Non-invasive Cardio-haemodynamic Assessment in Adult Emergency Department Patients with Sepsis

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by

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ABSTRACT

Title: **Non-invasive cardio-haemodynamic assessment in adult Emergency Department patients with sepsis.**

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Objective:
To explore the potential benefit of non-invasive cardio-haemodynamic variables in the management of sepsis in the Emergency Department (ED) by measuring their changes with normal treatment and their relationship to outcome.

Methods:
Study 1: Prospective cohort study of a convenience sample of adult ED patients with uncomplicated sepsis. Cardio-haemodynamic parameters were obtained using a Thoracic Electrical Bioimpedance (TEB) device. *Study 2:* Prospective cohort study of a convenience sample of adult ED patients with severe sepsis / septic shock. Cardio-haemodynamic parameters were obtained using a TEB device, transcutaneous Doppler ultrasound and Near-Infrared Spectroscopy. Measurements for both studies were taken on ED arrival, ED departure and after 24 hours, whilst patients received normal treatment. All patients were followed up for 30 days.

Results:
50 patients were enrolled in *study 1* and 73 patients in *study 2*. Septic patients had a significantly higher cardiac output and significantly lower stroke volume and systemic vascular resistance than non-septic ED controls. After 24 hours of normal treatment cardio-haemodynamic parameters of patients with uncomplicated sepsis and survivors from severe sepsis / septic shock began to normalise. In addition, patients with severe sepsis/septic shock had abnormal tissue oxygen saturation on ED arrival, which, in survivors normalised with treatment.

Conclusion:
This is the first description of cardio-haemodynamic parameters in septic patients at their entry to hospital (ED). Septic patients have initially abnormal haemodynamics and the ability to normalise haemodynamics and tissue oxygen saturation is associated with good outcome. This thesis has identified a number of parameters, which warrant validation to define their role as diagnostic or co-diagnostic biomarkers for sepsis and sepsis outcome.

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Dedicated to my little girl,

Hannah.

CONTRIBUTORSHIP

I conceived the idea for the MD project, conducted the literature review, designed the studies, prepared Ethics applications and attended the Ethics Committee meetings; managed the research projects, undertook the recruitment, data acquisition, data analysis, interpretation of findings and wrote the thesis.

Professor Tim Coats supervised the MD project from the preliminary to the final stage, provided advice on study design and Ethics application, attended Ethics Committee meetings, provided guidance on the structure of the thesis and reviewed and constructively commented on the thesis.

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ABBREVIATIONS AND ACRONYMS

95%CI	95% confidence interval
ACS	Acute coronary syndrome
AUROC	Area under the ROC curve
BP	Blood pressure
CaO_2	Arterial oxygen content
CI	Cardiac index
CO	Cardiac output
CVE	Cerebral vascular event
CVP	Central venous pressure
DO_2	Oxygen delivery
DPB	Diastolic blood pressure
ED	Emergency Department
EDV	End-diastolic volume
EGDT	Early goal directed therapy
ESV	End-systolic volume
ET%	Ejection time percentage
ETR	Ejection time ratio
FT	Flow time
GCS	Glasgow Coma Score
GI	Gastro-intestinal
HR	Heart rate
ICG	Impedance Cardiography
ICU	Intensive Care Unit
ISS	Injury Severity Score

LCW	Left cardiac work
LCWI	Left cardiac work index
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVET	Left ventricular ejection time
LVSWI	Left ventricular stroke work index
MAP	Mean arterial pressure
MD	Minute distance
MEDS	Mortality in Emergency Department Sepsis
MPG	Mean pressure gradient
NIRS	Near infrared spectroscopy
NNT	Numbers needed to treat
NPV	Negative predictive value
OT	Outflow tract
PAC-TD	Pulmonary artery catheter thermodilution
PE	Pulmonary embolus
PEP	Pre-ejection period
PPV	Positive predictive value
QI	Quality indicator
REC	Research & Ethics Committee
ROC	Receiver operating characteristics
RR	Respiratory rate
RVEDP	Right ventricular end-diastolic pressure

ScvO2	Central venous oxygen saturation
SD	Standard deviation
SI	Stroke index
SIRS	Systemic inflammatory response syndrome
SPB	Systolic blood pressure
SpO_2	Pulse oximetry oxygen saturation
SSC	Surviving Sepsis Campaign
StO_2	Tissue oxygen saturation
SV	Stroke volume
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
SVV	Stroke volume variation
TEB	Thoracic Electrical Bioimpedance
TFC	Thoracic fluid content
UO	Urine output
USCOM	Ultrasonic Cardiac Output Monitor
VO_2	Oxygen consumption
VP	Velocity peak
VTI	Velocity time integral
WCC	White cell count

GLOSSARY OF TERMS

Bias	Reflects a systematic error in the methods or conduct of the study.
Cardiac index	Cardiac output related to body surface area.
Cardiac output	Amount of blood pumped by the left ventricle per minute.
Conductivity	Measure of a tissue's (material's) ability to conduct an electric current.
Confidence Interval (95%)	A range of values around a point estimate that have a 95% probability of including the true value.
Confounding	Describes an error in the interpretation of findings.
Correlation Coefficient	Measure of strength of the linear relationship between two variables.
Cryptic Shock	State of shock with raised lactate and deceptively normal blood pressure.
Ejection time percentage	Percentage of cycle duration occupied by systolic ejection [aortic valve (AV) opening to closure divided by AV opening to opening x 100].
Ejection time ratio	Ratio of mechanical systole to heart rate.

Flow time	Equals systolic ejection time.
Gap analysis	Business resource assessment tool enabling a company to compare its actual with its potential performance.
Generalisability	Describes the extent to which research findings derived in one setting can be applied to other settings.
Impedance	Resistance that a system offers to an alternating electrical current.
Incidence	Number of new cases of a disease occurring in a population during a defined time.
Left cardiac work	Amount of work the left ventricle has to perform per minute to pump blood.
Left cardiac work index	Left cardiac work related to body surface area.
Left ventricular ejection time	Time interval between opening and closing of aortic valve (mechanical systole).
Left ventricular ejection time	Time interval from opening to closing of the aortic valve.
Likelihood ratio	The probability of a test result being seen in a patient with the disease relative to it being seen in an unaffected patient.

Mean pressure gradient	Presents the pressure gradient across the scanned heart valve.
Minute distance	The distance a blood cell travels in metres per minute.
Negative predictive value	Proportion of patients with a negative test result who genuinely do not have the disease.
Positive predictive value	Proportion of patients with a positive test who genuinely have the disease.
Pre-ejection period	Time interval from the onset of electrical stimulation of the ventricle to the opening of the aortic valve (electrical systole).
Prevalence	Total number of cases of the disease in a population at a given time.
Relative risk	Risk of an event relative to exposure $\mathrm{RR} = \frac{\text{Exposure group event rate}}{\text{Non} - \text{exposure group event rate}}$
Sensitivity	Proportion of patients with the disease who are correctly identified by the diagnostic test.
Sepsis	Systemic inflammatory response syndrome triggered by an infection.
Septic Shock	Sepsis with evidence of organ dysfunction.

Specificity	Proportion of patients without the disease who are correctly identified by the diagnostic test.
Stroke index	Stroke volume related to body surface area.
Stroke Volume	Define as the amount of blood ejected from the ventricle during one cardiac contraction.
Stroke volume variation	Percentage change of stroke volume between a group of beats.
Systemic vascular resistance	Resistance to the flow in the arterial system.
Thoracic fluid content	Represents the conductivity of the entire thorax and is an indicator of chest fluid status.
Velocity Peak	Peak velocity of the measured Doppler profile measured in m/s.
Velocity time integral	The distance (in cm) a single reflector travels per cycle.

1 INTRODUCTION

1.1 Opening Remarks

Sepsis is a major cause of morbidity and mortality worldwide and remains an ongoing challenge in medicine. Its incidence is steadily rising. Until 1992 there was no clear definition for sepsis and terms such as sepsis, septicaemia, septic syndrome or bacteraemia were used interchangeably.

In 1992 the American College of Chest Physicians and the Society of Critical Care Medicine consensus conference committee defined sepsis as a systemic inflammatory response syndrome (SIRS) triggered by an infection, leading to inadequate tissue oxygenation and organ perfusion.[1] SIRS is manifested by two or more of the following conditions: temperature >38°C or < 36°C, heart rate of > 90 beats per minute, respiratory rate of > 20 breaths per minute or white cell counts of $> 12.0 \times 10^9$/l or $< 4.0 \times 10^9$/l. Sepsis associated with dysfunction of one or more organs was defined as severe sepsis. Septic shock is a subset of severe sepsis. It is described as persistent sepsis-induced arterial hypotension (systolic blood pressure < 90 mmHg) with or without tissue hypoperfusion, characterised by lactic acidosis, oliguria or acute alteration in mental status, despite adequate intravenous fluid resuscitation (20mls/kg).

Sepsis is not a distinct disease but a complex dynamic syndrome that forms a continuum of clinical and pathophysiological severity with definable stages along this continuum that adversely affect patient's outcome. These critical stages are termed severe sepsis and septic shock and are associated with increased mortality.[2]

It took nearly a decade for the sepsis definition to be applied in day-to-day clinical practice. Even though awareness of sepsis has improved, early recognition and instigation of appropriate treatment at the patient's bedside is still inadequate. Unfortunately, it is not uncommon that the dynamic process of sepsis remains unrecognised until severe sepsis or septic shock has developed.

In 2001 Rivers and colleagues[3] published a randomised controlled trial demonstrating that mortality from sepsis can be significantly reduced if goal-driven resuscitation is commenced as early as in the Emergency Department. This concept is called early-goal-directed therapy (EGDT). It aims to achieve a balance between systemic oxygen delivery and oxygen demands, preventing global tissue hypoxia with subsequent organ failure. EGDT aims for pre-defined endpoints of central venous pressure (CVP), mean arterial pressure (MAP), urine output (UO) and central venous oxygen saturation ($ScvO_2$). Measurements of the CVP and $ScvO_2$ require the placement of a central venous catheter whilst arterial catheterisation is required for continuous MAP readings. Both procedures are not without risk to the patient and require time and expertise. This may be a drawback for its wider implementation in the UK Emergency Department which has a heavy work load and often overstretched resources.

The main difference between successful and futile goal-directed resuscitation in sepsis appears to be the time at which therapy had been commenced rather than the chosen resuscitation endpoint.[3-7] There is evidence to suggest that early initiation of haemodynamic optimisation with frequent reassessments, rather than achieving an invasive resuscitation endpoint, such as central venous oxygen saturation, improves clinical outcome from severe sepsis or septic shock.[8, 9] This raises an interesting question as to whether early goal directed therapy, using carefully chosen non-invasive

endpoints, would result in a similar outcome as demonstrated by Rivers and co-workers.

Non-invasive haemodynamic monitoring is safe, quick and feasible even in settings with limited resources. It has the potential to provide the clinician with essential information to guide goal-directed haemodynamic optimisation at the patient's bedside.

Over the last two decades a number of non-invasive methods assessing cardiovascular function or tissue oxygenation in critically ill patients have been explored, mainly as research tools.

There are three methods of non-invasive haemodynamic monitoring that have shown promising initial results in critically ill patients. These are Thoracic Electrical Bioimpedance (TEB), transcutaneous Doppler ultrasound and near-infrared spectroscopy (NIRS). However, it is not known whether any of these technologies might be useful in the early management of septic patients.

1.2 Epidemiology of sepsis

Data on the incidence of severe sepsis and septic shock is fragmented and incomplete. Over the last 5 decades there has been a reported decreasing incidence in gram-negative sepsis with gram positive and fungal pathogens being on the rise.[10, 11] The overall incidence of sepsis continues to climb and is currently believed to be 3 per 1,000 population with an expected annually increase of 1.5 %.[11, 12]

The major contributing factor for the rising incidence in the developed world is the aging population. The elderly (age ≥ 65 years) account for more than half of adult patients with severe sepsis and septic shock, and one third of these are nursing home residents.[12-14]

Unsurprisingly, there has been a steady increase in the number of intensive care unit (ICU) admissions due to severe sepsis or septic shock, with ICU admissions being associated with a 46% in-hospital mortality.[14, 15] Increase in multi-resistant strains, high-risk patients undergoing major surgery and the wider use of immunosuppressive therapy are likely to be contributing factors. ICU patients with septic shock were usually older, had a higher proportion of co-morbidities and had undergone recent surgery. They were found to have a 4-fold higher mortality than non-septic ICU patients.[14]

Not only are intensive care units faced with an increased number of septic patients; there is a growing pressure on Emergency Care Units to diagnose and manage sepsis. A recent survey in the United States highlighted that, contrary to previous belief, sepsis is far more likely to be community-acquired and that two thirds of patients with severe sepsis come through the Emergency Department.[13]

The death toll from sepsis remains unacceptably high. About 20 years ago an estimated 1,400 people died each day worldwide from sepsis.[1] This figure is likely to underestimate the magnitude of this public health burden owing to low diagnostic rates and the difficulty to track sepsis in many countries, since death is often attributed to the primary cause, such as pneumonia or cancer. A recent study from the U.S. reported more than 1 Million deaths from sepsis during a 7-year period, equating to approximately 400 sepsis related deaths per day in the U.S. alone.[16]

In comparison to other acute conditions such as myocardial infarction (MI) the mortality associated with sepsis has changed only slightly over the last decades. Severe sepsis is still associated with a mortality rate as high as 28.7 to 49.7%, similar to the in-hospital mortality seen in acute MI in the 1960's, before the implementation of successive life-saving treatments. [3, 10, 12, 17, 18]

The last decade saw the beginning of the decline in sepsis mortality as a result of improved diagnostic and therapeutic strategies.[10, 17, 19] Despite such progress, sepsis mortality remains unacceptably high. Likely reasons for this finding are the change in patient demographics with increasing number of elderly and high risk patients as well as an increase in antibiotic-resistant cases and the overall rising incidence of sepsis.

1.3 Standards of care for patients with sepsis

1.3.1 Improving care for septic patients

The discovery of Pencillin by Sir Alexander Flemming in 1928 set a benchmark in the management of sepsis saving millions of lives.[20] It marks the beginning of modern antibiotics. Even today, prompt and adequate antibiotic therapy combined with supportive therapy remains the mainstay of sepsis management.

The introduction of antibiotics into common clinical practice after World War II led to a significant decline in death from sepsis. In the 1950s the concept of the Intensive Care Unit (ICU) was introduced into the health care system, providing care to critically ill or injured patients. Unfortunately this had little effect on the outcome from sepsis. It was not until the end of the twentieth century when a number of landmark clinical trials introduced new or newly applied concepts of sepsis managements, that there was a further decrease in mortality.

The PROWESS study demonstrated in 2001 a 6.1% absolute reduction in mortality (NNT=16) in patients with severe sepsis treated with Drotrecogin alfa (recombinant human activated protein C).[21] Drotrecogin alfa, subsequently approved for the treatment of patients with severe sepsis, was found to be futile in patients with less severe disease but effective in septic patients with three or more organs failing.[22, 23]

In the same year *Rivers, et al.* published a randomised controlled trial with compelling evidence that 'Early goal-directed therapy' (EGDT) significantly reduced the mortality in patients with severe sepsis or septic shock (absolute risk reduction 16%).[3] EGDT is a concept that aims to prevent global tissue hypoxia with subsequent organ failure by

establishing a balance between systemic oxygen delivery and oxygen demands. It is a protocol-driven early intervention method that uses pre-defined values of central venous pressure (CVP), mean arterial pressure (MAP), urine output (UO) and central venous oxygen saturation ($ScvO_2$) as endpoints for resuscitation (Figure 1). EGDT uses CVP as a marker of intravascular filling and $ScvO_2$ as a surrogate marker for cardiac index, a parameter often referred to as measure for haemodynamic therapy.[3, 5]

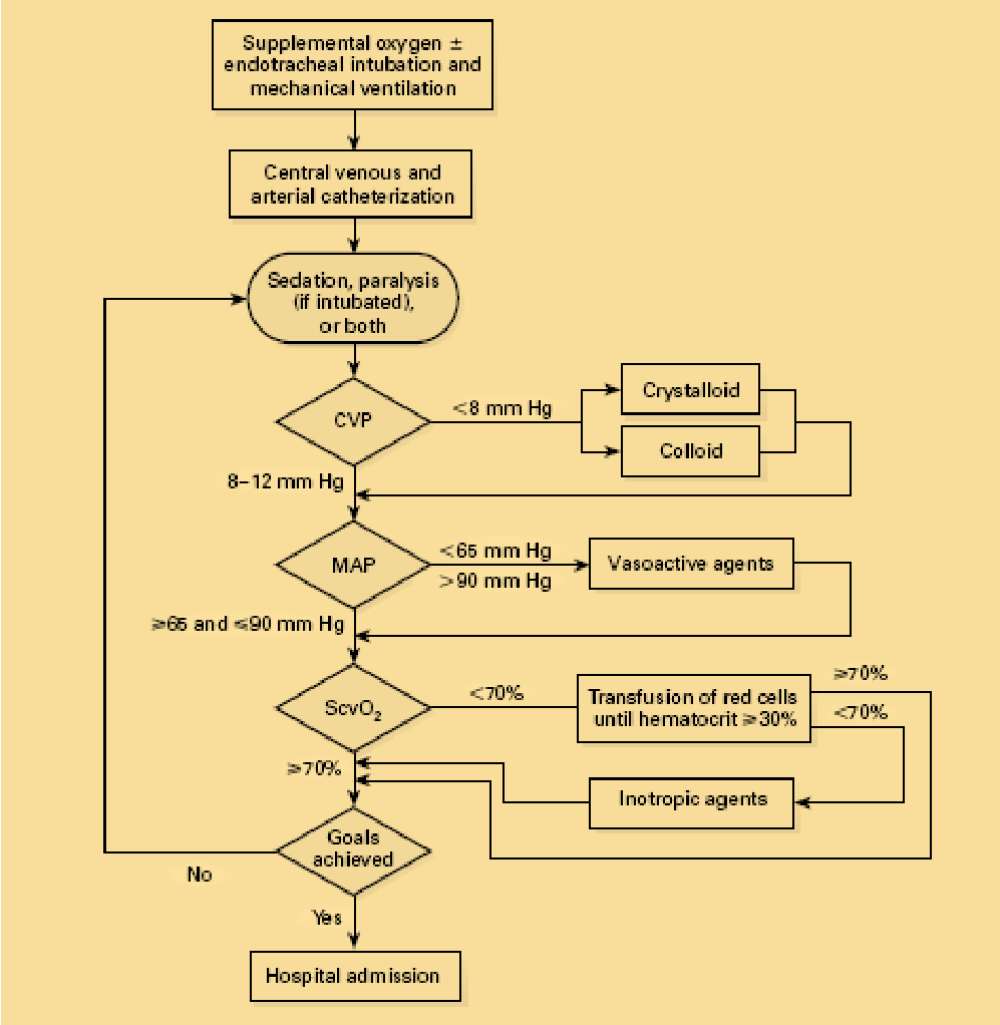

Figure 1. Protocol for Early Goal-Directed Therapy[3]

Rivers et al.[3] demonstrated that only six patients need to be treated following the EGDT protocol in order to save one life (NNT=6). An external validation of the EGDT

protocol using a 'before and after study' design found it to be similarly effective (NNT=11).[24] Though these figures are impressive, there remains scepticism about the magnitude of the effect amongst the wider medical community. The *Rivers et al.*[3] study is open to criticism. Not only does this single centre study lack generalisability but it also raises concerns about bias, given the unacceptable high mortality rate in the cohort receiving standard sepsis management. Nevertheless, *Rivers et al.*[3] deserve credit for their efforts to reduce mortality from sepsis by emphasising the importance of commencing effective sepsis management as early as possible.

Traditionally sepsis has been viewed as an 'intensive care unit' disease. However, it is now recognised that sepsis is a disease that demands critical care management at the earliest opportunity to improve outcome. For this to happen it would require greater awareness of sepsis and early clinical recognition by medical and nursing staff as well as the ability to instigate appropriate treatment in a timely manner. Furthermore, effective collaboration between 'in-house' specialities, particularly between emergency medicine and intensive care, is a key to facilitate improved sepsis management and outcome.[25]

To raise international awareness of the challenges associated with sepsis, the Surviving Sepsis Campaign (SSC), an international collaboration of health experts, was formed less than a decade ago. In 2004 the SSC committee published consensus guidelines for the management of severe sepsis providing guidance to the clinicians caring for septic patients.[26] These guidelines were extensively revised using the 'Grades of Recommendation, Assessment, Development and Evaluation' (GRADE) system which allows a structured assessment of the quality of evidence and of the strength of the recommendation.[27] Whilst in 2004 the SSC guidance was primarily focused on

the management of septic patients in intensive care units, the new guidelines allude to the fact that greater improvement would be achieved by better sepsis management in non-ICU settings.[26, 27]

The SSC was committed to a 25% relative reduction in mortality from severe sepsis by 2009.[28] This was to be achieved by changing clinical behaviour through the implementation of consensus guidelines known as 'sepsis bundles'. There were two bundles, the sepsis resuscitation bundle, which includes EGDT, and the sepsis management bundle.[29] The goal was, for these bundles to be implemented in all hospitals caring for the acutely ill to ensure consistent and evidence based management of patients with severe sepsis.

As expected, there were limitations to the widespread reliable implementation of the sepsis bundles, particularly, as initiation of invasive EGDT depends on local critical care facilities and expertise. However, if it would be possible for less invasive optimal endpoints to be substituted for CVP and $ScvO_2$ then compliance with the sepsis resuscitation bundle may markedly improve.

1.3.2 Sepsis bundles

The concept of care bundles, which is not unique to sepsis, originated from an extensive review of critical care literature aiming to identify interventions that improve patient outcomes.[30] A 'care bundle' is a group of several evidence based interventions which when applied in combination are expected to enhance clinical outcome. It is well known that the highest survival rate from a cardiac arrest can only be achieved when all components of the cardiac resuscitation bundle are applied as rapidly as possible. For a care bundle to be effective, the delivery of each element must be achievable in terms of resources, must be measurable, must be based on sound evidence and must not be a source of major controversy.[31]

The two sepsis bundles were created by the SSC as performance improvement tools. The 'sepsis resuscitation bundle', designed to be completed within six hours of identifying severe sepsis or septic shock, is most relevant to Emergency Care. This bundle is composed of a number of tasks which are essential to the care of patient with severe sepsis. These are measurement of serum lactate, obtaining blood cultures before administration of appropriate antibiotics, intravenous fluids and commencement of EGDT if indicated (Figure 2). It can be argued that early administration of appropriate antibiotics is one of the most important elements of this care bundle, as it has been shown to greatly reduce mortality.[32, 33] The SSC advocated that in severe sepsis or septic shock antibiotics should be given within one hour for patients in the ED. A recommendation which was recently reported to be strongly associated with improved outcome.[34]

The goals set out in the 'sepsis management bundle' are centred around the ICU management. They include administration of steroids, drotrecogin alfa (recombinant human activated protein C), glucose control and adequate inspiratory plateau pressures for ventilated patients. Completion of all tasks, if clinically indicated, must be accomplished within 24 hours of identifying severe sepsis or septic shock.

SEPSIS RESUSCITATION BUNDLE

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic, within 3 hrs of ED admission and within 1 hour of non-ED admission
4. In the event of hypotension and/or a serum lactate > 4 mmol/L
    a) Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
    b) Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4mmol/L
    c) Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
    d) Achieve a central venous oxygen saturation ($ScvO_2$) ≥ 70 % or mixed venous oxygen saturation (SvO_2) ≥ 65 %

Figure 2. Sepsis Resuscitation Bundle

Successful implementation of the sepsis resuscitation bundle into clinical practice presents a greater challenge. Whilst well established severe sepsis and septic shock are commonly encountered in intensive care units, identifying and treating the disease at its early stage is still challenging for medical staff. A recent UK study highlighted the effect of non-compliance with the sepsis resuscitation bundle on mortality in patients

with severe sepsis, demonstrating a two-fold increase in mortality in the non-compliant group (ARR 26%, NNT=4).[4] Is this an effect of poor compliance with a new guideline or is it lack of early identification of 'eligible' patients? As with any newly implemented clinical guideline, there are teething problems, many of which can be overcome by raising awareness, involving front line staff, setting up work-shops or creating networks to share experiences. These issues were extensively addressed through the international sepsis awareness programme led by the SSC. However, despite these efforts there was still only an up to three-fold improvement in compliance with sepsis bundle management and this was from a very low baseline.[34, 35]

A gap analysis performed in UK hospitals has shown that despite best efforts there are deficits in implementing the sepsis resuscitation bundle. To address this problem, 'Survive Sepsis UK' initiated the implementation of the so called 'Sepsis Six', six simple tasks which can be applied rapidly and easily by non-ICU staff in the ED or on the wards within the first hour of identifying severe sepsis (Figure3).[36]

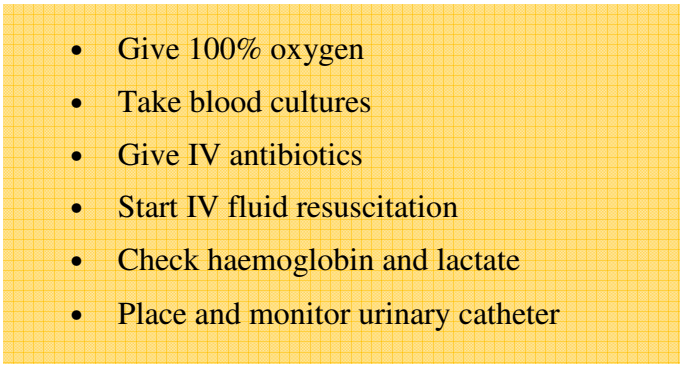

Figure 3. Sepsis Six

Compliance might be better using this more simplified approach. However, what these sepsis management strategies fail to address is the importance of early identifications of sepsis, since patients, who are not identified will not receive the SSC recommended treatment. Given the fact that there is no specific test or distinguishing feature for sepsis as there is e.g. myocardial infarct or stroke the early recognition of sepsis is difficult. Thus, one of the key issues to improve outcome from sepsis lies with the early identification of sepsis.

1.4 Pathophysiological concept of sepsis

Sepsis is the result of complex interactions of the host's inflammatory, immune and coagulation responses to the infecting microorganism. Initiation of the host's defence mechanisms results in activation of neutrophils and release of numerous inflammatory mediators. The circulating mediators cause direct or indirect tissue injury leading to increased vascular permeability, vasodilatation and activation of the coagulation cascade.[37] This results in redistribution and loss of circulatory blood volume due to fluid shift from the intravascular into the extravascular space. To compensate for these changes and to maintain oxygen supply to the tissues the RR and HR will increase. It is only at this stage that physiological deterioration manifests itself clinically. These physiological changes are an attempt to improve the oxygen content of the circulating blood and cardiac output. Whilst there may be a temporary improvement, these measures will not be able to sustain the tissues' oxygen demands for long.

As the disease process progresses hypotension, oliguria, tissue oedema and acute confusion will occur, indicating clinical decompensation. At this advanced stage of severe sepsis organ dysfunctions may be profound and irreversible, contributing to high morbidity and mortality. It has been shown that, once multiple organ dysfunction has occurred, instigation of goal-driven haemodynamic optimisation in an Intensive Care Unit does not significantly alter the patient's outcome.[5]

Whilst the traditional vital signs, such as heart rate, blood pressure, respiratory rate or oxygen saturation, as well as vital signs based scoring systems are of help in recognising clinical deterioration, the timing and magnitude of their derangement is not a true reflection of the underlying pathophysiological changes.

1.5 Sepsis and the cardiovascular system

1.5.1 Cardiovascular Physiology

The primary goal of the cardiovascular system is the delivery of adequate oxygen to the tissues in order to meet their metabolic demands. This is done by establishing a balance between oxygen consumption and oxygen delivery. Oxygen delivery (DO_2) is defined as the amount of oxygen made available to the body during one minute. It is equal to cardiac output multiplied by arterial oxygen content (CaO_2) (Equation 1).[38]

$$DO_2 = CO \times CaO_2$$

Equation 1. Oxygen delivery

In situations where there is an increasing oxygen demand by the tissues, this is usually met by an increase in cardiac output. Clearly, cardiac output plays a pivotal role in delivering oxygen to the tissues.

1.5.1.1 Regulation of cardiac output

Cardiac output (CO) is the amount of blood ejected by the heart during a one minute period and is imperative for maintaining blood pressure and oxygen delivery. Cardiac output is defined as heart rate (HR) multiplied by stroke volume (SV) (Equation 2) and if related to body surface area is referred to as cardiac index. It is measured in litres per minute, with the normal adult range being 4.0-8.0 l/min.[39]

$$CO = HR \times SV$$

Equation 2. Cardiac output

Although CO is determined by HR and SV, changes in HR will produce a greater effect on changes in CO, since HR may increase by up to 200% under physiological extremes, such as exercise, compared to an up to 50% increase in SV.[40] As HR increases CO will increase until a critical point is reached when any further increase in HR will result in a fall in CO. This is due to a HR related decrease in ventricular filling time leading to a reduction in end-diastolic volume (EDV) and therefore SV.

Heart rate is controlled by sympathetic and parasympathetic nervous system activity at the sino-atrial node whilst SV is regulated by three mechanisms; (1) preload, (2) afterload and (3) inotropy. The determinants of SV are depicted in Figure 4.

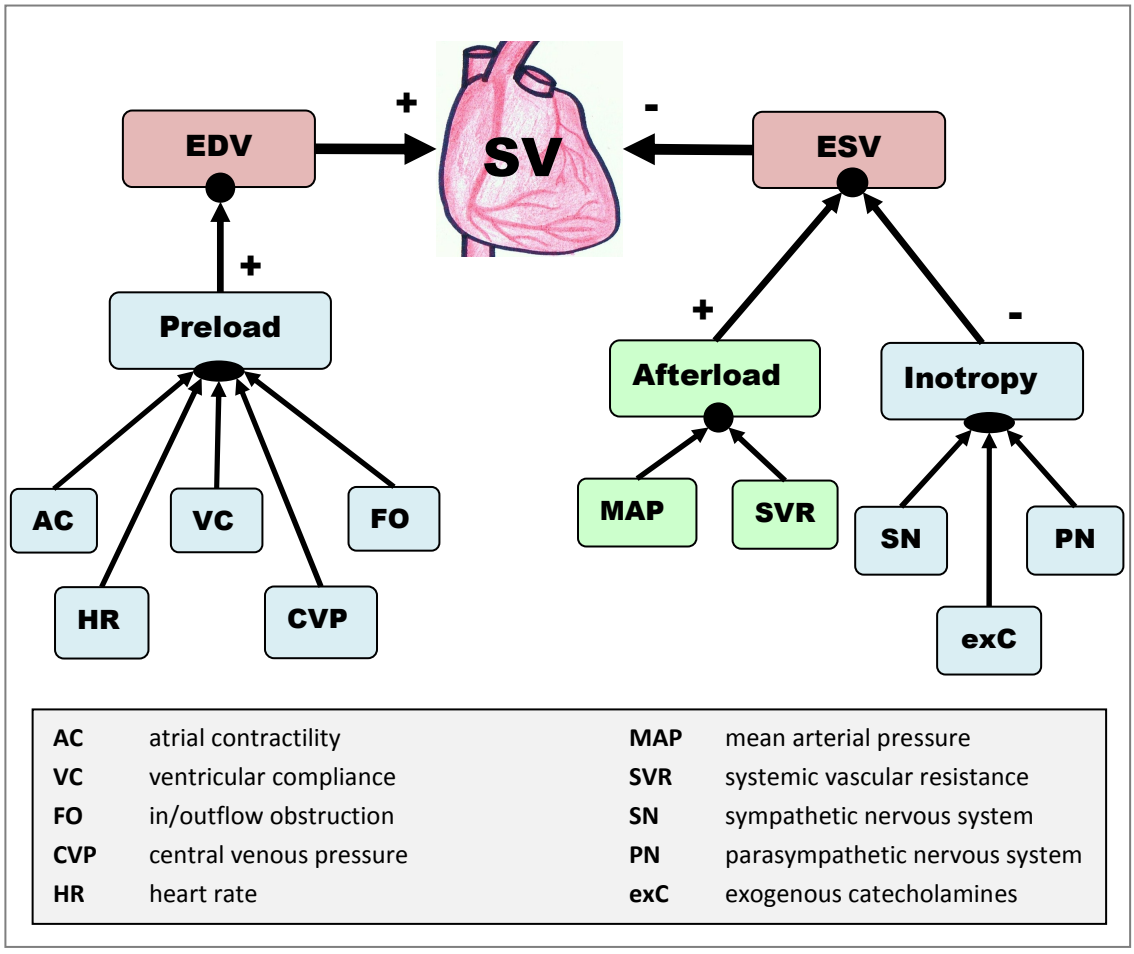

Figure 4. Determinants of stroke volume

(1) Preload is defined as the initial stretching of cardiac myocytes prior to contraction. Changes in preload alter EDV which has a positive effect on SV, thus an increase in preload will increase SV. Preload is predominantly affected by the central venous pressure (CVP) but there are a number of other factors, such as heart rate (HR), ventricular compliance (VC), atrial contractility (AC) and inflow or outflow obstruction (FO), that have an effect on preload.[40]

(2) Afterload can be described as the pressure against which the heart must contract in order to eject blood into the aorta. The two main factors affecting afterload are mean arterial pressure (MAP) and systemic vascular resistance (SVR). An increase in MAP or SVR will lead to an increase in afterload. This again will increase end-systolic volume (ESV) and thus decrease SV.

(3) Inotropy is often referred to as contractility. There are a number of factors influencing inotropy, the most important of which are activation of sympathetic (SN) or parasympathetic nerves (PN) as well as exogenous catecholamines (exC).[40] Whilst catecholamines have a positive inotropic effect, acetylcholine released via para-sympathetic nerve stimulation decreases inotropy.[40]

A further factor influencing the stroke volume is the Frank-Starling mechanism, which describes the relationship between stretching of cardiac myocytes, as a result of increased diastolic filling, and contractility.[40] It states that within certain limits an increase in preload will result in improved contractility producing a greater stroke volume and thus cardiac output.

1.5.1.2 Regulation of systemic vascular resistance

Systemic vascular resistance is defined as the resistance to blood flow offered by the systemic circulation. The major determinant of SVR is the vascular tone of small arteries and arterioles, the so called 'resistance vessels', although changes in blood viscosity also have an effect. An increase in vascular tone will lead to an increase in SVR. The vascular tone is generated by smooth muscle contraction within the wall of the vessel. A number of extrinsic and intrinsic factors, such as sympathetic nerves and endothelin-1, promote smooth muscle activation and vasoconstriction, whilst others, such as adenosine and endothelium-derived relaxing factor (nitric oxide), promote smooth muscle relaxation and vasodilatation.[40]

Systemic vascular resistance can be derived from cardiac output (CO), mean arterial pressure (MAP) and central venous pressure (CVP) (Equation 3). It is measured in units of dyne·sec/cm^5, with a normal range for adult of 1000 to 1500 dyne · sec/cm^5. [39]

$$SVR = \frac{MAP - CVP}{CO}$$

Equation 3. Systemic vascular resistance

1.5.2 Cardiovascular involvement in sepsis

The cardiovascular impairment in sepsis is complex and multifaceted. More than a century ago is was documented that septic illness affects the cardiovascular system and that the degree of disturbance is associated with the severity of the disease.[41] The traditional cardiovascular dysfunction seen in sepsis and septic shock was first described in 1951 by *Waisbren*.[42] He observed two distinct clinical stages of septic shock, the first being the hyperdynamic or high CO state characterized by fever, full bounding pulses, flushing and warm dry skin. The second being the hypodynamic state characterized by a thready pulse, oliguria, cold and clammy skin was thought to have a decreased CO. The traditional view was that patients with sepsis present initially in the hyperdynamic state and then either recover or progress to the pre-terminal hypodynamic shock state with decreased CO and elevated SVR.[43] Contrary to traditional beliefs *Wilson et al.* demonstrated in 1965 that septic shock is characterised by increased CO and decreased SVR, which is different from cardiogenic and haemorrhagic shock.[44]

1.5.2.1 Cardiac response

In an attempt to meet the body's increased oxygen requirements in sepsis the CO rises. This is achieved primarily by an increase in HR and to some extent by an increase in SV. It was initially thought that as septic shock deteriorates CO would decline and this was believed to be due to myocardial depression.[43] Myocardial depression in sepsis was thought to be associated with globally impaired myocardial perfusion causing myocardial ischaemia. This hypothesis was refuted by a number of studies demonstrating that the cause of myocardial dysfunction is not reduced coronary

perfusion but the effect of a circulating myocardial depressant factor.[45-47] The concept of a circulating myocardial depressant factor was first postulated by *Wiggers'* more than 60 years ago.[48] The existence of a myocardial depressant substance was first demonstrated in 1985 by *Parrillo et al*.[49] They found that by exposing in-vitro cardiac myocytes to a serum taken from a severely septic patient myocyte depression could be generated. Subsequently a number of circulating substances, such as cytokines, leucotrienes, nitric oxide and prostanoids, have been proposed to be linked to myocardial dysfunction in severe sepsis and septic shock.[50, 51] Of these cytokine mediators such as tumour necrosis factor - alpha (TNF- α) and interleukin - 1 beta (IL-1β) are considered to play a key role in the depression of myocardial contractility in sepsis.[52]

It has been shown that myocardial depression occurs within the first days of septic shock, characterised by dilatation of the left ventricle and a decrease in left ventricular ejection fraction. These changes were found to be transient in survivors.[53] Interestingly, despite myocardial depression the cardiac output of septic patients is usually normal or elevated, possibly a result of the low SVR obscuring the concomitant myocardial dysfunction.

Normal cardiac output is seen under normal physiological conditions while situations of physiological extremes, such as sepsis, demand an increase in cardiac output to meet increased metabolic requirements. It has been shown that inability to adequately augment CO in critical illness is associated with poor outcome.[54] Also, a persistently low CO in patients with septic shock, despite aggressive resuscitation, was found to increase mortality.[6, 55]

1.5.2.2 Peripheral circulation in sepsis

In sepsis there is typically a reduction in SVR as a result of vasodilatation of the small arteries and arterioles due to loss of sympathetic tone.[56] The peripheral vasodilatation is caused by a number of circulating mediators, such as nitric oxide and cytokines, and results in well-perfused warm skin as seen in the early phase of sepsis.[57]

At the later phase of severe sepsis or septic shock the progressing vasodilatation leads to blood pooling and microcirculation failure with maldistribution of blood flow and capillary leak, resulting in relative hypovolaemia and clinical hypotension. As sepsis progresses the peripheral vessels become refractory to vasopressor agents resulting in an even lower SVR and progressive hypotension.[58]

1.6 Non-invasive cardio-haemodynamic monitoring

Three non-invasive haemodynamic technologies have shown initial promising results in critically ill or injured patients. Two of these, Thoracic Electrical Bioimpedance and transcutaneous Doppler ultrasound, measure a variety of cardio-haemodynamic parameters, the third technology, near-infrared spectroscopy, measures tissue oxygen saturation. A detailed description of these three technologies is presented below.

1.6.1 Thoracic Electrical Bioimpedance

Thoracic electrical bioimpedance (TEB) also called impedance cardiography (ICG) is the study of cardiac functions determined from measurements of the electrical impedance of the thorax.[59] It is a non-invasive method of determining cardiac output, which allows continuous real-time assessment with no risk to the patient. It is immediately available, easy to use and cost-effective.

The first attempts to study the volume changes of the heart by placing the human body between two electrodes in an electrical circuit were described more than 100 years ago.[60, 61] However, it was not until 1940 when *Nyboer et al.* set the keystone for the use of electrical bioimpedance to measure cardiac function.[62] TEB, as a method to measure cardiovascular performance, gained increasing popularity in the 1960s when the original TEB system, the Minnesota impedance cardiograph, was developed for the National Aeronautics and Space Administration (NASA).[63] Since then TEB technology has undergone numerous transformations.

1.6.1.1 Electrophysiological Principles

Thoracic Electrical Bioimpedance is the electrical resistance of the thorax to a high-frequency and very-low amplitude alternating current (AC).

The fundamental principle behind electrical bioimpedance is based on Ohm's law. It states that impedance to current flow (Z) is equal to the voltage drop (E) between the two ends of the electrical circuit divided by the electrical current (I) (Equation 4).

$$Z = \frac{E}{I}$$

Equation 4. Ohm's law

Therefore, if the electrical current (I) remains constant, changes in impedance (Z) to flow are equal to changes in voltage drop (E) across the circuit. Furthermore, impedance (Z) is dependent on the resistivity (ρ), length (L) and cross sectional area (A) of the conductor (Equation 5).[59]

$$Z = \rho \times \frac{L}{A}$$

Equation 5. Impedance (1)

The conductor referred to is the thorax which, for simplicity, can be modelled as a cylinder.[59] Since the volume (V) of a cylinder is equal to the product of the cross-sectional area (A) and length (L), changes in impedance (Z) are related to changes in the volume (V) of the conductor (Equation 6).

$$V = A \times L$$

Equation 6. Volume of cylinder

Therefore, equation 5 changes to:

$$Z = \rho \times \frac{L^2}{V}$$

Equation 7. Impedance (2)

If a current is applied to a conductor it will seek the path of lowest resistivity. The thorax, an electrically inhomogeneous conductor, is primarily composed of tissues with a high resistivity (R), such as bone, fat, muscle air filled spaces and to a lesser extent of blood, which has the lowest resistivity in the human body (whole blood 130 Ω/cm , plasma 63 Ω/cm).[64, 65] Thus, when a constant alternating current is applied to the thorax it will primarily travel up the great vessels and any changes of impedance over time within the thorax will be related to dynamic changes of blood volume in the aorta and vena cava (Figure 5).[64, 65]

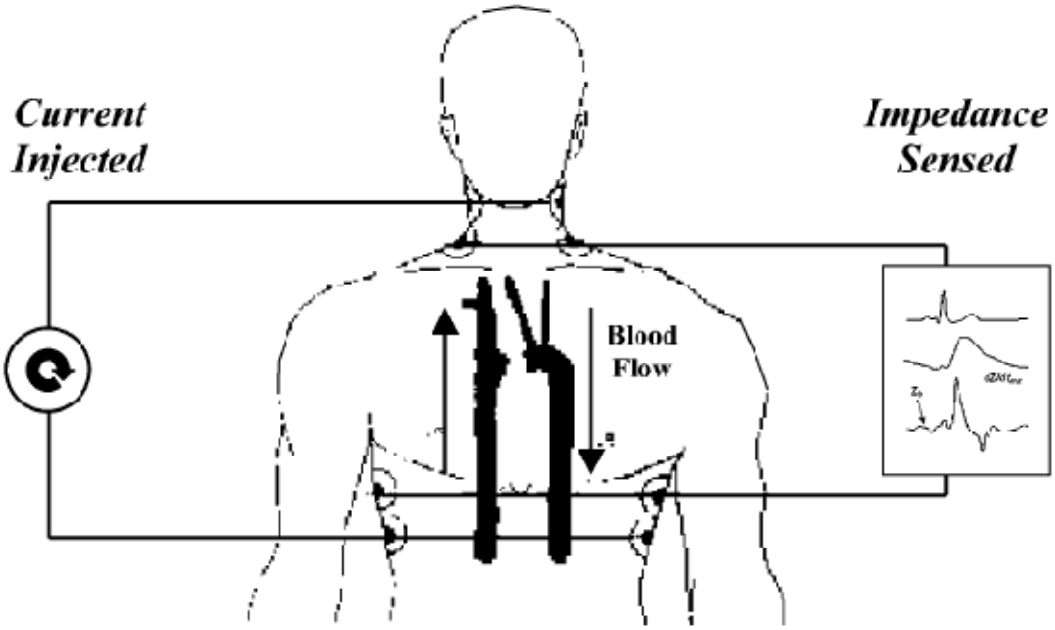

Figure 5. Transmitted and sensing current pathway [64]

The overall impedance of the thorax is composed of base impedance (Z_0), respiration impedance (Z_R) and haemodynamic impedance (Z_H) and has an average value of 25Ω (Equation 8).[64]

$$Z(t) = Z_O + Z_R(t)Z_H(t)$$

Equation 8. Impedance (Thorax)

Z_0, indicative of chest fluid volume, does not change suddenly with time, whereas Z_R and Z_H show variations during the cardiac cycle. The change in impedance induced by respiration is approximately 1Ω, which is as much as ten times higher than the blood

flow induced change in impedance (0.1 to 0.2Ω).[64] These changes are reflected in the impedance waveform (Delta Z) (Figure 6).

In order to overcome variability in impedance over time caused by respiration the first derivative of delta Z (dZ/dt) was introduced.[62, 66] This was a great advantage since, by applying this method, it has been shown that nearly all changes in thoracic impedance over time are due to blood volume and velocity changes in the thoracic aorta alone. The maximum deflection of the first derivative of delta Z is proportional to the peak flow in the ascending aorta.[67]

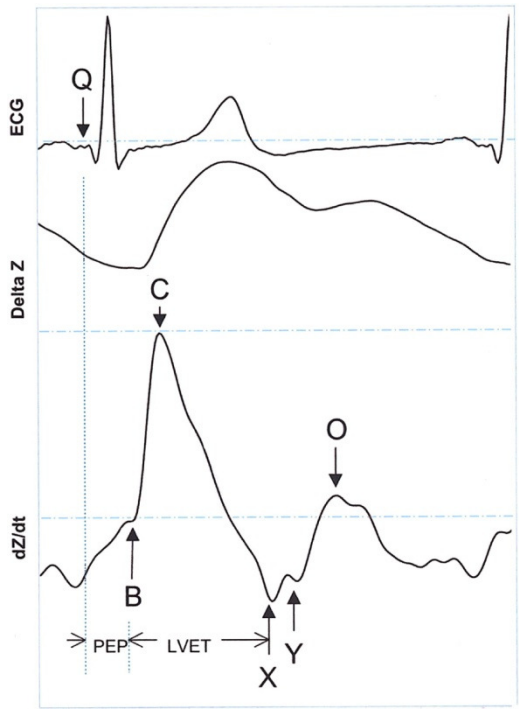

Figure 6. ECG and impedance waveforms [68]

The dZ/dt waveform reflects a number of physiological actions and allows measurement of various parameters.[69] PEP, the pre-ejection period, is measured from ventricular depolarisation (Q-point) to the aortic valve opening (B-point). The left ventricular ejection time (LVET) is measured from the opening of the aortic valve (B-point) to valve closure ('X'-point). The C-point reflects the maximal systolic flow $(dZ/dt)_{max}$. The Y-point represents closure of the pulmonary valve and the O-point indicates mitral valve opening.

Assuming that SV is proportional to the maximal systolic flow and the duration of the left ventricular ejection phase (LVET) it can be calculated using the following formula (Equation 9)[63, 67, 69]:

$$SV = V_{EPT} \times \frac{(\frac{dZ}{dt})_{max}}{Z_0} \times LVET$$

Equation 9. Stroke volume

This Bernstein/Scramek formula operates on the assumption that the thorax is geometrically modelled as a truncated cone which allows a better estimation of the electrically participating thoracic volume compared to the mere cylinder model used in previous formulas.[70] V_{EPT}, the volume of electrically participating thoracic tissue, is a personal constant and is determined by the patient's height, weight and gender.[67]

Cardiac output and cardiac index can be calculated by using the stroke volume derived from the first derivative of the impedance waveform.

Additional information can be gained from the base impedance (Z_0) which, not affected by the cardiac cycle, is an indicator of chest fluid volume. The reciprocal of (Z_0) is termed thoracic fluid content (TFC), a parameter that can be used to assess changes in intravascular and extravascular thoracic fluid.[71]

1.6.1.2 Validation

There are currently more than 200 TEB validation studies published. TEB has been evaluated in different clinical settings in a wide range of populations. Since there is no true 'gold standard' to measure cardiac output, different reference methods have been used to validate thoracic electrical bioimpedance measurements.[64, 72, 73] The majority of studies were validated against the pulmonary artery catheter thermodilution (PAC-TD) method which is widely accepted as the 'clinical gold standard'. Other reference techniques used were the Fick method, dye-dilution and echocardiography. Each reference technique lacks absolute accuracy and reproducibility in measuring the 'true' cardiac output, making agreement between two methods likely to be imperfect.[63, 74-77]

Furthermore, the validation studies differed considerably in their applied TEB methodology. This involved the use of different electrode configurations, values for resistivity of blood, differently modelled thoracic volume and different equations for calculating cardiac output.[66, 67, 73, 78] Also, the subjects studied varied greatly from healthy to critically ill patients. It may therefore not come as a surprise that the validation studies reached conflicting conclusions.

A large meta-analysis including 112 studies yielded an overall correlation coefficient r^2 of 0.67 (95% CI 0.64-0.71) which is similar to the cumulative correlation coefficient ($r^2 = 0.66$) found in a previous meta-analysis and in a recent literature review.[64, 73, 79]

Interestingly, TEB cardiac output correlated less well with PAC-TD in ICU patients compared to non-ICU patients ($r^2 = 0.64$ versus $r^2 = 0.77$). This is likely to be the result of the technical challenge to achieve correct electrode positioning due to dressings or CVP-lines.[79]

When reviewing validation studies in critically ill patients, utilising the same electrode configurations and SV equation as used in my research study, a satisfactory correlation between TEB and PAC-TD cardiac output measurements was found (Table 1).

Table 1. Correlation between TEB and PAC-TD

Author (year)	Reference Method	Patient group	r^2
Shoemaker (2006)[80]	PAC-TD	Trauma	0.84
Van De Water (2003)[63]	PAC-TD	Critically ill surgical	0.66
Shoemaker (1998)[81]	PAC-TD	Trauma, critically ill medical and surgical	0.73
Shoemaker (1994)[82]	PAC-TD	Critically ill	0.74
Shoemaker (1988)[83]	PAC-TD	Critically ill surgical	0.69
Appel (1986)[84]	PAC-TD	Critically ill surgical	0.69

Although there was not always a strong correlation ($r^2 < 0.8$) in cardiac output measurements between TEB and the PAC-TD method, TEB derived CO changes were

shown to closely follow changes in CO measured by thermodilution.[81] Furthermore, when comparing the intra-method variability of TEB cardiac output and PAC-TD cardiac output measurements TEB demonstrated better intra-patient reproducibility than thermodilution.[63]

Overall, when compared with the PAC-TD, TEB can be regarded as a reliable method to measure cardiac output, having demonstrated clinically acceptable accuracy and reproducibility. From a pragmatic point of view, it is probably even more important whether TEB is able to measure parameters and track dynamic changes that are related to a disease process or patient outcome.

1.6.1.3 Practical application

There are currently a number of thoracic electrical bioimpedance or impedance cardiography devices in use. The two current market leaders are the Niccomo™ Monitor (Medis. Medizinische Messtechnik GmbH) and the BioZ ®monitor (Cardio Dynamics). Both devices display, in real-time, non-invasive cardio-haemodynamic data. They requires four dual pre-gelled sensor patches, two of which are placed at the root of the patient's neck and two at the lateral aspect of the lower thorax (Figure 7). The outer electrodes (blue and orange) are used to transmit a constant alternating measurement current of high frequency (85kHz) and low amplitude (1mA). With this type of current the tissues are not excitable, minimising the risk of any physiological effect.[59] The inner electrodes (purple and green), placed inside the current path are used to receive the ECG signal, thus the heart rate and the thoracic impedance signal.

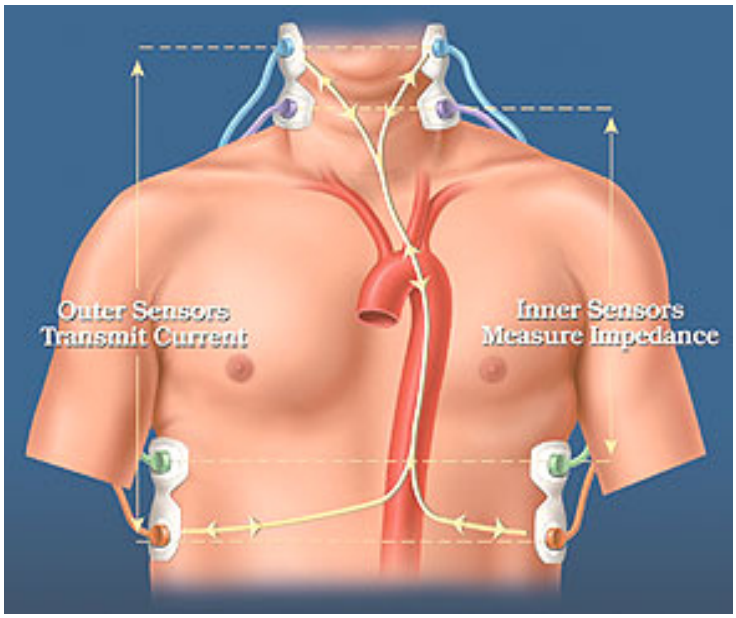

Figure 7. Electrode configuration [85]

1.6.1.4 Clinical applications

TEB monitoring has been investigated in a wide range of clinical conditions and settings. It has demonstrated a potential to assist diagnostic and therapeutic management of acutely and chronically ill patients. Its current use however, remains that of a research tool, for example:

Emergency Department

- Diagnostic tool to aid differentiation of acute dyspnoea[86-89]
- Haemodynamic assessment of critically ill patients[80, 90]
- Outcome prediction in critically ill emergency patients[91]
- Clinical decision-making tool[92]

In-patient

- Management of acute heart failure[93]

Out-patient

- To predict clinical deterioration and response to treatment in patients with heart failure[68, 94-96]
- To guide therapy in patients with hypertension[97-99]
- Monitoring tool in haemodialysis to prevent significant hemodynamic instability[100]
- Assessment aid in preeclampsia[101]

1.6.2 Transcutaneous Doppler ultrasound

The first description of the principle of modern Doppler ultrasound is attributed to Christian Doppler, an Austrian scientist. In 1843 he postulated that certain properties of light waves emitted from the stars depend on the relative motion of either the emitting source or the observer.[102] More than 100 years passed before the Doppler Effect became of practical relevance to medicine.

In medicine the Doppler concept was first employed to detect movements of the heart.[103] Subsequently, Satomura, a Japanese scientist, discovered that by transmitting a continuous ultrasonic beam through the skin surface it is possible to determine the character of blood flow within the blood vessel.[104] In the early 1960s transcutaneous Doppler ultrasound was gaining increasing popularity particularly as invasive cardio-vascular assessment methods were rather time consuming and not without risks to the patient.[105] The fact that Doppler ultrasound compared favourably with invasive circulatory methods when measuring relative flow values, set the foundation for the development of Doppler ultrasound as an attractive assessment tool.[106]

There are two main types of Doppler ultrasound systems, the continuous wave (CW) and pulse wave (PW) Doppler. They differ in their operating features and in the information they provide. The CW Doppler, as the name suggests, continuously transmits and receives ultrasound waves. Its main advantage is the ability to measure high blood flow velocities, thus providing information on haemodynamics. Its disadvantage is the lack of imaging capability thus providing no anatomical information about the examined structure. The PW Doppler uses a transducer that alternates between transmission and reception of ultrasound waves. The main

advantages of the PW Doppler is its ability to provide information on selected small segments along the ultrasonic beam as well as carrying out imaging alternatively with the Doppler.[107]

Currently transcutaneous Doppler ultrasound is used for the assessment of a wider spectrum of circulatory disorders, such as peripheral artery disease, acute venous thrombosis, cardiac valvular disease, and also for the evaluation of myocardial function.[105]

1.6.2.1 How does it work

Doppler ultrasound is based on the principle that the frequency of sound waves reflected from a moving object changes with the direction of motion in relation to the emitting source. This change in frequency is called the Doppler shift. The relationship between the Doppler shift of frequency (F_d) and the movement of a single object (V) can be expressed in the following equation (Equation 10):

$$F_d = \frac{2F_e \times V \times \cos\theta}{c}$$

Equation 10. Doppler shift of frequency

If the frequency of the emitting sound (F_e), the angle of the directed beam (θ) and the speed of sound through the tissues (c) are kept constant then the Doppler shift is directly proportional to the velocity of the moving object. Doppler shift of frequency (F_d) is highly dependent on the angle of the beam (θ). If the direction of the beam is

perpendicular to the blood flow, the Doppler signal is very poor with velocity measurements close to zero, whereas alignment of the ultrasound waves with the direction of blood flow gives the most accurate Doppler signal.

A Doppler ultrasound system consists of three elements, an emitter, a receiver and electronics. The emitting and receiver transducers are usually combined into one hand-held Doppler probe. The emitter produces an ultrasound beam which passes through the tissues and is reflected from moving red blood cells. Cells moving towards the transducer will create waves of higher frequency than those moving away from the transducer. The reflected waves are detected by the receiving transducer. The difference in frequency between the emitted and received ultrasound waves is analysed by the system's electronics and transformed into blood flow data.

There are three main factors that affect the Doppler signal these are air, bone and fat. Air, whether between transducer and skin or within the tissues, prevents any transmission of ultrasound waves and reflects the entire beam back to the transducer. Bony tissue absorbs the ultrasound waves completely, whereas adipose tissues absorb a proportion leading to a weakened Doppler signal.

1.6.2.2 Assessing cardio-haemodynamic function

The use of transcutaneous Doppler ultrasound as an 'Ultrasonic cardiac output monitor' (USCOM) to assess cardio-haemodynamic function is a recent addition to its array of applications.[108] CW Doppler ultrasound (frequency > 20,000 Hz) is applied to determine blood flow across the aortic or pulmonary outflow tract. This is done by measuring the distance that blood has travelled through the outflow tract in one heart

beat, which is referred to as the velocity time integral (vti). If the area of the outflow tract (OTa) is known then stroke volume (SV) can be calculated by applying the basic volume equation (Equation 11).

$$volume = area \times height$$

Equation 11. Volume equation

Applying this formula to the blood flow through the outflow tract leads to the stroke volume equation (Equation 12):

$$SV = OTa \times vti$$

Equation 12. Stroke volume

For the area across the aortic or pulmonary outflow tract (OT) to be calculated the OT diameter needs to be known (Equation 13).

$$OTa = \pi r^2 = \pi \times (D/2)^2$$

Equation 13. Outflow tract area

In adults and children the OT diameter has been shown to correlate linearly with body height.[109] Thus the OT diameter can be estimated using anthropometric normograms.

1.6.2.3 Validation

The ultrasonic cardiac output monitor (USCOM) was introduced into clinical use in 2001. Since then it has been evaluated in different clinical settings in adult and paediatric populations. The pulmonary artery catheter thermodilution (PAC-TD) method was the most commonly used reference technique. Although PAC-TD is considered to be the 'clinical gold standard' for assessing cardiac output it has to be remembered that it does not measure the 'true' cardiac output.[76, 77] Thus comparing any novel method with the 'old' standard requires careful interpretation.

A recently published review article attempted to compare the USCOM technique with currently used methods of measuring cardiac output, in particular with the PAC-TD.[110] This review included 16 studies, all of which had small numbers of patients. The studies were heterogeneous in design and population which precluded a meta-analysis. A number of the studies demonstrated a good correlation ($r^2 = 0.76$) between USCOM derived CO measurements and PAC-TD values, whilst others found poor agreement between the two methods. [111-115]

Further evidence has since emerged indicating acceptable agreement between USCOM and PAC-TD values in adult intensive care patients.[116-119] It has also been shown that USCOM is well suited to track intra-patient changes in CO over time.[118]

The lack of agreement between the two methods seen in some studies may have been a result of suboptimal Doppler flow signals due to intra-thoracic air in ventilated patients and inadequate beam alignment with the direction of the blood flow, which may have been caused by a lack of training.[110]

Given the current evidence the USCOM can be regarded as a feasible method for measuring cardio-haemodynamic parameters at the patient's bedside by a trained operator assessing non-ventilated patients.

1.6.2.4 Clinical Applications

The USCOM has been used in a range of clinical settings. It has been considered to be a feasible method to assess cardiac output and CO changes with treatment at the patient's bedside. It has been primarily used as a research tool in intensive care and to a limited extent in emergency medicine and paediatrics.[111, 113, 115, 117, 119-124]

1.6.3 Near Infrared Spectroscopy

The use of near infrared spectroscopy (NIRS) as a non-invasive method to measure oxygenation in human tissues was pioneered by Jöbsis in 1977. He noticed that biological tissues were transparent to the near infrared region of the electromagnetic spectrum, allowing sufficient photon transmission through the tissues to determine changes in oxyhaemoglobin and deoxyhaemoglobin.[125] In the 1990s NIRS gained increasing popularity in plastic and reconstructive surgery as a method of monitoring regional tissue oxygen saturation following flap surgery.[126, 127] The ability of NIRS to provide non-invasive information about local tissue oxygenation coupled with the development of a more sophisticated technology opened up a much wider clinical spectrum which focused on monitoring tissue oxygen as a marker of tissue hypoperfusion in critically ill and major trauma patients.[128-131]

1.6.3.1 Tissue oxygenation monitoring

Adequate tissue oxygen levels, essential for cell survival, rely on efficient oxygen delivery (DO_2) and oxygen consumption (VO_2) by the tissue. Oxygen delivery is a function of cardiac output (CO) and arterial oxygen content (CaO_2). It is influenced by a several factors: i) the oxygen content of the inspired gas mixture, ii) oxygen diffusion across the lung-blood barrier, iii) oxygen carrying capacity of the blood, iv) the body's capability to transport blood to the tissues and v) oxygen diffusion across the blood-tissue interface.

Impaired tissue oxygenation as a result of inadequate oxygen delivery to meet the tissues' demands is a feature of septic shock. Resuscitation efforts in sepsis

management aim to improve tissue oxygenation and to prevent prolonged global hypoxia. Assessing DO_2 or VO_2 in a clinical environment is cumbersome. Even invasive methods measuring mixed venous (SvO_2) or central venous oxygen saturation ($ScvO_2$) provide only a limited insight into oxygen utilisation in tissues. Furthermore, these systemic parameters of oxygenation may be normal despite significant regional hypoxia.[132]

Early correction of hypoxia, preventing a cascade of cellular and organ dysfunction, was found to significantly improve survival in patients with severe sepsis and septic shock.[3] A recent meta-analysis concluded that optimisation of tissue oxygenation in critically ill patients by optimising oxygen delivery reduces mortality.[133] This meta-analysis also highlighted that only early maximisation of oxygen delivery is associated with improved survival.[5, 6, 134] Paramount to all of this is however, the early detection of tissue hypoxia in sepsis, as delay in identification would defer strategies to optimise tissue oxygenation.

The central venous oxygen saturation ($ScvO_2$) is commonly used to gain information about the tissue oxygenation, although a thorough validation of how well it reflects oxygen delivery is lacking. Furthermore, $ScvO_2$ measurements require invasive monitoring which restricts its application to critical care units. Less cumbersome methods such as laser-Doppler flowmetry or orthogonal polarization spectral imaging are difficult to use at the patient's bedside. For a tissue oxygenation assessment method to be accepted into routine acute clinical care it would have to be non-invasive, whilst being rapid and easy to apply. The near infrared spectroscopy (NIRS) monitoring device (described below) seems to fit these criteria. Such a device would

provide the clinician at the bedside with instant information about the patient's tissue oxygenation.

1.6.3.2 How does it work

Near infrared spectroscopy (NIRS) is a non-invasive technology which is based on the spectrophotometric principles that relates the absorbance of light of a certain wavelength to the presence of a particular structure or chemical.[135] The fundamental principle behind NIRS is Beer's law. It states that the amount of light absorbed by a coloured substance is proportional to the concentration of the substance in solution.

NIRS uses the near infrared region of the electromagnetic spectrum, which is differently absorbed by oxygenated and deoxygenated haemoglobin. A sensor placed onto the skin scatters the near infrared light through the tissues below to a depth of up to 14 mm, where it is absorbed by haemoglobin.[136] The amount of light absorbed varies with the level of oxygenation. A photodetector which is placed in close proximity to the sensor (15mm) is used to detect the light that has not been absorbed (Figure 8). The incoming signal from the photodetector is analysed using the well described absorption spectra of oxygenated and deoxygenated haemoglobin to calculate the tissue oxygen saturation (StO_2).[136]

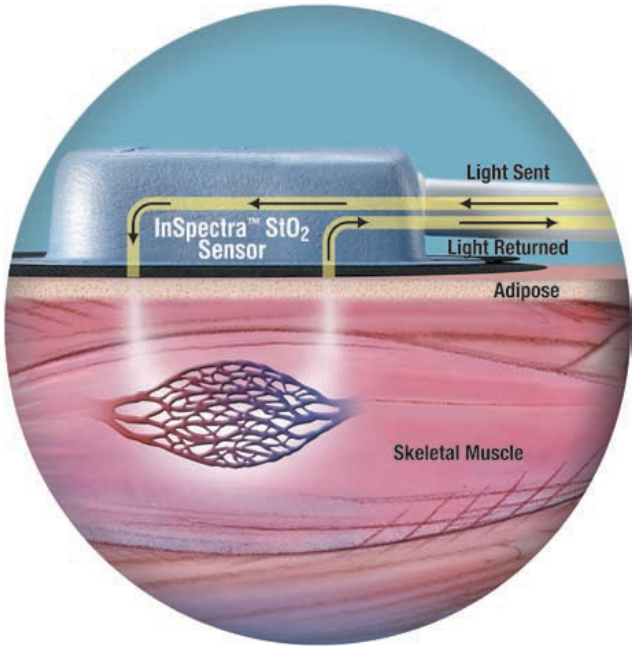

Figure 8. Principle of tissue oxygenation measurement[136]

1.6.3.3 How does StO_2 differ from SpO_2

StO_2 and SpO_2 (pulse oximetry oxygen saturation) are both non-invasive measures of oxygenation which can be easily obtained at the patient's bedside. They rely on the different light absorption characteristics of oxygenated and deoxygenated haemoglobin. Their main difference lies in where oxygenation is measured. Whilst pulse oximetry SpO_2 measures arterial oxygen saturation, StO_2 measures arterial and venous oxygen saturation and gives therefore a better reflection of oxygen delivery and consumption within the tissue.[137] Pulse oximetry SpO_2 is often referred to as a surrogate marker of systemic or global oxygen saturation whereas StO_2 is considered to be a measure of local oxygen saturation within the microcirculation. Therefore changes in StO_2 are more closely related to changes in the patient's tissue perfusion status, as opposed to SpO_2 which is a reflection of blood oxygenation and tends to

change once pulmonary or cardiac function are compromised. Additionally, SpO_2 readings require a pulsatile signal generated by the arterial blood flow.[136, 138]

1.6.3.4 Validation

There is no accepted 'gold standard' against which to validate StO_2 measurements. However, there are a number of very small studies which compared StO_2 against invasive $ScvO_2$ values. $ScvO_2$ is a commonly used target for haemodynamic optimisation. A study conducted in an ICU setting demonstrated significant correlation (r^2=0.79) between the two methods.[139] This finding was confirmed by a study amongst critically ill ED patients (r^2=0.74).[140]

1.6.3.5 Clinical application

Tissue oxygen saturation (StO_2) monitoring has been used as a research tool to assess microvascular dysfunction in critically ill patients suffering from major trauma, different types of shock, sepsis, heart failure; patients with compartment syndrome and those undergoing cardiac or reconstructive surgery.[128-131, 141-144] This monitoring modality has not been introduced into routine clinical practice. Data about the distribution of StO_2 values in healthy adults is limited. A study amongst healthy volunteers (n=707) found a thenar StO_2 of 87± 6% (mean ±SD).[131] In major trauma patients a StO_2 <75% in the first hour upon arrival in the ED was associated with multi-organ failure.[128]

1.7 Summary of Introduction

Several key aspects emerge from this introduction. Sepsis remains a major health care burden associated with a rising incidence and high mortality. The introduction of new sepsis management strategies has resulted in only small improvements. These strategies rely upon invasive monitoring to tailor treatment to predefined resuscitation targets. Such an approach is neither feasible nor practical in many EDs worldwide. Since early intervention in sepsis has shown to improve outcome, monitored goal directed therapy needs to start as soon as possible. However, for monitoring modalities to be applied as the patient reaches the hospital, they have to be safe, quick and easy to use. A number of non-invasive technologies have been developed and validated in different clinical settings and of these, three have shown promising results in critically ill patients. These are TEB, transcutaneous Doppler ultrasound and NIRS tissue oxygen saturation. However, the usefulness of any of these modalities in the early management of sepsis is not known.

1.8 General aims of this project

The overall aim of this thesis is to explore the potential benefit of different methods of non-invasive monitoring in the management of sepsis and severe sepsis / septic shock in the Emergency Department.

To justify a future therapeutic trial it would need to be shown that:

1. Patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED.
2. The abnormal cardio-haemodynamic parameters change towards normal with treatment.
3. The degree of initial abnormality is related to outcome (mortality).
4. Normalisation of cardio-haemodynamic parameters with treatment is related to outcome.

It would also be necessary to show:

5. Which non-invasive monitoring modality is most strongly related to outcome?

2 METHODOLOGY

2.1 Research Setting

This research project consists of two separate prospective studies amongst Emergency Department patients with differing severities of sepsis. The main body of research was carried out in the ED of the Leicester Royal Infirmary (LRI), a large urban teaching hospital. The follow up took place on hospital wards of the LRI, including the Intensive Care Unit, and the Leicester General Hospital (LGH). (A personal account of setting up and carrying out research in emergency care can be found in Appendix 1).

The LRI and the LGH are two of the three hospitals that form the University Hospitals of Leicester NHS Trust. All three hospitals receive acute patients but the LRI is the only hospital in Leicestershire that has an Emergency Department catering for a mixed urban and rural population. The ED at the LRI sees 400 patients per day on average, a quarter of which are children. It is the busiest single site ED in the UK and amongst the busiest EDs in Europe.[145]

The recruitment for the first study *'Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis'* took place between August and November 2007.

Data for the second study '*Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult Emergency Department patients with severe sepsis or septic shock'* was collected during two three-month periods between July 2008 and April 2009.

2.2 Study 1 – Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis

2.2.1 Study design and population

2.2.1.1 Study objectives

Primary objectives

1) To assess TEB cardio-haemodynamic parameters in septic patients and how they compare to non-septic ED patients.
2) To assess the change in TEB cardio-haemodynamic parameters in septic patients during normal management in the ED.

Secondary objectives

3) To assess the change in TEB cardio-haemodynamic parameters in septic patients after a 24 hour-period of treatment.
4) To determine the relationship between changes in TEB cardio-haemodynamic parameters and changes in conventional variables (mean arterial pressure and heart rate) in septic patients.

2.2.1.2 Design and selection of patients

This was a prospective observational cohort study amongst adult patients presenting to the Emergency Department at the Leicester Royal Infirmary with the clinical diagnosis of sepsis. Recruitment took place whenever the researcher (myself) was available which was usually daily between 0800 and 2000 hours. Potential participants were identified through the computerised Emergency Department database (EDIS) upon their arrival in the ED. Patients who met the inclusion criteria (see below) were approached by the researcher and the study was explained to them. Non-invasive cardio-haemodynamic monitoring using TEB was commenced as soon as possible. Informed consent was obtained from the patient as soon as clinically appropriate. Cardio-haemodynamic parameters were measured continuously throughout the patient's stay in the ED whilst they received normal therapy for sepsis. A further 10 minute measurement was obtained on the ward 24 hours after the initial TEB assessment. All readings were stored electronically and were not available to the treating clinician.

The age and gender matched controls were recruited amongst non-septic Emergency Department patients from the 'Minor' treatment area. They were only eligible for participation if their injury severity score was less than one (ISS $\leq$ 1) and their pain score assessment confirmed no or mild discomfort. This was to minimise any injury provoked cardiovascular changes that have been previously reported.[146] The control group underwent only one 10 minute TEB measurement.

Study population

- **Study group**

Inclusion criteria:

1. Age over 16 years
2. Clinical evidence of infection and two or more SIRS (Systemic inflammatory response syndrome) criteria:
    - Temperature > 38°C or < 36°C
    - Heart rate > 90/min
    - Respiratory rate > 20 breaths/min
    - WCC > 12.0×10^9/l or < 4.0×10^9/l

Exclusion criteria:

1. Need for immediate ventilatory support or surgery
2. Hypotension (systolic BP < 90 mm Hg)
3. Lactic acidosis (blood lactate ≥4mmol/l)
4. Administration > 500 ml of intravenous fluid
5. Pregnancy

- **Control group**

Inclusion criteria:

1. Age over 16 years (age-matched)
2. No evidence / suspicion of infection
3. Injury Severity Score (ISS) ≤ 1
4. No or mild discomfort (using validated pain score for assessment)

Exclusion criteria:

1. As for study group
2. Presence of any SIRS criteria

2.2.1.3 Data acquisition

Patients' eligible for participation were connected to the Thoracic Electrical Bioimpedance (TEB) monitor in order to commence cardio-haemodynamic measurements as soon as possible. A detailed description of data acquisition and the TEB monitor can be found in *section 2.4*.

2.2.1.4 Sample size calculation

From preliminary work amongst critically ill patients in the Emergency Department of the Leicester Royal Infirmary I discovered a standard deviation (SD) of 2.0 for TEB cardiac output. Assuming a power of 90% and an alpha of 0.05% with a SD of 2.0 to detect a minimum clinically significant difference of 2.0 in cardiac output (based on unpublished data) between septic patients and the control group, 44 patients would be required. Allowing for a 10% attrition rate would increase the sample size to 49 patients. To allow for equal numbers to be recruited in each group the sample size had to increase to 50. This sample size would have sufficient power to detect a clinically significant difference in change of cardiac output after intravenous fluid administration in the Emergency Department (paired data).

2.2.2 Study 1 – Objective 1

Comparison of TEB cardio-haemodynamic parameters between septic and non-septic ED patients

The first primary aim of this research project was to assess whether there exists a clinically significant difference in cardiac output measured using TEB between septic and non-septic ED patients. The detailed study methodology has been described in *section 2.2.1.*

Cardio - haemodynamic parameters of the study group patients taken on arrival in ED were compared with the measurements obtained from the age and gender matched control group. For each patient the median of the best 100 readings, as indicated by quality of signal, obtained within the first 10 minutes of recording were used for analysis. Comparison was made using the overall mean value of each parameter of the study and control group.

2.2.3 Study 1 – Objective 2

Change of TEB cardio-haemodynamic parameters in septic patients during normal treatment in the ED

The same patients and data as described for the study group in *section 2.2.1* were used. The study's sample size of 50 patients (*section 2.2.1.4*) gave sufficient power to detect a clinically significant difference in change of cardiac output, as paired data was used. Cardio-haemodynamic parameters taken on arrival and departure from the ED were compared. For the analysis the median of the best 100 measurements obtained for each patient within the first and last 10 minutes of recording in the ED were used. Comparison was made using the overall mean value of each parameter in the study group on arrival and departure from the ED.

2.2.4 Study 1 – Objective 3

Change of TEB cardio-haemodynamic parameters in septic ED patients after a 24-hour period of treatment

Again, the same study group patients as described in *section 2.2.1* were used. Cardio - haemodynamic parameters taken on arrival in the ED were compared with the measurements obtained after 24 hours of normal treatment. For the analysis the median of the best 100 measurements obtained for each patient within the first 10 minutes on arrival in the ED and during the 10 minute follow-up recording were used. Comparison was made using the overall mean value of each parameter in the study group on arrival in the ED and at 24 hours.

2.2.5 Study 1 – Objective 4

Relationship between changes in TEB cardio-haemodynamic parameters and changes in conventional MAP and HR in septic patients

A secondary aim of this study was to assess how changes in TEB cardio-haemodynamic data in septic ED patients compare with changes in conventional parameters such as heart rate and blood pressure. Comparisons were made using data taken on ED arrival, ED departure and at 24 hour follow up. The patients' data as described in *section 2.2.3 and 2.2.4* was used.

2.3 Study 2 – Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult Emergency Department patients with severe sepsis or septic shock

2.3.1 Study design and population

2.3.1.1 Study objectives

Primary objectives

1) To determine cardio-haemodynamic parameters in patients with severe sepsis / septic shock and how they compare to non-septic ED patients.

2) To assess the change in cardio-haemodynamic parameters in patients with severe sepsis / septic shock during normal management in the Emergency Department and after a 24 hour-period of treatment.

Secondary objectives

3) To determine the relationship between cardio-haemodynamic parameters in patients with severe sepsis / septic shock and outcome (length of survival / in-hospital mortality)

4) To assess the relationship between cardio-haemodynamic parameters and conventional variables (mean arterial pressure and heart rate) in severely septic patients

5) To compare simultaneous pairs of TEB and Doppler ultrasound cardiac output/index and stroke volume estimations in patients with severe sepsis / septic shock.

6) To assess the change in tissue oxygen saturation in patients with severe sepsis/septic shock before and after standard ED resuscitation; and to obtain initial data on the relationship between tissue oxygen saturation and clinical outcome.

2.3.1.2 Design and selection of patients

This was a prospective observational cohort study amongst adult patients (sixteen years or older) presenting to the Emergency Department at the Leicester Royal Infirmary with the clinical diagnosis of sepsis and evidence of organ dysfunction. Sepsis was defined according to the criteria of the International Sepsis Definitions Conference and organ dysfunction as one or more of the following: systolic blood pressure less than 90 mmHg, venous lactate equal or greater than 4mmol/l, reduced level of consciousness.[147] Venous lactate (Roche OMNI S, Roche Diagnostics Ltd) is available in the LRI Emergency Department as part of the routine near-patient blood tests analysis using the blood gas analyser.

Recruitment took place whenever the researcher (myself) was available which was usually daily between 0800 and 2000 hours. Senior nursing and medical staff in the ED were aware of the study and familiar with the inclusion criteria. Potential participants were identified through the computerised ED database (EDIS) upon their arrival in the Emergency Department and through the clinical staff, who were

encouraged to contact the researcher if any of their patients fulfilled the inclusion criteria. Potential candidates were screened for eligibility by the researcher, who was not involved in the clinical management of the patient. Patients eligible for participation were approached by the researcher and had the study explained to them. Non-invasive cardio-haemodynamic monitoring using TEB, tissue oxygen saturation (StO_2) and transcutaneous Doppler ultrasound was commenced as soon as possible. Informed consent was obtained as soon as clinically appropriate. Cardio-haemodynamic parameters were measured throughout the patient's stay in the Emergency Department whilst they received normal therapy. A further 10 minute measurement was obtained on the ward 24 hours after the initial cardio-haemodynamic assessment. All readings were stored electronically and were not available to the treating clinician.

The age and gender matched controls were recruited amongst non-septic Emergency Department patients from the 'Minor' treatment area. They were only eligible for participation if their injury severity score was less than one (ISS $\leq$ 1) and their pain score assessment confirmed no or mild discomfort. This was to minimise any injury provoked cardiovascular changes that have been previously reported.[146] The control group underwent only one 10 minute TEB measurement.

Study population

- **Study group**

Inclusion criteria:

1. Age over 16 years
2. Severe sepsis or septic shock (all 3 of the following)

   a. Clinical evidence of infection

   b. Two or more indicators of SIRS

   - Temperature > 38°C or < 36°C
   - Heart rate > 90/min
   - Respiratory rate > 20 breaths/min
   - WCC > 12.0 $\times 10^9$/l or < 4.0 $\times 10^9$/l

   c. Evidence of organ dysfunction

   (any of the following):

   - Lactate ≥ 4mmol/l
   - Systolic BP < 90mmHg
   - GCS <15

Exclusion criteria:

1. Need for immediate ventilatory support or surgery
2. Presence of an acute cerebral event, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, active gastrointestinal bleed, trauma
3. Known metastatic cancer
4. Pregnancy

- **Control group**

The same inclusion and exclusion criteria as used for the first study were applied (see *section 2.2.1.2*).

2.3.1.3 Data acquisition

Patients eligible for participation were immediately commenced upon cardio-haemodynamic monitoring. The three applied non-invasive modalities (TEB, Doppler ultrasound, NIRS tissue oxygen saturation) and the process of data acquisition are described in detail in *section 2.4.*

2.3.1.4 Sample size calculation

For Objective 1

From preliminary work amongst critically ill patients in our Emergency Department I found a standard deviation (SD) of 0.34 (for cardiac index). Assuming 80% power and alpha=0.05 with SD of 0.34 to detect a minimum clinically significant difference of 0.3 l/min/m^2 in cardiac index (based on published data [81, 91]) between patients with severe sepsis and the control group, 50 patients were required in total (25 in each group), including a 10% attrition rate.

For Objective 2

This sample size would have had sufficient power to detect a clinically significant difference in change of cardiac index (0.3 l/min/m^2) after treatment in ED and after 24 hours (paired data).

For Objective 3

As approximately 30% of septic patients were not expected to survive this would have given an approximately 1:2 ratio of non-survivors to survivors in the severe sepsis group. Assuming that out of 48 patients with severe sepsis/septic shock 16 would not

survive but 32 would, this would have provided a 80% power to detect a significant difference of 0.3 in cardiac index between survivors and non-survivors (SD 0.34, alpha=0.05). Therefore, 48 patients (54 allowing for 10% withdrawal rate) with severe sepsis were required to be recruited.

Overall

Thus for the study to be adequately powered to detect clinically significant differences in cardiac index (for primary and secondary outcomes) I had to recruit a minimum of 73 patients (48 with severe sepsis / septic shock and 25 controls). Using all 73 patients for the primary endpoint would have provided me with greater than 90% power to detect a difference of 0.3 in cardiac index between the severe sepsis group and the controls.

2.3.2 Study 2 – Objective 1

Comparison of cardio-haemodynamic parameters in ED patients with severe sepsis/septic shock and non-septic ED patients

The first primary question for this research project to answer was, whether there exists a clinically significant difference in cardiac index measured using TEB between ED patients with severe sepsis / septic shock and non-septic ED patients. The detailed methodology has been described in *section 2.3.1*.

TEB cardio - haemodynamic parameters of severely septic patients taken on arrival in the ED were compared with the snap-shot measurements obtained from the age and gender matched control group. For each patient the median of the best 100 readings, as shown by the quality indicator, obtained within the first 10 minutes of recording was calculated and used to compute the mean value for each cardio-haemodynamic parameter.

2.3.3 Study 2 – Objective 2

Change of cardio-haemodynamic parameters with normal treatment during the stay in the ED and after 24 hours

The other primary aim of study 2 was to assess the change in cardio-haemodynamic parameters of patients with severe sepsis / septic shock with treatment. The same patients and data as described for the study group in *section 2.3.1* was used. Comparisons were made between cardio-haemodynamic parameters recorded on arrival and departure from the ED and after 24 hours of normal treatment. For TEB parameters the median of the best 100 measurements, as indicated by quality signal, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow-up were used. During each assessment point a minimum of two transcutaneous Doppler measurements were carried out in close succession within 10 minutes. The reading with the best Doppler flow characteristics was used for analysis. Comparison was made using the overall mean value of each parameter from the study group on ED arrival and departure.

2.3.4 Study 2 – Objective 3

Relationship between cardio-haemodynamic parameters in patients with severe sepsis /septic shock and outcome

A secondary aim of this research project was to determine the relationship between cardio-haemodynamic parameters, 30 days in-hospital mortality and length of survival. The same patients and data as described for the study group in *section 2.3.1* were used.

TEB and Doppler cardio-haemodynamic parameters of survivors and non-survivors taken on ED arrival, ED departure and at 24 hours were compared. For TEB parameters the median of the best 100 measurements, as revealed by the quality indicator, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow up were used. For Doppler parameters the reading with the best flow characteristics obtained at each assessment point was used for analysis.

2.3.5 Study 2 – Objective 4

Relationship between TEB cardio-haemodynamic parameters and conventional heart rate and mean blood pressure

Another secondary aim of study 2 was to assess the relationship between cardio-haemodynamic parameters in ED patients with severe sepsis / septic shock and conventional parameters such as heart rate and blood pressure. The same patients and data as described for the study group in *section 2.3.1* were used. Comparisons were made using data taken on ED arrival, ED departure and at 24 hour follow up.

2.3.6 Study 2 – Objective 5

Comparison of simultaneous TEB and transcutaneous Doppler ultrasound cardio-haemodynamic measurements

The aim was to compare simultaneous pairs of TEB and Doppler measurements obtained at the three assessment points and to assess correlation and agreement between them. The same patients and data as described for the study group in *section 2.3.1* were used. For TEB parameters the median of the best 100 measurements, as revealed by the quality indicator, obtained for each patient within the first and last 10 minutes of recording in the ED and during the 10 minute follow up were used. For Doppler parameters the reading with the best flow characteristics obtained at each assessment point was used for analysis.

2.3.7 Study 2 – Objective 6

Determining tissue oxygen saturation in patients with severe sepsis or septic shock; its change with normal treatment and relationship to outcome

The final objective of study 2 was to determine tissue oxygen saturation (StO_2) in severely septic patients, how it changes with treatment and its correlation with pulse oximetry and cardio-haemodynamic parameters. This technology is at an early stage of development, thus no formal sample size calculation could be performed. Part of this final objective was also to explore the relationship between tissue oxygen saturation and in-hospital mortality.

The same patients and data as described for the study group in *section 2.3.1* were used. Tissue oxygen saturation was continuously recorded in the ED and followed up with a 10 minute measurement after 24 hours of treatment. For the purpose of analysis the median value obtained during the first and last five minutes of recording in the ED and during the follow up period was calculated for each patient.

2.4 Data acquisition using non-invasive modalities

Demographic data including anthropometric measures, past cardiovascular history and current drug history were documented for all recruited patients using a 'Patient Entry Form' (Appendix 2). Heart rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation (Propaq® CS monitor Welch Allyn Ltd), temperature and need for supplemental oxygen were obtained from the initial nurse assessment on patient's arrival in the ED.

2.4.1 Thoracic Electrical Bioimpedance (TEB)

TEB monitor

The Niccomo™ monitor (Medis Medizinische Messtechnik GmbH) was used to measure and calculate TEB cardio-haemodynamic parameters of all patients (Figure 9). Its inbuilt technology converts measured changes of thoracic impedance, which are the result of blood entering and leaving the aorta, into cardio-haemodynamic parameters (as described in *section 1.6.1*). The types of measured and calculated parameters are described in appendix 3. All recorded data was stored anonymously within the Niccomo™ and exported onto a computer for analysis.

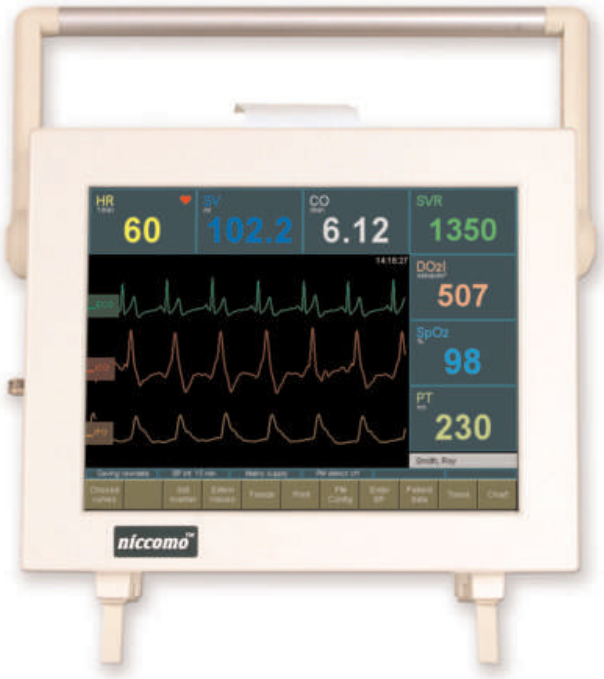

Figure 9. Niccomo™ monitor[148]

TEB data acquisition

The Niccomo™ monitor required the placement of four disposable pre-gelled dual sensor patches on the patient's thorax and neck. Prior to attaching the sensor patches, the patients skin was inspected to ensure it was not broken and then gently cleaned with an alcohol wipe (Uhs Alcotip Swab) and allowed to dry. In the meantime the patient's study number, height, weight, gender and age were entered into the Niccomo™ monitor.

The sensors were connected to colour coded electrode cables and then attached to the patient according to the manufacturer's instruction (Figure 10). The two neck sensors were placed opposite each other at the base of the neck in line with the earlobe. The thoracic sensors were positioned at the level of the xiphoid sternum between the anterior and posterior axillary line.

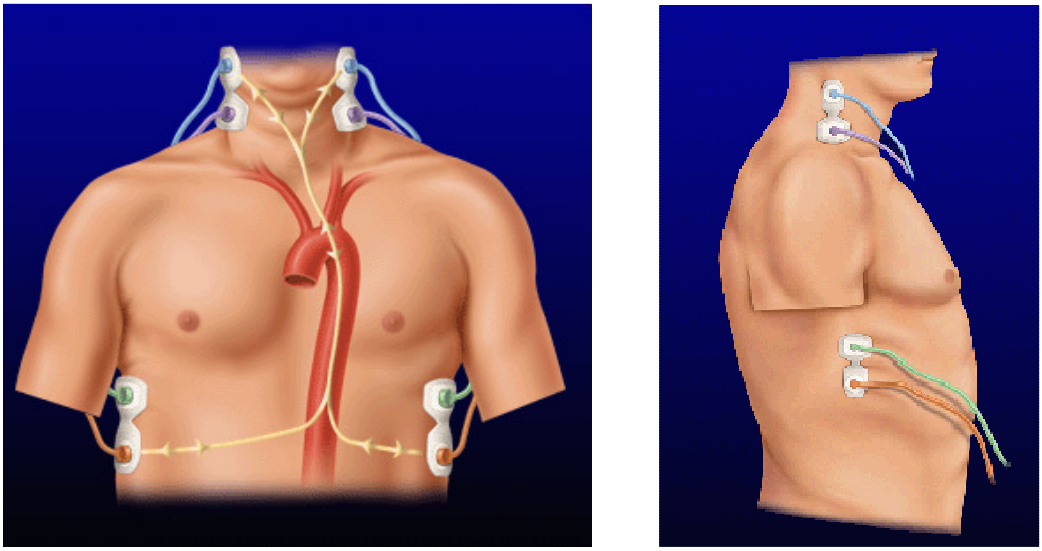

Figure 10. Sensor and electrode positioning [149, 150]

The outer electrodes (blue and orange) functioned as transmitters and the inner electrodes (purple and green) were used to receive the ECG and the thoracic impedance signals. Two LEDs built into a signal box within the electrode cable indicated whether a good contact was established between patient and monitor. A further quality indicator was displayed on the Niccomo™ screen, which gave an indication of the signal quality ranging from 0 to 100%. If the quality dropped below 50% then the measurements could not be relied upon. This was usually resolved by ensuring that the sensors were firmly attached to the patient and requesting that the patient would refrain from moving if possible. The quality of signal was displayed at all times throughout the recordings.

Before the measurements were commenced, a standard blood pressure cuff, plugged into the Niccomo™ device, was placed on the patient's arm. A blood pressure reading was taken every five minutes.

Patients enrolled in the study group were monitored continuously during their stay in the ED. For the calculation of SV, CO and CI, impedance signals of 16 heart beats were averaged (default setting of the Niccomo™ device) in order to eliminate the effect of respiration. SVR and MAP were calculated at 5-minute-intervals as they required a blood pressure measurement. All patients were followed up 24 hours later on the hospital ward where a further 10 minute recording took place.

The age and gender matched controls were recruited from the ED 'Minor' treatment area (as described in *sections 2.2.1 and 2.3.1*). Control group patients required a single 10 minute TEB measurement.

2.4.2 Transcutaneous Doppler Ultrasound

Doppler monitor

The USCOM (Ultrasonic Cardiac Output Monitor) was used to obtain intermittent transcutaneous Doppler Ultrasound measurement of cardiovascular parameters in patients with severe sepsis / septic shock. The USCOM is a portable unit consisting of a touch screen interface and a cleanable handheld transducer (Figure 11). The integrated software calculates cardio-haemodynamic parameters based on the measured Doppler flow profile across the aortic or pulmonary outflow tract. The obtained parameters are described in appendix 4. All recorded data was stored anonymously on the USCOM hard drive and transferred to a computer for analysis.

Figure 11. USCOM interface and transducer[107]

USCOM data acquisition

To obtain the required Doppler flow profile the transducer was placed at the patient's suprasternal notch (aortic valve) or alternatively along the left sternal edge at the level of the 3rd intercostal space (pulmonary valve). To gain access to the suprasternal notch the patient was positioned supine (Figure 12). The pulmonary outflow tract was accessible in supine as well as sitting patients who were unable to lie flat (Figure 13).

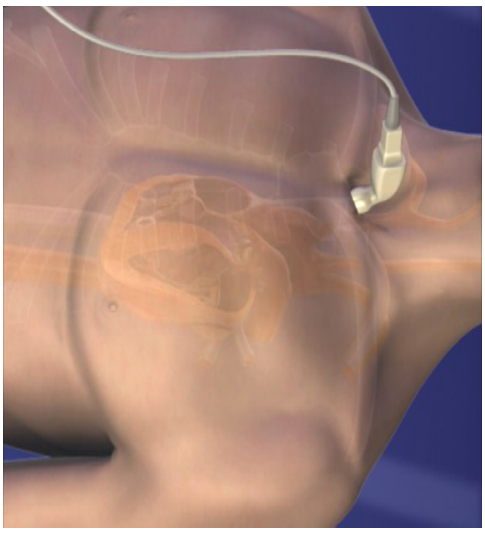

Figure 12. Transducer placement at the suprasternal notch (aortic window)[108]

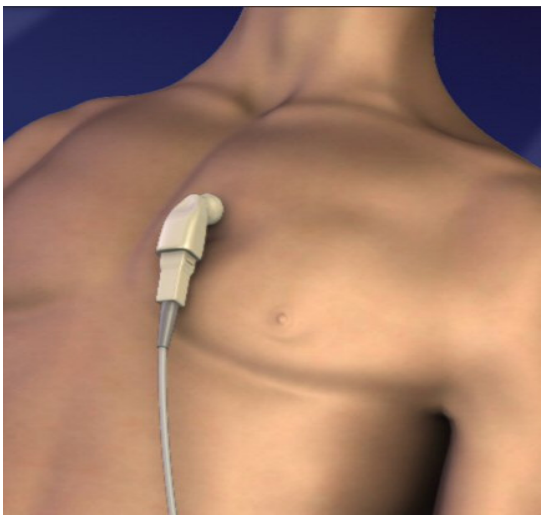

Figure 13. Transducer placement left sternal edge (pulmonary window)[108]

Prior to commencing measurements the patient's study number, height, weight, gender and age were entered into the interface unit and gel was applied to the flat face of the transducer. The patient's skin was inspected to ensure it was intact. The transducer was then firmly placed onto the skin and repositioned until a Doppler flow profile became visible on the screen of the interface unit. The angulation of the transducer was then carefully altered until a distinct triangular shaped flow profile was obtained. The angle was further adjusted aiming for maximum peak velocity (Figure 14).[151] Once an optimal profile was obtained it was saved on the hard drive. On average three consecutive measurements were recorded of which the one with the sharpest flow profile was selected for analysis.

The measurement took no longer than two minutes. Cardio-haemodynamic data was determined from the blood flow profile across the aortic or pulmonary valve using a height/weight dependent algorithm.

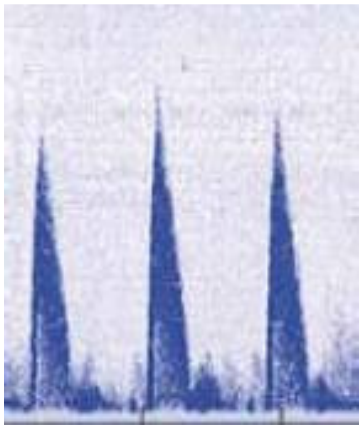

Figure 14. Example of optimal aortic valve Doppler profile.
A distinct triangular shape with straight and continuous sides converging at a sharp peak.

2.4.3 NIRS tissue oxygen saturation (StO_2)

StO_2 monitor

The portable InSpectra™ StO_2 monitor (Hutchinson Technology)[136] (Figure 15) was used to obtain continuous measurements of tissue oxygen saturation of all patients with severe sepsis / septic shock. This technology uses near-infrared (NIR) light and is based on the fundamental principle that oxygenated and deoxygenated haemoglobin have different light absorption spectra. Once the probe is positioned on the patient's thenar eminence (Figure 16) NIR light is sent into the skeletal muscle tissue below where it is absorbed by the tissue haemoglobin. Light that has not been absorbed returns as an optical signal and is analyzed to calculate the tissue oxygen saturation (StO_2).

Figure 15. InSpectra™ tissue oxygenation monitor[136]

StO_2 data acquisition

The InSpectra™ StO_2 tissue oxygenation monitor required the placement of a single disposable sensor patch on the patient's thenar eminence (Figure 16). Prior to attaching the sensor, the patient's skin was inspected to ensure that it was intact and then gently cleaned with an alcohol wipe (Uhs Alcotip Swab) and allowed to dry. The sensor unit contained an adhesive shield to facilitate attachment to the patient's skin and to protect measurements from ambient light interference. Once the sensor was attached to the patient it had to be connected to the optical cable before StO_2 monitoring could commence. StO_2 was monitored continuously throughout the patient's stay in the ED whilst normal treatment continued. A 10 minute follow-up StO_2 measurement was taken 24 hours later on the hospital ward.

Figure 16. Sensor position on thenar eminence[127]

2.5 Ethics & Consent

2.5.1 Ethical approval

Study 1 – *'Assessment of cardio-haemodynamic parameters in adult ED patients with uncomplicated sepsis'* was approved by the Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1 (REC Ref: 07/Q2501/56) on the 15th May 2007 (Appendix 5) and the University Hospitals of Leicester NHS Trust Research & Development department on the 19th June 2007 (Appendix 6).

Study 2 – *'Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult ED patients with severe sepsis / septic shock'* was approved by the Nottingham Research Ethics Committee 1 (REC Ref: 07/H0403/121) on the 17th December 2007 (Appendix7) and the University Hospitals of Leicester NHS Trust Research & Development department on the 22nd February 2008 (Appendix 8).

2.5.2 Consent procedure

Suitable patients were screened for eligibility by the 'Good Clinical Practice' trained researcher (myself). If there were no reasons for the patient to be excluded the patient was approached and the study was explained to them using a standard set of 'verbal prompts' (Appendix 9). If the patient did not object to participation in this study then non-invasive haemodynamic measurements were commenced, as recommended by the Ethics Committee. The patient was given a study summary sheet (Appendix 10) and if his/her clinical condition allowed a detailed information leaflet (Appendix 11). The

patient was offered the opportunity to ask any questions. Informed consent was obtained at the earliest appropriate time as judged by the researcher (myself).

If the patient was deemed to lack capacity for consent to participate in the study his / her personal consultee was approached. A personal consultee can be any person *'whom the person who lacks capacity would trust with important decisions about their welfare'* and who is capable and willing to act as the patient's personal consultee for the purpose of the study.[152] The study was explained to them and, if there were no objections to the patient's participation in the study, recording of measurements commenced. The personal consultee received a detailed information leaflet (Appendix 12) and was given the opportunity to ask any question. Informed consent/assent was obtained at the earliest appropriate time.

In situations where the patient was known to lack capacity, as the result of a chronic condition, and a personal consultee could, despite efforts, not be identified a R&D approved nominated consultee was approached.

Patients who were identified as suitable controls were required to have capacity to give informed consent in order to participate in this study. Once the study was explained to them by the researcher they were given the opportunity to read the patient information leaflet (Appendix 13) and to ask any questions.

All consent forms used is these studies had been approved by the Research and Ethics Committee (an example of the used consent forms is shown in appendix 14). Only patients for whom informed consent had been obtained were included in the study, all others were excluded and their recorded measurements deleted.

Withdrawals

Patients were allowed to withdraw from the study at any time without providing a reason. If they withdrew, they were given the opportunity to have the data, already collected, to be excluded from the study. However, if no request was made, data collected up to the point at which the patient withdrew was to be included in the analysis.

2.5.3 Adverse events monitoring

All three technologies are non-invasive methods to monitor cardio-haemodynamic variables. It was not envisaged that they would cause any adverse events. No adverse effects have been reported in the literature. It was possible that the ECG electrodes could irritate the skin, though this was unlikely. If I would have become aware that a participant was potentially being harmed because of taking part in the study then the study would have been stopped and investigated accordingly. If an adverse reaction had occurred and it was believed to be related to the study intervention then this would have been logged and reported.

2.5.4 Data protection

All data was collated and stored in the Emergency Medicine Academic Unit, at the Leicester Royal Infirmary. Patients were allocated a unique study number and a decoding record was kept securely within the department. Patient's confidentiality was maintained at all times.

2.6 Statistical analysis

Descriptive variables were presented as mean or median and 95% confidence interval (CI). The paired samples t-test was used to compare normally distributed continuous paired data, e.g. two sets of measurements from one cohort. To compare continuous unpaired data, such as septic with control patients, the independent samples t-test was chosen. The Kolmogorov-Smirnov-test was applied to test for normal distribution. Dichotomous variables were analysed using the Chi-square test. Two-tailed hypothesis testing was performed.

Kaplan-Meier- survival analysis was used to explore probability of survival in patients with severe sepsis / septic shock.

To test for diagnostic accuracy receiver operating characteristics (ROC) curves were constructed and the area under the ROC curve (AUROC) as predictor for mortality calculated.

To assess the correlation between two continuous variables the Pearson's coefficient was calculated. Linear regression was used to assess the direction and strength of the relationship between two continuous variables. To describe the agreement between two methods Bland-Altman plots were constructed.

All analysis was performed using Microsoft Office Excel 2007 and MedCalc®. The level of statistical significance was set at $p < 0.01$ (using the Bonferroni correction for multiple testing).

3 RESULTS

3.1 STUDY 1 – Assessment of cardio-haemodynamic parameters in adult Emergency Department patients with uncomplicated sepsis

3.1.1 General

Twenty nine patients who presented to the Emergency Department of the Leicester Royal Infirmary with features of sepsis during July and November 2007 were considered for inclusion. Two patients had to be excluded from enrolment in this study as one was given a working diagnosis of pulmonary embolus (PE), which was subsequently confirmed on CT pulmonary angiogram, and one patient was found to have diabetic ketoacidosis (DKA) without evidence of infection. A further two patients had to be excluded from the study, one for inability to gain informed consent and one due to a technical difficulty in recording measurements of adequate quality. Therefore 25 septic ED patients were included in the study.

The study population varied in their number of systemic inflammatory response syndrome (SIRS) criteria on arrival in the ED. There was a nearly equal distribution of patients with two (n=9), three (n=9) or four (n=7) SIRS parameters. The source of sepsis was most commonly the respiratory tract (n=10), followed by the urinary tract (n=5), skin/skeletal (n=4), abdomen (n=3), ENT/dental (n=2) and viral (n=1).

During the same study period twenty five control patients were recruited from the ED minor injury area. Figure 17 illustrates the flow of all patients through the study.

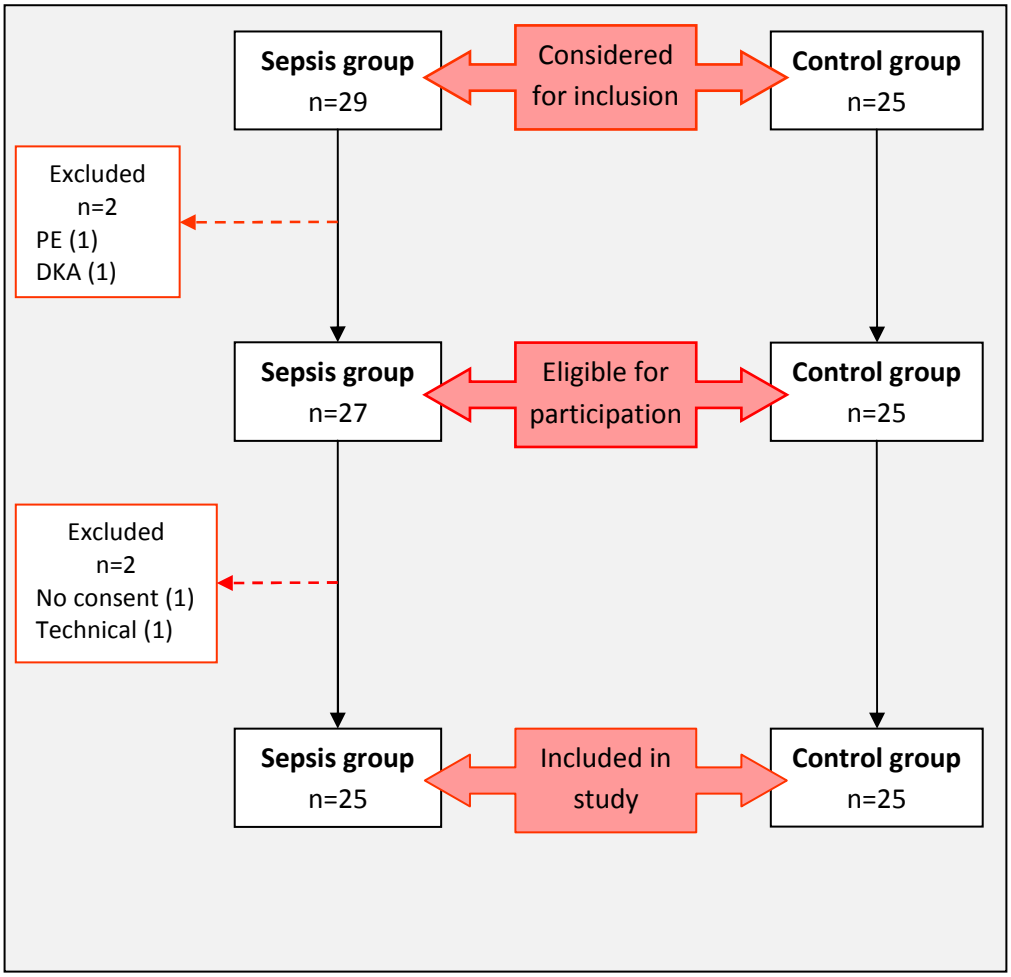

Figure 17. Flow diagram of study population

3.1.2 Study 1 – Results – Objective 1

Comparison of TEB cardio-haemodynamic parameters between septic and non-septic ED patients

Twenty five septic and twenty five non-septic control patients had TEB readings of adequate quality recorded and were included in the analysis. Both groups were well matched with regards to their demographics which are shown in Table 2.

Table 2. Characteristics of septic and control ED patients

Characteristic		Sepsis n=25	Control n=25	p-value
Age (yrs)		58 (48 – 67)	58 (48 – 67)	0.981
Gender, n (%)				
	Male	13 (52)	12 (48)	0.999
	Female	12 (48)	13 (52)	
Height (cm)		166 (161 – 172)	167 (162 – 172)	0.946
Weight (kg)		76 (69 – 83)	72 (67 – 78)	0.380

Values expressed as mean (95% confidence interval) unless stated otherwise

All septic patients had their conventional physiological measurements (heart rate, respiratory rate, blood pressure, oxygen saturation and temperature) taken as part of their routine assessment on arrival in the ED. These routine parameters were also obtained from all control patients prior to their enrolment in the study. Apart from SpO_2, parameters of septic patients differed significantly from those of the control cohort as depicted in Table 3.

Table 3. Routine physiological parameters on arrival in ED

Parameter	Sepsis n=25	Control n=25	p-value
Heart rate (min^{-1})	117 (110 – 124)	70 (66 – 74)	<0.001
Temperature (°C)	38.2 (37.5 – 39.0)	36.5 (36.3 – 36.7)	<0.001
Respiratory rate (min^{-1})	25 (21 – 28)	14 (13 – 15)	<0.001
Oxygen saturation (%)	97 (96 – 98)	98 (98 – 99)	0.067
Systolic blood pressure (mm Hg)	126 (115 – 136)	146 (140 – 152)	0.001

Values expressed as mean (95% confidence interval)

TEB measurements of septic patients were acquired as soon as possible after the patient's arrival in the ED. Non-septic control patients had their TEB readings taken during their stay in the ED minor injury area. On arrival in the ED septic patients had a significantly higher HR and a lower MAP than their non-septic controls. With regards to their cardio-haemodynamic measures ED patients with sepsis were found to have a significantly lower SV, SI and SVR compared to non-septic ED patients. Cardiac index was increased by 0.7 l/min/m^2 (95%CI 0.1 to 1.1) and cardiac output by 1.2 l/min (95%CI 0.1 to 2.4) in the septic cohort but this difference did not reach statistical significance. The TFC, a parameter primarily determined by the amount of intravascular, intra-alveolar and interstitial fluid in the thorax, was found to be similar in both cohorts. The TEB measurements of the control group were of slightly higher quality, as revealed by the quality indicator (QI). Table 4 gives a summary of the compared parameters, with those demonstrating statistical significance being shaded 'grey'.

Table 4. TEB parameters of septic and non-septic (control) patients on arrival in the ED

Parameter	Sepsis n= 25	Control n=25	p-value
QI (%)	89 (84 – 95)	94 (91 – 97)	0.116
CI (l/min/m^2)	3.8 (3.3 – 4.2)	3.1 (2.8 – 3.4)	0.013
CO (l/min)	6.9 (6.0 – 7.8)	5.7 (5.0 – 6.3)	0.029
SI (ml/m^2)	35 (31 – 39)	45 (41 – 49)	<0.001
SV (ml)	64 (56 – 73)	82 (72 – 91)	0.008
SVR (dynes·s·cm^{-5})	1071 (874 – 1269)	1435 (1263 – 1606)	0.006
MAP (mmHg)	89 (82 – 96)	100 (96 – 104)	0.007
TFC (1/kΩ)	29.0 (26.8 – 31.3)	27.0 (23.5 – 30.5)	0.319
HR (beats/min)	110 (103 – 117)	70 (66 – 74)	<0.001

Values expressed as mean (95% confidence interval)

The ability of each parameter to differentiate between septic and non-septic ED patients was tested using the receiver operating characteristics (ROC) analysis. The area under the ROC curve (AUROC), the ROC derived optimal cut-off and its sensitivity and specificity are presented in Table 5. The optimal cut-off was derived by giving equal value to sensitivity and specificity. The ROC curves for the three best performing parameters (AUROC >0.7), shaded in 'grey' in Table 5, are displayed in Figure 18.

Table 5. ROC derived values predictive of sepsis

Parameter	AUROC	Optimal cut-off	Sensitivity	Specificity
CI	0.702	> 3.0	80.0 (59.3-93.2)	52.9 (31.3-72.2)
CO	0.674	> 4.8	84.0 (63.9-95.5)	48.0 (27.8-68.7)
SI	0.743	≤ 39	64.0 (42.5-82.0)	68.0 (46.5-85.1)
SV	0.694	≤ 71	60.0 (38.7-78.9)	68.0 (46.5-85.1)
SVR	0.760	≤ 1174	72.0 (50.6-87.9)	72.0 (50.6-87.9)
TFC	0.643	> 26.6	64.0 (42.5-82.0)	56.0(34.9-75.6)

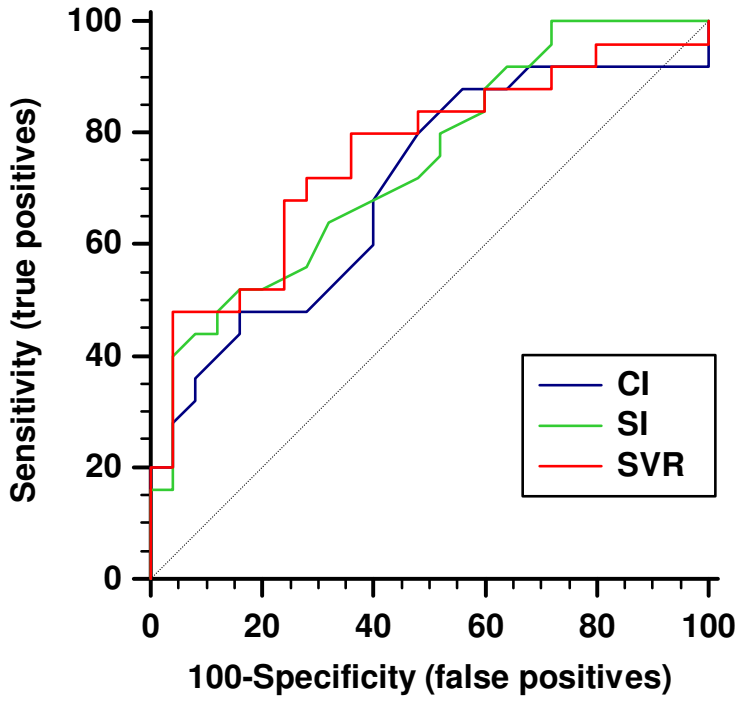

Figure 18. ROC curves for cardiac index, stroke index and systemic vascular resistance (ED arrival)

3.1.3 Study 1 – Results – Objective 2

Change of TEB cardio-haemodynamic parameters in septic patients with normal treatment in the ED

All septic patients were continuously monitored through the TEB device in addition to their conventional physiological observations whilst receiving normal treatment for sepsis. Treatment was administered at the discretion of the responsible clinician who had no access to the recorded TEB data. All septic patients received intravenous fluids and antibiotics and if clinically indicated supplemental oxygen in the ED, though there was no standard 'sepsis protocol' in place at the time of the study. Patients received on average 1144 millilitre (95%CI 893 to 1397) of intravenous fluids in the ED, equating to an average of 17 millilitre/kilogram bodyweight (95% CI 12 to 21).

TEB readings of adequate quality were successfully obtained for all included septic patients on arrival and departure from the ED. The comparison of arrival and departure measurements indicated, that the treatment given in the ED had very little immediate effect on changes in cardio-haemodynamic parameters (Table 6). Having said this, there were changes seen in CO and CI that were suggestive of a trend towards 'normal' values. Statistically significant changes were only observed for heart rate (HR) which was reduced by 11 beats/min (95% CI -15.6 to -5.6) and thoracic fluid content (TFC), which had increased by 2.6 per kilo ohm (95%CI 1.2 to 3.9) since patients' arrival in the ED.

Table 6. TEB measurements on arrival and departure from the ED

Parameter	ED arrival (n=25)	ED departure (n=25)	p-value
CI (l/min/m^2)	3.8 (3.3 – 4.2)	3.5 (3.1 – 3.9)	0.035
CO (l/min)	6.9 (6.0 – 7.8)	6.5 (5.6 – 7.4)	0.038
SV (ml)	64 (56 – 73)	67 (57 – 76)	0.265
SI (ml/m^2)	35 (31 – 39)	36 (31 – 40)	0.375
SVR (dynes·s·cm^{-5})	1071 (874 – 1269)	1112 (900 – 1325)	0.432
SVRI (dynes·s·cm^{-5} /m^2)	1957 (1577 – 2338)	2016 (1633 – 2398)	0.515
TFC (1/kΩ)	29.0 (26.8 – 31.3)	31.6 (28.8 – 34.4)	<0.001
HR (beats/min)	110 (103 -117)	99 (93 – 106)	<0.001
MAP (mmHg)	89 (82 – 96)	85 (79 – 90)	0.111
SBP (mmHg)	126 (115 – 136)	117 (108 – 125)	0.030
DBP (mmHg)	75 (69 – 82)	73 (68 – 79)	0.429
LCW (kg·m)	7.8 (6.6 – 9.1)	6.9 (5.9 – 7.8)	0.023
LCWI (kg·m/m^2)	4.2 (3.6 – 4.8)	3.7 (3.3 – 4.1)	0.026
PEP (ms)	83 (75 – 91)	83 (73 – 92)	0.905
LVET (ms)	242 (228 – 256)	256 (234 – 277)	0.060
ETR (%)	44 (41 – 46)	42 (39 – 44)	0.090
QI (%)	89 (84 – 95)	89 (83 – 94)	0.837

Values expressed as mean (95% confidence interval)

3.1.4 Study 1 – Results – Objective 3

Change of TEB cardio-haemodynamic parameters in septic ED patients after a 24-hour period of treatment

TEB measurements for 23 of the 25 septic patients were available after 24 hours of treatment. One patient had been discharged from hospital prior to the 24-hour follow-up assessment without the researcher being informed and one patient died shortly after departure from the ED. After admission to the ward patients received on average a further 1236 millilitres (95%CI 519 to 1953) of intravenous fluids over 24 hours. The paired TEB measurements obtained from the septic cohort on ED arrival and after 24 hours of treatment are presented in Table 7.

With normal treatment for sepsis the HR decreased significantly by 24 beats/min (95%CI -31 to -18) which, given the marginal changes in mean SV, resulted in a significant reduction in CI by 0.5 l/min/m^2 (95%CI -0.9 to -0.3). Significant changes were also seen in left ventricular ejection time (LVET), a marker of cardiac contractility, showing an increase by 40 milliseconds (95%CI 22 to 59) compared to ED arrival. There was a further increase of 3.4 per kilo ohm (95%CI 0.6 to 6.3) in the TFC by the end of 24 hours but this was not statistically significant. MAP and SVR showed no considerable changes during the first 24 hours of normal treatment.

Comparing the TEB measurements of the septic cohort obtained at 24 hours with the control data showed that nearly all parameters demonstrated a trend towards 'normal' values (Figure 19). This tendency was most noticeable for CI and CO where the difference between the septic cohort and controls was only 0.06 l/min/m^2 (95%CI -0.36 to 0.48) for cardiac index and 0.2 l/min (95%CI -0.8 to 1.2) for cardiac output.

Table 7. TEB measurements of septic patients on ED arrival and at 24 hour follow up

Parameter	ED arrival (n=23)	24 hour follow up (n=23)	p-value
CI (l/min/m^2)	3.7 (3.3 – 4.2)	3.2 (2.8 – 3.5)	<0.001
CO (l/min)	6.9 (5.9 – 7.9)	5.9 (5.2 – 6.6)	0.001
SV (ml)	64 (55 – 74)	69 (61 – 78)	0.102
SI (ml/m^2)	35 (31 – 39)	38 (34 – 42)	0.091
SVR (dynes·s·cm^{-5})	1089 (876 – 1302)	1152 (1021 – 1282)	0.449
SVRI (dynes·s·cm^{-5} /m^2)	1998 (1587 – 2409)	2108 (1861 – 2355)	0.479
TFC (1/kΩ)	28.8 (26.4 – 31.2)	32.2 (28.5 – 36.0)	0.020
HR (beats/min)	110 (102 – 117)	85 (79 – 92)	<0.001
MAP (mmHg)	90 (81 – 97)	87 (80 – 93)	0.418
SBP (mmHg)	127 (116 – 138)	123 (113 – 133)	0.440
DBP (mmHg)	76 (69 – 83)	74 (68 – 79)	0.394
LCW (kg·m)	7.9 (6.5 – 9.2)	6.5 (5.4 – 7.6)	0.003
LCWI (kg·m/m^2)	4.2 (3.6 – 4.8)	3.5 (3.0 – 4.0)	0.004
PEP (ms)	84 (75 – 93)	91 (82 – 100)	0.102
LVET (ms)	242 (226 – 257)	282 (259 – 305)	<0.001
ETR (%)	44 (41 – 46)	40 (37 – 42)	0.001
QI (%)	89 (83 – 94)	92 (87 – 97)	0.208

Values expressed as mean (95% confidence interval)

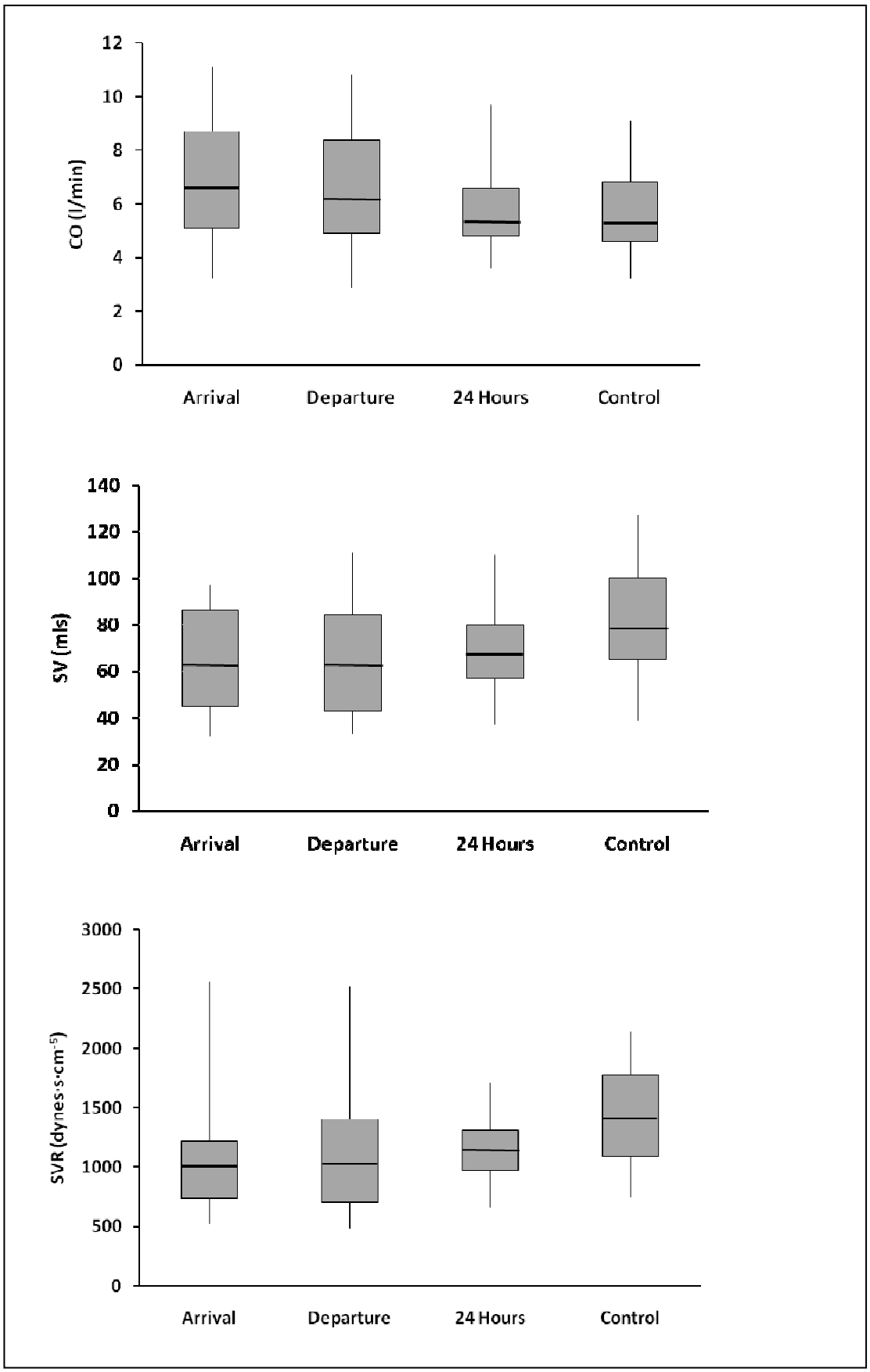

Figure 19. **Comparison of cardiac output, stroke volume and systemic vascular resistance in septic patients on ED arrival, ED departure, at 24 hour with non-septic controls**

3.1.5 Study 1 – Results – Objective 4

Relationship between changes in TEB parameters and changes in MAP and HR in patients with uncomplicated sepsis

Complete data sets were available from 23 septic patients. Comparisons were made between changes over 24 hours in measured cardio-haemodynamic and conventional circulatory parameters. CO and HR were both increased on arrival in the ED and decreased with treatment though the absolute and relative decrease in HR was more evident. The changes in SV were opposite to those of HR but less pronounced during the first 24 hours. Both, SVR and MAP were reduced in septic patients on their arrival in the ED compared to control and remained fairly static despite treatment.

Relative change over the first 24 hours whilst receiving normal treatment was calculated for each parameter and patient. The most significant changes were observed for HR -21.6% (95%CI -26.6 to -16.7) and CO -15.9% (95%CI -19.7 to -4.5). There was an increase in SV 12.7% (95%CI 1.1 to 24.4) and SVR 16.6% (95%CI -1.0 to 34.1), whilst there was no change in MAP -1.2% (95%CI -10.2 to 7.8%).

The strength of the relationship between relative changes in these parameters was assessed using Pearson's correlation coefficient (r) (Table 8). A poor relationship between changes in CO and changes in HR and MAP over the initial 24 hour period was demonstrated. There was a strong positive association between relative changes in SVR and MAP and a weak positive relationship between SVR and HR. A moderate negative association was found between changes in SV and HR, whereas changes in

SV were weakly negative associated with MAP. The graphical illustration of these relationships is shown in Figure 20. The scatter plot shows that changes in HR or MAP were unrelated to changes in CO, as indicated by the random spread of the data points and the linear approximation of their values parallel to the abscissa. Changes in SV and HR followed the expected inverse linear pattern with bigger increases in SV being associated with a greater decrease in HR. The strongest linear relationship is shown for changes in SVR and MAP, where data points are clustered around an almost diagonal line.

Table 8. Pearson's correlation coefficients for relative changes in TEB cardio-haemodynamic and conventional variables

	%ΔCO Arr/Dep	%ΔCO Arr/24hr	%ΔSVR Arr/Dep	%ΔSVR Arr/24hr	%ΔSV Arr/Dep	%ΔSV Arr/24hr	%ΔMAP Arr/Dep	%ΔMAP Arr/24hr
%ΔHR Arr/Dep	0.380		-0.049		-0.357		0.440	
%ΔHR Arr/24hr		-0.043		0.410		**-0.534**		**0.568**
%ΔMAP Arr/Dep	0.310		0.468		-0.040			
%ΔMAP Arr/24hr		-0.157		**0.819**		-0.424		
%ΔSV Arr/Dep	**0.710**		**-0.665**					
%ΔSV Arr/24hr		**0.847**		**-0.745**				
%ΔSVR Arr/Dep	**-0.681**							
%ΔSVR Arr/24hr		**-0.649**						

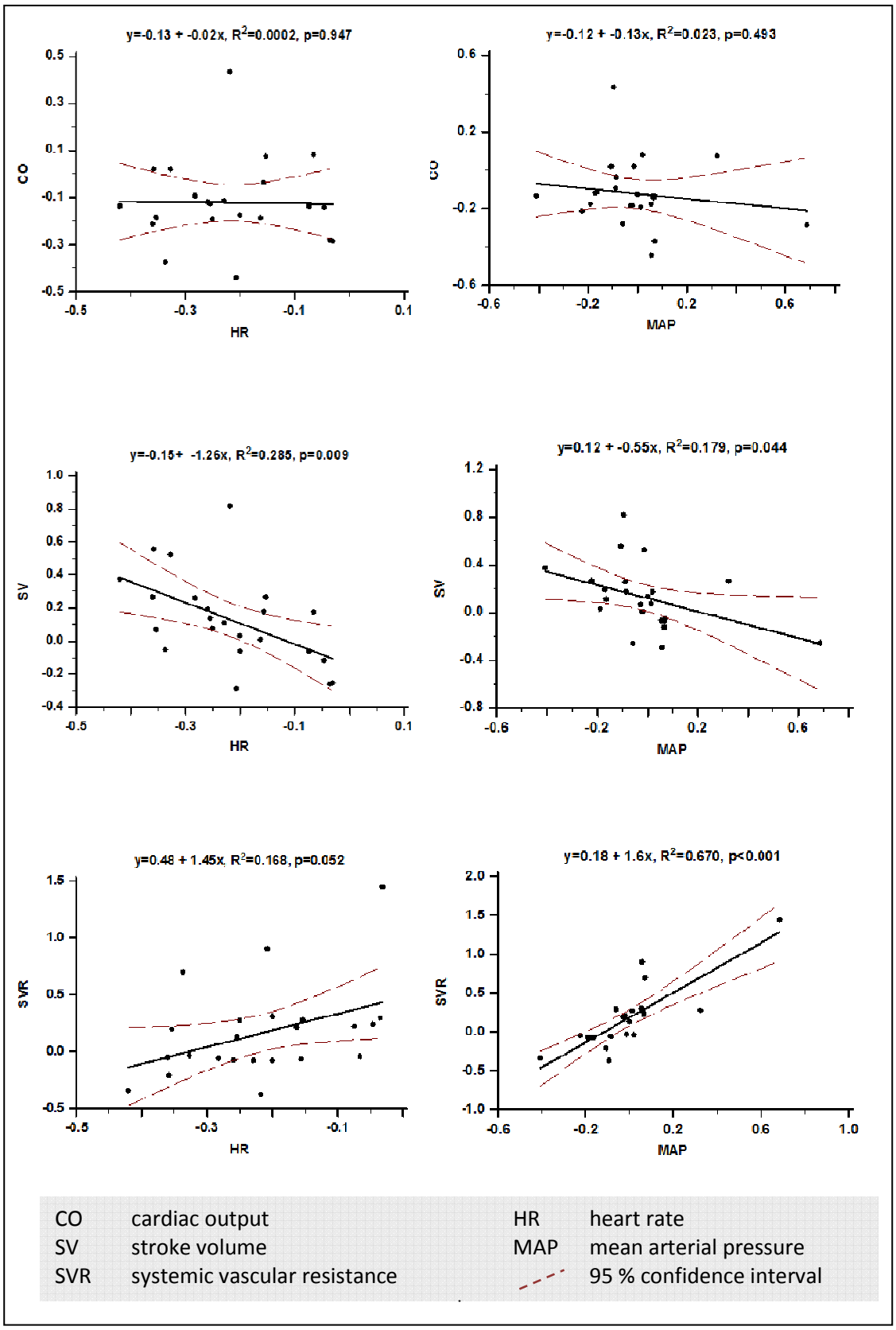

Figure 20. **Relationship between changes in cardio-haemodynamic and conventional parameters in septic patients with 24 hours of normal treatment**

3.2 STUDY 2 – Assessment of cardio-haemodynamic parameters and tissue oxygen saturation in adult ED patients with severe sepsis or septic shock

3.2.1 General

Ninety patients who presented to the Emergency Department with features of severe sepsis / septic shock between August 2008 to October 2008 and January 2009 to March 2009 were screened for inclusion. Forty patients were excluded as per the study's exclusion criteria. One further patient was unable to give informed consent due to lack of mental capacity and unavailability of a 'personal consultee'. Therefore forty nine patients were included in the study. The patients' flow through the study is illustrated in Figure 21.

Seventeen patients were classed as suffering from severe sepsis, fourteen from septic shock and eighteen from cryptic shock. The source of sepsis was most commonly the respiratory tract (n=32), followed by the urinary tract (n=9), abdomen (n=4), central nervous system (n=2), skin (n=1) and HIV related (n=1).

During the study period five more patients were recruited to the already existing control pool of non-septic ED patients. Out of this data pool twenty five patients, whose demographic data best matched those of the severe sepsis cohort, were chosen to form the control cohort for this study.

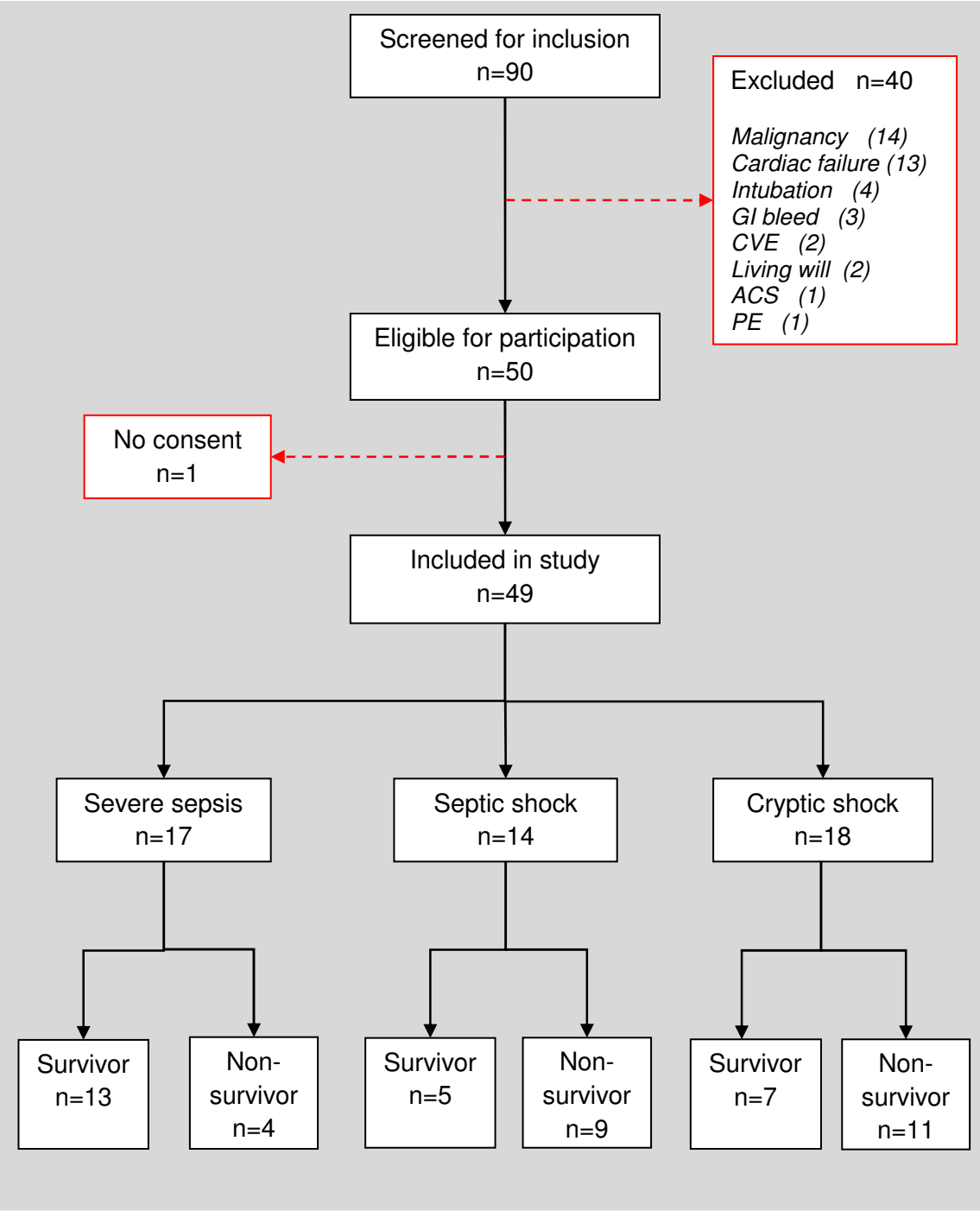

Figure 21. Flow diagram of study population

The mean age of the cohort studied was 71 years (95%CI 65 to 77) of which 35 (71%) were men. Their baseline characteristics are shown in Table 9. Nearly one quarter of patients were care home residents. Half of all patients suffered from chronic cardiovascular conditions, with hypertension being the most common.

Table 9. Characteristics of study participants

Characteristic		Study participants n=49
Age (yrs)		71 (65 – 76)
Gender, n (%)	**Male**	35 (71)
	Female	14 (29)
Height (cm)		170 (168 – 173)
Weight (kg)		74 (67 – 80)
Ethnicity, n (%)	**Asian**	7 (14)
	Caucasian	42 (86)
Care Home residency, n (%)		12 (24)
Past cardiovascular history, n (%)		
Any cardiovascular morbidity		24 (50)
Coronary artery disease		5 (10)
Myocardial infarct		8 (16)
Arrhythmias		6 (12)
Hypertension		11 (22)
Heart failure		2 (4)

Values expressed as mean (95% confidence interval) unless stated otherwise

The physiological observations taken on arrival in the ED clearly showed that the cohort was critically ill with an average early warning score (EWS) of 7, ranging from 3 to 12. More than three quarters of patients (78%) had three or more positive SIRS criteria when arriving in the ED. Nearly half of the patients (45%) were hypotensive

and 59% had a reduced level of consciousness on arrival in the ED. The near-patient venous lactate taken on arrival measured ≥ 4mmol in nearly two thirds (59%) of patients. Table 10 summarises the physiological parameters and blood results taken on ED arrival.

Table 10. Physiological and biological parameter on arrival in ED

Parameter	Study participants n=49
Physiology on ED arrival,	
GCS score*	14 (14 – 15)
Temperature (°C)*	38 (37.3 – 38.4)
Heart rate (min $^{-1}$)	116 (110 – 122)
Oxygen saturation (%)	96 (94 – 97)
Respiratory rate (min $^{-1}$)	30 (28 – 34)
Systolic blood pressure (mm Hg)	101 (94 – 109)
EWS	7.2 (6.6 – 7.7)
MEDS score	9.1 (8.0 – 10.2)
Need for supplemental oxygen, n (%)	35 (71)
Arrival blood results,	
White cell count (10^9/l)	16.5 (13.2 – 19.7)
Haemoglobin (g/l)	12.5 (12 – 13)
Platelet count (10^9/l)	273 (230 – 317)
Lactate (mmol/l)	5.0 (4.0 – 6.0)

Values expressed as mean (95% confidence interval)
*Median (95% confidence interval)
MEDS Mortality in Emergency Department Sepsis score

The observed mortality in this severe sepsis /septic shock cohort was 49% (n=24). One third of all deaths occurred within 24 hours of patients' arrival to the Emergency Department. Figure 22 illustrates the proportion of death within 24 hours, early (1 to 3 days), intermediate (4 to 13 days) and late (14 to 30 days) for this cohort. The survival

probability over time is shown in Figure 23. It illustrates that a patient's chance of survival reduced steeply by 30% within the first 72 hours of hospital admission.

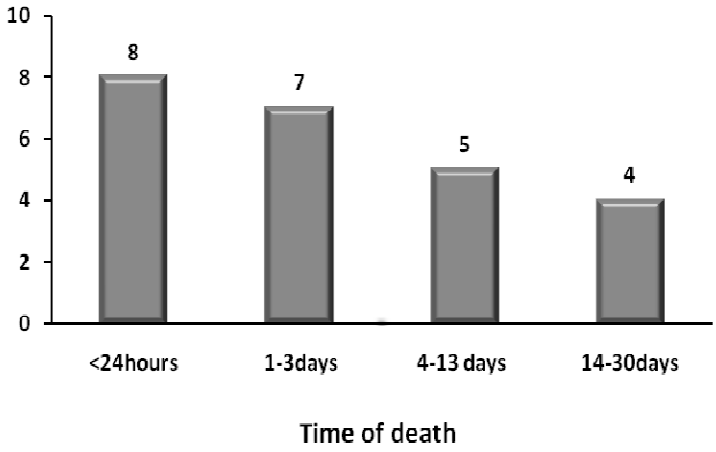

Figure 22. Number of deaths in relation to length of survival since arrival in the ED

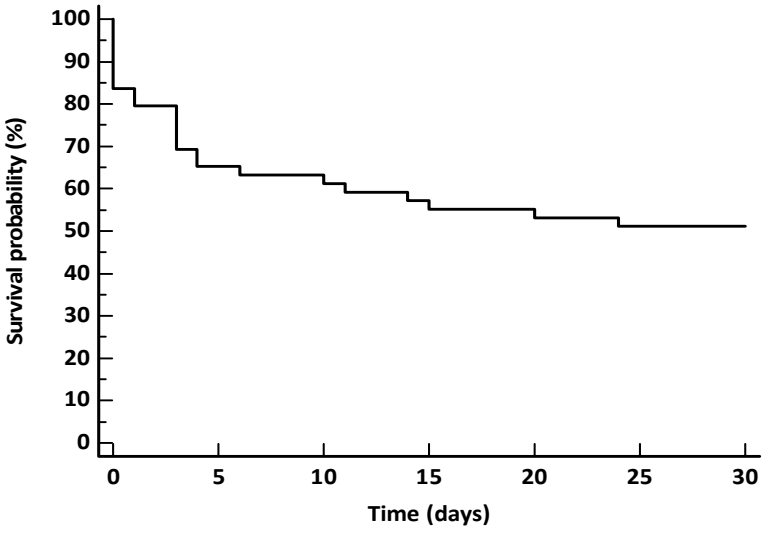

Figure 23. Probability of survival from sepsis with organ dysfunction over time

3.2.2 Study 2 – Results – Objective 1

Comparison of cardio-haemodynamic parameters in Emergency Department patients with severe sepsis or septic shock and non-septic ED patients

Forty eight of the forty nine study group patients had TEB measurements of adequate quality obtained upon their arrival in the ED. The control cohort consisted of twenty five patients. All of the seventy three patients were included in the analysis. Both groups were well matched in view of their demographics. There were proportionally more men in the study group but this was not statistically significant. Table 11 summarises their characteristics.

Table 11. Characteristics of study and control group

Characteristic		Severe sepsis /shock n= 48	Control n=25	p-value
Age (yrs)		71 (65 – 77)	69 (61 – 76)	0.603
Gender, n (%)	**Male**	35 (73)	15 (60)	0.385
	Female	13 (27)	10 (40)	
Height (cm)		171 (168 – 174)	169 (164 – 174)	0.445
Weight (kg)		74 (68 – 80)	74 (69 – 79)	0.994

Values expressed as mean (95% confidence interval) unless stated otherwise

The TEB measurements obtained in the control group were of higher quality than the study group measurements, as indicated by the quality index (QI). The difference however was not statistically significant and the quality index of all obtained TEB readings was well above the 50 % mark which is the manufacturer's recommended cut

off point for reliable data. The difference in CI between study group and control was 0.3 l/min/m^2. Though this was in keeping with the pre-defined minimum clinical significant difference it did not reach statistical significance, as the standard deviation was larger than anticipated. Patients with severe sepsis / shock were found to have a significantly lower SV and stroke index SI than their controls. Systemic vascular resistance was significantly lower in the study cohort as was the MAP. Severely septic patients had a significantly higher TFC, a parameter primarily determined by the amount of intravascular, intra-alveolar and interstitial fluids in the thorax. Table 12 gives an overview of all compared parameters.

Table 12. TEB parameters in severe sepsis/ septic shock on ED arrival compared to control

Parameter	Severe sepsis n= 48	Control n=25	p-value
QI (%)	84 (78 – 89)	93 (89 – 96)	0.015
CI (l/min/m^2)	3.4 (3.1 – 3.7)	3.1 (2.8 – 3.4)	0.135
CO (l/min)	6.4 (5.6 – 7.1)	5.7 (5.0 – 6.4)	0.215
SI (ml/m^2)	32 (29 – 35)	44 (40 – 49)	<0.001
SV (ml)	59 (53 – 64)	82 (72 – 91)	<0.001
SVR (dynes·s·cm^{-5})	984 (844 – 1123)	1466 (1279 – 1653)	<0.001
MAP (mmHg)	75 (70 – 81)	102 (97 – 108)	<0.001
TFC (1/kΩ)	31.5 (29.8 – 33.2)	26.4 (24.5 – 28.3)	<0.001
HR (beats/min)	111 (104 – 118)	71 (66 – 76)	<0.001

Values expressed as mean (95% confidence interval)

Comparison was also made between measurements available from the severe sepsis cohort at the 24 hour follow up (n=37) and the control group (Table 13). The lower number of severe septic patients at 24 hours was due to death (n=8), refusal to follow up (n=2) and equipment failure (n=1), section 3.2.3 contains a more detailed explanation. Despite these drop-outs both groups remained well matched in view of age (p=0.71), gender (p=0.21), height (p=0.23) and weight (p=0.58).

Table 13. TEB parameters in severe sepsis/ shock at 24 follow up compared to controls

Parameter	Severe sepsis n= 37	Control n=25	p-value
QI (%)	84 (78-90)	93 (89 – 96)	0.019
CI (l/min/m^2)	3.0 (2.7-3.2)	3.1 (2.8-3.4)	0.538
CO (l/min)	5.7 (5.0-6.4)	5.7 (5.0-6.4)	0.974
SI (ml/m^2)	35 (31-38)	44 (40-49)	0.001
SV (ml)	66 (58-75)	82 (72-91)	0.015
SVR (dynes·s·cm^{-5})	1075 (929-1221)	1466 (1279-1653)	0.003
MAP (mmHg)	76 (70-81)	102 (97- 108)	<0.001
TFC (1/kΩ)	38.6 (34.5-42.6)	26.4 (24.5-28.3)	<0.001
HR (beats/min)	87 (81-94)	71 (66-76)	<0.001

Values expressed as mean (95% confidence interval)

There was no statistical or clinical significant difference in CI or CO between the two groups. At 24 hours the severe sepsis cohort still had a significantly lower SVR and MAP as well as a higher HR compared to the control group. There was no statistical significant difference in SV but there was in SI. The severe sepsis group had at 24 hours a significantly higher TFC than the control cohort.

Receiver operating characteristics (ROC) analysis was used to assess the ability of each cardio-haemodynamic parameter to discriminate between severely septic and non-septic ED patients on arrival. The area under the ROC curve (AUROC), the ROC derived optimal cut-off and its sensitivity and specificity are presented in Table 14. The ROC curves for the four bests performing parameters with an AUROC greater than 0.7 (shaded in grey) are displayed in Figure 24.

Table 14. ROC derived values predictive of severe sepsis on ED arrival

Parameter	AUROC	Optimal cut-off	Sensitivity	Specificity
CI	0.588	> 3.1	54.8 (38.7-70.2)	60.0 (38.7-78.9)
CO	0.576	> 4.8	76.2 (60.5-87.9)	44.0 (24.4-65.1)
SI	0.810	≤ 37	76.2 (60.5-87.9)	76.0 (54.9-90.6)
SV	0.770	≤ 69	78.6 (63.2-89.7)	72.0 (50.6-87.9)
SVR	0.822	≤ 1094	79.0 (62.7-90.4)	80.0 (59.3-93.2)
TFC	0.740	> 27	76.2 (60.5-87.9)	64.0 (42.5-82.0)

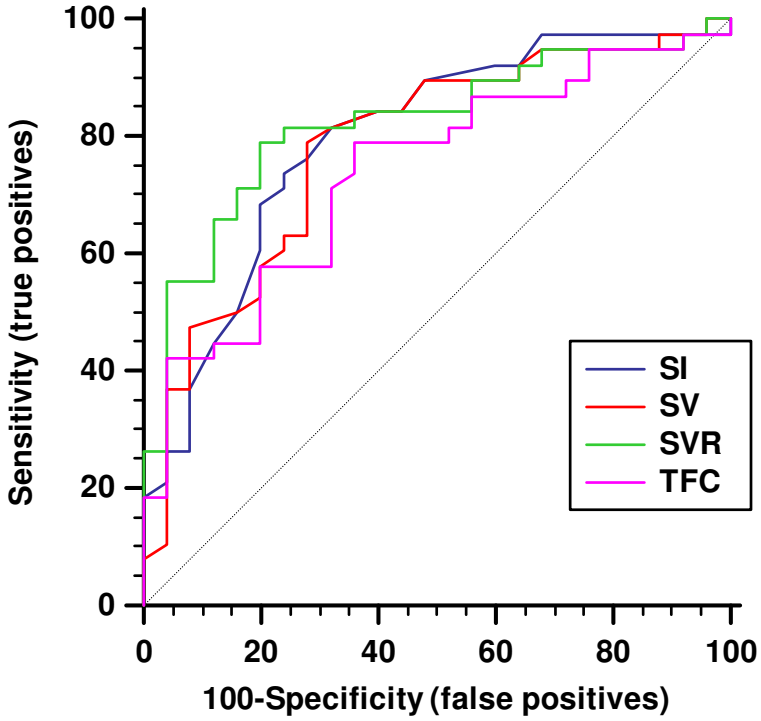

Figure 24. **ROC curves for stroke index, stroke volume, systemic vascular resistance and thoracic fluid content (ED arrival)**

3.2.3 Study 2 – Results – Objective 2

Change of cardio-haemodynamic parameters in severe sepsis / septic shock patients with normal treatment in the ED and after 24 hours

All patients were continuously monitored in the Emergency Department using the equipment as described under *section 2.4*, whilst receiving normal treatment for severe sepsis / septic shock. At the time of the study there was no standard sepsis protocol in place, hence treatment was given at the discretion of the clinician responsible. Clinicians had access to conventional monitoring equipment but not to the cardio-haemodynamic readings. All patients received intravenous fluids and antibiotics and, if clinically indicated, supplemental oxygen as part of their ED treatment. Patients received on average 1327 millilitres (95%CI 1051 to 1604) of intravenous fluid whilst in the ED equating to an average of 20 mls/kg bodyweight (95% CI 15 to 24). After admission to a hospital ward patients received on average a further 2234 millilitre (95%CI 1559 to 2910) of fluids within the first 24 hours. None of the patients received inotropic therapy, vasopressors or blood products whilst in the ED. Only one patient was temporarily commenced on Noradrenaline whilst on the intensive care unit but this had been discontinued well before the 24 hour follow up.

TEB measurements

TEB readings on arrival in the Emergency Department were successfully obtained for all but one patient who suffered from severe cervical spondylosis making the placement of the dual sensor patches impossible. Equipment failure prevented the

recording of TEB ED departure data for one patient. Therefore paired TEB data on arrival and departure from the ED was available for 47 patients. The obtained TEB recordings were all of acceptable quality remaining well above the 50% reliability mark throughout. Table 15 gives a summary of the recorded TEB parameters on arrival and departure from the ED.

Neither CI, CO, SV nor SVR were found to have changed significantly with normal treatment received in the ED. There was however, a significant increase in TFC and a significant decrease in left cardiac work (LCW), HR and blood pressure by the time the patient left the ED.

Table 15. TEB measurements of severely septic patients on ED arrival and departure

Parameter	ED arrival (n=47)	ED departure (n=47)	p-value
CI (l/min/m^2)	3.4 (3.1-3.7)	3.2 (2.9-3.5)	0.038
CO (l/min)	6.4 (5.6-7.1)	5.9 (5.3-6.5)	0.028
SV (ml)	60 (54-67)	60 (54-65)	0.789
SI (ml/m^2)	32 (29-35)	32 (30-35)	0.930
SVR (dynes·s·cm^{-5})	978 (833-1124)	872 (782-961)	0.121
SVRI (dynes·s·cm^{-5} /m^2)	1774 (1547-2001)	1614 (1460-1768)	0.126
TFC (1/kΩ)	31.7 (29.9-33.5)	34.2 (31.9-36.4)	<0.001
HR (beats/min)	110 (102-117)	102 (94-109)	<0.001
MAP (mmHg)	76 (70-82)	67 (61-73)	0.002
SBP (mmHg)	113 (104-122)	101 (93-109)	0.007
DBP (mmHg)	62 (57-67)	54 (49-60)	0.004
LCW (kg·m)	6.3 (5.0-7.5)	5.2 (4.2-6.3)	<0.001
LCWI (kg·m/m^2)	3.3 (2.7-3.9)	2.7 (2.2-3.2)	<0.001
PEP (ms)	84 (72-97)	85 (73-96)	0.978
LVET (ms)	237 (225-249)	250 (236-265)	0.060
ETR (%)	42 (40-44)	41 (39-43)	0.251
QI (%)	84 (79-90)	81 (74-88)	0.227

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

At the 24 hour assessment point only 41 patients were still alive, two of which had already been excluded from analysis. A further two patients refused follow up measurements, making 37 paired data available for comparing change over 24 hours. Table 16 gives a summary of measured TEB parameters on arrival in the ED and at the 24 hour follow up. Figure 25 depicts the changes during the first 24 hours using box and whisker plots for selected parameters.

The data shows that 24 hours of normal treatment resulted in a significant reduction in CI and CO which was mainly attributable to the significant decrease in HR as the SV remained essentially unchanged. There was a further significant increase in TFC reflecting the ongoing administration of intravenous fluids within the first 24 hours of hospital admission. Compared to ED arrival there was also a significant increase in the left ventricular ejection time (LVET), a marker of contractility. Though there was an increase in SV and SVR at 24 hours compared to arrival in the ED these changes were not significant.

The significant reduction in blood pressure (MAP, SBP or DBP) and in LCW found on departure from the ED had disappeared after 24 hours of normal treatment. This raises the question whether the decline seen on departure from ED was simply the effect of cardiovascular deterioration in those who died within 24 hours. However, when excluding these eight patient from the analysis altogether the significant difference in MAP (78 mmHg vs. 70 mmHg; p=0.008) and LCW (6.7kg m vs. 5.6kg m, p=0.003) between arrival and departure from the ED remained.

Table 16. TEB measurements in severely septic patients on ED arrival and at 24 hour follow up

Parameter	ED arrival (n=37)	24 hour follow up (n=37)	p-value
CI (l/min/m^2)	3.5 (3.1-3.9)	3.0 (2.7-3.2)	0.002
CO (l/min)	6.7 (5.8-7.6)	5.7 (5.0-6.4)	0.002
SV (ml)	64 (56-72)	66 (58-75)	0.502
SI (ml/m^2)	34 (30-39)	35 (31-38)	0.477
SVR (dynes·s·cm^{-5})	961 (775-1148)	1075 (929-1221)	0.223
SVRI (dynes·s·cm^{-5} /m^2)	1764 (1489-2038)	2006 (1792-2220)	0.147
TFC (1/kΩ)	31.4 (29.2-33.5)	38.6 (34.5-42.6)	<0.001
HR (beats/min)	107 (99-115)	87 (81-94)	<0.001
MAP (mmHg)	78 (70-85)	76 (70-81)	0.635
SBP (mmHg)	115 (103-127)	114 (104-124)	0.856
DBP (mmHg)	63 (57-70)	62 (57-66)	0.543
LCW (kg·m)	6.7 (5.1-8.3)	5.6 (4.5-6.6)	0.057
LCWI (kg·m/m^2)	3.5 (2.7-4.2)	2.9 (2.4-3.3)	0.056
PEP (ms)	81 (66-96)	83 (74-92)	0.808
LVET (ms)	243 (229-257)	277 (262-292)	0.002
ETR (%)	42 (40-45)	40 (37-41)	0.025
QI (%)	86 (81-91)	84 (78-90)	0.578

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

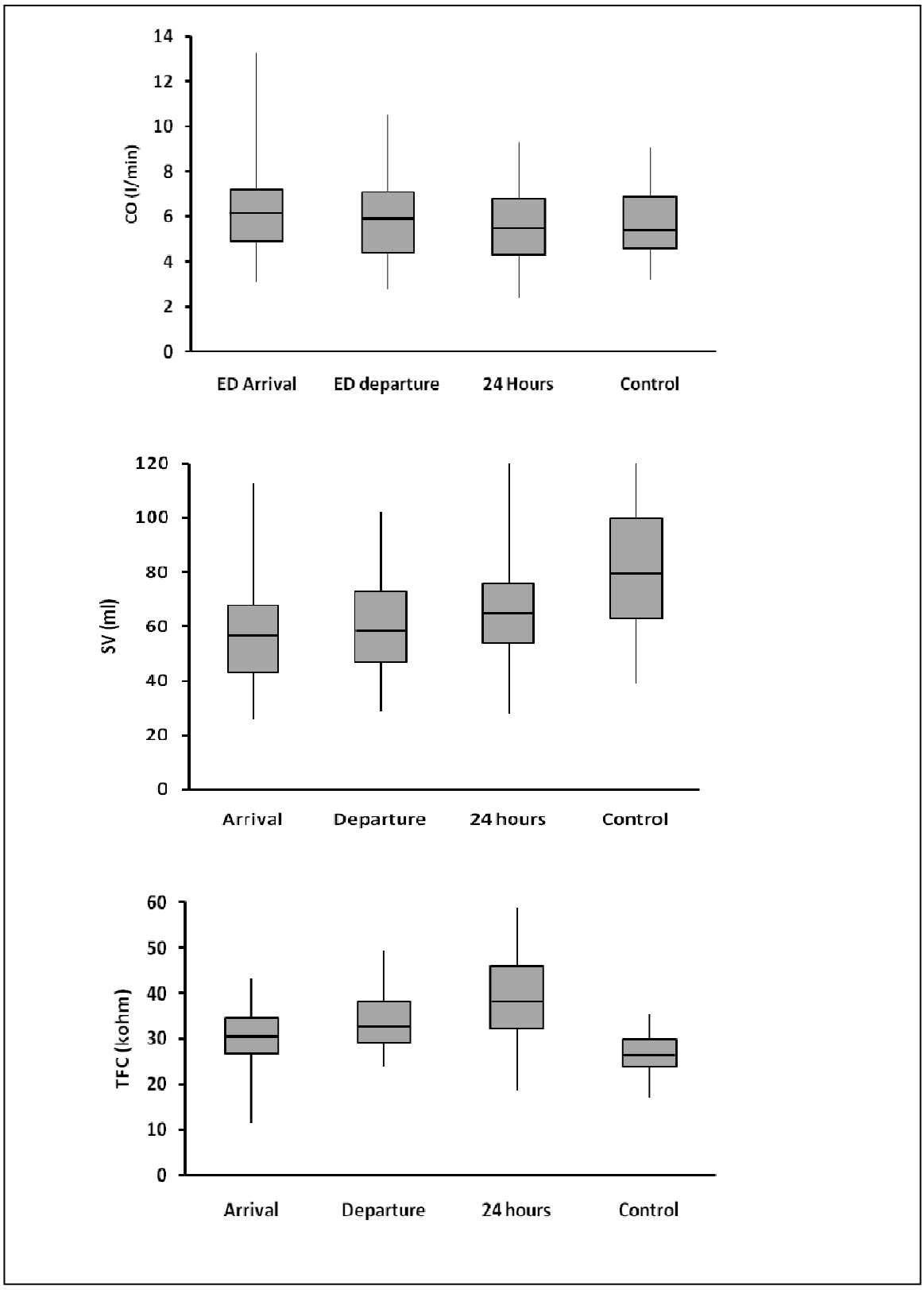

Figure 25. **Differences in cardiac output, stroke volume and thoracic fluid content in severely septic patients between measurement taken on ED arrival, ED departure and at 24 hour follow up; compared with control**

Transcutaneous Doppler measurements

Transcutaneous Doppler measurements were successfully obtained for 46 patients on arrival in the ED. Two sets of measurements were lost due to hardware system error and in one patient it was not possible to acquire a reading of acceptable quality. Paired measurements of the 46 patients taken on arrival and departure from the ED were compared and are presented in Table 17.

As with the TEB measurements there were no significant changes in Doppler cardiac output, cardiac index, stroke volume or stroke index during the patients' stay in the ED. Heart rate was the only parameter found to be significantly reduced on ED departure though the difference was not clinically meaningful.

Table 17. Doppler measurements on ED arrival and departure

Parameter	ED arrival (n=46)	ED departure (n=46)	p-value
CI (l/min/m^2)	3.8 (3.4-4.1)	3.6(3.2-4.0)	0.027
CO (l/min)	7.1 (6.4-7.8)	6.8 (6.1-7.5)	0.034
SV (ml)	67 (60-73)	67 (61-74)	0.605
SI (ml/m^2)	35 (32-38)	36 (32-39)	0.628
VP (m/s)	1.05 (0.97-1.13)	1.01 (0.92-1.09)	0.064
MPG (mmHg)	2.1 (1.8-2.4)	2.0 (1.7-2.4)	0.355
VTI (cm)	18.2 (16.5-19.9)	18.6 (16.7-20.4)	0.370
HR (beats/min)	109 (103-116)	103 (96-109)	<0.001
MD (m/min)	19.6 (17.7-21.5)	18.7 (16.8-20.7)	0.038
ET% (%)	49 (46-52)	48 (45-50)	0.217
FT (ms)	273 (261-284)	284 (270-298)	0.041
SVV (%)	38 (30-46)	34 (26-41)	0.264

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

Comparison was also made between Doppler measurements obtained on ED arrival and at 24 hour follow-up. From the 46 patients seven patients had died within the 24 hours and two patients refused further measurements. Therefore 37 paired readings were available for comparison. Table 18 summarises the data.

The data shows a significant reduction in Doppler CI and CO after a 24 hour period of normal treatment. Since SV remained essentially unchanged this reduction is a result of the decrease in HR which was statistically and clinically significant. There was also a significant increase in flow time (FT), also known as systolic ejection time, at 24 hours compared to arrival in the ED.

Table 18. Doppler measurements on Ed arrival and at 24 hour follow up

Parameter	ED arrival (n=37)	24 hour follow up (n=37)	p-value
CI (l/min/m^2)	3.8 (3.4-4.3)	3.4 (3.0-3.7)	0.001
CO (l/min)	7.3 (6.5-8.1)	6.4 (5.7-7.2)	0.001
SV (ml)	69 (62-76)	71 (64-78)	0.392
SI (ml/m^2)	36 (32-40)	37 (34-40)	0.423
VP (m/s)	1.07 (0.97-1.17)	0.98 (0.89-1.07)	0.009
MPG (mmHg)	2.1 (1.8-2.4)	2.0 (1.7-2.4)	0.355
VTI (cm)	18.6 (16.7-20.5)	19.6 (17.8-21.5)	0.114
HR (beats/min)	108 (101-115)	92 (85-98)	<0.001
MD (m/min)	20.0 (17.7-22.2)	17.8 (15.8-19.8)	0.004
ET% (%)	49 (46-52)	47 (44-49)	0.123
FT (ms)	274 (262-287)	310 (295-325)	<0.001
SVV (%)	36 (29-44)	23 (16-30)	0.007

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

3.2.4 Study 2 – Results – Objective 3

Comparison of cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis or septic shock

Twenty four out of the 49 patients died within 30 days of presenting to the ED with severe sepsis / septic shock (49% mortality). The majority of deaths (63%) occurred within 72 hours. Non-survivors were significantly older than survivors. They were more likely to be care home residents and to suffer from chronic cardiovascular illness than survivors though this was not found to be statistically significant. Table 19 shows the baseline characteristics of survivors and non-survivors from severe sepsis / septic shock.

Table 19. Baseline characteristics of survivors and non-survivors

Characteristic		Survivors n= 25	Non-survivors n=24	p-value
Age (yrs)		64 (54-74)	79 (74-85)	0.008
Gender, n (%)	**Male**	20 (80)	15 (62)	0.282
	Female	5 (20)	9 (38)	0.282
Height (cm)		174 (170-178)	166 (162-171)	0.006
Weight (kg)		77 (69-85)	70 (60-79)	0.238
Care home residency, n (%)		4 (16)	8 (33)	0.292
Past cardiovascular history, n (%)				
Any cardiovascular morbidity		9 (36)	15 (63)	0.109
Coronary artery disease		1(4)	4 (17)	0.306
Myocardial infarct		4 (16)	4 (17)	0.771
Arrhythmias		2 (8)	4 (17)	0.602
Hypertension		4 (16)	7 (29)	0.454
Heart failure		1 (4)	1 (4)	0.466

Values expressed as mean (95% confidence interval) unless stated otherwise

Physiological parameters taken on the arrival in the ED did not differ significantly between the two groups of patients. Non-survivors scored significantly higher on the 'Mortality in Emergency Department Sepsis' (MEDS) score and had a significantly higher venous lactate (Table 20).

Table 20. Conventional parameters on arrival in the Emergency Department

Parameter	Survivors n= 25	Non-survivors n=24	p-value
Physiological signs			
Temperature (°C)	38.1 (37.7-38.6)	37.4 (36.7-38.1)	0.062
Heart rate (min^{-1})	117 (109-124)	115 (106-125)	0.825
Oxygen saturation (%)	97 (95-98)	94 (92-97)	0.101
Respiratory rate (min^{-1})	28 (26-31)	33 (29-36)	0.064
Systolic blood pressure (mmHg)	106 (94-117)	97 (88-107)	0.262
Scoring systems			
EWS	6.7 (6.0-7.5)	7.7 (6.9-8.4)	0.072
MEDS score	7.5 (6.1-8.9)	10.8 (9.3-12.3)	0.002
Lactate (mmol/l)	3.7 (2.8-4.5)	6.3 (4.5-8.1)	0.007

Values expressed as mean (95% confidence interval)

When classifying the participants on their arrival in the Emergency Department in accordance to their degree of sepsis the severity of illness was greater amongst non-survivors (p=0.023). Sepsis related shock was seen in 83% of non-survivors (n=20) with cryptic shock being the most prevalent (n=11). Whereas, only half of the survivors (n=12) suffered from sepsis related shock of which seven cases were cryptic shock. The respiratory tract was the most common source of sepsis in both survivors (60%) and non-survivor (71%). There was a similar prevalence of uro-sepsis in both groups (survivors 20% and non-survivors 17%).

Non-survivors received on average more intravenous fluid in the Emergency Department than survivors ((1956mls (95%CI 1469 to 2444) vs. 1576mls (95%CI 1160 to 1993), p=0.226)). After leaving the ED non-survivors continued to receive more intravenous fluid compared to survivors within the first 24 hours ((2906mls (95%CI 2054 to 3759) vs. 1787mls (95%CI 808 to 2765), p=0.101)).

TEB measurements

TEB cardio-haemodynamic measurements on arrival in the ED were available for 48 patients of whom there were 23 non-survivors and 25 survivors. Table 21 compares TEB parameters of both cohorts taken on arrival in the ED. Survivors had an increased cardiac index (ΔCI=0.3; 95%CI -0.3 to 1.0) and cardiac output (ΔCO=1.3; 95%CI -0.1 to 2.7) compared to non-survivors. Though the difference in CI was clinically significant it did not reach statistical significance. There were no statistically significant differences in any of the other TEB parameters between the two groups on arrival in the ED.

ED departure measurements were available for 47 patients (23 non-survivors and 24 survivors). The comparisons of both cohorts are presented in Table 22. Following normal treatment for sepsis in the ED the differences in cardiac index and output as seen on arrival had diminished. Apart from the left ventricular filling time (LVET) and the ejection time ratio (ETR) there were no statistically significant differences between survivors and non-survivors on departure from the ED.

Within 24 hours of presenting to the ED with severe sepsis / septic shock eight patients had died and two of the survivors refused to participate in the follow-up

measurements. Thus data from 37 patients (15 non-survivors and 22 survivors) were available for comparison at 24 hours (Table 23). There was a noticeable difference in the SV, which in survivors had started to normalise and was thus significantly greater than in non-survivors (ΔSV=21; 95%CI 5 to 36). No other significant differences were found between the two cohorts.

Table 21. TEB measurements of survivors and non-survivors on ED arrival

Parameter	Survivors (n=25)	Non-survivors (n=23)	p-value
CI (l/min/m^2)	3.6 (3.1-4.0)	3.3 (2.8-3.7)	0.291
CO (l/min)	7.0 (5.9-8.1)	5.7 (4.7-6.6)	0.061
SV (ml)	65 (55-75)	53 (46-61)	0.063
SI (ml/m^2)	33 (29-37)	31 (27-34)	0.377
SVR (dynes·s·cm^{-5})	906 (699-1112)	1075 (878-1273)	0.224
SVRI (dynes·s·cm^{-5} /m^2)	1712 (1392-2032)	1817 (1496-2137)	0.632
TFC (1/kΩ)	31.2 (28.5-33.9)	31.8 (29.4-34.2)	0.736
HR (beats/min)	111 (102-120)	111 (99-123)	0.988
MAP (mmHg)	76 (68-83)	75 (66-84)	0.859
SBP (mmHg)	115 (102-129)	105 (93-116)	0.219
DBP (mmHg)	61 (55-67)	62 (54-70)	0.783
LCW (kg·m)	6.5 (5.2-7.9)	5.5 (3.4-7.5)	0.339
LCWI (kg·m/m^2)	3.3 (2.7-3.9)	3.1 (2.0-4.2)	0.664
PEP (ms)	76 (69-83)	92 (68-116)	0.191
LVET (ms)	231 (214-247)	240 (221-259)	0.448
ETR (%)	42 (39-45)	43 (40-46)	0.689
QI (%)	89 (85-93)	77 (67-88)	0.028

Values expressed as mean (95% confidence interval)

Table 22. TEB measurements of survivors and non-survivors on ED departure

Parameter	Survivors (n=24)	Non-survivors (n=23)	p-value
CI (l/min/m^2)	3.2 (2.8-3.5)	3.2 (2.7-3.7)	0.841
CO (l/min)	6.2 (5.4-6.9)	5.6 (4.6-6.7)	0.388
SV (ml)	62 (54-71)	57 (49-65)	0.364
SI (ml/m^2)	32 (28-35)	33 (29-36)	0.728
SVR (dynes·s·cm^{-5})	851 (732-971)	922 (780-1065)	0.422
SVRI (dynes·s·cm^{-5} /m^2)	1635 (1429-1840)	1609 (1357-1860)	0.866
TFC (1/kΩ)	33.2 (29.9-36.5)	35.2 (32.0-38.5)	0.352
HR (beats/min)	101 (92-110)	102 (90-115)	0.889
MAP (mmHg)	68 (60-75)	67 (58-76)	0.960
SBP (mmHg)	104 (93-115)	98 (88-108)	0.434
DBP (mmHg)	54 (47-61)	55 (46-64)	0.798
LCW (kg·m)	5.3 (4.2-6.4)	5.1 (3.3-6.9)	0.828
LCWI (kg·m/m^2)	2.7 (2.2-3.2)	2.8 (1.9-3.6)	0.834
PEP (ms)	89 (68-109)	83 (71-94)	0.605
LVET (ms)	230 (217-244)	273 (248-297)	0.003
ETR (%)	38 (35-41)	44 (40-48)	0.009
QI (%)	89 (83-94)	72 (59-85)	0.014

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

Table 23. TEB measurements of survivors and non-survivors at 24 hour follow-up

Parameter	Survivors (n=22)	Non-survivors (n=15)	p-value
CI (l/min/m^2)	3.0 (2.7-3.4)	2.8 (2.2-3.4)	0.393
CO (l/min)	6.1 (5.2-7.0)	5.0 (3.8-6.2)	0.099
SV (ml)	74 (63-85)	53 (44-63)	0.004
SI (ml/m^2)	37 (33-42)	30 (25-36)	0.023
SVR (dynes·s·cm^{-5})	989 (853-1123)	1263 (883-1642)	0.055
SVRI (dynes·s·cm^{-5} /m^2)	1893 (1688-2098)	2224 (1559-2889)	0.169
TFC (1/kΩ)	37.1 (31.2-43.0)	41.1 (35.9-46.2)	0.274
HR (beats/min)	84 (76-92)	94 (83-104)	0.136
MAP (mmHg)	76 (68-83)	75 (66-84)	0.914
SBP (mmHg)	115 (104-127)	108 (93-124)	0.433
DBP (mmHg)	61 (55-67)	61 (53-69)	0.906
LCW (kg·m)	5.9 (4.5-7.3)	4.7 (3.4-5.9)	0.135
LCWI (kg·m/m^2)	2.9 (2.4-3.5)	2.6 (2.0-3.2)	0.411
PEP (ms)	79 (71-87)	89 (67-111)	0.268
LVET (ms)	289 (271-306)	257 (231-282)	0.033
ETR (%)	39 (37-42)	40 (35-44)	0.924
QI (%)	88 (80-97)	77 (67-88)	0.108

Values expressed as mean (95% confidence interval)

Areas shaded grey highlight statistically significant differences

Figure 26 illustrates the chronological patterns of selected cardio-haemodynamic parameters of survivors and non-survivors during the first 24 hours since arrival in the ED. Survivors had a persistently higher CO and SV whereas SVR and TFC were higher in non-survivors.

CO measured on arrival in the ED was higher in survivors than in non-survivors or non-septic controls (red dotted line). Within 24 hours of treatment the CO of survivors had decreased reaching a similar value as seen in controls whilst CO of non-survivors had further declined.

SV was reduced in survivors and more so in non-survivors compared with non-septic controls. Whilst there was a marked improvement in SV in survivors after 24 hours SV remained seriously reduced in non-survivors. When comparing the change in SV over time between survivors and non-survivors there was no significant difference in ΔSV on ED departure (ΔSV= -1.9; 95%CI -11.1 to 7.4, p=0.688). However, after 24 hours of initial sepsis management, there was a statistically significant difference in ΔSV between survivors and non-survivors (ΔSV= 17.0; 95%CI 8.5 to 25.5, p<0.001).

SVR was lower in survivors on arrival in the ED and increased only marginally during the first 24 hours. In contrast, SVR of non-survivors increased to nearly the control value after 24 hours of treatment.

TFC on arrival in the ED was increased in both cohorts compared to the mean value of the control group. During the first 24 hours there was a steady rise in TFC in survivors and non-survivors which, considering the amount of intravenous fluids administered to both groups of septic patients, was to be expected.

LCW, an indicator of the amount of work performed by the left ventricle each minute, was markedly lower in non-survivors, declining steadily during the first 24 hours. Survivors exhibited a higher LCW on ED arrival, this reached a similar value to non-survivors on ED departure but rose again within 24 hours of treatment.

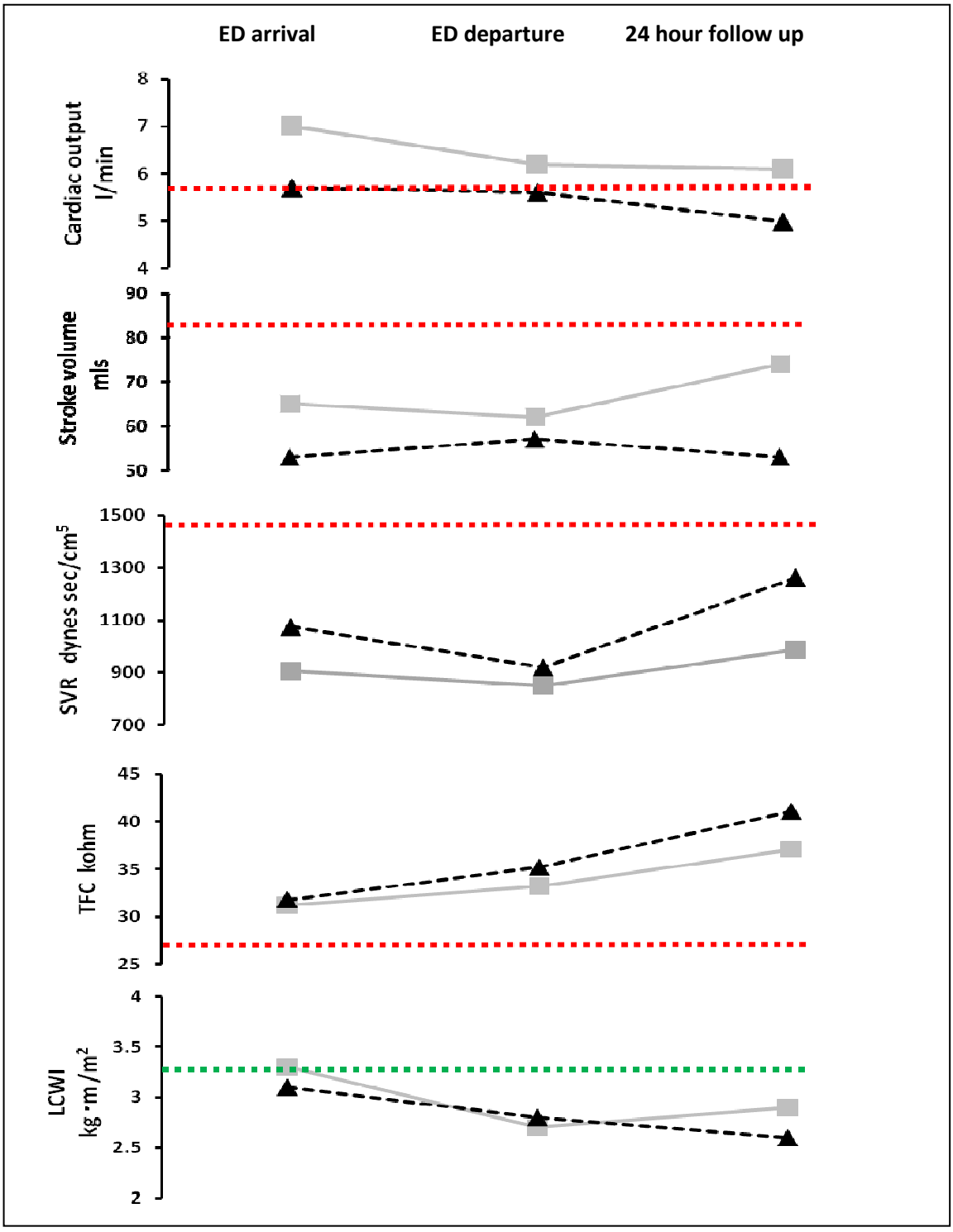

Figure 26. Patterns of cardio-haemodynamic parameters of survivors (grey solid line) and non-survivors (black scattered line).

Grey squares (■) represent mean values in survivors; black triangles (▲) mean values in non-survivors; red dashed lines represent the mean value of the non-septic control; green dashed line represents smallest value of the 'Normal range'[153].

The ability of each TEB parameter to discriminate survivors from non-survivors was tested using the receiver operating characteristics (ROC) analysis. The area under the ROC curve (AUROC) for each parameter is shown in Table 24. Parameters with an AUROC greater than 0.7 are highlighted in grey colour.

Table 24. Area under the ROC curve for TEB parameters

Parameter	ED arrival	ED departure	24 hour
CI (l/min/m^2)	0.603 (0.441-0.751)	0.491 (0.330-0.654)	0.577 (0.384-0.754)
CO (l/min)	**0.702** (0.541-0.833)	0.594 (0.427-0.746)	0.646 (0.451-0.811)
SV (ml)	0.647 (0.484-0.788)	0.588 (0.421-0.741)	**0.754** (0.563-0.892)
SI (ml/m^2)	0.566 (0.404-0.718)	0.531 (0.367-0.691)	**0.706** (0.512-0.857)
SVR (dynes·s·cm^{-5})	0.656 (0.482-0.804)	0.588 (0.417-0.745)	0.641 (0.443-0.810)
SVRI (dynes·s·cm^{-5} /m^2)	0.565 (0.392-0.727)	0.515 (0.348-0.680)	0.576 (0.379-0.756)
TFC (1/kΩ)	0.527 (0.367-0.683)	0.585 (0.419-0739)	0.620 (0.425-0.790)
HR (beats/min)	0.480 (0.323-0.639)	0.510 (0.347-0.671)	**0.701** (0.507-0.853)
MAP (mmHg)	0.534 (0.361-0702)	0.518 (0.348-0.685)	0.492 (0.303-0.683)
SBP (mmHg)	0.605 (0.428-0.763)	0.545 (0.373-0.709)	0.593 (0.396-0.771)
DBP (mmHg)	0.514 (0.342-0.684)	0.494 (0.326-0.663)	0.538 (0.344-0.724)
LCW (kg·m)	0.669 (0.492-0.816)	0.565 (0.393-0.727)	**0.636** (0.438-0.806)
LCWI (kg·m/m^2)	0.625 (0.448-0.780)	0.519 (0.349-0.686)	0.581 (0.384-0.760)
PEP (ms)	0.546 (0.384-0.702)	0.474 (0.314-0.637)	0.557 (0.366-0.737)
LVET (ms)	0.582 (0.418-0.734)	**0.721** (0.556-0.851)	**0.734** (0.542-0.878)
ETR (%)	0.564 (0.401-0.718)	**0.721** (0.556-0.851)	0.457 (0.275-0.648)

ROC curves were constructed for the best performing parameters. On arrival in the ED only cardiac output was found to have a good discriminatory power (Figure 27). Giving equal value to sensitivity and specificity, a CO of greater than 5.1 l/min was found to be the optimal derived cut-off to discriminate between survival and death. This was found to be 81.8% sensitive (95%CI 59.7 to 94.8) and 55.0% specific (95%CI 31.5 to 76.9) for survival. It had a positive likelihood ratio (LR+) of 1.82, negative likelihood ratio (LR-) of 0.33, a positive predictive value (PPV) of 66.7 and a negative predictive value (NPV) of 73.3.

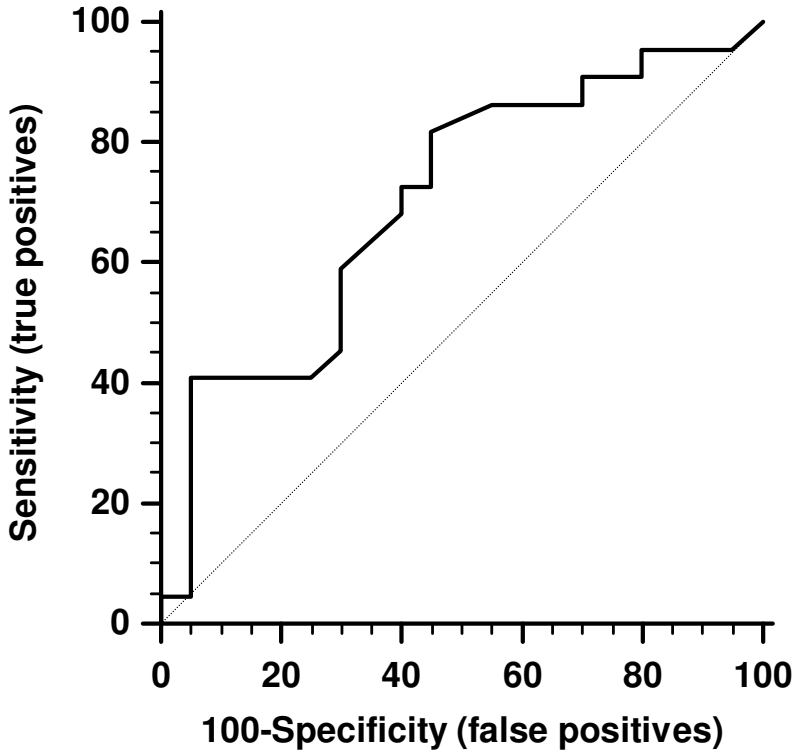

Figure 27. Receiver operating characteristics curve for cardiac output (ED arrival)

On departure from the ED there were two parameters with a good discriminatory power for survival, left ventricular ejection time (LVET) and ejection time ratio (ETR). Figure 28 presents the ROC curves for both parameters. The optimal cuff-off derived from the ROC for LVET to discriminate between survival and death was 260 or less and for ETR 41 or less. A LVET of ≤260 was 95.2% sensitive (95%CI 76.2 to 99.9) and 42.1% specific (95%CI 20.3 to 66.5) for survival. It had a LR+ of 1.65, a LR- of 0.11, a PPV of 64.5 and a NPV of 88.9. An ETR of ≤41 had a sensitivity of 76.2% (95%CI 52.8 to 91.8), a specificity of 68.4% (95%CI 43.4 to 87.4), a LR+ of 2.41, a LR- of 0.35, a PPV of 72.7 and a NPV of 72.2.

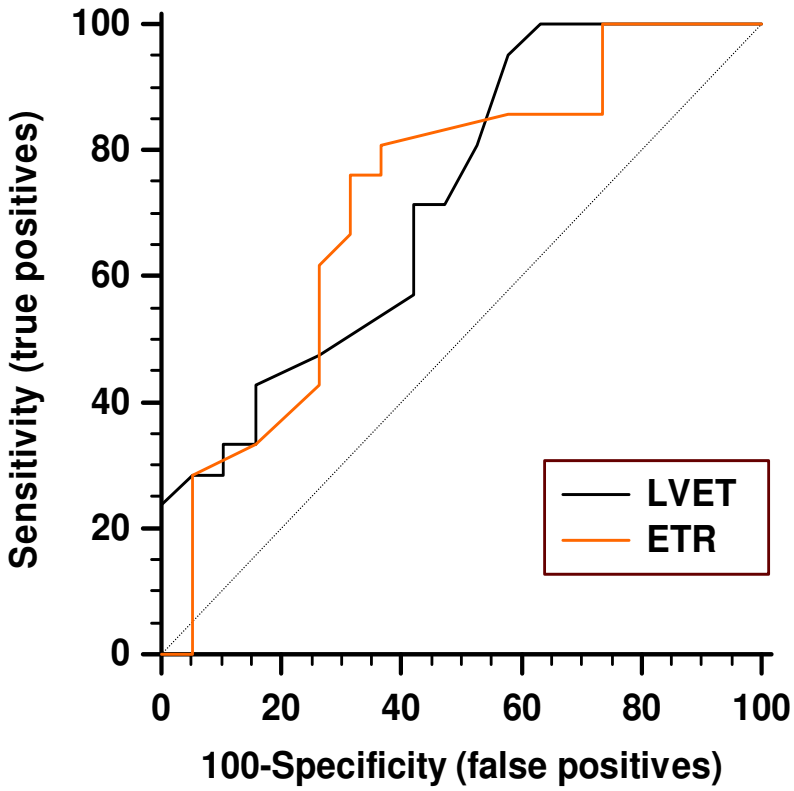

Figure 28. Receiver operating characteristics curves for LVET and ETR (ED departure)

At the 24 hour follow-up assessment there were four parameters with good discriminating qualities, the best of which was the SV followed by LVET, SI and HR. The ROC curves of all four parameters are presented in Figure 29. The ROC derived optimal cut-off for each parameter and its sensitivity, specificity, LR+, LR-, PPV and NPV are shown in Table 25. None of the identified cut-offs had a high sensitivity. HR was found to have the highest specificity (100%) and highest PPV (100%) for survival followed by the SV (91% and 91% respectively). Interestingly, whilst a low LVET on ED departure was found to be predictive of survival from severe sepsis the opposite applied after 24 hours of treatment.

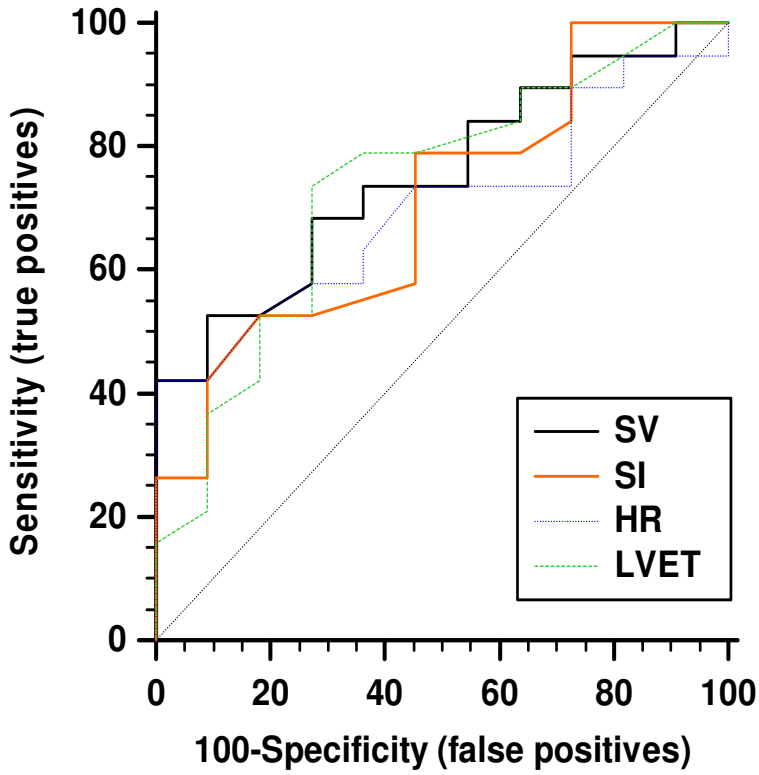

Figure 29. ROC curves for stroke volume, stroke index, heart rate and left ventricular ejection time (at 24 hours)

Table 25. ROC derived values predictive of survival at 24 hours

Parameter	Optimal cut-off	Sensitivity	Specificity	LR+	LR-	PPV	NPV
SV	>67	52.6 (28.9-75.6)	90.9 (58.7-99.8)	5.79	0.52	90.9	52.6
LVET	>265	73.7 (48.8-90.9)	72.7 (39.0-94.0)	2.7	0.36	82.4	61.5
SI	>37	52.6 (28.9-75.6)	81.8 (48.2-97.7)	2.89	0.58	83.3	50.0
HR	≤76	42.1 (20.3-66.5)	100 (71.5-100)	Infinite	0.58	100	50.0

Transcutaneous Doppler measurements

Transcutaneous Doppler readings on arrival in the ED were available for 46 patients of whom 23 survived. Table 26 depicts Doppler parameter of survivors and non-survivors taken on their arrival in the ED. Similar to TEB measurements survivors were found to have a markedly higher CO and SV than non-survivors. There was also a noticeable difference in mean pressure gradient (MPG) which was distinctively higher in survivors.

ED departure measurements were available for 43 patients (22 survivors and 21 non-survivors). Table 27 compares the measured parameters of both cohorts. Following the initial resuscitative treatment in the ED there was now a statistical significant difference in SV between survivors and non-survivors. Cardiac output remained markedly higher in survivors, as did MPG. Survivors had a higher velocity time integral (VTI) and peak velocity (VP), a marker of contractility.

Table 26. Doppler measurements of survivors and non-survivors on ED arrival

Parameter	Survivors (n=23)	Non-survivors (n=23)	p-value
CI (l/min/m^2)	4.0 (3.4 – 4.6)	3.4 (3.0 – 3.8)	0.085
CO (l/min)	7.7 (6.6 – 8.7)	6.2 (5.3 – 7.0)	0.028
SV (ml)	72 (62 – 82)	58 (50 – 65)	0.022
SI (ml/m^2)	38 (33 – 43)	32 (28 – 36)	0.057
VP (m/s)	1.12 (0.97 – 1.27)	0.96 (0.89 – 1.04)	0.051
MPG (mmHg)	2.4 (1.8 – 2.9)	1.7 (1.5 – 2.0)	0.033
VTI (cm)	19.5 (16.8 – 22.2)	16.5 (14.5 – 18.4)	0.063
HR (beats/min)	108 (100 – 117)	110 (100 – 121)	0.779
MD (m/min)	21.1 (17.9 – 24.3)	17.7 (15.7 – 19.7)	0.065
ET% (%)	50 (46 – 54)	48 (44 – 51)	0.436
FT (ms)	278 (264 – 291)	266 (247 – 285)	0.312
SVV (%)	36 (23 – 50)	40 (31 – 49)	0.658

Values expressed as mean (95% confidence interval)

Table 27. Doppler measurements of survivors and non-survivors on ED departure

Parameter	Survivors (n=22)	Non-survivors (n=21)	p-value
CI (l/min/m^2)	3.8 (3.3 – 4.4)	3.4 (2.9 – 3.8)	0.174
CO (l/min)	7.4 (6.4 – 8.5)	6.2 (5.3 – 7.1)	0.070
SV (ml)	76 (65 – 86)	59 (52 – 65)	0.006
SI (ml/m^2)	39 (33 – 45)	32 (29 – 35)	0.037
VP (m/s)	1.09 (0.94 – 1.23)	0.93 (0.87 – 0.99)	0.048
MPG (mmHg)	2.4 (1.7 – 3.0)	1.6 (1.4 – 1.8)	0.029
VTI (cm)	20.5 (17.3 – 23.7)	16.5 (14.9 – 18.1)	0.030
HR (beats/min)	100 (91 – 109)	106 (96 – 116)	0.371
MD (m/min)	20.2 (16.9 – 23.4)	17.2 (15.2 – 19.3)	0.122
ET% (%)	47 (43 – 50)	49 (45 – 53)	0.462
FT (ms)	287 (265 – 309)	281 (261 – 301)	0.669
SVV (%)	32 (24 – 40)	35 (23 – 48)	0.592

Values expressed as mean (95% confidence interval)

Following 24 hours of treatment eight patients had died and two survivors refused further measurements leaving a total of 36 assessments available for comparison (Table 28). At this stage there was very little difference in CO between survivors and non-survivors. Though there was a subtle increase in SV in both cohorts, but this did not affect the distinct difference between survivors and non-survivors. The heart rate was more reduced in survivors, which would have contributed to the decreased difference in CO between the two cohorts.

Table 28. Doppler measurements of survivors and non-survivors at 24 hours

Parameter	Survivors (n=20)	Non-survivors (n=16)	p-value
CI (l/min/m^2)	3.4 (2.8 – 3.9)	3.3 (2.8 – 3.9)	0.909
CO (l/min)	6.6 (5.6 – 7.6)	6.2 (5.0 – 7.4)	0.612
SV (ml)	78 (68 – 88)	62 (54 – 70)	0.017
SI (ml/m^2)	40 (35 – 45)	33 (29 – 37)	0.058
VP (m/s)	1.00 (0.86 – 1.14)	0.96 (0.84 – 1.07)	0.596
MPG (mmHg)	2.0 (1.5 – 2.6)	1.7 (1.3 – 2.1)	0.302
VTI (cm)	21.3 (18.3 – 24.2)	17.6 (15.7 – 19.4)	0.042
HR (beats/min)	86 (77 – 94)	100 (90 – 110)	0.027
MD (m/min)	18.0 (14.9 – 21.0)	17.6 (14.8 – 20.4)	0.872
ET% (%)	45 (42 – 48)	49 (44 – 54)	0.132
FT (ms)	320 (299 – 341)	297 (277 – 318)	0.124
SVV (%)	18 (13 – 23)	28 (15 – 41)	0.133

Values expressed as mean (95% confidence interval)

The receiver operating characteristics (ROC) analysis was used to test the ability of each Doppler derived parameter to predict outcome from sepsis. The area under the ROC curve (AUROC) for each parameter is shown in Table 29. Parameters with a good predictability, as indicated by an AUROC greater than 0.7, are highlighted in 'grey'.

Table 29. AUROC values for transcutaneous Doppler parameters

Parameter	ED arrival	ED departure	24 hour
CI (l/min/m^2)	0.651 (0.497 – 0.786)	0.605 (0.444 – 0.751)	0.491 (0.321 – 0.662)
CO (l/min)	0.698 (0.545 – 0.825)	0.698 (0.539 – 0.828)	0.606 (0.430 – 0.764)
SV (ml)	0.685 (0.532 – 0.814)	0.737 (0.581 – 0.859)	0.767 (0.591 – 0.894)
SI (ml/m^2)	0.651 (0.489 – 0.791)	0.717 (0.557 – 0.845)	0.696 (0.515 – 0.842)
VP (m/s)	0.637 (0.475 – 0.780)	0.666 (0.504 – 0.804)	0.530 (0.351 – 0.702)
MPG (mmHg)	0.653 (0.491 – 0.793)	0.677 (0.515 – 0.813)	0.602 (0.421 – 0.766)
VTI (cm)	0.682 (0.520 – 0.817)	0.702 (0.541 – 0.833)	0.708 (0.528 – 0.851)
HR (beats/min)	0.542 (0.387 – 0.692)	0.576 (0.416 – 0.725)	0.731 (0.558 – 0.865)
MD (m/min)	0.653 (0.497 – 0.789)	0.626 (0.465 – 0.768)	0.495 (0.325 – 0.666)
ET% (%)	0.542 (0.387 – 0.691)	0.515 (0.358 – 0.670)	0.612 (0.436 – 0.770)
FT (ms)	0.622 (0.465 – 0.762)	0.529 (0.371 – 0.683)	0.650 (0.473 – 0.801)
SVV (%)	0.575 (0.413 – 0.726)	0.503 (0.345 – 0.661)	0.585 (0.404 – 0.751)

Values expressed as mean (95% confidence interval)

3.2.5 Study 2 – Results – Objective 4

Relationship between TEB cardio-haemodynamic and conventional parameters

The chronological patterns of cardiac output, stroke volumes, systemic vascular resistance, heart rate and mean arterial pressure during the first 24 hours after arrival in the ED were compared and are illustrated in Figure 30. HR and CO were both elevated on ED arrival and decreased nearly parallel over the first 24 hour period reaching, by then, near normal values. The SV, which was very low on ED arrival, gradually increased over time following an opposite pattern to HR and CO. Changes in SVR and MAP followed a similar pattern. Both were reduced on arrival in the ED, reached their lowest point on ED departure and increased again by the end of the first 24 hours.

Pearson's correlation coefficient was used to assess the relationship between the cardio-haemodynamic and the conventional parameters at the three assessment points. Table 30 contains the correlation coefficients (r) for all pairs of variables. There was no strong correlation between any of the parameters. HR was found to have a weak positive association with CO and a negligible negative association with SV and SVR. MAP was weakly correlated with CO and SV on departure from the ED and at 24 hours whilst the correlation was negligible on ED arrival. Systemic vascular resistance and mean arterial pressure were found to have a weak positive association on arrival and departure from the ED and virtually no correlation at 24 hours.

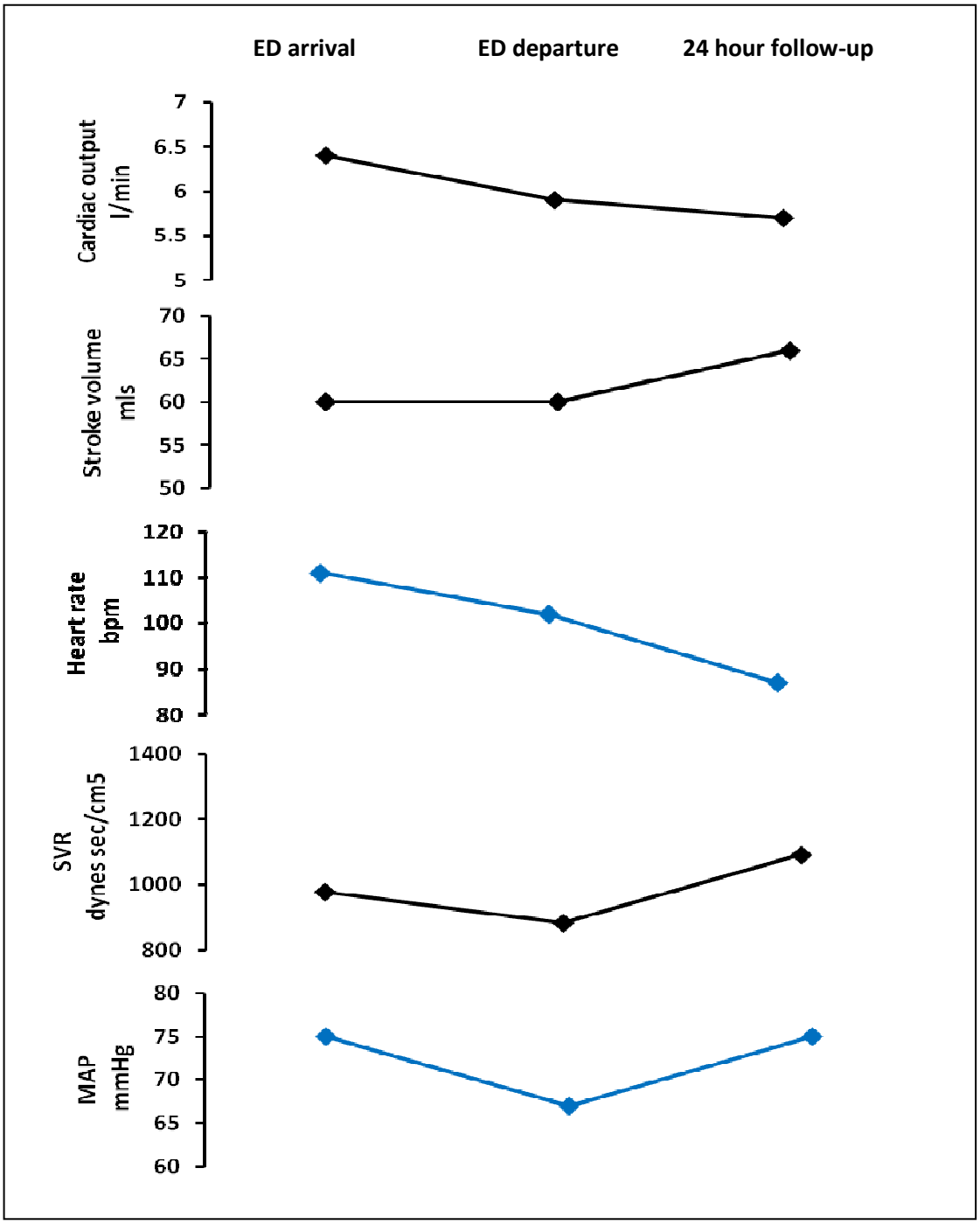

Figure 30. **Patterns of cardio-haemodynamic and conventional parameters in patients with severe sepsis or septic shock**

Table 30. Pearson's correlation coefficients for cardio-haemodynamic and conventional variables

	CO ED arr	**CO** ED dep	**CO** 24 hrs	**SV** ED arr	**SV** ED dep	**SV** 24 hrs	**SVR** ED arr	**SVR** ED dep	**SVR** 24 hrs
HR ED arr	0.286			-0.269			-0.130		
HR ED dep		**0.510**			-0.264			-0.329	
HR 24 hrs			0.306			-0.239			-0.189
MAP ED arr	0.259			0.210			0.407		
MAP ED dep		0.460			0.358			0.342	
MAP 24 hrs			0.418			0.395			0.134

Ability of parameters to discriminate between good and poor outcome

Area under the ROC curve values (*section 3.2.4* Table 24) were used to compare the ability of cardio-haemodynamic parameters, conventional HR and BP to discriminate between good and poor outcome from severe sepsis or septic shock. Conventional HR and MAP taken on arrival and departure from the ED were not able to differentiate survivors form non-survivors. CO however, was found to be a good discriminator for outcome in severely septic patients on arrival in the ED but not so for subsequent assessments. Both SV and HR were found to be helpful in distinguishing between survivors and non-survivors after 24 hours of treatment whereas SVR and MAP were found to be of no help.

3.2.6 Study 2 – Results – Objective 5

Comparison of simultaneous TEB and transcutaneous Doppler ultrasound cardio-haemodynamic measurements

Cardio-haemodynamic measurements using TEB and transcutaneous Doppler ultrasound (USCOM) were obtained simultaneously on patients' arrival and departure from the ED and after 24 hours. TEB readings on ED arrival and departure were available for forty seven patients compared to forty six transcutaneous Doppler assessments. At the 24 hour follow up a total of thirty seven TEB and USCOM measurements were successfully obtained. Both devices measured an array of parameters and five of these were identical. These were CO, CI, SV, SI and HR, and a comparison was made of all five variables.

Measurements obtained using TEB were generally lower than their simultaneous acquired USCOM values. This trend remained unchanged throughout the 24 hour assessment period and is illustrated in Figure 31. USCOM measurements are shown as black squares (■) and TEB values as grey diamonds (◆). The graphs illustrate that when comparing the TEB and USCOM measurements for the entire cohort the patterns of change were very similar.

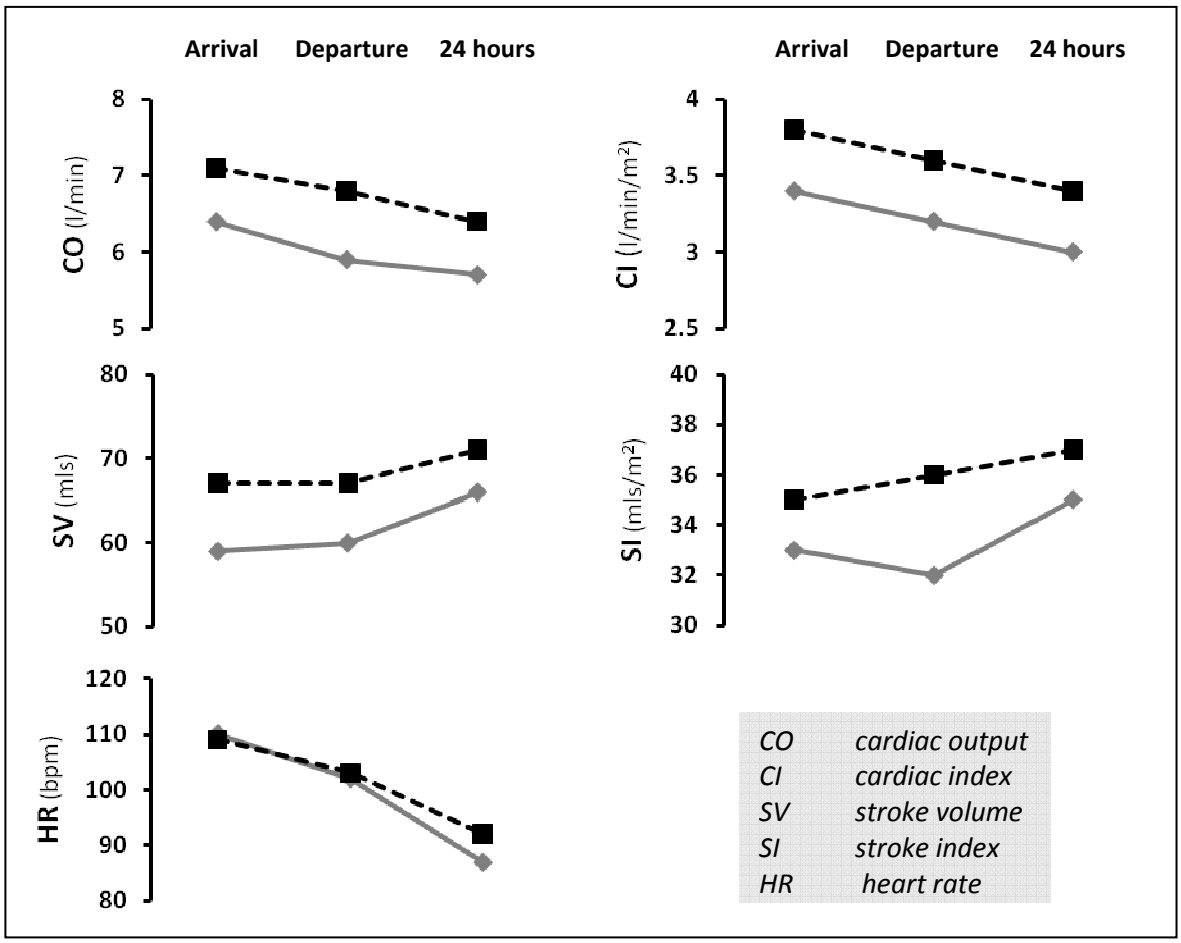

Figure 31. Chronological patterns of TEB (◆) and USCOM (■) parameters

To assess the strength of the association between each of the matched TEB and USCOM variables the Pearson's correlation coefficient was used, assuming a linear relationship. The strongest association was found for HR followed by CO, whereas TEB and USCOM stroke index measurements were only weakly correlated. Table 31 contains the Pearson's correlation coefficient (r) for each matched variable.

Table 31. Pearson's correlation coefficients

	ED arrival	ED departure	24 hour follow up
Cardiac output	0.804	0.746	0.673
Cardiac index	0.679	0.619	0.462
Stroke volume	0.713	0.534	0.650
Stroke index	0.518	0.302	0.412
Heart rate	0.940	0.909	0.982

Graphical illustrations of the strength of the relation and the agreement between paired TEB and USCOM measurement of CO, SV and HR obtained during the three assessment points are shown in Figure 32. Though there appears to be an acceptable to good correlation for the three measured variables the agreement between measurements was less than perfect as indicated by the wide limits of agreements (mean ± 2SD) of the Bland-Altman plots with several measurements outside this range. The mean difference between TEB and USCOM measurements was always less than 'zero' which points to the fact that TEB tends to give lower readings than USCOM.

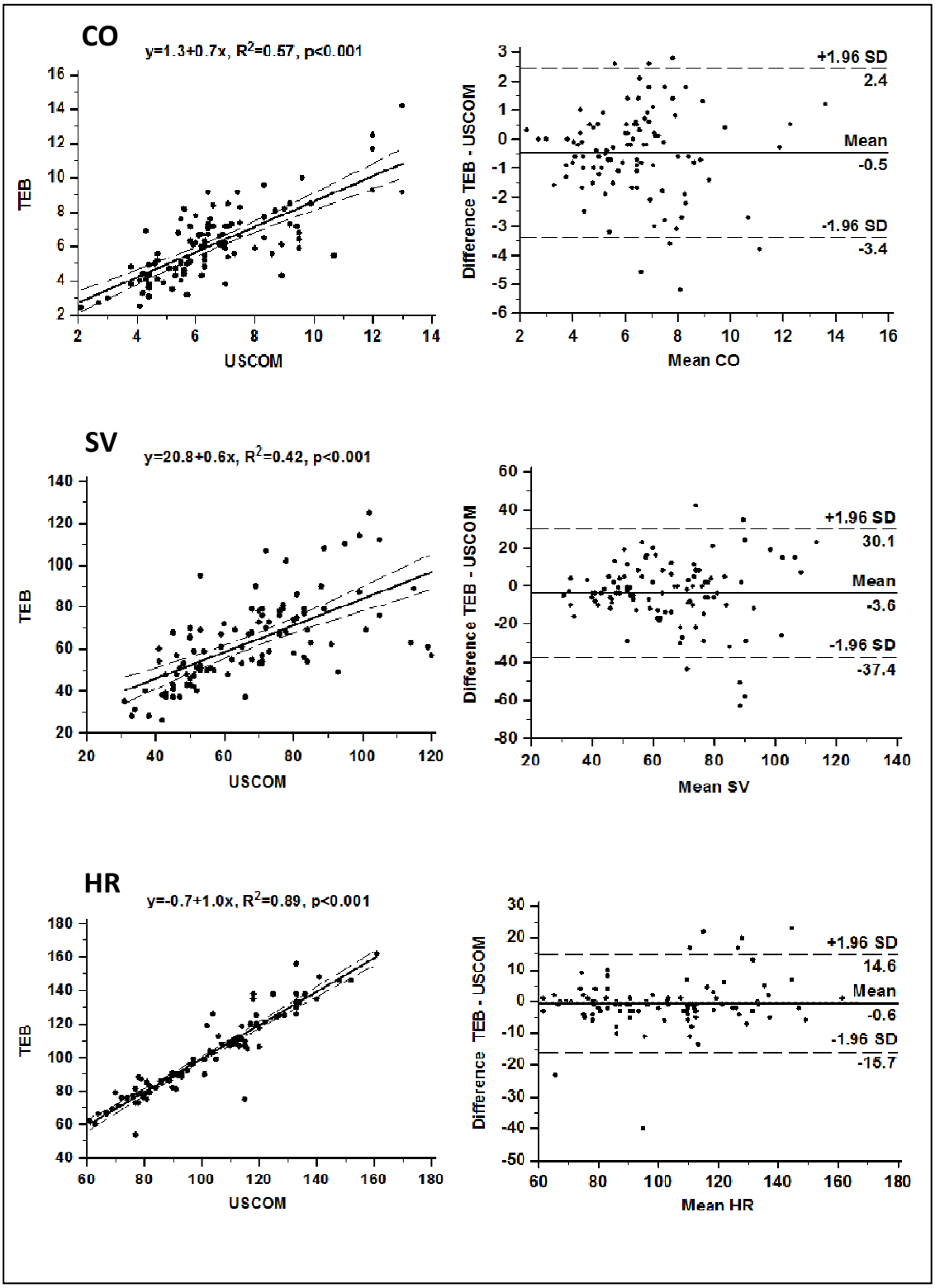

Figure 32. **Relationship between paired TEB and USCOM cardiac output (CO), stroke volume (SV) and heart rate (HR) measurements presented as Scatter and Bland-Altman plots**

3.2.7 Study 2 – Results – Objective 6

Assessment of tissue oxygen saturation in severely septic ED patients; its change with normal treatment and relationship to outcome

3.2.7.1 Tissue oxygen saturation in severely septic ED patients

Tissue oxygen saturation (StO_2) measurements were obtained for all forty nine patients during their stay in the Emergency Department. The mean StO_2 for the entire cohort on arrival in the ED was 72% (95%CI 69 to 75) which on departure from the ED had increased to 75% (95%CI 72 to 78; p=0.061).

At the 24 hour follow up StO_2 data for thirty nine patients was available as eight patients had died and two had refused to participate in the final assessment. The StO_2 for the remaining cohort after 24 hour of normal treatment increased to 77% (95%CI 73 to 80).

The StO_2 in patients (n=18) with cryptic shock, a condition characterised by global ischaemia, a raised lactate and a deceptively normal blood pressure, was 72% (95%CI 68 to 76) for arrival in the ED and 74% (95%CI 67 to 80) for departure from the ED. Neither of these was significantly different from severely septic 'non-cryptic shock' patients (p=0.916, p=0.570 respectively).

3.2.7.2 *Comparison of tissue oxygen saturation in survivors and non-survivors from severe sepsis*

Survivors and non-survivors from severe sepsis / septic shock were identical in their StO_2 measurements (72%) on arrival in the ED. Whilst in survivors StO_2 (78%) improved with normal treatment for sepsis in the ED, it remained unchanged in non-survivors (72%). This difference was still present after 24 hours of normal treatment on the hospital wards. Table 32 summarises the StO_2 values recorded in both cohorts.

Table 32. Tissue oxygen saturation in survivors and non-survivors from severe sepsis / septic shock

	Survivors (n=25)*	Non-survivors (n=24)*	p-value
ED arrival	72 (68-76)	72 (68-76)	0.974
ED departure	78 (74-81)	72 (66-78)	0.079
24 hour follow up	81 (77-84)	73 (68-78)	0.015

*reduced number of participants at 24 hour follow up resulting in n=23 survivors and n=16 non-survivors

Whereas StO_2 in survivors (p=0.006) changed significantly with treatment administered in the ED, the change in non-survivors was insignificant (p=0.936). After leaving the ED StO_2 in survivors continued to improve, reaching normal values, whilst there was very little change in non-survivors (p=0.164).

Patients who survived for less than 24 hours had a markedly reduced StO_2 (65%) on arrival and departure from the ED (64%) compared to patients who died at a later stage (75% and 76% respectively). In survivors, those who required a hospital stay of seven

days or less had a higher StO_2 on arrival in the ED and a greater improvement within the first 24 hours compared to those who spent more than seven days in hospital. Figure 33 illustrates the various patterns of tissue oxygen saturation measurements in short and long stay survivors (scattered and solid red lines) and early and late non-survivors (solid and scattered black lines).

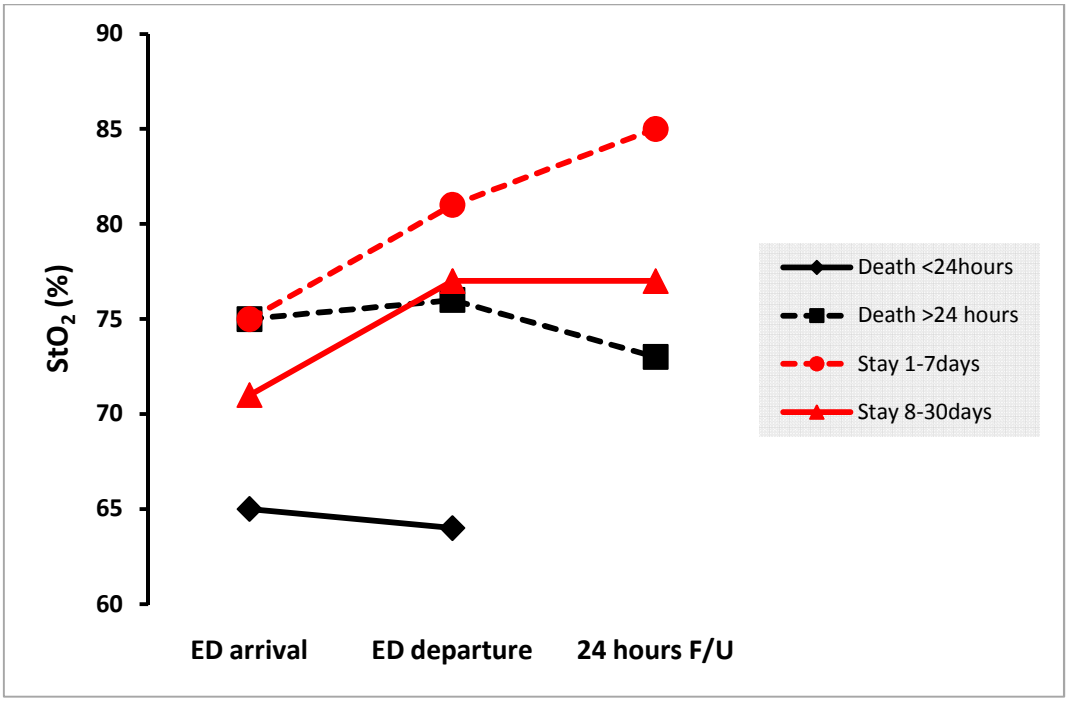

Figure 33. Changes in StO_2 in early and late non-survivors and survivors with short and long hospital stay

StO_2 on arrival in the ED was found to be a poor discriminator between death and survival in patients presenting with severe sepsis / septic shock (AUROC=0.512). Its differentiating power was slightly better on departure from the ED (AUROC=0.634). However, when used to predict early death (<24 hours) StO_2 on arrival and departure from the ED was found to perform well ($AUROC_{EDarr}$=0.735, 95%CI 0.589 to 0.851; $AUROC_{EDdep}$=0.768, 95%CI 0.626 to 0.877).

3.2.7.3 *Relationship between StO_2 and pulse oximetry oxygen saturation (SpO_2)*

StO_2 and SpO_2 readings were available at all three assessment points. Changes in StO_2 and SpO_2 over time followed a different pattern as illustrated in Figure 34. On arrival in the ED SpO_2 was found to be within the normal range in survivors ((97% (95%CI 95 to 98)) and non-survivors ((95% (95%CI 92 to 97)) whereas StO_2 was markedly reduced in all patients. With normal treatment administered in the ED there was a marked improvement in StO_2 in survivors (p=0.006) whilst SpO_2 ((97% (95%CI 95 to 99), p=0.564)) did not change. Contrary to this, in non-survivors, StO_2 remained unchanged on departure from the ED (p=0.936) whilst SpO_2 had slightly increased ((97% (95%CI 94 to 99), p=0.276)). At the 24-hour follow-up survivors had normal StO_2 and SpO_2 measurements compared to readings below the normal range seen in non-survivors.

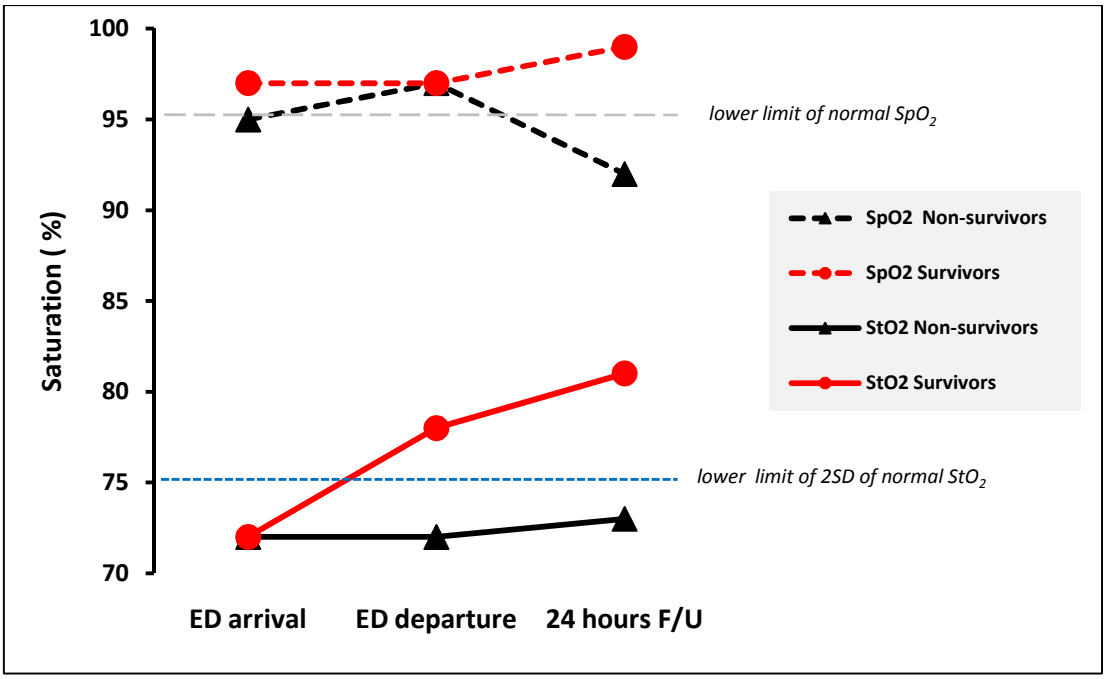

Figure 34. Changes in StO_2 and SpO_2 in survivors and non-survivors during the first 24 hours

When plotting the StO_2 and SpO_2 measurements taken on arrival and departure from the ED into a scatter diagram (Figure 35) there was no association between the two parameters. This was confirmed by the Pearson's correlation coefficient which was r=0.111 for ED arrival and r=0.020 for ED departure.

StO_2 on arrival and departure from the ED was found to be only marginally better than SpO_2 in discriminating between survivors and non-survivors as demonstrated by the areas under the ROC curve (Table 33).

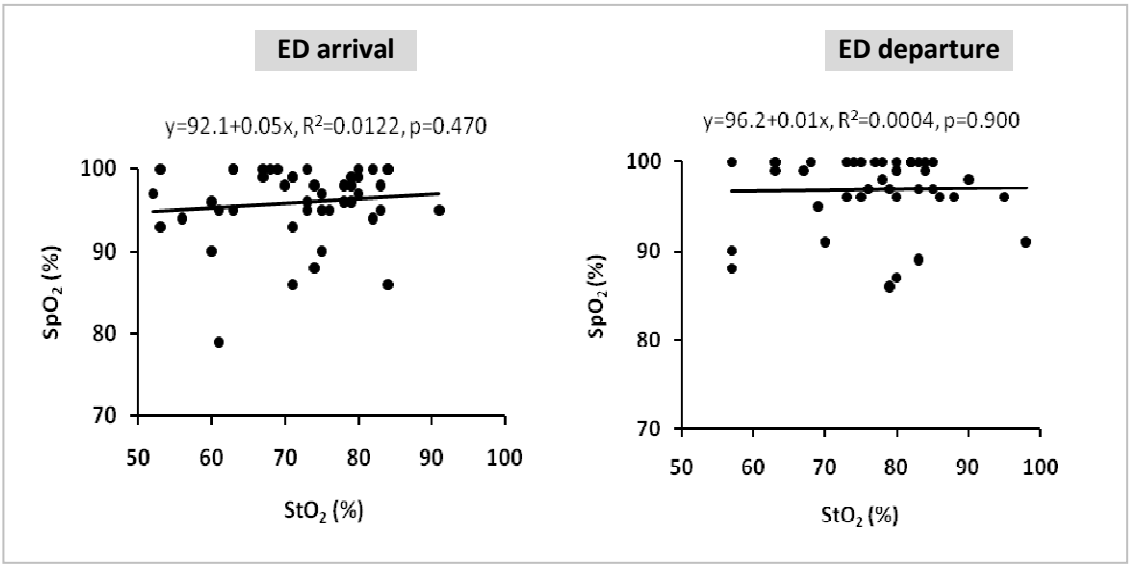

Figure 35. Relationship between tissue oxygen saturation (StO_2) and pulse oximetry oxygen saturation (SpO_2) on arrival and departure from the ED

Table 33. Area under the ROC curve values for tissue oxygen saturation and pulse oximetry oxygen saturation on arrival and departure from the ED

Parameter	AUC	95% CI
StO_2 $ED_{arrival}$	0.571	0.407 – 0.724
StO_2 $ED_{departure}$	0.634	0.484 – 0.767
SpO_2 $ED_{arrival}$	0.534	0.372 – 0.691
SpO_2 $ED_{departure}$	0.489	0.330 – 0.650

3.2.7.4 *Relationship between StO_2 and cardio-haemodynamic parameters*

TEB and Doppler data obtained on patient's arrival was used to assess the relationship between StO_2 and haemodynamic parameters. As illustrated by the Pearson's correlation coefficient (Table 34) there was no strong association between StO_2, reflecting local oxygenation, and any of the global haemodynamic parameters. There was however, a weak positive relationship between StO_2 and SV and a weak negative between StO_2 and SVR.

Table 34. Pearson's correlation coefficients for StO_2 and haemodynamic variables

	CO	CI	SV	SI	SVR	SVRI	HR	MAP	TFC
TEB	0.147	0.116	0.211	0.189	-0.352	-0.315	-0.175	-0.200	-0.030
Doppler	0.322	0.182	0.315	0.005	--	--	-0.001	--	--

4 DISCUSSION

These two studies were undertaken to explore the benefit of non-invasive monitoring in the management of sepsis and septic shock in the Emergency Department, a phase in which previous data is very sparse. The general aims of this thesis, as stated on page 44, will be considered.

4.1 To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

The results of both studies have shown that patients presenting to the ED with uncomplicated (study 1) or severe sepsis (study 2) have a measurable difference in their TEB cardio-haemodynamic indices compared to non-septic ED patients.

Septic patients in both studies were found to have an increased CI and CO whereas SV and SVR were significantly reduced in comparison to controls. In addition, severely septic patients had a markedly reduced StO_2. HR was significantly increased to the same level in both septic cohorts. Mean arterial pressure was significantly reduced in both septic cohorts with a more pronounced reduction in the severely septic cohort. These findings are in keeping with the well described haemodynamic state of sepsis characterized by increased cardiac output and low SVR, but have not been previously well documented in the early stages of sepsis management. Figure 36 depicts the overall physiological derangements seen in severely septic patients on arrival to the Emergency Department.

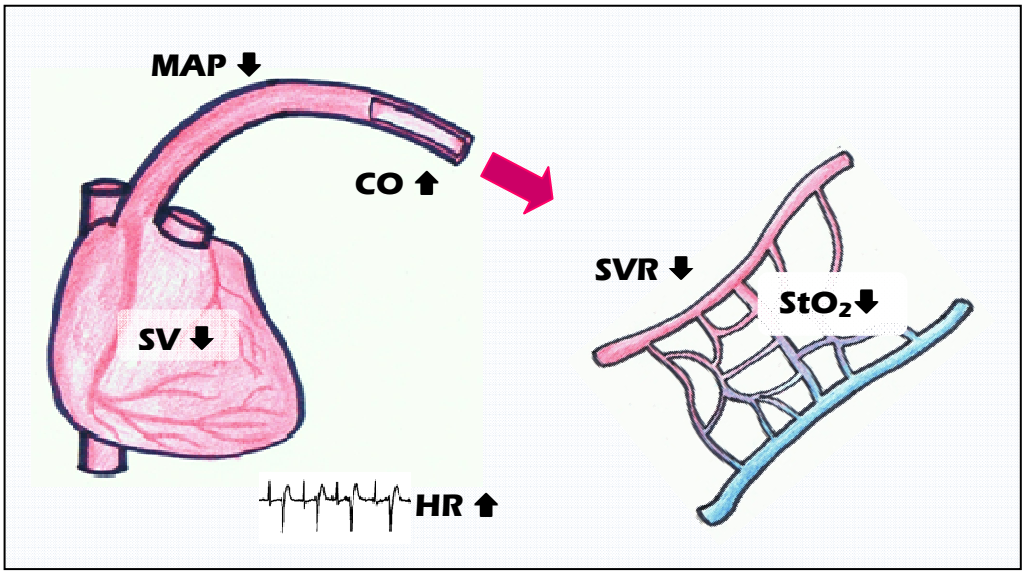

Figure 36. Physiological derangements in septic patients on ED arrival compared to controls

Cardiac output. CO, a determinant of oxygen delivery to the tissues, increases in clinical conditions where there is a greater oxygen demand by the tissues, such as sepsis. Although the tissue's oxygen requirement increases with more severe disease, severely septic patients in my study demonstrated a smaller increase in CO and CI compared to patients with uncomplicated sepsis. It could be argued that with disease progression the ability to augment CO is impaired thus a smaller increase in CO was observed in severely septic patients. Another contributing factor could be due to age related changes of cardiac function. It has been shown that cardiac function and therefore cardiac output decreases with age.[154, 155] Since severely septic patients were on average ten years older than the uncomplicated sepsis cohort, their baseline CO would have likely been lower. Such age related cardiac impairment may have contributed to the smaller increase in CO in the severe sepsis cohort.

Heart rate. Tachycardia, a recognised feature of sepsis, is believed to be a response to cardiac underfilling, fever and adrenergic stimulation. Whilst an increase in heart

rate has the potential to increase cardiac output it also causes restriction of diastolic filling and subsequently a reduction in stroke volume. Interestingly, both septic cohorts mounted a nearly identical tachycardic response but a greater reduction in SV was seen in the severely septic group. This implies that the observed difference in cardiac output must be mainly attributable to SV changes.

Stroke volume. Currently there is conflicting evidence as to whether SV diminishes with age. Earlier studies suggested a decline in SV with age but this was not confirmed in a more recent publication.[156-158] Since the severely septic cohort was older their SV at baseline may have been lower than that of the uncomplicated sepsis cohort. However, increasing age has been shown to affect the ability of the heart to respond to stress. Considering the increased prevalence of cardiovascular disease in the elderly, the haemodynamic changes seen with ageing are likely to be a combination of physiological ageing and chronic cardiovascular disease. Two recent studies of SV in exercise have shown that the ability to augment and maintain SV at increased exercise intensity was found to be impaired in older men and women.[159, 160]

Although it has been demonstrated that SV increases as a result of physical stress this is not the case in sepsis. Contrary to earlier belief that SV is maintained in sepsis, recent ICU studies reported a reduction in left ventricular SV.[53, 161, 162] Stroke volume, a main component of CO, is regulated by the difference in end diastolic volume (EDV) and the end-systolic volume (ESV). When exposed to physical stress younger people increase their SV predominantly through a decrease in ESV, whereas in the elderly the increase in SV occurs through an increase in EDV with ESV remaining fairly static.[163]

How might this explain the changes seen in my patients? In sepsis, as a result of intravascular fluid depletion, venous return is commonly reduced. With venous return being a major determining factor of preload, a fall in venous return will reduce the preload and therefore the EDV. A reduction in EDV will subsequently lower the SV, as observed in both of my studies. A reduction in SV may also be attributable to an increase in the ESV which is regulated by cardiac contractility and afterload. Myocardial contractility is difficult to measure in real life but a number of studies using an experimental sepsis model have demonstrated depressed myocardial contractility.[164, 165] In the light of these findings it would seem likely that the combination of impaired cardiac contractility and reduced preload results in a decreased SV in septic patients regardless of age.

Systemic vascular resistance. Reflecting primarily peripheral arteriolar tone, SVR is a commonly used estimate of afterload. I found a reduced SVR in sepsis with a greater decline in those with severe sepsis / septic shock, thus septic patients are likely to have had a reduced afterload. As previously mentioned, afterload is the second key determinant of ESV. Under normal physiological conditions a reduction in afterload would lead to a decrease in ESV and therefore to an increase in SV. This however, appears not to apply to sepsis where changes in SVR were not found to have an effect on SV.[166]

Though cardiovascular dysfunction is a recognised manifestation of sepsis, clinical data on cardiac physiology in sepsis, particularly during the pre-intensive care unit stage, is sparse. Current understanding of the cardiovascular changes in sepsis and septic shock rely upon studies undertaken in ICU settings and animal studies.[53, 161, 162, 164, 165, 167] Not only were their findings of limited applicability to septic ED patients

they also convey conflicting results. Whilst earlier studies[166, 167] found a normal left ventricular ejection fraction and a normal SV in septic patients, a more recent study[162] described the exact opposite.

There may be a number of reasons for these inconsistent findings. Firstly, the studied populations were very heterogeneous, most likely due to lack of defined criteria for sepsis and septic shock. Control groups were either poorly defined or historical data was used instead. The timing of the haemodynamic evaluations varied and in some cases measurements were obtained after patients had been stabilised and received adequate fluid resuscitation. Finally, studies used different methods to assess cardiovascular function. Despite their differences the general consensus is that in sepsis myocardial function is impaired. Furthermore, it is thought that the degree of myocardial functional impairment is related to sepsis severity.[168]

Despite the evidence of altered cardio-haemodynamics in sepsis the underlying patho-physiological mechanisms are not yet clearly understood. Several factors and mechanism are thought to be responsible, of which circulating mediators, such as cytokines and nitrous oxide, are believed to play a key part.[168] Mitochondrial dysfunction has also been described in sepsis and was found to be related to illness severity and outcome. Other mechanisms considered are microcirculatory and metabolic changes as well as contractile and autonomic dysfunction which are likely to be mediated by circulating inflammatory compounds.[168] Until there is better understanding of the pathophysiological causes for sepsis induced myocardial depression, clinical management needs to focus on patient identification and initiation of directed and supportive therapy at the earliest stage.

Thoracic Fluid Content. Microvascular hyperpermeability is considered to be a feature of sepsis. Though this phenomenon has been confirmed by experimental studies the clinical diagnosis of capillary leakage at the patients' bedside remains challenging.[169] To date there is no published data on the use of TFC to evaluate fluid distribution in sepsis. TFC is determined by intra- and extravascular fluid within the chest. Under normal physiological conditions fluid will be predominantly located intravascularly. In sepsis however, the extent of extravascular fluid increases as a result of mediator induced progressive capillary hyperpermeability. In my study the TFC of patients with uncomplicated sepsis did not differ significantly from controls, which is likely to indicate the absence of any major fluid shift. Severely septic patients however, had a significantly higher TFC value on arrival in the ED than non-septic controls. Since sepsis is characterised by relative and absolute hypovolaemia the measured elevated TFC is highly indicative of pulmonary capillary leakage. My data suggests that TFC measurements may serve as a bedside method to diagnose capillary leak syndrome in patients with sepsis.

Tissue oxygen saturation. Study data on StO_2 was only available for the severely septic cohort. However, when compared with published 'normal' StO_2 values (healthy volunteers) severely septic patients had markedly reduced StO_2 measurements on arrival in the ED. This implies that patients with severe sepsis or septic shock have a measurable microcirculatory dysfunction and inadequate tissue oxygenation prior to the initiation of any treatment. This important secondary outcome finding is further discussed in *sections 4.3.2 and 4.4.2.*

[4.1] SUMMARY – To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

Prior to this thesis there was no published data on early cardio-haemodynamic changes in septic patients before administration of any treatment. When comparing septic patients to normal controls my work shows that they have clearly abnormal haemodynamic parameters. This thesis provides the first evidence that even patients with uncomplicated sepsis, who are not haemodynamically compromised by conventional measurements, have significantly altered SV and SVR compared to non-septic ED patients. The data also shows that severely septic ED patients have a measurable microcirculatory dysfunction as indicated by the abnormal StO_2 values on arrival in the ED.

4.2 To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

4.2.1 Change of cardio-haemodynamic parameters in septic ED patients with normal treatment in the ED

In uncomplicated sepsis, resuscitation in the ED did not result in important differences between most of the TEB cardio-haemodynamic variables obtained on arrival and departure from the ED. There were, however, two exceptions TFC and HR which showed a statistically significant increase and decrease respectively.

Severely septic patients exhibited a similar degree of change in their cardio-haemodynamics following the resuscitative management in ED. In addition, the severely septic cohort demonstrated a significant fall in MAP and left cardiac work (LCW). Interestingly, in spite of a decrease in heart rate and an anticipated increase in venous blood volume owing to the administration of intravenous fluids to all septic patients in the ED, an important change in SV was not observed. This was surprising as I had expected SV to increase with treatment.

Under normal conditions an increase in venous blood volume will result in an increase in central venous pressure (CVP), a parameter commonly used as a surrogate marker for cardiac preload. CVP reflects the right ventricular end-diastolic pressure (RVEDP) which, in the absence of left ventricular impairment (ejection fraction >50%), mirrors changes in the left ventricular end diastolic pressure (LVEDP).[170] Thus it would be expected that an increase in central venous blood volume would result, to some extent, in an increase in left ventricular end diastolic volume (LVEDV) and therefore SV, if

the left ventricular end systolic volume (LVESV) was kept constant. An increase in SV was not observed in either of the septic cohorts and there are a number of possible explanations for this.

Firstly the amount of fluid given in the ED was likely to have been too small to sufficiently augment the CVP and thus the preload. Severely septic patients received on average 1.3 litre of crystalloid fluid whilst in the ED, which is less than half of the amount that was given to the control arm in the 'Early goal directed therapy' (EGDT) study[3] and about one third of that given to the EGDT intervention group[3, 24].

Secondly, even if the administration of intravenous fluids resulted in an increase in CVP this may not have had the effect on preload that would have been expected under normal conditions. A recent paper had shown that patients with septic shock failed to augment their LVEDV, as measured by transthoracic echocardiography, despite venous volume expansion to a CVP of greater than 12mmHg.[162] This is contrary to earlier studies using a combination of thermodilution and radionuclide angiography, which described an increase in LVEDV owing to volume loading. [53, 171] Though all three studies included patients with septic shock, their diagnostic criteria varied, as did the timing of the measurements and the treatment given to the patients. *Parker et al.*[53] studied a very young cohort with an average age of 43.6 years. With advancing age the ventricles become stiffer, ventricular compliance declines and myocardial relaxation time increases, resulting in impaired filling.[155] This may explain why *Parker et al.*[53] observed an 100% increase in LVEDV in their relatively young septic shock patients whereas others[162, 171] studying older septic shock patients found only a minimal or no increase in LVEDV.

A third reason for the lack of increase in SV amongst septic patients in my research study could be impaired cardiac contractility. This theory is supported by a previously published study looking at quantifying ventricular contractility amongst septic patients.[167] The authors assessed the response to an intravenous fluid load in patients with uncomplicated sepsis, septic shock and non-septic critical illness by measuring changes in left ventricular stroke work index (LVSWI), which is a marker of contractility. They found that septic patients had a much smaller increase in LVSWI than controls following the fluid load and that patients with septic shock were barely able to augment their LVSWI which was significantly lower compared to controls. This would suggest that patients with severe sepsis have an abnormal cardiac response to fluid resuscitation due to a markedly reduced ventricular contractility.

There are some parallels between these findings and the changes seen in the patient data presented in this thesis. Since LVSWI is a function of stroke index (SI), measured changes in SI will be reflected in LVSWI. Similar to *Ognibene et al.*[167] I found that patients with uncomplicated sepsis demonstrated a minor increase in stroke volume whilst severely septic patients were unable to show any SV augmentation despite administration of intravenous fluids. This would suggest that from the early stage of sepsis ventricular contractility is impaired and that cardiac performance is not noticeably improved by increasing CVP through venous volume load. This may also explain, why in severe sepsis, fluid resuscitation targeted to a fixed CVP endpoint had no significant impact on hospital mortality.[34]

In my study severely septic patients became more hypotensive despite initial fluid resuscitation in the ED. Given the fact that severe sepsis is a state of profound

intravascular deficit the worsening hypotension is likely to be a combination of inadequate fluid therapy, increasing vasodilatation and microvascular leakage.

Though fluid resuscitation received in the ED may have not been adequate to augment the systemic blood pressure of severely septic patients there was a measurable increase in their fluid status as indicated by the rise in TFC. Thoracic fluid content is primarily determined by the amount of intravascular, intra-alveolar and interstitial fluids in the thorax. It is not commonly used to evaluate a patient's fluid status. The current understanding about the association between TEB derived TFC and thermodilution parameters is limited to the findings of a few studies with very small sample sizes. Whilst one study[172] in chronic heart failure patients found a moderate positive correlation between TFC and left ventricular diastolic pressures two other studies[173, 174] found that TFC did not correlate with pulmonary capillary wedge and right atrial pressures. Though there is lack of correlating TFC with established invasive modalities TEB TFC measurements were found to be of value in the assessment of the fluid status in critically ill ED patients.[175] This has been confirmed by a more recent study demonstrating that TFC is a reliable measurement of thoracic fluid status and tracks fluid changes well.[71]

Although this research project was not designed to assess the effect of intravenous fluid administration, the data from both septic cohorts imply that there is a weak positive correlation between the amount of fluids given per kg/bodyweight and absolute changes in TFC whilst in the ED. This association was more pronounced in the uncomplicated sepsis group (r^2=0.48 vs. r^2=0.32) which may be explained by the persistent peripheral vasodilatation and global microvascular leakage in severe sepsis or septic shock. Considering the existing challenge to assess fluid therapy of septic

patients in routine clinical practice the potential of TFC to monitor fluid resuscitation warrants further exploration.

Another parameter believed to be indicative of fluid responsiveness in critically ill patients is stroke volume variation (SVV). SVV, a naturally occurring phenomenon due to respiration, is thought to decrease in response to an increase in preload. Current evidence, which is based on mechanically ventilated surgical patients using semi-invasive techniques, is inconsistent though there is a trend in favour of the usefulness of SVV in this selective group of patients.[176-179] The results from my research project do not support the use of transcutaneous Doppler ultrasound derived SVV to predict fluid responsiveness given the lack of association between SVV and changes in SV (r^2<0.01). Possible explanations for this are the variability in respiratory pattern of spontaneously breathing critically ill patients and the earlier described sepsis induced myocardial dysfunction.

The resuscitative management in the ED resulted in an overall improved StO_2 amongst severely septic patients, just reaching the lower limit of the 'normal' range for StO_2. This finding concurs with the concept of improved tissue oxygenation by restoring tissue perfusion through fluid resuscitation. Interestingly, though initial fluid resuscitation resulted in a noticeable improvement in microcirculatory function this was not observed for macrocirculatory perfusion markers, such as SVR or MAP.

4.2.2 Change of cardio-haemodynamic parameters in septic ED patients after 24 hours of normal treatment

Whilst there were negligible changes in haemodynamic parameters following the treatment period in the ED in both septic cohorts subsequent sepsis management over 24 hours resulted in a significant reduction in CO, CI and HR and an increase in left ventricular ejection time (LVET). StO_2 measurements of severely septic patients were within the normal range, an important though not statistical significant change from the initial assessment. Figure 37 illustrates the physiological status of severely septic patients compared to normal, after the initial 24 hour sepsis management. Whereby the width of the arrow signifies the extent of abnormality and the direction of the arrow indicates the directional change from normal.

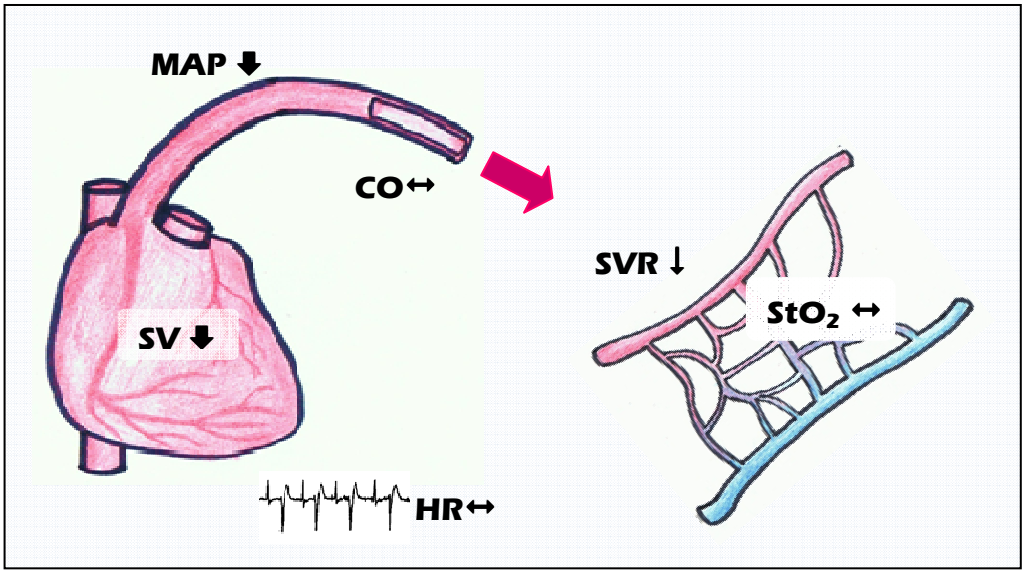

Figure 37. Physiological parameters after 24 hours of treatment compared to controls

The reduction in CO and CI was mainly attributable to the decline in HR as SV remained low. LVET, a function of ventricular contractility, represents the isotonic phase of the ventricular systole.[180] It is generally accepted that LVET is inversely proportional to HR.[181] For this reason the increase in LVET observed in both studies was most likely the result of HR reduction rather than a result of improved contractility. This assumption is supported by the fact that SV and SI remained essentially unchanged despite 24 hours of treatment, thus endorsing the concept of prolonged myocardial depression in sepsis.

After 24 hours of sepsis management there was a significant increase in TFC amongst severely septic patients but virtually no change in patients with uncomplicated sepsis. Despite patients with severe sepsis / septic shock receiving, on average, one third more intravenous fluids than those with uncomplicated sepsis the proportional increase in TFC was far greater than would have been expected based upon the absolute fluid administration. A likely explanation for this observation would be ongoing or even worsening pulmonary capillary hyperpermeability over 24 hours leading to an increase in extravascular fluid.

[4.2] SUMMARY – To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

My data shows that initial resuscitative treatment in uncomplicated or severe sepsis does not result in pronounced immediate changes in patients' haemodynamics. However, when assessed after the initial 24 hour treatment period cardio-

haemodynamic parameters of patients with uncomplicated or severe sepsis began to normalise. This trend towards 'normality' was more pronounced in patients with uncomplicated sepsis, a finding which was not unexpected. Though, after 24 hours of treatment, septic patients were found to have near normal HR and CO their cardiac function had not returned to normal, as indicated by the persistently low SV.

TFC continued to rise during the 24 hours treatment period, which was most evident in severely septic patients, indicative of increased capillary hyperpermeability.

Contrary to the pattern of change seen in haemodynamic parameters, StO_2, a marker of microcirculatory function, was found to reach near normal values with initial fluid resuscitation. These patterns, observed and presented in this thesis for the first time, substantiate the concept that restoration of the microcirculatory function precedes that of the macrocirculation.

4.3 To determine whether the degree of initial abnormality is related to outcome

4.3.1 Comparison of initial cardio-haemodynamic parameters in survivors and non-survivors from severe sepsis / septic shock

Survivors and non-survivors were very similar in their baseline characteristics with the exception for age. Non-survivors were found to be significantly older than those surviving septic illness. No significant differences were seen in their initial conventional physiological parameters or 'Early Warning Score' (EWS) results. There were however, differences in their mean 'Mortality in Emergency Department Sepsis' (MEDS) score and venous lactate measurement, with values being significantly higher in non-survivors.

No statistically significant differences in initial cardio-haemodynamic parameters were found between survivors and non-survivors. Though not significant, there was a noticeable difference in CO and SV (Figure 38).

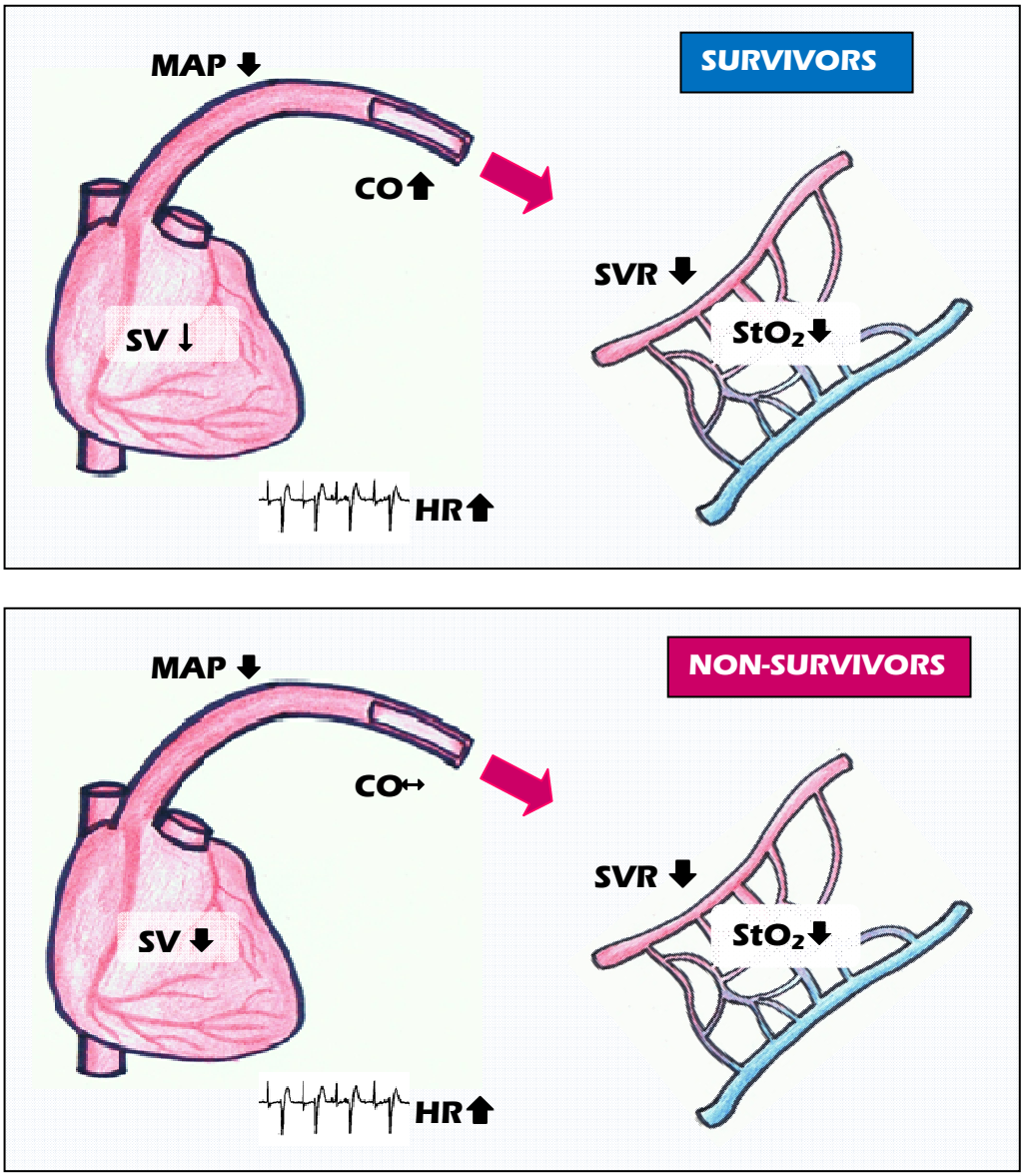

Figure 38. **Physiological state of survivors and non-survivors on ED arrival compared to controls**

Whilst survivors demonstrated the ability to augment their CO in response to sepsis, this ability was lacking in non-survivors, who were merely able to maintain a CO similar to the control group. This concurs with the findings of a recently published study reporting a significantly lower cardiac index in non-survivors from severe sepsis.[182] *Napoli et al.*[182] hypothesised that the difference in CI may be the result of inadequate fluid resuscitation since non-survivors received on average 530mls less.

Though this is plausible it was unlikely to be the cause in the *Napoli et al.*[182] study given the very similar CVP measurements (10.3 versus 10.0) in both cohorts. A more likely explanation for the observed greater CO in patients with a favourable outcome from severe sepsis / septic shock is a lesser degree of myocardial depression and thus a smaller decrease in SV.

The data from my study has shown that SV was reduced in all severely septic patients and though the reduction was far greater in non-survivors, it did not reach statistical significance. This said, the lack of statistical power may have caused a type II error given the wide 95% confidence intervals. In view of this and the fact that a difference in SV of 18% would be deemed clinically meaningful further exploration in a future trial is needed.

Since all initial measurements were taken prior to fluid administration, fluid under-resuscitation does not appear to play a pivotal role. Other factors that affect stroke volume are contractility, compliance and afterload. Interestingly, left ventricular ejection time (LVET) a marker of contractility was found to be no different in relation to outcome. Systemic vascular resistance, an estimate of afterload, was insignificantly lower in survivors and may have contributed to some extent to the larger SV seen in survivors. Though ventricular compliance was not measured in this research study it is conceivable that impaired compliance had an effect on SV differences seen in this research study. This concept is supported by a number of previous studies indicating an impaired ventricular compliance in septic patients as a result of abnormal ventricular filling and relaxation.[183-185]

Contrary to previous beliefs[43] initial heart rate was not found to be related to outcome. In fact, HR was identical in both groups. The view that initial HR predicts outcome from severe sepsis and septic shock is based on two studies from the 1980s.[186, 187] Since both studies had been conducted in intensive care units and initial measurements were commenced once circulatory shock was present, describing their finding as 'initial' is misleading and not reflective of changes seen in the very early phase of sepsis.

Of all measured haemodynamic parameters, TEB cardiac output demonstrated the best discriminatory power for survival on ED arrival, as indicated by the AUROC (0.702). Though CO may be an useful early predictor of outcome from severe sepsis, the identified optimal cut off for cardiac output greater than 5.1 l/min in favour of survival, lacks sufficient sensitivity (82%) and specificity (55%) to be used as a 'rule out' or 'rule in' tool.

4.3.2 Comparison of initial tissue oxygen saturation (StO_2) in survivors and non-survivors

Tissue oxygen saturation (StO_2) was seriously impaired in all severely septic patients on their arrival in the ED prior to the initiation of treatment, hence initial StO_2 measurements were not found to be predictive of outcome.

Tissue oxygen saturation provides information about oxygenation within the microcirculation. It has become evident that microcirculatory dysfunction plays a key role in the pathogenesis of sepsis and that the derangement is more severe in patients with the worst outcome.[188-190] These findings are based on ICU patients with severe

sepsis or septic shock who were already receiving treatment. As such they do not provide information on early microcirculatory changes in severe sepsis.

In contrast to the findings of my research, a recent prospective study of high-risk trauma patients showed that tissue oxygen saturation measured upon their arrival in the Emergency Room predicts development of multiple organ failure and death.[191] This concept of early determination of poor outcome had been initially confirmed in a porcine haemorrhagic shock model.[192]

In neither sepsis nor trauma is the complex pathogenesis responsible for microcirculatory disturbance clearly understood. The complex interactions of different biological structures and processes within the body are thought to be responsible for the microvascular dysfunction in sepsis. Circulating inflammatory mediators, such as cytokines, are believed to play a pivotal role, alongside activated dysfunctional complement and coagulation cascades and leucocytes.[193, 194] As a knock-on effect endothelial permeability increases, thrombosis and sludging of red blood cells in the microvasculature develops. This leads to an impaired microvascular blood flow and oxygen delivery, a fact that has been confirmed by the StO_2 measurements of my study. Observed changes in StO_2 in the severely septic cohort are further discussed in *section 4.4.2.*

[4.3] SUMMARY – To determine whether the degree of initial abnormality is related to outcome

The results of my thesis demonstrate that survivors from severe sepsis / septic shock do not differ significantly in their degree of initial abnormality in haemodynamics and StO_2 compared to non-survivors. However, patients with a favourable outcome had a higher CO and a lesser reduction in SV on arrival in the ED. Given the wide confidence intervals, these findings warrant further exploration as they may identify a group of patients who may benefit from a different sepsis management. A future trial should not only focus on initial CO and SV measurements but also on the dynamic changes in response to initial resuscitative treatment to determine their potential to guide early sepsis management.

4.4 To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

4.4.1 Comparison of cardio-haemodynamic parameters following normal treatment in survivors and non-survivors from severe sepsis / septic shock

As depicted in *section 4.1* septic patients had deranged cardio-haemodynamic values compared to non-septic controls. It was further shown in *section 4.2* that administration of normal treatment resulted in measurable though not significant changes. Previous studies amongst critically ill ED patients have demonstrated that normalisation of cardiovascular and tissue perfusion markers was associated with a good outcome.[82, 91] It was therefore anticipated that patients with a good outcome would display a normalisation of their cardio-haemodynamic parameters.

Of those patients presenting with uncomplicated sepsis to the ED all but one survived (4% mortality). With initial treatment this cohort showed a clear trend towards normalisation of cardio-haemodynamic parameters with the exception of TFC.

In contrast, the chronological patterns of cardio-haemodynamic parameters of severely septic patients differed depending on the patient's outcome. The pattern in survivors of severe sepsis / septic shock was similar to that seen in uncomplicated sepsis, with a trend to normality in cardiovascular parameters over 24 hours. In contrast, non-survivors did not show this normalisation with continuing abnormality of CO, SV and StO_2. Figure 39 illustrates the observed physiological state seen in survivors and non-

survivors after 24 hours of treatment. The overall lack of improvement in myocardial function as seen in non-survivors is likely to be a reflection of irreversible cardiac dysfunction due to sepsis. These observations, the first in the emergency care phase, are consistent with previous ICU studies describing irreversible depression of cardiac function in patients succumbing to septic shock.[53, 161, 195]

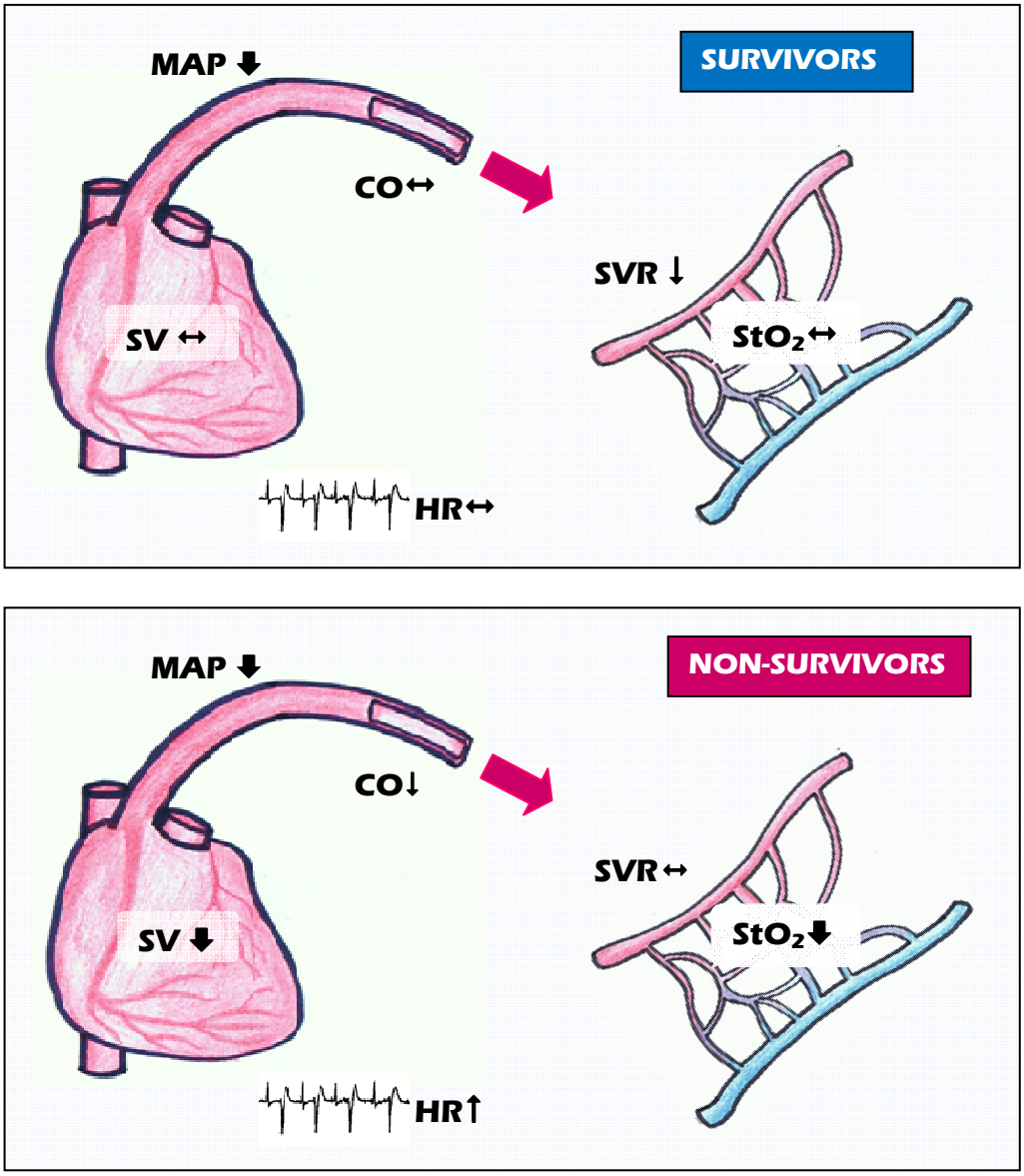

Figure 39. **Physiological state of survivors and non-survivors after 24 hours of treatment compared to controls**

Since survival appears to be associated with the ability to improve cardiac performance would a more aggressive treatment approach alter the prognosis of those with a potentially poor outcome? According to a study in septic ICU patients non-survivors failed to augment their cardiac function despite the administration of inotropic agents, suggesting serious and potentially irreversible myocardial depression.[196] Even if prevention of disease progression may not be possible, early identification of septic patients with a poor prognosis will aid clinical decision making, even if this is simply to decide on the ceiling of treatment.

As for TFC, this parameter continued to increase with treatment in survivors and non-survivors. Non-survivors had a higher TFC and had received more intravenous fluids, although neither finding was statistically significant. Though early aggressive fluid resuscitation within the first hours of sepsis presentation was found to be associated with a good outcome, subsequent aggressive fluid administration may actually be harmful.[3, 197] Most of the infused fluid will eventually disperse into the extravascular space, a process which is expedited in sepsis due to increased vascular permeability, hence exacerbating tissue oedema and worsening organ perfusion. Whilst these are valid points they are unlikely to be applicable to the patients of my research study, since none of the patients received excessive amounts of intravenous fluids compared to other studies[3, 197].

Contrary to what would have been expected, after 24 hours of treatment, non-survivors had a markedly higher SVR, approaching the value found in normal controls. The impact of sepsis on SVR and its association with outcome from sepsis has not been studied in depth in clinical settings. There is evidence to suggest that poor outcome from septic shock is linked with a low SVR.[198, 199] Systemic vascular resistance,

defined as resistance to the blood flow offered by the systemic circulation, is predominantly determined by the calibre of the arterioles. A number of sepsis models have demonstrated that endothelial-derived nitric oxide plays an important role in the flow regulation of arterioles.[200, 201] There is also evidence that altered synthesis and release of nitric oxide and disruption of endothelial signalling affecting the dilator control mechanisms for arterioles, contributes to a decreased SVR in sepsis.[202] A possible explanation for the higher than expected SVR in severely septic patients in my research study may be the fact that TEB SVR was calculated using MAP and CO rather than being measured. Since SVR is inversely proportional to CO and non-surviving septic patients had a markedly lower CO their calculated SVR would have been higher since the MAP was nearly identical in both cohorts.

4.4.2 Comparison of change in tissue oxygen saturation (StO_2) following normal treatment in survivors and non-survivors

A key finding of this research project is the measurable normalisation of StO_2, a marker of microcirculatory function, in survivors following the initial treatment, whilst macrocirculatory parameters were only starting to demonstrate a trend towards 'normal' after 24 hours of sepsis management.

Until recently the assessment of microcirculatory changes in critically ill patients was limited due to the need for cumbersome measuring equipment. The use of StO_2 monitoring has been described in different cohorts of critically ill patients such as trauma and septic ICU patients.[128-131, 203-205] Nearly all studies concluded that StO_2 values were lower in critically ill patients compared to healthy controls and some suggested that low StO_2 values were predictive of poor outcome. Two recently

published studies assessing StO_2 in severely septic ICU patients found no difference in baseline StO_2 measurements in survivors and non-survivors from severe sepsis / septic shock but a significantly lower StO_2 reperfusion slope in non-survivors after three minutes of induced arterial ischemia.[130, 205]

Two other ICU studies looked at StO_2 values without induced ischemia in severely septic patients after completion of the EGDT resuscitation treatment.[203, 204] They found that low StO_2 values were associated with poor outcome despite early optimisation of haemodynamic parameters.

Data on the microcirculatory assessment of septic patients in the ED is sparse. A recent study utilising orthogonal polarisation spectral imaging to visualise sublingual microcirculation in ED patients with severe sepsis reported greater microcirculatory derangement in non-survivors from an early stage, defined as 'within 6 hours of commencing early goal directed therapy'.[206] Those findings are in keeping with the results from my research study of persistently low StO_2 readings in non-survivors despite normal resuscitative treatment.

The fact that StO_2 in survivors began to normalise with initial resuscitative treatment in the ED, as demonstrated in my study, indicates that patients with a good prognosis have the ability to rapidly improve their microcirculatory derangement, whilst those with a poor outcome lack this type of response. This raises the question as to whether septic patients, who fail to respond to normal ED treatment, as measured by lack of improvement in StO_2, would have their prognosis improved by a therapeutic strategy that targets early optimisation of StO_2.

[4.4] SUMMARY – To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

The ability to normalise cardio-haemodynamic parameters and StO_2 with treatment is associated with a good outcome. Whilst StO_2 of survivors reached a near normal value with the initial resuscitation such immediate effect was not observed for macrocirculatory parameters. Within 24 hours of treatment survivors from severe sepsis demonstrated a trend towards normal for nearly all haemodynamic parameters, a pattern similar to that seen in patients with uncomplicated sepsis. Non-survivors however, lacked this ability, which is likely to be a reflection of ongoing serious cardiac dysfunction.

4.5 To determine which non-invasive monitoring modality is most strongly related to outcome

Early risk stratification in sepsis is crucial to improve outcome given the high morbidity and mortality associated with severe sepsis / septic shock. Owing to the heterogeneity of the clinical manifestation of sepsis, early risk stratification remains challenging and conventional physiological and laboratory parameters were not found to be helpful.[207] There is a clear need for clinically useful biomarkers to aid identification of high risk septic patients.

My research is the first study to assess the cardio-haemodynamic response to severe sepsis / septic shock in its early phase, by using a range of non-invasive technologies, and how this response is related to outcome. Two of the modalities, TEB and transcutaneous Doppler, provided a wide range of cardio-haemodynamic parameters. The third device measured tissue oxygen saturation, a marker of microcirculatory function.

My work shows that, as expected, the cardio-haemodynamic responses to sepsis are complex and not homogenous. There was evidence of cardiovascular and microcirculatory dysfunction amongst all patients with severe sepsis / septic shock, with a distinct pattern for survival. Early measurements in the ED showed that survivors predominantly exhibited a high CO with a lesser reduction in SV and low SVR whereas non-survivors primarily demonstrated a 'normal' CO with a low or normal SVR. There was no difference in StO_2 on ED arrival.

In response to the initial ED sepsis management a distinct pattern emerged for SV and StO_2. Following the initial and the subsequent 24 hour treatment, survivors demonstrated the ability to augment their stroke volume and to normalise their tissue oxygenation whereas both parameters remained unchanged in non-survivors.

There is no previous published data comparing StO_2 and SpO_2. Though both are measures of oxygenation, StO_2 reflects oxygenation within the microcirculation whereas SpO_2 is a surrogate marker of global oxygenation. The distinct chronological pattern of StO_2 from the early phase of sepsis heralds the fact of ongoing impaired microcirculatory oxygenation in patients with poor outcome, despite having normal SpO_2 values. This concurs with the concept of sepsis induced tissue hypoxia preceding global hypoxia. It further suggests that StO_2 can provide early prognostic information about outcome from severe sepsis / septic shock and has the potential to aid identification of patients who would benefit from more intensive therapy.

Contrary to previous beliefs my data has shown that severely septic patients have a reduced SV, with the greatest reduction in non-survivors. This concurs with a recent study by *Napoli et al.*[182]. The changes in SV over time exhibited a distinct pattern for survival whereby survivors had the ability to augment their SV in response to treatment but non-survivors did not; an observation which supports the concept of reversible myocardial dysfunction in survivors from sepsis originally described by *Parker et al.*[53].

Both TEB and USCOM measured SV. Overall both technologies measured higher values in the surviving cohort though TEB measurements were persistently lower. The cause of this discrepancy is not clear. Given the fact that signal acquisition using the

USCOM was not always perfect due to the patients' habitus or inability to remain still during the measurement, underestimation of haemodynamic values would have been expected. Underestimation of haemodynamic parameters by the TEB method due to motion artefacts is a possibility, although measurements obtained in this research project had higher values than those of a comparable cohort in the *Napoli et al.*[182] study.

The study was powered to detect a difference in cardiac index for survival. Though the predetermined minimal clinical significant difference for CI of $\geq$ 0.3 l/min/m^2 was observed on ED arrival, this lacked statistical significance due to higher than expected variation. In subsequent measurements this difference was even smaller. This is contrary to a very recent study using TEB in a cohort of ED patients (n=55) eligible for EGDT, where survivors had a significantly higher CI (3.2 vs. 2.3, p=0.02) following ED resuscitation.[182] Noticeably, non-survivors in the *Napoli et al.*[182] study had a surprisingly low mean heart rate (67 bpm) which was very different to the HR of 102 bpm found in non-survivors after ED sepsis management in my study. This in itself may explain the disparate findings. (Personal communication with Dr Napoli did not offer any further explanation.)

As expected conventional parameters such as HR, BP and SpO_2 did not show a distinct pattern for survival on arrival or departure from the ED. At the 24 hour follow up HR and SpO_2 differed for survival, but interestingly there was no distinct difference for BP. Since hypotension is believed to be associated with worse outcome from sepsis, non-survivors were expected to have a lower BP than survivors. Even sepsis related non-sustained hypotension (systolic BP <100mmHg) was reported to be associated with a threefold higher risk of mortality.[208] This is much higher than in my severe

sepsis study, where the association between hypotension and mortality was weak (relative risk of death of 1.2).

[4.5] SUMMARY – To determine which non-invasive monitoring modality is most strongly related to outcome

Predicting patient outcome based on parameters taken on arrival in the ED is difficult. Of all measured haemodynamic parameters CO and its determinant SV were found to be the best discriminatory variables for survival on ED arrival, an observation that concurs with the concept of worse myocardial dysfunction in patients with poor outcome. With the instigation of initial sepsis treatment macrocirculatory parameters (CO and SV) lost their discriminating ability, whilst another variable, StO_2, showed a distinct pattern for survival. This pattern continued throughout the initial 24 hour treatment period and is indicative of early normalisation of the sepsis induced microcirculatory derangement. At the end of the 24 hour treatment period of all the cardiovascular parameters, only SV demonstrated a distinct pattern for survival.

My work demonstrates that these parameters, in particular StO_2 and SV, have the potential to act as biomarkers of poor outcome and thus enable the identification of high risk patients who may have their prognosis improved by a more intensive treatment strategy.

5 CONCLUSIONS

5.1 Research findings

This thesis examined cardio-haemodynamic parameters in septic ED patients and explored their potential value in the early management of sepsis and septic shock. Five general aims were addressed in this thesis, the finding for each of these objectives were:

[1] To determine whether patients with sepsis have abnormal cardio-haemodynamic parameters on arrival in the ED compared with normal controls

a) This research project has shown that ED patients with sepsis / septic shock have measurable abnormal cardio-haemodynamic indices on arrival in the ED. The direction of physiological derangement was the same for patients with uncomplicated or severe sepsis.

b) Septic patients were found to have a higher cardiac output and cardiac index than the age and gender matched control group patients, but these differences were not statistically significant.

c) Stroke volume and stroke index in both septic cohorts was significantly lower than in the age and gender matched control group. This is likely to be a reflection of impaired myocardial contractility, a feature of sepsis induced myocardial depression.

d) Systemic vascular resistance was found to be significantly lower in both septic cohorts. This reduction was most pronounced for patients with severe sepsis / septic shock.

e) Septic patients of both groups were found to be tachycardic, exhibiting a heart rate which was significantly higher than that of control group patients. Mean arterial pressure remained within the accepted normal range for patients with uncomplicated sepsis but was significantly reduced in patients with severe sepsis / septic shock.

f) Severely septic ED patients had a measureable microcirculatory dysfunction on arrival in the Emergency Department, as indicated by the markedly reduced tissue oxygen saturation (StO_2) measurements. It is not known whether patients with uncomplicated sepsis have a similar abnormality.

In light of these findings I hypothesise that early identification of septic patients may be improved by including haemodynamic parameters and StO_2 measurement as part of the initial assessment in the ED.

[2] To determine whether abnormal cardio-haemodynamic parameters normalise with treatment

g) Initial resuscitative management in the ED did not result in important immediate changes in cardio-haemodynamic parameter of patients with uncomplicated or severe sepsis. However, this lack of change might have been masked by the relatively small amount of fluid resuscitation that was given.

h) After 24 hours of sepsis management a trend towards 'normal' haemodynamics emerged in both septic cohorts. This trend was more pronounced in patients with uncomplicated sepsis.

i) Following the initial ED management tissue oxygen saturation of severely septic patients demonstrated a trend towards 'normal' values, which is likely to be a reflection of the beginning of microcirculatory improvement following treatment.

[3] To determine whether the degree of initial abnormality is related to outcome

j) No statistically significant differences in initial cardio-haemodynamic or StO_2 measurements taken on arrival in the ED were found between survivors and non-survivors. However, survivors had a greater cardiac output owing to a lesser reduction in stroke volume, suggestive of a lesser degree of myocardial dysfunction in patients with a favourable prognosis. These findings warrant further exploration using cardiac output and stroke volume as biomarkers to define a high risk group.

[4] To determine whether normalisation of cardio-haemodynamic parameters with treatment is related to outcome

k) Following early resuscitative sepsis management StO_2 measurements improved in survivors, reaching the lower end of the normal range, but remained abnormal in non-survivors. Thus in patients with a good prognosis the microcirculatory

derangement responded well to initial sepsis management raising the question whether non-responders may have their prognosis improved by a more intensive approach to early sepsis resuscitation.

l) Patients with uncomplicated sepsis (4% mortality), demonstrated a clear trend towards normalisation of cardio-haemodynamic indices with 24 hours of treatment. A similar pattern was seen in survivors from severe sepsis / septic shock (49% mortality). Patients who did not show a tendency to normalise within 24 hours had a poor outcome. The overall lack of improvement in cardiovascular function, as seen in non-survivors, is likely to be indicative of ongoing myocardial dysfunction.

[5] To determine which non-invasive monitoring modality is most strongly related to outcome

m) Of all studied parameters StO_2 and SV were most strongly related with outcome from severe sepsis / septic shock. SV was found to have good discriminatory power for survival throughout the initial 24 hours. This ability to discriminate was strongest at the end of the initial 24 hour sepsis management period. Though StO_2 on arrival in the ED lacked discriminating power for survival, a distinct outcome related pattern for StO_2 emerged following the initial resuscitative treatment with early normalisation in survivors.

SUMMARY OF CONCLUSION

This thesis is the first description of cardio-haemodynamic parameters in septic patients at their entry to hospital (ED). The data shows that septic patients have initially abnormal haemodynamics and abnormal tissue oxygen saturation which is indicative of macro and microcirculatory derangements. The study also demonstrates that the microcirculatory function starts to normalise in survivors after the initial resuscitative treatment in the ED whilst haemodynamic parameters, reflecting the macrocirculation, remained abnormal. Another key finding is, that the initially abnormal cardio-haemodynamic parameters began to normalise after 24 hours of treatment and that the failure to show signs of normalisation was associated with poor outcome.

Of all the parameters studied the two variables most strongly related to outcome were StO_2 and SV. Both parameters warrant further exploration to define their role as biomarkers for early disease progression and poor outcome. This might identify a group of high risk patients, who may have their outcome improved by a more intensive treatment strategy.

Any future trial will need also to focus on dynamic changes of haemodynamic parameters, in particular SV and StO_2 in response to initial resuscitative treatment to determine their potential to guide early sepsis management.

What is already known on this topic

- Septic shock is characterised by increased cardiac output and low systemic vascular resistance (ICU phase)
- Early instigation of appropriate sepsis management improves outcome from sepsis
- Sepsis management directed at CVP and SvO_2 does not improve outcome from sepsis
- One quarter of septic patients progress to severe sepsis / septic shock

What this thesis adds

- Septic shock is characterised by increased cardiac output and low systemic vascular resistance (ED phase)
- Septic patients, who are not haemodynamically compromised by conventional measurements, have abnormal cardio-haemodynamic parameters prior to instigation of treatment
- Ability to normalise cardio-haemodynamic parameters with initial treatment is related to good outcome
- Normalisation of microcirculatory function precedes that of the macrocirculation
- StO_2 and stroke volume are strongly related to outcome from sepsis and have the potential to act as biomarkers to indentify high risk patients

5.2 Limitations

There are a number of limitations to this research project. A potential weakness of both studies was the use of a convenience sample. Convenience sampling is known for its potential to create bias and may account for the higher proportion of male patients recruited to the severely septic cohort. However, a consecutive sample would have not been feasible owing to the fact that the entire recruitment and data acquisition was carried out by a single researcher (myself).

Despite every effort, follow up was incomplete. Whilst only two patients from the uncomplicated sepsis group were lost to follow up (n=1 death; n=1 drop out), there were 10 attritions in the severe sepsis group (n=8 deaths; n=2 drop outs). This could have resulted in an under or overestimation of the observed difference in haemodynamics between cohorts.

Lack of standard sepsis management could have caused confounding, resulting in an erroneous interpretation of the studies' findings. Whilst this is a potential risk for any observational study it is less likely to have had an important effect, since early resuscitative treatment was very similar regardless of outcome.

Though the researcher was not involved in the direct clinical care of the patients enrolled in either study, given their observational nature, there is the potential that the researcher's presence may have influenced the care the patients received (Hawthorne effect). This may have had an impact on patient's mortality and as such the results may have underestimated the true difference in cardio-haemodynamic parameters between survivors and non-survivors.

Although both studies were based on sample size calculations there was greater variance within the groups than expected causing overall lack of power. This may have caused a type II error as indicated by the relatively wide confidence intervals, which encompass clinically significant differences.

30-day in-hospital mortality was used as the primary endpoint for assessing the relationship and predictability of cardio-haemodynamic parameters on mortality from severe sepsis or septic shock. However, there may have been multiple other factors that contributed to the death of a patient.

There may be limitations to the generalisability of the findings. Firstly, all enrolled patients received clinical care in keeping with normal local practice but this may differ considerably from sepsis management in other departments. Secondly, strict exclusion criteria were used in order to explore the value of non-invasive cardio-haemodynamic parameters and tissue oxygen saturation in the early management of sepsis. Therefore the results of this thesis may not be generalisable to other groups of patients.

5.2 The next stage

This thesis has identified a number of areas that warrant further exploration in future trials:

Co-diagnostic / therapeutic intervention

1) This thesis has identified a number of parameters, StO_2 and SV being the most promising, which have the potential to act as biomarkers for disease progression and poor outcome. To validate the link between these potential biomarkers and clinical outcome a multi-centre prospective study of broadly defined septic ED patients receiving standard sepsis management is needed.

2) The data of this thesis also shows that normalisation of haemodynamics with treatment is associated with good outcome. This generates the question as to whether high risk patients may have their prognosis improved by using a treatment strategy targeted at normalisation of specific haemodynamic biomarkers, such as StO_2 or SV. To explore this hypothesis a study would be required to determine the relationship between specific biomarkers as therapeutic endpoints and clinical outcome.

3) Once biomarker based resuscitation / therapeutic endpoints have been identified a therapeutic trial comparing early sepsis management directed by non-invasive haemodynamic (biomarker) endpoints versus conventional management is warranted.

4) Since sepsis is a complex clinical condition using a single biomarker may not yield optimal discriminatory power. However, combining haemodynamic and biochemical biomarkers, such as lactate clearance or brain natriuretic peptide, in a

predictive model may significantly enhance disease progression and outcome predictability. Once a predictive model has been derived from a prospective data set, internal and external validation of this model, ideally, as part of a multi-centre study will be required.

Diagnostics

4) Since septic patients were found to have clearly abnormal haemodynamics, as demonstrated in this thesis, a diagnostic study is needed to determine the role of clinically useful haemodynamic biomarkers to aid early diagnosis of sepsis at the point of entering the Emergency Department.

6 REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. *Chest.* 1992;101:1644-1655.

2. Russell RA. Management of sepsis. *N Engl J Med.* 2006;355(16):1699-1713.

3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.

4. Gao F, T. M, Daniels DF, et al. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care.* 2005;9:R765-R770.

5. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-orientated hemodynamic therapy in critically ill patients. *N Engl J Med.* 1995;333:1025-1032.

6. Tuchschmidt J, Fried J, Astiz M, et al. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest.* 1992;102:216-220.

7. Hayes MA, Timmins AC, Yau E, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330:1717-1722.

8. Gunn SR, Fink MP, Wallace B. Equipment review: The success of early goal-directed therapy for septic shock prompts evaluation of current approaches for monitoring the adequacy of resuscitation. *Crit Care.* 2005;9:349-359.

9. Jones AE, Brown MD, Trzeciak S, et al. The effect of a quantative resuscitation strategy on mortality in patients with sepsis: A meta-analysis *Crit Care Med.* 2008;36(10):2734-2739.

10. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? *Crit Care Med.* 1998;26:2078-2086.

11. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348(16):1546-1554.

12. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care *Crit Care Med.* 2001;29:1303-1310.

13. Wang HE, Shapiro NI, Angus DC, et al. National estimates of severe sepsis in the United States emergency departments. *Crit Care Med.* 2007;35(8):1928-1936.

14. Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock. *Am J Respir Crit Care Med.* 2003;168:165-172.

15. Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occuring in the first 24 hours in intensive care units in England, Wales, and Northern Irland. *Crit Care Med.* 2003;31:2332-2338.

16. Wang HE, Devereaux RS, Yealy DM, et al. National variation in the United States sepsis mortality: a descriptive study. *International Journal of Health Geographics.* 2010;9:9.

17. Harrison D, Welch C, Eddleston J. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care.* 2006;10(2):R42.

18. The Task Force on the management of acute myocardial infarction of the European Society of Cardiology. Acute myocardial infarction: pre-hospital and in-hospital management. *Eur Heart J.* 1996;17(1):43-63.

19. Vincent J-L, Abraham E, Annane D, et al. Reducing mortality in sepsis: new directions. *Crit Care.* 2002;6(Suppl 3):S1-S18.

20. Fleming A. On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of B. influenzae. *Br J Experimental Path.* 1929;10:226-236.

21. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med.* 2001;344(10):699-709.

22. Abraham E, Laterre P-F, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and low risk of death. *N Engl J Med.* 2005;353(13):1332-1341.

23. Rowan KM, Welch C, North E, et al. Drotrecogin alfa (activated): real-life use and outcomes for the UK. *Crit Care.* 2008;12:R58.

24. Jones AE, Focht A, Horton JM, et al. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest.* 2007;132:425-432.

25. Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest.* 2006;129:225-232.

26. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for managment of severe sepsis and septic shock. *Crit Care Med.* 2004;32(3):858-873.

27. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for the management of severe sepsis and septic shock. *Crit Care Med.* 2008;36(1):296-327.

28. Slade E, Tamber PS, Vincent J-L. The Surviving Sepsis Campaign: raising awareness to reduce mortality. *Crit Care.* 2003;7:1-2.

29. Surviving Sepsis Campaign. *http://www.survivingsepsis.org/.* Accessed 04 August 2008.

30. Berenholtz SM, Dorman T, Ngo K, et al. Qualitative review of intensive care unit quality indicators. *J Crit Care.* 2002;17(1):1-15.

31. Daniels R. Severe sepsis care bundles Emergency Care Specialist Library. National Library for Health. http://www.library.nhs.uk/Default.aspx; 2007.

32. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest.* 2000;118:146-155.

33. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.

34. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med.* 2010;38(2):367-374.

35. Reade MC, Huang DT, Bell D, et al. Variability in management of early severe sepsis. *Emerg Med J.* 2010;27:110-115.

36. Survive Sepsis.org. *http://www.survivesepsis.org/.* Accessed 07 August 2008.

37. Daniels R. Pathophysiology of sepsis. Emergency Care Specialist Library; 2007.

38. Guyton AC, Hall JE. *Textbook of medical physiology*. Philidelphia: W.B. Saunders; 1998.

39. AnaesthesiaUK. *www.anaesthesiauk.com*. Accessed 12 August 2008.

40. Klabunde RE. *Cardiovascular physiology concepts*. Baltimore: Lippincott Williams & Wilkins; 2005.

41. Romberg E, Paessler H, Bruhns C, et al. Untersuchungen ueber die allgemeine Pathologie und Therapie der Kreislaufstoerung bei acuten Infectionskrankheiten. *Arch Klin Med.* 1899;64:652-714.

42. Waisbren BA. Bacteremia due to gram-negative bacilli other than the salmonella: A clinical and therapeutic study. *Arch Intern Med.* 1951;88:467-488.

43. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock. *Crit Care Clin.* 2000;16(2):251-287.

44. Wilson RF, Thal AP, Kindling PH, et al. Hemodynamic measurements in septic shock. *Arch Surg.* 1965;91(1):121-129.

45. Reilly JM, Cunnion RE, Burch-Whitman C, et al. A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. *Chest.* 1989;95:1072-1080.

46. Young JD. The heart and circulation in severe sepsis. *Br J Anaesth.* 2004;93(1):114-120.

47. Cunnion RE, Schaer GL, Parker MM, et al. The coronary circulation in human septic shock. *Circulation.* 1986;73:637-644.

48. Wiggers CJ. Myocardial depression in shock: a survey of cardiodynamic studies. *Am Heart J.* 1947;33:633-650.

49. Parrillo JE, Burch C, Shelhamer JH, et al. A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. *J Clin Invest.* 1985;76:1539-1553.

50. Merx MW, Weber C. Sepsis and the heart. *Circulation.* 2007;116:793-802.

51. Court O, Kumar A, Parrillo JE, et al. Clinical review: Myocardial depression in sepsis and septic shock. *Crit Care.* 2002;6(6):500-508.

52. Kumar A, Thota V, Dee L, et al. Tumor necrosis factor-alpha and interleukin-1 beta are responsible for in vitro myocardial cell depression induced by serum from humans with septic shock. *J Exp Med.* 1996;183(3):949-958.

53. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med.* 1984;100:483-490.

54. Shoemaker WC, Montgomery ES, Kaplan E, et al. Physiologic patterns in surviving and non-surviving shock patients. *Arch Surg.* 1973;106:630-636.

55. Clowes GHA, Vuviniv M, Weidner MG. Circulatory and metabolic alterations associated with survival or death in peritonitis. *Ann Surg.* 1966;163(6):866-884.

56. Bone RC. Gram-negative sepsis. Background, clinical features, and intervention. *Chest.* 1991;100:802-808.

57. Harris RL. Manifestations of sepsis. *Arch Intern Med.* 1987;147:1895-1906.

58. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med.* 2004;32(9):1928-1948.

59. Patterson RP. Fundamentals of impedance cardiography. *IEEE Engng Med and Biol* 1989:35-38.

60. Cremer M. Ueber die Registrierung mechanischer Vorgaenge auf elektrischem Wege, speziell mit Hilfe des Saitengalvanometers und Saitenelektrometers. *Muenchen Med Wochenschrift.* 1907;54:1629.

61. Bonjer FH, Van Den Berg JW, Dirken MNJ. The origin of the variations of body impedance occurring during the cardiac cycle. *Circulation.* 1952;6:415-420.

62. Tsadok S. The historical evolution of bioimpedance. *AACN Clin Issues.* 1999;10(3):371-384.

63. Van De Water JM, Miller TW, Vogel RL, et al. Impedance cardiography: The next vital sign technology? *Chest.* 2003;123:2028-2033.

64. Summers RL, Shoemaker WC, Peacock WF, et al. Bench to bedside: Electrophysiologic and clinical principles of noninvasive hemodynamic monitoring using impedance cardiography. *Acad Emerg Med.* 2003;10(6):669-680.

65. Cotter G, Moshkovitz Y, Kaluski E, et al. Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical impedance. *Chest.* 2004;125:1431-1440.

66. Kubicek WG, Karnegis JN, Patterson RP, et al. Development and evaluation of an impedance cardiac output system. *Aerosp Med.* 1966;37:1208-1212.

67. Bernstein DP. A new stroke volume equation for thoracic electrical bioimpedance: Theory and rationale. *Crit Care Med.* 1986;14:904-909.

68. Packer M, Abraham WT, Mehra MR, et al. Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. *J Am Coll Cardiol.* 2006;47:2245-2252.

69. Medis. Niccomo Manual. Ilmenau: Medzinische Messtechnik GmbH; 2005.

70. Fortin J, Habenbacher W, Heller A, et al. Non-invasive beat-to-beat cardiac output monitoring by an improved method of transthoracic bioimpedance measurements. *Comput Biol Med.* 2006;36(11).

71. Van De Water JM, Mount BE, Chandra KM, et al. TFC (thoracic fluid content): A new parameter for assessment of changes in chest fluid volume. *Am Surg.* 2005;71(1):81-86.

72. Gonzalez J, Delafosse C, Fartoukh M, et al. Comparison of bedside measurement of cardiac output with the thermodilution method and the Fick method in mechanically ventilated patients. *Crit Care.* 2003;7:171-178.

73. Raaijmakers E, Faes TJC, Scholten RJPM, et al. A meta-analysis of three decades of validating thoracic impedance cardiography. *Crit Care Med.* 1999;27(6):1203-1213.

74. Tan HL. Evaluation of cardiac output monitoring devices: clarity or confusion? *Crit Care Resusc.* 2006;8(4):277-278.

75. Sramek BB. Thoracic electrical bioimpedance measurement of cardiac output. *Crit Care Med.* 1994;22(8):1337-1339.

76. Stetz CW, Miller RG, Kelly GE, et al. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Respir Dis.* 1982;126:1001-1004.

77. McIntyre RW. Cardiac output by thermodilution. *JAMA.* 1985;254(17):2413.

78. Van der Meer BJM, Woltjer HH, Sousman AM, et al. Impedance cardiography. Importance of the equation and the electrode configuration. *Intensive Care Med.* 1996;22:1120-1124.

79. Fuller HD. The validity of cardiac output measurements by thoracic impedance: a meta-analysis. *Clin Invest Med.* 1992;15:103-112.

80. Shoemaker WC, Wo CCJ, Chien L-C, et al. Evaluation of invasive and noninvasive hemodynamic monitoring in trauma patients. *J Trauma.* 2006;61:844-854.

81. Shoemaker WC, Belzberg H, Wo CCJ, et al. Multicenter study of noninvasive monitoring systems as alternatives to invasive monitoring of acutely ill emergency patients. *Chest.* 1998;114(6):1643-1652.

82. Shoemaker WC, Wo CCJ, Bishop MH, et al. Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. *Crit Care Med.* 1994;22(12):1907-1912.

83. Shoemaker WC, Appel PL, Kram HB, et al. Multicomponent noninvasive physiologic monitoring of circulatory function. *Crit Care Med.* 1988;16(5):482-490.

84. Appel PL, Kram HB, MacKabee J, et al. Comparison of measurements of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. *Crit Care Med.* 1986;14(11):933-935.

85. ImpedanceCardiography.com. *http://www.impedancecardiography.com.* Accessed 30 July 2008.

86. Peacock WF, Summers RL, Vogel RL, et al. Impact of impedance cardiography on diagnoses and therapy in emergent dyspnea: The ED-IMPACT trial. *Acad Emerg Med.* 2006;13(4):365-371.

87. Springfield C, Sebat F, Johnson D, et al. Utility of impedance cardiography to determine cardiac vs. noncardiac cause of dyspnea in the emergency department. *Congest Heart Fail.* 2004;10(2 suppl2):14-16.

88. Barcarse E, Kazanegra R, Chen A, et al. Combination of B-type natriuretic peptide levels and non-invasive hemodynamic parameters in diagnosing congestive heart failure in the Emergency Department. *Congest Heart Fail.* 2004;10(4):171-176.

89. Vorwerk C, Jeyanithi H, Coats TJ. Thoracic electrical bioimpedance: a tool to determine cardiac versus non-cardiac causes of acute dyspnoea in the emergency department *Emerg Med J.* 2010;27:359-363.

90. Veale WN, Morgan JH, Beatty JS, et al. Hemodynamic and pulmonary fluid status in the trauma patient: are we slipping? . *Am Surg.* 2005;71(8):621-625.

91. Shoemaker WC, Wo CJ, Chan L, et al. Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. *Chest.* 2001;120:528-537.

92. Summers RL, Thompson JR. Impact of the inclusion of noninvasive cardiac output as a vital sign on medical decision making in the Emergency Department. *Am J Clin Med.* 2006;3(4):3-6.

93. Mehra MR. Optimizing outcomes in the patient with acute decompensated heart failure. *Am Heart J* 2006;151(3):571-579.

94. Demarzo AP, Calcin JE, Kelly RF, et al. Using impedance cardiography to assess left ventricular systolic function via postural change in patients with heart failure. *Prog Cardiovasc Nurs.* 2005;20(4):163-167.

95. Luthje L, Drescher T, Zenker D, et al. Detection of heart failure decompensation using intrathoracic impedance monitoring by triple-chamber implantable defibrillator. *Heart Rhythm.* 2005;2(9):997-999.

96. Yu CM, Wang L, Chau E, et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. *Circulation.* 2005;112(6):841-848.

97. Smith RD, Levy P, Ferrario CM. Value of noninvasive hemodynamics to achieve blood pressure control in hypertensive subjects. *Hypertension.* 2006;47:769-775.

98. Sharman DL, Gomes CP, Rutherford JP. Improvement in blood pressure control with impedance cardiograph-guided pharmacologic decision making. *Congest Heart Fail.* 2004;10:54-58.

99. Taler SJ, Augustine J, Textor SC. A hemodynamic approach to resistant hypertension. *Congest Heart Fail.* 2000;6(2):36-39.

100. Wynne JL, Ovadje LO, Akridge CM, et al. Impedance cardiography: A potential monitor for hemodialysis. 2006;133(1):55-60.

101. Scardo JA, Ellings J, Vermillion ST, et al. Validation of bioimpedance estimates of cardiac output in preeclampsia. *Am J Obstet Gynecol.* 2000;183(4):911-913.

102. Doppler C. Ueber das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels. *Abhandlungen der königlich böhmischen Gesellschaft der Wissenschaften.* 1843;2:465-482.

103. Roguin A. Christian Johann Doppler: the man behind the effect. *Br J Radiol.* 2002;75:615-619.

104. Satomura S. Study of flow patterns in peripheral arteries by ultrasonics [English Summary]. *J Acoust Soc Japan.* 1959;29:151-158.

105. Wyse RKH. Clinical diagnosis by transcutaneous Doppler ultrasound. *Postgrad Med J.* 1982;58:197-211.

106. Sequeira RF, Light LH, Cross G, et al. Transcutaneous aortovelography. A quantitative evaluation. *Br Heart J.* 1976;38:443-450.

107. Kisslo JA, Adams DB. Principles of Doppler echocardiography. *Echo in context. http://www.echoincontext.com/doppler01/doppler01_01.asp*. Accessed 4 February 2009.

108. USCOM -The Basics. USCOM Ltd. Published April 2008.

109. Nidorf SM, Picard M, Triulzi M, et al. New perspectives in the assessment of cardiac chamber dimensions during development and adulthood. *JACC.* 1992;19(5):983-988.

110. Meyer S, Todd D, Wright I, et al. Review article: Non-invasive assessment of cardiac output with portable continuous-wave Doppler ultrasound. *Emerg Med Australas.* 2008;20:201-208.

111. Tan HL, Pinder M, Parson R, et al. Clinical evaluation of USCOM ultrasonic cardiac output monitor in cardiac surgical patients in intensive care unit. *Br J Anaesth.* 2005;94(3):287-291.

112. Arora D, Chand R, Mehta Y, et al. Cardiac output estimation after off-pump coronary artery bypass: a comparison of two different techniques. *Ann Cardiol Anaesth.* 2007;10(132-136).

113. Chan JS, Segara D, Nair P. Measurement of cardiac output with a non-invasive continuous wave Doppler device versus the pulmonary artery catheter: a comparative study. *Crit Care Resusc.* 2006;8(4):309-314.

114. Chand R, Mehta Y, Trehan N. Cardiac output estimation with a new Doppler device after off-pump coronary bypass surgery. *J Cardiothorac Vasc Anaesth.* 2006;20:315-319.

115. Knobloch K, Lichtenberg A, Winterthaler M, et al. Noninvasive cardiac output determination by two-dimensional independent Doppler during and after cardiac surgery. *Ann Thorac Surg.* 2005;80:1479-1484.

116. Su BC, Yu HP, Yang MW, et al. Reliability of a new ultrasonic cardiac output monitor in recipients of living donor liver transplantation. *Liver Transpl.* 2008;14(7):1029-1037.

117. Van Lelyveld-Haas LE, van Zanten AR, Borm GF, et al. Clinical validation of the non-invasive cardiac output monitor USCOM-1A in critically ill patients. *Eur J Anaesthesiol.* 2008;25(11):917-924.

118. Wong LS, Yong BH, Young KK, et al. Comparison of the USCOM ultrasound cardiac output monitor with pulmonary artery catheter thermodilution in patients undergoing liver transplantation. *Liver Transpl.* 2008;14(7):1038-1043.

119. Su BC, Lin CC, Su CW, et al. Ultrasonic cardiac output monitor provides accurate measurements of cardiac output in recipients after liver transplantation. *Acta Anaesthesiol Taiwan.* 2008;46(4):171-177.

120. Brierley J, Peters MJ. Distinct hemodynamic patterns of septic shock at presentation to pediatric intensive care. *Pediatr.* 2008;122:752-759.

121. Dey I, Sprivulis P. Emergency physicians can reliable assess emergency department patient cardiac output using the USCOM continuous wave Doppler cardiac output monitor. *Emerg Med Australas.* 2005;17(3):193-199.

122. Knirsch W, Kretschmar O, Tomaske M, et al. Cardiac output measurements in children: comparison of the Ultrasound Cardiac Output Monitor with

thermodilution cardiac output measurements. *Intensive Care Med.* 2008;34(6):1060-1064.

123. Stemmler HJ, Weigert O, Gruener N, et al. Non-invasive hemodynamic monitoring in critically ill patients. Initial experience with the ultrasonic cardiac output monitoring (USCOM) device and correlation to invasive measurements. *Intensivmedizin und Notfallmedizin.* 2007;44(6):366-371.

124. Thom O, Taylor D, Wolfe R, et al. A comparison of the USCOM cardiac output monitor with base excess for detecting occult hypoperfusion in emergency department trauma patients. *Ann Emerg Med.* 2008;51(4):473.

125. Jobis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science.* 1977;198(4323):1264-1267.

126. Irwin MS, Thorniley MS, Dore CJ, et al. Near infra-red spectroscopy: a non-invasive monitor of perfusion and oxygenation within the microcirculation of limps and flaps. *Br J Plastic Surg.* 1995;48:14-22.

127. Stranc MF, Sowa MG, Abdulrauf B, et al. Assessment of tissue viability using near-infrared spectroscopy. *Br J Plastic Surg.* 1998;51:210-217.

128. Cohn SM, Nathens AB, Moore FA, et al. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma.* 2007;62(1):44-55.

129. Creteur J. Muscle StO2 in critically ill patients. *Curr Opin Crit Care.* 2008;14(3):361-366.

130. Creteur J, Carollo T, Soldati G, et al. The prognostic value of muscle StO2 in septic patients. *Int Care Med.* 2007;33(9):1549-1556.

131. Crookes BA, Cohn SM, Bloch S, et al. Can near-infrared spectroscopy identify the severity of shock in trauma patients? *J Trauma.* 2005;58(4):806-816.

132. Hameed SM, Aird WC, Cohn SM. Oxygen delivery. *Crit Care Med.* 2003;31(12 Suppl.):S658-S667.

133. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med.* 2002;30(8):1686-1692.

134. Alia I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. *Chest.* 1999;115:453-461.

135. Simonson SG, Piantadosi CA. Near-infrared spectroscopy. *Crit Care Clinics.* 1996;12(4):1019-1029.

136. InSpectra™StO2 Tissue Oxygenation monitor. *http://www.htibiomeasurement.com/technology.asp*. Accessed 09 October 2008.

137. Beilman GJ, Blondet JJ. Near-infrared spectroscopy-derived tissue oxygen saturation in battlefield injuries: a case series report. *World J Emerg Surg.* 2009;4:25.

138. Jubran A. Pulse oximetry. *Crit Care.* 1999;3:R11-R17.

139. L'Her E, Goetghebeur D, Tonnelier JM, et al. Correlation between noninvasive oxygen tissue saturation (StO2) measurements by near-infrared spectroscopy and invasive central venous saturation (SvO2). *American Thoracic Society International Conference.* San Diego; 2005.

140. Crawford J, Otero R, Goyal N, et al. Near infrared spectroscopy to assess systemic perfusion in the critically ill. *Crit Care Med.* 2007;35(12):A254.

141. Arbabi S, Brundage SI, Gentilello LM. Near-infrared spectroscopy: A potential method for continuous, transcutaneous monitoring for compartmental syndrome in critically injured patients. *J Trauma.* 1999;47(5):829-833.

142. Sanders J, Martin D, Smith A, et al. Tissue oxygen saturation during anaesthesia, cardiopulmonary bypass and intensive care stay for cardiac surgery. *Crit Care.* 2008;12(Suppl 2):S28.

143. Strahovnik I, Podbregar M. Measurement of skeletal muscle tissue oxygenation in the critically ill. *Signa Vitae.* 2008;3(1):43-50.

144. Moore FA, Nelson T, McKinley BA, et al. Massive transfusion in trauma patients: Tissue hemoglobin oxygen saturation predicts poor outcome. *J Trauma.* 2008;64(4):1010-1023.

145. *University Hospitals of Leicester. Annual Review 2007/2008.* 2008.

146. Anderson ID, Little RA, Irving MH. An effect of trauma on human cardiovascular control: Baroreflex suppression. *J Trauma.* 1990;30(8):974-981.

147. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-1256.

148. Medis. Niccomo Brochure. Ilmenau: Medzinische Messtechnik GmbH; 2004.

149. Medis. *www.medis-de.com/en/icg.html*. Accessed 18 July 2008.

150. CardioDynamics. *http://www.cardiodynamics.com/cdprod40.html*. Accessed 3 Februar 2009.

151. USCOM - Quick guide.: USCOM Ltd. Published April 2008.

152. Guidance on nominating a consultee for research involving adults who lack capacity to consent. Department of Health; 2008.

153. de Cleva R, Herman P, D'albuquerque LAC, et al. Pre-and postoperative systemic hemodynamic evaluation in patients subjected to esophagogastric devascularization plus splenectomy and distal splenorenal shunt: A comparative study in schistomomal portal hypertension. *World J Gastroenterol.* 2007;13(41):5471-5475.

154. Luisada AA, Bhat PK, Knighten V. Changes of cardiac output caused by aging: An impedance cardiographic study. *Angiology.* 1980;31:75-81.

155. Wei JY. Age and the cardiovascular system. *N Engl J Med.* 1992;327(24):1735-1739.

156. Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation.* 1955;12:557-566.

157. Geokas MC, Lakatta EG, Makinodan T, et al. The aging process. *Ann Intern Med.* 1990;113(6):455-466.

158. Julius S, Amery A, Whitlock LS, et al. Influence of age on the hemodynamic response to exercise. *Circulation.* 1967;36:222-230.

159. Proctor DN, Beck KC, Shen PH, et al. Influence of age and gender on cardiac output-VO2 relationships during submaximal cycle ergometry. *J Appl Physiol.* 1998;84:599-605.

160. Hossack KF, Bruce RA. Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. *J Appl Physiol.* 1982;53(4):799-804.

161. Ellrodt AG, Riediger MS, Kimchi A, et al. Left ventricular performance in septic shock: Reversible segmental and global abnormalities. *Am Heart J.* 1985;110(2):402-409.

162. Jardin F, Fourme T, Page B, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. *Chest.* 1999;116:1354-1359.

163. Cheitlin MD. Cardiovascular physiology - changes with aging. *Am J Geriatric Cardiol.* 2003;12(1):9-13.

164. Ren J, Ren BH, Sharma AC. Sepsis-induced depressed contractile function of isolated ventricular myocytes is due to altered calcium transient properties. *Shock.* 2002;18(3):285-288.

165. Tao W, Deyo DJ, Traber DL, et al. Hemodynamic and cardiac contractile function during sepsis caused by cecal ligation and puncture in mice. *Shock.* 2004;21(1):31-37.

166. Calvin JE, Driedger AA, Sibbald WJ. An assessment of myocardial function in human sepsis utilizing ECG gated cardiac scintigraphy. *Chest.* 1981;80(5):579-586.

167. Ognibene FP, Parker MM, Natanson C, et al. Depressed left ventricular performance. Response to volume infusion in patients with sepsis and septic shock. *Chest.* 1988;93(5):903-910.

168. Rudiger A, Singer M. Mechanism of sepsis-induced cardiac dysfunction. *Crit Care Med.* 2007;35(6):1599-1608.

169. Marx G. Fluid therapy in sepsis. *Eur J Anaesthesiol.* 2003;20:429-442.

170. Weyland A, Gruene F. Kardiale Vorlast und zentraler Venendruck. (Cardiac preload and central venous pressure) *Anaesthesist.* 2009;58:506-512.

171. Schneider AJ, Teule GJJ, Groneveld ABJ, et al. Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: A combined hemodynamic and radionuclide study. *Am Heart J.* 1988;116(1):103-112.

172. Albert NM, Hail MD, Li J, et al. Equivalence of the bioimpedance and thermodilution methods in measuring cardiac output in hospitalized patients with advanced, decompensated chronic heart failure. *Am J Crit Care.* 2004;13(6):469-479.

173. Drazner MH, Thompson B, Rosenberg PB, et al. Comparison of impedance cardiography with invasive hemodynamic measurements in patients with heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol.* 2002;89:993-995.

174. Funk M, Nystroem KV, Riordan M, et al. Bioimpedance monitoring in patients with heart failure. *Eur J Cardiovasc Nurs.* 2005;4:51-52.

175. Saunders CE. The use of transthoracic electrical bioimpedance in assessing thoracic fluid status in emergency department patients. *Am J Emerg Med.* 1988;6(4):337-340.

176. Hofer CK, Muller SM, Furrer L, et al. Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest.* 2005;128:848-854.

177. Reuter DA, Kirchner A, Felbinger TW, et al. Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. *Crit Care Med.* 2003;31(5):1399-1404.

178. Wiesenack C, Prasser C, Rodig G, et al. Stroke volume variation as an indicator of fluid responsiveness using pulse contour analysis in mechanically ventilated patients. *Anesth Analg.* 2003;96:1254-1257.

179. Zimmermann M, Feibicke T, Keyl C, et al. Accuracy of stroke volume variation compared with pleth variability index to predict fluid responsiveness in mechanically ventilated patients undergoing major surgery. *Eur J Anaesthesiol.* 2010;27(6):555-561.

180. Modak S, Banerjee PK. Studies of left ventricular function by systolic time intervals on exposure to dry immersion. *Ind J Aerospace Med.* 2004;48(2):48-56.

181. Hahn J-O, McCombie D, Reisner A, et al. Adaptive left ventricular ejection time estimation using multiple peripheral pressure waveforms. *Proc 27th Conference on Engineering in Medicine and Biology, Shanghai, China.* 2005:2383-2386.

182. Napoli AM, Machan JT, Corl K, et al. The use of impedance cardiography in predicting mortality in emergency department patients with severe sepsis and septic shock. *Acad Emerg Med.* 2010;17:452-455.

183. Jafri SM, Lavine S, Field BE, et al. Left ventricular diastolic function in sepsis. *Crit Care Med.* 1990;18(7):709-714.

184. Munt B, Jue J, Gin K, et al. Diastolic filling in human severe sepsis: an echocardiographic study. *Crit Care Med.* 1998;26(11):1829-1833.

185. Poelaert J, Declerck C, Vogelaers D, et al. Left ventricular systolic and diastolic function in septic shock. *Intensive Care Med.* 1997;23(5):553-560.

186. Azimi G, Vincent J-L. Ultimate survival from septic shock. *Resuscitation.* 1986;14:245-253.

187. Parker MM, Shelhamer JH, Natanson C, et al. Serial cardiovascular variables in survivors and non-survivors of human septic shock: Heart rate as an early predictor of prognosis. *Crit Care Med.* 1987;15(10):923-929.

188. De Backer D, Creteur J, Preiser J-C, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med.* 2002;166:98-104.

189. Ince C. The microcirculation is the motor of sepsis. *Crit Care.* 2005;9(Suppl 4):S13-S19.

190. Sakr Y, Dubois M-J, De Backer D, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med.* 2004;32(9).

191. Cohn SM, Nathens AB, Moore FA, et al. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock. *J Trauma.* 2007;62(1):44-54.

192. Tayler JH, Mulier KE, Myers DE, et al. Use of near-infrared spectroscopy in early determination of irreversible hemorrhagic shock. *J Trauma.* 2005;58:1119-1125.

193. Mohammed I, Nonas SA. Mechanisms, detection and potential management of microcirculatory disturbances in sepsis. *Crit Care Clin.* 2010;26:393-408.

194. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nature Reviews Immunology.* 2008;8:776-787.

195. Etchecopar-Chevreuil C, Francois B, Clavel M, et al. Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. *Intensive Care Med.* 2008;34(2):250-256.

196. Hayes MA, Timmins AC, Yau EH, et al. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med.* 1997;25(6):926-936.

197. Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: Less is more. *Chest.* 2008;133:252-263.

198. Groeneveld ABJ, Nauta JJP, Thijs LG. Peripheral vascular resistance in septic shock: its relation to outcome. *Intensive Care Med.* 1988;14:141-147.

199. Winslow EJ, Loeb HS, Rahimtoola SH, et al. Hemodynamic studies and results of therapy in 50 patients with bacteremic shock. *Am J Med.* 1973;54:421-432.

200. Myers PR, Parker JL, Tanner MA, et al. Effects of cytokines tumor necrosis factor alpha and interleukin 1 beta on endotoxin-mediated inhibition of endothelium-derived relaxing factor bioactivity and nitric oxide production in vascular endothelium. *Shock.* 1994;1(1):73-78.

201. Wang P, Ba ZF, Chaudry IH. Endothelium-dependent relaxation is depressed at the macro- and microcirculatory levels during sepsis. *Am J Physiol.* 1995;269:R988-R994.

202. Tucker JJ, Wilson MA, Wead WB, et al. Microvascular endothelial cell control of peripheral vascular resistance during sepsis. *Arch Surg.* 1998;133:1335-1345.

203. Leone M, Blidi S, Antonini F, et al. Oxygen tissue saturation is lower in nonsurvivors than in survivors after early resuscitation of septic shock. *Anesthesiology.* 2009;111(2):366-371.

204. Lima A, van Bommel J, Jansen TC, et al. Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients *Crit Care.* 2009;13(Suppl 5):S13.

205. Payen D, Luengo CL, Heyer L, et al. Is thenar tissue hemoglobin oxygen saturation in septic shock related to macrohemodynamic variables and outcome. *Crit Care.* 2009;13(Suppl 5):S6.

206. Trzeciak S, Dellinger RP, Parrillo JE, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med.* 2007;49(1):88-98.

207. Glickman SW, Cairns CB, Otero RM, et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis *Acad Emerg Med.* 2010;17:383-390.

208. Marchick MR, Kline JA, Jones AE. The significance of non-sustained hypotension in emergency department patients with sepsis. *Intensive Care Med.* 2009;35(7):1261-1264.

APPENDICES

Appendix 1. Applying research methodology in the acute setting

Conducting research in critically ill Emergency Department patients presents a number of challenges. There are issues with ethical approval, identification/recruitment, obtaining consent, meeting clinical and research needs and patient follow up, to name just a few. After securing funding, the biggest hurdle to overcome is getting a favourable decision from the Research and Ethics committees, which is not uncommonly hinged upon the informed consent procedure. Informed consent is a process that should allow patients adequate time to make an informed decision. Whilst this is feasible in an out-patient setting it is impossible to apply to research in critical illness, where most patients are physically and mentally unable to follow such a lengthy process. There are probably several ways to overcome this problem, the approach that I have used in this research project is described as follows.

After convincing the Research and Ethics committee of the importance of my proposed research I had to attain their approval of the proposed informed consent process. The approach that I found successful was by attending the Ethics Committee meeting and describing a patient's journey through the research, with emphasis upon the conflict between meeting their clinical needs and obtaining informed consent in the Emergency Department, since most patients would have been to unwell to give informed consent. It was the lay person who felt that approaching such ill patients, even for limited (provisional) consent, would be inappropriate and that, considering the non-invasive nature of the research, measurements should be commenced at the earliest suitable time after having explained the study in very brief and simple terms using 'Verbal

prompts' (Appendix 9) to the patients. Informed consent was then to be sought once the patient's condition had improved. This approach allowed me to enrol patients who at the time of recruitment would have not been able to provide informed consent.

Since sepsis would also affect patients who permanently lack capacity or may result in lack of capacity in cases with poor outcome, ethical approval was obtained for a 'Personal Consultee' (formerly personal representative) who was to be approached for their assent to the patient's participation in the study. During the study it became apparent that despite a reasonable effort it was not always possible to identify a 'Personal Consultee' and approval for a 'Nominated Consultee' (formerly legal representative) was sought.

Identifying suitable patients as soon as they arrived in the ED was another challenge. Though the ED had an electronic patient's data base displaying the patient's presenting complaint this information, in terms of identifying patients with sepsis, was not particularly helpful. Furthermore, suitable patients arrived at unpredictable times thus it would not have been feasible for a single researcher to be present at all times in the ED. To address this shortfall awareness amongst ED staff needed to be raised. This was done by spending most of my time in ED at the beginning of the project to personally explain the research project to members of staff and encouraging them to participate in the identification process. Other methods used were the display of the research's inclusion criteria in the department, handing out pocket cards to staff and regular email up-dates about the project's progress.

It was anticipated that connecting a patient to two additional monitors plus performing transcutaneous Doppler measurement may be problematic and might potentially interfere with clinical care, fortunately this was not the case.

The experience I have gained from carrying out clinical research in a busy Emergency Department is very valuable. Being aware of potential difficulties and having developed strategies to overcome these obstacles will assist me in both the delivery and supervision of Emergency Care research in the future.

Appendix 2. Patient Entry Form

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5646
Fax: 0116 204 7935

STUDY:

Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine
Principal Researcher : Dr C Vorwerk, Specialist Registrar Emergency Medicine

PATIENT ENTRY FORM

INFORMATION ABOUT TRIAL ENTRY

Date: / / 2009	Arrival Time: __ : __ hrs	Recruitment Time: __ : __ hrs
Study explained to	Patient Y / N	Representative Y / N
Consent obtained from (circle) • Patients • Representative	Date: / / 2009 Time: __ : __ hrs	By: .....
IF consent not obtained in ED explain why:		

INFORMATION ABOUT THE PATIENT

ED identification number	S _ _ _ _ _ _ _	Trial number	NASA* S __ __
Date of birth:	__ __ / __ __ / 19 __ __	Age	__ __ years
Weight	__ __ __ Kg	Height	__ __ __ cm
Gender	Female	Male	

* S for study group *C for control group

INFORMATION ABOUT PATIENT'S **PAST MEDICAL HISTORY**

IHD / CAD	MI	Arrthythmia	Hypertension	Heart failure	Terminal illness (what type ?)

INFORMATION ABOUT PATIENT'S **CURRENT DRUG HISTORY**

B-blocker	ACE inhibitor	Ca- channel blocker	Nitrates	Diuretics

INFORMATION ABOUT PATIENT'S **SOCIAL HISTORY**

Lives at Home	Warden controlled	Nursing Home

Appendix 3. TEB parameters measured in this thesis

Parameter		Unit
CI	Cardiac index	l/min/m^2
CO	Cardiac output	l/min
SV	Stroke volume	ml
SI	Stroke volume index	ml/m^2
SVR	Systemic vascular resistance	(dynes·s·cm^{-5})
SVRI	Systemic vascular resistance index	(dynes·s·cm^{-5} /m^2)
TFC	Thoracic fluid content	1/kΩ)
HR	Heart rate	beats/min
MAP	Mean arterial pressure	mmHg
SBP	Systolic blood pressure	mmHg
DBP	Diastolic blood pressure	mmHg
LCW	Left cardiac work load	kg·m
LCWI	Left cardiac work load index	kg·m/m^2
PEP	Pre-ejection period	ms
LVET	Left ventricular ejection time	ms
ETR	Ejection time ratio	%
QI	Quality indicator	%

Appendix 4. Doppler parameters measured in this thesis

Parameter		Unit
CI	Cardiac index	l/min/m^2
CO	Cardiac output	l/min
SV	Stroke volume	ml
SI	Stroke volume index	ml/m^2
VP	Peak Velocity	m/s
MPG	Mean pressure gradient	mmHg
VTI	Velocity time integral	cm
HR	Heart rate	beats/min
MD	Minute distance	m/min
ET%	Ejection time percentage	%
FT	Flow time	ms
SVV	Stroke volume variation	%

Appendix 5. Ethics approval – Study 1

NHS

National Research Ethics Service

Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1

1 Standard Court
Park Row
Nottingham
NG1 6GN
Telephone: 01159123344 Ext: 68575
Facsimile: 01159123300

15 May 2007

Professor Timothy Coats
Professor of Emergency Medicine
Leicester University
Emergency Department, Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW

Dear Professor Coats,

Full title of study: **Assessment of cardiac output in septic adult patients usingnon-invasive Thoracic Electrical Bioimpedance**

REC reference number: **07/Q2501/56**

Thank you for your letter of 23 April 2007, 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.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		15 February 2007
Investigator CV		12 February 2007
Protocol	1.0	31 January 2007
Peer Review		01 February 2007
Participant Information Sheet: Patient Information Leaflet (control group)	2.0	16 April 2007
Participant Information Sheet: Patient Information Leaflet	2.0	16 April 2007
Participant Information Sheet: Summary Information Leaflet (patient)	1.0	16 April 2007

Participant Consent Form: Study Group	2.0	16 April 2007
Participant Consent Form: Control Group	2.0	16 April 2007
Response to Request for Further Information		23 April 2007
e mail from S Stevens - sample size calculations		17 January 2007
letter from Mr J Banerjee		22 December 2006
summary and flowchart	1	17 January 2007
Patient Assessment Form	1.0	16 April 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

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.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/Q2501/56	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr C Edwards/Ms L Ellis
Chair/Co-ordinator

Email: Linda.ellis@nottinghamshirecounty-tpct.nhs.uk

Enclosures: *Standard approval conditions*
Site approval form

Copy to: R&D office for NHS care organisation at lead site - University Hospitals Leicester NHS Trust

Appendix 6. R&D approval – Study 1

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH AND DEVELOPMENT

Director: Professor D Rowbotham
Assistant Director: John Hampton
Co-ordinator: C Cannaby
Direct Dial: 0116 258 4614
Fax No: 0116 258 4226
EMail: chris.cannaby@uhl-tr.nhs.uk

Leicester General Hospital
Gwendolen Road
Leicester
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Tel: 0116 249 0490
Fax: 0116 258 4666
Minicom: 0116 258 8188

19 June 2007

Professor Timothy Coats
A&E Dept
LRI
Infirmary Square
LE1 5WW

Dear Professor Coats

ID: 10294 **Assessment of cardiac output in septic adult patients using non-invasive Thoracic Electrical Bioimpedance**

LREC Ref: 07/Q2501/56 **MREC Ref:**

Sponsor UHL NHS Trust
Funder Departmental funds

Please note that Trust Indemnity ceases on: 19/08/2008

As you are aware all research undertaken within the NHS requires both a favourable ethical opinion from an independent ethics committee, and R&D Approval from each NHS Trust it is taking place within. We have received confirmation that your study has gained a favourable opinion from the local Ethics Committee. All papers submitted have also been reviewed by University Hospitals of Leicester NHS Trust R&D Office and I am pleased to confirm NHS R&D Approval from the Trust, on the following conditions:

- All papers submitted to this office are followed to the letter; should any amendments or changes be required these must be submitted to this office.
- Only researchers detailed on the second page of this letter are to be involved in the study. If this changes, the changes must be submitted to this office as a non-substantial amendment.
- Your study is now covered by NHS Indemnity, as required, and excluding aspects covered by external indemnity, e.g. ABPI, University. This indemnity is in place to the above date – the end date you supplied. Should you wish your study to extend past this date you must notify the R&D Office, as not doing so would mean you are no longer covered to conduct your research. One method for this is through Annual Reports, see over page.
- Ongoing Pharmacovigilance and safety reporting is essential in all research studies. Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) must be reported appropriately and timely. Please ensure you are aware of our SOP on Safety Reporting which is available on the UHL R&D web pages: http://www.uhl-tr.nhs.uk/our-services/research--development
- Your application detailed resources to be used in this study, you must ensure the budget detailed is followed as the Trust will not cover any additional costs associated to this research.
- If honorary research contracts have been issued it is your responsibility to ensure this/these are kept up to date.

Reporting Requirements
Within University Hospitals of Leicester we are keen to encourage well structured, good quality research; to ensure this high standard is achieved and maintained we are keen to make you aware of national and local reporting requirements:

- Annual & Final Reports on the progress are required each year, or final on completion. These reports are needed by both the R&D Office and local Ethics Committee. Templates for these reports are available on the R&D & NRES website, and we look forward to the receipt of these on the anniversary of your ethics approval, and on the completion of your study.
- Additionally Annual Safety Reports are required for CT-IMP (Clinical Trials of Investigational Medicinal Products) studies and should be submitted to the MHRA annually 60 days prior to the anniversary of MHRA Approval.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities and have attached to this letter, forming part of your R&D approval, an information sheet to ensure you are aware of these responsibilities.

The R&D Office is keen to support research, researchers and facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust please feel welcome to contact this office again. The Trust wishes you success with your research.

Below is a list of the Researchers Approved to work on this Application within UHL

Professor Timothy Coats

Dr Christiane Vorwerk

Yours sincerely

John Hampton

Assistant Director for Research and Development

Appendix 7. Ethics approval – Study 2

NHS
National Research Ethics Service

Nottingham Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 01159123344 Ext: 39368
Facsimile: 01159123300

17 December 2007

Professor Timothy J Coats
Professor of Emergency Medicine
Leicester University
Emergency Department Academic Unit,
Leicester Royal Infirmary
Leicester, LE1 5WW

Dear Professor Coats,

Full title of study: **Assessment of cardio-haemodynamics in adult Emergency Department patients with severe sepsis or septic shock.**
REC reference number: **07/H0403/121**

Thank you for your letter of 05 December 2007, 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.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		31 July 2007
Investigator CV		14 November 2007
Investigator CV - Chief Investigator		26 June 2007
Protocol		
Summary/Synopsis		

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority.

Peer Review		28 June 2007
Statistician Comments		25 June 2007
Participant Information Sheet: Patient Summary	1.0	22 June 2007
Participant Information Sheet: Patient Control Group	1.0	22 June 2007
Participant Information Sheet: Patient Study Group	1.0	22 June 2007
Participant Information Sheet: Deceased Patients' Relatives	2.0	05 December 2007
Participant Information Sheet: Patient's Relatives	3.0	05 December 2007
Participant Consent Form: Assent form	3.0	05 December 2007
Participant Consent Form: Patient Control Group	1.0	22 June 2007
Participant Consent Form: Patient Study Group	1.0	22 June 2007
Response to Request for Further Information		05 December 2007
Response to Request for Further Information		19 November 2007
Verbal Prompts		
Declaration proforma awareness of research guidelines -C Vorwerk		09 November 2006
Declaration proforma awareness of research guidelines - T Coates		25 July 2007
Section 30 supplementary form		

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

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 Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

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@nationalres.org.uk .

07/H0403/121	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

P. Wheat

Dr K Pointon / Ms T Wheat
Chair / Coordinator

Email: trish.wheat@nottspct.nhs.uk

Enclosures: *Standard approval conditions*
Site approval form

Copy to: R&D office for NHS care organisation at lead site - UHL

Appendix 8. R&D approval – Study 2

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH AND DEVELOPMENT

Director: Professor D Rowbotham
Assistant Director: John Hampton
Co-ordinator: C Cannaby
Direct Dial: 0116 258 4614
Fax No: 0116 258 4226
EMail: chris.cannaby@uhl-tr.nhs.uk

Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Tel: 0116 249 0490
Fax: 0116 258 4666
Minicom: 0116 258 8188

22 February 2008

Professor Timothy Coats
A&E Dept
LRI
Infirmary Square
LE1 5WW

Dear Professor Coats

ID: 10407 **Assessment of cardio-haemodynamics in adult Emergency Department patients with severe sepsis or septic shock.**

Sponsor UHL NHS Trust
Funder Departmental funding

Please note that Trust Indemnity ceases on: 22.11.09

As you are aware all research undertaken within the NHS requires both a favourable ethical opinion from an independent ethics committee, and R&D Approval from each NHS Trust it is taking place within. We have received confirmation that your study has gained a favourable opinion from the local Ethics Committee. All papers submitted have also been reviewed by University Hospitals of Leicester NHS Trust R&D Office and I am pleased to confirm NHS R&D Approval from the Trust, on the following conditions:

- All papers submitted to this office are followed to the letter; should any amendments or changes be required these must be submitted to this office.
- Only researchers detailed on the second page of this letter are to be involved in the study. If this changes, the changes must be submitted to this office as a non-substantial amendment.
- Your study is now covered by NHS Indemnity, as required, and excluding aspects covered by external indemnity, e.g. ABPI, University. This indemnity is in place to the above date – the end date you supplied. Should you wish your study to extend past this date you must notify the R&D Office, as not doing so would mean you are no longer covered to conduct your research. One method for this is through Annual Reports, see over page.
- Ongoing Pharmacovigilance and safety reporting is essential in all research studies. Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) must be reported appropriately and timely. Please ensure you are aware of our SOP on Safety Reporting which is available on the UHL R&D web pages: http://www.uhl-tr.nhs.uk/our-services/research--development
- Your application detailed resources to be used in this study, you must ensure the budget detailed is followed as the Trust will not cover any additional costs associated to this research.
- If honorary research contracts have been issued it is your responsibility to ensure this/these are kept up to date.

Reporting Requirements
Within University Hospitals of Leicester we are keen to encourage well structured, good quality research; to ensure this high standard is achieved and maintained we are keen to make you aware of national and local reporting requirements:

- Annual & Final Reports on the progress are required each year, or final on completion. These reports are needed by both the R&D Office and local Ethics Committee. Templates for these reports are available on the R&D & NRES website, and we look forward to the receipt of these on the anniversary of your ethics approval, and on the completion of your study.
- Additionally Annual Safety Reports are required for CT-IMP (Clinical Trials of Investigational Medicinal Products) studies and should be submitted to the MHRA annually 60 days prior to the anniversary of MHRA Approval.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities and have attached to this letter, forming part of your R&D approval, an information sheet to ensure you are aware of these responsibilities.

The R&D Office is keen to support research, researchers and facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust please feel welcome to contact this office again. The Trust wishes you success with your research.

Below is a list of the Researchers Approved to work on this Application within UHL

Professor Timothy Coats

Dr Christiane Vorwerk

Yours sincerely

John Hampton

Assistant Director for Research and Development

Appendix 9. Verbal Prompts

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5168
Fax: 0116 204 7935

Study Title: **Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.**

Name of Researchers: Professor Tim Coats
Dr Chris Vorwerk
Emergency Department, Leicester Royal Infirmary

VERBAL PROMPTS

Septic patients presenting to the Emergency department at the Leicester Royal Infirmary, who meet the inclusion criteria of this research study, but who are too unwell to give informed consent, will have the study explained to them by a member of the research team. If verbal consent is given the monitoring will be commenced and formal consent will be obtained at a later stage. The explanation will be tailored to the individual patient using the following template.

'Dear (name of patient) we are currently doing a research study in our emergency department looking at how the heart is working in patients who have an infection. This involves the use of a special heart and oxygen monitor and needs me to put an entire 5 sticky patches (like the ECG test that you have had done). Two patches will be placed on the neck, two on the chest and one on the thumb. This special machine will then measure how the normal treatment which you will receive in the Emergency Department is reduces the extra work your heart is doing. Taking part in this study will not affect your treatment. I will explain things in more detail when you are feeling better, but is okay if I go ahead and record this special type of ECG? '

The patient will be connected to the special monitor and the measurement will start. However, if it is felt that the additional monitoring may cause any distress to the patient, then the measurement will be stopped. (Previous experience with this technique has re-assured us that this has not yet happened.)

Appendix 10. Summary Information Leaflet

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5646
Fax: 0116 204 7935

SUMMARY INFORMATION LEAFLET (patient)

Study Title:

Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find better ways of treating patients with sepsis, which is a severe illness caused by an infection. Despite advances in Medicine it can be difficult to properly diagnose and treat patients with sepsis. We hope that the use of a special monitoring machine, similar to an ECG machine, will improve the care of patients with sepsis in the future.

You have been chosen to participate in this study, because you are suffering from sepsis. Participation is entirely voluntary and you are free to withdraw from the research at any time. This will have no effect on the standard of care you receive. If you decide to take part in this research study, you will be connected to an additional monitor which will measure what your heart is doing whilst your body is fighting off an infection and whilst your are receiving treatment for it. In order to obtain those measurements we will have to place ECG electrode patches (sticky patches) onto your neck and chest and one onto your thumb. Your normal treatment will continue throughout. In order to assess how the normal treatment, which you receive, is reducing the extra work your heart is doing, we would need monitor you for 24 hours.

There are no known risks using this type of monitoring machine. There are no advantages or disadvantages for you in taking part in this study. However we hope that the information obtained from this study will improve the care and clinical management of patient, suffering from a similar condition to yours, in the future.

Your participation in this study and any data obtained about you will be kept strictly confidential.

Should you decide to participate in this study you will be given a detailed information sheet about this research study. You will also have the opportunity to ask any questions and to discuss any concerns with a member of the research team.

We would like to take this opportunity to thank you for reading this.

Prof Tim Coats
Professor of Emergency Medicine
Division of Cardiovascular Science
Leicester University

Dr Chris Vorwerk
Research Registrar
Emergency Department
Leicester Royal Infirmary

Appendix 11. Patient Information Leaflet (study group)

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5646
Fax: 0116 204 7935

PATIENT INFORMATION LEAFLET

Study Title:

Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of septic patients. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.
Please take time to read the following information carefully and discuss it with others 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 would wish to take part.

What is the purpose of this study?
Each year more than a million people suffer from sepsis, which is a severe illness caused by an infection. Despite advances in medicine it can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why have I been chosen?
You have been chosen, because you are suffering from an infection which caused sepsis.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. Participation is entirely voluntary and you are free to withdraw from the research at any time without giving a reason. A decision to withdraw 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?
The study will not affect the normal treatment which you will receive. None of your treatment will be delayed or changed. You will be connected to an additional monitor that will allow us to measure how your heart is working whilst your body is fighting off an infection. In order to obtain such measurement we will have to place sensor patches (sticky patches) onto your chest and neck and one onto your thumb. To assess how the normal treatment, which you receive, is reducing the extra work your heart is doing, we would need to monitor you continuously for 24 hours. We will also carry out three 2-minute recordings of your heart using an ultrasound machine, with the ultrasound probe being placed onto your neck.

What do I have to do?
You do not have to do anything different whilst the measurements are conducted.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the sticky patches may irritate the skin, however this is unlikely. If we become aware that a participant might potentially being harmed because of taking part in this study then the study will be stopped and investigated accordingly.

What are the possible benefits of being in this study?
There are no direct advantages for you in taking part in this study. However we hope that the information obtained from this study will improve the care and clinical management of patient, suffering from a similar condition to yours, in the future.

What if new information becomes available?
The short duration of this research study makes such an event less likely, however should new information become available, your research doctor will discuss it with you. If you decide to withdraw from the study your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If you are harmed as a direct consequence of taking part in this study, you will be covered by Leicester University Hospitals NHS Trust's indemnity. Compensation arrangements apply to negligent harm only. 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 NHS complaints mechanisms would be available to you.

What information will you collect about me?
We will need your weight, height, date of birth and blood pressure. We will also need to know whether you suffer from any heart problems and whether you take any medication for your heart.

Will my taking part in the research study be kept confidential?
Yes, all information about you and your participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen to the results of the research study?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about you will not be included and there will be no way that you could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the committee is satisfied that you rights will be respected, that risks have been reduced to an minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?

.

Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 258 5168 email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168 email: Tim.Coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for reading this.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.

Appendix 12. Consultee Information leaflet

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5646
Fax: 0116 204 7935

RELATIVE / LEGAL REPRESENTATIVE INFORMATION LEAFLET

Study Title:

Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Prof TJ Coats, Professor of Emergency Medicine

Your relative is invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of patients with sepsis. Before you decide for your relative to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others 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 would wish for your relative to take part.

What is the purpose of this study?
Each year more than a million people suffer from Sepsis, which is a severe illness caused by an infection. Sepsis can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why has my relative been chosen?
Your relative has been chosen, because he/she is suffering from sepsis.

Does my relative have to take part?
It is up to you to decide whether or not your relative should take part in the research study. If you decide for your relative to take part you will be asked to sign an 'assent' form. Participation is entirely voluntary and your relative is free to withdraw from the research at any time without giving a reason. A decision to withdraw or a decision not to take part, will not affect the care your relative receives.

What will happen to my relative if he/ she takes part?
Your relative will be connected to an additional monitor that will allow us to measure how the heart is working whilst the body is fighting off an infection. In order to obtain such measurement we will have to place 4 sensor patches (sticky patches) onto chest and neck and one onto the thumb. To assess how the normal treatment, which your relative receive, is reducing the extra work your heart is doing, we would need to leave the monitor connected for 24 hours. We will also carry out three 2-minute recordings of the heart using an ultrasound machine, with the ultrasound probe being placed onto the neck. The study will not affect in any way the normal treatment which your relative will receive.

What does my relative have to do?
Your relative will not have to do anything different whilst the measurements are conducted.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the sticky patches may irritate the skin, however this is unlikely. If we become aware that a participant might potentially being harmed because of taking part in this study then the study will be stopped and investigated accordingly.

What are the possible benefits of being in this study?
There are no direct advantages in taking part in this study. However we hope that the information obtained from this study will improve the care of septic patient in the future.

What if new information becomes available?
The short duration of this research study makes such an event very unlikely, however should new information become available, the research doctor will discuss it with you.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If your relative is harmed as a direct consequence of taking part in this study, he/she will be covered by Leicester University Hospitals NHS Trust's indemnity. Compensation arrangements apply to negligent harm only. If you wish to complain, or have any concerns about any aspect of the way you have been approached or the way your relative ahs been treated during the course of this study, the normal NHS complaints mechanisms would be available to you.

What information will you collect about my relative?
We will need his/her weight, height and date of birth. We will also need to know whether your relative suffers from any heart problems and whether he/she takes any medication for heart problems.

Will my relative's taking part in the research study be kept confidential?
Yes, all information about your relative and his/her participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen when the research is finished?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about your relative will not be included and there will be no way that your relative could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that your relative will not come to any harm if he/she takes part. However approval means that the committee is satisfied that your relative's rights will be respected, that risks have been reduced to an minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?

.

Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 258 5168 email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168 email: Tim.Coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for considering your relative's participation in this study.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.

Appendix 13. Patient Information Leaflet (control group)

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5646
Fax: 0116 204 7935

PATIENT INFORMATION LEAFLET
(CONTROL GROUP)

Study Title:

Assessment of cardio-haemodynamics in adult patients with severe sepsis or septic shock.

Principal Investigator: Professor TJ Coats, Professor of Emergency Medicine

You are invited to take part in a research study, carried out at the Leicester Royal Infirmary to find ways to improve the management of septic patients. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.
Please take time to read the following information carefully and discuss it with others 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 would wish to take part.

What is the purpose of this study?
Each year more than a million people suffer from sepsis, which is a severe illness caused by an infection. Despite advances in medicine it can be difficult to diagnose and to properly treat sepsis. It is important to find better ways of managing patients with sepsis. We hope, that the use of a special monitoring machine, which will give us more information than the routine observation (such as blood pressure, heart rate), will help to improve the care of septic patients in the future.

Why have I been chosen?
In order to assess what the heart is doing during sepsis, we will need to obtain measurements about the heart from patients who are not seriously ill. You have been chosen, because you do not suffer from an infection/sepsis and your age and gender matches one of the septic patients in the research study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. Participation is entirely voluntary and you are free to withdraw from the research at any time without giving a reason.

What will happen to me if I take part?
Taking part in the study will have no impact on the treatment you receive in the Emergency Department. You will be connected to a special monitor that will allow us to measure how your heart is working. In order to obtain such measurement we will have to place ECG electrodes (sticky patches) onto your chest and neck. After the 10minutes-recording your participation in this study will end.

What do I have to do?
During the measurement, which will take about 10 minutes, we would like you to sit still and talk as little as possible.

What are the possible disadvantages and risks of taking part?
There are no known risks using this type of monitoring device. It is possible that the ECG electrodes may irritate the skin, however this is unlikely. If we become aware that a participant might potentially being harmed because of taking part in this study then the study will be stopped and investigated accordingly.

What are the possible benefits of being in this study?
There are no benefits for you in taking part in this study. However we hope that the information obtained from this study will improve the care and clinical management of patient, suffering from sepsis in the future.

What if there is a problem?
If you are concerned about any aspect of the study you should ask to speak to the researcher, who will do their best to answer your questions. Please see contact details provided at the end of the information leaflet. If you are harmed as a direct consequence of taking part in this study, you will be covered by Leicester University Hospitals NHS Trust's indemnity. Compensation arrangements apply to negligent harm only. 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 NHS complaints mechanisms would be available to you.

What information will you collect about me?
We will need your weight, height, date of birth and blood pressure. We will also need to know whether you suffer from any heart problems and whether you take any medication for your heart.
Measured data on how your heart is working will be kept and used to form a reference database for future projects.

Will my taking part in the research study be kept confidential?
Yes, all information about you and your participation in this study will be kept strictly confidential. The only people allowed to look at the information are the members of the research team. Data for the research study will be stored securely and will be anonymised.

What will happen to the results of the research study?
We will publish the results of the study in a medical journal, so that other doctors can benefit from the knowledge, but personal information about you will not be included and there will be no way that you could be identified. We will send you a copy if you wish.

Who is organising and funding the research?
The Academic Department of Emergency Medicine, which is part of the Division of Cardiovascular Science, Leicester University.

Who has reviewed this study?
All research that involves NHS patients must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the committee is satisfied that you rights will be respected, that risks have been reduced to an minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If I have any questions regarding this study or wish to express any concerns, who can I contact?

.

Dr Chris Vorwerk, Research Registrar, Emergency Department, Leicester Royal Infirmary
Tel: 0116 258 5168 email: chris.vorwerk@uhl-tr.nhs.uk

Prof Tim Coats, Professor of Emergency Medicine, Division of Cardiovascular Science, Leicester University
Tel: 0116 2585168 email: Tim.Coats@uhl-tr.nhs.uk

We would like to take this opportunity to thank you for reading this.

If you decide to participate in this research project you will be given a copy of this information sheet and a signed consent form to keep.

Appendix 14. Consent Form – Study 2

University Hospitals of Leicester NHS
NHS Trust

Emergency Department
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0116 258 5168
Fax: 0116 204 7935

Centre number:
Patient Identification Number for this trial:
Study Number:

CONSENT FORM
(Study Group)

Study Title: **Assessment of cardio-haemodynamics in adult ED patients with severe sepsis or septic shock.**

Name of Researchers: Professor Tim Coats
Dr Chris Vorwerk
Emergency Department, Leicester Royal Infirmary

Please initial box

1. I confirm that I have read and understand the information sheet dated 22nd June 2007. (Version 1.0) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation 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 responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

3 copies required: one copy for patient; one for researcher; one to be kept with hospital notes

TEBAS 2 Study Patient Consent Form (SG) Version 1.0 dated 22/06/2007

Appendix15. MD related / derived publications /presentations

Publications

Vorwerk C, Loryman B, Coats T, et al. **Prediction of mortality in adult emergency department patients with sepsis.** Emerg Med J 2009;**26**:254-258

Vorwerk C, Jeyanithi H, Coats, TJ. **Thoracic electrical bioimpedance: a tool to determine cardiac versus non-cardiac cayses of acute dyspnoea in the emergency department.** Emerg Med J 2010;**27**:359-363

Vorwerk C, Coats TJ. **Protocol driven sepsis management—time for a rethink?** Emerg Med J emj.2010.101808 Published Online First: 2 November 2010

Abstracts

Vorwerk C, Coats T. **Predictive value of tissue oxygen saturation upon mortality in Emergency Department patients with sepsis.** Crit Care Med 2011; (accepted for publication)

Vorwerk C. **Normalisation of tissue oxygen saturation in ED patients with severe sepsis or septic shock is related to mortality**. Emerg Med J 2009;26 (Suppl I)**:**A6

Vorwerk C, Coats T. **Non-invasive cardio-haemodynamic assessment in septic Emergency Department patients.** Emerg Med J 2008;25 (Suppl II):A2

Oral presentations

Vorwerk C. **Normalisation of tissue oxygen saturation in ED patients with severe sepsis or septic shock is related to mortality.** CEM conference, Roderick Little Prize Session, London Sept 2009.

Vorwerk C. **Non-invasive cardio-haemodynamic assessment in septic Emergency Department patients.** CEM conference, Roderick Little Prize Session, Dublin Sept 2008.