2006).

Research in brain injured children has also reported a high incidence of cardiac arrhythmias, including ventricular tachycardias (Bourdages et al., 2010). In this study, however, no child manifested asystole, atrioventricular block, AA or ventricular fibrillation. Arrhythmias occurred in the absence of primary cardiovascular trauma, and were more common in hypothermic patients.

Following traumatic subarachnoid haemorrhage, cardiac arrhythmias and myocardial ischaemia were again demonstrated in approximately half of the 35 individuals recruited to the study (Baffoun et al., 2011).

Although a very limited investigation with errors in reporting and statistical analysis, the authors also found a Troponin I rise in 12 patients which was independently associated with increased mortality.

A retrospective review of all blunt trauma patients with severe head injury (head AIS 3≤) and lesser injuries to the remainder of body regions (AIS <3) revealed Troponin I rises in nearly a third (29.8%) of the study cohort (Salim et al., 2008). Both admission and peak Troponin I elevations were associated with a lower Glasgow Coma Scale (GCS), higher ISS and

greater mortality when compared to individuals with normal biomarker levels. Peak, but not admission, Troponin I was an independent predictor or mortality (OR 8.5, 95% CI 3.46-22.15, $p<0.001$).

Although this study did not explicitly examine the relationship between chest injury and Troponin I release, patients with severe thorax trauma were excluded from the analysis. Accordingly, it supports the notion that secondary cardiac injury occurs in trauma, albeit following head injury in such cases.

BNP levels may also rise following neurological trauma, and may correspond to both hyponatraemia and elevated intracranial pressure (ICP) (Wu et al., 2011). Elevations in NT-proBNP have also been noted in both the plasma and cerebrospinal fluid of brain injured patients (Kirchhoff et al., 2006), and may be associated with higher ICP measurements (ICP >15 mmHg).

To date, catecholamines and sympathetic overactivity have been amongst the most widely implicated mediators of secondary cardiac injury following head injury (Samuels, 2007). This may explain the survival benefits of beta-blockers seen in limited studies of patients with neurological trauma (*Table 1.2*).

1.8 Cardiac Disease and Trauma

Increasing age is associated with poorer survival following injury. Trauma patients over the age of 45 years have worse outcomes and this increases linearly with age. All cause mortality in individuals over 60 years may approach up to 20% (Tornetta et al., 1999), and those over 65 have a two to threefold higher risk of death than younger individuals (Taylor et al., 2002).

Higher death rates are not only seen in-hospital but are observed over the course of several years following the index injury (Claridge et al., 2010, Laupland et al., 2010, Davidson et al., 2011).

A factor leading to the increased death rate of older trauma patients is the presence of co-morbidity. The isolated influence of heart disease on survival following injury is controversial, however.

1.8.1 Cardiac Disease and Survival in Trauma

Not only the presence but the number of pre-morbid conditions may influence the death rate in trauma (Bamvita et al., 2007). In this study of all acute trauma deaths within 30 days of emergency department (ED) arrival, a bivariate statistical model initially revealed cardiac disease as a predictor of death. When adjusted for using multivariate regression, conversely, heart conditions no longer remained significantly associated with survival. However, cardiac disease led to death in 19.2% of cases, making it the third highest cause of death in this study sample (although individual diagnoses were not specified).

In a larger investigation of a Japanese population, only the presence of congestive heart failure alone was linked to a greater death rate, but this was itself limited to two specific groups of injured patients, namely those with an ISS of 1-15 and an ISS of 16-24 (Shoko et al., 2010). Overall, however, cardiac disease per se was not associated with increased death rates in this cohort of adult trauma patients.

In conjunction, an earlier study of injured individuals over the age of 65 years revealed that the presence of cardiac disease was not generally associated with increased odds of death. Only congestive heart failure was predictive of poorer survival, but solely in older patients who presented following a fall (Grossman et al., 2002).

Prior research designed to determine the factors which influence outcome in the elderly also assessed the effect of pre-existing medical conditions. In a comparison of older (age ≥65 years) versus (vs.) younger patients (<65 years), increasing age was associated with worsening survival (Smith et al., 1990). The presence of co-morbidity, including cardiac disease, did not affect mortality. Similar studies in older individuals admitted to a surgical ICU (Horst et al., 1986) and in injured patients over the age of 70 (Oreskovich et al., 1984) reached identical conclusions.

In a more recent report of trauma patients with severe injury, cardiovascular disease in isolation was not associated with a higher risk of death (Efron et al., 2008). When considered in combination with statin use, however, the presence of a diseased heart negatively influenced survival.

A landmark study in the field highlighted that the presence of ischaemic heart disease nearly doubled the risk of death in adult trauma patients (Morris et al., 1990). However, the detrimental impact of the condition was lost in older and more severely injured patients. In those over the age of 65 years with an ISS ≥13, the presence of any pre-morbid condition had no longer any significant effect on mortality.

In contrast, perhaps the only prospective study in trauma examining the influence of co-morbidity on outcome revealed a positive association between pre-morbid conditions, including cardiac disease, and mortality (Milzman et al., 1992). This relationship remained true even after controlling for both ISS and age. The effect of co-morbidity on survival was most pronounced in younger, less severely injured patients.

Moreover, in a study of the moderately injured (mean ISS of 10.7), older individuals were more likely to suffer late mortality when compared to younger patients (Perdue et al., 1998). In individuals over the age of 65 years, the presence of pre-existing cardiovascular disease was not only associated with higher death rates, but was additionally related to other poorer outcomes including cardiac, respiratory, renal, and infectious complications.

These findings were reinforced by work in more severely injured patients (ISS ≥16), which demonstrated that heart disease and indeed peripheral vascular disease were associated with higher mortality even after adjusting for age and severity of injury (Wutzler et al., 2009).

However, an earlier paper reported that when the mortality of patients over 50 years of age was analysed in relation to ISS (Mcgwin et al., 2004), heart disease only had a marked impact on those less injured (ISS 1-15), and to a lesser extent those with severe injuries (ISS 16-25). In critically injured patients (ISS ≥26), heart disease did not significantly influence outcome.

These findings were supported by a British study of adult trauma patients, which demonstrated that the presence of co-morbidity was associated with a negative impact on survival only in mildly and moderately injured patients (Hollis et al., 2006). In patients with an ISS <16, cardiovascular disease was associated with a seven-fold increase in death (OR 7.0, 95% CI 5.1-9.6, $p<0.001$). Conversely, pre-existing medical conditions had no significant effect on mortality in the severely injured. Amongst this cohort, cardiovascular disease was the most common co-morbidity, affecting nearly a third of the population. Strokes were included in these figures, however, so the true incidence of cardiovascular disease alone was not revealed.

Again in the UK, multiple studies conducted by the same author revealed that cardiovascular disease was the most prevalent type of co-morbidity observed in injured patients, and was consistently associated with a

significant increase in the death rate following trauma (Wardle, 1999). Nonetheless, these findings were subject to regional differences in public health and cannot therefore be assumed to represent the trend throughout the UK, nor indeed the rest of the world.

Most recently, poorer long-term survival after major injury was demonstrated in a non-validated predictive model of co-morbidity in trauma (Niven et al., 2012). Cardiopulmonary disease accounted for 26% of deaths at one year, but in contrast, led to only 6% of fatalities during hospitalisation after the index event. Nonetheless, the study did not isolate cardiac disease from respiratory illness (including chronic obstructive pulmonary disease), thus it provided little further indication of the independent effect of heart conditions on survival after trauma.

Indeed the only research to investigate specifically the relationship between cardiac disease in isolation and trauma was a dedicated retrospective database analysis of nearly 6000 patients (Ferraris et al., 2010). Approximately 43% of survivors and 69% of non-survivors were documented as having pre-morbid cardiovascular disease. Amongst the deaths from trauma, 236 (33%) had an adequate medical history. Although multiple cardiovascular diseases and medications were associated with increased death rates, only three remained significant when adjusted for using multivariate analysis; pre-morbid warfarin use, beta-blockade and congestive heart failure. Although these were associated with decreased survival, their effects were less when compared to more traditional risk factors such as age, GCS and ISS.

1.8.2 Limitations of the Literature on Cardiac Disease and Trauma

While some studies are suggestive of increased mortality in injured patients with cardiovascular disease, the isolated effect of heart conditions on post-traumatic survival remains nonetheless inconclusive.

There are only a relatively small number of trauma papers that have reported the effect of pre-morbid disease on outcome, and just one has specifically investigated cardiac disease in isolation.

Furthermore, many of the studies' findings are conflictive, and all are subject to limitations. Most of the evidence is derived from observational, retrospective database analyses which enable the investigation of large study populations. However diagnoses are based on coding criteria such as those of the ICD-9-CM. Consequently, these studies are dependent on accurate documentation, and vulnerable to the latitude of definitions of heart disease, such that none can discriminate the actual level of physiological derangement and physical limitation associated with each cardiac diagnosis. Furthermore, such methodology precludes patients with existing, but undiagnosed, cardiovascular disease. Consequently, the true incidence of heart disease, including both symptomatic and asymptomatic presentations, is not known in trauma.

Studies have varied in their patient populations and assessment of cardiovascular conditions rendering them difficult to compare and contrast. None have specifically investigated atherosclerotic disease despite it being amongst the most prevalent of cardiovascular pathology. Finally, many papers have limited their inclusion criteria to patients aged 60 years or over, thus neglecting younger individuals either with, or at risk of, cardiovascular disease (Grundy et al., 1999). Accordingly, the true incidence and impact of cardiac disease on survival in trauma patients remains unknown.

1.8.3 Cardiac Medications and Outcome in Trauma

In addition to cardiac disease, several clinical studies have investigated the influence of cardiac medications, and particularly beta-blockers, on outcomes following injury.

Overall the evidence is favourable and suggests that the pre-morbid use of beta-blockers is associated with improved survival. This is perhaps most notable in patients with head injuries, wherein beta-blockers are proposed to attenuate the deleterious effects of the sympathetic hyperactivity and catecholamine surges that occur in neurological trauma. The benefits of statin therapy are less clear (*Table 1.2*).

Table 1.2. Beta-blockers and Statins in Trauma - Summary of Evidence

Study	Medication	Trauma Population	Effect on Outcome
(M. Martin, 2005)	Beta-blockers	Critically injured	Improved survival
(Cotton, 2007)	Beta-blockers	Severe head injuries	Improved survival
(Arbabi, 2007)	Beta-blockers	Patients on beta-blockers (initiated in hospital or pre-morbid)	Improved survival (most notable in severe head injury)
(Riordan, 2007)	Beta-blockers	Severe head injuries with heart rate monitoring for first 24 hours on ICU	Non-significant association with survival
(Neideen, 2008)	Beta-blockers	Patients aged >65 years	Increased mortality in patients without head injury No difference in those with head injury
(Salim, 2008)	Beta-blockers	Severe head injuries with Troponin I measurement	Improved survival
(Inaba, 2008)	Beta-blockers	Isolated head injury	Improved survival (especially in head injuries >55 years)
(Ferraris, 2010)	Beta-blockers	Patients aged >20 years	Increased mortality
(Schroeppel, 2010)	Beta-blockers	Blunt traumatic brain injuries	Improved survival
(Hadjizacharia, 2011)	Beta-blockers	Critically injured	Improved survival in patients with AA treated with beta-blockers
(Bukur, 2012)	Beta-blockers	Surgical ICU admissions without severe head injury	Improved survival
(Efron, 2008)	Statins	Patients with at least one severely injured body region	Improved survival only in those >65 years with no cardiovascular disease
(Neal, 2009)	Statins	Patients aged >55 years	No difference in survival Higher risk of MODS in statin users
(Schneider, 2011)	Statins	Patients aged >65 years with severe head injury	Improved survival and functional recovery at one year

The evidence on the benefits of these medications, however, is limited to a handful of studies. These investigations are mostly retrospective and thus vulnerable to errors in documentation and reporting of medication use. Results are restricted to specific injured cohorts, and are not directly translatable to general trauma populations.

Although papers describe the class of drugs investigated, they fail to mention the specific type of medication used, despite the variety of pharmaceutical effects that the family of beta-blockers have. Doses are not reported, and the timing of administration variable.

Finally, the literature has not yet established whether the pre-morbid use of these medications is associated with differing outcomes in trauma patients when compared to their initiation in hospital following injury.

1.9 Summary

Trauma is an important cause of death and disability worldwide. Nonetheless, it is a poorly funded field characterised by a lack of research. The relationship of trauma with the heart is an area of study particularly neglected.

Experimental evidence has demonstrated that trauma and haemorrhage may provoke a profound systemic inflammatory response characterised by increased levels of pro-inflammatory factors, with subsequent cardiac injury and dysfunction. However, the experimental evidence is limited and not directly translational to clinical practice.

Only a handful of dedicated clinical studies have investigated whether trauma can lead to secondary cardiac injury and dysfunction. Although some of the studies are suggestive, findings lack unanimity (*Table 1.3*). In addition, the outcomes associated with secondary cardiac injury in trauma remain uncertain.

Much of the clinical evidence is derived from retrospective studies, and primarily limited to small numbers of critically injured patients only. Clinical manifestations of secondary cardiac injury are restricted to isolated diagnoses, whilst biomarker studies have investigated single markers, despite evidence in the non-trauma literature that multiple biomarker panels might be more effective (McCann et al., 2009). Furthermore the timings of biomarker sampling in relation to injury chronology have not been described precisely.

The relationship between pre-existing heart disease and outcome in trauma is inconclusive. Studies are conflictive and have relied on existing diagnoses of heart disease using database analyses. Only one paper has reported the effect of heart disease specifically in isolation on survival.

Table 1.3. Summary of Dedicated Clinical Studies of Secondary Cardiac Injury and Dysfunction in Trauma

Study	Design (n)	Trauma Population	Variable	Incidence (%)	Risk Factors	Evidence of Secondary Cardiac Injury?
(Edouard, 1998)	Prospective cohort (17)	Critically injured	Troponin I	35	Not identified	Yes
(Moosikasuwan, 2000)	Retrospective cohort (11,866)	All	MI	0.04	Not identified	No
(Edouard, 2004)	Prospective cohort (728)	Critically injured	Troponin I	12	Not identified	No
(Ismailov, 2005)	Retrospective cohort (1,051,081)	All	MI	3.10	Chest/abdominal/pelvic trauma	Yes
(M. Martin, 2005)	Retrospective cohort (1,081)	Critically injured	Troponin I	29	Base excess ISS Deranged physiology	Yes
(Seguin, 2006)	Prospective cohort (293)	Critically injured	AF	5.5	Age >40 years >3 body regions injured Catecholamine use SIRS Deranged physiology	Yes
(Lagi, 2008)	Prospective cohort (106)	Mildly injured & no pre-morbid cardiac disease	Troponin I	16	Not identified	No
(Kirchhoff, 2008)	Prospective cohort (26)	Critically injured	BNP	100	Not identified	Yes
(Hadjizacharia, 2011)	Retrospective cohort (3,499)	Critically injured	AA	6	Age >55 years	Yes
(Sangha, 2012)	Prospective cohort (59)	Severely injured children	Troponin I	27	Chest injury and ISS	No

In conclusion, no study has attempted to link all clinical manifestations of secondary cardiac injury with multiple biomarker evidence. In the event of the existence of this condition, the outcomes associated with it are not yet fully understood.

The pathological processes, notably inflammation, together with the risk factors that might lead to secondary cardiac injury have been not investigated. The trauma populations at risk of the condition have not been identified.

Finally, the true incidence and effect of coronary heart disease on survival requires dedicated investigation.

Consequently the theme of trauma associated cardiac injury and dysfunction represents an important and novel target for investigation.

1.10 Project Aims

The overall research objective was to investigate the relationship between trauma and the heart. Specifically, this project aimed to:

1) Identify the existence of a trauma induced secondary cardiac injury (TISCI) and determine its impact on the outcome of severely injured patients

2) Establish if there is an association between inflammation and the development of a trauma induced secondary cardiac injury, and determine whether inflammation combined with cardiac injury is associated with poorer survival

3) Describe the features of a trauma induced secondary cardiac injury, and identify its risk factors in all adult trauma patients

4) Identify the overall incidence of coronary heart disease in older trauma patients, and establish its association with survival after injury

CHAPTER TWO

Trauma Induced Secondary Cardiac Injury

2.1 Introduction

Direct trauma to the heart is known to lead to cardiac injury and dysfunction (Amino et al., 2009, Ismailov et al., 2007). It remains controversial, however, if trauma may cause secondary cardiac injury, and if it does, whether this results in adverse outcomes for patients.

There is circumstantial evidence to support the existence of indirect injury to the heart following trauma, and a few studies have described secondary cardiac events in injured patients. In a retrospective review of over a million individuals, the risk of post-traumatic MI was found nearly to double following pelvic or abdominal trauma (Ismailov et al., 2005). This observation was independent of confounding factors. The development of AA has been reported in trauma patients, irrespective of the severity of thoracic injury. AA occurred in six percent (n=210 of 3499) of injured patients on a critical care unit, and were independently associated with higher mortality (Hadjizacharia et al., 2011). The only significant risk factor for developing an arrhythmia was age (>55 years). Seguin found similarly that the incidence of AF was just over five percent in critically injured patients, and identified age, catecholamine use, the presence of SIRS and the severity of overall injury and physiological derangement as the contributing risk factors for AF (Seguin et al., 2006). Patients with AF suffered a higher death rate, but in contrast to the aforementioned study, this was not statistically significant.

In the trauma literature, heart specific biomarkers have also been investigated in research attempting to identify both the severity and significance of secondary cardiac injury in trauma.

Troponin I, found in heart muscle, is a specific biomarker of myocardial injury. Raised levels of Troponin I have been identified in patients after trauma and may be associated with both an increased risk of ACEs and death (Lagi et al., 2008, M. Martin et al., 2005).

NT-proBNP is secreted primarily by the ventricles of the heart in response to excessive stretch. It is a sensitive biomarker of cardiac injury.

Measured 24 hrs after trauma, NT-proBNP levels have been shown to correlate significantly with a decreased cardiac index and MODS (Kirchhoff et al., 2008).

In experimental animal models, secondary cardiac injury and dysfunction have also been identified following trauma-haemorrhage. Inflammation and ischaemia-reperfusion injury have been implicated repeatedly in their pathogenesis (Yang et al., 2004, Mizushima et al., 2000b, Li et al., 2007).

In addition, there is a growing body of indirect, non-trauma related clinical evidence to suggest that cardiac dysfunction is associated with deranged physiological states. Myocardial injury has been demonstrated after post-partum haemorrhage, critical illness and sepsis and is related to poorer outcomes, including higher death rates (Karpati et al., 2004, Lim et al., 2006, Post et al., 2008, Quenot et al., 2005, Wu et al., 2004).

Although these studies are suggestive of post-traumatic secondary cardiac injury and dysfunction, no research has yet investigated the development of cardiac events in trauma patients in combination with biochemical evidence of cardiac injury.

Previous biomarker studies have measured isolated markers only, and these have been done later in the clinical course, when elevations might have been caused by mechanisms other than trauma. Moreover, many of these analyses have calculated a threshold level of the biomarker for prediction of outcome, despite the fact that associations between biomarkers and outcome are usually continuous. Reporting of inaccurately large effect sizes may have thus resulted.

Additional research is further limited by studies including only small numbers of patients, examining isolated cardiac diagnoses (such as MI) or by virtue of using retrospective database analyses. Lastly, few investigations have reported outcomes.

The existence and clinical relevance of TISCI, therefore, continues to remain in doubt.

2.2 Study Aims

The overall study objective was to determine the existence of TISCI and if present, to establish whether it was associated with worse clinical outcomes.

Specifically, the *first* aim was to identify the incidence of post-traumatic ACEs in a group of severely injured patients.

Second, to ascertain whether there was biochemical evidence of myocardial injury early after trauma and if present, establish whether this was associated with the development of ACEs.

Third, to identify which factors correlated with the development of a TISCI in terms of injury characteristics and degree of shock on admission.

Finally, to assess whether a TISCI was associated with higher mortality in trauma patients.

2.3 Materials and Methods

The research project complied with the Declaration of Helsinki. It was reviewed and granted ethical approval by East London and the City Research Ethics Committee 1.

2.3.1 Study Design and Setting

A retrospective cohort study of severely injured patients admitted to an ITU. The project was performed at The Royal London Hospital, a major urban trauma centre in the UK (Davenport et al., 2009).

2.3.2 Study Population

All adult trauma patients (>15 years) who had an abnormal primary survey were eligible for inclusion, and were prospectively recruited into the Activation of Coagulation and Inflammation in Trauma 2 (ACIT 2) study when research personnel were present (08:00-20:00 daily) (Davenport et al., 2011).

Exclusion criteria were arrival in the ED more than two hours after injury, the administration of over 2000 millilitres (mls) of intravenous fluid prior to ED arrival, and transfer from another hospital. Patients were retrospectively excluded if they declined to give consent to use research samples collected.

Patients recruited into ACIT 2 and subsequently admitted to the ICU between January 2008 and January 2010 were retrospectively selected and enrolled into this study.

2.3.3 Data Collection

Data were prospectively collected on patient demographics, injury time and mechanism, time of arrival in the ED, baseline vital signs and daily physiological data, body regions AIS, ISS and survival.

Each participant was retrospectively reviewed for the presence of ACEs using inpatient notes, critical care charts, pathology records and the hospital trauma registry.

2.3.4 Outcomes

The two study outcomes were ACEs and in-hospital death and patients were followed up from admission until death or discharge. An ACE was defined as any of the following diagnoses; cardiac death, myocardial infarction, angina, arrhythmia and cardiogenic shock. Diagnoses were based on a combination of ECG, echocardiogram or other specialist cardiac investigations.

Death was recorded as 28-day mortality of any cause, and patients discharged from hospital before 28 days were assumed to be alive at day 28.

2.3.5 Blood Collection

Five millilitres of blood was drawn from either the femoral vein or the antecubital fossa along with standard trauma laboratory tests. Baseline blood (0 hr) was drawn prior to any hospital intervention and taken within 20 minutes (mins) of arrival to the ED, and inside of two hours from injury. Further samples were collected at 24 and 72 hrs thereafter.

Blood was drawn into a 4.5 ml citrated vacutainer (0.109M + buffered sodium citrate 3.2%, Becton Dickinson, Plymouth, UK). The citrated blood was centrifuged for ten minutes at 1750 g (relative centrifuge force) within one hour of collection. Plasma was removed and then further spun for ten minutes at 1750 g before being transferred into 0.6 ml Eppendorf tubes and subsequently frozen at -80 degrees Celsius (°C) until ready for processing.

2.3.6 Biomarker Assays

2.3.6.1 Selection of Biomarkers

Plasma was collected to measure levels of H-FABP, BNP and Troponin I as evidence of cardiac injury. A panel of biomarkers was selected based on research that this may be more effective than single assays in the diagnosis and prognosis of cardiac damage (McCann et al., 2009).

Furthermore, such novel methodology sought to improve upon the limitations of prior relevant literature restricted to the study of single isolated markers.

H-FABP may be the earliest and most sensitive biomarker to rise following myocardial cell damage (McMahon et al., 2012). It is a predictor of poor outcomes including mortality and risk of future adverse events in non-trauma states (Viswanathan et al., 2010, Jo et al., 2012). In trauma, H-FABP has only been described in the experimental literature (Clements et al., 2010), where it was found to be a good early marker of cardiac injury. Consequently, its use in the clinical setting is a novel but clinically relevant and appropriate method for the detection of secondary cardiac damage in injured patients.

BNP was selected as this is a sensitive indicator of cardiac injury, and has prognostic value in the prediction of both ACEs and survival in non-traumatic conditions (Post et al., 2008, Meyer et al., 2007, Choi et al., 2009, Charpentier et al., 2004, Kistorp et al., 2005). It is used frequently in the clinical setting and may be easily measured in hospital. In addition, BNP has been described in the trauma literature (Stewart et al., 2007, Friese et al., 2007) and has also been investigated in the context of secondary cardiac injury (Kirchoff et al., 2008). As such, its inclusion into this study enabled validation of its results and contrast with previous work.

Troponin I was chosen because it is currently the most heart specific biomarker in use in clinical practice. Moreover, the bulk of research on second cardiac injury in trauma has been undertaken using Troponin I (Lagi et al., 2008, M. Martin et al., 2005, Monaghan et al., 2012, Edouard et al., 1998, Edouard et al., 2004, Sangha et al., 2012). Again this facilitated comparison and assessment of this study's findings with the existing literature in this field.

Individual biomarker ELISA (Enzyme-Linked Immunosorbent Assay) kits were selected based on a number factors. These included practical protocols, with optimisation procedures compatible with the resources

available and the nature of blood collection and storage. Existing validation of each kit prior to selection was sought in the published literature, and the assays were further opted for based on their sensitivity to the substrate and their precision (*Tables 2.1-2.3*).

2.3.6.2 Inter- and Intra-Coefficients of Variation of Each Biomarker Kit

Table 2.1. Heart-type Fatty Acid Binding Protein (Hycult biotech Cat No. HK402)

Inter		Intra	
OD	*CV (%)*	*OD*	*CV (%)*
0.097	7.3	0.106	4.5
0.216	6.5	0.243	2.2
0.499	5.3	0.556	6.1
1.145	4.7	1.232	5.0
2.160	3.2	2.298	4.6
2.914	1.9	2.996	3.2

OD=optical density

Table 2.2. B-type Natriuretic Peptide (BNP Fragment EIA Biomedica Cat No. BI-20852)

Inter		Intra	
BNP (fmol/ml)	*CV (%)*	*BNP (fmol/ml)*	*CV (%)*
320	4.4	320	6.5
666	3.8	666	4.0

Table 2.3. Troponin I (Troponin I [human cardiac-specific] Life Diagnostics, Cat No.2010)

Inter		Intra	
Troponin I (ng/ml)	*CV (%)*	*Troponin I (ng/ml)*	*CV (%)*
5.88	4.8	5.93	3.7
24.56	4.7	24.3	5.6
48.91	4.6	44.9	4.0
85.81	4.4	89.80	2.8

2.3.6.3 Materials

- Cardiac biomarker ELISA kits (detailed below)
- Distilled water
- Alarm clock
- Vortex stirrer
- Plate mixer
- Plate washer (automatic)
- Polyprolene tubes
- Calibrated ELISA plate
- Calibrated micropipettes and disposable tips

2.3.6.4 Assay Protocols

Heart-type Fatty Acid Binding Protein **(Hycult biotech Cat No. HK402)**

96 microtitre wells coated with antibody unspecified by manufacturer.

1. Plasma samples selected and thawed for five minutes in water bath at 37 °C
2. 96-well plate schematic/template and polyprolene tubes labelled accordingly (blank/standards/samples/control)
3. Tracer diluted to either 1:5 or 1:10 using kit dilution buffer
4. 50 microlitres (µl) of duplicate standard/sample/control added to relevant wells in plate
5. Adhesive cover placed over plate and incubated at room temperature for 60 mins
6. Plate washed x4 with wash buffer using plate washer
7. 100 µl Tetramethylbenzidine substrate added to each well
8. Plate covered with aluminium foil and left at room temperature for 15 mins
9. 100 µl of stop solution (oxalic acid) added to each well
10. Absorbance of each well read at 450 nanometre (nm) within 30 mins of step 9

Calculation of results:

The absorbance (OD) at 450 nm was measured using a spectrophotometre. A standard curve was obtained by plotting absorbance versus corresponding concentrations of H-FABP standards. Concentrations of the samples were determined from the standard curve using GraphPad PRISM v5 (GraphPad Software Inc, San Diego, CA, USA) in accordance with both the manufacturer and GraphPad Prism instructions.

Mean absorbance was converted to picogram per millilitre (pg/ml) using non-linear regression. This was then corrected for dilution and final results reported in nanogram per millilitre (ng/ml).

B-type Natriuretic Peptide **(BNP Fragment EIA Biomedica Cat No. BI-20852)**

96 microtitre wells coated with polyclonal anti-BNP fragment.

1. Plasma samples selected and thawed for five minutes in a water bath at 37 °C
2. 96-well plate schematic/template and polyprolene tubes labelled accordingly (blank/standard/sample/control)
3. 200 µl assay buffer added to blank well
4. 200 µl added to standard/diluted sample/diluted control, in duplicate into respective wells. (Standard=synthetic human BNP fragment).
5. 50 µl of conjugate (synthetic BNP fragment-HRPO) added to each well (except blank)
6. Plate covered and incubated at 4 °C in dark for 24 hrs
7. Plate washed x5 with wash buffer
8. 200 µl of Tetramethylbenzidine added to each well
9. Plate covered with aluminium foil and left at room temperature for 20 mins
10. 50 µl of stop solution (sulphuric acid) added to each well
11. Absorbance of each well read at 450 nm immediately

Calculation of results:

Results were calculated using the same methods described for H-FABP (above), although mean absorbance was converted to femtomole per milliliter (fmol/ml) using non-linear regression.

***Troponin I* (Troponin I [human cardiac-specific] Life Diagnostics, Cat No.2010)**

96 microtitre wells coated with mouse monoclonal anti-Troponin I.

1. Plasma samples selected and thawed for five minutes in water bath at 37 °C
2. 96-well plate schematic/template and polyprolene tubes labelled accordingly (blank/standard/sample/control)
3. 100 µl dispensed of standards, samples and controls in duplicate to each well
4. 100 µl dispensed of enzyme conjugate reagent (mouse monoclonal anti-Troponin I conjugated to horseradish peroxidase in Tris Buffer solution with preservatives) in each well
5. Mixed thoroughly for 30 secs
6. Incubated at room temperature for 90 mins
7. Plate washed x5 with distilled water
8. 100 µl of Tetramethylbenzidine added to each well and mixed for five seconds
9. Incubated at room temperature for 20 mins
10. 100 µl of stop solution (hydrochloric acid) added to each well
11. Gently mixed for 30 secs
12. Absorbance of each well read at 450 nm within 15 mins

Calculation of results:

Data were collected as absorbance (OD) in duplicate at 450 nm, plotted against the dose and a standard curve fitted by 2nd order polynominal fit analysis using GraphPad PRISM v5 (GraphPad Software Inc, San Diego, CA, USA) in accordance with both the manufacturer and GraphPad Prism instruction manual. Mean absorbance was converted to ng/ml.

2.3.7 Statistical Analysis

All statistical analyses were performed using GraphPad PRISM v5 (GraphPad Software Inc, San Diego, CA, USA).

Normal-quantile plots were used to test for normality. Non-parametric data are expressed as medians with interquartile (IQR) ranges unless otherwise specified.

These were compared using Mann-Whitney U and Kruskal-Wallis. Proportions were assessed using Fisher's exact test and Chi Squared test for trend.

Spearman correlation coefficient was used to examine the linear relationship between head AIS and BNP and Troponin I levels, and biomarker levels and thorax AIS, ISS, lactate and SBP.

A two-sided p value of less than 0.05 was considered significant.

2.4 Results

One hundred and thirty five patients were included into this study and characteristics are described in Table 2.4 overleaf.

2.4.1 Incidence and Features of Adverse Cardiac Events

Eighteen patients (13.3%) had twenty ACEs during admission, of which the majority (65%) were supra-ventricular arrhythmias (*Figure 2.1*).

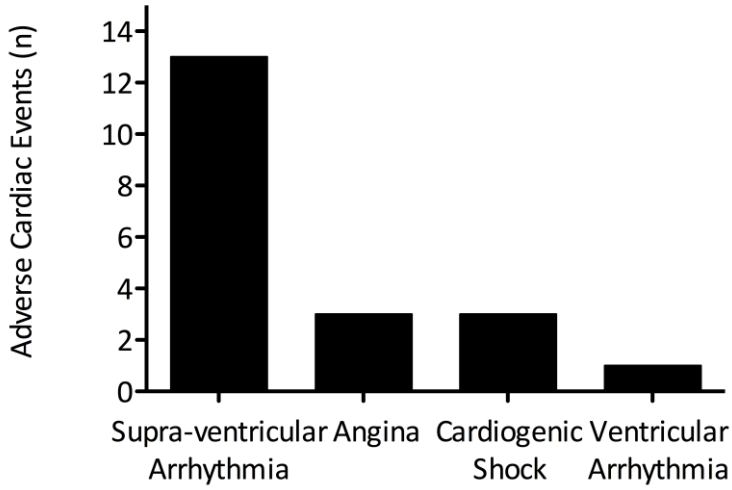


Figure 2.1. Numbers of adverse cardiac events by diagnosis

Patients with ACEs were older (64 years vs. 37, p<0.001) and more likely to have known heart disease (22% vs. 1.8%, p=0.003, *Table 2.4*). However, five patients (28%) who sustained an ACE were below the age of 50, and 13 (72%) had no previous history of heart disease, and were not on any regular medication.

The presence of pre-existing heart disease was related to the risk of a cardiac event in-hospital (*Table 2.4*). In contrast, patients with heart disease were not placed at a significantly higher rate of death (p=1.000).

Table 2.4. Patient Demographics, Characteristics and Outcomes

	All	No ACE	ACE	p Value
Number	135	117	18	n/a
Male, *n (%)*	106 (79)	92 (79)	14 (78)	1.000
Age, years	40 (25-56)	37 (24-53)	64 (42-72)	**<0.001**
Pre-injury Diagnoses, n (%)				
Heart disease	6 (4.4)	2 (1.8)	4 (22)	**0.003**
Diabetes	5 (3.7)	3 (2.6)	2 (11)	0.132
Hypertension	8 (5.9)	7 (5.9)	1 (5.5)	1.000
Hypercholesterolemia	5 (3.7)	4 (3.4)	1 (5.5)	0.517
PVD	2 (1.5)	0 (0.0)	2 (11)	**0.017**
CVA	2 (1.5)	1 (0.9)	1 (5.5)	0.249
Pre-injury Medication, n (%)				
Aspirin	6 (4.4)	2 (1.8)	4 (22)	**0.003**
Anti-hypertensives	4 (2.9)	3 (2.6)	1 (5.5)	0.439
Statins	5 (3.7)	3 (2.6)	2 (11)	0.132
Metformin	1 (0.7)	1 (0.9)	0 (0)	1.000
Insulin	2 (1.5)	2 (1.7)	2 (11)	0.083
Injury Characteristics				
Injury Severity Score	23 (13-30)	22 (13-30)	29 (19-35)	0.069
AIS Body Regions				
Head and neck	1 (0-4)	1 (0-4)	2 (0-4)	0.469
Face	0 (0-1)	0 (0-1)	0 (0-1)	0.182
Thorax	3 (0-4)	3 (0-4)	3 (0-4)	0.348
Extremity	2 (0-3)	2 (0-3)	3 (0-3)	0.395
Abdomen/pelvis	0 (0-2)	0 (0-2)	0 (0-2)	0.433
Admission Physiology				
SBP, mmHg	134 (62-220)	134 (62-220)	108 (63-160)	**0.049**
SBP <90 mmHg, *n (%)*	26 (19.3)	19 (14.1)	7 (39)	**0.047**
GCS	15 (14-15)	13 (7-15)	14 (11-15)	0.191
Lactate, mmol/L	2.2 (1.3-3.5)	2.2 (1.3-3.5)	3.1 (1.4-3.6)	**0.043**
Outcomes				
ICU stay, days	5 (2-10.5)	4 (2-8)	11 (4.5-18.5)	**0.005**
Hospital stay, days	14 (5-28)	14 (5-27)	19.5 (5-37)	0.385
Mortality, *n (%)*	28 (20.7)	20 (17)	8 (44.5)	**0.008**

Data are presented as median (interquartile range) unless otherwise stated. Comparisons are between the No ACE and ACE cohorts. PVD=Peripheral Vascular Disease, CVA=Cerebrovascular Accident, mmol/L=millimoles per litre.

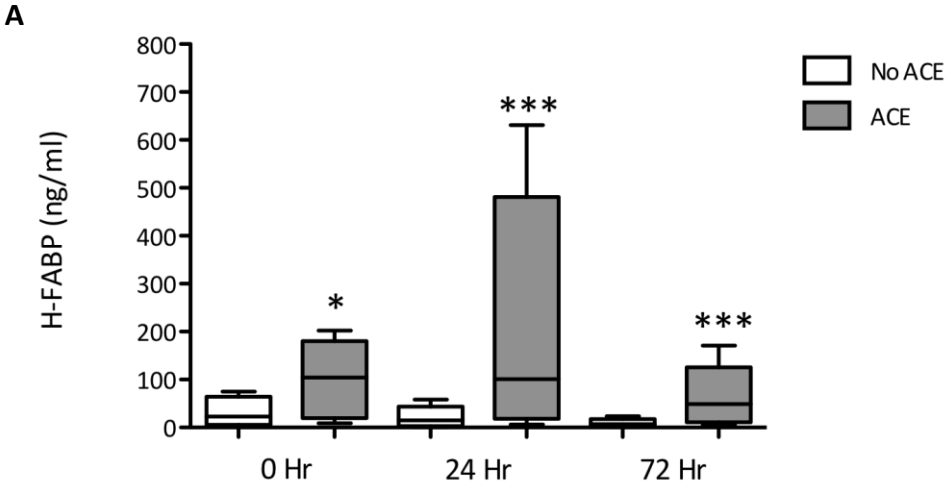
2.4.2 Biomarkers and Adverse Cardiac Events

Overall, H-FABP levels were highest on admission but by 72 hrs were below normal range. BNP levels peaked at 72 hrs, with lowest values observed on admission. Maximum Troponin I levels were observed at 0 hr.

Immediately on arrival to the ED, and hence within two hours of injury, patients showed elevations in plasma levels of the three cardiac biomarkers.

Admission levels of H-FABP were 3.2 times higher in patients with ACEs compared to those without (104.4 ng/ml vs. 32.4, p=0.022, *Figure 2.2 A*). BNP levels were also greater in individuals who had a cardiac event (573.0 fmol/ml vs. 407.0, p=0.004, *Figure 2.2 B*). H-FABP and BNP remained higher at 24 and 72 hrs in patients who developed ACEs (*Figure 2.2 A&B*).

Troponin I levels were no higher on admission blood samples. At 24 and 72 hrs, however, levels became significantly elevated in patients who suffered ACEs compared to those who did not (*Figure 2.2 C*).



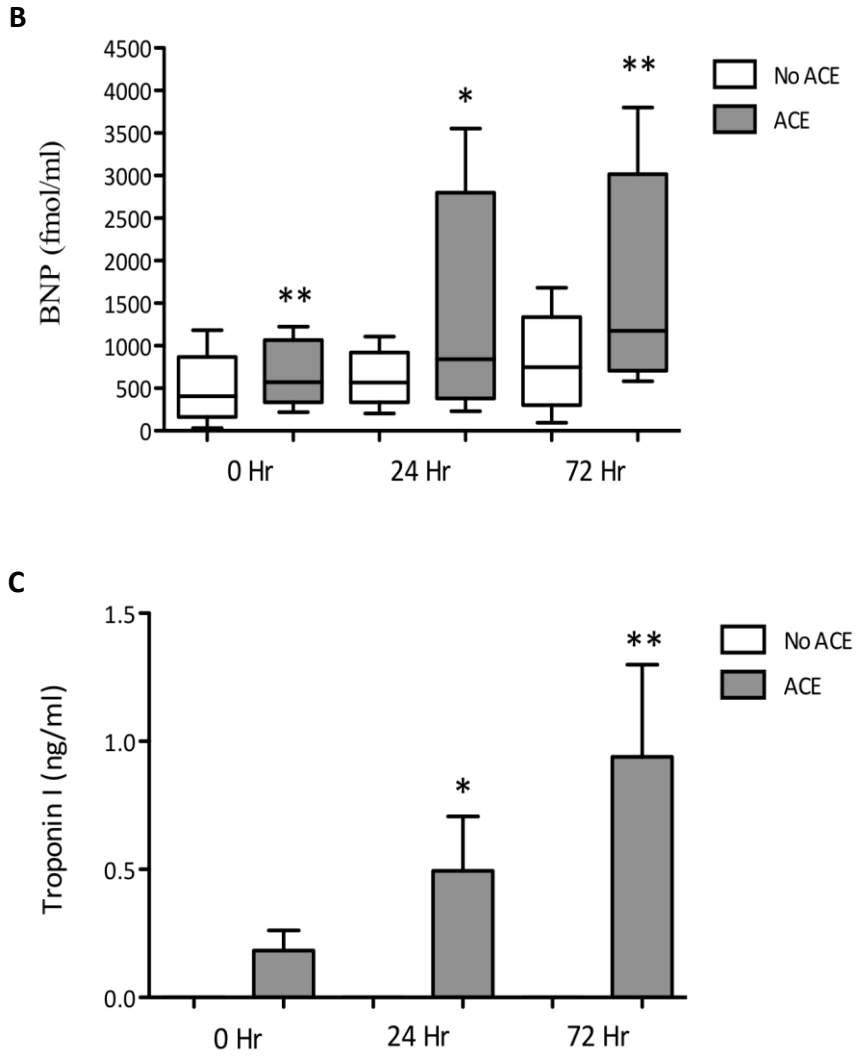


Figure 2.2 A-C. Biomarker concentrations in patients without and with ACEs

Box and whisker plots show median (horizontal line within box), interquartile range (box) and range (error bars). **A:** Patients with an ACE had higher concentrations of H-FABP at all three time points (*hr 0* 104.4 ng/ml [IQR 30.2-158.3] vs. 32.4 [IQR 14.3-75.4]; *hr 24* 101.2 ng/ml [IQR 31.7-473.3] vs. 15.1 [IQR 6.6-29.9]; *hr 72* 49.9 ng/ml [IQR 17.5-80.3] vs. 6.3 [IQR 3.7-11.9]). **B:** BNP in patients with ACEs was also higher at all time points (*hr 0* 573 fmol/ml [IQR 407-1111] vs. 453 [IQR 297-818.7]; *hr 24* 840 fmol/ml [IQR 533.3-2725] vs. 567 [IQR 461.8-731.3]); *hr 72* 1175 fmol/ml [IQR 831-2943.7] vs. 747 [IQR 287.5-1350]). **C:** Troponin I levels were significantly higher at 24 hrs (0 ng/ml [IQR 0-0.5] vs. 0 [IQR 0-0]) and 72 hrs (0 ng/ml [IQR 0-0.9] vs. 0 [IQR 0-0]) in patients with ACEs, but were no different at hr 0 (0 ng/ml (IQR 0-0.2] vs. 0 [IQR 0-0], p=0.102). *p<0.05, **p<0.01, ***p<0.001.

2.4.3 The Relationship Between Adverse Cardiac Events and Injury

There was no relationship between ACEs and injury to any specific body region (*Table 2.4*). In particular, there was no association between chest trauma and the likelihood of developing ACEs. The largest group of patients (n=6, 33%) who had a cardiac event had no injury to the thorax. This demonstrated that ACEs were not the product of direct trauma to the heart, and that a secondary process must be implicated (*Figure 2.3*).

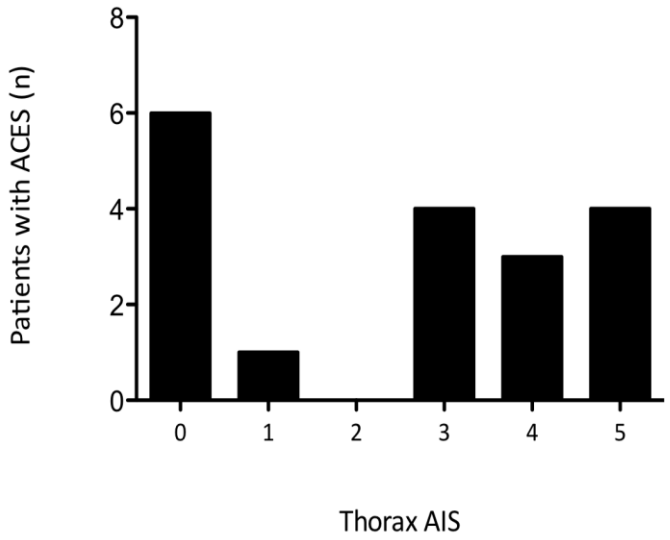


Figure 2.3. The number of ACEs in each category of chest injury

No relationship between ACEs and the severity of mechanical chest injury was observed, revealing ACEs were secondary in nature (p=0.392).

There was a trend towards increasing numbers of ACEs with worsening ISS, and the largest group of patients with a cardiac event were critically injured and found in the highest ISS category. Nonetheless, the relationship between ACEs and the severity of overall injury was not statistically significant (*Figure 2.4*).

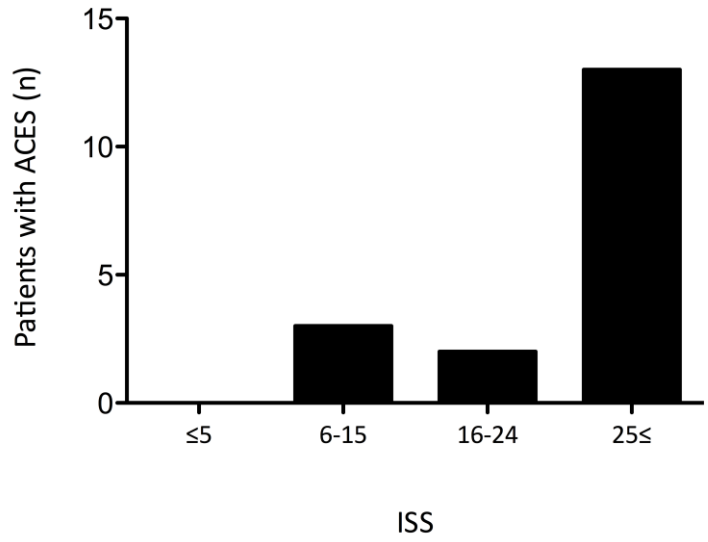


Figure 2.4. The relationship between ACEs and overall injury (ISS)
There was a non-significant trend towards increasing numbers of ACEs with worsening ISS (p=0.052).

2.4.4 Biomarkers and Injury

H-FABP correlated to the severity of mechanical chest injury (Thorax AIS) on admission (r=0.47, 95% CI 0.32-0.61; p<0.001), at 24 hrs (r=0.40, 95% CI 0.22-0.55; p<0.001) and once again at 72 hrs (r=0.29, 95% CI 0.08-0.47; p<0.01).

There was no correlation, however, between thorax AIS scores and either BNP or Troponin I on admission (r=-0.05, 95% CI -0.23-0.12; p=0.535 and r=0.02 95% CI -0.17-0.20; p=0.862, respectively). At 24 and 72 hrs, BNP continued to demonstrate no relationship to chest injury (r=-0.05, 95% CI -0.13-0.25; p=0.535 and r=0.10 95% CI -0.11-0.29; p=0.324, respectively). Equally Troponin I at 24 hrs (r=-0.15, 95% CI -0.05-0.33; p=0.126) and 72 hrs (r=0.06 95% CI -0.14-0.26; p=0.527) had no correlation to thorax AIS.

H-FABP levels correlated with the overall severity of injury (*Table 2.5*). Conversely, neither BNP nor Troponin I exhibited such an association to ISS (*Table 2.5*).

Table 2.5. Correlation between Biomarkers and ISS

	Time Point (Hr)	Spearman r (95% CI)	p Value
H-FABP	0	0.37 (0.20 - 0.52)	**<0.001**
	24	0.38 (0.20 - 0.54)	**<0.001**
	72	0.33 (0.13 - 0.51)	**0.001**
BNP	0	0.05 (-0.13 - 0.22)	0.593
	24	0.12 (-0.07 - 0.31)	0.205
	72	0.12 (-0.09 - 0.31)	0.245
Troponin I	0	0.03 (-0.16 - 0.21)	0.790
	24	0.15 (-0.04 - 0.33)	0.112
	72	0.01 (-0.19 - 0.21)	0.968

These results demonstrated that elevations in BNP and Troponin I were neither the product of direct chest injury, nor the total extent of injury.

ACEs and both BNP and Troponin I release have been associated hitherto with traumatic brain injury (Kirchhoff et al., 2006, Stewart et al., 2007, Salim et al., 2008). In this cohort of patients, however, there was no significant difference between the severity of traumatic head injury in individuals with or without ACEs (*Table 2.4*).

Furthermore, no such association was observed between either of the two biomarkers with head trauma on admission, nor indeed at any subsequent time point (*Table 2.6*).

Table 2.6. Correlation between BNP and Troponin I and Head and Neck AIS

	Time Point (Hr)	Spearman r (95% CI)	p Value
BNP	0	0.13 (-0.05 - 0.30)	0.149
	24	-0.01 (-0.28 - 0.09)	0.320
	72	-0.08 (-0.27 - 0.13)	0.441
Troponin I	0	0.05 (-0.13 - 0.24)	0.569
	24	-0.07 (-0.26 - 0.11)	0.441
	72	-0.03 (-0.23 - 0.16)	0.736

2.4.5 Adverse Cardiac Events, Biomarkers and Shock

Shock showed an equivocal association with ACEs. Half the patients (n=9, 50%) with ACEs presented with low systolic blood pressure (SBP <100mmHg), compared to nearly a quarter (n=25, 21%) of individuals without cardiac events. As such, ACEs were associated with hypotension (SBP <100 mmHg 26% vs. 9% SBP ≥100 mmHg, p=0.017).

The greatest number of cardiac events was found in the highest lactate quartile, and there was a vague trend towards higher numbers of ACEs with increasing lactate levels.

Nonetheless the relationship between lactate and ACEs was not quite statistically significant (*Figure 2.5*).

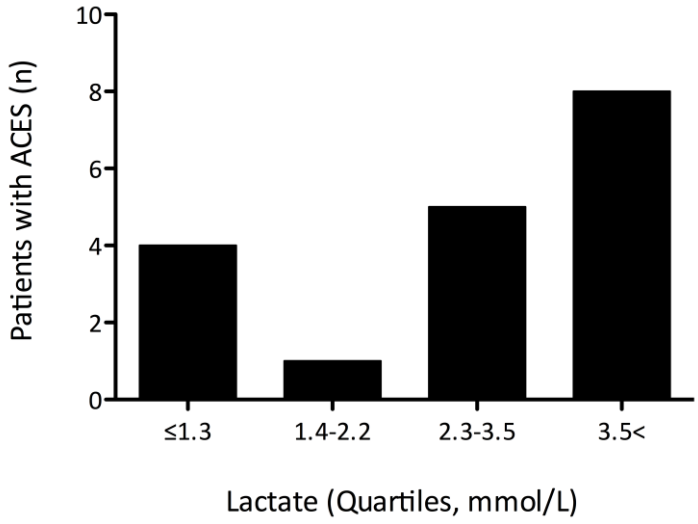


Figure 2.5. Number of patients with ACEs per admission lactate quartile

A pattern of increasing ACEs was observed with higher lactate values, although the association was not significant, p=0.053.

The association between biomarkers and shock on admission was inconclusive (*Table 2.7*). H-FABP correlated with lactate and showed an inverse relationship with SBP. BNP exhibited no association with either marker of shock. Troponin I showed a positive correlation to lactate only.

Table 2.7. Correlation between Biomarkers and Admission Lactate and SBP

	Biomarker	Spearman r (95% CI)	p Value
Lactate	H-FABP	0.27 (0.07 - 0.43)	**0.003**
	BNP	-0.02 (-0.19 - 0.16)	0.845
	Troponin I	0.24 (0.06 - 0.41)	**0.009**
SBP	H-FABP	-0.43 (-0.57 - -0.27)	**<0.001**
	BNP	0.02 (-0.16 - 0.19)	0.810
	Troponin I	-0.11 (-0.28 - 0.08)	0.256

2.4.6 Adverse Cardiac Events, Biomarkers and Mortality

Cardiac events were associated with significant mortality. The incidence of death approached 50% in the ACE cohort, and was over double that of the group in whom no cardiac event occurred (*Figure 2.6*).

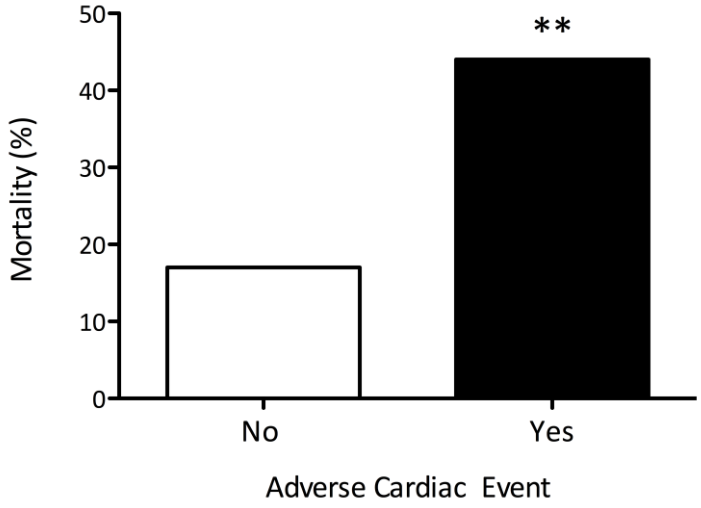


Figure 2.6. The relationship between ACEs and death

ACEs were associated with significant mortality, **p<0.01.

Median levels of H-FABP were higher in non-survivors at all three time points, although values did not reach statistical significance (*Figure 2.7*).

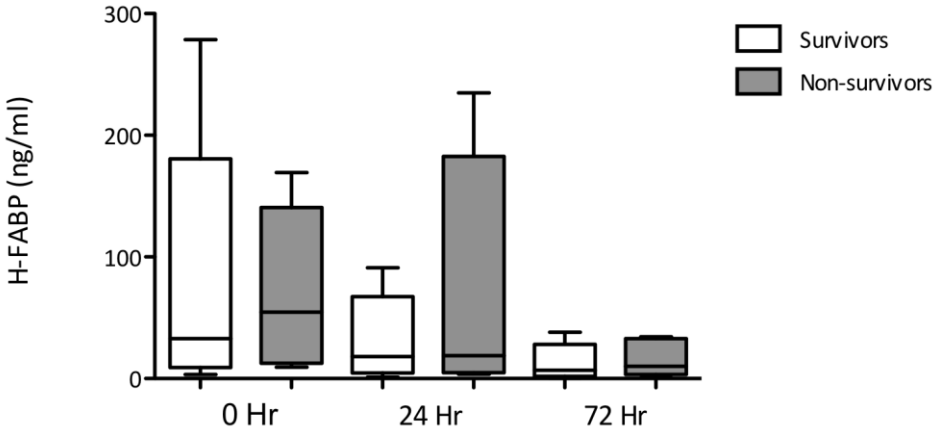


Figure 2.7. The relationship of H-FABP with death

Box and whisker plot shows median (horizontal line within box), interquartile range (box) and range (error bars). H-FABP levels were lower throughout in survivors compared to non-survivors, although not statistically significant (*hr 0* 32.8 ng/ml [IQR 14.8-177.5] vs. 54.6 [IQR 16.3-142.8], p=0.315; *hr 24* 18.2 ng/ml [IQR 8.05-65.0] vs. 18.8 [IQR 6.2-181.7], p=0.869; *hr 72* 6.8 ng/ml [IQR 3.9-17.8] vs. 10.2 [IQR 6.5-34.4], p=0.312).

BNP was associated with death at all three time frames (*Figure 2.8*).

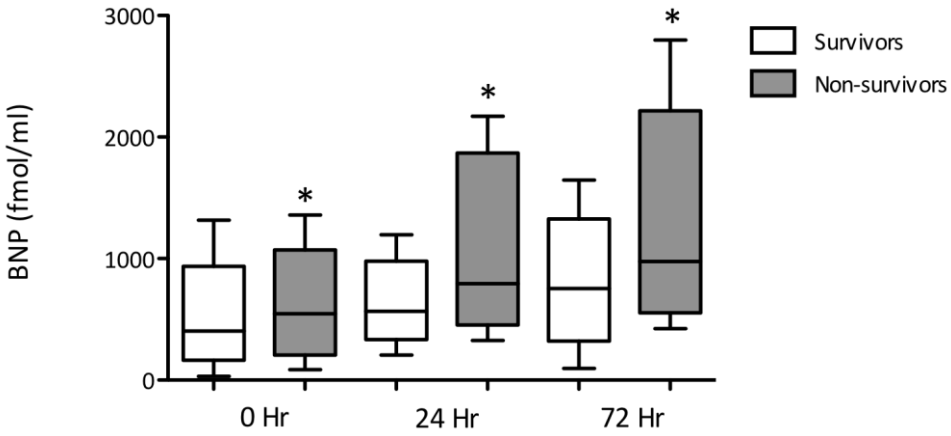


Figure 2.8. The relationship of BNP with death

Box and whisker plot shows median (horizontal line within box), interquartile range (box) and range (error bars). BNP levels were significantly greater in non-survivors on admission (546 fmol/ml [IQR 191.7-1066.6] vs. 403 [IQR 167-920]) at 24 hrs (794 fmol/ml [IQR 420.8-1837.7] vs. 567 [IQR 275-962.5]) and at 72 hrs (977 fmol/ml [IQR 684-2150] vs. 753 [IQR 475-1275]). *p<0.05.

Admission Troponin I levels were associated with survival, but no differences between survivors and patients who died were observed on either 24 or 72 hrs blood samples (*Figure 2.9*).

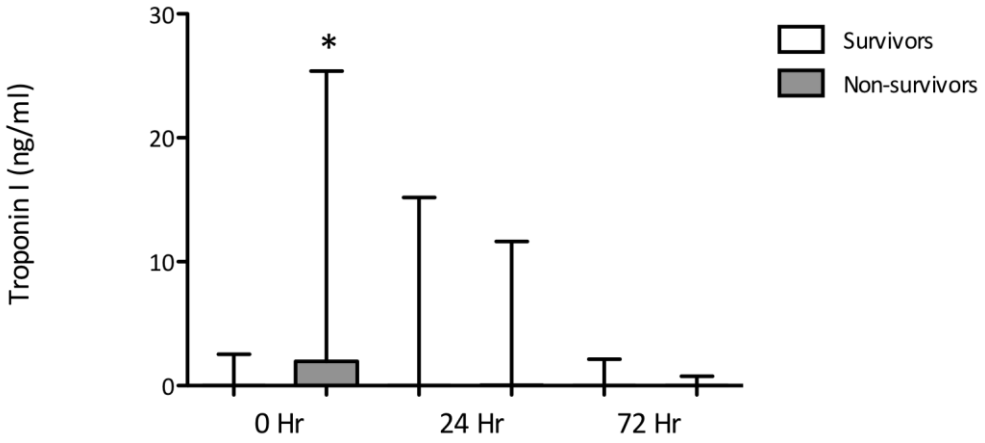


Figure 2.9. The relationship of Troponin I with death

Box and whisker plot shows median, interquartile range and range. Hour 0 Troponin I levels were higher in non-survivors (0 ng/ml [IQR 0-1.9] vs. 0 [IQR 0-0], *p<0.05), although no further differences between the two groups were noted (*hr 24* 0 ng/ml (IQR 0-0] vs. 0 [IQR 0-0], p=0.939; *hr 72* 0 ng/ml (IQR 0-0] vs. 0 [IQR 0-0], p=0.643).

2.5 Discussion

There is evidence that cardiac injury and dysfunction occur as a result of critical illness states, and that their development is associated with poorer patient outcome. Experimental research has shown that that the heart is susceptible to secondary injury following trauma-haemorrhage, whilst limited investigations in injured patients have hinted at a harmful and indirect relationship between trauma and the heart.

This study is now the first in trauma to have shown both the clinical manifestations of cardiac dysfunction combined with a panel of biochemical evidence of cardiac injury. The investigation is subject to robust methodology, including adherence to and guidance from the REMARK guidelines on biomarker studies (Mallett et al., 2010). Consequently, the results of this research add to the limited current evidence and knowledge by identifying the existence of a TISCI. This analysis implied that TISCI might not be uncommon, and may be associated with both significant and increased mortality.

Neither cardiac injury nor ACEs arose as a direct result of thoracic injury, thus demonstrating that trauma may have an indirect, secondary effect on the heart. Previous studies (M. Martin et al., 2005, Edouard et al., 1998) have also shown that cardiac injury is not associated with thoracic trauma, whilst others have revealed that ACEs occur independent of chest injury (Hadjizacharia et al., 2011, Ismailov et al., 2005, Seguin et al., 2006). Taken all into account, the evidence indicates that pathological processes beyond direct myocardial damage are implicated in the cause of TISCI.

ACEs demonstrated a trend towards worsening injury severity. This relationship was not statistically significant, perhaps as a consequence of the relatively small survey population, but nonetheless remains an association that has been recognised previously (M. Martin et al., 2005, Seguin et al., 2006).

Severely injured patients are more likely to present with adrenergic stress, shock and reperfusion injury and generally experience a greater inflammatory response.

They are therefore more susceptible to SIRS and subsequently MODS. Such pathological processes have been proposed in leading to cardiac dysfunction in non-trauma states, and so their role in driving TISCI requires investigation.

Pre-existing cardiac disease was linked with the development of an ACE, but not associated with death. However, only a minority of patients had a diagnosis of heart disease prior to injury and this association was seen in a very small number of individuals in this retrospective study. Accordingly, future larger analyses will need to clarify the true effect of pre-morbid heart disease on the outcomes of injured patients.

Patients diagnosed with an ACE were significantly older and more shocked, but were well matched in terms of injury characteristics with those in whom no cardiac event was diagnosed. Nonetheless, the difference in age may be a factor between the two groups, with older patients being at greater risk of asymptomatic heart disease. The presence of this may have triggered an ACE, precipitated by the periods of physiological stress and haemodynamic disturbances caused by trauma (Sprung et al., 2000, Reich et al., 1999).

Although neither the incidence nor sequelae of asymptomatic cardiac disease in trauma are known, the condition does not provide a likely explanation for ACEs seen in the younger patients among this cohort. The development of a cardiac event, certainly amongst these individuals, is likely to be driven by alternative mechanisms.

In experimental research, increased expression and levels of cardiac IL-6 (Yang et al., 2004, Nickel et al., 2009) and TNFα (Cai et al., 2009) result from trauma-haemorrhage with a subsequently deleterious impact on cardiac function. In mice, the daily administration of IL-18 leads to interstitial fibrosis and myocyte hypertrophy.

This causes increased ventricular stiffness (Platis et al., 2008). Furthermore, circulating TNFα in plasma taken from animals subject to mechanical trauma and given to normal cardiomyocytes from non-traumatised animals has been shown to lead to cardiomyocyte apoptosis (Li et al., 2007).

These findings support the notion that inflammation could be an aetiological factor in the clinical development of a TISCI. The role of inflammation in TISCI warrants, therefore, detailed exploration in a dedicated clinical study.

The analysis suggested a relationship between TISCI and shock, but was by no means conclusive. ACEs were associated with low SBP, and demonstrated a non-significant trend towards higher lactate levels. Both H-FABP and Troponin I were correlated to lactate levels, but only H-FABP showed any statistically relationship with SBP. BNP was unrelated to shock. Consequently, there remain unanswered questions regarding TISCI and shock, and further the associated pathogenic processes resulting from the integrated roles of ischaemia-reperfusion, free radical production and adrenergic stress as culprits in the development of this condition.

There are potential implications of these results for clinical practice. In general terms, cardiac dysfunction is amongst the most well recognised targets for therapeutic intervention, and beta-blockers are now recommended in selected elderly patients undergoing major elective surgery (Auerbach et al., 2002). In some studies of trauma patients, the presence of pre-existing cardiac disease, and in particular congestive heart failure, has been linked to an increase in mortality (Ferraris et al., 2010).

Research reporting the use of cardiac medication in injured patients has revealed conflicting results describing both increased and decreased mortality and morbidity rates following trauma (Arbabi et al., 2007, Cotton et al., 2007, Efron et al., 2008, Neal et al., 2009, Neideen et al., 2008).

Although most of the evidence regarding beta-blockers in injured patients is retrospective in nature, the majority of papers report a survival benefit in patients who are beta-blocked prior to trauma. To date, this has been most evident in studies examining survival following head injury, where it is suggested that these drugs might exert their protective effects through the abrogation of the detrimental effects of catecholamine surges.

In turn, this may also lead to a reduction in bone marrow dysfunction, systemic inflammation and myocardial oxygen demand (Elhassan et al., 2011).

This study provides additional evidence that a significant number of patients are at risk of ACEs after trauma. In conjunction with other published data (M. Martin et al., 2005, Lagi et al., 2008, Hadjizacharia et al., 2011), this research also highlights the clinical relevance of TISCI by demonstrating the poorer outcomes associated with the condition.

Accordingly, in the event that the pathways of TISCI are better understood and an "at risk" population identified, studies in the future might better elucidate the use of selected therapeutic intervention in certain individuals, and enable a consensus on the use of cardiac medication in trauma patients. In particular, the benefit of beta-blockers in improving outcomes following trauma merits further investigation in larger prospective studies.

2.6 Limitations

Although patients, blood samples and much of the information were collected prospectively, individuals enrolled into this analysis were retrospectively selected and assessed for ACEs. It is possible, therefore, that the analysis was subject to measurement bias because the identification of ACEs was reliant on the events being accurately documented. As a result, there is the potential for misclassification of ACEs, with the additional likelihood that the incidence of these amongst patients in this cohort is in fact higher.

Furthermore, some patient data were not available, including individual left ventricular function prior to trauma. Patients with ACEs were older, more often diabetic and on more medication. Thus trauma may have in fact simply exposed pre-existing cardiac disease that was not identified pre-injury. Although this could not have been discerned in this study, it is possible that ACEs were the manifestation of such a process.

Injury to the heart was demonstrated through the abnormal elevation of cardiac biomarkers but without visualising the heart or assessing its function. Echocardiograms or ECGs were not performed on admission in patients in this study, and hence this research was limited by an inability to rule out causes for biomarker rises such as pre-existing heart failure or an MI. However, raised BNP has been shown in injured patients without heart failure, and a high incidence of pre-injury MI is very unlikely in this patient group.

The exact cause of death in this cohort of patients was not known and therefore whether and how TISCI contributed to the mode of death remains unclear.

Finally, the study looked only at a specific group, namely severely injured patients. Accordingly results might not be representative of all trauma patients, and may not reflect the true incidence and outcomes associated with TISCI.

2.7 Conclusions

This is the first study to have provided both clinical and multiple biomarker evidence identifying the existence of TISCI, and to have demonstrated its association with poorer outcomes.

Future prospective studies are needed to characterise fully the exact nature, incidence, risk factors, and outcomes associated with TISCI. In particular post-traumatic ACEs should be investigated in a larger prospective study. Such research should be undertaken in all trauma patients, and not remain limited to the critically ill.

The processes implicated in driving this condition should be investigated, and in particular, the role of inflammation, so that eventually targeted management strategies may be developed to lessen the burden of TISCI in trauma patients.

CHAPTER THREE

Trauma Induced Secondary Cardiac Injury and Inflammation

3.1 Introduction

In conjunction with the evidence presented in *Chapter Two*, a growing body of literature points to the existence and clinical significance of TISCI. The pathological mechanisms that lead to this condition have not yet been fully identified.

Research in trauma patients has revealed associations between TISCI and the degree of injury and physiological stress (Edouard et al., 1998, M. Martin et al., 2005), age (Hadjizacharia et al., 2011), body region injured (Ismailov et al., 2005), catecholamine use and SIRS (Seguin et al., 2006). Although separate clinical entities, these factors are all linked together by inflammation. Specifically, they either trigger it, or are the product of it.

Injury provokes a systemic inflammatory response which may cause MODS, the leading cause of late death in trauma (Dewar et al., 2009). In a prospective study of critically injured patients, a link between inflammation and secondary cardiac dysfunction was demonstrated (Seguin et al., 2006). Individuals who developed AF were more likely to experience SIRS, in addition to other conditions associated with inflammation such as shock, sepsis and higher catecholamine use (Batistaki et al., 2008). Most recently, an association between infection and cardiac injury was described in trauma, and implied the existence of infection-related, inflammatory driven cardiac dysfunction in critically injured patients (Monaghan et al., 2012).

In SIRS and subsequently MODS, inflammation dominates and cardiovascular dysfunction is frequent (Jastrow et al., 2009, Maier et al., 2007, Moore et al., 1996). Inflammation is known to reduce cardiac function (Prabhu, 2004) and SIRS causes myocardial depression, contractile dysfunction and decreased afterload (Ungureanu-Longrois et al., 1995, R. S. Martin et al., 2005).

Experimental research has identified that trauma-haemorrhage leads to secondary cardiac injury and dysfunction and has explored many of the

mechanisms implicated. To date, the role of inflammation has been the predominant interest of most of these studies.

Investigations have concentrated particularly on the relationship between the pro-inflammatory cytokines IL-6 and TNFα and cardiac damage, and explored the pathways through which these effects are exerted (Yang et al., 2004, Li et al., 2007, Sato et al., 2007). Experiments designed to inhibit these damaging pathways have demonstrated that the suppression of inflammatory sequences leads to restored cardiac function (Nickel et al., 2009, Mizushima et al., 2000a, Kan et al., 2008, Zou et al., 2008).

Although the experimental literature is suggestive, it is not translational to the clinical setting. The evidence is based on rodent data from small numbers of healthy animals, in models of tissue injury and shock specifically designed to lead to cardiac damage and dysfunction. The experimental data is thus limited in its applicability to a heterogeneous cohort of injured patients.

Currently in the trauma literature, only one study has described an association between rises in pro-inflammatory cytokines, namely TNFα, IL-6 and IL-8, with secondary cardiac injury (Jiang et al., 1997). The analysis, however, was flawed by the inclusion of only small patient numbers, and through the use of an unreliable and dated biomarker of cardiac injury (CPK).

The causes of TISCI have not been elucidated. Based on existing experimental data, inflammation is most widely implicated. Consequently, the association between cytokines, inflammation and secondary cardiac injury and dysfunction represents an important and novel area for research.

3.2 Study Aims

The overall objective of this study was to determine if there was an early association between inflammation and TISCI in trauma patients, and explore the impact of this relationship on survival.

Specifically, the *first* aim was to investigate whether there was an association between acute markers of inflammation and subsequent development of ACEs.

Second, to investigate if there was an early correlation between inflammatory markers and elevations in biomarkers of cardiac injury.

Finally, to determine whether activation of inflammation combined with biomarker evidence of cardiac injury on admission was associated with a higher in-hospital mortality rate.

3.3 Materials and Methods

This project identified patients and used blood samples that were collected as part of the ongoing prospective ACIT 2 project. ACIT 2 was granted ethical approval by East London and the City Research Ethics Committee 1. All data and samples used in this study were consented for.

3.3.1 Study Design and Setting

A retrospective cohort study of severely injured patients admitted to an ICU. The project was performed at The Royal London Hospital, a major urban trauma centre in the United Kingdom.

3.3.2 Study Population

This study is undertaken in the same cohort of patients described in *Chapter Two* (*Section 2.3.2*). This selection was based on investigating the role of inflammation in a trauma population with established evidence of TISCI.

3.3.3 Data Collection

Data collection is detailed in *Chapter Two* (*Section 2.3.3*).

3.3.4 Outcomes

The two study outcomes were ACEs and in-hospital death. An ACE included any one of the following diagnoses; supra-ventricular arrhythmias, ventricular arrhythmias, acute coronary syndrome (ACS) and cardiogenic shock. Diagnoses were made and documented by a senior intensivist or cardiologist blinded to study outcomes.

Death was recorded as 28-day mortality of any cause. Patients discharged from hospital before 28 days were assumed to be alive at day 28.

3.3.5 Blood Collection

Blood collection is described in *Chapter Two* (*Section 2.3.5*).

3.3.6 Inflammatory Marker Analysis

A panel of common cytokines which included TNFα, IL-6 and IL-8, together with interferon gamma (IFNγ), interleukin 10 (IL-10), interleukin 12 (IL-12) and interleukin 1 beta (IL-1β) was selected in order to screen the association between inflammation and ACEs.

Thereafter, the three pro-inflammatory cytokines TNFα, IL-6 and IL-8 were isolated and investigated in further detail in order to translate experimental evidence into the clinical context. Their selection was based on the existing literature demonstrating the role of these three in leading to cardiac injury and dysfunction in various disease states (Vallejo et al., 2004, Emura et al., 2010, Li et al., 2007, Yang et al., 2006, Jiang et al., 1997).

Plasma cytokine quantification was performed on participants' blood using a commercially available Multiplex pro-inflammatory cytokine analysis platform on a SECTOR® Imager 2400 (Mesoscale Discovery, Maryland, USA). Measurements were undertaken in accordance with the manufacturer's protocol. All samples were performed in duplicate. A standard curve was prepared using the standard cytokine solution provided, to achieve a range from 0.6 – 2500 pg/ml. This range was well within the detection limits of the apparatus. Unknown concentrations were obtained from the standard curve using the inbuilt Mesoscale software.

Cytokine analysis was performed by Joanna Manson, a fellow researcher, as part of an ACIT substudy.

There is no defined normal range of these cytokines in a heterogeneous population such as trauma patients. Accordingly, a control group was established and included individuals who had a normal base deficit (≤2 mEq/L) with no or minimal evidence of injury (ISS ≤5).

Eight patients were identified using these criteria (*Table 3.1*) and were excluded from any subsequent analyses. Cytokines were deemed elevated when values exceeded the median values of the control group listed overleaf.

- **TNFα** 2.32 pg/ml, IQR 1.74-4.18
- **IL-6** 10.45 pg/ml, IQR 1.41-55.02
- **IL-8** 5.38 pg/ml, IQR 2.56-12.16

Table 3.1. Control Group Characteristics and Admission Cytokine Levels

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8
Gender	F	M	M	M	M	M	M	M
Age, years	47	27	43	40	59	37	28	62
Injury Characteristics								
Mechanism	B	B	P	B	B	B	B	B
ISS	4	5	1	1	4	5	5	4
Thorax AIS	0	0	0	0	0	2	0	0
Admission Physiology								
SBP, mmHg	178	220	124	132	135	132	156	161
Heart rate, bpm	69	118	121	82	120	88	130	100
Base excess, mEq/L	2	1.5	1.2	-3.2	-0.4	0.6	0.1	1.2
Admission Cytokine Levels (pg/ml)								
TNFα	2.01	2.27	2.36	1.46	3.27	1.65	4.48	5.48
IL-6	38.62	1.06	5.68	0.32	60.48	2.44	15.22	90.38
IL-8	4.29	2.58	1.84	2.55	12.33	6.48	24.01	11.63
28 day Survival								
	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive

Pt=patient, F=female, M=male, B=blunt, P=penetrating, bpm=beats per minute.

3.3.7 Biomarker Assays

H-FABP, BNP and Troponin I were selected as markers of cardiac injury. Biomarker analysis is detailed in *Chapter Two* (*Section 2.3.6*). For the purposes of this study, elevated levels of H-FABP were defined as ≥20 ng/ml, BNP as ≥300 fmol/ml and Troponin I as ≥0.03 ng/ml.

These levels were based on a combination of the ELISA kit manufacturers' guidelines and existing literature defining both normal and abnormal values of these biomarkers.

3.3.8 Statistical Analysis

Data analyses were performed using SPSS version 20 (SPSS Inc., Chicago IL). Statistical significance was set as a two tailed p value of <0.05.

Data are presented as medians with interquartile ranges, unless otherwise specified. Non-parametric data were compared using the Mann Whitney U test. Correlation between biomarkers and cytokines was performed using Spearman correlation. Proportions were analysed using Fisher's exact test and Chi Squared test for trend.

Simple univariate regression determined the correlation of cytokines with age. To discover the independent association between H-FABP (as the earliest marker of cardiac injury) and inflammation on admission, multiple linear regression analysis was applied. The enter method was used with the probability of F set at $p<0.05$ to enter and $p>0.1$ for removal. H-FABP represented the dependent variable, and age, ISS, base excess and hour 0 levels of TNFα, IL-6 and IL-8 were the predictor variables.

The final aim was to investigate whether on admission, evidence of cardiac injury (defined by an elevated level of H-FABP, BNP or Troponin I) combined with activation of inflammation (demonstrated by an elevated level of TNFα, IL-6 or IL-8) was predictive of in-hospital death. Accordingly, patients were divided into four distinct groups:

1. Patients with normal biomarker and normal cytokine values.
2. Patients with an elevated biomarker value and a normal cytokine level.
3. Patients with a normal biomarker level and an elevated cytokine value.
4. Patients with both an elevated biomarker and elevated cytokine level.

Group 1 was used as the control group (Relative Risk [RR]=1) and the relative risk of in-hospital death was calculated among the remaining three groups based on comparisons to the first.

3.4 Results

One hundred and thirty five patients were recruited to the study. Eighteen (13.3%) individuals had an ACE during admission, and 28 patients (20.7%) died. Patient characteristics are summarised in Table 3.2.

Table 3.2. Patient Characteristics, Adverse Cardiac Events and Outcomes

	All	No ACE	ACE	p Value
Number	135	117	18	n/a
Male *n (%)*	106 (79)	92 (79)	14 (78)	1.000
Age, years	40 (16-89)	37 (16-89)	64 (23-88)	**<0.001**
ISS	23 (13-30)	22 (13-30)	29 (19-35)	0.069
Thorax AIS	3 (0-4)	3 (0-4)	3 (0-4)	0.348
Admission SBP, mmHg	134 (62-220)	134 (62-220)	108 (63-160)	**0.049**
Admission GCS	15 (14-15)	13 (7-15)	14 (11-15)	0.191
Type of ACE, n (%)				
Supra-ventricular arrhythmia	13 (9.6)	n/a	13 (65)	n/a
Ventricular arrhythmia	1 (0.74)	n/a	1 (5)	n/a
Acute coronary syndrome	3 (2.2)	n/a	3 (15)	n/a
Cardiogenic shock	3 (2.2)	n/a	3 (15)	n/a
Outcomes				
ICU stay, days	5 (2-11)	4 (2-8)	11 (5-19)	**0.005**
Hospital stay, days	14 (5-28)	14 (5-27)	20 (5-37)	0.385
Mortality, *n (%)*	28 (21)	20 (17)	8 (45)	**0.008**

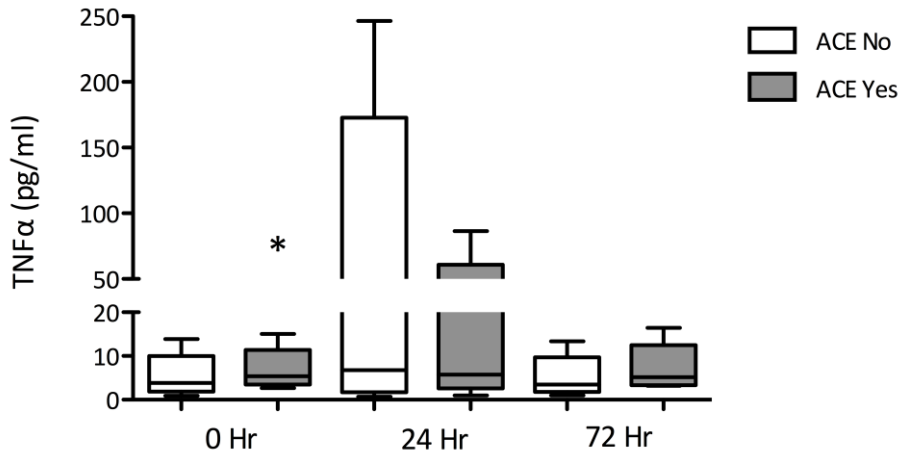
Data are presented as median (interquartile range) unless otherwise stated. Comparisons are between the No ACE and ACE cohorts.

3.4.1 Inflammation and Adverse Cardiac Events

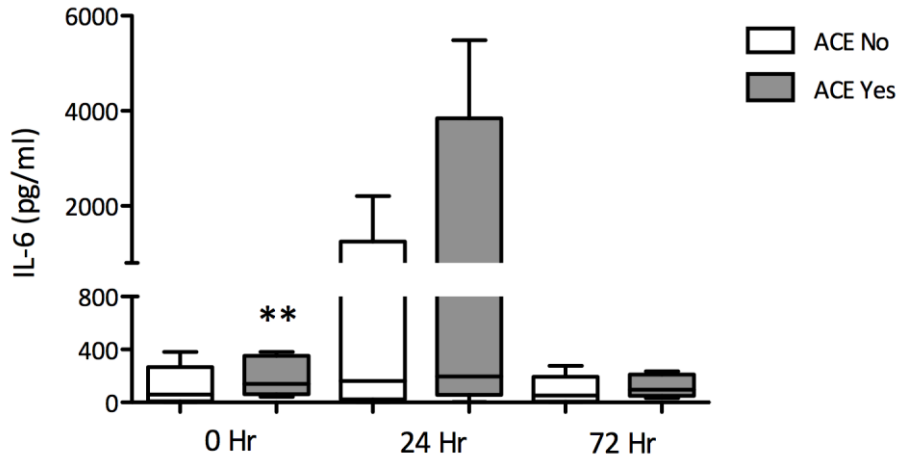
Amongst this cohort of severely injured patients, the cytokines TNFα, IL-6, IL-8 and IL-1β demonstrated an association with ACEs (*Figure 3.1 A-D*).

Immediately on admission, and hence within two hours of injury, plasma levels of TNFα, IL-6 and IL-8 were all significantly higher in patients who subsequently developed an ACE in-hospital compared to those who did not (*Figure 3.1 A-C*).

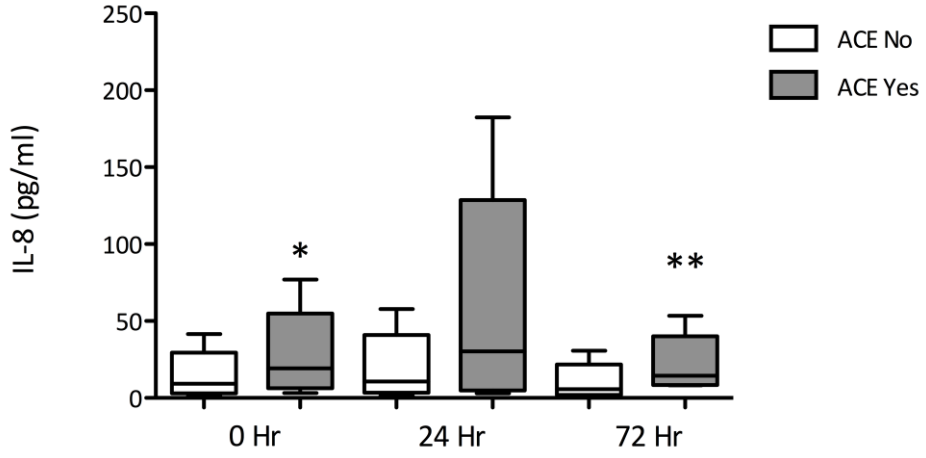
A


TNFα (pg/ml)
250
200
150
100
50
20
10
0
*
0 Hr
24 Hr
72 Hr
ACE No
ACE Yes

B


IL-6 (pg/ml)
6000
4000
2000
800
400
0
**
0 Hr
24 Hr
72 Hr
ACE No
ACE Yes

C


IL-8 (pg/ml)
250
200
150
100
50
0
*
**
0 Hr
24 Hr
72 Hr
ACE No
ACE Yes

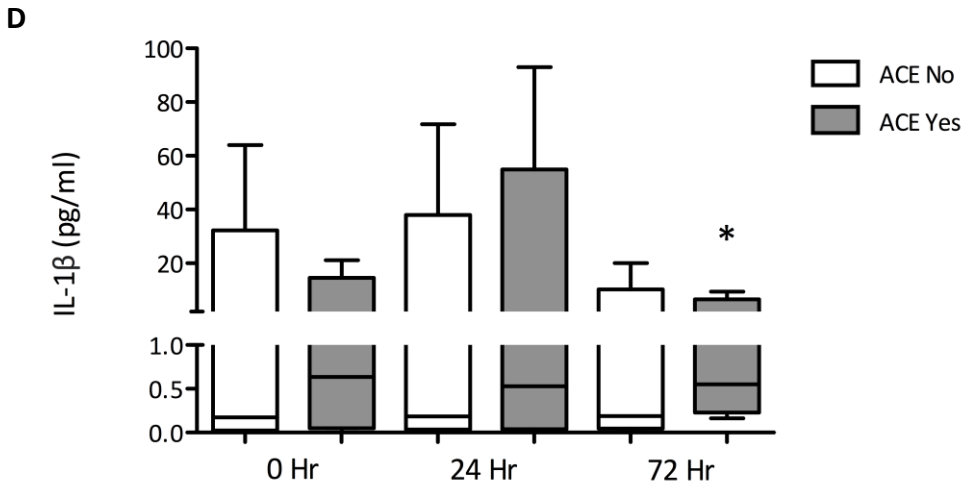


Figure 3.1. A-D. Relationship of TNFα, IL-6, IL-8 and IL-1β with adverse cardiac events

Box and whisker plots show median (horizontal line within box), interquartile range (box) and range (error bars). **A**: Admission TNFα levels were higher in ACE patients (5.42 pg/ml [IQR 4.34-10.50] vs. 3.84 [IQR 2.86-9.28]), but no differences were noted at 24 hrs (5.01 pg/ml [IQR 1.95-58.05] vs. 5.62 [IQR 1.34-167.80], p=0.935) or 72 hrs (4.79 [IQR 3.95-11.11] vs. 2.56 pg/ml [IQR 1.76-8.67], p=0.119). **B**: ACE patients had greater levels of IL-6 on admission (85.37 pg/ml [IQR 44.72-308.94] vs. 24.39 [IQR 4.07-247.97]). There were no differences between the two groups at 24 hrs (146.34 pg/ml [IQR 24.34-3762.05] vs. 126.02 [IQR 24.39-1159.79], p=0.390) and 72 hrs (96.46 pg/ml [IQR 66.19-186.00] vs. 51.80 [IQR 12.22-146.34], p=0.087). **C**: In patients with ACEs, admission (19.33 pg/ml [IQR 9.56-52.43] vs. 9.18 [IQR 4.71-24.65]) and 72 hrs (14.50 pg/ml [IQR 8.87-36.81] vs. 5.85 [IQR 3.25-19.44]) levels of IL-8 were higher. 24 hrs levels were no different (30.26 pg/ml [IQR 6.80-127.08] vs. 10.64 [IQR 5.29-36.81], p=0.098). **D**: Patients with a cardiac event had significantly higher levels of IL-1β at 72 hrs (0.55 pg/ml [IQR 0.29-5.94] vs. 0.19 [IQR 0.09-8.92]), but there were no significant differences between the two groups on admission (0.64 pg/ml [IQR 0.09-12.90] vs. 0.17 [IQR 0.05-29.81], p=0.130) or at 24 hrs (0.52 pg/ml [IQR 0.08-53.69] vs. 0.19 [IQR 0.07-36.78], p=0.333). *p<0.05, **p<0.01.

Although all cytokine values were highest at 24 hrs, there were no significant differences in levels between the two groups of patients at this time point.

However, the median IL-8 level at 24 hrs was 2.8 times higher in patients with ACEs than in those without. Moreover both IL-8 and IL-1β levels were statistically greater in ACE patients at 72 hrs (*Figure 1 C&D*).

Conversely, there were no significant differences in IFNγ, IL-10 and IL-12 levels between patients who experienced an ACE in-hospital compared to those who did not (*Table 3.3*).

Table 3.3. Levels of IFNγ, IL-10 and IL-12 and Adverse Cardiac Events

	Time Point (Hr)	No ACE	ACE	p Value
IFNγ (pg/ml)	0	0.74 (0.21-1.85)	1.79 (0.36-10.16)	0.185
	24	2.21 (0.31-11.11)	2.37 (0.08-20.24)	1.000
	72	0.47 (0.17-8.22)	0.85 (0.40-5.77)	0.284
IL-10 (pg/ml)	0	48.52 (9.29-106.10)	30.15 (14.84-135.4)	0.603
	24	10.03 (2.33-29.08)	16.13 (5.30-78.28)	0.370
	72	3.88 (1.13-11.98)	8.33 (5.09-20.37)	0.113
IL-12 (pg/ml)	0	1.06 (0.44-5.19)	0.79 (0.17-9.21)	0.296
	24	4.15 (0.13-36.01)	2.06 (0.577-70.39)	0.485
	72	0.67 (0.15-5.54)	2.63 (0.46-24.40)	0.152

Data are presented as median (interquartile range).

Patients with cardiac events were significantly older (*Table 3.2*). Univariate linear regression was performed, therefore, to determine whether age was a confounder for those cytokines associated with ACEs and age (*Table 3.4*).

The analysis revealed that overall, age was not a confounder for higher cytokine levels. Only 24 hr levels of IL-8 correlated significantly. In patients with cardiac events, therefore, raised cytokine values were not the product of older age.

Table 3.4. Relationship of Cytokines with Age

	Time Point (Hr)	Beta Coefficient	p Value
TNFα	0	-0.48	0.302
	24	-0.01	0.617
	72	0.86	0.140
IL-1β	0	-0.13	0.569
	24	0.03	0.084
	72	0.40	0.507
IL-6	0	0.07	0.376
	24	0.02	0.100
	72	0.09	0.649
IL-8	0	0.48	0.408
	24	0.01	**0.019**
	72	0.13	0.060

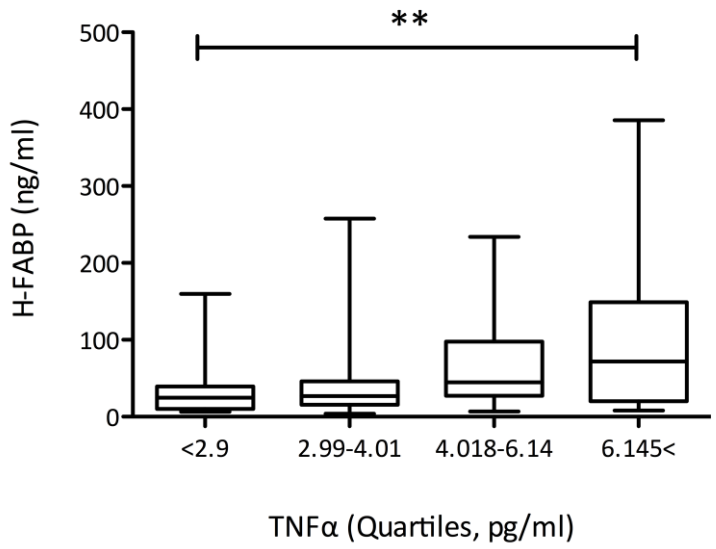
3.4.2 Inflammation and Cardiac Injury

The relationship between levels of the pro-inflammatory cytokines TNFα, IL-6 and IL-8 with the biomarkers of cardiac injury was examined on admission, and again at 24 and 72 hrs.

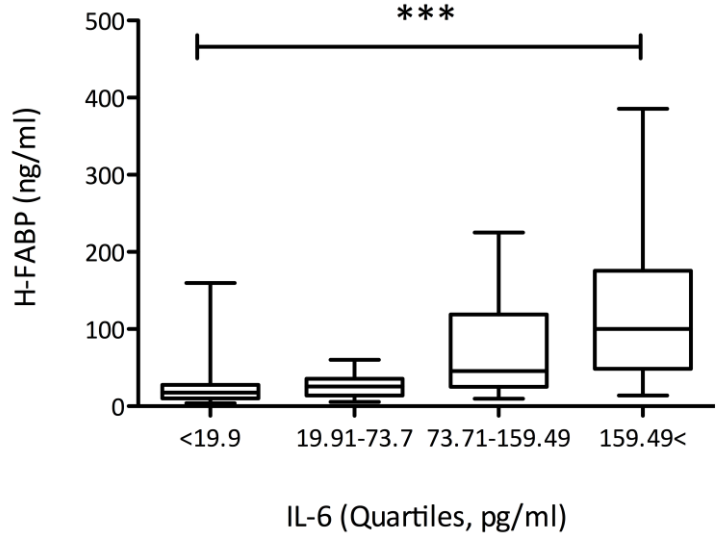
Admission levels of H-FABP correlated with admission levels of TNFα, IL-6 and IL-8 (*Figure 3.2 A-C*).

Within two hours of injury, therefore, incremental rises in each cytokine were associated with elevations in H-FABP, thereby providing evidence of a relationship between inflammation and cardiac injury.

A


**
500
400
300
200
100
0
H-FABP (ng/ml)
<2.9
2.99-4.01
4.018-6.14
6.145<
TNFα (Quartiles, pg/ml)

B


***
500
400
300
200
100
0
H-FABP (ng/ml)
<19.9
19.91-73.7
73.71-159.49
159.49<
IL-6 (Quartiles, pg/ml)

C

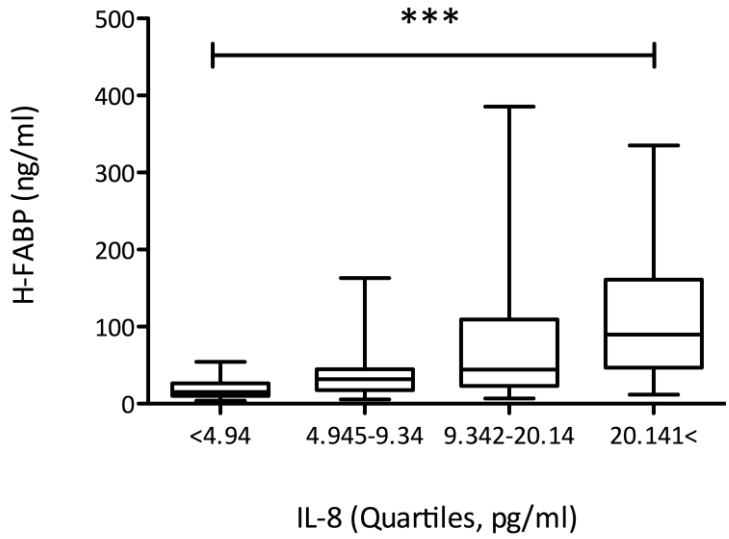


Figure 3.2. A-C. Correlation between admission levels of cytokines and H-FABP

Box and whisker plots show median (horizontal line within box), interquartile range (box) and range (error bars). **A**: TNFα and H-FABP (24.70 ng/ml [10.40-39.53] vs. 26.85 [15.58-46.18] vs. 44.60 [27.10-97.50] vs. 71.95 [20.40-149.90]). **B**: IL-6 and H-FABP (17.90 ng/ml [10.30-27.75] vs. 25.70 [14.10-35.80] vs. 45.70 [25.13-118.80] vs. 100.20 [48.40-175.80]). **C**: IL-8 and H-FABP (15.00 ng/ml [10.05-26.28] vs. 32.00 [17.90-44.60] vs. 44.40 [22.95-109.40] vs. 89.95 [46.68-160.90]). **p<0.01, ***p<0.001.

The correlation between all the cytokines and the biomarkers is shown in Table 3.5 overleaf. IL-8 levels correlated with plasma levels of H-FABP at all time points. IL-6 was associated with rises in H-FABP not only on admission, but also at 72 hrs. TNFα correlated with H-FABP only at 0 hr.

There was no correlation, however, between either TNFα, IL-6 or IL-8 and BNP at any point. Similarly, the three cytokines demonstrated no association with Troponin I on admission, or at any subsequent time frame (Table 3.5).

Early activation of inflammation was thus associated with release of H-FABP into the plasma, and this relationship may persist for at least 72 hrs after injury.

Table 3.5. Correlation between Cytokine Levels and Biomarkers

	Time (Hr)	H-FABP	BNP	Troponin I
TNFα	0	0.41 (0.2 - 0.55) ***p<0.001***	0.14 (-0.07 - 0.34) *p=0.174*	0.06 (-0.16 - 0.27) *p=0.585*
	24	0.22 (-0.06 - 0.47) *p=0.118*	-0.15 (-0.41 - 0.13) *p=0.272*	0.14 (-0.14 - 0.4) *p=0.318*
	72	0.27 (-0.02 - 0.52) *p=0.062*	0.25 (-0.03 - 0.49) *p=0.069*	-0.12 (-0.37 - 0.18) *p=0.466*
IL-6	0	0.63 (0.48 - 0.74) ***p<0.001***	0.09 (-0.12 - 0.29) *p=0.375*	0.07 (-0.14 - 0.3) *p=0.491*
	24	0.25 (-0.03 - 0.5) *p=0.073*	-0.07 (-0.34 - 0.21) *p=0.613*	0.07 (-0.20 - 0.34) *p=0.615*
	72	0.44 (0.17 -0.65) ***p=0.002***	0.01 (-0.27 - 0.29) *p=0.920*	-0.03 (-0.31 - 0.25) *p=0.842*
IL-8	0	0.62 (0.47 - 0.74) ***p<0.001***	0.16 (-0.05 - 0.36) *p=0.114*	0.03 (-0.2 - 0.24) *p=0.772*
	24	0.28 (-0.03 - 0.52) ***p=0.044***	-0.16 (-0.42 - 0.12) *p=0.257*	0.05 (-0.23 - 0.32) *p=0.716*
	72	0.40 (0.16 - 0.64) ***p=0.002***	0.26 (-0.02 - 0.51) *p=0.059*	-0.02 (-0.29 - 0.27) *p=0.909*

Data presented as Spearman r value (95% confidence intervals) with *p values*.

In order to adjust for the positive relationship between H-FABP and inflammation on admission, multiple regression analysis was subsequently performed. H-FABP was entered as the dependent variable and age, ISS, base excess, TNFα, IL-6 and IL-8 were examined as the covariates (*Table 3.6*). The model was a fair fit (R^2=0.342) and the overall association was significant (F[4,85]=11.030, p<0.001).

Table 3.6. The Relationship Between H-FABP and the Covariates

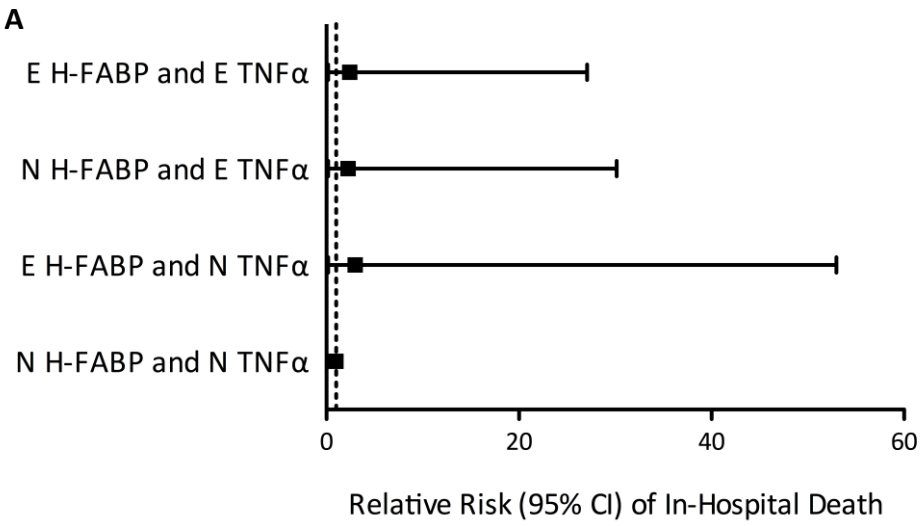
Variable	Beta Coefficient	p Value
Age	0.367	<0.001
Base excess	-0.131	0.198
ISS	0.188	<0.05
TNFα	-0.234	0.539
IL-6	0.206	<0.05
IL-8	0.064	0.511

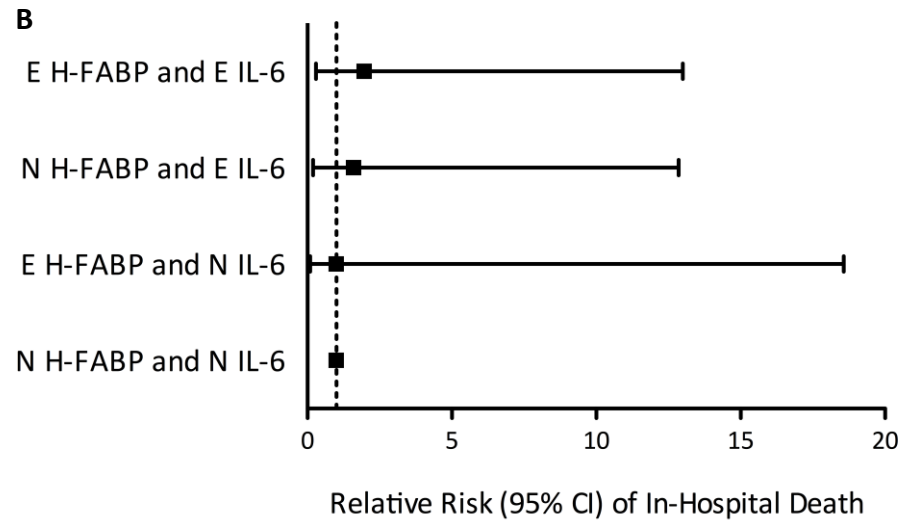
The analysis revealed that age, ISS and IL-6 were all independent predictors of an increased H-FABP. In contrast, base excess, TNFα and IL-8 were not associated with the biomarker.

Thus in addition to older age and increasing tissue injury, evidence of inflammation on admission independently predicted cardiac injury (using H-FABP levels) in this cohort of trauma patients.

3.4.3 Inflammation, Cardiac injury and Survival

On admission plasma samples, patients who presented with an elevated H-FABP combined with an elevation in any of the three cytokines were not placed at an increased risk of in-hospital death (*Figure 3.3 A-C*).





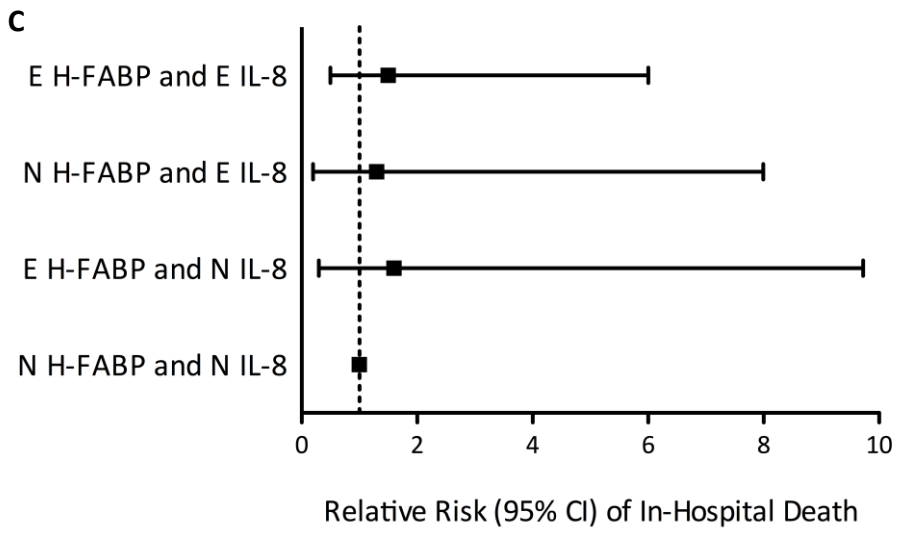


Figure 3.3. A-C. The relationship between inflammation and H-FABP on admission with in-hospital mortality

Relative risk of death (with 95% Confidence Intervals) is shown for each group (N=normal level, E=elevated level). Hashed line indicates a relative risk of 1. **A:** H-FABP and TNFα. (E H-FABP and N TNFα, p=1.000, N H-FABP and E TNFα, p=1.000, E H-FABP and E TNFα, p=0.566). **B**: H-FABP and IL-6. (E H-FABP and N IL-6, p=1.000, N H-FABP and E IL-6, p=1.000, E H-FABP and E IL-6, p=0.448). **C**: H-FABP and IL-8. (E H-FABP and N IL-8, p=0.618, N H-FABP and E IL-8, p=1.000, E H-FABP and E IL-8, p=0.526).

On hour 0 plasma samples, patients who presented with an elevated BNP in combination with evidence of high levels of inflammation were not found to be placed at an increased risk of in-hospital death.

In particular, a high BNP level combined with an elevated TNFα on admission was not associated with a higher risk of death in this patient population (*Figure 3.4*).

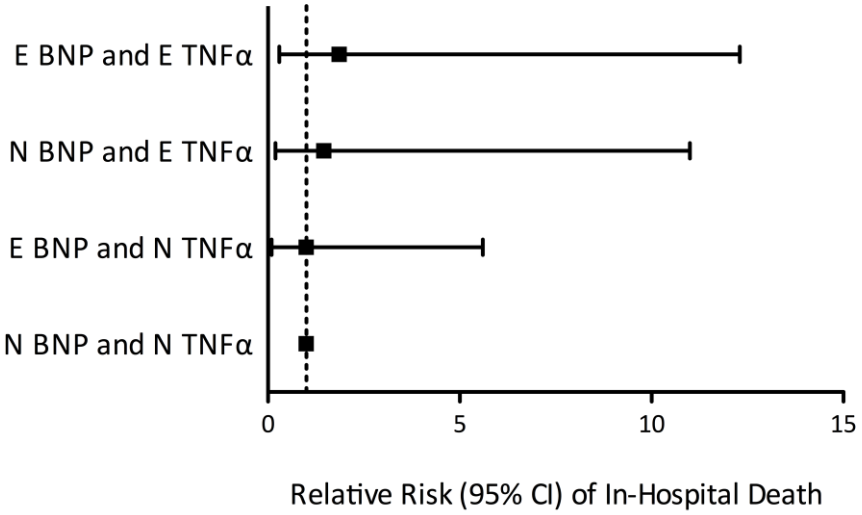
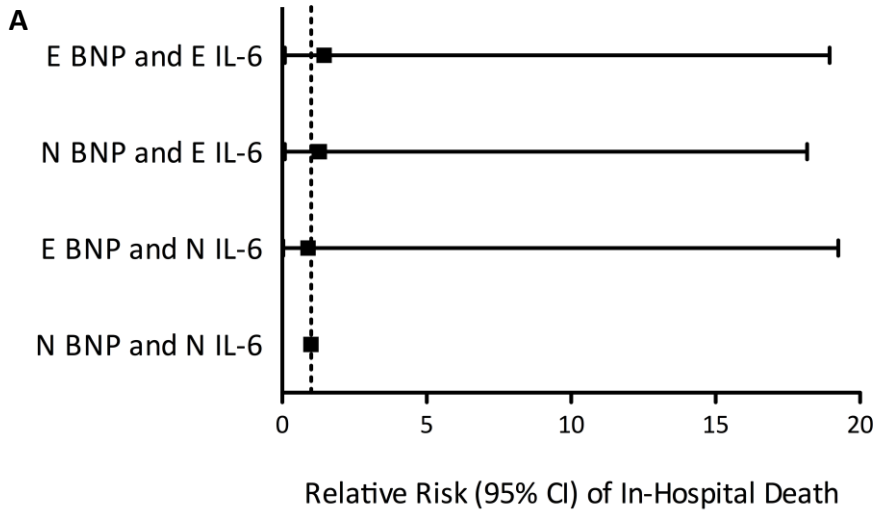


Figure 3.4. The relationship between TNFα and BNP on admission with in-hospital mortality

Relative risk of death (with 95% Confidence Intervals) is shown for each group (N=normal level, E=elevated level). Hashed line indicates a relative risk of 1. E BNP and N TNFα, p=1.000, N BNP and E TNFα, p=1.000, E BNP and E TNFα, p=0.493.

Similarly, neither the combination of an elevated BNP with elevated IL-6, nor a raised BNP and raised IL-8 produced significantly higher relative risks of in-hospital death compared to the other groups in the analysis (*Figure 3.5 A&B*).



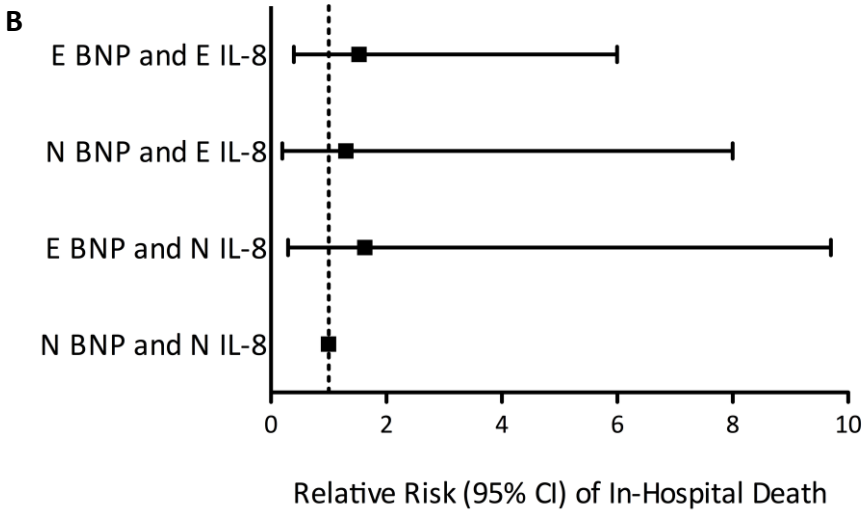


Figure 3.5. A & B. The relationship between IL-6 and IL-8 with BNP on admission with in-hospital mortality

Relative risk of death (with 95% Confidence Intervals) is shown for each group (N=normal level, E=elevated level). Hashed line indicates a relative risk of 1. **A**: BNP and IL-6. (E BNP and N IL-6, p=1.000, N BNP and E IL-6, p=1.000, E BNP and E IL-6, p=0.768). **B**: BNP and IL-8. (E BNP and N IL-8, p=1.000, N BNP and E IL-8, p=1.000, E BNP and E IL-8, p=0.605).

Furthermore, no differences between any of the groups were elucidated. No single BNP and cytokine combination was associated with an increased risk of in-hospital mortality.

However, when demonstrated by an elevated Troponin I concentration, early evidence of cardiac injury combined with evidence of hyperacute activation of inflammation was associated with a significantly greater relative risk of in-hospital death in this severely injured trauma population.

Specifically, patients with an elevated Troponin I and an elevated TNFα on admission were placed at the highest risk of death when compared to the other groups (*Figure 3.6*).

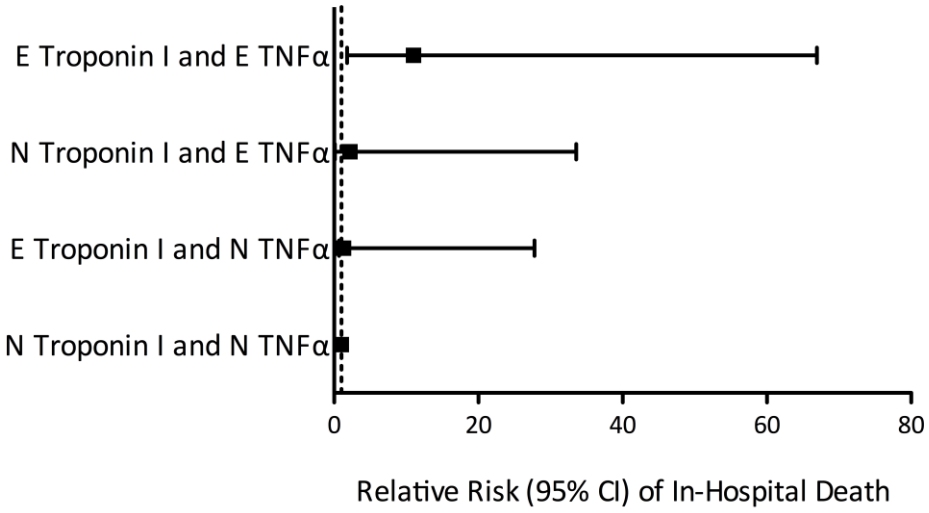
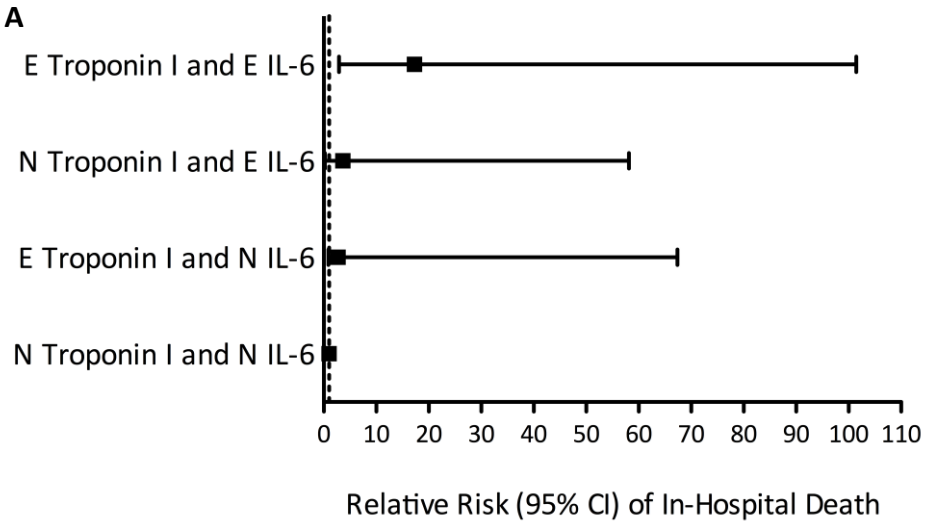


Figure 3.6. The relationship between TNFα and Troponin I on admission with in-hospital mortality

Relative risk of death (with 95% Confidence Intervals) is shown for each group (N=normal level, E=elevated level). Hashed line indicates a relative risk of 1. E Troponin I and N TNFα, p=0.091, N Troponin I and E TNFα, p=0.546, E Troponin I and E TNFα, p=0.015.

Patients with a raised Troponin I and either a raised IL-6 or IL-8 were also placed at the greatest risk of death (*Figure 3.7 A&B*).



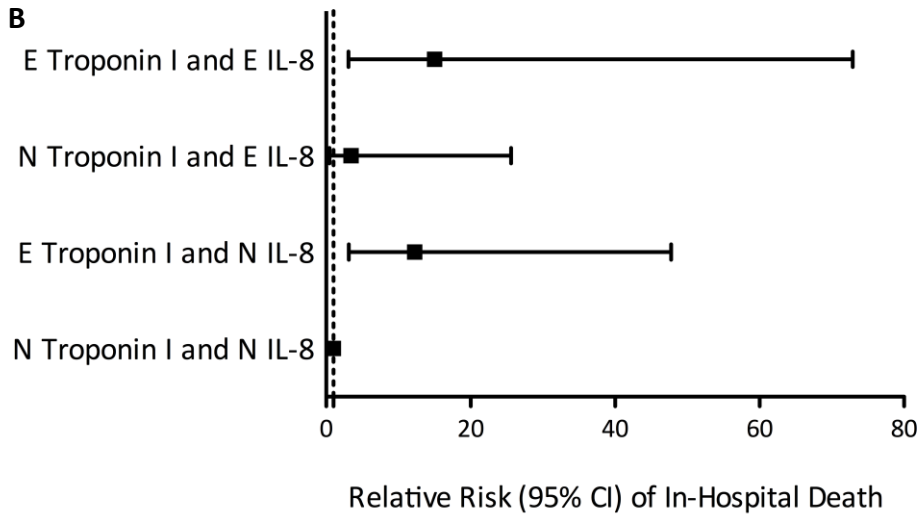


Figure 3.7. A & B. The relationship between IL-6 and IL-8 with Troponin I on admission with in-hospital mortality

Relative risk of death (with 95% Confidence Intervals) is shown for each group (N=normal level, E=elevated level). Hashed line indicates a relative risk of 1. **A**: Troponin I and IL-6. (E Troponin I and N IL-6, p=0.871, N Troponin I and E IL-6, p=0.297, E Troponin I and E IL-6, p=0.001). **B**: Troponin I and IL-8. (E Troponin I and N IL-8, p=0.002, N Troponin I and E IL-8, p=0.176, E Troponin I and E IL-8, p=0.008).

Critically injured patients who presented on admission with both an elevated Troponin I and an elevated cytokine were found to have at least a ten fold greater risk of death compared to patients in the other groups. Individuals with a raised Troponin I and a normal IL-8 on 0 hr plasma samples level also had a significantly higher risk of death.

3.5 Discussion

Increasingly there is evidence to suggest that trauma may lead to the development of cardiac injury and dysfunction in the absence of direct damage to the heart. The condition, TISCI, may be associated with worse clinical outcomes, although the pathological mechanisms that cause it are not known. As such, the purpose of this study was to be the first to identify the relationship between TISCI and acute inflammation.

The project completed all its aims, and revealed that in severely injured patients, clinical and biochemical evidence of secondary cardiac injury was associated with inflammation. Specifically, activation of inflammation within two hours of injury was associated with the subsequent development of ACEs, and was correlated with H-FABP release. Finally, this study demonstrated that on admission, the combination of inflammation and cardiac injury may place trauma patients at a higher risk of in-hospital death.

These new findings are corroborated by existing clinical evidence. Studies have shown that trauma leads to activation of inflammation, including the production of IL-6, IL-8 and TNFα (Moore et al., 1996, Maier et al., 2007, Jastrow et al., 2009, Spielmann et al., 2001). This may in turn lead to SIRS and MODS. In injured patients, an association between AF and SIRS has been previously demonstrated, as well as relationships with other conditions related to high levels of inflammation (Seguin et al., 2006).

However, while supportive of the link between inflammation and post-traumatic cardiac dysfunction, the study referenced above examined only a single cardiac diagnosis, and did not investigate the association with secondary cardiac injury. Furthermore, the aim of their analysis was to investigate the incidence and risk factors associated with AF exclusively, and hence inflammation was only measured in terms of clinical correlates (e.g. SIRS, higher catecholamine use).

In contrast to previous research, this study is therefore not only strengthened by investigating the association of inflammation with all

manifestations of cardiac dysfunction, but is also the first to combine this with a panel of specific markers of cardiac injury.

Further, through the measurement of both cytokines and biomarkers, the link between inflammation and cardiac injury in this project was demonstrated objectively and quantitatively.

The findings of an association between inflammation and cardiac injury are substantiated by a Japanese review of autopsy cases of patients with MODS (Emura et al., 2010). High levels of IL-6, IL-8 and TNFα were found in blood taken directly from the heart and this was associated with evidence of cardiac myocyte necrosis. None of the patients in the Japanese study were trauma victims, but these results nevertheless support an association between MODS, inflammation and cardiac injury.

Furthermore, the Japanese study mitigates a weakness of this project. Because only peripheral blood was sampled, the cytokines measured in this analysis were within the systemic circulation and were not localised to any specific organ or tissue. The postmortem investigation demonstrated that in MODS, inflammation occurs within the heart itself and causes cardiac injury. It provided, therefore, evidence that the associations revealed in this study have a direct pathological basis.

As such, the results of this analysis combined with the autopsy findings lead to the hypothesis that cardiac dysfunction might be implicated in the late deaths observed in trauma patients with MODS. Future projects should establish whether this is the case.

Non-trauma based research further supports the results of this study, and inflammation has been widely implicated in cardiac disease and failure (Chen et al., 2008, Hohensinner et al., 2011). C-reactive protein (as a marker of systemic inflammation), for example, may be independently associated with AF, and levels might also be predictive of future episodes (Aviles et al., 2003).

The findings presented in this study of early differences in cytokine levels in patients with cardiac dysfunction contrasted to those without are not

new. Individuals with acutely decompensated heart failure have been shown to have significantly higher admission IL-6, TNFα and IL-1β levels compared to controls without cardiovascular disease (Suzuki et al., 2005). Moreover, IL-6 values may correlate significantly with the severity of the disease, and TNFα levels are higher in decompensated patients. However, such differences have not been demonstrated previously in injured patients. Consequently, this study adds new evidence to the existing body of literature in this narrow field of trauma research.

Experimental models have investigated the role of inflammation and the mechanisms through which it leads to cardiac injury following trauma-haemorrhage (Vallejo et al., 2004, Mizushima et al., 2000, Nickel et al., 2009, Li et al., 2007, Yang et al., 2004, Sato et al., 2007). These have revealed in animals almost identical cytokine responses to trauma over parallel time frames.

Specifically, TNFα levels peak an hour and a half after non-lethal mechanical trauma, and lead to cardiomyocyte apoptosis through overproduction of cytotoxic reactive oxygen and nitrogen species (Li et al., 2007). In addition, the upregulation of IL-6 in cardiomyocytes may occur within two hours of trauma-haemorrhage and is associated with decreased cardiac output, stroke volume and left ventricular performance (Yang et al., 2004, Yang et al., 2007, Yang et al., 2006). Myocardial damage may occur within three hours of ischaemia-reperfusion, and results in the subsequent activation of inflammasomes and IL-1β production (Kawaguchi et al., 2011).

Although the basic science research ratifies the results of this study, it also highlights a weakness of this project, namely its failure to demonstrate the precise mechanistic processes leading to TISCI. At this stage, only inferences can be drawn from the experimental evidence, which suggests that inflammation causes mainly functional and not structural changes to the heart. These cause decreased contractility and myocardial depression.

Because cytokines also generate cardiomyocyte injury and apoptosis through oxidative and nitrative stresses, these in turn may generate or further compound existing cardiac dysfunction. Notwithstanding, further investigation is required in patients to determine the precise mechanisms through which inflammation causes TISCI.

This study has provided new understandings regarding the interaction of early cardiac injury, inflammation and in-hospital mortality. Prior investigation of inflammation in injured individuals has shown that certain cytokine profiles in trauma may be predictive of death (Hranjec et al., 2010), whilst Troponin I is a recognised predictor of poor outcome in many disease states (Kim et al., 2002, King et al., 2005, Wu et al., 2004). Similarly, improved prediction of in-hospital mortality has been demonstrated when the inflammatory status is added to a model designed to predict death in trauma patients (Park et al., 2008). In Park's study this was combined with coagulation, but it suggests that the synergism of inflammation with organ injury or body system failure might be a risk factor for increased mortality.

Although the result of a preliminary retrospective analysis, the findings of this research may provide some potential explanations to the survival benefits observed in patients on certain cardiac medications. Both statins and beta-blockers have been associated with improved function and survival in selected studies (Efron et al., 2008, Schneider et al., 2011, Arbabi et al., 2007, Cotton et al., 2007, M. Martin et al., 2005). Although most widely used for preserving cardiac function and lowering cholesterol, both have significant anti-inflammatory properties. In addition, severely injured younger females have been shown to have a lower incidence of MODS, sepsis and lesser plasma cytokine levels compared to male counterparts (Frink et al., 2007). This observation has been postulated to be the result of the protective effects of oestrogen on the immune response, and further suggests the detrimental effect of inflammation on organ function.

Animal data has also shown both increased survival (Cai et al., 2009) and restoration of cardiac function (Tsai et al., 2011) when downregulating the inflammatory response to trauma-haemorrhage. Furthermore, TNFα blockade in pigs may attenuate or even prevent myocardial dysfunction in those animals with significant increases in plasma TNFα following resuscitation after cardiac arrest (Niemann et al., 2010).

In combination with the evidence presented above, this study generates an additional hypothesis of an association between survival with preservation of cardiac function and attenuation of inflammation, and encourages further research in this area.

Finally, the analysis revealed that early activation of inflammation was associated with H-FABP release, but not Troponin I or BNP. Although the reasons behind this discordance are uncertain, these results might be a reflection of both the different kinetics and mechanisms of release of the biomarkers, particularly in the acute stages. H-FABP appears in the circulation more rapidly than Troponin I and BNP following damage to the heart, and is the earliest, most sensitive biomarker to rise following cardiac injury (McMahon et al., 2012). It follows, therefore, that this marker was most likely to show an association with inflammation on admission blood samples, which were taken within two hours of injury.

Troponin I, however, is the most specific indicator of myocardial injury (Babuin et al., 2005), and so perhaps heart damage may not have always been present in spite of elevated H-FABP levels. This might also explain why only a combination of Troponin I with the cytokines was predictive of survival, given that a rise in this biomarker was most likely to have indicated cardiac injury. H-FABP and BNP elevations may have been less specific to the heart.

3.6 Limitations

The study is subject to a number of limitations. Firstly, because of the retrospective identification of ACEs, the reported incidence and nature of the cardiac events in this project may have been inaccurate. Such methodology will most likely have led to the under-reporting of ACEs, and this in turn may have altered the statistical accuracy of the results presented.

Cardiac dysfunction was described in terms of ACEs, but was not demonstrated in each individual case by imaging or functional studies such as echocardiography. In future research, the use of such modalities should be employed to characterise more accurately not only the nature but also the degree of the cardiac abnormalities induced by trauma.

All ACEs were grouped together, in spite of the observation of multiple cardiac diagnoses. Nonetheless, it was the aim of this study to describe all the events witnessed in this cohort of critically injured patients, and investigate their overall association with inflammation. It is possible, however, that specific cardiac events are associated with different initiating factors, and so the involvement of inflammation may be greater or lesser according to each individual diagnosis.

Only the acute relationship between inflammation and TISCI was examined. Although the bulk of evidence has investigated primarily the early relationships and characteristics of the inflammatory response to trauma, future research would benefit from identifying the more protracted relationship between inflammation and TISCI.

It is possible that many of the inconsistencies between H-FABP, BNP and Troponin I were a consequence of the study being underpowered by too few patients in the analysis, given that many of the trends are similar but lack statistical significance.

A further limitation of the study is that whilst it demonstrated an association between inflammation and TISCI, the mechanistic,

pathological link between the two was not demonstrated, and requires further characterisation.

Moreover, the findings of an association between inflammation and post-traumatic cardiac injury and dysfunction were demonstrated using a handful of cytokines, despite the fact that there exists greater numbers of inflammatory markers. However, the purpose of this study was to examine this association using the markers of inflammation most commonly referenced to in the existing literature, which are those that have been shown to rise following trauma and are associated with cardiac damage.

These results are specific to a cohort of critically injured patients. Such individuals are in all likelihood more susceptible to cardiac injury, and exposed to higher levels of inflammation. Consequently, the association described between inflammation and TISCI in this cohort is potentially subject to other confounding variables, including higher ISS scores and greater inotrope use for example. As such, these findings might not be applicable to less seriously injured trauma patients.

Lastly, although the relationship between cardiac injury (using H-FABP) and inflammation (IL-6) was demonstrated in an adjusted multivariate regression analysis model, the R^2 value was relatively low, and few predictor variables were included. Future research would benefit correspondingly from larger studies designed to collect prospective data on all potentially confounding variables.

3.7 Conclusions

This study of critically injured trauma patients has revealed an acute association between inflammation and clinical and biochemical evidence of secondary cardiac injury. In addition, this project has provided evidence that on admission, patients who presented with a combination of elevated cytokine levels and cardiac injury were at increased risk of in-hospital death.

This research will serve as a base for future work. These include larger prospective studies undertaken to understand better the relationship between inflammation and TISCI over a longer time period. Additionally, analyses are required of the mechanistic pathways leading to secondary cardiac injury and dysfunction that are driven by inflammation.

Ultimately, this work should lead to trials of therapeutic avenues designed to minimise the morbidity and mortality associated with TISCI. In the first instance, these should be directed at downregulating inflammation and preserving cardiac function.

CHAPTER FOUR

Adverse Cardiac Events in a General Trauma Population: A Prospective Study

4.1 Introduction

Clinical evidence suggests that trauma can lead to secondary cardiac injury and dysfunction (TISCI) which may be associated with poorer patient outcomes (Kirchhoff et al., 2008, Hadjizacharia et al., 2011, Moosikasuwan et al., 2000, Ismailov et al., 2005, Seguin et al., 2006, M. Martin et al., 2005, Lagi et al., 2008, Edouard et al., 1998).

The evidence supporting the existence of TISCI is limited, however. Much of the research is retrospective in nature, and conducted in specific populations, such as critically injured patients (M. Martin et al., 2005) or individuals with mild trauma (Lagi et al., 2008). Although certain studies are prospective, they have included relatively small numbers of individuals (Edouard et al., 1998, Kirchhoff et al., 2008), or have investigated the features of a single diagnosis (AF) in a selected patient cohort (Seguin et al., 2006). Larger studies are mainly constrained to retrospective database reviews which have only examined specific diagnoses in isolation, such as AA (Hadjizacharia et al., 2011) or MI (Ismailov et al., 2005).

In *Chapter Two*, the existence of TISCI was further identified. Nonetheless, the detection of ACEs was performed retrospectively, and remained limited to a selected group of patients, namely those admitted to an ICU.

On the basis of previous research, therefore, it remains inconclusive as to whether a general trauma population is susceptible to ACEs following injury. If so, the epidemiology, clinical features and outcomes of these events are uncertain, and the risk factors for their development poorly determined.

Moreover, the precise nature of ACEs in all categories of trauma patients has not been fully established hitherto. In particular, no research has examined whether there is a correlation between ACEs in injured patients and a stress induced cardiomyopathy, commonly referred to as Takotsubo's.

Currently in trauma, Takotsubo's cardiomyopathy has only been described in a couple of case reports (Vergez et al., 2009, Morita et al., 2010).

It is an acute and reversible cardiac disorder characterised by left ventricular dysfunction and is usually triggered by stressful physical or psychological events (Prasad et al., 2008). Although the pathophysiology is not known, dysfunctional metabolism of fatty acids, mitochondrial disturbances, stress-induced catecholamine release with subsequent cardiac stunning and vasoconstriction of the coronary arteries leading to microvascular dysfunction have all been proposed (Akashi et al., 2008).

Takotsubo's may well be implicated in trauma patients who develop cardiac events, given these individuals are exposed to significant physical and psychological stress following injury. H-FABP levels are increased after trauma (*Chapter Two*), and this may mirror derangement of fatty acid metabolism in the heart. In addition, trauma causes mitochondrial changes (Zhang et al., 2010) and injured patients are exposed to high levels of both circulating endogenous and exogenous catecholamines. Finally, trauma can lead to shock, which results in systemic haemodynamic changes including vasoconstriction.

Patients with Takotsubo's may present with symptoms of an ACS or be asymptomatic. The disorder may manifest with arrhythmias, heart failure, ECG changes, cardiogenic shock or death, likening the presentation of many of the patients with ACEs in *Chapter Two*.

The most characteristic feature of the syndrome is apical ballooning of the left ventricle in association with diminished left ejection fraction. Although there is no consensus on the diagnostic specifications for Takotsubo's cardiomyopathy, the Mayo criteria are commonly referred to (*Table 4.1*).

In spite of the possible association between Takotsubo's syndrome and post-traumatic ACEs, the relationship connecting the two has yet to be formally established.

Table 4.1. Mayo Criteria for a Diagnosis of Takotsubo's Cardiomyopathy

1	Transient hypokinesis, akinesis, or dyskinesis of left ventricular mid segments with or without apical involvement; regional wall motion abnormalities extend beyond a single epicardial vascular distribution; stressful trigger is often, but not always present
2	Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3	New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac Troponin
4	Absence of Phaeochromocytoma or Myocarditis

For a diagnosis of Takotsubo's, all four criteria must be met (Taken from Prasad et al., 2008).

4.2 Study Aims

The overall study objective was to confirm the existence of TISCI and further define the features of ACEs in a general trauma population.

The *first* aim was to determine the epidemiology and clinical features of ACEs in a non-specific cohort of injured patients.

Second, to determine whether post-traumatic ACEs were the manifestation of Takotsubo's syndrome.

Third, to compare the characteristics of patients with and without ACEs.

Fourth, to examine the outcomes associated with ACEs in a general cohort of injured patients.

Finally, to identify the risk factors associated with the development of ACEs in all injured patients.

4.3 Materials and Methods

This study is an analysis of data generated from the Trauma Associated Cardiac Injury and Dysfunction A (TACID A) research programme. TACID is a large observational study created and designed to investigate TISCI in detail, including its longer-term outcomes.

TACID received ethical approval from the Cambridgeshire 3 Research Ethics Committee the 3rd of September 2010 (REC reference number: **10/H0306/47**).

4.3.1 Study Setting

This study was performed at the Royal London Hospital, a major trauma centre in the United Kingdom.

4.3.2 Study Design

A prospective cohort study of all injured patients admitted to the hospital in the 16 months between the 15th September 2010 and 31st December 2011.

4.3.3 Study Population

The inclusion criteria incorporated all adult trauma patients (>15 years) who initiated trauma team activation (*Table 4.2*) and presented with an abnormal primary survey.

Individuals suitable for inclusion were prospectively recruited to TACID when research personnel were present (08.00 hrs to 21.00 hrs daily).

Exclusion criteria included the following:

- Patients transferred from other hospitals
- Not expected to survive >72 hrs
- Pregnant
- Patients <16 years of age
- Prisoners
- Trauma team leader deemed recruitment inappropriate

Table 4.2. Trauma Team Activation Criteria

History of
Person hit by train
Person trapped under vehicle
Fatality in same vehicle as occupant
Occupant ejected from vehicle
Fall from >2 metres
Presentation with
Amputation proximal to wrist or ankle
Spinal trauma with altered neurology
Chest trauma with altered physiology
Polytrauma with burns
GCS <14 or Respiratory Rate <10 or >29 or Systolic BP <90
Penetrating trauma from neck to groin or proximal to elbow or knee
Clinical suspicion of
Open or depressed skull fracture
Pelvic fracture
Major haemorrhage

4.3.4 The Process of Consent

On admission, most severely injured patients present unconscious either as a result of trauma or as a consequence of intubation. Conscious individuals may be temporarily incapacitated due to anxiety, pain, psychological distress or as a result of alcohol or drug intoxication.

Accordingly, a hierarchy of consent was established and approved by the Cambridgeshire 3 Research Ethics Committee to enable recruitment of trauma patients to this study.

On admission to the ED, trauma team leaders (ED Consultants or Registrars), all of whom were independent to this study, acted as the patient's advocate and were thus appointed their Professional Legally Appointed Representative (PLAR).

If consent was granted by the PLAR and the individual recruited, continued participation was sought from the patient as a priority. Participants were examined daily to determine capacity.

Until such time as the patient had capacity, next of kin acted as the Consultee (Legally Appointed Representative), and were asked to consider the wishes of the patient.

Patients and Consultees were provided with detailed information sheets and time to consider involvement in the study. If consent was refused or retracted by either the patient or Consultee, then participation was withdrawn.

If a patient died before personally giving consent, the Consultee was approached for permission to continue the use of samples and patient data for the study. In cases where no Consultee was identified, and the patient either died or suffered such disability that they remained incapacitated, samples and data remained in the study. If the patient was not identified or no next of kin were found, samples and data also remained in the study.

A record was kept on a secure database of all consent procedures and patient reviews. Conversations with participants and Consultees, together with consent were documented in the patient's medical notes.

4.3.5 Data Collection

Data were prospectively collected on patient demographics, injury time and mechanism, time of arrival in the ED, baseline vital signs and daily physiological data, ISS, AIS and survival.

Each participant was reviewed daily for the presence and timing of ACEs until either death or discharge. In patients in whom an ACE was diagnosed, Troponin T levels were measured according to standard hospital protocols (normal value <30 ng/L) and further ECGs performed. Where possible, echocardiograms were undertaken. In addition, the TACID study protocol dictated the collection of an admission ECG (within a maximum of two hours of injury), followed by further examinations at 24 and 72 hrs after admission.

4.3.6 Study Definitions

An ACE included any of the following diagnoses; MI, new onset left or right bundle branch block (LBBB or RBBB), ACS, cardiac death, arrhythmia or cardiogenic shock.

Diagnoses were made and documented by senior intensivists or cardiologists based on a combination of clinical evidence, cardiac biomarker (Troponin T) values, ECGs, echocardiograms or other specialist cardiac investigations. These clinicians were both independent of the study and blinded to its outcomes.

Death was recorded as 28-day mortality of all causes. Patients discharged from hospital before 28 days were assumed to be alive at day 28.

4.3.7 Statistical Analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago IL). Data are presented as medians with interquartile ranges, unless otherwise specified. Non-parametric data were analysed using Mann-Whitney U and Kruskal-Wallis. Student's t-test was used to compare parametric data. Fisher's exact test, chi-square, or chi-squared test for trend was used to compare categorical data. Pearson's correlation coefficient was used to correlate ejection fraction with death.

A binary logistic regression model was created to identify patient risk factors for the development of ACEs. Initial analysis examined unadjusted effects of possible predictor variables using univariate statistics. Thereafter, a binary logistic model was undertaken and contained both categorical and continuous predictor variables. Variables were added in a stepwise regression analysis with significance levels set at $p<0.05$ to enter and $p>0.1$ for removal. The following variables were included: age, SBP, thorax AIS, lactate, base excess, the presence of either cardiac disease, diabetes or hypertension pre-injury, ISS and pre-hospital administration of Tranexamic Acid.

A two-sided p value of less than 0.05 was considered significant.

4.4 Results

One hundred and ninety nine patients were recruited during the 16 month study period. Characteristics are described in Table 4.3.

Table 4.3. Patient Demographics, Injuries and Admission Physiology

	All	No ACE	ACE	p Value
Number	199	169	30	n/a
Male, *n (%)*	164 (82.4)	143 (84.6)	21 (70)	0.068
Age, years	37 (26-52)	36 (24-49)	50 (30-61)	**0.010**
Mechanism, Blunt *n (%)*	158 (79.4)	130 (76.9)	28 (93)	**0.049**
Injury Characteristics				
Injury Severity Score	18 (9-30)	16 (9-26)	31 (25-42)	**<0.001**
Head and neck AIS	0 (0-3)	0 (0-2)	3 (0-4)	**0.004**
Face AIS	0 (0-1)	0 (0-1)	0 (0-2)	0.516
Thorax AIS	2 (0-3)	1 (0-3)	3 (3-4)	**<0.001**
Extremity AIS	2 (0-3)	2 (0-3)	3 (0-3)	**0.016**
Abdomen/pelvis AIS	0 (0-2)	0 (0-2)	0 (0-2)	0.339
Admission Physiology				
SBP, mmHg	125 (109-144)	129 (114-145)	102 (77-124)	**<0.001**
SBP <90 mmHg, *n (%)*	30 (15)	16 (9.5)	14 (46)	**<0.001**
GCS	15 (11-15)	15 (12-15)	11 (5-14)	**<0.001**
Lactate, mmol/L	2.1 (1.3-3.7)	2 (1.3-3.4)	3.7 (1.8-7.7)	**0.003**
Outcomes				
ICU stay, days	0 (0-5)	0 (0-2)	12 (6-17)	**<0.001**
Hospital stay, days	8 (3-21)	7 (2-15)	27 (14-46)	**<0.001**
Mortality, *n* (%)	17 (8.5)	11 (6.5)	6 (20)	**0.026**

Data are presented as median (interquartile range) unless otherwise stated. Comparisons are between the No ACE and ACE cohorts.

4.4.1 Epidemiology and Clinical Features of Adverse Cardiac Events

Thirty (15%) individuals had an ACE in hospital. Of these, arrhythmias were the most frequently observed. In most cases, these were supra-ventricular in nature (*Figure 4.1*).

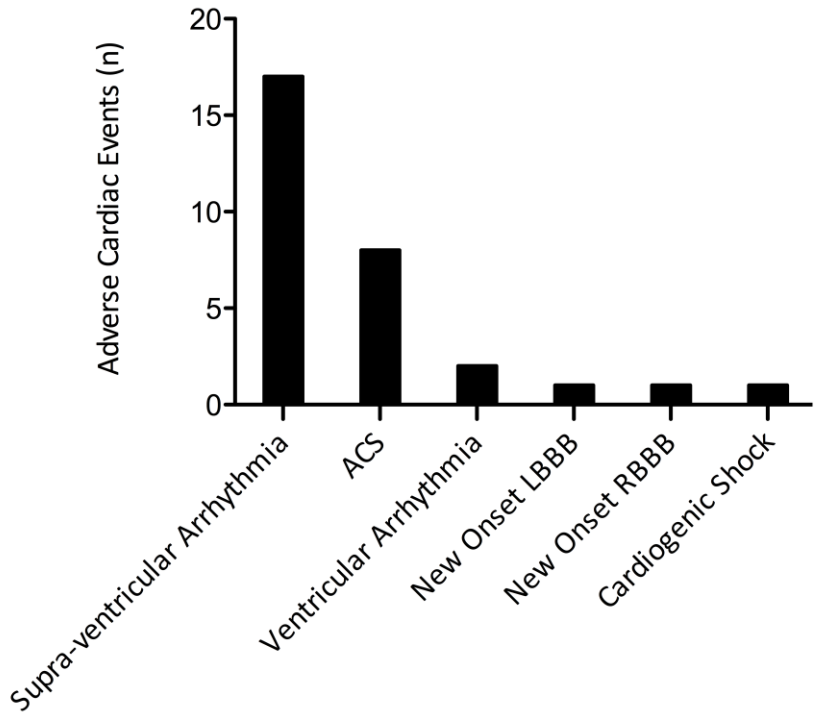


Figure 4.1. Numbers of adverse cardiac events by diagnosis

The median time from admission to the development of an ACE was three days (IQR 2-5 days), and the majority (n=24, 80%) occurred within five days of admission (*Figure 4.2*).

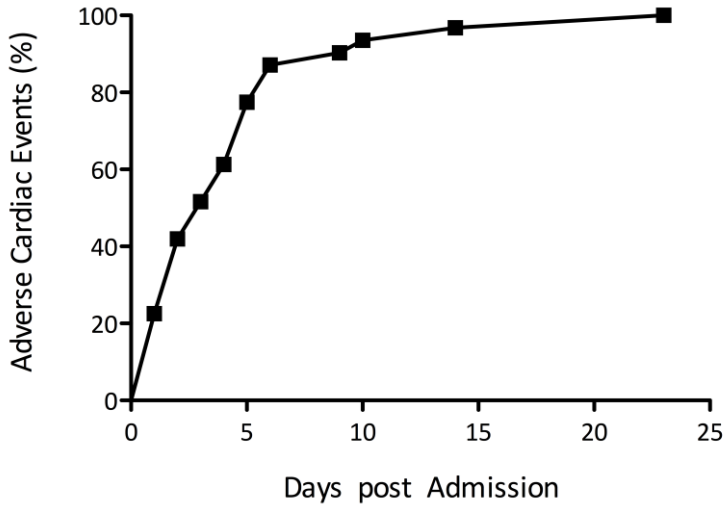


Figure 4.2. Percentage of ACEs occurring each day post admission

For the most part, admission ECGs (n=18, 60%) were normal in patients who subsequently developed an ACE in-hospital (*Figure 4.3*). Moreover, the nature of ECG changes was not predictive of the type of ACE subsequently observed.

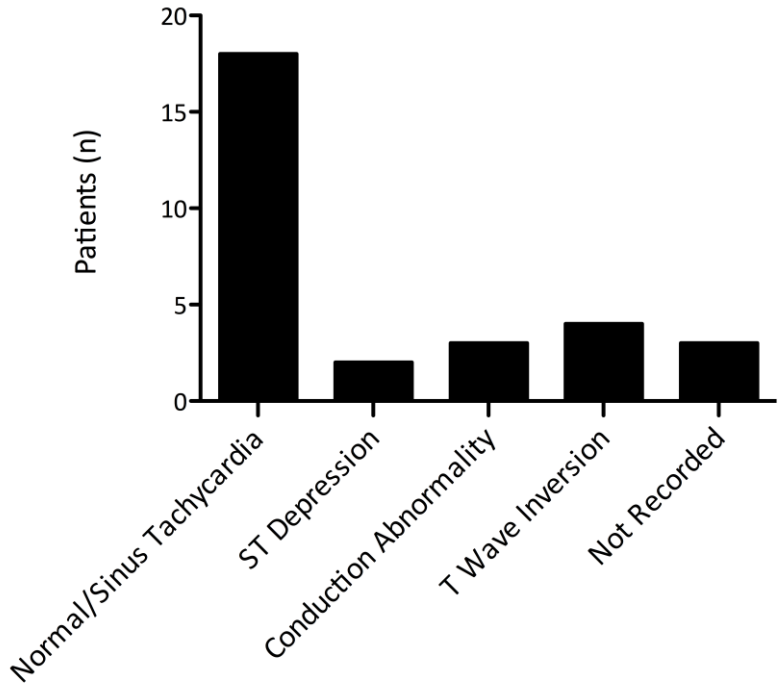


Figure 4.3. Admission ECG findings in patients who developed an ACE

Twenty one (70%) patients who had an ACE had an echocardiogram (transthoracic n=19, transoesophageal n=2). Of the remaining nine individuals, echocardiograms were not performed acutely following their ACE because of either death shortly after the cardiac event (n=3), or individuals were in theatre or undergoing intervention (n=2). In the last four cases, chest wounds or dressings prohibited transthoracic examination. Findings of these investigations are summarised in Table 4.4 overleaf.

In only two cases, a small reactive pericardial effusion was diagnosed but not a single patient had evidence of blunt cardiac injury or contusion. In addition, in no case was left apical wall ballooning observed (*Table 4.4*).

Table 4.4. Echocardiogram Findings in Patients with Adverse Cardiac Events

Findings	Frequency, n (%)
Ejection Fraction	
Normal	18 (86)
Reduced	3 (14)
Left Ventricle	
Appearance	
Normal	16 (76)
Hypertrophied (mild)	5 (24)
Function	
Normal	15 (71)
Dyskinetic	4 (19)
Hyperdynamic	2 (10)
Right Ventricle	
Appearance	
Normal	18 (86)
Dilated (mild)	2 (10)
Not visualised	1 (4)
Function	
Normal	14 (67)
Decreased	5 (24)
Hyperdynamic	1 (4)
Septum	
Normal	15 (71)
Hypertrophied	1 (4)
Hypokinetic (Basal)	3 (14)
Dyskinetic	1 (4)
Not reported	1 (4)
Pericardium	0 (0)
Normal	19 (90)
Effusion (small)	2 (10)
Traumatic Valve Injury	0 (0)
Left Ventricular Ballooning	0 (0)
Contusion	0 (0)

Ten patients (48%) had an entirely normal study and no individual who had an ACE had a markedly abnormal echocardiogram.

The majority of those who had an ACE retained normal cardiac function on echocardiography (mean ejection fraction=65%, standard deviation [SD] 9.6).

Furthermore, there were no differences in the type of cardiac events between those with completely normal studies in comparison to those with abnormalities.

Based on Pearson's correlation coefficient, ejection fraction was not correlated with death (r^2=0.015, 95% CI -0.56-0.36).

In eight patients (38%), the echocardiogram was reported as a limited study. This was either due to poor subcostal views (n=4, 50%), inadequate apical views (n=3, 37%) or positioning (one patient in a Rotorest, 13%).

Troponin T levels were measured in 25 (83%) patients following their diagnosis of an ACE. Figure 4.4 shows a scatter plot of the values. Seven patients (28%) had a normal Troponin T value after their event, although the median Troponin T value in this group was mildly raised above the normal range (61 ng/L, IQR 10-160).

There was no difference in Troponin T values in those with or without an abnormal echocardiogram (median Troponin T 21 ng/L, IQR 10-194.7 vs. 97.95 ng/L, IQR 45.75-192.0, p=0.411 respectively).

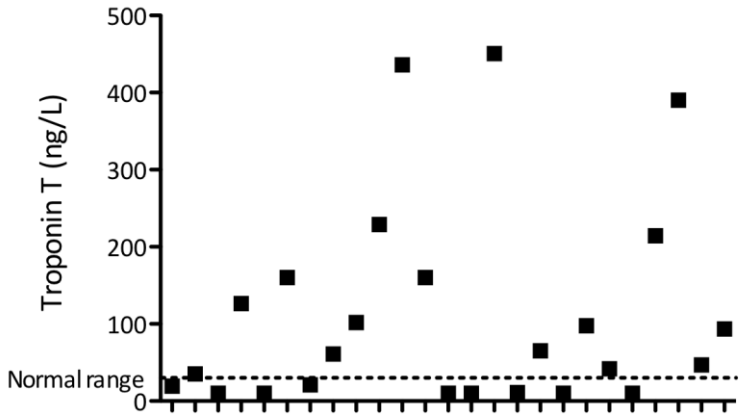


Figure 4.4. Scatter plot of Troponin T values in patients with ACEs

Each graduation on the x axis represents a single patient.

4.4.2 Adverse Cardiac Events and Takotsubo's Syndrome

Based on the Mayo diagnostic criteria (*Table 4.1*), there was evidence in four of the patients (13%) with ACEs that post-traumatic cardiac events could have been the manifestation of Takotsubo's Syndrome. These individuals had left ventricular wall dyskinesis (criterion 1), although in no cases was the classical left apical ballooning observed. No patient had an angiogram, and hence obstructive coronary disease was not ruled out in this study (criterion 2).

All of these individuals developed new ECG changes (two patients with ACS and two with arrhythmia) and all four had rises in Troponin T (criterion 3). No patient had a diagnosis of myocarditis and although phaeochromocytomas were not actively ruled out, not a single individual exhibited evidence of the condition (criterion 4).

4.4.3 Characteristics of Patients With and Without Adverse Cardiac Events

The ACE cohort was more severely injured compared to the non-ACE group (ISS 31 vs. 16, $p<0.001$) and had higher thorax AIS scores (3 vs. 1, $p=0.006$). Patients with cardiac events were older, and were more shocked on admission with lower GCS scores (*Table 4.3*).

In terms of co-morbidity, only the incidence of diabetes and hypertension were significantly greater in the ACE population. There was, however, no significant difference in the incidence of pre-morbid heart disease between the ACE and no ACE cohorts (*Table 4.5*).

The pre-morbid use of anti-platelet therapy and insulin was higher in those patients who had a cardiac event. There were no further significant differences in documented medication use pre-injury between the two populations (*Table 4.5*).

Table 4.5. Pre-morbid Diagnoses and Medications

	All	No ACE	ACE	p Value
Number	199	169	30	n/a
Pre-morbid Diagnoses				
Heart disease	9 (5)	7 (4)	2 (7)	0.627
Diabetes	8 (4)	6 (3.5)	2 (7)	**<0.001**
Hypertension	21 (10.5)	14 (8.3)	7 (23)	**0.022**
Hypercholesterolemia	15 (7.5)	10 (6)	5 (17)	0.055
PVD	1 (0.5)	0 (0)	1 (3)	0.151
CVA	3 (1.5)	3 (1.7)	0 (0)	1.000
Pre-morbid Medications				
Anti-platelet	7 (3.5)	3 (1.7)	4 (13)	**0.012**
Anti-hypertensives	18 (9)	13 (7.6)	5 (17)	0.158
Statins	15 (7.5)	10 (6)	5 (17)	0.055
Diuretics	3 (1.5)	1 (0.6)	2 (7)	0.061
Anticoagulants	2 (1)	1 (0.6)	1 (3)	0.279
Vasodilators	2 (1)	2 (1)	0 (0)	1.000
Anti-arrhythmics	0 (0)	0 (0)	0 (0)	n/a
Oral Hypoglycaemics	4 (2)	3 (1.7)	1 (3)	0.483
Insulin	2 (1)	0 (0)	2 (7)	**0.022**

Data are presented as absolute number (percentage). Comparisons are between the No ACE and ACE cohorts. PVD=Peripheral Vascular Disease, CVA=Cerebrovascular Disease.

Patients who developed an ACE were more likely to have been administered Tranexamic Acid pre-hospital (OR 2.5, 95% CI 1.1-6.2), and in general required significantly more cardiac medication during their admission (*Figure 4.5*).

Individuals who had a cardiac event needed more pressure support through the use of inotropes and vasopressors. These patients also had higher glycaemic control requirements, and were more often prescribed hypoglycaemics such as insulin.

Indeed, only the in-hospital prescription of anti-platelet agents such as Aspirin was no different between the two groups (*Figure 4.5*).

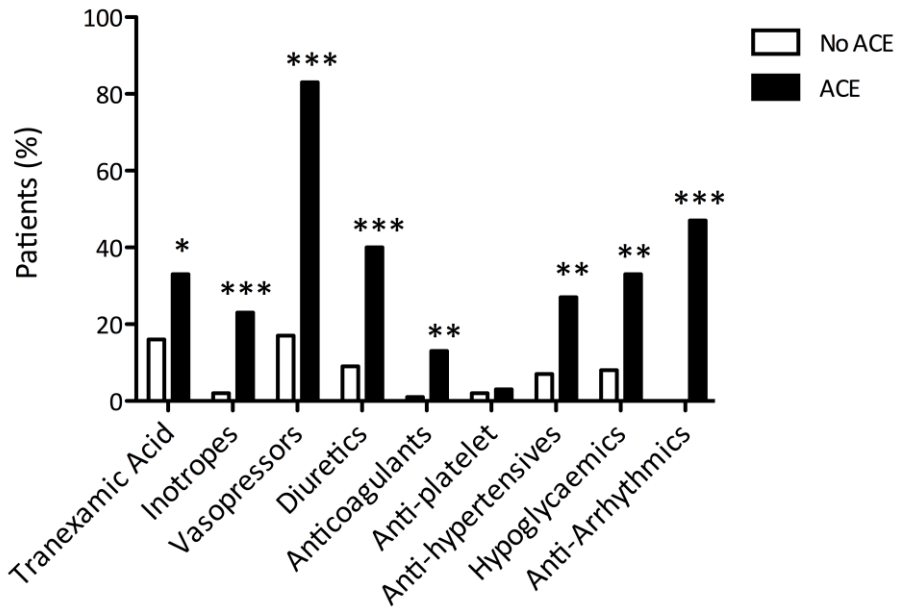


Figure 4.5. Medication requirements of the No ACE and ACE cohorts

Tranexamic Acid was administered pre-hospital by a dedicated trauma physician. All other medications were prescribed according to clinical requirements during admission. *p<0.05, **p<0.01, ***p<0.001.

4.4.4 Adverse Cardiac Events and Outcomes

ACEs were associated with poorer outcomes in this population of general trauma patients.

Cardiac events were related to nearly a four fold longer length of hospital stay (27 days vs. 7, p<0.001). Moreover, 26 patients with ACEs (87%) required an intensive care admission compared to 36 individuals (21%) from the cohort in whom no cardiac events occurred (p<0.001). ACEs were also associated with a significantly increased length of ICU stay (*Table 4.3*).

ACEs were related to higher mortality and patients who had a cardiac event were three times more likely to die (OR 3.6, 95% CI 1.2-10.6) compared to the group in whom no ACE was observed (*Figure 4.6*).

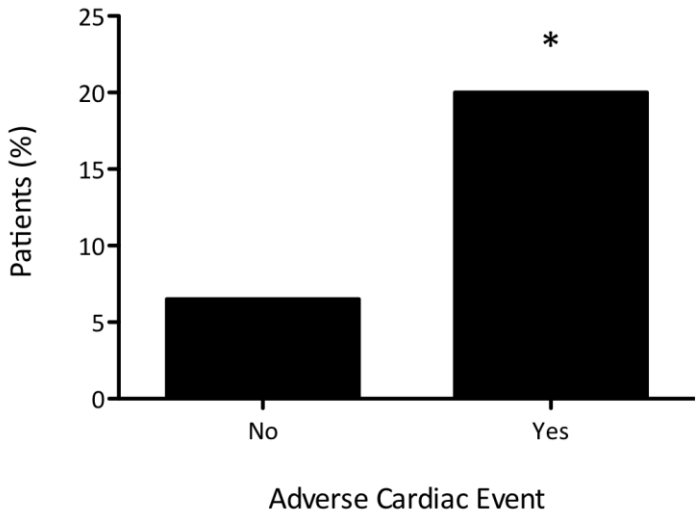


Figure 4.6. The mortality rate in patients with and without ACEs *p<0.05.

There was a clinical difference between the timing of death in the deceased ACE and no ACE individuals. Overall, patients who had a cardiac event died much later during their admission, although the discrepancy was not statistically significant (p=0.149, *Figure 4.7*).

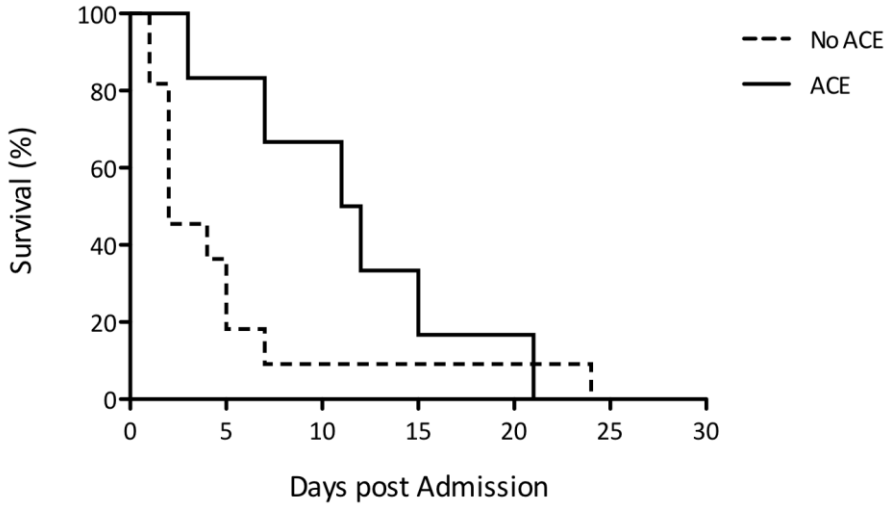


Figure 4.7. Timing of death of the deceased patients

There was, however, a significant difference between the two groups' median date of death (ACEs: day 11 of admission, IQR 6-17 vs. no ACE: day 2, IQR 2-5, p=0.026).

4.4.5 Adverse Cardiac Events and Risk Factors

Table 4.6 shows crude and adjusted odds ratios for each of the predictors of ACEs in this cohort of injured patients. The R^2 value was 42% (Nagelkerke R Square 0.416) which suggested that the risk model was a good forecaster of cardiac events amongst this trauma cohort.

Table 4.6. Crude Odds Ratios and Adjusted Multivariate Predictors of Adverse Cardiac Events in 199 Trauma Patients

Variable	Crude OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Mechanism, blunt	4.07 (0.92 - 17.89)	0.064	2.84 (0.39 – 20.64)	0.301
Age, years	1.03 (1.01 - 1.05)	**0.011**	1.02 (1.01 – 1.04)	**0.019**
SBP, mmHg	0.97 (0.95 - 0.98)	**<0.001**	0.99 (0.99 – 1.01)	0.190
Thorax AIS	1.59 (1.24 - 2.04)	**<0.001**	1.24 (0.85 – 1.82)	0.264
ISS	1.07 (1.04 - 1.11)	**<0.001**	1.06 (1.02 – 1.09)	**0.001**
Lactate, mmol/L	1.26 (1.11 - 1.44)	**<0.001**	1.21 (0.89 – 1.63)	0.219
Base excess, mEq/L	0.84 (0.78 - 0.91)	**<0.001**	0.87 (0.81 – 0.94)	**<0.001**
Cardiac disease	0.41 (0.10 - 1.69)	0.218	0.48 (0.66 – 3.39)	0.468
Hypertension	3.17 (1.16 - 8.70)	**0.028**	3.88 (0.88 – 17.04)	0.072
Diabetes	1.83 (0.35 - 9.55)	0.614	4.99 (0.46 – 53.86)	0.186
Tranexamic Acid	2.58 (1.08 - 6.13)	**0.041**	2.27 (0.56 – 8.33)	0.259

Three predictors of post-traumatic ACEs were identified. These were increasing age, worsening severity of injury (ISS) and decreasing base excess (indicating tissue hypoperfusion or shock).

Based on this model, however, the cardiac events that developed in this cohort of patients were not associated with the severity of chest injury. This demonstrated that post-traumatic ACEs were the not the result of direct, primary heart damage, and hence were secondary in nature.

Furthermore, cardiac events were unrelated to the presence of heart disease pre-injury, revealing that the ACEs observed in this study population were not the product of trauma merely exacerbating existing cardiac disease.

4.5 Discussion

The identification and description of ACEs that occurred in all categories of injured patients was undertaken in this prospective cohort study. In conjunction with limited prior research, these results demonstrated that trauma leads to secondary cardiac events, and that these are associated with poorer patient outcomes. Accordingly, this study confirmed the existence of TISCI.

Although undertaken prospectively in a more general cohort of patients, this investigation mirrored the findings of *Chapter Two*, namely that cardiac events occur in approximately 15% of all trauma admissions. It also substantiated the observation that post-traumatic ACEs are most commonly supra-ventricular arrhythmias.

Echocardiograms performed in individuals with ACEs demonstrated that no single patient had evidence of blunt cardiac injury, such as myocardial contusion, traumatic valve injury or septal rupture, for example. These findings demonstrated that ACEs in this injured population were thus the product of a secondary process, and not the result of direct chest trauma. Additionally, when adjusted for in multivariate analysis, thoracic injury was not found to be a risk factor for ACEs, thereby reinforcing the secondary nature of these cardiac events.

Takotsubo's cardiomyopathy causes secondary cardiac dysfunction following stressful triggers, and may lead to arrhythmias, ECG changes, Troponin rises and symptoms of ACS (Akashi et al., 2008, Prasad et al., 2008).

It is possible that secondary cardiac events in trauma could have been the result of Takotsubo's, although the findings of this study are suggestive in only a handful of cases. Four patients demonstrated left ventricular dyskinesis in conjunction with ECG changes and Troponin rises, although none had echocardiographic evidence of left apical ballooning. In addition, in no individual was a comment on the state of the coronary arteries possible.

As such, this study provided limited evidence for Takotsubo's leading to ACEs in injured patients, and in the event, only in a minority of cases.

Given that the echocardiogram findings did not support any evidence of significant macrostructural changes to the heart, and ACEs were not due to mechanical disruption of cardiac tissue, other pathological factors must have been at play. The processes leading to cardiac dysfunction must therefore occur on a microstructural level, be it cellular, molecular or both. These conclusions are supported by the findings of *Chapter Three,* indicating the role of inflammation in the pathogenesis of TISCI.

Furthermore, in *Chapter Three*, the relationship between TISCI and inflammation was demonstrated in the acute setting. The significance of the acute nature of this association is reaffirmed in this study given that 80% of ACEs had occurred within five days of admission.

Injury severity and shock on admission were identified as risk factors for the development of ACEs. This was established in a robust regression model, based on a significant R^2 value and the inclusion of over ten outcomes in the analysis (Harrell et al., 1996).

These findings are supported by previous clinical studies (M. Martin et al., 2005, Seguin et al., 2006, Ismailov et al., 2005) and animal models which both have demonstrated cardiac injury and dysfunction following trauma and shock. Such clinical states are known to stimulate an inflammatory response, and higher ISS and shock are risk factors for the development of SIRS, a state of systemic inflammation.

SIRS may lead to MODS, the leading cause of late death in the critically injured, and most of the individuals with TISCI died later in hospital. These patients also had a higher incidence of ICU admission, with a longer length of stay. As such they were also more likely to experience MODS. Taken these observations into consideration, this investigation thus further suggested the association of inflammation with TISCI, and leads again to the hypothesis that post-traumatic secondary cardiac dysfunction may be implicated in the significant mortality related to MODS.

In trauma patients, age as a risk factor for ACEs has been shown in previous research, (Seguin et al., 2006, Hadjizacharia et al., 2011, Ismailov et al., 2005) and is again supported by the findings of this study.

Age is a significant predictor of cardiovascular events based on the Framingham Risk Score, and is associated with poorer survival following injury (Tornetta et al., 1999, Taylor et al., 2002). Although the precise mechanisms for these worse outcomes in elderly trauma patients are not known, this study implied that cardiac dysfunction might be a relevant factor.

In accordance with the findings of *Chapter Two* together with previously published literature on the subject, this investigation revealed both the existence of a cohort of injured patients at risk of TISCI, coupled with its association with poorer outcome. Consequently, this evidence supports the need for further research investigating interventions aimed at mitigating the harmful effects of secondary cardiac injury and dysfunction in trauma.

Beta-blockers, for example, have largely been shown to confer a survival advantage to older patients (Arbabi et al., 2007, Bukur et al., 2012). This evidence is mostly in traumatic head injury (Cotton et al., 2007, Inaba et al., 2008), and the result of multivariable regression analyses of retrospective database reviews. Nonetheless, these drugs may represent a suitable first line of inquiry. In the first instance, older, shocked and more severely injured patients should be targeted, and investigated in large randomised trials.

Patients with ACEs had a higher incidence of ICU admission which was combined with a longer length of intensive care stay compared to non-ACE patients. Individuals with cardiac events also had significantly greater requirements for vasoactive drugs, and were more often prescribed cardiac medications and insulin. The higher incidence and degree of critical illness following injury in individuals with ACEs indicated that although this study was performed in a general cohort of

trauma patients, TISCI remains a condition primarily limited to the critically injured. Whilst critical illness might not be a risk factor per se, it appears to be a useful marker of those patients at risk of secondary cardiac damage after injury.

The majority of patients who developed ACEs had a normal ECG on admission, and hence suggested that unless blunt cardiac injury is suspected, ECGs may be of limited value in the initial assessment of the patient. Even if they provided evidence of heart disease, this study showed that pre-morbid cardiac disease did not predict patients at risk of in-hospital ACEs. This observation has been noted previously in the literature (Seguin et al., 2006, Hadjizacharia et al., 2011).

As such the study revealed that trauma is in itself an entity that precipitates cardiac events. Post-traumatic ACEs are not, perhaps contrary to expectation, simply the result of injury aggravating pre-existing cardiovascular disease. Although in *Chapter Two* heart disease was associated with ACEs, this relationship was identified in much smaller numbers and was not adjusted for, thereby representing a limitation of that study.

4.6 Limitations

There are several limitations to this study. In the first instance, the investigation substantiated the existence of TISCI through the demonstration of trauma induced ACEs, but did not provide evidence of cardiac injury through biomarker rises. However, blood samples had been acquired prospectively in *Chapter Two*, and were analysed accurately using ELISA techniques.

ACEs, conversely, were recorded retrospectively and hence were more likely subject to recall error. As such, prospective and contemporaneous documentation of ACEs was necessary to demonstrate the existence of TISCI, given that cardiac injury through biomarker rises had already been reliably demonstrated in *Chapter Two*.

In over a third of patients, the echocardiogram views were noted as limited, and therefore could not have provided comprehensive information on cardiac function and appearance. In addition, few transoesophageal examinations were carried out, despite this modality providing more accurate and detailed information on the heart and vessels. However, ultrasonographers documented only that which they could accurately see, and solely these findings were reproduced in the results section of this chapter, giving a reliable overview of the heart in trauma.

Diagnostic criteria for Takotsubo's require evidence of normal coronary arteries in the presence of the other signs and symptoms of the disorder. None of the study patients underwent coronary angiography or detailed coronary imaging, so the diagnosis of this syndrome amongst this cohort could neither be conclusively ruled in or out.

In spite of this, coronary angiography for the purposes of this research would not have been appropriate because there are serious potential risks associated with the procedure. Given many patients were active and young, however, it is unlikely they would have pre-existing coronary

artery disease. Nonetheless, the incidence of atherosclerosis in trauma populations is not known, and requires investigation.

Since most of the patients were unconscious on the ICU when ACEs were diagnosed, none were able to report any symptoms including chest pain, thus restricting the ability to further diagnose cardiac events or Takotsubo's syndrome.

Finally, the influence of smoking in leading to cardiac disease is well documented. This investigation failed to record a history of smoking amongst the study population, despite the fact it may be a relevant risk factor for the development of ACEs. Its effect on outcome and its relationship to secondary cardiac events in trauma should be determined by other studies.

4.7 Conclusions

This is the first prospective study to have investigated the epidemiology and features of all ACEs in all categories of injured patients. It confirmed the existence of TISCI.

Cardiac events occurred in about 15% of trauma patients, primarily in those who were critically ill. ACEs were associated with worse outcomes, including higher death rates, and risk factors for their development included older age, shock on admission and severity of injury. Cardiac events were not the product of pre-existing cardiac disease, but in some cases may have been a manifestation of Takotsubo's syndrome.

Future research should examine the appearance and function of the heart following post-traumatic ACEs using more detailed imaging, such as transoesophageal echocardiography or cardiac magnetic resonance imaging (MRI). The latter would also enable an assessment of the coronary arteries. A smoking history should be elucidated from all patients.

Because an "at-risk" population for TISCI has been identified, studies should examine therapeutic interventions such as beta-blockers aimed at improving the poor outcomes associated with this condition.

CHAPTER FIVE

Coronary Artery Calcium and Trauma

5.1 Introduction

Both coronary heart disease (CHD) and trauma are leading causes of death internationally. Trauma accounts for nearly six million fatalities annually (WHO, 2009), whilst CHD is the commonest cause of death worldwide (WHO, 2007). In the US around 16.3 million people have symptomatic CHD (Roger et al., 2011). In the UK, over two million live with the disease (BHF, 2011). Previous chapters in this thesis have focused on the effect of trauma on the heart. Yet research on trauma associated cardiac injury and dysfunction must also consider the effect of pre-morbid heart disease on outcome following injury.

Existing evidence in trauma has described the effect of co-morbidity on survival and has shown that both the presence and number of pre-injury conditions may lead to higher death rates (Bamvita et al., 2007). The impact of pre-existing heart disease on post-traumatic survival has been the subject of only a handful of limited studies, however, and remains uncertain still.

Several retrospective analyses in trauma patients, for instance, have shown associations between pre-morbid heart disease and poorer survival (Morris et al., 1990, Perdue et al., 1998, Wutzler et al., 2009, Milzman et al., 1992). Conversely, conflicting evidence has suggested that the presence of cardiac disease pre-injury has no influence on mortality (Grossman et al., 2002, Horst et al., 1986, Smith et al., 1990), or has only a limited effect in selective patient cohorts (Mcgwin et al., 2004, Hollis et al., 2006, Shoko et al., 2010).

To date, just one single study in trauma has focused on the relationship between cardiac disease in isolation and survival (Ferraris et al., 2010). In addition, the impact of CHD on post-traumatic mortality has been measured solely in those with a documented cardiac diagnosis, and therefore predominantly symptomatic patients. A significantly higher number of injured individuals are likely to present with asymptomatic, subclinical heart disease, although studies have so far neglected to

investigate this category of patients. Consequently, the true incidence of CHD in a trauma population is not known.

Moreover, research has yet to reveal the impact of CHD in trauma and include all documented cases of the disease, including those with asymptomatic or subclinical CHD. If subclinical heart disease, combined with symptomatic disease, does indeed lead to higher death rates, its presence would require screening for as part of the assessment of the older trauma population. Thereafter, studies would be required designed to improve the poorer survival seen in such patients, including trials of therapeutic intervention.

Currently the difficulty with measuring both the epidemiology and impact of all types of CHD in trauma is that individuals with asymptomatic disease are unlikely to present with an established diagnosis. Moreover, injured patients are very frequently admitted unconscious or unable to give a history. Markers of CHD that include subclinical disease must therefore be determined.

On Computerised Tomography (CT) scans of the chest, the presence of calcium in the coronary arteries is an indicator of subclinical CHD (Wexler et al., 1996). It directly correlates with atherosclerotic plaques on histological examination (Rumberger et al., 1995). Furthermore, an absence of coronary artery calcium (CAC) tends to rule out luminal obstructive disease (Simons et al., 1992).

Thirteen years ago, Agatston (Agatston et al., 1990) demonstrated that CAC can be easily and accurately scored on CT scans, and subsequent studies have demonstrated an association between high coronary artery calcium scores (CACS) with an increased risk of ACEs, in both symptomatic and subclinical presentations of heart disease (Keelan et al., 2001, Arad et al., 1996, Arad et al., 2000, Detrano et al., 2008, Polonsky et al., 2010, Lamonte et al., 2005). More recently, there is evidence that CACS (CACS=Agatston score) are predictive of all cause mortality in patients with heart disease (Ostrom et al., 2008, Raggi et al., 2008, Budoff et al.,

2007) and may provide valuable screening assessments of the heart in non-cardiac illnesses such as HIV (D'ettorre et al., 2011) and aortic aneurysms (Stolzmann et al., 2009).

Accordingly, CACS represents a suitable marker of CHD in trauma. Until now, however, CACS have been calculated using dedicated software.

No studies have attempted to estimate CACS both in the absence of dedicated cardiac scanning and in the context of non-cardiac related disease.

Therefore the true incidence and impact on mortality of pre-morbid CHD in injured patients, determined by the extent of CAC on CT scans of the chest, represents a significant and original target for research.

5.2 Study Aims

The overall objective of this study was to determine the global incidence of CHD in older trauma patients, and to investigate its association with survival after injury.

Specifically, the *first* aim was to establish the feasibility of using trauma triage CT scans performed on admission to assess the quantity and severity of CAC.

Second, to describe the incidence of CHD using CACS in a trauma population aged 45 years or over.

Third, to compare the general features and characteristics of injured patients with and without CAC on their trauma CT scans of the chest.

The *final* aim was to determine whether either the presence or extent of CAC, as a marker of both subclinical and symptomatic CHD, was associated with increased in-hospital mortality in older injured patients.

5.3 Materials and Methods-Part A

This study was conducted in two stages, namely parts A and B. Part A was a training and validation exercise. In the first instance, the burden of calcium was examined on existing non-trauma CT scans with an established formal calcium score. This was followed by a validation assignment, whereby the investigators' capacity to interpret and agree on the CACS was measured. On completion of part A, Part B was undertaken. This second stage was designed to investigate the study aims, and involved the assessment of calcium on CT scans of injured patients and its association with mortality.

To ensure the scientific validity of this study, a second researcher (Kathryn Oakland) was invited to interpret the scan images in both Parts A and B.

5.3.1 Training

Both investigators reviewed and familiarised themselves with the features of 200 CT scans of the heart with formal calcium scores (Agatston scores) performed in patients with known coronary atherosclerosis. These images were obtained by the cardiology team and were undertaken independently for the purpose of assessment of the coronary arteries in patients with symptomatic heart disease. These 200 scans were selected at random from the list of patients found in the cardiology database.

The scans were undertaken using a second generation dual-source CT scanner (SOMATOM Definition Flash, Siemens, Forchheim, Germany). These heart scans were performed at the London Chest Hospital, and were acquired with a prospectively ECG-triggered technique at 40% of the cardiac cycle when the patient's heart rate was higher than 75 beats per minute, otherwise with a high pitch spiral technique.

Scan parameters were as follows: collimation 0.6 mm, x-ray tube voltage 120 kilovolts (kV), x-ray tube current 250 milliamperes (mA). Three millimetre thick images were reconstructed at an increment of 1.5 mm.

MSCT datasets were analysed using a dedicated workstation (syngo MultiModality Workplace, Siemens, Erlangen, Germany) and specific software (syngo Calcium Scoring, Siemens, Germany) was used to measure calcium score on non-enhanced images.

5.3.2 Validation

Once familiar with the characteristics of the 200 formal CT calcium scores, a different set of 50 cardiac CT scans were then selected at random from the database to validate the ability of each observer to estimate accurately a CACS.

These 50 scans had also been undertaken previously to evaluate non-trauma patients with symptomatic heart disease and each had already been ascribed a formal Agatston score. The two investigators assessed these scans independently, and whilst blinded to both one another's estimates and the formal Agatston score.

Each investigator gave both a numeric score (estimated CACS) based on the quantity of calcium in the coronary arteries and a grade. Grades were awarded on the basis of the calcium score (*Table 5.1*).

Table 5.1. Grades of Calcium Based on Corresponding Calcium Score

Calcium Score	Calcium Grade
0	None
1-100	Mild
101-400	Moderate
401-1000	Severe
1001≤	Extensive

These grades were based on the American College of Cardiology Foundation/American Heart Association guidelines (Greenland et al., 2007).

5.3.3 Inter-observer Agreement

In this validation exercise, the agreement between the two observers was excellent for both grade (kappa coefficient, κ=0.82) and score (*Figure 5.1*).

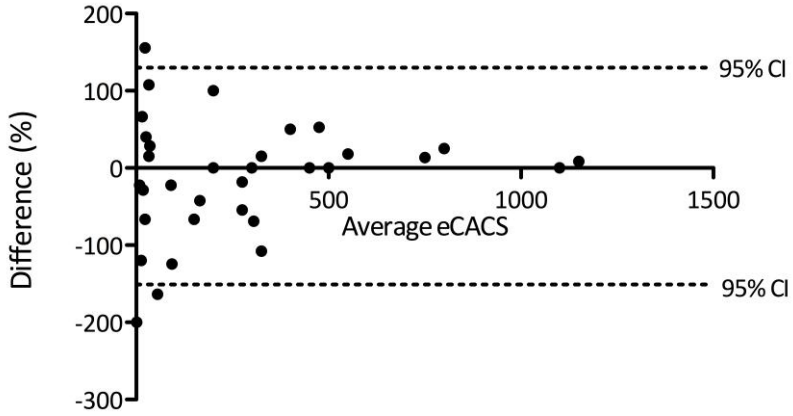


Figure 5.1. Bland Altman plot of inter-observer agreement in validation exercise

There was excellent agreement between the two observers' scores in the 50 patients selected at random with formal Agatston scores (Bias=-10.6, SD of bias 71.67).

Agreement between the first observer and grade based on the formal Agatston score was excellent (κ=0.80) and between the second observer and formal grade was good (κ=0.64).

These statistics revealed that observers could independently and reliably estimate the score and grade of coronary artery calcium. Consequently, the ability to interpret the CTs was validated, and Part B of the study could be undertaken robustly.

5.4 Materials and Methods-Part B

Based on guidance from the National Research Ethics Service, ethical approval for this study was not required (NRES, 2011).

5.4.1 Study Design and Setting

A single centre retrospective cohort study performed at the Royal London Hospital.

5.4.2 Study Population

Inclusion criteria were all trauma patients aged 45 years or over who presented to the hospital between 1st January 2009 and 1st January 2011. The age selection was based on Framingham Data describing the respective contribution of age to cardiovascular risk in men and women (Grundy et al., 1999). The only exclusion criterion was individuals without a CT scan of the chest.

Patients were identified retrospectively from the hospital trauma registry. This has been prospectively collecting detailed and contemporaneous data on every trauma patient who has presented to the Royal London Hospital since 2003.

5.4.3 Indication for CT in Study Patients

Scans had been performed as part of the initial and emergency assessment of patients following trauma, and were formulated to diagnose and qualify the severity of traumatic injures.

CTs were indicated in patients who presented with severe injuries, abnormal physiology or with a significant traumatic mechanism. Reasons for not performing a CT included patients deemed too physiologically unstable to scan, or those not for further treatment because of anticipated and imminent death. The trauma team who were both independent and blinded to this study's outcomes requested all scans. All CTs were undertaken within three hours of arrival to the ED and were performed by the hospital radiology department.

5.4.4 CT Scan Protocol in Trauma

All CT scans were performed on a Siemens SOMATOM Sensation 64 slice scanner (Siemens Medical Solutions, Forchheim, Germany).

Patients were placed supine and entered the scanner head first with arms above their heads whenever possible. The scans covered from above the lung apices to below the pelvis.

The delay between the start of contrast medium administration and the start of scanning was obtained using an automated bolus triggering technique (CARE bolus, Siemens Medical Solutions). In all patients, 80 mls of Visipaque contrast was used (Visipaque 270, GE Healthcare, Milwaukee, WI, USA) and injected at a rate of 2-3 mls/sec with a scan delay of 50 secs.

Data were acquired in a cranio-caudal direction with the following scanning parameters: 120/260 kV tube voltage, collimation 24 x 1.2 mm, 0.5 secs rotation time and 5 mm increment and 5 mm reconstructed section thickness. A smooth reconstruction thickness (B31f) was used for initial reconstruction, followed by reconstructions using the settings of soft tissue fine, lung, bone fine, coronal lung, coronal thorax and abdomen, coronal spine/pelvis and sagittal spine.

5.4.5 CT Scan Interpretation

All patients who met study inclusion and exclusion criteria were identified and their admission CT scans were located and reviewed using the NHS Picture Archiving and Communication System (PACS).

Thereafter, both authors reviewed each CT scan independently and a CACS was estimated. Based on the CACS, a grade of calcium in the coronary vessels was then awarded (between none and extensive).

CAC was defined as an intra-coronary artery plaque of a minimum of three millimetres of high attenuation. The total score was calculated from the sum of the estimated calcium content of the three major coronary arteries.

These were the left, including the main and anterior descending (LAD), the circumflex (Cx), and the right coronary (RCA, *Figure 5.2*). Both the number (0-3) and identity of vessels containing calcium plaques were also documented in each patient.

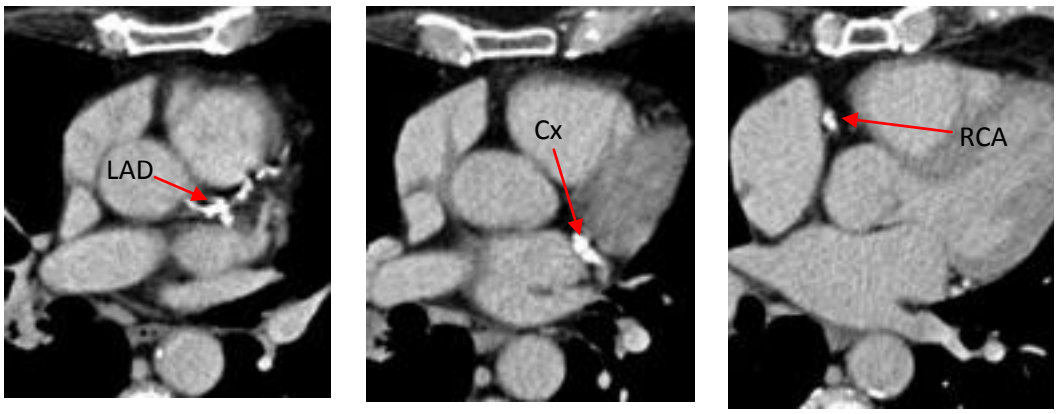


Figure 5.2. Axial views of the heart on a trauma CT scan

The presence of coronary artery calcium in the LAD, the Cx and the RCA is demonstrated.

Interpretation of the scans was performed with observers blind to all patient characteristics, outcomes and each other's measurements until assessment of the CT scans was complete in its entirety.

5.4.6 Data Collection

Data on patient demographics and baseline physiology, injury characteristics, ISS and mortality were collected from the hospital trauma registry and from individual patient clinical records.

5.4.7 Study Outcome

The study endpoint was death, defined as death of any cause occurring in-hospital. For the purposes of analysis, patients surviving to hospital discharge were assumed to have survived.

5.4.8 Statistical Analysis

All data analyses were performed using SPSS version 20 (SPSS Inc., Chicago IL). Normal-quartile plots were used to test for normality.

Non-parametric continuous data are reported as median with interquartile range and categorical data reported as absolute number and percentage.

Mann-Whitney U or Kruskal-Wallis tests were used to compare numerical data and Fisher's exact test, chi-square, or chi-squared test for trend was used to compare categorical data.

Regression analysis was used to identify the risk factors for death in this patient group. Initially, univariate statistics were performed to examine the unadjusted effects of potential predictor variables. A subsequent binary logistic model containing both categorical and continuous predictor variables was conducted, and variables were added in a stepwise regression analysis. Significance levels were set at $p<0.05$ to enter and $p>0.1$ for removal. The following variables were included: age, gender, base excess, GCS, the presence of pre-morbid disease, mechanism of injury, SBP, ISS and the CACS.

Using Fisher's exact test, univariate analyses were conducted for mortality rates based on the grade of coronary artery calcium. To adjust for age and injury severity, patients were divided into two age categories (<65 years and ≥65 years, in accordance with existing literature) and analyses were performed after stratification of ISS into four subgroups (≤5, 6-15, 16-24, 25≤).

Kappa coefficient was used to test inter-observer reliability for nominal data (http://justusrandolph.net/kappa, accessed 24/10/12) and Bland-Altman plots were used to interpret inter-observer agreement for continuous data.

Statistical significance was set as a two tailed p value of <0.05.

5.5 Results

Over the two year study period, 880 trauma patients met the inclusion criteria. Four hundred and five (46%) of these patients did not have a CT scan of the chest, and were excluded from any further analyses.

The medical records of one patient who had had a CT thorax could not be traced, and therefore that individual was also disqualified from any further analysis (*Figure 5.3*).

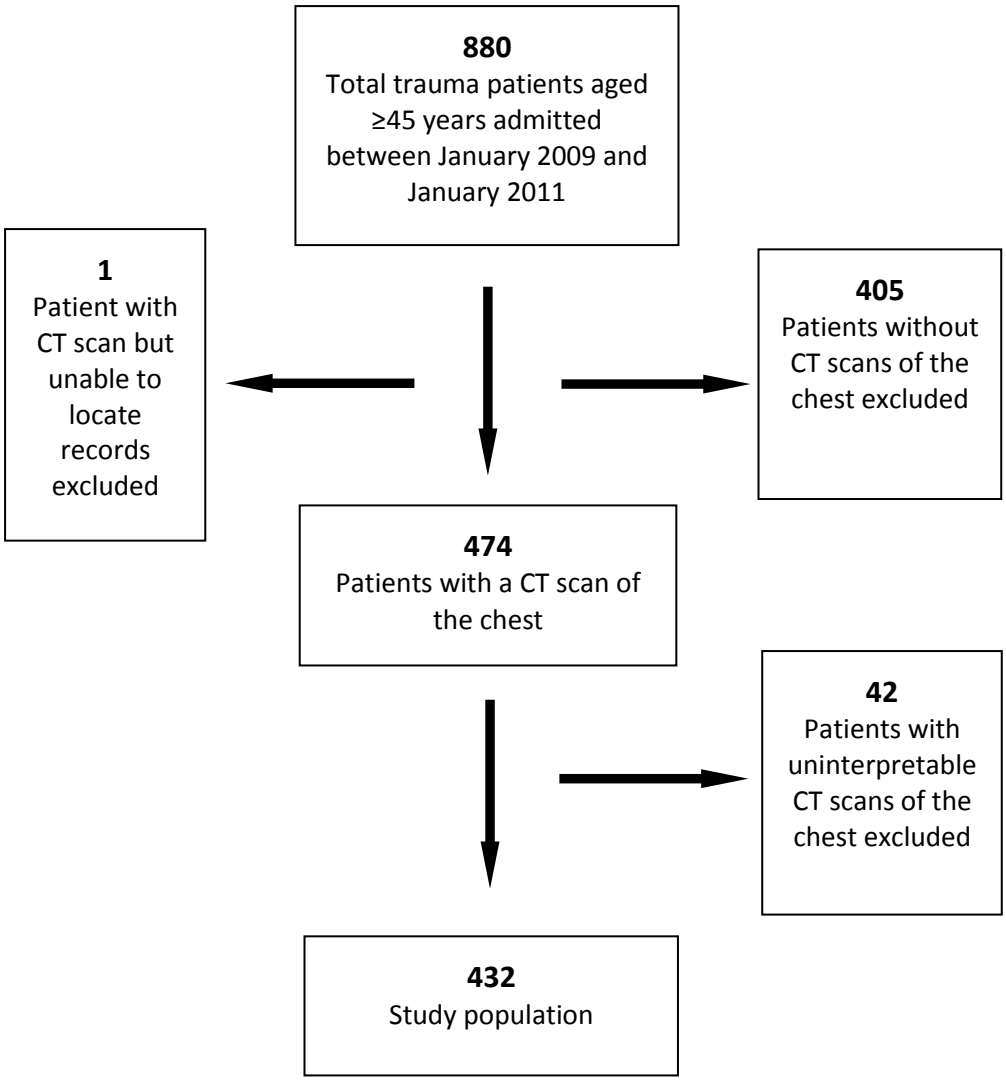


Figure 5.3. Flow diagram depicting selection of study population

5.5.1 Feasibility of Trauma CT scans in Determining Calcium Score

Of the 474 patients who had a CT scan of the thorax on admission, 432 (91%) had sufficiently clear images of the heart and coronary arteries to enable reliable assessment of calcium score and grade.

The interpretation of the remaining 42 scans was not possible due to artefact from chest drains, other external devices or movement, and so these patients were further excluded.

Authors were independently unanimous in their agreement ($\kappa=1$) in identifying those images that could and could not be assessed further for the purposes of this study. In just over 90% of trauma CT scans, therefore, an assessment of calcium score and grade was feasible.

5.5.2 Study Population

The study population comprised of some 432 patients. In total, 41 (9.5%) individuals died. Overall, patients were severely injured but were not shocked on admission. Patient characteristics are described in Table 5.2.

Table 5.2. Study Population Characteristics

Number	432
Male *n (%)*	345 (80)
Age, years	56 (45-94)
Injury Characteristics	
Blunt mechanism *n (%)*	392 (91)
Injury Severity Score	16 (8-25)
Admission Physiology	
SBP, mmHg	134 (138-154)
HR, bpm *mean (SD)*	84 (68-99)
GCS	14 (8-15)
Base Deficit, mEq/L	1.6 (4 - -1)
Outcomes	
Hospital stay, days	4 (1-17)
Mortality, *n (%)*	41 (9.5)

Data presented as median (interquartile range) unless otherwise stated.

One hundred and seventy eight patients (41%) presented with one or more documented co-morbidities on admission. Of these, hypertension was the most common diagnosis amongst the study population (*Table 5.3*).

Table 5.3. Documented Patient Co-morbidities on Admission

Diagnosis	Frequency, n (%)
Hypertension	55 (12.7)
Hypercholesterolemia	23 (5.5)
Diabetes	27 (6.5)
Coronary Heart Disease	26 (6)
Valve Disease	3 (0.7)
PVD including AAA	11 (2.5)
Cerebrovascular Accident	16 (3.7)
Renal Disease	6 (1.5)
Respiratory Disease	22 (5)
Mental Illness	30 (7)
Malignancy	10 (2.5)
Neurological Disease	21 (4.9)
Gastro-Intestinal & Liver Disease	8 (1.8)
Orthopaedic	13 (3)
Musculoskeletal	3 (0.7)
Blood Disorders	3 (0.7)
Thyroid Disorders	2 (0.5)
Chronic Infection	2 (0.5)

PVD=Peripheral Vascular Disease, AAA=Abdominal aortic aneurysm.

5.5.3 Incidence of Coronary Artery Calcium on Trauma CT

One hundred and thirty seven patients (32%) had no calcium in their coronary arteries (Ca^0 group), whilst the remainder (n=295, 68%) had evidence of CHD with a calcium score of one or greater (Ca^+ group). The Ca^+ group was older (60 years, IQR 45-94 vs. 50 years, IQR 45-76, $p<0.001$) and included higher numbers of patients with co-morbidities (132 patients vs. 46, $p=0.035$, respectively).

Total lengths of hospital stay were not significantly different between the Ca^+ and Ca^0 groups (12 days IQR 3-25 vs. 6 days IQR 2-25, $p=0.08$ respectively).

5.5.4 Characteristics of Patients with Coronary Artery Calcium

The median overall CACS was 53 (range 1-1250), and the largest group of patients had a grade of mild coronary artery calcium (*Table 5.4*).

Table 5.4. Patient Characteristics Based on Coronary Artery Calcium Grade

	None	Mild	Moderate	Severe	Extensive	p Value
Number *(%)*	137 (31.2)	139 (32.2)	75 (17.4)	64 (14.8)	17 (3.9)	**<0.001**
Age, years	50 (47-56)	53 (45-89)	64 (45-94)	70 (46-91)	77 (58-91)	**<0.001**
Gender, male *n (%)*	107 (78)	115 (83)	56 (75)	51 (80)	16 (94)	0.568
Co-morbidities *n (%)*	46 (33)	38 (27)	43 (57)	42 (66)	9 (53)	**<0.001**
ISS	13 (2-25)	12 (5-28)	17 (9-29)	15 (9-27)	20 (3-32)	0.268
GCS	15 (12-15)	15 (11-15)	14 (11-15)	14 (10-15)	14 (12-15)	0.754
BP, mmHg *mean (SD)*	135 (37)	137 (34)	136 (28)	147 (41)	123 (34)	0.059
Base Excess, mEq/L	1.3 (-0.8-4)	1.1 (-1.3-3.8)	2.3 (-0.05-4)	2.1 (-1.9-5.5)	1.4 (-0.9-2.8)	0.578
CACS	0 (0-0)	45 (20-70)	190 (130-290)	617.5 (500-763)	1100 (1048-1150)	**<0.001**
Vessels	0 (0-0)	1 (1-2)	2 (2-3)	3 (3-3)	3 (3-3)	**<0.001**
Hospital stay, days	6 (2-25)	8 (2-20)	17 (5-30)	16 (4.5-25)	14 (1.5-48.5)	**0.008**

Data presented as median (interquartile range) unless otherwise stated. Comparisons are made across all groups.

The median number of calcified vessels was two. The artery most commonly affected was the Circumflex and calcium was seen in this vessel in 229 (53%) patients. Calcification was observed in the LAD in 219 (51%) and the RCA in 162 (38%) individuals.

5.5.5 Coronary Artery Calcium and Mortality

5.5.5.1 Overall Study Mortality

Patients with evidence of CHD had a higher mortality rate compared to those without, but differences were not significant (p=0.597, *Figure 5.4*).

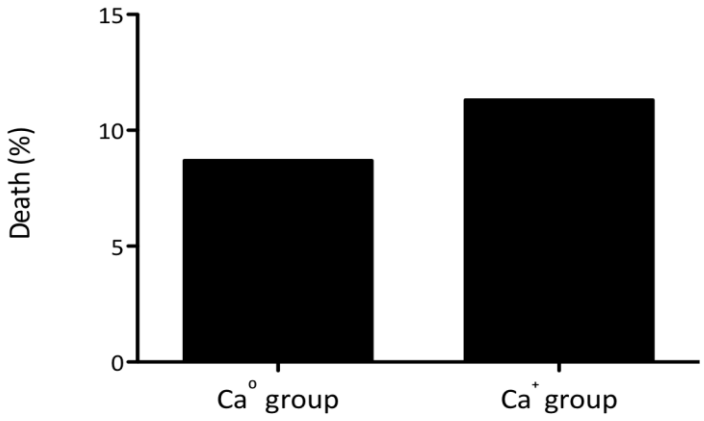


Figure 5.4. Death rate based on the absence or presence of coronary artery calcium

No significant difference in the overall death rate between patients without CAC (Ca^0 group) compared to those with evidence of CHD (Ca^+ group) was observed.

The death rate in each coronary artery calcium quartile is shown in Figure 5.5.

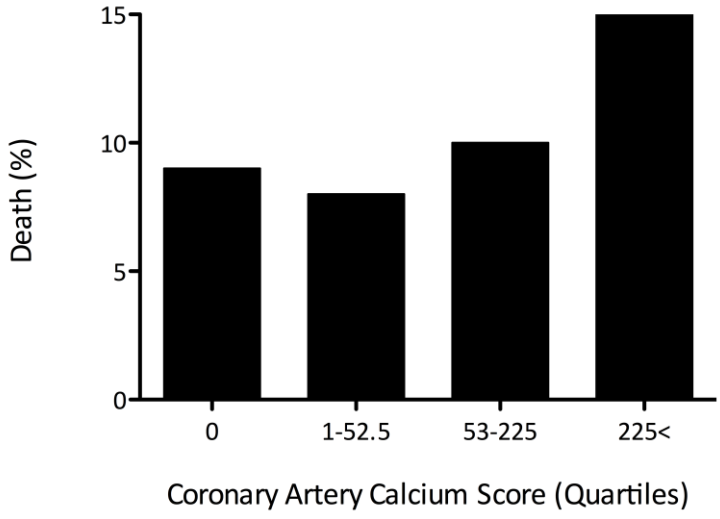


Figure 5.5. Death rate per coronary artery calcium score quartile (p=0181)

The death rate was greatest in patients in the highest CACS quartile, and there was a trend towards poorer survival with increasing calcium score. The differences were not, however, statistically significant (*Figure 5.5*).

In order to identify the clinical variables independently associated with mortality in this study population, a binary logistic regression model was created (*Table 5.5*). The model was a good predictor of death amongst this cohort with an R^2 value of 48% (Nagelkerke R Square 0.481).

Table 5.5. Predictors of Death in Trauma Patients Over the Age of 45

Variable	Crude OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age, years	0.95 (0.93-0.98)	**<0.001**	0.93 (0.89-0.97)	**0.012**
Gender, male	0.39 (0.19-0.78)	**0.007**	0.95 (0.33-2.67)	0.092
ISS	0.93 (0.91-0.96)	**<0.001**	0.96 (0.94-1.01)	0.180
BE, mEq/L	1.19 (1.11-1.27)	**<0.001**	1.13 (1.04-1.22)	**0.004**
GCS	1.29 (1.20-1.39)	**<0.001**	1.29 (1.16-1.44)	**<0.001**
SBP, mmHg	1.01 (1.00-1.02)	**<0.001**	1.00 (0.99-1.01)	0.356
Pre-morbid disease	1.74 (0.91-3.32)	0.092	1.25 (0.48-3.23)	0.655
Mechanism, blunt	0.23 (0.03-1.69)	0.147	1.34 (0.34-6.54)	0.967
CACS	0.99 (0.99-1.00)	0.282	1.00 (0.99-1.01)	0.757

Three predictors of death were identified amongst the patients in this study. These were age, base excess and GCS. Based on both univariate and multiple regression analysis, however, the CACS was not independently associated with mortality. This revealed that in this population of older trauma patients, CHD was not a risk factor for in-hospital death.

5.5.5.2 Mortality and Coronary Artery Calcium Grade

The mortality rate in each individual CAC grade group was around 10% or less. Only patients with evidence of severe CAC had markedly higher death rates, although the differences were not statistically significant (p=0.157, *Figure 5.6*).

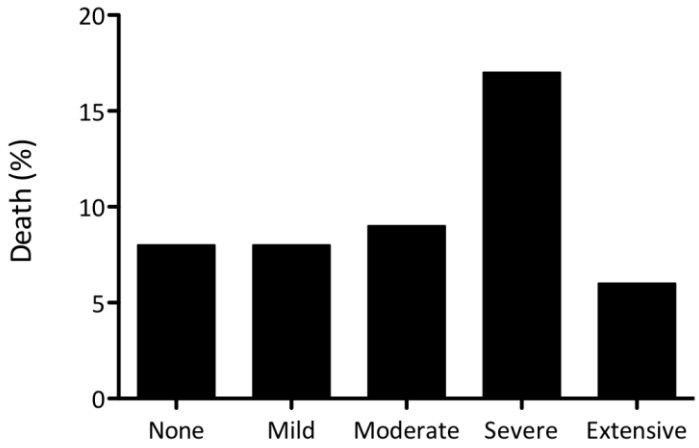


Figure 5.6. Death rates according to grade of coronary artery calcium

In addition, only a grade of severe CAC on admission trauma CT was associated with significantly higher odds of death. Those with otherwise mild, moderate or extensive CAC were found to have no significant differences compared to those patients without evidence of calcification (*Figure 5.7*).

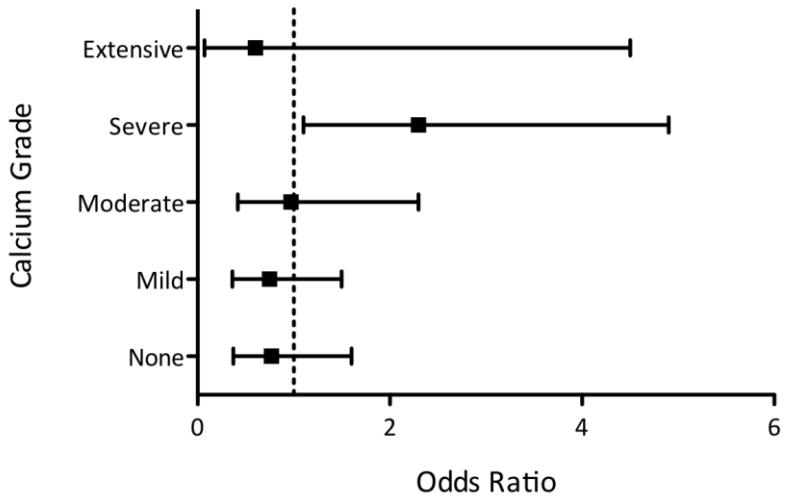


Figure 5.7. Odds ratios of death (with 95% CI) according to grade of coronary artery calcium

Only patients with severe CAC were placed at significantly higher odds of in-hospital death.

5.5.5.3 Coronary Artery Calcium Grade and Mortality Adjusted for Age and ISS

The CAC grade, even after adjusting for age and ISS, was not associated with higher mortality in this study population.

Amongst the younger patients, there was no statistical or clinically relevant pattern of mortality according to the calcium grade even after ISS was adjusted for (*Table 5.6*).

Table 5.6. Odds Ratio of Mortality per Calcium Grade Stratified by Injury Severity Score in Patients Aged <65 Years

	ISS <5	ISS 6-15	ISS 16-24	25≤ ISS
None	1.28 (0.17-9.52) *p=1.000*	0.54 (0.02-13.55) *p=1.000*	0.85 (0.05-14.40) *p=1.000*	0.56 (0.14-2.24) *p=0.529*
Mild	0.14 (0.01-2.71) *p=0.136*	4.83 (0.19-121.9) *p=0.389*	2.33 (0.14-39.85) *p=0.525*	0.97 (0.29-3.29) *p=1.000*
Moderate	3.08 (0.28-33.26) *p=0.363*	2.07 (0.08-53.66) *p=1.000*	1.65 (0.07-39.13) *p=1.000*	1.58 (0.37-6.69) *p=0.683*
Severe	13.33 (0.93-191.3) *p=0.135*	2.86 (0.11-74.41) *p=1.000*	2.71 (0.11-68.30) *p=1.000*	4.00 (0.59-26.75) *p=0.176*
Extensive	n/a	n/a	n/a	0.54 (0.03-10.62) *p=1.000*

Data presented as odds ratio (95% confidence intervals) with *p values*. n/a=There was no patient <65 years with an extensive calcium grade and an ISS <25 in this cohort.

Within the older population, there were no patients within the mild injury category (ISS <5). Only those with severe injuries (ISS 16-24) demonstrated a non-significant pattern of increasing odds of death with higher grades of calcification.

In all other respects, however, there was similarly no evidence of a relationship between the grade of CAC and death. This remained true irrespective of the degree of injury (*Table 5.7*).

Table 5.7. Odds Ratio of Death per Calcium Grade Stratified by Injury Severity Score in Patients Aged 65≤ Years

	ISS <5	ISS 6-15	ISS 16-24	25≤ ISS
None	n/a	6.33 (0.17-231.3) *p=1.000*	1.24 (0.04-34.23) *p=1.000*	3.90 (0.56-26.94) *p=0.303*
Mild	n/a	1.48 (0.05-41.58) *p=1.000*	1.34 (0.07-35.07) *p=1.000*	1.10 (0.28-5.31) *p=1.000*
Moderate	n/a	0.72 (0.03-19.36) *p=1.000*	1.43 (0.08-26.91) *p=1.000*	0.33 (0.06-1.78) *p=0.276*
Severe	n/a	4.87 (0.18-128.9) *p=0.400*	1.83 (0.10-34.87) *p=1.000*	1.11 (0.26-4.67) *p=1.000*
Extensive	n/a	2.52 (0.08-74.87) *p=1.000*	2.20 (0.07-70.48) *p=1.000*	1.08 (0.09-13.15) *p=1.000*

Data presented as odds ratio (95% confidence intervals) with *p values*. n/a=There was no patient ≥65 years with an ISS <5 in this study population.

5.5.5.4 Mortality According to Vessel Involvement

Patients with calcium in all three coronary arteries had the highest incidence of death, although this was not significant (p=0.173, *Figure 5.8*).

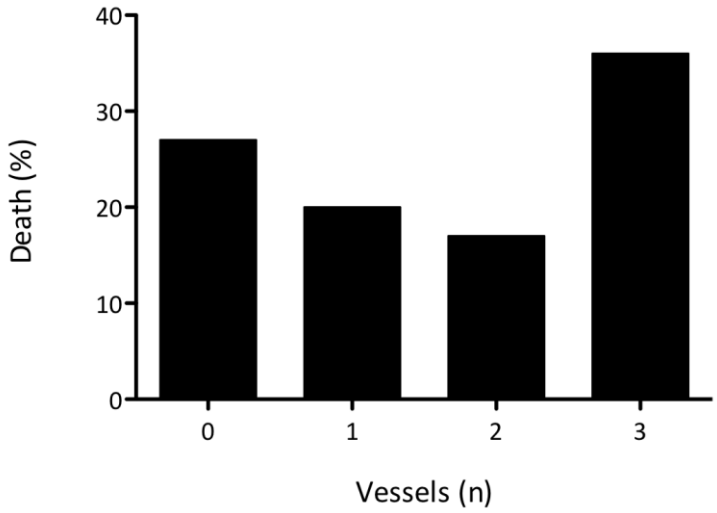


Figure 5.8. Mortality according to number of calcified vessels observed

Moreover, increasing numbers of coronary vessels with calcium involvement was not associated with higher odds of death (*Figure 5.9*).

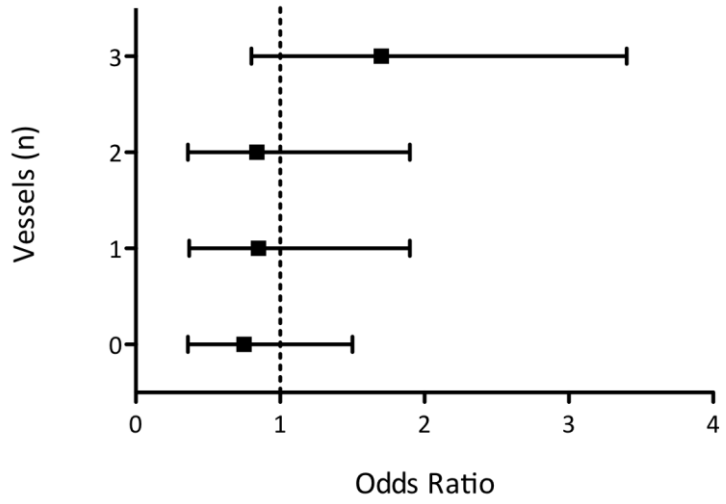


Figure 5.9. Odds ratios of death (with 95% CI) according to number of calcified coronary vessels.

No significant differences in the odds of death were observed based on the number of calcified vessels involved.

Finally, there was no association between mortality and any one particular vessel with calcification (*Table 5.8*).

Table 5.8. Relationship of Each Coronary Artery with Mortality

Vessel	Mortality Rate	OR of Death (95% CI)	p Value
Left Anterior Descending	11.5%	0.61 (0.32-1.18)	0.165
Circumflex	11.8%	0.53 (0.26-1.07)	0.078
Right Coronary Artery	12.3%	0.78 (0.41-1.51)	0.507

5.5.6 Inter-observer Agreement

The results of the inter-observer agreement analyses revealed that the estimation of the CAC load on the CT scans of the study patients was both reliable and reproducible.

There was good agreement between the CACS of the two observers with 399 (92%) of estimates falling within the 95% Confidence Intervals (*Figure 5.10*).

Where there was disagreement, this was predominantly in patients with a lower CACS and as the score increased, so did the inter-observer concordance (*Figure 5.10*).

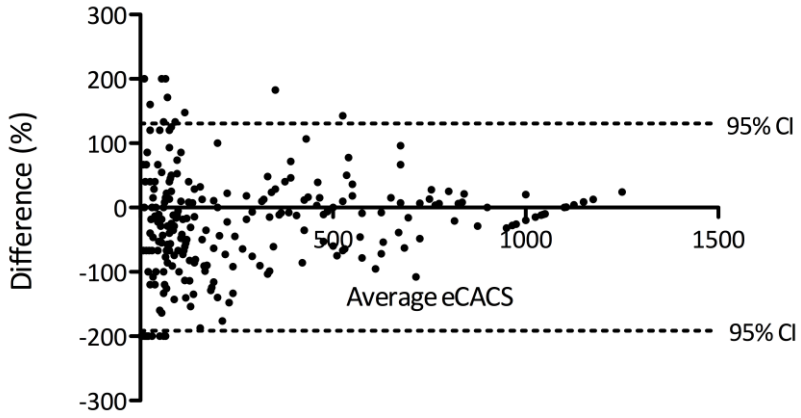


Figure 5.10. Bland Altman plot of inter-observer agreement of estimated coronary artery calcium scores

There was good inter-observer agreement in the scores of the 432 trauma patients' CT scans (Bias=30.5, SD of bias 82.18).

There was substantial agreement between observers when analysing grade of CAC (κ=0.74). Where discrepancies existed between observers, only in seven patients (1.6%) was the difference by more than one estimated grade.

5.6 Discussion

This study is the first to have demonstrated that an estimation of the CACS on CT is feasible, not only in the absence of dedicated cardiac scanning but also in the context of trauma. Using these assessments, this research indicated the true incidence of CHD in a trauma population aged 45 years or over approaches nearly 70%. Finally, and perhaps contrary to expectations, an increase in the distribution and severity of CAC was not, for the most part, associated with an increased in-hospital mortality following injury.

Although scan interpretation was subjective in nature, this study revealed that estimated scores and grades correlated appropriately with expected patient characteristics of increasing levels of coronary calcium, such as older age and greater numbers of co-morbidities (Wexler et al., 1996, Budoff et al., 2007). Furthermore, CAC assessments were possible in just over 90% of trauma patients with a CT scan of the thorax, and substantial agreement between the two observers' scores and grades was demonstrated, thus validating this technique.

This novel finding has implications for future work not only in trauma, but also in other specialties. Using these estimates, patients having a CT chest for non-cardiac related disease could be screened for the incidence and severity of CHD. Additionally, because the measurements did not rely on patients presenting with signs and symptoms of heart disease, calcium estimates could be used to detect the true incidence of atherosclerotic heart disease in any given population.

CAC was present in over two thirds of the study cohort. Whilst this is a considerably higher incidence compared to much of the existing published data on incidental findings on trauma CTs (Van Vugt et al., 2011, Barrett et al., 2009, Devine et al., 2010), these previous studies have also included much younger patients who will not have developed signs of coronary artery disease.

Other research, including those examining the role of statins and beta blockers on outcome in trauma (Schneider et al., 2011, Neideen et al., 2008, Neal et al., 2009, Efron et al., 2008, Cotton et al., 2007, Arbabi et al., 2007) have described the incidence of a number of cardiac diseases in trauma populations, although only a single investigation has described heart disease in isolation (Ferraris et al., 2010). In all cases, however, these studies have identified pre-morbid cardiac diagnoses only, but none have acknowledged either the incidence or additional contribution to outcome of patients with subclinical CHD. Accordingly, these papers have reported fewer cases of heart disease amongst their populations.

It is particularly useful in the trauma setting to screen for cardiovascular disease, given that patients are mostly unable to give a full medical history or are unconscious on arrival to hospital. To demonstrate evidence of underlying cardiac disease, therefore, may be a useful adjunct to enable appropriate allocation of resources and the subsequent planning of relevant management strategies, such as the early involvement of cardiology specialists.

Although survival was the study outcome, it is worth noting that patients with higher CACS and evidence of CHD tended to have longer lengths of hospital stay. By association, it is probable that these patients were more unwell and consumed greater hospital resources. In selected studies, injured patients on beta-blocker therapy have improved outcomes, notably survival (M. Martin et al., 2005, Hadjizacharia et al., 2011, Arbabi et al., 2007, Cotton et al., 2007). Although this protective effect is most apparent following head injury, it is possible that a secondary and previously unrecognised benefit of these drugs is the treatment and stabilisation of patients with subclinical CHD, which in turn might lead to improved outcomes. Future studies should therefore determine whether the treatment of subclinical CHD in trauma is beneficial overall.

In contrast, isolated levels of CAC were not generally predictive of survival and only patients with severe CACS were placed at an increased odds of death.

These findings not only support results presented in *Chapter Two*, but are corroborated by much of the literature demonstrating patients with cardiac disease are not exposed to a higher risk of death following injury (Shoko et al., 2010, Bamvita et al., 2007, Smith et al., 1990, Oreskovich et al., 1984, Horst et al., 1986). This finding may have been a consequence of survival bias, however. Patients who will have died in the acute setting will not have had a CT scan, and older patients with higher CACS may have been exposed to higher death rates on admission. They will not have been included into this study therefore (Meisler et al., 2011).

Given the disproportionately fewer numbers of individuals with extensive CAC in this analysis, it is also likely that patients with very high CACS are older and die from cardiac related disease, and are perhaps less likely to be exposed to trauma.

The study did reveal that patients with evidence of severe CAC were at a higher odds of death, but it is possible that the study was underpowered given the findings are otherwise contrary to some of the other published data on survival with heart disease in trauma (Ferraris et al., 2010, Morris et al., 1990, Perdue et al., 1998, Wutzler et al., 2009, Milzman et al., 1992).

Furthermore, evidence on the prognostic value of CACS on mortality has often followed up patients over the course of several years (Ostrom et al., 2008). It would be valuable in future studies, therefore, to analyse whether the estimated CACS is more predictive of the higher longer-term death rates seen in trauma patients.

5.7 Limitations

In the first instance, the study could have been subject to inaccurate documentation of patient characteristics and outcomes because of its retrospective nature.

Secondly, survival was the primary endpoint examined amongst this trauma cohort. In order to achieve a clearer insight into the effects of pre-existing heart disease on the outcomes of injured patients, additional endpoints should be studied in future, including the risk of ACEs, given that that is where the bulk of evidence on calcium scoring currently lies.

Conclusions of this study were derived from calcium score estimates and not objectively calculated values. In addition, calcium scores were not formally computed using dedicated software to verify the estimates. Although it was one of the aims of this study to determine whether calcium score estimates could be made and usefully applied, it does mean that at this stage that the findings of this study can only be generalised. Formal calcium scoring of non-cardiac CTs is also not possible, however, and so it would not be feasible to objectively measure Agatston scores for the purposes of a study such as this.

While the agreement between observers was substantial, in a few cases where there was disagreement, certain scores led to grades moving from one category to another. Accordingly, patients may have been categorised incorrectly to a group, and thus inappropriately influenced the numbers and outcomes associated with each calcification grade (e.g. mild CAC incorrectly labelled moderate or vice versa).

There is evidence within the statistical analyses that the study may have been underpowered. This was perhaps most apparent when determining the odds ratio for death in each calcium score grade after adjusting for age and ISS.

The confidence intervals were very wide in places, and suggested this investigation lacks sufficient numbers of patients to achieve statistical

significance. Indeed, although a large overall study population, there were only 17 patients in the group with extensive CAC, for example.

There were also no patients in certain categories, such as deceased patients ≥65 years with an ISS <5, and this will have led to incomplete data analyses. As a result of all these, the statistical validity of the results may have been undermined, and thus the strength of the overall study conclusions weakened.

Nonetheless, because findings from this pilot study were novel and designed in part to assess the global incidence of CHD, including those subclinical cases, a power calculation to estimate the study population size could not have been undertaken. As a consequence of this work, future research will now be able to compute a sufficiently well powered study.

Finally, the median ISS in this patient cohort was 16 demonstrating this analysis was undertaken in predominantly severely injured patients. Moreover, no older patient with an ISS <5 died. It is difficult, therefore, to draw conclusions from this investigation on the influence of pre-morbid cardiac disease on survival in mild trauma.

In spite of the fact that the findings of this study are supported by some prior research in the field, much of the previous evidence that has revealed a negative impact of cardiac disease on survival has shown that this effect is most marked in less injured patients. The high overall ISS of this study population meant that the findings of these latter studies could neither be confirmed nor refuted. Future analyses should therefore include more patients with mild injury.

5.8 Conclusions

Trauma CT scans performed on admission in older injured patients may be used to estimate the CACS and grade. These estimates suggested that the incidence of CHD, inclusive of all presentations, approaches 70% in injured patients aged 45 years or over. Finally, the presence and extent of CAC, and therefore CHD, was generally neither predictive nor associated with all cause in-hospital mortality in an older trauma cohort.

Further studies should ensure sufficient statistical power, and examine not only in-hospital mortality but also longer term survival. Furthermore, the presence of CAC should be assessed as a risk factor for ACEs in trauma.

CHAPTER SIX

Conclusions

6.1 Summary of Findings

This thesis has achieved all the aims described in *Chapter One*, and has led to significant and novel contributions to the body of knowledge on trauma associated cardiac injury and dysfunction.

Chapter Two identified the existence of a "Trauma Induced Secondary Cardiac Injury-TISCI", and demonstrated its association with poorer outcomes. This included significantly higher death rates.

Chapter Three revealed a relationship between TISCI and acute inflammation. It also demonstrated that on admission, evidence of cardiac injury combined with high levels of inflammation may be associated with an increased risk of in-hospital mortality in trauma.

Chapter Four confirmed both the existence of TISCI and its link to increased mortality. Detailed characteristics of ACEs were reported, including evidence that cardiac events were not a manifestation of a stress induced (Takotsubo's) cardiomyopathy. In addition, the chapter revealed the risk factors associated with the development of ACEs, namely increasing age and ISS and shock (worsening base excess). Finally, the study showed that pre-morbid heart disease was not an independent predictor of secondary ACEs in trauma.

Lastly, *Chapter Five* reported that CT scans of the chest undertaken in trauma patients may be assessed for the presence and degree of coronary artery calcium, as a surrogate marker of CHD. Although the incidence of this disease in an older trauma population approached 70%, its presence did not significantly impact on survival outcomes.

A summary of the principal findings of this thesis is illustrated in Figure 6.1.

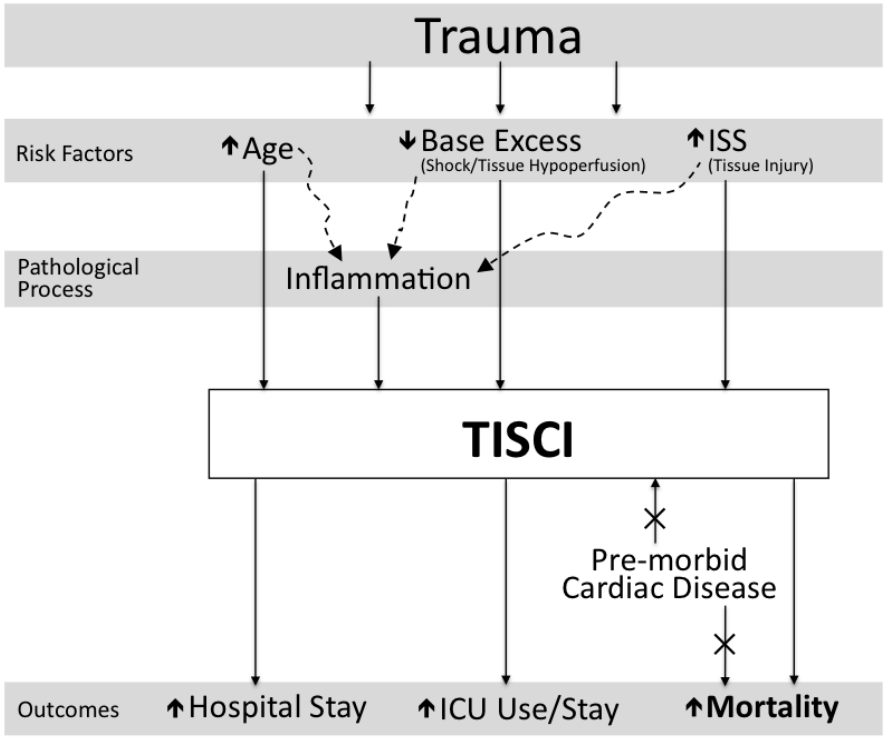


Figure 6.1. Trauma associated cardiac injury and dysfunction: an illustrative summary of the principal findings of this thesis

Full arrows show the associations, or when crossed the non-associations demonstrated in this dissertation. Dashed arrows show putative relationships not examined by this research project.

6.2 Strengths and Limitations

6.2.1 Strengths of the Research Project

There are several key strengths to this research project, which is believed to be the largest dedicated global study of trauma associated cardiac injury and dysfunction to date.

This work is the only investigation to have identified TISCI through the combination of clinical and multiple biomarker evidence. Previous work has focused on either isolated clinical diagnoses (Hadjizacharia et al., 2011, Moosikasuwan et al., 2000, Ismailov et al., 2005, Seguin et al., 2006) or single biomarker studies (M. Martin et al., 2005, Edouard et al., 2004, Edouard et al., 1998, Lagi et al., 2008), but none have yet combined the two.

The prospective evidence gathered from a larger, unrelated cohort of injured patients in *Chapter Four* mirrored the retrospective findings of *Chapter Two*. Consequently, perhaps the single greatest strength of this work is to have presented conclusive verification of TISCI, a relevant and important clinical entity.

In contrast to prior research in the field (Hadjizacharia et al., 2011, Ismailov et al., 2005, Seguin et al., 2006), this thesis contains currently the only prospective data examining all ACEs in a general trauma population. Using multivariate analysis in a robust statistical model, the project identified the risk factors for post-traumatic secondary cardiac events in trauma. These findings not only build upon the limited current knowledge of the field, but more importantly will now enable clinicians to identify those patients at risk of TISCI following trauma.

This research project includes the first clinical study to investigate fully the role of inflammation in TISCI, and thus begin to translate the findings of existing experimental evidence (Yang et al., 2006, Nickel et al., 2009, Horton et al., 2000, Liu et al., 2011) into the wider clinical context.

By means of a novel and innovative technique, this is the only study to examine the epidemiology of CHD in trauma and encompass all spectrums of the disease.

Furthermore, the method evolved and developed is one that may be replicated and used to assess CHD in other medical specialties in the future.

A significant achievement of this project is to have set up the single largest ongoing prospective study of its kind. Using robust methodology and effective recruitment procedures "Trauma Associated Cardiac Injury and Dysfunction-TACID" continues to examine all aspects of the secondary effects of trauma on the heart. In conjunction, a further key strength of this work was the development and application of an ethical and functional process of consent in injured patients. Although notoriously difficult to undertake and traditionally prohibitive to research in trauma, this system remains in place and enables ongoing data collection.

The chief legacy of this thesis is to have produced translational and clinically applicable data that reveals significant and tangible opportunities for future research, most conspicuously in targets for therapeutic intervention in TISCI. This project provides novel insights and thus represents an important step in leading potentially to a reduction in the burden of morbidity and mortality associated with trauma.

6.2.2 Limitations of the Research Project

There are, however, notable limitations to the work presented in this dissertation. Most of the studies were dependent on retrospective data collection. Accordingly, there existed the potential for misclassification of cardiac events which may have led to subsequent inaccuracies in the diagnoses of post-traumatic ACEs. Furthermore, such methodology may have resulted in an inaccurate estimation of the incidence of such occurrences.

Nonetheless, whilst it is possible that ACEs were more widespread, the prospective findings in *Chapter Four* suggested that the retrospective data

capture was a comprehensive and accurate reflection of the epidemiology of post-traumatic cardiac events.

The diagnosis of cardiac injury and dysfunction were based predominantly on clinical and biomarker evidence. Few patients with TISCI were investigated with detailed imaging studies, which would have provided additional and more complete information on cardiac morphology and function. As such this represents another limitation of the research methodology.

The measurement of coronary artery calcium on CT in *Chapter Five* was based on subjective assessments using a non-validated technique. Consequently, there would have been inevitable errors in reporting the extent of cardiac calcification in patients. Based on the Bland-Altman charts demonstrating the discrepancies between observers, these were most likely in individuals with lower calcium scores.

Finally, many of the conclusions of this thesis are based on associations in relatively small study populations. Although larger than many previous investigations, the existing data would benefit from substantiation in future studies with greater statistical power.

6.3 Future Work

The research presented in this thesis revealed the existence of a trauma induced secondary cardiac injury that is associated with poorer outcome. Although an association with inflammation was shown, the pathophysiological mechanisms driving this condition are not fully understood. Future work should investigate the cellular structure of the heart in TISCI, and identify which organelles and microscopic processes are disrupted in leading to such cardiac damage. Mitochondria and endoplasmic reticulum together with apoptosis and autophagy represent appropriate targets for preliminary investigation. Whilst initially performed in animal studies, corroboration in human hearts should be undertaken pending ethical approval. Furthermore, postmortem analyses would determine if and how TISCI leads to the death of injured patients.

Prospective experimental and clinical research should also conduct detailed cardiac imaging studies such as MRI and positron emission tomography (PET) to yield further information on the appearance, structure and function of the heart in TISCI.

Investigations should examine why increased age, shock and tissue injury are independent predictors of TISCI. They should determine which pathological processes responsible for cardiac injury they initiate.

Further outcomes associated with TISCI require exploration, including longer-term end points (such as one, five and ten year mortality and economic cost, for example). This would also establish if TISCI is a chronic condition, and implicated in the higher protracted death rates seen in trauma patients.

The novel technique used to assess coronary artery calcium should be validated. This could be done using existing cardiac scanning software designed to measure calcification objectively in the heart. In addition, this research did not reveal the impact of CHD on other outcomes in trauma, such as the development of ACEs. Indeed the influence of CHD on long-term survival remains unknown. Future work should establish these.

Ultimately, the aim of the research both presented and generated in this thesis will be to identify opportunities to reduce the mortality and morbidity associated with trauma.

These include the trial of therapeutic interventions such as cardiac medication. Beta-blockers are recommended agents in the treatment of life threatening conditions such as MI, and the evidence presented in this thesis might represent the first step in the eventual justification and initiation of a future randomised clinical trial of such medication in trauma.

Finally, increasing age, shock and tissue injury were found to be the risk factors linked to TISCI. None of these aspects, however, are exclusive to trauma, and indeed they are common to a number of other medical specialties. As such, this thesis justifies research in non-trauma fields (such as all major surgery) to determine whether secondary cardiac injury and dysfunction exists in such areas, and whether it is also responsible for negative impacts on outcome.

6.4 Conclusions

This thesis has completed all the study aims. It has revealed that trauma induces a secondary cardiac injury and that this is related to poorer outcome. Increasing age, shock and tissue injury are independent predictors, whilst inflammation is associated with TISCI. Although coronary heart disease is widespread in older trauma patients, it has no significant impact on in-hospital mortality.

REFERENCES

Adams, J. E., Bodor, G. S., Dávila-Román, V. G., Delmez, J. A., Apple, F. S., Ladenson, J. H., Jaffe, A. S. (1993). Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation,* 88(1): 101-106.

Agatston, A. S., Janowitz, W. R., Hildner, F. J., Zusmer, N. R., Viamonte, M., Detrano, R. (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology,* 15(4): 827-832.

Akashi, Y. J., Goldstein, D. S., Barbaro, G., Ueyama, T. (2008). Takotsubo Cardiomyopathy: a new form of acute, reversible heart failure. *Circulation,* 118(25): 2754-2762.

Alhadi, H. A., Fox, K. A. (2004). Do we need additional markers of myocyte necrosis: the potential value of heart fatty-acid-binding protein. *QJM,* 97(4): 187-198.

Amino, M., Yoshioka, K., Morita, S., Iizuka, S., Otsuka, H., Yamamoto, R., Aoki, H., Aizawa, T., Ikari, Y., Nasu, S., Hatakeyama, K., Iino, M., Kodama, I., Inokuchi, S., Tanabe, T. (2009). One-year follow-up and convalescence evaluated by nuclear medicine studies and 24-hour holter electrocardiogram in 11 patients with myocardial injury due to a blunt chest trauma. *The Journal of Trauma, Injury, Infection, and Critical Care,* 66(5): 1308-1310.

Andrassy, M., Volz, H. C., Igwe, J. C., Funke, B., Eichberger, S. N., Kaya, Z., Buss, S., Autschbach, F., Pleger, S. T., Lukic, I. K., Bea, F., Hardt, S. E., Humpert, P. M., Bianchi, M. E., Mairbaurl, H., Nawroth, P. P., Remppis, A., Katus, H. A., Bierhaus, A. (2008). High-mobility group box-1 in ischemia-reperfusion injury of the heart. *Circulation,* 117(25): 3216-3226.

Andreoli, A., Di Pasquale, G., Pinelli, G., Grazi, P., Tognetti, F., Testa, C. (1987). Subarachnoid hemorrhage: frequency and severity of cardiac arrhythmias. A survey of 70 cases studied in the acute phase. *Stroke,* 18(3): 558-564.

Apple, F., Falahati, A., Paulsen, P. (1997). Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I. *Clinical Chemistry* 43(11): 2047-51.

Arad, Y., Spadaro, L. A., Goodman, K., Lledo-Perez, A., Sherman, S., Lerner, G., Guerci, A. D. (1996). Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. *Circulation,* 93(11): 1951-1953.

Arad, Y., Spadaro, L. A., Goodman, K., Newstein, D., Guerci, A. D. (2000). Prediction of coronary events with electron beam computed tomography. *Journal of the American College of Cardiology.* 36(4): 1253-60.

Arbabi, S., Campion, E. M., Hemmila, M. R., Barker, M., Dimo, M., Ahrns, K. S., Niederbichler, A. D., Ipaktchi, K. & Wahl, W. L. (2007). Beta-blocker use is associated with improved outcomes in adult trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 62(1): 56-62.

Arenberg, H. (1943). Traumatic heart disease: a clinical study of 250 cases of non-penetrating chest injuries and their relation to cardiac disability. *Annals of Internal Medicine,* 19(2): 326-346.

Artucio, H., Pereira, M. (1990). Cardiac arrhythmias in critically ill patients: epidemiologic study. *Critical Care Medicine,* 18(12): 1383-8.

Asensio, J. A., Berne, J. D., Demetriades, D., Chan, L., Murray, J., Falabella, A., Gomez, H., Chahwan, S., Velmahos, G., Cornwell, E. E., Belzberg, H., Shoemaker, W., Berne, T. V. (1998). One hundred five penetrating cardiac injuries: a 2-year prospective evaluation. *The Journal of Trauma, Injury, Infection, and Critical Care,* 44(6): 1073-1082.

Auerbach, A. D., Goldman, L. (2002). Beta-blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA : the journal of the American Medical Association,* 287(11): 1435-1444.

Aviles, R. J., Martin, D. O., Apperson-Hansen, C., Houghtaling P. L, Rautaharju, P., Kronmal, R. A., Tracy, R. P., Van Wagoner, D. R., Psaty, B. M., Lauer, M. S., Chung, M. K. (2003). Inflammation as a risk factor for atrial fibrillation. *Circulation,* 108(24): 3006-3010.

Ba, Z. F., Hsu, J. T., Chen, J., Kan, W. H., Schwacha, M. G., Chaudry, I. H. (2008). Systematic analysis of the salutary effect of estrogen on cardiac performance after trauma-hemorrhage. *Shock,* 30(5): 585-589.

Babu, G. G., Wood, A., O'Callaghan, P., Masani, N. D., Bleasdale, R. A. (2009). The complete array of electrocardiogram abnormalities secondary to myocardial contusion in a single case. *Europace,* 11(11): 1557-1559.

Babuin, L., Jaffe, A. S. (2005). Troponin: the biomarker of choice for the detection of cardiac injury. *Canadian Medical Association Journal,* 173(10): 1191-1202.

Baffoun, N., Lakhdhar, R., Baccar, K., Djebari, K., Kaddour, C. (2011). Cardiac injury in traumatic subarachnoid hemorrhage: a prospective study in 35 patients. *La Tunisie médicale,* 89(2): 184-187.

Bahloul, M., Chaari, A. N., Kallel, H., Khabir, A., Ayadi, A., Charfeddine, H., Hergafi, L., Chaari, A. D., Chelly, H. E., Ben Hamida, C., Rekik, N., Bouaziz, M. (2006). Neurogenic pulmonary edema due to traumatic brain injury: evidence of cardiac dysfunction. *American journal of critical care : an official publication, American Association of Critical-Care Nurses,* 15(5): 462-470.

Baker, S. P., O'Neill, B., Haddon, W Jr., Long, W. B. (1974). The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *The Journal of Trauma, Injury, Infection, and Critical Care,* 14(3): 187-196.

Bamvita, J. M., Bergeron, E., Lavoie, A., Ratte, S., Clas, D. (2007). The impact of premorbid conditions on temporal pattern and location of adult blunt trauma hospital deaths. *The Journal of Trauma, Injury, Infection, and Critical Care,* 63(1): 135-141.

Barrett, T. W., Schierling, M., Zhou, C., Colfax, J. D., Russ, S., Conatser, P., Lancaster, P., Wrenn, K. (2009). Prevalence of incidental findings in trauma patients detected by computed tomography imaging. *American Journal of Emergency Medicine,* 27(4): 428-435.

Batistaki, C., Kostopanagiotou, G., Myrianthefs, P., Dimas, C., Maatsota, P., Pandazi, A., Baltopoulos, G. (2008). Effect of exogenous catecholamines on tumor necrosis factor alpha, interleukin-6, interleukin-10 and beta-endorphin levels following severe trauma. *Vascular Pharmacology,* 48(2-3): 85-91.

Beck, C. S., Bright, E. F. (1933). Changes in the heart and pericardium brought about by compression of the legs and abdomen. *Journal of Thoracic Surgery,* 2: 616.

Bedi, U., Arora, R. (2007). Cardiovascular manifestations of posttraumatic stress disorder. *Journal of the National Medical Association,* 99(6): 642-9.

BHF. (2011). Trends in coronary heart disease 1961-2011. British Heart Foundation.

Bourdages, M., Bigras, J. L., Farrell, C. A., Hutchison, J. S., Lacroix, J. (2010). Cardiac arrhythmias associated with severe traumatic brain injury and hypothermia therapy. *Pediatric Critical Care Medicine,* 11(3): 408-14.

Budoff, M. J., Shaw, L. J., Liu, S. T., Weinstein, S. R., Mosler, T. P., Tseng, P. H., Flores, F. R., Callister, T. Q., Raggi, P., Berman, D. S. (2007). Long-term prognosis associated with coronary calcification. *Journal of the American College of Cardiology,* 49(18): 1860-1870.

Bukur, M., Lustenberger, T., Cotton, B., Arbabi, S., Talving, P., Salim, A., Ley, E. J., Inaba, K. (2012). Beta-blocker exposure in the absence of significant head injuries is associated with reduced mortality in critically ill patients. *American Journal of Surgery,* 204(5): 697-703.

Cai, B., Deitch, E. A., Grande, D., Ulloa, L. (2009). Anti-inflammatory resuscitation improves survival in hemorrhage with trauma. *The Journal of Trauma, Injury, Infection, and Critical Care,* 66(6): 1632-1640.

Cameron, C. M., Purdie, D. M., Kliewer, E. V., Mcclure, R. J. (2005). Long-term mortality following trauma: 10 year follow-up in a population-based sample of injured adults. *The Journal of Trauma, Injury, Infection, and Critical Care,* 59(3): 639-646.

CDC. (2010). Injury prevention and control: data and statistics. The ten leading causes of death and injury. Centre for Disease Control and Prevention.

Cebelin, M. S., Hirsch, C. S. (1980). Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. *Human Pathology,* 11(2): 123-32.

Chalkley, D., Cheung, G., Walsh, M., Tai, N. (2011). Deaths from trauma in London-a single centre experience. *Emergency Medicine Journal,* 28(4): 305-309.

Charpentier, J., Luyt, C. E., Fulla, Y., Vinsonneau, C., Cariou, A., Grabar, S., Dhainaut, J. F., Mira, J. P., Chiche, J. D. (2004). Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. *Critical Care Medicine,* 32(3): 660-665.

Chatpun, S., Cabrales, P. (2011). Cardiac systolic function recovery after hemorrhage determines survivability during shock. *The Journal of Trauma, Injury, Infection, and Critical Care,* 70(4): 787-793.

Chen, D., Assad-Kottner, C., Orrego, C., Torre-Amione, G. (2008). Cytokines and acute heart failure. *Critical Care Medicine,* 36(1 Suppl): S9-S16.

Choi, J. H., Cho, D. K., Song, Y. B., Hahn, J. Y., Choi, S., Gwon, H. C., Kim, D. K., Lee, S. H., Oh, J. K., Jeon, E. S. (2009). Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery. *Heart,* 96(1): 56-62.

Chong, C. P., Lam, Q. T., Ryan, J. E., Sinnappu, R. N., Lim, W. K. (2008). Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. *Age and Ageing,* 38(2): 168-174.

Christensen, M. C., Nielsen, T. G., Ridley, S., Lecky, F. E., Morris, S. (2008a). Outcomes and costs of penetrating trauma injury in England and Wales. *Injury,* 39(9): 1013-1025.

Christensen, M. C., Ridley, S., Lecky, F. E., Munro, V., Morris, S. (2008b). Outcomes and costs of blunt trauma in England and Wales. *Critical Care,* 12(1): R23.

Ciesla, D. J., Moore, E. E., Johnson, J. L., Burch, J. M., Cothren, C. C., Sauaia, A. (2005). A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Archives of Surgery*, 140(5): 432-8.

Claridge, J. A., Leukhardt, W. H., Golob, J. F., Mccoy, A. M., Malangoni, M. A. (2010). Moving beyond traditional measurement of mortality after injury: evaluation of risks for late death. *Journal of American College of Surgeons,* 210(5): 788-794.

Clements, P., Brady, S., York, M., Berridge, B., Mikaelian, I., Nicklaus, R., Gandhi, M., Roman, I., Stamp, C., Davies, D., Mcgill, P., Williams, T., Pettit, S., Walker, D.; Ilsi Hesi Cardiac Troponins Working Group, Turton J. (2010). Time course characterization of serum cardiac Troponins, Heart Fatty Acid-binding Protein, and morphologic findings with Isoproterenol-induced myocardial injury in the rat. *Toxicologic Pathology,* 38(5): 703-714.

Cothren, C. C., Moore, E. E., Hedegaard, H. B., Meng, K. (2007). Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World Journal of Surgery,* 31(7): 1507-11.

Cotton, B. A., Snodgrass, K. B., Fleming, S. B., Carpenter, R. O., Kemp, C. D., Arbogast, P. G., Morris Jr, J. A. (2007). Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. *The Journal of Trauma, Injury, Infection, and Critical Care,* 62(1): 26-35.

Davenport, R., Manson. J., De'Ath, H., Platton, S., Coates, A., Allard, S., Hart, D., Pearse, R., Pasi, J., MacCallum, P., Stanworth, S., Brohi, K. (2011). Functional definition and characterization of acute traumatic coagulopathy. *Critical Care Medicine,* 39(12): 2652-8.

Davenport, R. A., Tai, N., West, A., Bouamra, O., Aylwin, C., Woodford, M., Mcginley, A., Lecky, F., Walsh, M. S., Brohi, K. (2009). A major trauma centre is a specialty hospital not a hospital of specialties. *British Journal of Surgery,* 97(1): 109-117.

Davidson, G. H., Hamlat, C. A., Rivara, F. P., Koepsell, T. D., Jurkovich, G. J., Arbabi, S. (2011). Long-term survival of adult trauma patients. *JAMA : the journal of the American Medical Association,* 305(10): 1001-1007.

Dellegrottaglie, S., Pedrotti, P., Pedretti, S., Mauri, F., Roghi, A. (2008). Persistent myocardial damage late after cardiac contusion: depiction by cardiac magnetic resonance. *Journal of Cardiovascular Medicine,* 9(11): 1177-1179.

Detrano R, Guerci, A. D., Carr, J. J., Bild, D. E., Burke, G., Folsom, A. R., Liu, K., Shea, S., Szklo, M., Bluemke, D. A., O'leary, D. H., Tracy, R., Watson, K., Wong, N. D., Kronmal, R. A. (2008). Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *New England Journal of Medicine,* 358(13): 1336-45.

D'ettorre, G., Francone, M., Mancone, M., Ceccarelli, G., Ascarelli, A., Vullo, F., Baroncelli, S., Galluzzo, M. C., Catalano, C., Strano, S., Fedele, F., Mastroianni, C., Palmisano, L., Vullo, V. (2011). Significant coronary stenosis detected by coronary computed angiography in asymptomatic HIV infected subjects. *Journal of Infection,* 64(1): 82-8.

Devine, A. S., Jackson, C. S., Lyons, L., Mason, J. D. (2010). Frequency of incidental findings on computed tomography of trauma patients. *The Western Journal of Emergency Medicine,* 11(1): 24-27.

Dewar, D., Moore, F. A., Moore, E. E., Balogh, Z. (2009). Postinjury multiple organ failure. *Injury,* 40(9): 912-918.

Edouard, A. R., Benoist, J. F., Cosson, C., Mimoz, O., Legrand, A., Samii, K. (1998). Circulating cardiac troponin I in trauma patients without cardiac contusion. *Intensive Care Medicine,* 24(6): 569-573.

Edouard, A. R., Felten, M. L., Hebert, J. L., Cosson, C., Martin, L., Benhamou, D. (2004). Incidence and significance of cardiac troponin I release in severe trauma patients. *Anesthesiology,* 101(6): 1262-1268.

Efron, D. T., Sorock, G., Haut, E. R., Chang, D., Schneider, E., Mackenzie, E., Cornwell III, E. E., Jurkovich, G. J. (2008). Preinjury statin use is associated with improved in-hospital survival in elderly trauma

patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 64(1): 66-74.

Elhassan, I. O., Hannoush, E. J., Sifri, Z. C., Jones, E., Alzate, W. D., Rameshwar, P., Livingston, D. H., Mohr, A. M. (2011). Beta-blockade prevents hematopoietic progenitor cell suppression after hemorrhagic shock. *Surgical Infections,* 12(4): 273-278.

Elrifai, A. M., Bailes, J. E., Shih, S. R., Dianzumba, S., Brillman, J. (1996). Characterization of the cardiac effects of acute subarachnoid hemorrhage in dogs. *Stroke,* 27(4): 737-41.

Emura, I., Usuda, H. (2010). Histopathological and cytological examination of autopsy cases with multiple organ dysfunction syndromes. *Pathology International,* 60(6): 443-451.

Evans, J. A., Wessem, K. J. P., Mcdougall, D., Lee, K. A., Lyons, T., Balogh, Z. J. (2009). Epidemiology of traumatic deaths: comprehensive population-based assessment. *World Journal of Surgery,* 34(1): 158-163.

Ferraris, V. A., Ferraris, S. P., Saha, S. P. (2010). The relationship between mortality and preexisting cardiac disease in 5,971 trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 69(3): 645-652.

Finkelstein, E.A., Corso, P.S., Miller, T. R. (2006). The incidence and economic burden of injuries in the United States. Oxford University Press.

Friese, R. S., Dineen, S., Jennings, A., Pruitt, J., Mcbride, D., Shafi, S., Frankel, H., Gentilello, L. M. (2007). Serum B-Type Natriuretic Peptide: a marker of fluid resuscitation after injury? *The Journal of Trauma, Injury, Infection, and Critical Care,* 62(6): 1346-1351.

Frink, M., Pape, H. C., Van Griensven, M., Krettek, C., Chaudry, I. H., Hildebrand, F. (2007). Influence of sex and age on MODS and cytokines after multiple injuries. *Shock,* 27(2): 151-156.

Greenland, P., Bonow, R. O., Brundage, B. H., Budoff, M. J., Eisenberg, M. J., Grundy, S. M., Lauer, M. S., Post, W. S., Raggi, P., Redberg, R. F, Rodgers, G. P., Shaw, L. J., Taylor, A. J., Weintraub, W. S; American College of Cardiology Foundation Clinical Expert Consensus Task

Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography. (2007). ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain. *Journal of the American College of Cardiology,* 49(3): 378-402.

Grossman, M. D., Miller, D., Scaff, D. W., Arcona, S. (2002). When is an elder old? Effect of preexisting conditions on mortality in geriatric trauma. *The Journal of Trauma: Injury, Infection, and Critical Care,* 52(2): 242-246.

Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., Fuster, V. (1999). Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation,* 100(13): 1481-1492.

Guan, D. W., Zhang, X. G., Zhao, R., Lu, B., Han, Y., Hou, Z. H., Jia, J. T. (2007). Diverse morphological lesions and serious arrhythmias with hemodynamic insults occur in the early myocardial contusion due to blunt impact in dogs. *Forensic Science International,* 166(1): 49-57.

Hadjizacharia, P., O'keefe, T., Brown, C. V., Inaba, K., Salim, A., Chan, L. S., Demetriades, D., Rhee, P. (2011). Incidence, risk factors, and outcomes for atrial arrhythmias in trauma patients. *American Surgeon,* 77(5): 634-639.

Hamdani, N., Kooij, V., van Dijk, S., Merkus, D., Paulus, W. J., Remedios, C. D., Duncker, D. J., Stienen, G. J., van der Velden, J. (2008). Sarcomeric dysfunction in heart failure. *Cardiovascular Research*, 77(4): 649-58.

Harada, A., Sekido, N., Akahoshi, T., Wada, T., Mukaida, N., Matsushima, K. (1994). Essential involvement of interleukin-8 (IL-8) in acute inflammation. *Journal of Leukocyte Biology,* 56(5): 559-564.

Harrell, F. E., Lee, K., Mark, D. B. (1996). Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy and measuring and reducing errors. *Statistics in Medicine,* 15(4): 361-387.

Hassoun, H. T., Kone, B. C., Mercer, D. W., Moody, F. G., Weisbrodt, N. W., Moore, F. A. (2001). Post-injury multiple organ failure: the role of the gut. *Shock,* 15(1): 1-10.

Hohensinner, P. J., Niessner, A., Huber, K., Weyand, C. M., Wojta, J. (2011). Inflammation and cardiac outcome. *Current Opinion in Infectious Diseases,* 24(3): 259-264.

Hollis, S., Lecky, F., Yates, D. W., Woodford, M. (2006). The effect of pre-existing medical conditions and age on mortality after injury. *The Journal of Trauma, Injury, Infection, and Critical Care,* 61(5): 1255-1260.

Horst, H. M., Obeid, F., Sorensen,V. J., Bivins, B. A. (1986). Factors influencing survival of elderly trauma patients. *Critical Care Medicine,* 14(8): 681-684.

Horton, J. W., Maass, D., White, J., Sanders, B. (2000). Nitric oxide modulation of TNF-alpha-induced cardiac contractile dysfunction is concentration dependent. *AJP. Heart and Circulatory Physiology,* 278(6): H1955-65.

Hranjec, T., Swenson, B. R., Dossett, L. A., Metzger, R., Flohr, T. R., Popovsky, K. A., Bonatti, H. J., May, A. K., Sawyer, R. G. (2010). Diagnosis-dependent relationships between cytokine levels and survival in patients admitted for surgical critical care. *Journal of the American College of Surgeons,* 210(5): 833-844.

Hsieh, Y. C., Yang, S., Choudhry, M. A., Yu, H. P., Bland, K. I., Schwacha, M. G., Chaudry, I. H. (2005a). Flutamide restores cardiac function after trauma-hemorrhage via an estrogen-dependent pathway through upregulation of PGC-1. *AJP: Heart and Circulatory Physiology,* 290(1): H416-H423.

Hsieh, Y. C., Yang, S., Choudhry, M. A., Yu, H. P., Rue, L. W 3rd., Bland, K. I., Chaudry, I. H. (2005b). PGC-1 upregulation via estrogen

receptors: a common mechanism of salutary effects of estrogen and flutamide on heart function after trauma-hemorrhage. *AJP: Heart and Circulatory Physiology,* 289(6): H2665-H2672.

Hsieh, Y. C., Yu, H. P., Suzuki, T., Choudhry, M. A., Schwacha, M. G., Bland, K. I., Chaudry, I. H. (2006). Upregulation of mitochondrial respiratory complex IV by estrogen receptor-β is critical for inhibiting mitochondrial apoptotic signaling and restoring cardiac functions following trauma–hemorrhage. *Journal of Molecular and Cellular Cardiology,* 41(3): 511-521.

Hsu, J. T., Kan, W. H., Hsieh, C. H., Choudhry, M. A., Bland, K. I., Chaudry, I. H. (2009). Mechanism of salutary effects of estrogen on cardiac function following trauma-hemorrhage: Akt-dependent HO-1 up-regulation. *Critical Care Medicine,* 37(8): 2338-2344.

Inaba, K., Teixeira, P. G., David, J. S., Chan, L. S., Salim, A., Brown, C., Browder, T., Beale, E., Rhee, P., Demetriades, D. (2008). Beta-blockers in isolated blunt head injury. *Journal of the American College of Surgeons,* 206(3): 432-438.

Ismailov, R. M., Ness, R. B., Redmond, C. K., Talbott, E. O., Weiss, H. B. (2007). Trauma associated with cardiac dysrhythmias: results from a large matched case-control study. *The Journal of Trauma, Injury, Infection, and Critical Care,* 62(5): 1186-1191.

Ismailov, R. M., Ness, R. B., Weiss, H. B., Lawrence, B. A., Miller, T. R. (2005). Trauma associated with acute myocardial infarction in a multi-state hospitalized population. *International Journal of Cardiology,* 105(2): 141-146.

Ismailov, R. M., Weiss, H. B., Ness, R. B., Lawrence, B. A., Miller, T. R. (2005). Blunt cardiac injury associated with cardiac valve insufficiency: trauma links to chronic disease? *Injury,* 36(9): 1022-1028.

Jastrow, K. M., Gonzalez, E. A., Mcguire, M. F., Suliburk, J. W., Kozar, R. A., Iyengar, S., Motschall, D. A., Mckinley, B. A., Moore, F. A., Mercer, D. W. (2009). Early cytokine production risk stratifies trauma patients

for multiple organ failure. *Journal of the American College of Surgeons,* 209(3): 320-331.

Jian, B., Yang, S., Chaudry, I. H., Raju, R. (2012). Resveratrol improves cardiac contractility following trauma-hemorrhage by modulating Sirt1. *Molecular Medicine,* 18: 209-214.

Jian, B., Yang, S., Chen, D., Zou, L., Chatham, J. C., Chaudry, I., Raju, R. (2011). Aging influences cardiac mitochondrial gene expression and cardiovascular function following hemorrhage injury. *Molecular Medicine,* 17(5-6): 542-9.

Jiang, J. X., Tian, K. L., Chen, H. S., Zhu, P. F., Wang, Z. G. (1997). Plasma cytokines and endotoxin levels in patients with severe injury and their relationship with organ damage. *Injury,* 28(8): 509-513.

Jo, Y. H., Kim, K., Lee, J. H., Rhee, J. E., Lee, J. H., Kang, K. W., Rim, K. P., Hwang, S. S., Park, H. M. (2012). Heart-type fatty acid–binding protein as a prognostic factor in patients with severe sepsis and septic shock. *American Journal of Emergency Medicine,* 30(9): 1749-55.

Kan, W. H., Hsu, J. T., Ba, Z. F., Schwacha, M. G., Chen, J., Choudhry, M. A., Bland, K. I., Chaudry, I. H. (2008). p38 MAPK-dependent eNOS upregulation is critical for 17-estradiol-mediated cardioprotection following trauma-hemorrhage. *AJP: Heart and Circulatory Physiology,* 294(6): H2627-H2636.

Karalis, D. G., Victor, M. F., Davis, G. A., McAllister, M. P., Covalesky, V. A., Ross, J. J. Jr., Foley, R. V., Kerstein, M. D., Chandrasekaran, K. (1994). The role of echocardiography in blunt chest trauma: a transthoracic and transesophageal echocardiographic study. *The Journal of Trauma: Injury, Infection, and Critical Care,* 36(1): 53-58.

Karpati, P. C., Rossignol, M., Pirot, M., Cholley, B., Vicaut, E., Henry, P., Kévorkian, J. P., Schurando, P., Peynet, J., Jacob, D., Payen, D., Mebazaa, A. (2004). High incidence of myocardial ischemia during postpartum hemorrhage. *Anesthesiology,* 100(1): 30-6.

Kawaguchi, M., Takahashi, M., Hata, T., Kashima, Y., Usui, F., Morimoto, H., Izawa, A., Takahashi, Y., Masumoto, J., Koyama, J., Hongo, M.,

Noda, T., Nakayama, J., Sagara, J., Taniguchi, S., Ikeda, U. (2011). Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation,* 123(6): 594-604.

Keel, M., Trentz, O. (2005). Pathophysiology of polytrauma. *Injury,* 36(6): 691-709.

Keelan, P. C., Bielak, L. F., Ashai, K., Jamjoum, L. S., Denktas, A. E., Rumberger, J. A., Sheedy Ii, P. F., Peyser, P. A., Schwartz, R. S. (2001). Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation,* 104(4): 412-417.

Kia, M., Cooley, A., Rimmer, G., Macdonald, T., Barber, K., Manion, P., Shapiro, B., Socey, J., Iddings, D. (2006). The efficacy of B-type atriuretic peptide for early identification of blood loss in traumatic injury. *The American Journal of Surgery,* 191(3): 353-357.

Kim, L., Martinez, E., Faraday, N., Dorman, T. (2002). Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation,* 106(18): 2366-71.

King, D., Codish, S., Novack, V. & Barski, L. (2005). The role of cardiac troponin I as a prognosticator in critically ill medical patients: a prospective observational cohort study. *Critical Care,* 9(4): R390-5.

Kirchhoff, C., Leidel, B. A., Kirchhoff, S., Braunstein, V., Bogner, V., Kreimeier, U., Mutschler, W., Biberthaler, P. (2008). Analysis of N-terminal pro-B-type natriuretic peptide and cardiac index in multiple injured patients: a prospective cohort study. *Critical Care,* 12(5): R118.

Kirchhoff, C., Stegmaier, J., Bogner, V., Buhmann, S., Mussack, T., Kreimeier, U., Mutschler, W., Biberthaler, P. (2006). Intrathecal and systemic concentration of NT-proBNP in patients with severe traumatic brain injury. *Journal of Neurotrauma,* 23(6): 943-949.

Kistorp, C., Raymond, I., Pedersen, F., Gustafsson, F., Faber, J., Hildebrandt, P. (2005). N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality

and cardiovascular events in older adults. *JAMA : the Journal of the American Medical Association,* 293(13): 1609-1616.

Lagi, A., Meucci, E., Cencetti, S. (2008). Outcome of patients with elevated cardiac troponin I level after mild trauma. *The American Journal of Emergency Medicine,* 26(2): 248.e3-e5.

Lamonte, M. J., Fitzgerald, S. J., Church, T. S., Barlow, C. E., Radford, N. B., Levine, B. D., Pippin, J. J., Gibbons, L. W., Blair, S. N., Nichaman, M. Z. (2005). Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *American Journal of Epidemiology,* 162(5): 421-429.

Laupland, K. B., Svenson, L. W., Grant, V., Ball, C. G., Mercado, M., Kirkpatrick, A. W. (2010). Long-term mortality outcome of victims of major trauma. *Injury,* 41(1): 69-72.

Lee, M. A., Yatani, A., Sambol, J. T., Deitch, E. A. (2008). Role of gut-lymph factors in the induction of burn-induced and trauma-shock-induced acute heart failure. *International Journal of Clinical and Experimental Medicine,* 1(2): 171-80.

Levin, E. R., Gardner, D. G., Samson, W. K. (1998). Natriuretic peptides. *The New England Journal of Medicine,* 339(5): 321-328.

Li, S., Jiao, X., Tao, L., Liu, H., Cao, Y., Lopez, B. L., Christopher, T. A., Ma, X. L. (2007). Tumor necrosis factor-alpha in mechanic trauma plasma mediates cardiomyocyte apoptosis. *AJP: Heart and Circulatory Physiology,* 293(3): H1847-H1852.

Li, S., Tao, L., Jiao, X., Liu, H., Cao, Y., Lopez, B., Luan, R. H., Christopher, T., Ma, X. L. (2007). TNFα-initiated oxidative/nitrative stress mediates cardiomyocyte apoptosis in traumatic animals. *Apoptosis,* 12(10): 1795-1802.

Lim, W., Cook, D. J., Griffith, L. E., Crowther, M. A., Devereaux, P. J. (2006). Elevated cardiac troponin levels in critically ill patients: prevalence, incidence, and outcomes. *American Journal of Critical Care : an official publication, American Association of Critical-Care Nurses,* 15(3): 280-8.

Liu, S., Yin, T., Wei, X., Yi, W., Qu, Y., Liu, Y., Wang, R., Lian, K., Xia, C., Pei, H., Sun, L., Ma, Y., Lau, W. B., Gao, E., Koch, W. J., Wang, H., Tao, L. (2011). Downregulation of adiponectin induced by tumor necrosis factor α is involved in the aggravation of posttraumatic myocardial ischemia/reperfusion injury. *Critical Care Medicine,* 39(8):1935-43.

Maier, B., Lefering, R., Lehnert, M., Laurer, H. L., Steudel, W. I., Neugebauer, E. A., Marzi, I. (2007). Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma. *Shock,* 28(6): 668-674.

Mallett, S., Timmer, A., Sauerbrei, W., Altman, D. G. (2010). Reporting of prognostic studies of tumour markers: a review of published articles in relation to REMARK guidelines. *British Journal of Cancer,* 102(1)**:** 173-180.

Manson, J., Thiemermann, C., Brohi, K. (2011). Trauma alarmins as activators of damage-induced inflammation. *British Journal of Surgery,* 99(Suppl 1): 12-20.

Martin, M., Mullenix, P., Rhee, P., Belzberg, H., Demetriades, D., Salim, A. (2005). Troponin increases in the critically injured patient: mechanical trauma or physiologic stress? *The Journal of Trauma, Injury, Infection, and Critical Care,* 59(5): 1086-1091.

Martin, R. S., Kincaid, E. H., Russell, H. M., Meredith, J. W., Chang, M. C. (2005). Selective management of cardiovascular dysfunction in posttraumatic SIRS and sepsis. *Shock,* 23(3): 202-208.

McCann, C. J., Glover, B. M., Menown, I. B., Moore, M. J., McEneny, J., Owens, C. G., Smith, B., Sharpe, P. C., Young, I. S., Adgey, J. A. (2009). Prognostic value of a multimarker approach for patients presenting to hospital with acute chest pain. *American Journal of Cardiology,* 103(1): 22-28.

Mcgwin, G. Jr., Maclennan, P. A., Fife, J. B., Davis, G. G., Rue III, L. W. (2004). Preexisting conditions and mortality in older trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 56(6): 1291-1296.

Mcleod, A. A., Neil-Dwyer, G., Meyer, C. H., Richardson, P. L., Cruickshank, J., Bartlett, J. (1982). Cardiac sequelae of acute head injury. *British Heart Journal,* 47(3): 221-226.

McMahon, C. G., Lamont, J. V., Curtin, E., McConnell, R. I., Crockard, M., Kurth, M. J., Crean, P., Fitzgerald, P. (2012). Diagnostic accuracy of heart-type fatty acid–binding protein for the early diagnosis of acute myocardial infarction. *American Journal of Emergency Medicine,* 30(2): 267-74.

Meisler, R., Thomsen, A. B., Theilade, P., Abildstrøm, H., Borge, P., Treschow, M., Korsgaard, G. M., Rasmussen, S. W., Bødtker, S., Sylvest, A., Rasmussen, L. S. (2011). Age-related differences in mechanism, cause, and location of trauma deaths. *Minerva Anestesiologica,* 77(6): 592-597.

Meng, X., Harken, A. H. (2002). The interaction between Hsp70 and TNF-alpha expression: a novel mechanism for protection of the myocardium against post-injury depression. *Shock,* 17(5): 345-353.

Meyer, B., Huelsmann, M., Wexberg, P., Karth, G. D., Berger, R., Moertl, D., Szekeres, T., Pacher, R., Heinz, G. (2007). N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. *Critical Care Medicine,* 35(10): 2268-2273.

Meyers, D. G., Hoestje, S. M., Korentager, R. A. (2003). Incidence of cardiac events in burned patients. *Burns,* 29(4): 367-368.

Milzman, D. P., Boulanger, B., Rodriguez, A., Soderstrom, C. A., Mitchell, K. A., Magnant, C. M. (1992). Pre-existing disease in trauma patients: a predictor of fate independent of age and injury severity score. *The Journal of Trauma, Injury, Infection, and Critical Care,* 32(2): 236-43.

Mizushima, Y., Wang, P., Jarrar, D., Cioffi, W. G., Bland, K. I. & Chaudry, I. H. (2000a). Preinduction of heat shock proteins protects cardiac and hepatic functions following trauma and hemorrhage. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology,* 278(2): R352-R359.

Mizushima, Y., Wang, P., Jarrar, D., Cioffi, W. G., Bland, K. I., Chaudry, I. H. (2000b). Estradiol administration after trauma-hemorrhage improves cardiovascular and hepatocellular functions in male animals. *Annals of Surgery,* 232(5): 673-9.

Monaghan, S. F., Adams Jr., C. A., Stephen, A. H., Connolly, M. D., Gregg, S. C., Machan, J. T., Cioffi, W. G., Heffernan, D. S. (2012). Infections after trauma are associated with subsequent cardiac injury. *Journal of Trauma and Acute Care Surgery,* 73(5): 1079-1085.

Moore, F. A., Sauaia, A., Moore, E. E., Haenel, J. B., Burch, J. M., Lezotte, D. C. (1996). Postinjury multiple organ failure: a bimodal phenomenon. *The Journal of Trauma, Injury, Infection, and Critical Care,* 40(4): 501-10;.

Moosikasuwan, J. B., Thomas, J. M., Buchman, T. G. (2000). Myocardial infarction as a complication of injury. *Journal of the American College of Surgery,* 190(6): 665-70.

Morgan Jones, M., Grant, J. (2011). Complex trauma research in the UK-A rapid review of the funding landscape. Rand Europe.

Morita, S., Inokuchi, S., Yamagiwa, T., Aoki, H., Nakagawa, Y., Yamamoto, I. (2010). Tako-Tsubo-like left ventricular dysfunction with ST-segment elevation after central spinal cord injury: A case report. *Journal of Emergency Medicine,* 39(3): 301-304.

Morris, J. A., Mackenzie, E. J., Edelstein, S. L. (1990). The effect of preexisting conditions on mortality in trauma patients. *JAMA : the Journal of the American Medical Association,* 263(14): 1942-1946.

NAO. (2010). Major trauma care in England. Report by the Comptroller and Auditor General. National Audit Office.

Napolitano, L. M., Ferrer, T., Mccarter, R. J., Scalea, T. M. (2000). Systemic inflammatory response syndrome score at admission independently predicts mortality and length of stay in trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 49(4): 647-52.

National Trauma Institute. (2010). The Case for Trauma Funding.

Neal, M. D., Cushieri, J., Rosengart, M. R., Alarcon, L. H., Moore, E. E., Maier, R. V., Minei, J. P., Billiar, T. R., Peitzman, A. B., Sperry, J. L. (2009). Preinjury statin use is associated with a higher risk of multiple organ failure after injury: a propensity score adjusted analysis. *The Journal of Trauma, Injury, Infection, and Critical Care,* 67(3): 476-484.

Neideen, T., Lam, M., Brasel, K. J. (2008). Preinjury beta blockers are associated with increased mortality in geriatric trauma patients. *The Journal of Trauma: Injury, Infection, and Critical Care,* 65(5): 1016-1020.

NRES. (2011). Changes to the remit of Research Ethics Committees. National Research Ethics Service.

Nickel, E. A., Hsieh, C. H., Chen, J. G., Schwacha, M. H., Chaudry, I. H. (2009). Estrogen suppresses cardiac IL-6 after trauma-hemorrhage via a hypoxia-inducible factor 1 alpha-mediated pathway. *Shock,* 31(4): 354-358.

Niemann, J. T., Youngquist, S., Rosborough, J. P., Shah, A. P., Phan, Q. T., Filler, S. G. (2010). Infliximab attenuates early myocardial dysfunction after resuscitation in a swine cardiac arrest model. *Critical Care Medicine,* 38(40): 1162-1167.

Niven, D. J., Kirkpatrick, A. W., Ball, C. G., Laupland, K. B. (2012). Effect of comorbid illness on the long-term outcome of adults suffering major traumatic injury: a population-based cohort study. *American Journal of Surgery,* 204(2): 151-6.

Office for National Statistics. (2005). Mortality Statistics, causes 2005. DH2: no32, London.

Oreskovich, M. R., Howard, J., Copass, M. K., Carrico, C. J. (1984). Geriatric trauma: injury patterns and outcome. *The Journal of Trauma, Injury, Infection, and Critical Care,* 24(7): 565-72.

Ostrom, M. P., Gopal, A., Ahmadi, N., Nasir, K., Yang, E., Kakadiaris, I., Flores, F., Mao, S. S., Budoff, M. J. (2008). Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *Journal of the American College of Cardiology,* 52(16): 1335-1343.

Park, M. S., Salinas, J., Wade, C. E., Wang, J., Martini, W., Pusateri, A. E., Merrill, G. A., Chung, K., Wolf, S. E., Holcomb, J. B. (2008). Combining early coagulation and inflammatory status improves prediction of mortality in burned and nonburned trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 64(2 Suppl): S188-S194.

Perdue, P. W., Watts, D., Kaufmann, C. R., Trask, A. l. (1998). Differences in mortality between elderly and younger adult trauma patients: geriatric status increases risk of delayed death. *The Journal of Trauma, Injury, Infection, and Critical Care,* 45(4): 805-10.

Peter, J., Kirchner, A., Kuhlisch, E., Menschikowski, M., Neef, B., Dreßler, J. (2006). The relevance of the detection of troponins to the forensic diagnosis of cardiac contusion. *Forensic Science International,* 160(2-3): 127-133.

Platis, A., Yu, Q., Moore, D., Khojeini, E., Tsau, P., Larson, D. (2008). The effect of daily administration of IL-18 on cardiac structure and function. *Perfusion,* 23(4)**:** 237-242.

Polonsky, T. S., Mcclelland, R. L., Jorgensen, N. W., Bild, D. E., Burke, G. L., Guerci, A. D., Greenland, P. (2010). Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA : the Journal of the American Medical Association,* 303(16)**:** 1610-1616.

Post, F., Weilemann, L. S., Messow, C. M., Sinning, C., Münzel, T. (2008). B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. *Critical Care Medicine,* 36(11)**:** 3030-3037.

Prabhu, S. D. (2004). Cytokine-induced modulation of cardiac function. *Circulation Research,* 95(12)**:** 1140-1153.

Prasad, A., Lerman, A., Rihal, C. S. (2008). Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *American Heart Journal,* 155(3)**:** 408-417.

Probst, C., Zelle, B. A., Sittaro, N. A., Lohse, R., Krettek, C., Pape, H. C. (2009). Late death after multiple severe trauma: when does it occur and

what are the causes? *The Journal of Trauma, Injury, Infection, and Critical Care,* 66(4)**:** 1212-1217.

Quenot, J. P., Le Teuff, G., Quantin, C., Doise, J. M., Abrahamowicz, M., Masson, D., Blettery, B. (2005). Myocardial injury in critically ill patients: Relation to increased cardiac troponin I and hospital mortality. *Chest,* 128(4)**:** 2758-2764.

Raggi, P., Gongora, M. C., Gopal, A., Callister, T. Q., Budoff, M., Shaw, L. J. (2008). Coronary artery calcium to predict all-cause mortality in elderly men and women. *Journal of the American College of Cardiology,* 52(1)**:** 17-23.

Reich, D. L., Bodian, C. A., Krol, M., Kuroda, M., Osinski, T. & Thys, D. M. (1999). Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. *Anesthesia and Analgesia,* 89(4)**:** 814-822.

Riezzo, I., Pomara, C., Neri, M., Rossi, G., Fineschi, V. (2008). Cardiac contusion: ending myocardial confusion in this capricious syndrome. *International Journal of Cardiology*, 128(3): 107-10.

Riordan Jr, W. P., Cotton, B. A., Norris, P. R., Waitman, L. R., Jenkins, J. M., Morris Jr, J. A. (2007). Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. *The Journal of Trauma, Injury, Infection, and Critical Care,* 63(3)**:** 503-511.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Adams, R. J., Berry, J. D., Brown, T. M., Carnethon, M. R., Dai, S., De Simone, G., Ford, E. S., Fox, C. S., Fullerton, H. J., Gillespie, C., Greenlund, K. J., Hailpern, S. M., Heit, J. A., Ho, P. M., Howard, V. J., Kissela, B. M., Kittner, S. J., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Makuc, D. M., Marcus, G. M., Marelli, A., Matchar, D. B., Mcdermott, M. M., Meigs, J. B., Moy, C. S., Mozaffarian, D., Mussolino, M. E., Nichol, G., Paynter, N. P., Rosamond, W. D., Sorlie, P. D., Stafford, R. S., Turan, T. N., Turner, M. B., Wong, N. D., Wylie-Rosett, J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (2011). Heart Disease

and Stroke Statistics--2011 Update: A Report From the American Heart Association. *Circulation,* 123(4)**:** e18-e209.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., Bravata, D. M., Dai, S., Ford, E. S., Fox, C. S., Fullerton, H. J., Gillespie, C., Hailpern, S. M., Heit, J. A., Howard, V. J., Kissela, B. M., Kittner, S. J., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Makuc, D. M., Marcus, G. M., Marelli, A., Matchar, D. B., Moy, C. S., Mozaffarian, D., Mussolino, M. E., Nichol, G., Paynter, N. P., Soliman, E. Z., Sorlie, P. D., Sotoodehnia, N., Turan, T. N., Virani, S. S., Wong, N. D., Woo, D., Turner, M. B.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (2012). Heart Disease and Stroke Statistics--2012 Update: A Report From the American Heart Association. *Circulation,* 125(1): e2-e220.

Rumberger, J. A., Simmons, D. B., Fitzpatrick, L. A., Sheedy, P. F., Schwartz, R. S. (1995). Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation,* 92(8)**:** 2157-2162.

Saini, H. K., Xu, Y. J., Zhang, M., Liu, P. P., Kirshenbaum, L. A., Dhalla, N. S. (2005). Role of tumour necrosis factor-alpha and other cytokines in ischemia-reperfusion-induced injury in the heart. *Experimental and Clinical Cardiology,* 10(4)**:** 213-222.

Sakka, S G., Huettemann, E., Giebe, W., Reinhart K. (2000). Late cardiac arrhythmias after blunt chest trauma. *Intensive Care Medicine,* 26(6)**:** 792-5.

Salim, A., Hadjizacharia, P., Brown, C., Inaba, K., Teixeira, P. G. R., Chan, L., Rhee, P., Demetriades, D. (2008). Significance of troponin elevation after severe traumatic brain injury. *The Journal of Trauma, Injury, Infection, and Critical Care,* 64(1)**:** 46-52.

Sambol, J. T., Lee, M. A., Caputo, F. J., Kawai, K., Badami, C., Kawai, T., Deitch, E. A., Yatani, A. (2008). Mesenteric lymph duct ligation prevents trauma/hemorrhage shock-induced cardiac contractile dysfunction. *Journal of Applied Physiology,* 106(1)**:** 57-65.

Samuels, M. A. (2007). The Brain-Heart Connection. *Circulation,* 116(1)**:** 77-84.

Sangha, G. S., Pepelassis, D., Buffo-Sequeira, I., Seabrook, J. A., Fraser, D. D. (2012). Serum troponin I as an indicator of clinically significant myocardial injury in paediatric trauma patients. *Injury,* 43(12): 2046-50.

Sato, H., Tanaka, T., Kasai, K., Kita, T., Tanaka, N. (2007). Role of p38 mitogen-activated protein kinase on cardiac dysfunction after hemorrhagic shock in rats. *Shock,* 28(3): 291-299.

Sauaia, A, Moore, F. A., Moore, E. E., Moser, K. S., Brennan, R., Read, R. A., Pons, P. T. (1995). Epidemiology of trauma deaths: a reassessment. *The Journal of Trauma, Injury, Infection, and Critical Care,* 38(2): 185-93.

Schneider, E. B., Efron, D. T., Mackenzie, E. J., Rivara, F. P., Nathens, A. B., Jurkovich, G. J. (2011). Premorbid statin use is associated with improved survival and functional outcomes in older head-injured individuals. *The Journal of Trauma, Injury, Infection, and Critical Care,* 71(4)**:** 815-819.

Schroeppel, T. J., Fischer, P. E., Zarzaur, B. L., Magnotti, L. J., Clement, L. P., Fabian, T. C., Croce, M. A. (2010). Beta-adrenergic blockade and traumatic brain injury: protective? *The Journal of Trauma, Injury, Infection, and Critical Care,* 69(4)**:** 776-782.

Schultz, J. M., Trunkey, D. D. (2004). Blunt cardiac injury. *Critical Care Clinics,* 20(1)**:** 57-70.

Seguin, P., Laviolle, B., Maurice, A., Leclercq, C., Mallédant, Y. (2006). Atrial fibrillation in trauma patients requiring intensive care. *Intensive Care Medicine,* 32(3)**:** 398-404.

Seguin, P., Signouret, T., Laviolle, B., Branger, B., Mallédant, Y. (2004). Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. *Critical Care Medicine,* 32(3)**:** 722-726.

Semenas, E., Nozari, A., Wiklund, L. (2010). Sex differences in cardiac injury after severe haemorrhage and ventricular fibrillation in pigs. *Resuscitation,* 81(12)**:** 1718-1722.

Sharma, S. Jackson, P. G., Makan, J. (2004). Cardiac troponins. *Journal of Clinical Pathology,* 57(10)**:** 1025-1026.

Shimizu, T., Szalay, L. S., Hsieh, Y. C., Suzuki, T., Choudhry, M. A., Bland, K. I., Chaudry, I. H. (2006). A role of PPAR-γ in androstenediol-mediated salutary effects on cardiac function following trauma-hemorrhage. *Annals of Surgery,* 244(1)**:** 131-138.

Shoko, T., Shiraishi, A., Kaji, M., Otomo, Y. (2010). Effect of pre-existing medical conditions on in-hospital mortality: analysis of 20,257 trauma patients in Japan. *Journal of the American College of Surgeons,* 211(3)**:** 338-346.

Shorr, R., Crittenden, M., Indeck, M., Hartunian, S., Rodriguez, A. (1987). Blunt thoracic trauma analysis of 515 patients. *Annals of Surgery,* 206(2)**:** 200-205.

Simons, D. B., Schwartz, R. S., Edwards, W. D., Sheedy, P. F, Breen, J. F., Rumberger, J. A. (1992). Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. *Journal of the American College of Cardiology,* 20(5)**:** 1118-26.

Smith, D. P., Enderson, B. L., Maull, K. I. (1990). Trauma in the elderly: determinants of outcome. *Southern Medical Journal,* 83(2)**:** 171-7.

Søreide, K., Krüger, A. J., Vårdal, A. L., Ellingsen, C. L., Søreide, E., Lossius, H. M. (2007). Epidemiology and contemporary patterns of trauma deaths: changing place, similar pace, older face. *World Journal of Surgery,* 31(11): 2092-103.

Spielmann, S., Kerner, T., Ahlers, O., Keh, D., Gerlach, M., Gerlach, H. (2001). Early detection of increased tumour necrosis factor alpha (TNFα) and soluble TNF receptor protein plasma levels after trauma reveals associations with the clinical course. *Acta Anaesthesiologica Scandinavica,* 45(3)**:** 364-370.

Sprung, J., Abdelmalak, B., Gottlieb, A. (2000). Analysis of risk factors for myocardial infarction and cardiac mortality after major vascular surgery. *Anesthesiology,* 93(1)**:** 129-40.

Stangl, V., Baumann, G., Stangl, K., Felix, S. B. (2002). Negative inotropic mediators released from the heart after myocardial ischaemia-reperfusion. *Cardiovascular Research,* 53(1)**:** 12-30.

Stephens, G. A. (1922). Three thoracic emergencies. *The Lancet,* 200(5183)**:** 1382-1383.

Stewart, D., Waxman, K., Brown, C. A., Schuster, R., Schuster, L., Hvingelby, E. M., Kam, K., Becerra, S. (2007). B-Type Natriuretic Peptide levels may be elevated in the critically injured trauma patient without congestive heart failure. *The Journal of Trauma, Injury, Infection, and Critical Care,* 63(4)**:** 747-750.

Stolzmann, P., Phan, C., Desbiolles, L., Lachat, M., Pfammatter, T., Marincek, B., Prokop, M., Alkadhi, H. (2009). The heart of patients with aortic aneurysms: evidence from cardiac computed tomography. *Interactive Cardiovascular and Thoracic Surgery,* 9(5)**:** 769-773.

Suzuki, H., Sato, R., Sato, T., Shoji, M., Iso, Y., Kondo, T., Shibata, M., Koba, S., Katagiri, T. (2005). Time-course of changes in the levels of interleukin 6 in acutely decompensated heart failure. *International Journal of Cardiology,* 100(3)**:** 415-420.

Sybrandy, K. C., Cramer, J. M., Burgersdijk, C. (2003). Diagnosing cardiac contusion: old wisdom and new insights. *Heart,* 89(5)**:** 485-489.

Tanabe, M., Crago, E. A., Suffoletto, M. S., Hravnak, M., Frangiskakis, J. M., Kassam, A. B., Horowitz, M. B., Gorcsan, J. (2008). Relation of elevation in cardiac Troponin I to clinical severity, cardiac dysfunction, and pulmonary congestion in patients with subarachnoid hemorrhage. *American Journal of Cardiology,* 102(11)**:** 1545-1550.

Tang, A. L., Inaba, K., Branco, B. C., Oliver, M., Bukur, M., Salim, A., Rhee, P., Herrold, J., Demetriades, D. (2011). Postdischarge complications after penetrating cardiac injury: a survivable injury with a high postdischarge complication rate. *Archives of Surgery,* 146(9)**:** 1061-1066.

Tao, L., Liu, H R., Gao, F., Qu, Y., Christopher, T A., Lopez, B l., Ma, X l. (2005). Mechanical traumatic injury without circulatory shock causes

cardiomyocyte apoptosis: role of reactive nitrogen and reactive oxygen species. *AJP: Heart and Circulatory Physiology,* 288(6)**:** H2811-H2818.

TARN (2006). An Overview. Trauma Audit and Research Network.

Taylor, M. D., Tracy,. J. K., Meyer, W., Pasquale, M., Napolitano, L. M. . (2002). Trauma in the elderly: intensive care unit resource use and outcome. *The Journal of Trauma, Injury, Infection, and Critical Care,* 53(3)**:** 407-14.

Tornetta, P. 3rd., Mostafavi, H., Riina, J., Turen, C., Reimer, B., Levine, R., Behrens, F., Geller, J., Ritter, C., Homel, P. (1999). Morbidity and mortality in elderly trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* 46(4)**:** 702-6.

Tsai, Y. F., Liu, F. C., Lau, Y. T., Yu, H. P. (2011). Role of Akt-dependent pathway in Resveratrol-mediated cardioprotection after trauma-hemorrhage. *Journal of Surgical Research,* 176(1): 171-7.

Turan, A. A., Karayel, F. A., Akyildiz, E., Pakis, I., Uzun, I., Gurpinar, K., Atilmis, U., Kir, Z. (2010). Cardiac injuries caused by blunt trauma: an autopsy based assessment of the injury pattern. *Journal of Forensic Sciences,* 55(1)**:** 82-84.

Ungureanu-Longrois, D., Balligand, J. L., Kelly, R. A., Smith, T. W. (1995). Myocardial contractile dysfunction in the systemic inflammatory response syndrome: role of a cytokine-inducible nitric oxide synthase in cardiac myocytes. *Journal of Molecular and Cellular Cardiology,* 27(1)**:** 155-167.

Vallejo, J. G., Nemoto, S., Ishiyama, M., Yu, B., Knuefermann, P., Diwan, A., Baker, J. S., Defreitas, G., Tweardy, D. J., Mann, D. L. (2004). Functional significance of inflammatory mediators in a murine model of resuscitated hemorrhagic shock. *AJP: Heart and Circulatory Physiology,* 288(3)**:** H1272-H1277.

Van Snick, J. (1990). Interleukin-6: an overview. *Annual Review of Immunology,* 8**:** 253-278.

Van Vugt, R., Dekker, H. M., Deunk, J., Van Der Vijver, R. J., Van Vugt, A. B., Kool, D. R., Brink, M. Edwards, M. J. (2011). Incidental findings on

routine thoracoabdominal computed tomography in blunt trauma patients. *The Journal of Trauma, Injury, Infection, and Critical Care,* [Epub ahead of print].

Vergez, M., Pirracchio, R., Mateo, J., Payen, D., Cholley, B. (2009). Tako Tsubo cardiomyopathy in a patient with multiple trauma. *Resuscitation,* 80(9)**:** 1074-1077.

Viswanathan, K., Kilcullen, N., Morrell, C., Thistlethwaite, S. J., Sivananthan, M. U., Hassan, T. B., Barth, J. H., Hall, A. S. (2010). Heart-Type Fatty Acid-Binding Protein predicts long-Term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are Troponin-negative. *Journal of the American College of Cardiology,* 55(23)**:** 2590-2598.

Wang, M., Baker, L., Tsai, B. M., Meldrum, K. K., Meldrum, D. R. (2005). Sex differences in the myocardial inflammatory response to ischemia-reperfusion injury. *AJP: Endocrinology and Metabolism,* 288(2)**:** E321-E326.

Wardle, T. D. (1999). Co-morbid factors in trauma patients. *British Medical Bulletin,* 55(4)**:** 744-756.

Wexler, L., Brundage, B., Crouse, J., Detrano, R., Fuster, V., Maddahi, J., Rumberger, J., Stanford, W., White, R., Taubert, K. (1996). Coronary artery calcification: Pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. *Circulation,* 94(5)**:** 1175-1192.

WHO. (2004). Burden of Disease: DALYs. World Health Organization.

WHO. (2008). The top ten causes of death. Fact Sheet No 310. World Health Organization.

WHO. (2009). Global forum on trauma care. World Health Organization

Wu, T. T., Yuan, A., Chen, C. Y., Chen, W. J., Luh, K. T., Kuo, S. H., Lin, F. Y., Yang, P. C. (2004). Cardiac troponin I levels are a risk factor for mortality and multiple organ failure in noncardiac critically ill patients and have an additive effect to the APACHE II score in outcome prediction. *Shock,* 22(2)**:** 95-101.

Wu, X., Sha, H., Sun, Y., Gao, L., Liu, H., Yuan, Q., Zhang, T., Zhu, J., Zhou, L., Hu, J. (2011). N-Terminal Pro-B-Type Natriuretic Peptide in patients with isolated traumatic brain injury: a prospective cohort study. *The Journal of Trauma, Injury, Infection, and Critical Care,* 71(4)**:** 820-825.

Wutzler, S., Maegele, M., Marzi, I., Spanholtz, T., Wafaisade, A., Lefering, R; Trauma Registry of the German Society for Trauma Surgery. (2009). Association of Preexisting Medical Conditions with In-Hospital Mortality in Multiple-Trauma Patients. *Journal of American College of Surgeons.,* 209(1)**:** 75-81.

Yang, S., Choudhry, M. A., Hsieh, Y. C., Hu, S., Rue, L. W., Bland, K. I., Chaudry, I. H. (2006). Estrus cycle: influence on cardiac function following trauma-hemorrhage. *AJP: Heart and Circulatory Physiology,* 291(6)**:** H2807-H2815.

Yang, S., Hu, S., Choudhry, M. A., Rue III, L. W., Bland, K. I., Chaudry, I. H. (2007). Anti-rat soluble IL-6 receptor antibody down-regulates cardiac IL-6 and improves cardiac function following trauma–hemorrhage. *Journal of Molecular and Cellular Cardiology,* 42(3)**:** 620-630.

Yang, S., Hu, S., Hsieh, Y. C., Choudhry, M. A., Rue III, L. W., Bland, K. I., Chaudry, I. H. (2006). Mechanism of IL-6-mediated cardiac dysfunction following trauma-hemorrhage. *Journal of Molecular and Cellular Cardiology,* 40(4)**:** 570-579.

Yang, S., Zheng, R., Hu, S., Ma, Y., Choudhry, M. A., Messina, J. L., Rue, L. W., Bland, K. I., Chaudry, I. H. (2004). Mechanism of cardiac depression after trauma-hemorrhage: increased cardiomyocyte IL-6 and effect of sex steroids on IL-6 regulation and cardiac function. *AJP: Heart and Circulatory Physiology,* 287(5)**:** 2183-2191.

Yoshida, K., Ogura, Y., Wakasugi, C. (1992). Myocardial lesions induced after trauma and treatment. *Forensic Science International,* 54(2)**:** 181-9.

Yu, H. P., Hsieh, Y. C., Suzuki, T., Choudhry, M. A., Schwacha, M. G., Bland, K. I., Chaudry, I. H. (2007). The PI3K/Akt pathway mediates

the nongenomic cardioprotective effects of estrogen following trauma-hemorrhage. *Annals of Surgery,* 245(6)**:** 971-977.

Yu, H. P., Shimizu, T., Choudhry, M. A., Hsieh, Y. C., Suzuki, T., Bland, K. I., Chaudry, I. H. (2006). Mechanism of cardioprotection following trauma-hemorrhagic shock by a selective estrogen receptor-β agonist: up-regulation of cardiac heat shock factor-1 and heat shock proteins. *Journal of Molecular and Cellular Cardiology,* 40(1)**:** 185-194.

Zhang, Q., Raoof, M., Chen, Y., Sumi, Y., Sursal, T., Junger, W., Brohi, K., Itagaki, K., Hauser, C. J. (2010). Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature,* 464(7285)**:** 104-107.

Zou, L., Yang, S., Champattanachai, V., Hu, S., Chaudry, I. H., Marchase, R. B., Chatham, J. C. (2008). Glucosamine improves cardiac function following trauma-hemorrhage by increased protein O-GLcNAcylation and attenuation of NF-kappa B signaling. *AJP: Heart and Circulatory Physiology,* 296(2)**:** H515-H523.

Zou, L., Yang, S., Hu, S., Chaudry, I. H., Marchase, R. B., Chatham, J. C. (2007). The protective effects of Pugnac on cardiac function after trauma-hemorrhage are mediated via increased protein O-GlcNAc levels. *Shock,* 27(4)**:** 402-408.

Appendix I

Trauma Associated Cardiac Injury and Dysfunction (TACID)

Study Proposal

Barts and the London School of Medicine & Dentistry

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Synopsis

"Trauma Associated Cardiac Injury and Dysfunction" (TACID) is a programme designed to investigate cardiac-specific outcomes following major trauma. Trauma and heart disease are two of the world's most prevalent conditions and are the leading causes of death and disability. There is emerging evidence that trauma may have adverse effects on the heart, leading to long-term cardiac dysfunction and poor outcomes. Furthermore, as the elderly remain active for longer, they are more likely to sustain serious injury. Elderly patients are known to have worse outcomes following injury and pre-existing cardiovascular disease may contribute to this. Early identification of at-risk patients and cardiac dysfunction may allow targeted therapeutic intervention and reduce death and disability associated with major trauma.

We will assess the effect of trauma on the healthy heart; looking at the independent impact of direct cardiac trauma, extra-thoracic trauma and systemic hypotension on short and long term cardiac function. We will also investigate the influence of trauma on the diseased heart, investigating the contribution of pre-morbid cardiovascular disease on short and long-term outcomes in trauma patients. We hope to identify the optimal investigations for screening and delineation of post-traumatic cardiac injury. Finally, we wish to determine a reliable, sensitive and specific biomarker of cardiac trauma which may be used alone or in conjunction with other simple investigations to screen for cardiovascular risk following injury.

The initial investigations are structured as observational (A) and feasibility (B) studies to inform the design and conduct of subsequent larger cohort studies. Patients at risk of cardiac dysfunction will be enrolled into the study. These patients will have significant chest trauma, major extra-thoracic trauma, systemic shock or have risk factors for pre-existing cardiac disease. Patients expected not to survive the first 72 hours will be excluded.

In TACID (A), initially and at 24 hours, patients will have an ECG and a blood sample taken for markers of cardiac injury.

Patients with an adverse cardiac event will receive a transthoracic echocardiogram within the first 3 days.

Individuals will be followed up during the course of their admission for any cardiac-related morbidity. At discharge patients will have their current and premorbid disability and quality of life assessed using validated scoring systems. Patients who are alive at 12 months will be contacted to ascertain their current general and cardiac-specific health and quality of life.

A smaller subset of the above patients, in the order of 50, will be enrolled into TACID (B), a feasibility study to examine the role of more detailed cardiac investigations in the screening and diagnosis of cardiac injury and dysfunction. In addition to the above investigations patients will have a cardiac MRI scan. These patients will also undergo cardio-pulmonary exercise testing (CPEx) prior to discharge. At twelve months they will undergo further 24-hour Holter monitoring, Echo, MRI and CPEx testing and blood samples.

Study Aims & Hypotheses

Aim 1: To identify the effect of trauma on the healthy heart.

Hypothesis: 1A

Direct chest injury results in cardiac dysfunction. These patients have significant long-term cardiac dysfunction and worse outcomes.

Hypothesis: 1B

Severe tissue injury results in cardiac dysfunction. These patients have significant long-term cardiac dysfunction and worse outcomes.

Hypothesis: 1C

Systemic shock results in cardiac dysfunction. These patients have significant long-term cardiac dysfunction and worse outcomes.

Aim 2: To determine the effect of trauma on the diseased heart.

Hypothesis: 2A

The presence of pre-morbid cardiac disease results in worse outcomes in trauma patients.

Hypothesis: 2B

The presence of atherosclerotic disease, or its individual risk factors, results in worse outcomes in trauma patients.

Hypothesis: 2C

Pre-morbid cardiac medical therapy improves outcomes following trauma in at-risk patients.

Aim 3: To identify useful screening and diagnostic investigations for the presence of post-injury cardiac dysfunction.

Hypothesis: 3A

ECG is the most appropriate screening test for significant cardiac dysfunction following injury.

Hypothesis: 3B

Echo is the most appropriate screening test for significant cardiac dysfunction following injury.

Hypothesis: 3C

Echo is the most appropriate diagnostic tool of significant cardiac dysfunction following injury and its associated prognosis.

Hypothesis: 3D

CPEx testing is the most appropriate diagnostic tool of significant cardiac dysfunction following injury.

Hypothesis: 3E

Cardiac MRI is the most appropriate diagnostic tool of significant cardiac dysfunction following injury.

Aim 4: To identify the most reliable biomarker of cardiac trauma and subsequent cardiac dysfunction

Hypothesis: 4A

Troponin I is a sensitive biomarker of cardiac trauma and levels are predictive of the extent of cardiac dysfunction and subsequent cardiac complications.

Hypothesis: 4B

Heart type fatty acid binding protein (H-FABP) is a more sensitive, specific and reliable assessor of the presence of cardiac trauma and longer term outcomes.

Hypothesis: 4C

Brain Natriuretic Peptide (BNP) is a more sensitive, specific and reliable assessor of the presence of cardiac trauma and longer term outcomes.

Hypothesis: 4D

A combination of biomarkers, ECG and/or Echo is an effective screening tool for cardiac dysfunction following trauma.

Background

Trauma and heart disease are two of the world's most prevalent conditions and are leading causes of death and disability. There is emerging evidence that trauma may have adverse effects on the heart, leading to long-term cardiac dysfunction and poor outcomes. Furthermore, as the elderly remain active for longer, they are more likely to sustain serious injury. Elderly patients are known to have worse outcomes following injury and pre-existing cardiovascular disease may contribute to this. Early identification of at-risk patients and cardiac dysfunction may allow targeted therapeutic intervention and reduce death and disability associated with major trauma.

Trauma is the leading cause of death in those aged between one and forty. For every death due to injury, there are approximately two patients left with serious permanent disabilities[1]. Trauma is a serious financial burden to the NHS with a mean hospital cost per blunt trauma patient estimated at £9,530, and penetrating at £7,983[2,3] . Cardiovascular disease is the world's leading cause of death. In the UK, coronary heart disease is the single biggest killer with approximately 110,000 deaths in England alone[4].

Despite occurring together with increasing frequency, very little is known about the combination of trauma and cardiovascular disease. There is also a paucity of clinical evidence on the effect of trauma on the healthy heart. There is a reasonable body of laboratory evidence to suggest that trauma and its consequences have a significant detrimental effect on cardiac function, even when the heart is not directly injured in the event.

Studies have shown that trauma patients' risk of death following discharge is approximately twice as high as age and sex matched uninjured cohorts for up to ten years post injury[5]. Amongst the former, cardiovascular disease may account for nearly 25% of these deaths[6]. Most often, these are young active members of society with little or no associated background illnesses. Prior to injury, these patients typically lead healthy lives with normal life expectancies.

The reasons why this cohort is more likely to die once they have recovered from the acute injury are therefore crucial to establish. Cardiac dysfunction as a result of trauma may contribute either wholly or in part to these poor outcomes and therefore may represent an important target for preventing post-injury death and disability.

Certain retrospective studies suggest that patients with cardiovascular disease may have worse outcomes following injury. Patients over the age of 45 have worse outcomes following trauma, which increases linearly as patients get older. One study has shown that all cause mortality in trauma patients over 60 approached 20%[7]. Moreover, those over 65 have a two to threefold higher risk of death and worse outcomes than younger individuals[8]. These patients are presumed to have 'less physiological reserve' without a specific understanding on why they are less able to cope with trauma. Roughly 22% of our annual trauma team activations comprise patients over 45 (n=230) and those over 60 nearly 10% (n=90). These patients are in large numbers and are representative of significant trauma case loads in society. The effects of trauma on a diseased heart may lead to increased early and late deaths or long-term cardiac-related disability. Trauma-induced cardiac dysfunction may also have other systemic effects influencing outcomes in the elderly.

Data on trauma patients with pre-existing coronary heart disease remains scarce in spite of the prevalence of this disease and its burden on the NHS. According to the British Heart Foundation, in 2006 the prevalence of Coronary Heart Disease rose from 3.6% in those aged 45 to 54 to 28.6% in those aged 75 or over.

The true rate of asymptomatic cardiac disease is higher in all likelihood, as are risk factors such as diabetes and hypertension. A better understanding of the impact of background coronary artery disease or heart failure in the context of injury may lead to improved survival and reduced disability in this increasing patient population.

There is circumstantial evidence that patients on cardiovascular medication (beta blockers, statins) may have an improved outcome following injury. This data comes from very limited retrospective studies.

Prospective studies are needed to assess whether this effect is real and whether they may hold therapeutic potential for patients after injury.

The existence and severity of post traumatic cardiac disability is a poorly explored phenomenon in spite of the impact on both the individual and society. Patients' exercise tolerance and ability to return to their pre-injury existence are not well known. Patients who remain inactive and unable to work are more susceptible to mental health problems and developing diseases at later stages in life. They represent significant cost to the NHS yet the prevalence and extent of cardiac disability following injury has not been quantified. The study will seek to identify the degree to which patients have cardiac dysfunction following trauma and the impact this has on their activities of daily living. The assessment of post-traumatic cardiac physiology, through CPEx testing, imaging and patient surveys will enable a better understanding of the impact and significance of longer term abnormal cardiac function secondary to injury.

Background

Aim 1: To identify the effect of trauma on the healthy heart

Trauma is the leading killer of young people. There is evidence that chest injuries and haemorrhage can lead to longer term cardiac dysfunction. This might lead to a higher protracted risk of death in discharged trauma patients due to cardiovascular diseases and a reduction in function due to cardiac disability.

Hypothesis 1A:

- Clinical data have shown that direct blunt chest trauma results in cardiac injuries in up to a third of cases. Longer term follow up of these subjects has shown a greater susceptibility to potentially fatal cardiac events and a decline in cardiac function in up to 50% of patients with injuries to the heart[9]. In patients 65 or over, significant chest injuries were shown to cause adverse outcomes in 16% of the cohort[10].
- The numbers in these studies are small, however, and the degree to which chest trauma affects cardiac function and the duration of this effect requires quantifying and qualifying. It has also not been established whether cardiac function, if disrupted, ever returns to normal.

Hypothesis 1B:

- Cardiovascular and respiratory dysfunction account for over half the mortality of patients with severe traumatic brain injury where death is not neurological in origin[11]. Multiply severely injured patients, as defined by an injury severity score (ISS) >15 are known to have worse short and long-term outcomes.
- The impact, however, of severe tissue injury on the heart has not been fully explored and myocardial function of these patients following discharge has not been examined over the long term.

Hypothesis 1C:

- In clinical studies, cardiac ischaemia occurs in over 50% of patients with postpartum bleeding and cardiac dysfunction occurs in sepsis and SIRS[12,13]. Animal models have confirmed that trauma haemorrhage results in acute cardiac dysfunction through a variety of inflammatory and other pathways[14,15,16, 17,18].
- Few studies have verified this phenomenon in trauma and the duration and extent of cardiac dysfunction remains unknown.

A small number of studies have examined the effect of both shock and severe generic trauma on the heart and little is known on longer term outcomes in these patients and the degree and length to which cardiac physiological function is affected. Moreover, there remains a paucity of evidence on the effect of direct trauma to the heart. There is a lack of data on why trauma patients are more susceptible to death at later stages and how this might be prevented. It is not known who represents a high-risk patient for subsequent cardiac complications.

Establishing these facts will result in a better understanding on the effect of trauma on the heart thereby potentially enabling in the future a significant reduction in both cardiac associated morbidity and mortality following trauma.

Aim 2: Assess the effect of trauma on the diseased heart

There is some retrospective data to suggest that patients with pre-existing cardiovascular disease fare worse in trauma. The presence of diabetes is associated with worse morbidity outcomes whilst there are suggestions that cardiovascular medications may have protective effects in trauma patients.

Hypothesis 2A:

- There is a little retrospective evidence that patients with pre-existing heart disease have worse outcomes in trauma.

- Age, with greater associated co-morbidities is a risk factor for higher death rates, longer hospital stay and poorer outcomes.

  Detailed evidence on the impact of pre-injury cardiovascular disease is lacking including its true incidence, and the short and longer term outcome of this specific group of patients is not known.

Hypothesis 2B:

- There is evidence that diabetics have worse morbidity compared to age and injury severity matched counterparts[19]. Furthermore, poor glycaemic control has been shown to result in poorer outcomes in SIRS and sepsis.
- Few studies, however, have analysed in detail the impact that risk factors such as hypertension and hypercholesterolaemia have in trauma patients.

Hypothesis 2C:

- There may be a protective effect associated with pre-trauma B-blockers. Statins are associated with improved in-hospital survival amongst older patients following injury[20,21].
- There remain, however, many questions on the effect that cardiovascular medicines have on outcomes. It has not been examined whether all severely injured patients should be prescribed any or a combination of cardiovascular medications.

In spite of the massive health implications of both heart disease and trauma, very little is known on what effect pre-existing cardiac illness has on injured patient outcomes. There is sparse evidence on both short and long term outcomes in patients with heart disease pre-injury, and whether outcomes are influenced by diabetic and cardiovascular medications. Identifying whether these patients are at greater risk of mortality and morbidity would then provide impetus for developing means of improving survival and minimising the longer term effects of injury.

It would also facilitate further studies identifying the role of cardiac and diabetic medications, and whether these have a role in all trauma patients and not just those with coronary artery disease or diabetes.

Aim 3: To identify useful screening and diagnostic investigations for the presence of post-injury cardiac dysfunction.

ECGs and Echos are used in current clinical practice to detect cardiac injuries. They are safe, cheap and reliable. MRI perfusion scans are useful diagnostic investigations in trauma although seldom used. CPEx has not been explored.

Little is known on these investigations abilities' to prognosticate or screen cardiac injuries.

Hypothesis: 3A

- ECGs have been shown in many studies to be a reasonable indicator of cardiac injury and may correlate with severity of injury and outcome. Cheap, quick and safe to patients, ECGs are now commonly used in the detection of cardiac injuries, mostly following blunt chest trauma.
- The extent to which ECGs are useful screening tools in post-injury cardiac dysfunction is vague. Cardiac abnormalities following trauma may manifest on ECGs, and may continue to do so at least twelve months post injury. The sensitivity and specificity of ECGs to independently screen for cardiac dysfunction needs confirmation.

Hypothesis: 3B & 3C

- There is good evidence that the diagnosis of cardiac injuries using echocardiograms is reliable. Identification of cardiac function, volume status and wall abnormalities have been evaluated in the intensive care setting and the investigation is both safe and cheap[22].
- Echocardiograms have not been extensively used in the diagnosis of post traumatic cardiac dysfunction and evidence on the subject remains insufficient

Hypothesis: 3D

- The use of CPEx to assess cardiopulmonary physiological function is now commonplace in patients planned for major elective surgery. Its ability to detect cardiac dysfunction to this end is well documented and relied upon.
- The role of CPEx testing has not been assessed in trauma and therefore the extent to which patient's exercise tolerance and cardiac function following trauma are compromised is not known.

Hypothesis: 3E

- MRI is safe and can discriminate between cardiac contusions and peri-traumatic myocardial infarctions.
- There is also evidence to suggest that MR stress testing may indicate patients at risk of future cardiac events which might validate its use as a screening tool of cardiac dysfunction[23].
- The use of MRI as an investigation in the screening and diagnosis of cardiac dysfunction has not been attempted in trauma patients.

In spite of the volume of evidence demonstrating that the above imaging modalities are effective in demonstrating cardiac damage, there is little evidence assessing their ability to detect cardiac dysfunction in trauma patients. In addition, little is known on the optimal timing of undertaking these investigations, which is most reliable, and finally which would give the best indication of patients at risk of cardiac complications in the longer term.

Aim 4: To identify the most reliable biomarker of cardiac trauma and subsequent cardiac dysfunction

Troponin I is used in clinical practice as a biomarker of cardiac injury, particularly in blunt chest trauma. Studies have shown it to be specific but poorly sensitive. Other cardiac biomarkers such as Troponin T and CK-MB have been demonstrated to be relatively invalid indicators of cardiac dysfunction and are discouraged in the literature[24]. There is no significant current evidence on both BNP and H-FABP in trauma.

Hypothesis: 4A

- Troponin I has been shown to be a biomarker of cardiac damage both in studies of trauma and critical care[25]. In critical care, following orthopaedic and vascular surgery and in sepsis, a rise in Troponin I may be suggestive of increased mortality and cardiac complications[26,27,28].
- The extent to which Troponin I is sensitive and the significance of its levels are still not fully known. Objective parameters indicating prediction of death or likelihood of future adverse cardiac events have not been set.

Hypothesis: 4B

- There is mounting evidence that H-FABP is a reliable biomarker of myocardial infarction and other acute coronary syndromes. Furthermore, there is increasing data demonstrating its ability to detect long term mortality and cardiac events[29,30,31].
- H-FABP has not been investigated in trauma.

Hypothesis: 4C

- B type Natriuretic Peptide has been studied in sepsis and with regard to cardiac surgery and failure. On the one hand its use is discouraged whilst conversely other studies have endorsed its role in detecting myocardial injury[32,33].
- Little is known on its validity both in detecting myocardial injuries and as a prognostic indicator in trauma.

Hypothesis: 4D

- Studies have demonstrated that when used in combination Troponin I and ECGs are sensitive detectors of cardiac injury. The grouping of Troponin I with other biomarkers is no more sensitive than the former in isolation.
- The use of H-FABP/BNP/Troponin I together has not been assessed nor indeed has the use of routine screening Echos as a screening tool of cardiac damage.

Moreover, a sufficiently reliable combination of tests to indicate future adverse cardiac outcomes remains undetermined.

A highly sensitive biomarker of cardiac trauma remains undiscovered. Furthermore, the extent to which Troponin I has prognostic value in subsequent cardiac events in patients following injury is not known. A sensitive and specific combination of cardiac biomarkers and tests has not been elucidated.

Goals and Expected Outcomes

Overall Goal

Both the short and long term effects on the heart of severe trauma, shock and direct cardiac injury remain largely unknown. By undertaking this study, we hope to identify what happens to patients following injury and whether clinical or subclinical cardiac dysfunction exists and contributes to poorer mortality and morbidity outcomes. By following these patients over the course of a year, we will establish whether myocardial damage persists, and what, if any, consequence that has. We will examine post-traumatic exercise tolerance and cardiac disability and determine why patients die at later stages following injury, and whether the heart is implicated.

This research will establish "at risk" groups of subsequent cardiac mortality and morbidity following trauma and which investigations will best ascertain risk and prognosis. In undertaking this research, we aim to provide baseline data to enable future larger prospective studies to be undertaken. Using this data, research could examine, as an example, the utility of cardiac medications in trauma and thus expand knowledge and improve care in this poorly understood area.

Aim1:

- Understand the long and short term effects of direct trauma to the heart
- Determine the impact of shock on cardiac function
- Establish the consequence of severe generic trauma on myocardial behaviour
- Identify areas which require further research on the matter of preventable long term death and disability from trauma

Aim 2:

- Establish the effect of pre-morbid heart disease on trauma outcomes

- Establish the effect of hypertension, hypercholesterolaemia and diabetes and age on trauma outcomes
- Encourage further research on the mechanisms behind why these patients have worse outcomes
- Analyse means of reducing the impact of trauma on this cohort
- Determine the impact of cardiovascular medications on trauma outcomes

Aim 3:

- Establish which investigation best assesses cardiac dysfunction and its prognosis
- Determine the best time frame in which to undertake particular imaging modalities
- Provide clinicians with universal guidance on the assessment of myocardial damage in trauma.
- Highlight which patients need close follow up and cardiological supervision

Aim 4:

- Determine the sensitivity of Troponin I in detecting traumatic myocardial injury
- Establish the reliability of Troponin I as a prognostic indicator
- Determine the reliability of H-FABP in the detection and prognostication of cardiac injuries
- Determine the reliability of BNP in the detection and prognostication of cardiac injuries
- Improve the detection of cardiac injuries and better determine who is at risk of cardiac complications
- Establish those who do not require admission for surveillance or cardiac monitoring and eventually reduce the cost of unnecessary inpatient stays
- To validate a combination of biomarkers

TACID (A)

Prospective Cohort Study of Cardiac Dysfunction in Trauma (numbers anticipated = approx. 300)

Inclusion criteria

- Trauma patients meeting trauma team activation criteria

Exclusion criteria

- Not expected to survive > 72 hours
- Pregnant
- Prisoners
- Patients under 16 years of age

Interventions

- Blood sampling: Baseline, 24 hours & 72 hours
- ECG: Baseline, 24 & 72 hours
- Echocardiogram in patients with adverse cardiac events
- Premorbid cardiac risk factors, medications, cardiac-specific disability/Quality of Life

Outcomes

- Cardiac events during admission (arrythmias, infarctions, failure, angina and cardiac death)
- Requirement for cardiac medication during admission (B-blockers, inotropes, diuretics, Ca channel blockers, ACE inhibitors, Angiotensin II inhibitors)
- Mortality (30 day, six months and one year)
- Length of hospital stay, length of ITU stay, ventilator free days
- Cardiac-specific disability/ Quality of Life at discharge or 30 days (whichever is first)

TACID (B)

Comprehensive Cardiac Assessment Feasibility Sub study

In addition to the former, a subgroup of 50 patients from the cohort above will be recruited into a more comprehensive cardiac assessment sub study.

Inclusion criteria

Subset of patients from cohort above with one or more of the following:

- Severe thoracic injury (AIS>3)
- Severe extra-thoracic injury (ISS > 24)
- Severe traumatic brain injury (AIS>2)
- Severe systemic shock (Systolic BP < 80 during ED phase)
- Age 60 or over
- Known significant heart disease or cardiovascular risk factors
- Evidence of cardiac injury on admission/24 hr ECG, cardiac enzymes, CT
- Evidence of pre-existing cardiovascular disease on admission investigations

Exclusion criteria

- Patients without consent
- Prisoners
- Patients transferred from other hospitals
- Patients likely to have difficulty with study related tasks

Investigations (Table 1)

- Echo – At 24 hours and again at 12 months
- ECG – Admission, 24hrs, 72hrs and 12 months
- Blood sampling - Admission, 24hrs, 72hrs and 12 months
- CT Calcium score calculated if patient has a CT Chest on clinical grounds
- Cardiac MRI - Within first 14 days and at 12 months
- Cardiopulmonary Exercise testing Prior to discharge and at 12 months

- Patients with pre-existing cardiovascular disease and/or risk factors will have CT Coronary Angiography

Outcomes

- In-hospital cardiac events (arrythmias, infarctions, failure, angina and cardiac death)
- Requirement for cardiac support/medication in-hospital
- Discharge or 30-day cardiac disability/Quality of Life
- 12-month disability
- Length of hospital stay, length of ITU stay, ventilator free days
- Mortality (30 day, six months and one year)

Table 1. Summary of Cardiac Assessment Feasibility Sub study

	Admission	**24 hours**	**72 hours**	**3-14 days**	**Discharge**	**12 months**
Biomarkers	✓	✓	✓	X	X	✓
ECG	✓	✓	✓	X	X	✓
CT chest	✓	X	X	X	X	X
Echo	X	✓	X	X	X	✓
MRI	X	X	X	✓	X	✓
CPEx	X	X	X	X	✓	✓
Questionnaire	X	X	X	X	✓	✓

Proposed Outcome Surveys

1. Minnesota
2. SF-36
3. EQ-5D

Procedures

All investigations, with the exception of the CT scan, will be performed at least twice in order to compare the results of the test in the acute and the longer term settings. This will permit a comparison of cardiac morphology and function in these time frames, and indicate the best period in which to perform these investigations in future, outside the context of this study.

Blood Samples (TACID A&B)

Trauma patients will have blood samples drawn to measure Troponin I, H-FABP and BNP levels. Samples will be drawn on admission, at 24 and 72 hours and thereafter at twelve months.

There is discomfort associated with having blood taken and certain patients have needle phobia. Whenever possible we will therefore coordinate our blood draws with those of clinical need, to reduce the number of needle-sticks. Most major trauma patients have an arterial or central line placed and hence most blood draws will involve no pain.

Electrocardiogram (ECG) (TACID A&B)

An ECG will be performed on admission, at 24 and 72 hours and at twelve months. ECGs are performed on admission in trauma patients regardless of the study and the result of this initial investigation may be a determinant of whether the patient is enrolled in the research. ECGs are cheap and safe and cause no distress to patients. They can be performed very quickly and therefore impose minimal time delays on patients awaiting transfer to theatre, angiography or other investigations. The purpose of repeating this test at various stages of seeing the patient is to determine whether ECG changes incurred as a result of traumatic damage to the heart reverse, and in the event, in what time frame. In addition, in those who have abnormal ECGs prior to injury, we seek to determine whether any changes occur in their traces and over what period this may occur.

Computerised Tomography (CT) chest (TACID A&B)

A CT of the chest will be performed on admission in all trauma patients in whom it is clinically indicated. This decision will be made by the trauma team leader, independent of this study. If this scan is abnormal, the patient will be included in the project, on the basis that they either have evidence of pre-existent heart disease, or that changes incurred as a result of the traumatic episode are sufficient as to indicate significant chest trauma. Only the CT scan performed on admission will be interpreted for the purposes of this research, although others may be undertaken during the patient's admission if clinically required. A CT chest is associated with large doses of radiation and this is why we will not request the investigation unless clinically warranted. Transfer to the CT room and into the scanner itself is associated with time delays and is potentially hazardous to patients with spinal injuries. Furthermore access to the patient during scanning can be problematic.

Given the difficulties and potential dangers with CT, we will only request Calcium scores in patients who clinically require the investigation and will not undertake it independently for the purposes of the study only.

There is evidence, however, in the literature that in spite of the radiation, a CT scan is usually indicated in severely injured patients given its sensitivity and superiority to chest radiographs and other imaging modalities in detecting abnormalities of the heart, lungs, great vessels and mediastinum.

Echocardiogram (Echo) (TACID A&B)

A transthoracic Echo will be performed in patients with adverse cardiac events (A) or after 24 hours and at 12 months (B). This investigation will provide a cheap, reliable and safe means of assessing the heart, both in terms of structure, appearance and function. There can be discomfort to the patient when applying the probe to an injured chest wall, although the technician will ensure the patient has good analgesia and will undertake the study with due care to minimise this effect.

Echo will highlight new cardiac problems due to trauma, whilst also indicating patients with pre-existing heart disease with wall and valve defects, morphological abnormalities and lowered ejection fractions. The investigation may be of clinical benefit to patients by giving their treating doctors information on cardiac function and volume status. It will provide us with data on acute cardiac dysfunction and the structural changes that may occur as a result of both direct cardiac trauma and generic injury and shock. Twelve months later, images can be compared with the admitting investigation and provide the study with information on what the long-term consequences of trauma are on heart appearance and function.

Magnetic Resonance Imaging (MRI) (TACID B only)

MRI perfusion studies will be performed between 3 and 14 days and again at twelve months. The purpose of the MRI will be to assess myocardial blood flow and the degree of cardiac injury. The rationale for timing the scan at least three days post admission is to ensure that patients are being scanned when deemed clinically stable, when the process of imaging the trauma patient places them at minimal risk. As with CT, transferring patients to MRI can be problematic and care needs to be taken with monitoring and anaesthetic equipment. Once in the scanner, patients are difficult to access. We will ensure, therefore, that patients are transferred to MRI only when they are awake, stable, self-ventilating and accompanied by appropriately trained staff that can safely monitor patients throughout the process of scanning, from ward transfer to moving the patients in and out of the MRI suite. This first MRI will be conducted no later than two weeks post admission in order to ensure we get images that will reflect the acute state of the heart. Although not routinely used, MRIs are sometimes required in patients with head and spinal injuries and in the event, we will combine perfusion scans with those of the spinal tract. At twelve months, we will compare the MRI images to those on admission and assess, if any, the degree to which

cardiac morphology and function has changed. There is also evidence to suggest that MRI perfusion scans have prognostic value in cardiac disease. Hence we will combine images with the patient's physiological state and any cardiac events that may occur over the course of the year over which we will follow them up to determine the extent to which this is true.
MRI is a safe investigation, contra-indicated only in patients with non-compatible metal work. Naturally these patients will be excluded from this test, but all others will be scanned if they consent.

Cardio-Pulmonary Exercise Testing (CPEx) <u>(TACID B only)</u>

CPEx testing will be used for the first time in trauma. The purpose of this test will be to assess the patient's exercise tolerance following a traumatic episode. CPEx is now routinely used in the routine pre-operative assessment of older patients with significant co-morbidities about to undergo major surgery. There is no evidence in the literature of contra-indications and certainly anecdotally this is a safe test. There will be a doctor at all times with the patient during this investigation and thus the individual will be medically supervised throughout CPEx testing.

It will be conducted prior to the discharge of the patient and again at one year following the patient's injury. We will be assessing the individual for evidence of decreased exercise tolerance, with lowered cardiopulmonary physiological ability.

This will determine whether and to what extent trauma causes longer term cardiac disability.

Questionnaires <u>(TACID A&B)</u>

The questionnaires used are most appropriate to trauma patients and have been validated to this end. Patients will be asked to complete them on discharge and at one year post injury. The purpose of the questionnaire is to obtain a subjective assessment of the patient's state, both in the acute and longer term setting.

Risks & Benefits

Risks

All aspects of the study will always be undertaken minimising patient risk and discomfort. Patient care will never be compromised or delayed for the purposes of the study. The risks of blood sampling include potential bruising at the site of venepuncture and discomforts limited to needle puncture (where no arterial line is already in place).

Computerised Tomography scans are well described sources of radiation with small but nevertheless measurable cancer risks. Patients in the study will have only one CT scan performed and this will be indicated on the basis of their mechanism of injury and clinical state on presentation to the Emergency Department. No additional CT imaging will be performed for the study however further scans may be clinically indicated during the course of the patients' admission independent of the study.

Echocardiography is widely reported throughout the literature as both a safe and useful clinical tool. The complications of this procedure, when performed as a transoesophageal approach, however, primarily relate to the gastrointestinal, cardiovascular, and respiratory systems, and include infection, toxic drug reaction, local reaction through contamination of the probe, and ultrasound cavitation. For this reason we will be only using transthoracic Echos.

Magnetic Resonance Imaging is a safe and well tolerated procedure with only few patients at risk of claustrophobic symptoms during scanning. Naturally, scans will not be undertaken in all those for whom MRI is contra-indicated (implants, pacemakers etc…).

There is no evidence in the literature of risks associated with CPEx testing.

We will record all adverse events associated with the study and review them both as they occur and collectively at monthly intervals.

Participation in research may involve some degree of loss of privacy. This risk will be minimised, however, by our data protection methods.

Furthermore, we are not performing any tests that may subsequently result in significant personal, financial or social detriment to our research subjects. We will make every effort to ensure that our data is secure and patients' privacy is protected.

Benefits

Because this is primarily an observational study, there will be no direct benefit to patients. The study reveals, however, the potential to identify those with previously unrecognised cardiac disease, thereby facilitating the process of further managing these patients and controlling risk factors for cardiovascular disease. This may in time lead to a subsequent reduction in cardiac events.

Patients are also given the opportunity to be followed up over a longer and more intensive course than patients outside the study thus providing the former with greater support and prolonged medical input.

In terms of benefits to society, trauma remains the leading cause of death in patients between 1 and 40 years of age, and is the 5th most frequent cause of death overall.

The World Health Organization predicts that by 2020 road traffic accidents alone will be the 3rd leading cause of death worldwide. To better comprehend, therefore, the physiological responses to shock and generic trauma from a cardiac perspective will enable, in future, the better delivery of care of this large cohort of patients.

As mentioned previously, Coronary Heart Disease is the leader killer in the UK, and by better understanding its impact in the trauma patient we hope that society will benefit through the evolution of care of these patients. A large database will result from this study, and should facilitate further investigations in this field. Eventually, through this research, we will hopefully understand the role of cardiac medications in trauma, the effect of shock on the diseased heart and may even be able to stratify and prognosticate injured patients with heart disease to name but a few examples.

Furthermore, once the study is completed we hope to demonstrate how best to identify the presence of cardiac dysfunction or injury and how to quantify it. We will highlight the best time frame under which to undertake this and what prognosis to expect. This will help guide clinicians on who needs admission and who is safe to be discharged, who needs follow up and who does not. This targeted approach will help relieve some of the financial and resources burden incurred through inappropriate admissions and investigations. It will direct doctors towards those at risk of adverse cardiac events thereby ensuring these patients are managed in such a way as to minimise long term morbidity and mortality resulting from the heart.

Risk to Benefit Analysis

Patients may have unrecognised heart disease diagnosed and thus will benefit from secondary preventative measures that can be implemented to avoid subsequent cardiac events. They will also be followed up more intensely and longer than would ordinarily be the case.

The bulk of the study is observational, and the interventions undertaken place the patients at no or minimal harm and inconvenience. The project has been designed to reduce discomfort and any risks to the study subjects. Patients care will not be compromised in any way for the purposes of the study.

Consent

Informed Consent will be obtained by the chief investigator or co-investigators. If patients are deemed unable to consent for themselves a legally authorised representative will be asked to give permission to enrol the patient into the study. The Trauma Team Leader, independent of the research, will give consent on behalf of the patient for the first blood draw, ECG and CT chest which will take place during resuscitation in the Emergency Department. Emergency consent only will be required for this cohort, enrolled into the larger cohort study.

All trauma patients routinely have bloods taken in the resuscitation room during the primary survey and thus this study will induce no extra stress or morbidity as a result of blood drawn for the study. An ECG is performed as standard during resuscitation and poses no risk to the patient.

If a CT is deemed necessary by the trauma team leader, as is the case in all severely injured patients, it will be performed on clinical grounds and data required for the study can be elucidated from these images. The trauma patient is therefore not inappropriately exposed to radiation for the purposes of research.

Where patients are awake with relatively minor injuries, and deemed able to give informed consent to take part in the research we will undertake this as soon as possible. However, as we are able to use blood from the initial draw for trauma management, and ECGs and CT will be clinically indicated, we will still request a professional legally appointed representative consent. To consent a patient in the initial phases of trauma evaluation would be difficult and might compromise patient care.

This research study focuses on both the early and later stages of injury, from admission through to twelve months post trauma. The majority of severely injured trauma patients present unconscious from a traumatic brain injury, hypovolaemic shock, intubated in the prehospital phase of their care or acutely in the emergency department. These patients form an

important cohort of the study as we seek to determine whether patients with severe injury develop post-traumatic cardiac dysfunction. These patients are likely to be enrolled into the sub-study and will therefore need to consent for themselves, and agree to be followed up over the course of the year. Patients who are not unconscious have recently been through a major psychologically disturbing event, may have been a victim of violence and are frequently in pain. Hence they may be unable to comprehend, or it may be inappropriate to discuss the details of a complex research trial at this time.

The patient will be examined regularly to determine if and when he/she is able to consent for himself/herself even if surrogate consent has already been obtained. While the duration of unconsciousness for trauma patients is very variable, most will regain consciousness in 2-10 days. When awake, the trial and all study procedures performed and yet to be completed will be explained to the patient. Subjects will once again be given the option to give consent to continue participation or to withdraw from the study. Until the patient is able to consent for themselves the consent from the patient's legally authorised representative will be sought.

All study procedures already performed in addition to those yet to be completed will be explained, and their consent for ongoing participation will be requested. They will also be informed that they have the right to deny continued involvement on the patient's behalf.

If a patient remains unidentified, the police and hospital social workers will continue to assist the investigator in identification of the patient. Daily attempts to locate family to discuss the patient's condition and study involvement will be made. Documentation of these attempts will be made in the patient's medical record.

A quarterly report will be sent to the LREC regarding the Consent Process. It will include the number of subjects entered into the study, the quantity of whom consented prior to entry, the number of subjects for whom

consent was waived, the number of subjects or surrogates who later refused or agreed to continue in the study and ongoing study results available.

Bibliography

1. https://www.tarn.ac.uk/content/images/53/Overview%2006.pdf (Accessed 06/06/09)
2. Michael C Christensen, Saxon Ridley, Fiona E Lecky, Vicki Munro, Stephen Morris. Outcomes and costs of blunt trauma in England and Wales. Crit Care. 2008;12(1):R23
3. Christensen MC, Nielsen TG, Ridley S, Lecky FE, Morris S. Outcomes and costs of penetrating trauma injury in England and Wales. Injury. 2008 Sep;39(9):1013-25
4. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Healthcare/Longtermconditions/Vascular/Coronaryheartdisease/DH_120 (Accessed 09/06/09)
5. Cameron CM, Purdie DM, Kliewer EV, McClure RJ. Long-term mortality following trauma: 10 year follow-up in a population-based sample of injured adults. J Trauma. 2005 Sep;59(3):639-46
6. Probst C, Zelle BA, Sittaro NA, Lohse R, Krettek C, Pape HC. Late death after multiple severe trauma: when does it occur and what are the causes? J Trauma. 2009 Apr;66(4):1212-7
7. Tornetta P 3rd, Mostafavi H, Riina J, Turen C, Reimer B, Levine R, Behrens F, Geller J, Ritter C, Homel P. Morbidity and mortality in elderly trauma patients. J Trauma. 1999 Apr;46(4):702-6
8. Taylor MD, Tracy JK, Meyer W, Pasquale M, Napolitano LM. Trauma in the elderly: intensive care unit resource use and outcome. J Trauma. 2002 Sep;53(3):407-14
9. Amino M, Yoshioka K, Morita S, Iizuka S, Otsuka H, Yamamoto R, Aoki H, Aizawa T, Ikari Y, Nasu S, Hatakeyama K, Iino M, Kodama I, Inokuchi S, Tanabe T. One-Year Follow-Up and Convalescence Evaluated by Nuclear Medicine Studies and 24-Hour Holter Electrocardiogram in 11 Patients With Myocardial Injury Due to a Blunt Chest Trauma. J Trauma. 66(5):1308-1310, May 2009
10. Lotfipour S, Kaku SK, Vaca FE, Patel C, Anderson CL, Ahmed SS, Menchine MD. Factors associated with complications in older adults

with isolated blunt chest trauma. West J Emerg Med. 2009 May;10(2):79-84

11. Kemp CD, Johnson JC, Riordan WP, Cotton BA. How we die: the impact of nonneurologic organ dysfunction after severe traumatic brain injury. Am Surg. 2008 Sep;74(9):866-72
12. Karpati PC, Rossignol M, Pirot M, Cholley B, Vicaut E, Henry P, Kévorkian JP, Schurando P, Peynet J, Jacob D, Payen D, Mebazaa A. High incidence of myocardial ischemia during postpartum hemorrhage. Anesthesiology . 2004 Jan;100(1):30-6
13. Rossi MA, Celes MR, Prado CM, Saggioro FP. Myocardial structural changes in long-term human severe sepsis/septic shock may be responsible for cardiac dysfunction. Shock. 2007 Jan;27(1):10-8
14. Meng X, Harken AH. The interaction between Hsp70 and TNF-alpha expression: a novel mechanism for protection of the myocardium against post-injury depression. Shock. 2002 May;17(5):345-53
15. Nickel EA, Hsieh CH, Chen JG, Schwacha MG, Chaudry IH. Estrogen suppresses cardiac IL-6 after trauma-hemorrhage via a hypoxia-inducible factor 1 alpha-mediated pathway. Shock. 2009 Apr;31(4):354-8
16. Yang S, Zheng R, Hu S, Ma Y, Choudhry MA, Messina JL, Rue LW 3rd, Bland KI, Chaudry IH. Mechanism of cardiac depression after trauma-hemorrhage: increased cardiomyocyte IL-6 and effect of sex steroids on IL-6 regulation and cardiac function. Am J Physiol Heart Circ Physiol. 2004 Nov;287(5):H2183-91
17. Platis A, Yu Q, Moore D, Khojeini E, Tsau P, Larson D. The effect of daily administration of IL-18 on cardiac structure and function. Perfusion. 2008 Jul;23(4):237-42
18. Luyun Zou, Shaolong Yang, Voraratt Champattanachai, Shunhua Hu, Irshad H. Chaudry, Richard B. Marchase, and John C. Chatham. Glucosamine improves cardiac function following trauma-hemorrhage by increased protein *O*-GlcNAcylation and attenuation

of NF-κB signalling. Am J Physiol Heart Circ Physiol. Feb 2009; 296: H515 - H5239

19. Ahmad R, Cherry RA, Lendel I, Mauger DT, Service SL, Texter LJ, Gabbay RA. Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg. 2007 Jul;142(7):613-8
20. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, Niederbichler AD, Ipaktchi K, Wahl WL. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma. 2007 Jan;62(1):56-61
21. Efron DT, Sorock G, Haut ER, Chang D, Schneider E, Mackenzie E, Cornwell EE 3rd, Jurkovich GJ. Preinjury statin use is associated with improved in-hospital survival in elderly trauma patients. J Trauma. 2008 Jan;64(1):66-73
22. Gunst M, Ghaemmaghami V, Sperry J, Robinson M, O'Keeffe T, Friese R, Frankel H. Accuracy of cardiac function and volume status estimates using the bedside echocardiographic assessment in trauma/critical care. J Trauma. 2008 Sep;65(3):509-23.
23. Hundley WG, Morgan TM, Neagle CM, Hamilton CA, Rerkpattanapipat P, Link KM. Magnetic Resonance Imaging Determination of Cardiac Prognosis. Circulation. 2002 Oct 29;106(18):2328-33
24. Ferjani M, Droc G, Dreux S, Arthaud M, Goarin JP, Riou B, Coriat P. Circulating Cardiac Troponin T in Myocardial Contusion. Chest. 1997 Feb;111(2):427-33
25. Velmahos, George C. MD; Karaiskakis, Marios MD; Salim, Ali MD; Toutouzas, Konstantinos G. MD; Murray, James MD; Asensio, Juan MD; Demetriades, Demetrios MD, PhD. Normal Electrocardiography and Serum Troponin I Levels Preclude the Presence of Clinically Significant Blunt Cardiac Injury. J Trauma. 2003 Jan;54(1):45-50

26. Mehta NJ, Khan IA, Gupta V, Jani K, Gowda RM, Smith PR. Cardiac troponin I predicts myocardial dysfunction and adverse outcome in septic shock. Int J Cardiol. 2004 May;95(1):13-7

27. Ausset S, Auroy Y, Lambert E, Vest P, Plotton C, Rigal S, Lenoir B, Benhamou D. Cardiac troponin I release after hip surgery correlates with poor long-term cardiac outcome. Eur J Anaesthesiol. 2008 Feb;25(2):158-64

28. Kim, Lauren J. MPH; Martinez, Elizabeth A. MD; Faraday, Nauder MD; Dorman, Todd MD; Fleisher, Lee A. MD; Perler, Bruce A. MD; Williams, G. Melville MD; Chan, Daniel PhD; Pronovost, Peter J. MD, PhD. Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients. Circulation. 2002 Oct 29;106(18):2366-71

29. Kilcullen N, Viswanathan K, Das R, Morrell C, Farrin A, Barth JH, Hall AS; EMMACE-2 Investigators. Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. J Am Coll Cardiol. 2007 Nov 20;50(21):2061-7

30. Ishii J, Ozaki Y, Lu J, Kitagawa F, Kuno T, Nakano T, Nakamura Y, Naruse H, Mori Y, Matsui S, Oshima H, Nomura M, Ezaki K, Hishida H. Prognostic value of serum concentration of heart-type fatty acid-binding protein relative to cardiac troponin T on admission in the early hours of acute coronary syndrome. Clin Chem. 2005 Aug;51(Hadjizacharia et al.):1397-404

31. Nakata T, Hashimoto A, Hase M, Tsuchihashi K, Shimamoto. Human heart-type fatty acid-binding protein as an early diagnostic and prognostic marker in acute coronary syndrome. Cardiology. 2003;99(2):96-104

32. Provenchère S, Berroeta C, Reynaud C, Baron G, Poirier I, Desmonts JM, Iung B, Dehoux M, Philip I, Bénessiano J. Plasma brain natriuretic peptide and cardiac troponin I concentrations after adult cardiac surgery: association with postoperative cardiac dysfunction and 1-year mortality. Crit Care Med. 2006 Apr;34(4):995-1000

33. Charpentier J, Luyt CE, Fulla Y, Vinsonneau C, Cariou A, Grabar S, Dhainaut JF, Mira JP, Chiche JD. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med. 2004 Mar;32(3):660-5

Appendix II

Cambridgeshire 3 Research Ethics Committee
Victoria House
Capital Park
FULBOURN
Cambridge
CB21 5XB

Telephone: 01223 597597
Facsimile: 01223 597645

03 September 2010

Professor Karim Brohi
Consultant in Trauma, Vascular & Critical Care Surgery
Royal London Hospital
Trauma Clinical Academic Unit
Royal London Hospital
Whitechapel Road, London
E1 1BB

Dear Professor Brohi

Study Title:	**Trauma Associated Cardiac Injury, Dysfunction & Death (TACIDD)**
REC reference number:	**10/H0306/47**

Thank you for your letter of 23 August 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The

favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Investigator CV: Karim Brohi		07 June 2010
Protocol	1.1	02 June 2010
REC application	3	03 June 2010
Covering Letter		04 June 2010
Study Flowchart		07 June 2010
Letter from Sponsor		01 June 2010
GP/Consultant Information Sheets	1.1	02 June 2010
Participant Information Sheet: Information Sheet A - Subject	1.2	30 July 2010
Participant Consent Form: TACIDD A professional legally appointed representative consent form	1.2	30 July 2010
Response to Request for Further Information		23 August 2010
Participant Information Sheet: Information Sheet B - Subject	1.2	30 July 2010
Participant Information Sheet: Information Sheet C Consultee	1.2	30 July 2010
Participant Information Sheet: Information Sheet D - Consultee	1.2	30 July 2010
Participant Consent Form: A	1.1	02 June 2010
Participant Consent Form: Tissue	1.2	30 July 2010
Participant Consent Form: A -Subject	1.2	30 July 2010
Participant Consent Form: B -Subject	1.2	30 July 2010
Participant Consent Form: TACIDD B professional legally appointed representative consent form	1.2	30 July 2010
Evidence of insurance or indemnity: Barts & The London		01 June 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

1. Notifying substantial amendments
2. Adding new sites and investigators
3. Progress and safety reports
4. Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0306/47	**Please quote this number on all correspondence**

Yours sincerely

Mr John Richardson
Chair

Email: lynda.mccormack@eoe.nhs.uk

Enclosures:	"After ethical review – guidance for researchers"
Copy to:	Mr Gerry Leonard R&D Department Queen Mary Innovation Centre Walden Street London E1 2EF

Appendix III

Barts and The London NHS
NHS Trust

Patient information sheet

DIRECTORATE OF SURGERY AND ANAESTHESIA
ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Information Sheet A – Subject
Version 1.2, 30/07/2010

Cambridgeshire 3 Research Ethics Committee
REC number: 10/H0306/47

Title: Trauma Associated Cardiac Injury and Dysfunction (TACID A)
Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Date: ___/___/_____
Subject Name: _____. NHS Ref: _____ Study Ref: _____

Introduction

You are being invited to take part in a research study. This research will help us to improve the care of patients who suffer severe injuries in the future. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Why is this research being carried out?

Trauma (serious injury) is a serious health problem worldwide. Once discharged home, trauma patients are more likely to be limited in their daily activities compared to similar people who have not been injured. Injury, shock and blood loss may damage the heart, which might lead to the above. If this is the case, the extent and frequency of heart damage and dysfunction in trauma patients is not known, and we hope that this research will help us to determine if, who and how significantly the heart might be affected by trauma.

Coupled with this, we want to find out what happens to trauma patients who already have diseased hearts before injury, and compare their outcomes to similar patients with normal healthy hearts.

Why have I been chosen?

On ___ - ___ - _____ (date), you were injured and admitted to the Royal London Hospital. At the time, you were unable to give informed consent. When you arrived in the emergency department, a full trauma team of doctors and nurses attended to you. The trauma team leader, who is not part of this research study, gave consent as your representative. As part of the immediate management, a heart trace (ECG) was performed and blood taken and sent to the laboratory for analysis. A small amount of extra blood (approximately 1 teaspoonful) was drawn and saved for research purposes. We are now asking for your consent to allow us to use the samples we have collected and to continue to participate in the study, since all the procedures have not yet been completed.

Do I have to take part?

No, participation is completely voluntary. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to continue with the study the following will happen:

1. We will store and process the samples we have already collected.
2. We will continue to collect blood samples and heart traces (ECGs) until the 3rd day in hospital. 3 of each in total. Each blood sample is equivalent to 1 teaspoonful, and the total amount of blood drawn over 3 days is less than 1 fluid ounce. Wherever possible we will draw the blood out of a line already in a blood vessel, or coincide the blood draw with tests required for your care, in order to minimise any discomfort from the procedure.
3. We will perform an echocardiogram (Echo) during your admission, at a time that is convenient to you and medically appropriate. An Echo is an ultrasound of the heart, and will give us information on the appearance and function of your heart.
4. This will take approximately 30 minutes, and is undertaking by placing some jelly on your chest followed by a probe that produces the images. It is very safe, but if the chest wall is injured, can be a little uncomfortable.

We will give you painkillers if this is the case, which will allow the test to be performed pain free.

5. When you go home, or at 30 days after your accident, we will ask you to fill in a questionnaire designed to assess your health perception. It is easy to complete and should take no more than 10 minutes.
6. We also need permission to access your health records, so that we can assess your health one year after your accident. This information is confidential, and will only be seen by the research team. It will only be used for the purpose described above in this study.

What do I have to do?

If you agree to continue with the study the following will happen:

1. We will collect ___ (number) of further blood samples and ___ ECGS from you, on _____(date/times)

2. We will perform an Echo at a convenient time to you during the course of your admission.

What are the possible disadvantages and risks of taking part in the study?

There are no long-term risks to you from participating in this study. The specific risks associated with each investigation are as follows:

1. Blood samples:
   The risks of drawing blood include temporary discomfort from the needle stick and bruising.
2. Echocardiogram:
   There is no risk to your health from an Echo, however, if you have chest wall injuries, you may find the procedure a little uncomfortable. We will give you painkillers if this is the case and only proceed when you are happy for us to do so.

What are the possible benefits of taking part in the study?

In the event that we detect an abnormality with your heart, we will refer you with your consent to a specialist in order to ensure you get appropriate care and follow up. In addition, we hope that the information we get will help to improve the care of trauma patients in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This Completes Part I.

If the information in Part 1 has satisfied you and you are considering continuing in the study, please read the additional information in Part 2 before making any decision.

Date: ___/___/_____ Researcher Initial: _____

PART 2

What will happen if I don't want to carry on with the study?

If you decide, at any time, to withdraw from the study all study procedures will be stopped immediately. Any information and samples that have already been collected will be processed as part of the study unless you wish to have your samples withdrawn from the study, in which case we will destroy them. Your decision will in no way result in a change in the type or quality of care you subsequently receive.

What if I am not happy about the study?

We will only make very minor changes to the way we look after you. It is extremely unlikely that this small change to normal practice would cause any problems. However, if taking part in this study harms you, there is no special compensation arrangement. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email pals@bartsandthelondon.nhs.uk. You can also visit PALS by asking at any hospital reception.

Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential and will be stored securely in coded form. If you consent to take part in the research, the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. Only authorised personnel such as researchers and research auditors will have access to the data. Any subsequent use of the samples will have to be performed with approval from a research ethics committee, otherwise the samples will be destroyed.

What will happen to the samples that I give?

We would like your permission to store your blood samples for further research. Any further use of your samples outside of this research study will have to be approved by a research ethics committee.

What will happen to the results of the research study?

We hope to publish the results in a scientific journal. It will not be possible to identify any individual who has taken part from this scientific report. Copies of the report will be available on request.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given ethical approval by the Cambridgeshire 3 Research Ethics Committee.

Who can I contact for further information?

1. If you require further information about the study, please contact the TACID study offices via the Trauma Surgery secretary at 020 7377 7000, x7695 or email: Henry.De'Ath@bartsandthelondon.nhs.uk
2. If you require impartial, local advice, please contact the Patient Advice and Liaison Service, telephone: 020 7943 1335 or e-mail: pals@bartsandthelondon.nhs.uk

Thank you for taking the time to read this sheet.

Date: ___/___/_____ Researcher Signature: _____

Appendix IV

Information for Consultee

Barts and The London NHS
NHS Trust

DIRECTORATE OF SURGERY AND ANAESTHESIA
ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Information Sheet C - Consultee
Version 1.2, 30.07.2010

Cambridgeshire 3 Research Ethics Committee
REC number: 10/H0306/47

Title: Trauma Associated Cardiac Injury and Dysfunction (TACID A)
Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Date: ___/___/_____
Subject Name: _____. NHS Ref: _____ Study Ref: _____

Introduction

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research. To help decide if he/she should join the study, we would like to ask your opinion whether or not they would want to be involved. We would ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may make about participating in research. These should take precedence. If you are unsure about the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility. The following information is the same as would have been provided to your relative/friend.

Why is this research being carried out?

Trauma (serious injury) is a serious health problem worldwide. Once discharged home, trauma patients are more likely to be limited in their daily activities compared to similar people who have not been injured. Injury, shock and blood loss may damage the heart, which might lead to the above. If this is the case, the extent and frequency of heart damage and dysfunction in trauma patients is not known, and we hope that this research will help us to determine if, who and how significantly the heart might be affected by trauma.

Coupled with this, we want to find out what happens to trauma patients who already have diseased hearts before injury, and compare their outcomes to similar patients with normal healthy hearts.

Why have they been chosen?

On ___ - ___ - _____ (Greenland P), your relative or significant other was injured and admitted to the Royal London Hospital. At the time, they were unable to give informed consent. When they arrived in the emergency department, a full trauma team of doctors and nurses attended to them. The trauma team leader, who is not part of this research study, gave consent as their representative. As part of the immediate management, a heart trace (ECG) was performed and blood taken and sent to the laboratory for analysis. A small amount of extra blood (approximately 1 teaspoonful) was drawn and saved for research purposes. We are now asking for your consent to allow us to use the samples we have collected and to allow their continued participation in the study, since all the procedures have not yet been completed.

Do I have to agree?

No, participation is completely voluntary. It is up to you to decide whether or not your relative/significant other should take part. If you do, you will be given this information sheet to keep and be asked to sign a declaration form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your relative/significant other receives.

What will happen to them if they take part?

1. If you agree to continue with the study the following will happen:
2. We will store and process the samples we have already collected.
3. We will continue to collect blood samples and heart traces (ECGs) until the 3rd day in hospital. 3 of each in total. Each blood sample is equivalent to 1 teaspoonful, and the total amount of blood drawn over 3 days is less than 1 fluid ounce. Wherever possible we will draw the blood out of a line already in a blood vessel, or coincide the blood draw with tests required for their care, in order to minimise any discomfort from the procedure.
4. We will perform an echocardiogram (Echo) during the admission, at a time that is convenient and medically appropriate. An Echo is an ultrasound of the heart, and will give us information on the appearance and function of the heart. This will take approximately 30 minutes, and is undertaking by placing some jelly on the patient's chest followed by a probe that produces the images.

It is very safe, but if the chest wall is injured, can be a little uncomfortable. We will give painkillers if this is the case, which will allow the test to be performed pain free.

5. When home, or at 30 days after the accident, we will ask your relative or significant other to fill in a questionnaire designed to assess their health perception. It is easy to complete and should take no more than 10 minutes.
6. We also need permission to access their health records, so that we can assess their health one year after your accident. This information is confidential, and will only be seen by the research team. It will only be used for the purpose described above in this study.

What do they have to do?

If you agree to continue with the study the following will happen:

1. We will collect ___ (number) of further blood samples and ___ ECGS from them, on_____(date/times)
2. We will perform an Echo at a convenient time to you during the course of his/her admission.

What are the possible disadvantages and risks of taking part in the study?

There are no long-term risks to you from participating in this study. The specific risks associated with each investigation are as follows:

1. Blood samples:

The risks of drawing blood include temporary discomfort from the needle stick and bruising.

2. Echocardiogram:

There is no risk to their health from an Echo, however, if they have chest wall injuries, they may find the procedure a little uncomfortable. We will give them painkillers if this is the case and only proceed when they are happy for us to do so.

What are the possible benefits of taking part in the study?

In the event that we detect an abnormality with your relative/significant other's heart, we will refer them with your consent to a specialist in order to ensure they get appropriate care and follow up. In addition, we hope that the information we get will help to improve the care of trauma patients in the future.

What if there is a problem?

Any complaint about the way you or your relative have been dealt with during the study or any possible harm they might suffer will be addressed. The detailed information on this is in Part 2.

Will taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about your relative/significant other will be handled in confidence. The details are included in Part 2.

This Completes Part I.

If the information in Part 1 has satisfied you and you are considering continuing in the study, please read the additional information in Part 2 before making any decision.

Date: ___/___/_____ Researcher Initial: _____

PART 2

What will happen if I don't want them to carry on with the study?

If you or your relative/significant other decides, at any time, to withdraw from the study all study procedures will be stopped immediately. Any information and samples that have already been collected will be processed as part of the study unless you wish to have their samples withdrawn from the study, in which case we will destroy them. Your decision will in no way result in a change in the type or quality of care they subsequently receive.

What if I am not happy about the study?

We will only make very minor changes to the way we look after your relative/significant other. It is extremely unlikely that this small change to normal practice would cause any problems. However, if they are harmed by taking part in this study, there is no special compensation arrangement. If they are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you or your relative have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care they have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email pals@bartsandthelondon.nhs.uk. You can also visit PALS by asking at any hospital reception.

Will taking part in the study be kept confidential?

All information collected during the course of the research will be kept strictly confidential and will be stored securely in coded form. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you and your relative have under this Act. Only authorised personnel such as researchers and research auditors will have access to the data. Any subsequent use of the samples will have to be performed with approval from a research ethics committee, otherwise the samples will be destroyed.

What will happen to the samples that are given?

We would like your permission to store his/her blood samples for further research. Any further use of the samples outside of this research study will have to be approved by a research ethics committee.

What will happen to the results of the research study?

We hope to publish the results in a scientific journal. It will not be possible to identify any individual who has taken part from this scientific report. Copies of the report will be available on request.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given ethical approval by the Cambridgeshire 3 Research Ethics Committee.

Who can I contact for further information?

1. If you require further information about the study, please contact the ACIT Study offices via the Trauma Surgery secretary at 020 7377 7000, ext7695 or email: Henry.De'Ath@bartsandthelondon.nhs.uk

2. If you require impartial, local advice, please contact the Patient Advice and Liaison Service, telephone: 020 7943 1335 or e-mail: pals@bartsandthelondon.nhs.uk

Thank you for taking the time to read this sheet.

Date: ___/___/_____ Researcher Signature: _____ _____

Appendix V

Trauma Associated Cardiac Injury and Dysfunction (A)

Trauma patients are eligible for participation in TACID A trial unless they meet one of the following:

- **Patients transferred from other hospitals**
- **Not expected to survive <72 hours**
- **Pregnant**
- **Patients <16**
- **Prisoners**
- **Trauma team leader deems recruitment inappropriate**

Patient Name _

Patient ID _ _ _ _ _ _ _ _ _ _ _ _

DOB _ _/_ _/__ Approximate Age _ _

Date Recruited _ _/_ _/_ _ Time of Baseline Blood/ECG _:_

I, as trauma team leader, fully understand the TACID A research study and informed consent process. I have read the consent documents and have provided consent in my capacity as a professional legally appointed representative of the above named patient and am independent of the trial.

Name _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Title _ _ _ _ _ _ _ _ _

Signature _ _ _ _ _ _ _ _ _ _ _ _ _ _

Appendix VI

Barts and The London NHS
NHS Trust

DIRECTORATE OF SURGERY AND ANAESTHESIA
ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Consent Form A – Subject

Version 1.2, 02.06.2010

Cambridgeshire 3 Research Ethics Committee

REC number: 10/H0306/47

Title: TRAUMA ASSOCIATED CARDIAC INJURY AND DYSFUNCTION (A)

Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Please initial box to indicate agreement

1. I confirm that I have read and understood the information sheet dated 30.07.2010 (version 1.2) for the above study and have had the opportunity to ask questions. I have been given a copy of the patient's information sheet to keep. [ ]

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

3. I understand that sections of any of my medical notes may be looked at by professional individuals involved in this study or by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that my personal data will be processed and stored securely in compliance with the 1998 Data Protection Act. [ ]

4. I agree to take part in the above study. [ ]

Name of patient	Date	Signature

I have explained this in terms which, in my judgement, are suited to the understanding of the patient.

Name of person taking consent (if different from Investigator)	Date	Signature

Investigator	Date	Signature

Appendix VII

Barts and The London NHS
NHS Trust

DIRECTORATE OF SURGERY AND ANAESTHESIA
ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Consultee Declaration Form C

Version 1.2, 30.07.2010

Cambridgeshire 3 Research Ethics Committee

REC number: 10/H0306/47

Title: TRAUMA ASSOCIATED CARDIAC INJURY AND DYSFUNCTION (A)

Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Please initial box to indicate agreement

1. I confirm that I have read and understood the information sheet dated 30.07.2010 (version 1.2) for the above study and have had the opportunity to ask questions. I have been given a copy of the consultee information sheet to keep. [ ]

2. I understand that his/her participation in this study is voluntary and that I am free to withdraw him/her at any time, without giving reason, without their medical care or legal rights being affected. [ ]

3. I understand that sections of any of his/her medical notes may be looked at by professional individuals involved in this study or by regulatory authorities where it is relevant to them taking part in research. I give permission for these individuals to have access to his/her records. I understand that his/her personal data will be processed and stored securely in compliance with the 1998 Data Protection Act. [ ]

4. I agree to allow my relative/significant other take part in the above study. [ ]

Name of Patient	Relationship	
Name of Consultee	Date	Signature

I have explained this in terms which, in my judgement, are suited to the understanding of the patient.

Name of person taking consent (if different from Investigator)	Date	Signature
Investigator	Date	Signature