Diagnostic Investigation of Shock (DiPS study)

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The thesis is submitted in partial fulfilment of the requirement for the degree of MD

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Dedication

To

My parents and my beloved sister

Declaration

Declaration This thesis is the result of my own independent work, except where otherwise stated, and the views expressed are my own. Other sources are acknowledged by explicit references. The thesis has not been edited by a third party beyond what is permitted by Cardiff University's Use of Third-Party Editors by Research Degree Students Procedure.

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Abbreviation List

ACCP American College of Clinical Pharmacy

ACE Angiotensin-converting enzyme

ACS Acute coronary syndrome

ADHER Acute decompensated heart failure registry

ADHF Acute decompensated heart failure

ALL Acute lymphocytic leukaemia

AMD Age related macular degeneration

AMED Association of Management Education and Development

AMI Acute myocardial infarction

AMP Adenosine monophosphate

AMU Acute medical unit

APACHE Acute physiology and chronic health evaluation

APC Angiotensin presenting cell

ARISE Australasian Resuscitation Sepsis Evaluation

ATLS Adult trauma life support

AUC Area under the curve

AURC Area under receiver curve

AUROC Area under receiver operating curve

AVPU Awake verbal pain unresponsive

BE Base excess

BP Blood pressure

BSA Body surface area

C4 Complement 4

CA9 Cancer antigen 9

CABG Coronary artery bypass graft

CCO Continuous Cardiac output

CCU Coronary care unit

CI Confidence interval

CINAHL Cumulative Index of Nursing and Allied Health Literature

CO Cardiac output

CO2 Carbon dioxide

COPD Chronis obstructive pulmonary disease

CORTICUS Corticosteroid Therapy of Septic Shock

CP Chest pain

CPI Cardiac power index

CPO Cardiac power

CPR C-reactive protein

CS Cardiogenic shock

CSA Cross sectional area

CT Computed tomography

CUB C1r/C1s, UEGF, BMP1

CVP Central venous pressure

CW Cardiac power

CWD Chronis wasting disease

DA Dopamine antagonist

DBP Diastolic blood pressure

DCO Diffusing capacity for Carbon Monoxide

DGU Documented in registry of German Trauma Registry

DI Diabetes insipidus

DIC Disseminated intravascular coagulation

DO2 Oxygen delivery

DVT Deep vein thrombus

ECHO Echocardiogram

ECMO Extracorporeal membrane oxygenation

ECOM Endotracheal cardiac output monitoring

ED Emergency department

EDM Esophageal Doppler monitor

EDV End diastolic volume

EGDT Early goal directed therapy

EMBASE Excerpta Medica data BASE

ESC European society of cardiology

ESICM European society of intensive care

ET Ejection time

EW Early warning

EWS Early warning score

FFP Fresh frozen plasma

FT Fractional time

FVII Factor seven

GBP Pound sterling

GCS Glasgow coma scale

GDT Goal directed therapy

GUSTO Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery

H2 Hydrogen

HDU High dependency unit

HES Hyper-eosinophilic syndrome

HR Heart rate

HRT Hormone replacement therapy

IABP Intra-aortic balloon pump

ICU Intensive care unit

IM Intra-muscular

ITRP International Technology Recommendation Panel

ITU Intensive care unit

IV Intravenous

IVC Inferior vena cava

JACC Journal of American cardiology

KK3

LA Left atrium

LiPS Li Priori of Sock

LV Left ventricle

LVAD Left ventricular assist device

LVEDAI Left ventricular end diastolic area index

LVEDP Left ventricular end diastolic pressure

LVEF Left ventricular ejection fraction

LVET Left ventricular ejection time

LVOT Left ventricular outflow tract

MAP Mean arterial pressure

MAX Maximum

MCS Multiple chemical sensitivity

MD Minute distance

MEWS Modified early warning score

MHZ Mega Hertz

MI Myocardial infarction

MIP Maximum intensity projection

MP Molecular pathology

MRI Magnetic resonance imaging

MTPG Mother Teresa College of Pharmacy

NEWS National early warning score

NHS National health service

NICE National institute of clinical excellence

NIHR National Institute of Health Research

NO Nitric oxide

NPSA National Patient Safety Agency

NRMI National Remote Medical Imaging

NSTEMI Non-ST elevation myocardial infarction

O2 Oxygen

OTD Oncology therapeutic development

PA Pulmonary artery

PAC Pulmonary artery catheter

PAP Pulmonary artery pressure

PAWP Pulmonary artery wedge pressure

PCI Percutaneous Coronary intervention

PCWP Pulmonary capillary wedge pressure

PE Pulmonary embolism

PH Power of hydrogen

PKR Potential kinetic ratio

PLR Passive leg raising

PLT Platelet

PMD Pelizaeus-Merzbacher disease

PPCI Primary Percutaneous Coronary intervention

PPV Pulse pressure variation

PRAM Paediatric Respiratory Assessment Score

PRBC Packed red blood cell

PS Pulmonary stenosis

PV Pulmonary vein

PVR Pulmonary vascular resistance

PW Pulse wave

PY5 Phosphonopyridoxyl - AMINO- PENTANOIC ACID

RA Right atrium

RAAS Renin Angiotensin system

RAP Right atrium pressure

RBC Red blood cell

RCP Royal College of Physician

RCT Randomised controlled trial

ROC Receiver operating curve

RPM Remote patient monitoring

RR Respiratory rate

RV Right ventricle

RVEDP Right ventricular end diastolic pressure

RVSWI Right ventricular systolic work index

SBP Systolic blood pressure

SCCM Society of Critical Care Medicine

SCI Science Citation Index

SCLK

SD Standard deviation

SH Social history

SI Serious incidence

SIRS Systemic inflammatory response syndrome

SMII Smith-Madigan inotropy index

SO2 Sulfur dioxide

SOAP Sepsis Occurrence in Acutely Ill Patients

SOFA Sequential organ failure assessment score

SS4 Starch Synthase 4

SSC Systemic sclerosis

ST ST segment

STEMI ST elevation myocardial infarction

SV Stroke volume

SVI Stroke volume index

SVR Stroke volume resistance

SVRI Stroke volume resistance index

SVS Superior vena cava

SVV Stroke volume variability

SW Stroke work

TARN Trauma Audit and Research Network

TBI Traumatic brain injury

TEE Transoesophageal echocardiogram

TP Tissue plasminogen

USCOM Ultrasonic cardiac output monitor

VASST Vasopressin versus Norepinephrine infusion in septic shock trial

VO2 Volume of Oxygen

VR Ventricular rate

VTI Velocity time integral

WHO World health organization

Abstract

Background:

Despite advancement in diagnostic and therapeutic measures, mortality of shock remains high. Identifying patients at highest risk of deterioration is of great interest to clinicians. The main purpose of this study is to investigate the diagnostic ability of USCOM as a feasible, Doppler-based technique in ED. Also, to assess how USCOM improves identification and classification of shock at early stages and help clinician gestalt. At last, to validate Li priori definition of shock; in different settings and assess clinician gestalt.

Methods:

Study was held at University Hospital of Wales. Ethics approval was sought from Wales Research Ethics Committee II with authority to approve projects involving adults lacking capacity to consent. All adult patients aged ≥ 18 years old, with initial NEWS score of ≥ 3, were recruited within one hour of ED arrival.

Results:

A total of 359 patients, 46.5% male, were included in the analysis. SVV was found to be the only independent predictor of poor outcome (*P* value: 0.021, AUC: 0.62, sensitivity and specificity: 60% and 56% respectively). Based on proposed haemodyanmic criteria, analysis of grouped data showed that there is no significant association between shock groups and mortality (*P* value: 0.52). Using regression analysis, LiPS additive score was validated in internal and external settings, with high performance ability (*P* value: 0.0006, 0.0003 and 0.005, AUC: 0.77, 0.71 and 0.62 in three cohorts respectively). DiPS as a novel diagnostic model of shock, uses a combination of physiological and laboratory values, and shown to have excellent diagnostic ability in predicting outcome, (AUC of 0.813, accuracy: 83.3% and *P* value < 0.0001). LiPS diagnostic tool did not agree with clinical impression of shock. However, USCOM and clinicians had acceptable agreement on diagnosis of (Possible) shock. SVV is an independent predictor of shock outcome. DiPs as a quantitative measure of shock can be used parallel to LiPS to improve detection and risk stratification of shock in ED.

Conclusion:

SVV is an independent predictor of shock outcome. DiPs as a quantitative measure of shock can be used parallel to LiPS to improve detection and risk stratification of shock in ED.

Key words:

DiPS: Diagnostic Investigation and Prediction of Shock. LiPS: Li Priori Shock, SVV: Stroke Volume Variability, USCOM: Ultrasonic cardiac output monitor

"Every writer on shock has his own ideas as to its nature: I have not broken the tradition."

W. B. Cannon (1923)

Chapter 1

Background & Introduction

In this chapter, I will be writing on history of shock and how most recent definitions of shock been developed. I will be discussing different types of shock, their aetiology, epidemiology and pathophysiology. I will be highlighting the importance of diagnosing shock at early stages with regards to prognosis and outcome, with focus on development of various scoring systems, which aimed to enable clinicians at front line diagnosing shock in an easier and quicker manner. I would briefly touch base on comparison of these scoring systems and published data on diagnostic ability of each score. Subsequently, I will be discussing pharmacological or mechanical treatment strategies, being used up to this date in treating different types of shock. I expand that by mention of diagnostic and risk stratification criteria of Early Goal Directed therapy (EGDT), which enables detection of patients at risk and most likely to benefit from early treatment. And at last, I will be illustrating the importance of haemodynamic parameters in diagnosis of shock and monitoring treatment. I included a summary on development of USCOM, its features and how haemodynamic variables such as stroke volume, systemic vascular resistance and cardiac output could be measured in an easy, cost-effective, and harmless way, using ultrasound technology. This chapter will end by description of unmet need for this study, unanswered questions and study objectives and hypothesis.

1.1 History of shock

The word “shock” was never used before 1743. However, Hippocrates used the word “exemia“to describe a condition where the human body is drained of blood. [1] The word “choc“was first used by Henri-François Le Dran's, a French surgeon, in 1740. He used it to describe a reaction which resulted from the impact of a missile. [2] Prior to this time there is no record of the word shock being used to describe a clinical syndrome. Le Dran's wrote a document, which was then translated to English in 1743. It defined Shock as a neurological phenomenon, related to gun wound injury which manifests itself as commotion or agitation and is eventually followed by fatal consequences. [2]

Between Le Dran's work and the mid-19th century Georges James Guthrie, a British surgeon who served in the Spanish war of independence, expanded the conception of shock to include both the direct result of trauma and the physiological response of a body to trauma. [3] Twenty years later in 1848, a French surgeon; Velpeau M, in a Lancet article explaining management of wounded victims during the Paris revolution, described a sequence of physiological responses after gunshot wound, and the first stage of this sequence was characterised as the “shock” resulting from the wound. [4]

Both of these authors used the word “reaction”, for the time during which, a patient is still responsive to medical treatment. They meant if shock means the neurophysiological response to injury, then reaction means the physiological recovery after shock. During 1861 to 1865 American surgeons of the American civil war realised that shock can be caused by different mechanisms and recognised that shock is a physiological response to injury in general. The treatments they recommended were intended to push patients to that state of reaction. [5] Surgeons such as Professor Julian J Chisolm prescribed stimulants such as alcohol, ammonia and caffeine to treat patients with hypovolemic or haemorrhagic shock. [5] Despite the many experiments and pages of written work on medical and surgical history of American rebellion war, the word shock had limited use during the period.

In 1868, Edwin Morris, a physician at Union Infirmary, now known as Greenwich District Hospital, London reviewed everything that was written on the topic of shock and described it as a “clinical syndrome”, which results from the work of multiple organ including the brain, spinal cord, heart and kidneys. [5] Morris emphasised the need for a thorough knowledge of physical properties and the nervous system in order to treat shock. [6] Over the late 19th century, shock as a “nervous” phenomenon gained more attention. The effect of autonomic system and its effect on cardiovascular system was described by a French physiologist named Claude Bernard. This coincided with the first accurate measurement of blood pressure and the recognition that the central nervous system and the autonomic system are responsible for the adjustment and maintenance of blood pressure as well as systemic blood perfusion. [7] Thirteen years later, Mansell-Moullin expanded on the idea and devoted an entire book of “On the Pathophysiology of Shock”, to describe shock as a primarily nervous phenomenon. [8] He was particularly interested in the idea of mesenteric nerves being the forebrain of hypotension seen in shock. Between 1890 and 1925 two theories around the pathophysiology of shock emerged. Dr George Crile, a famous American surgeon, reported that vasoconstriction occurs after haemorrhage and burns in dogs. [9] He believed that afferent stimulation and expectation of noxious stimuli by the higher centres of the brain are the key factors in shock. Hence, he concluded that adequate sedation and analgesia are essentials in treating shocked patients. [10] The second theory was based on the work of Yandell Henderson, a Yale University physiologist, who observed that animals suffering from bleeding and saw that they have lower than normal partial pressure of carbon dioxide in their blood. [11] He understood that hypocarbia is a result of tachycardia and therefore pathological hyperventilation is an important factor in shock. Henry Janeway and Ebrahim Ewing at Bellevue Hospital of New York combined the two hypotheses and after extensive experimentation on dogs, they concluded that reflexive hyperventilation, after severe injury results in hypocarbia, promotes splenic vasodilation. They also concluded that blood pooling in splenic vessels results in missing blood from circulation, hypotension, and shock. [12]

World War I provided another opportunity for scientists to investigate shock under very difficult conditions. In 1918, when America joined the war, American and British scientists established a joint commission to study battlefield shock. William Bayliss from the University of London and Walter Cannon from University of Massachusetts were amongst these names. [13]

Cannon supported the theory of “missing blood” and believed that there is pooling of blood within the body in response to shock, which results in a marked reduction in circulating blood volume. [14] Both Cannon and Bayliss reported on the efficacy of a number of intravenous solutions including synthetic colloid solutions and in 1831 normal saline was first used in the treatment of hypovolemia owing to cholera. [15] By the end of World War I, shock was considered a 2-stage phenomenon: 1) primary shock; which occurs immediately after wound injury and is a neurologic phenomenon; 2) secondary shock which develops later due to toxins elaborated by the wound itself. [16] It was believed that pooling of the blood in certain capillary beds, results in the phenomenon of ‘‘missing blood’’ and is the main culprit for hypotension and tissue hypoperfusion.

Alfred Blalock, a well-known American surgeon, rejected the theory of “missing blood”. Blalock compared weights of the experimental and control limbs amputated through the proximal thigh and divided the pelvis and lumbar spine. He found the added weight of the injured limb accounted for all observed hypovolemia. Hence, he concluded that there was no missing blood or missing fluid at all. He also excluded the theory of central nervous injury as an important cause of shock. [17] Blalock described shock as an “acute circulatory failure” and for the first time in the history of shock, as a topic of investigation, defined five distinct physiological responses for shock which later translated to different types of shock; 1) hematogenic shock (hypovolemic), 2) neurogenic shock, 3) vasogenic shock (including both anaphylactic and septic shock), 4) cardiogenic shock; and 5) ‘‘unclassified conditions.’’ Blalock paid a major contribution to shock and between 1927 and 1942 published 44 articles on the topic.

Towards the end of 1940s various studies showed significant outcome improvement by infusing Ringer or Normal Saline solutions to human and animal victims of shock. [18], [19] John Dillon, also working on a dog model, confirmed the superiority of resuscitation of haemorrhagic shock with a partial replacement of shed blood together with large volumes of lactated Ringer’s solution. [20] Research on resuscitation with crystalloid solutions and blood continued and towards the end of 1970s it was widely understood that an aggressive approach is required for a successful resuscitation. During the 1990s the research continued on pathophysiology of shock at the molecular level and the word ‘‘shock’’ continued to be used to describe haemodynamically unstable patients since its appearance as a medical term in 1743. Despite all the advancements in medicine, shock remained an important clinical challenge. The pathophysiology of shock has continued to evolve and continues to do so, but the clinical “syndrome” has not changed. Knowledge of clinical descriptions and definitions is clearly useful for clinicians routinely dealing with the syndrome and its fatal and irreversible consequences.

1.2 Definition of shock

In 2013, Vincent JL. *et al*, defined the latest conceptual definition of shock as “global insufficiency of tissue perfusion leading to inadequate oxygen and nutrients delivery to meet the needs of the tissues”. [21] Shock is a syndrome and is usually characterised by hypotension, tachycardia, and clinical signs of tissue hypoperfusion, which are apparent through the three “windows” [22] of the body; skin (cold, cyanotic and clammy) kidneys; (low urine output of <0.5 ml per kilogram of body weight per hour), and nervous system; (altered mental state, which typically includes obtundation, disorientation, and confusion). This is in addition to presence of hyperlactatemia (levels above 1.5 mmol per litre), which indicates abnormal cellular oxygen metabolism. Shock is a life-threatening emergency, which requires urgent and rapid assessment, diagnosis, and treatment. [23] It is a common condition and affects one third of intensive care patients. [24]

1.3 Pathophysiology of shock

Vincent JL. *et al*. [21] classified the pathophysiology of shock into two main groups, as the following definitions:

Cardiac: This includes types of shock caused by low cardiac output and hence poor oxygen delivery. This group includes hypovolemic shock (from internal or external fluid or blood loss), cardiogenic shock (from acute myocardial infarction, end-stage cardiomyopathy, advanced structural or valvular heart disease, myocarditis, or cardiac arrhythmias), and obstructive shock (from pulmonary embolism, cardiac tamponade, or tension pneumothorax).

Non-cardiac: This includes distributive shock where the problem is peripheral and caused by reduced systemic vascular resistance (SVR) leading to altered oxygen extraction. In this type of mechanism cardiac output is usually high however it can also be low due to myocardial depression. Between 2003 to 2007, Becker *et al,* examined the effect of Dopamine vs Norepinephrine in treatment of shock in 1679 patients admitted to emergency department (ED) in a multi-centre, randomised-controlled trial and they showed that distributive-septic shock is present in 62%, distributive, non-septic in 4%, hypovolemic in 16%, cardiogenic in 16% and obstructive shock is present in 2% of the patients. [25] Previous research showed that septic shock is the commonest cause of shock. [21], [26], [27], However, patients with acute circulatory failure often have a combination of these mechanisms. For example, a patient with distributive shock from severe pancreatitis, anaphylaxis, or sepsis may also have combined hypovolemia and cardiogenic shock resulted from myocardial depression. **(Figure 1.1)**

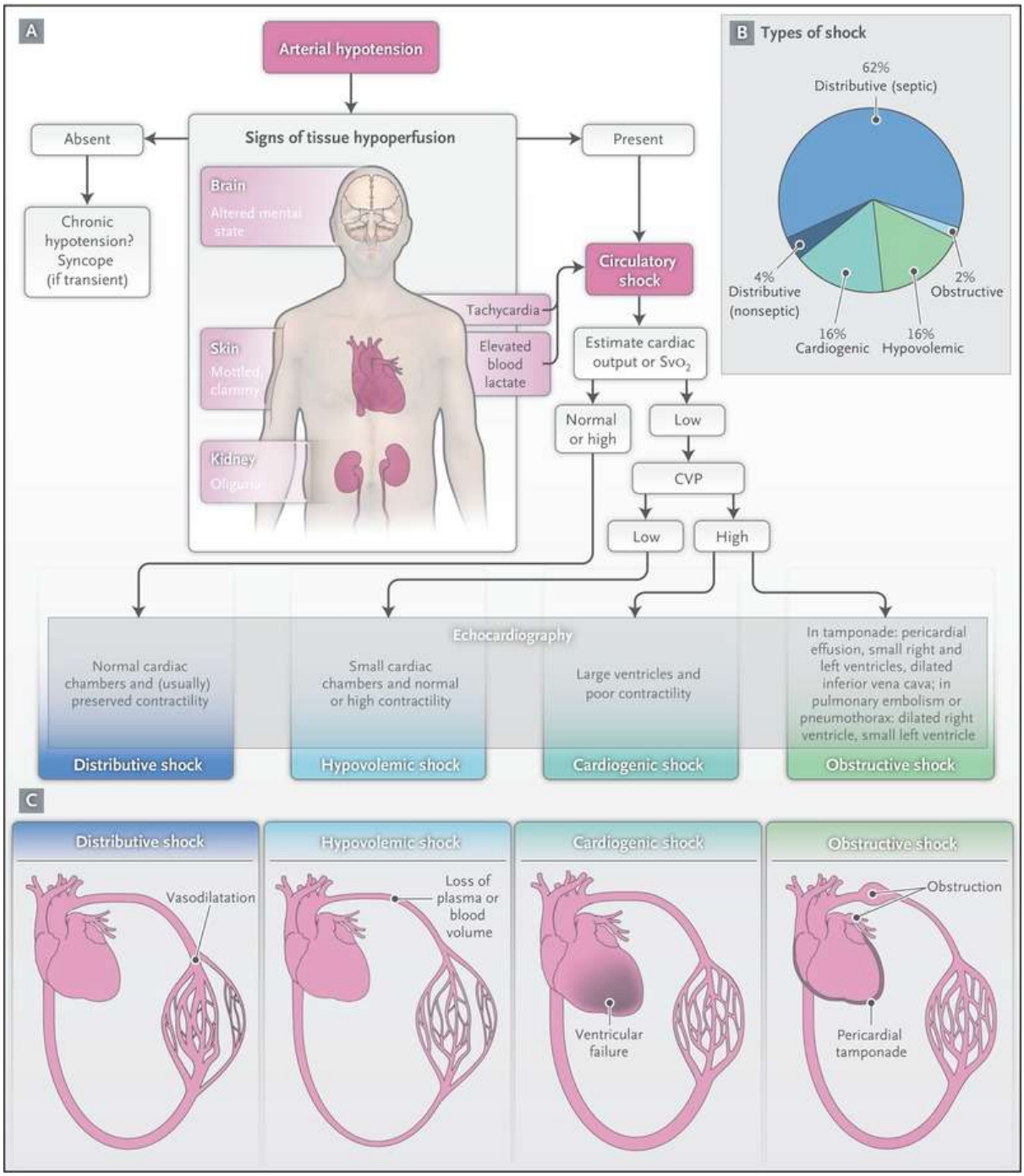


Figure 1.1: Initial Assessment of Shock States. What is shown here is an algorithm for the initial assessment of a patient in shock **(Panel A)**, relative frequencies of the main types of shock **(Panel B)**, and schematic representations of the four main types of shock **(Panel C).** The algorithm starts with the most common presentation (i.e., arterial hypotension), but hypotension is sometimes minimal or absent. **Abbreviations:** CVP: central venous pressure, and SvO2: mixed venous oxygen saturation. Adopted from Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013 Oct31;369 (18):1726-34.

1.4 Types of shock

1.4.1 Distributive (vasodilatory) shock

Moranville MP. *et al*, [28] characterised distributive shock by reduction in systemic vascular resistance (SVR) due to vasodilatation with or without decrease in cardiac output (CO). Systemic vasodilation leads to decreased blood flow to the brain, heart, and kidneys causing damage to vital organs. Leakage of fluid from capillaries into the surrounding tissues further complicates the clinical picture in distributive shock. [29] Most common causes of distributive shock are sepsis and anaphylaxis. Less common causes are neurogenic shock, adrenal insufficiency, and capillary leak syndrome. Drug overdose or toxicity should always be considered, particularly in context of potent vasodilators such as calcium channel blockers, beta-blockers and Hydralazine or Nitrates. [30], [31], [32]

1.4.1.1 Septic shock

Definition and Pathophysiology

The most recent definition of sepsis as per the 45th Critical Care Congress in 2016 defines sepsis as a “life-threatening condition caused by dysregulated host immune response to infecting pathogen”. [33] Septic shock is defined as sepsis-induced hypotension (systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mmHg or a decrease in SBP of > 40 mmHg), despite adequate fluid resuscitation along with evidence of hypoperfusion. Perfusion defects may include lactic acidosis (lactic acid > 4 mmol/L), oliguria, or altered mental status. There are two main pathophysiological response to the pathogen, one being release of systemic cytokines, resulting in vasodilation and fluid leak from capillaries, and the second being development of pro-coagulant state. [34] If left untreated sepsis can advance to disseminated intravascular coagulation (DIC). [28] Alongside this, the pathogen plays a significant role by attacking the host defence mechanism, adhering to epithelia surfaces, invading, and destroying cells.

Epidemiology

Sepsis is thought to kill 52,000 people a year in the United Kingdom (UK). National Health Service (NHS) digital data obtained by the Press Association shows that there were 350,344 recorded hospital admissions with a first or second diagnosis of sepsis in 2017 and 2018, up from 169,125 three years earlier. [35] These included 38,401 admissions among children aged four and under, up from 30,981 in 2015 and 2016. [35] The mortality rates of septic shock extend to 50%. [34] The long-term prognosis is usually poor; only approximately 30% survive the first year after hospital admission. [36]

1.4.1.2 Anaphylactic shock

Anaphylaxis is an immunoglobulin (IgE)-mediated, rapid-onset systemic allergic reaction. It is a life- threatening acute hypersensitivity reaction which can be defined as a rapidly evolving, generalised, multi-system, allergic reaction. [34] In anaphylaxis the patient has a history of previous exposure to an antigen, resulting in IgE formation, attached to the surface of mast cells in the tissues and basophils in the blood. Second exposure to same allergen will lead to IgE-mediated release of histamine from mast cells and basophils, leading to systemic vasodilation and capillary fluid leak. [37] Anaphylaxis can happen within minutes, delayed (after hours post exposure) or can be biphasic and happen in four to eight hours post exposure. [28] The median time between exposure and cardiac arrest can be five to fifteen minutes and the most common cause of death is normally airway obstruction followed by hypotension. [38] Same as other types of shock it is associated with hypoxia (cyanosis or partial pressure of oxygen (PaO2) < 92%), hypotension (SBP < 90mmHg), or neurologic phenomenon (confusion or loss of consciousness).

Epidemiology

Anaphylactic shock is the second most common cause of distributive shock. [34] The incidence of anaphylaxis in the UK is increasing, with a reported increase in hospital admissions for anaphylaxis from 1 to 7 cases per 100,000 populations per year between 1992 and 2012. [39] An estimated 20 deaths from anaphylaxis are reported each year in the UK. [40]

1.4.1.3 Neurogenic shock

Neurogenic shock is attributed to disruption of the autonomic pathways within the spinal cord. [41] This leads to vasodilation caused by reduced SVR and hypotension. Neurogenic shock is most commonly seen in victims of spinal cord injuries (SCI). In a setting of sympathetic denervation and increased vagal tone it will end in paradoxical bradycardia which can progress to complete heart block or cardiac arrest. [42] In a study of 75 patients with penetrating SCI, only 24% were hypotensive in the field and only 7% of patients had neurogenic shock. Only 22% of patients who were hypotensive had neurogenic shock as a cause of hypotension. [43] A further study of 408 patients with both blunt and penetrating trauma, reveals that the incidence of hypotension (<100 mmHg) is 4.5% in 107 neurologically intact spinal injuries (most had associated injuries to account for the shock), 20.7% in 111 with incomplete SCIs and 31.6% in 190 with complete cord lesions. [44] There is no universally accepted definition of neurogenic shock. One paper has defined it as a systolic BP < 100 mmHg and a heart rate of < 80 beat per minute (bpm) in a patient without other obvious cause. [43] Another paper has defined hypotension in spinal cord injury as a systolic BP < 90 mmHg. [45] Neurogenic shock can happen soon after cord injury but often happens several weeks after. [28] **(Figure1.2)**

Epidemiology

A retrospective analysis of Trauma Audit and Research Network (TARN) studied 490 patients with isolated spinal injury between 1989 and 2003. They reported that the incidence of neurogenic shock in cervical cord injuries was 19.3% (95% CI: 14.8-23.7%). The incidence of neurogenic shock in thoracic and lumbar cord injuries were 7% (CI: 3-11.1%) and 3% (CI: 0-8.85%) respectively. [46]

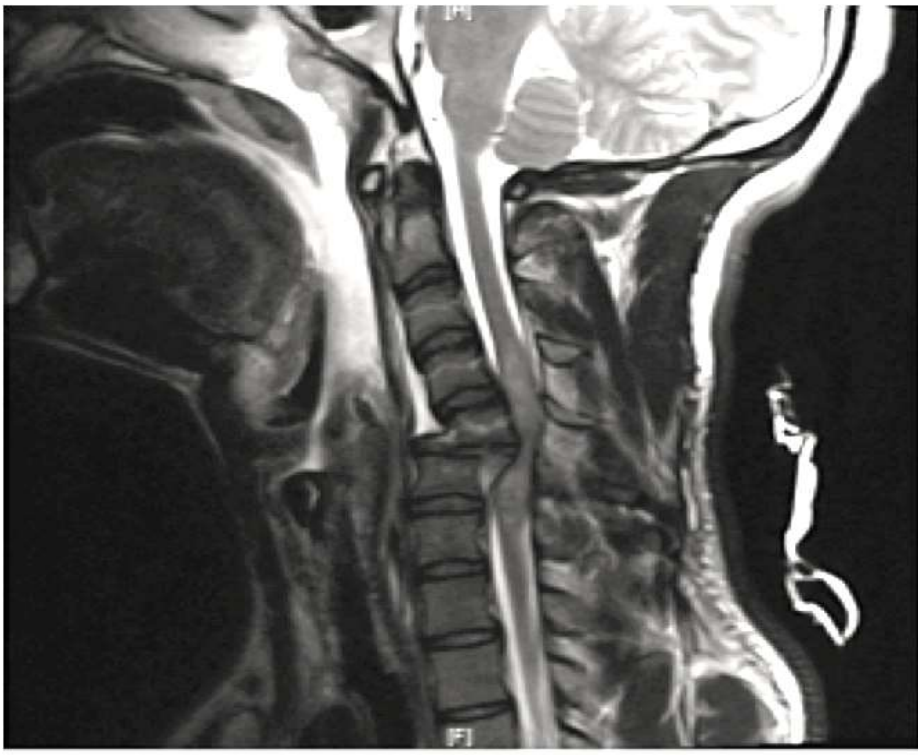


Figure1.2: Magnetic resonance imaging (MRI) of cervical spinal cord injury at level of C4. The image show protrusion of vertebrae towards spinal cord causing compression. Adopted from https://www.orthobullets.com.

1.4.1.4 Adrenergic shock

Lack of Cortisol results in decreased alpha-1 receptor expression on arterioles and causes vasodilation. This can be seen in context of pituitary or adrenal insufficiency and in patients on chronic steroid therapy who stopped their treatment suddenly. [47] Adrenergic shock can also occur in Pheochromocytoma, which is a rare tumour that secretes excessive amounts of catecholamines. [48] Pheochromocytoma manifests with tachycardia, sweating, headaches, and fluctuating blood pressure in most cases. Patients are hypertensive in almost 70% of the times but hypotension can also happen in Epinephrine-secreting pheochromocytomas. [49], [50] Bergland BE. *et al*, reviewed 539 cases with pheochromocytoma and found shock on presentation in 11(2%) of these patients. [51] Hypotension, increased capillary permeability together with myocardial depression as a result of vasospasm, and chronic ischemia are key physiological findings in shock associated with pheochromocytoma. [48] Necrosis and haemorrhage inside the tumour itself can also result in shock. Unrecognised cases have poor prognosis and rapid assessment, and haemodynamic support is required to prevent further progression of shock. [48]

1.4.1.5 Capillary leak syndrome

Systemic Capillary Leak Syndrome (SCLK) was first described in 1960 by Clarkson *et al*. [52] The syndrome is associated with vascular endothelial dysfunction, hypoalbuminemia, and decreased oncotic pressure leading to fluid loss from the blood into the interstitium followed by tissue hypoperfusion and hypoxia. [53] SCLK is not very common and there are reports on only 150 published cases. [54], [55]. Extreme cases can be fatal. Clinical diagnosis includes the presence of severe hypoalbuminemia, haemoconcentration, and development of oedema without evidence of fluid overload. There would be no evidence of cardiac dysfunction, abnormal C-reactive protein (CRP) or isolated pathogen on blood cultures same as no evidence of abnormal IgE or eosinophilia. Strong clinical suspicion, confirmation of haemoconcentration with paradoxical hypoalbuminemia, and exclusion of other causes of shock in this case are warranted. [56]

1.4.2 Hypovolemic shock

Hypovolemic shock caused by severe hypovolemia and decreased peripheral perfusion. If left untreated, these patients can develop ischemic injury of vital organs, leading to multi-system organ failure. [57] Zelman *et al*, characterised hypovolemic shock by loss of 15% or more of intravascular volume. [58] Unlike most internal organs which can lose up to 50% of their functional mass before organ failure becomes apparent, loss of as little as 30 to 40% of total blood volume can result in life-threatening circulatory failure. [28] Hypovolemic shock either results from haemorrhage or fluid loss. It is important to establish aetiology in order to plan on replacement of blood or fluid at early stages and avoid further deterioration. Water loss normally happens through gastrointestinal, renal, skin loss or third space sequestration. Volume loss through gastrointestinal happens during retractable vomiting, diarrhoea, or external drainage via stoma or fistulas. Fluid loss through kidneys happens as a result of excessive diuresis, diabetes insipidus (DI), osmotic diuresis in diabetes mellitus and during a variety of parenchymal and tubular nephropathies. Any interruption of skin barrier ends in excessive volume loss through skin and finally third spacing happens when too much of intravascular fluid leaks from intravascular space to extravascular space, for instance in intestinal obstruction, pancreatitis, obstruction of a major venous system. [59] Haemorrhagic shock can happen as a result of severe blood loss secondary to trauma, maternal, gastrointestinal, perioperative haemorrhages or ruptured aneurysms. [60] Based on the most recent Advanced Trauma Life Support (ATLS) document published by American College of Surgeons (ACS) in 2013, hypovolemic shock can be classified into four groups based upon an estimated blood loss and corresponding vital signs including mental state, blood pressure and pulse rate. [61] **(Table 1.1)** The ACS defines massive haemorrhage as a loss of total blood volume within a 24-hour period or loss of half of the blood volume in a 3-hour period. [62], [63] However, recent

analyses from the Trauma Register Deutschen Gesellschaft für Unfallchirurgie (DGU) and the Trauma Audit Research Network (TARN) registry questioned the classification's validity. [64], [65] Hence, a large retrospective analysis of 40888 patients with multiple trauma; with or without traumatic brain injury (TBI) between 2002 and 2013 took place by Fröhlich M. and colleagues. The proposed use of shock index (SI), which is a readily available index and calculated by dividing heart rate by systolic blood pressure to identify patients at risk of needing blood products with or without TBI. [66], **(Table 1.2)**

Table 1.1. Classification of hypovolemic shock based on American College of Surgeons proposed classification.

	Class I	Class II	Class III	Class IV
Volume of blood Loss	<750 ml (<15%)	750-1500 ml (15 - 30%)	1500-2000 ml (30 - 40%)	>2000 ml (> 40%)
Heart rate (bpm)	Normal	>100	>120	>140
Respiratory rate	Normal	20 - 30	30 - 40	>35
Systolic blood Pressure **Palpable pulse**	Normal Radial palpable	Normal Radial palpable	Reduced Radial pulse not palpable	Reduced Carotid palpable +/-
Neurological Status	Alert	Anxious	Confused	Lethargic
Urine Output (ml/h)	Normal	20-30	5-15	Minimum

Proposed classification based on amount of volume loss, heart rate, respiratory rate, systolic blood pressure, ability to fill the pulse, neurological status and urine output. **Abbreviations:** bpm: beats per minute. Adopted from N Engl *J Med* 2014; 370:1683-1693.

Table 1.2. Classification of hypovolemic shock based on the shock index.

Shock class	Class I	Class II	Class III	Class IV
Severity of shock	No shock	Mild shock	Moderate shock	Severe shock
SI at admission	< 0.6	≥ 0.6 to <1	≥ 1 to <1.4	≥ 1.4
Need for blood products	Observe	Consider use of blood products	Prepare transfusion	Prepare massive transfusion

Proposed classification based on severity of shock, shock index at admission and need for blood transfusion, divides shock into four different class, when class I represent no shock and class IV represent severe shock. **Abbreviations:** SI: shock index. Adopted from Fröhlich M. et al. Is the shock index, based classification of hypovolemic shock applicable in multiple injured patients with severe traumatic brain injury? An analysis of the Trauma Register DGU. Resuscitation and Emergency Medicine. 2016; 24:148.

Pathophysiology

Depletion of intravascular volume, whether by extracellular fluid loss or blood loss would lead to compensatory mechanisms and increased sympathetic tone resulting in increased heart rate, increased peripheral vasoconstriction and cardiac contractility. [60] The first changes in vital signs seen in hypovolemic shock is an increase in diastolic blood pressure with narrowed pulse pressure. [28], [60] As volume status continues to decrease, systolic blood pressure drops. As a result, oxygen delivery to vital organs is unable to meet oxygen demand. Aerobic metabolism turns to anaerobic metabolism, resulting in lactic acidosis. As sympathetic drive increases, blood flow is diverted from other organs to preserve blood flow to the heart and brain. This would act as a vicious cycle and stimulates tissue ischemia and worsening of lactic acidosis. [60] Devastating consequences of haemorrhagic shock and uncontrolled bleeding are acidosis, hypothermia, and coagulopathy. [67] These abnormalities are referred to as the ‘‘lethal’’ triad because each element exacerbates the other and in combination can rapidly lead to death if haemorrhage is not controlled. [68], [69], [70], [71]

Epidemiology

Hypovolemic shock is most common in intensive care units. [60] Annually, 1.9 million people in the world lose their lives due to haemorrhage and its consequences. [60] In a prospective, observational study of 5210 adult trauma patients aged 16 years and over admitted to one of the 22 trauma centers in England and Wales over 22 months, 442 patients had major haemorrhage, 80·8% were severely injured and 33·0 % had massive haemorrhage as per study criteria (Patients who received at least 4 units of PRBCs in the first 24 hours were classified as having major haemorrhage, and those receiving 10 units or more as having massive haemorrhage). The results were extrapolated to an overall estimated incidence of 83 per million for major haemorrhage and 23 per million for massive haemorrhage in England and Wales. A greatly increased likelihood of major haemorrhage was identified in older patients. The likelihood of suffering injury with haemorrhage was consistent across all age groups until the age of 65 years, after which it almost doubled to 196 per million for major haemorrhage and 50 per million for massive haemorrhage. [72]

1.4.3 Cardiogenic Shock

Cardiogenic shock (CS) has been defined as a state of tissue hypoxia caused by reduced systemic cardiac output in the presence of adequate intravascular volume. [73] Despite advances in reperfusion therapy and mechanical circulatory support treatments, mortality among patients with cardiogenic shock remained high and around 30 to 50%. [74], [75], [76] Several studies establish hemodynamic criteria for cardiogenic shock and defined it by hypotension (SBP < 80-90 mmHg or MAP: 30 mmHg lower than baseline) with severe reduction in cardiac index ([CI] < 1.8 L/min/m2 without or < 2.0 to 2.2 L/min/m2 with supportive measures) and adequate or elevated filling pressure (e.g., Left ventricular end-diastolic pressure (LVEDP) > 18 mmHg or Right ventricular end-diastolic pressure (RVEDP) > 10-15 mmHg). [77], [78], [79], [80], [81], [82], [83], [84], [85], [86]

Aetiology

The most common cause of cardiogenic shock is extensive acute myocardial infarction. [87], [88] Shock secondary to acute myocardial infarction (MI) can happen early post presentation with MI or in the later stages. [89], [90] The most common cause of MI is acute ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI). [91], [92] Mechanical complications of MI, such as acute mitral regurgitation, rupture of the interventricular septum, or rupture of the free wall can lead to cardiogenic shock. Other causes of cardiogenic shock include myocarditis, end-stage cardiomyopathy, myocardial contusion, septic shock with severe myocardial depression, myocardial dysfunction after prolonged cardiopulmonary bypass, valvular heart disease, and hypertrophic obstructive cardiomyopathy. **(Table 1.3)** A summary of the randomised **SHOCK** trail **(*SH*ould we emergently revascularize of *O*ccluded *C*oronaries for shoc*K*),** which examined the benefit of early revascularization in 302 patients with cardiogenic shock secondary to acute myocardial infarction showed that the predominant cause of shock is left ventricular failure; 74.3% followed by acute, severe mitral regurgitation; 8.3%, ventricular septal rupture; 4.6%, isolated right ventricular shock; 3.4%, tamponade and rupture; 1.7% and other causes; 8%. It estimated that 55% of infarctions were anterior, 46% were inferior, 21% were posterior, and 50% were in multiple locations. [93] SHOCK trial showed that the median time from presentation with MI to cardiogenic shock is five hours. Angiographic evidence most often demonstrates multi-vessel coronary artery disease (left main occlusion in 29% of patients **(Figure 1.3)**, three-vessel disease in 58% of patients, two-vessel disease in 20% of patients, and one-vessel disease in 22% of patients). [94] Risk factors for developing cardiogenic shock include age > 75 years, female gender, history of hypertension, diabetes, previous acute coronary syndrome, multi-vessel coronary artery disease, presence of heart failure, low systolic blood pressure (SBP < 80 mmHg), and rapid heart rate (>100 beats/min). [95], [96], [97].

Table 1.3. Causes of cardiogenic shock and their sub-types.

Acute myocardial infarction	Loss of > 40% of myocardial mass	
	Loss of < 40% of myocardial mass with associated tachycardia	
	Mechanical defects	Acute ventricular septal rupture
		Papillary muscle rupture
		Chordal rupture
		Free wall rupture
Cardiomyopathy	Severe dilated cardiomyopathy	
	Hypertrophic cardiomyopathy	
Valvular disease	Aortic stenosis, Mitral stenosis, Aortic and mitral regurgitation, ascending aortic dissection, prosthetic valve dysfunction, obstruction by vegetation or thrombosis, valve trauma and iatrogenic.	
Pericardial disease	Cardiac tamponade	
Severe myocarditis		
Myocardial contusion		
Prolonged cardiopulmonary bypass		
Post cardiotomy shock		
Iatrogenic		

Table represent different causes of cardiogenic shock and their common sub-types. Adopted from Gowda M. R. Cardiogenic shock: Basics and clinical considerations. International Journal of Cardiology. 2008;123 (3):221-8.

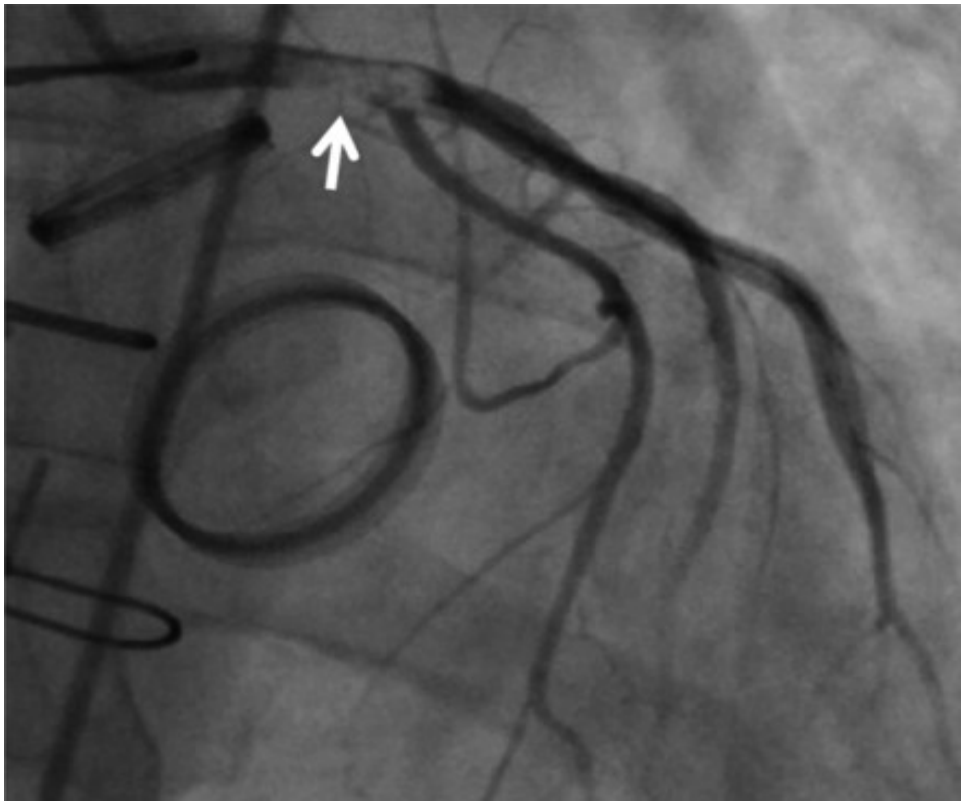


Figure 1.3. Coronary angiography revealed a large filling defect within the left main coronary artery of a patient presented with ST-elevation myocardial infarction and cardiogenic shock. Adopted from Jaffe R, et al. Left Main Coronary Artery Occlusion Due to Thrombus Embolization from a Prosthetic Mitral Valve. JACC. 2013; 6(7): 43-44.

Pathophysiology

Damage to myocardium most likely as a result of ischemia would lead to myocardial depression and ventricular dysfunction, which in turn results in reduced contractibility and catastrophic reduced cardiac output (CO). Multifactorial processes beyond cardiac function are implicated in CS. Chronic systolic heart failure patients express ventricular dilation to maximise stroke volume (SV) and CO through Frank-Starling forces. [98] This adaptive mechanism, however, does not occur acutely in patients with MI and CS. Low blood flow and reduced tissue hypoperfusion perpetuate adrenergic sympathetic system leading to peripheral vasoconstriction in order to maintain blood flow to vital organs and prevent cerebral and myocardial tissue death. The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in exacerbating CS via production of angiotensin II, which is a potent vasoconstrictor. Aldosterone release causes water and salt retention in an attempt to increase preload, LV filling, and CO. [99], [100] These responses increase myocardial workload, afterload, and preload, in addition to causing reduced coronary artery perfusion which culminates in myocardial stress and increased oxygen demand. These compensatory mechanisms subsequently worsen ischemia and are followed by pathological vasodilation as a

result of increased systemic inflammatory markers such as nitric oxide, interleukins and tumour necrosis factors. [28] The SHOCK trial showed that median systemic vascular resistance (SVR) in patients with CS and without suspected sepsis or systemic inflammatory response (SIRS) negative, was inappropriately low, suggesting involvement of other vasodilatory factors in pathophysiology of CS. Unless CS is not interrupted by adequate treatment strategy it continues to lead to significant hypoperfusion, multi-organ failure and death. [101]

Epidemiology

The incidence of cardiogenic shock is ~40 000 to 50 000 patients per year in the USA and ~60 000 to 70 000 in Europe. [102] Despite, advances in treatment and use of percutaneous coronary intervention or coronary artery bypass grafting, catecholamines, fluids, intra-aortic balloon pumping (IABP), and mechanical assist devices, the mortality of cardiogenic shock remains high and reaches 50%. [102] Approximately 5% to 8% of STEMI and 2% to 3% of Non-STEMI (NSTEMI) cases result in cardiogenic shock. [103]. Between 1997 and 2012 database of the Collège des Utilisateurs de Bases de données en Réanimation (CUB-Réa), which prospectively collects data from ICUs in the greater Paris area, identified 316,905 ICU admissions, from which 19416 (6.1%) exhibited CS, with incidence increasing from 4.1% to 7.7% ($P < 0.001$). [104] Among patients with myocardial infarction, shock is more likely to develop in those who are elderly, diabetic, have anterior infarction, or have a history of previous MI, peripheral vascular disease, and cerebrovascular disease. [105], [106], [107], [108]

1.4.4 Obstructive shock

Cox *et al*, defined obstructive shock as acute obstruction of blood flow in the cardiovascular system, which is characterised by impairment of diastolic filling or excessive afterload. [109] This obstruction results in reduced cardiac output and clinical symptoms and signs of shock.

Aetiology

The most common causes generally include tension pneumothorax, cardiac tamponade, and pulmonary embolism. Also included in this category, and more specific to paediatrics, are congenital heart diseases characterised by left ventricular outflow tract obstruction, including critical aortic stenosis, coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome. [109]

Pathophysiology and epidemiology

1.4.4.1 Tension pneumothorax

In tension pneumothorax (TP) complete collapse of lungs and great vessels occur as a result of pathological accumulation of air in the thoracic cavity. Tension pneumothorax acts as mechanical obstruction leading to profound reduction in venous return and cardiac output resulting in tissue hypoperfusion and death. [109] In 1997 Barton and colleagues described pathophysiology of pneumothorax in a ventilated swine model and showed that complete occlusive mechanical compression is suggested by equalisation of the Mean Intrathoracic Pressure (MIP) and Central Venous Pressure (CVP). Barton described this as a very late event the same as overt hypotension. [110] Early signs of respiratory collapse include respiratory distress, tachypnoea, and hypoxia. Pneumothorax can be primary or secondary to existing lung conditions such as trauma, asthma, cystic fibrosis, chronic obstructive respiratory disease, and pneumonia. [111] Pneumothorax only causes obstructive shock when it turns into tension pneumothorax. A radiographic analysis of 370 patient's chest X ray and high-resolution CT scans, showed incidence of 16.2% (60/370) with TP. In this study the diagnostic criteria for tension pneumothorax was defined as 1) hemodynamic compromise accompanied by tachycardia, tachypnoea, sweating, hypotension and pallor, 2) hemodynamic improvement and release of gas after tube thoracostomy, 3) mediastinal shifting including trachea deviation toward the opposite site of the pneumothorax, a pushed cardiac silhouette, crossing over the spine of air density,

compression, shifting of left cardiac border, and flattening of the diaphragmatic contour, 4) return of the shifted mediastinal structure after tube thoracostomy. [112]

1.4.4.2 Pulmonary embolism

A massive pulmonary embolism (PE) has a profound impact on gas exchange and haemodynamics. [109], **(Figure 1.5)** Obstruction to blood flow through the pulmonary artery results in increased dead space ventilation, where affected lung segments are ventilated but not perfused. Pulmonary embolism increases right ventricular (RV) afterload, resulting in an increase in RV end-diastolic volume (EDV). This affects left ventricular haemodynamics through ventricular interdependence. Increasing right heart pressures bows the interventricular septum into the left ventricle (LV) and impairs diastolic filling, resulting in decreased LV preload and subsequently diminished cardiac output, hypotension, and shock. [113], [114] In PE vasoconstriction, mediated by the release of thromboxane A2 and serotonin, contributes to increase in pulmonary vascular resistance (PVR). [115] Anatomical obstruction and hypoxic vasoconstriction in the affected lung area leads to further increase in PVR, and a proportional decrease in arterial compliance. This together with the obstructive effect of PE in circulation contributes to progressive right ventricular dilatation and failure as explained above. **(Figure 1.4)** Harjola *et al*, described the contemporary management of acute right failure and defined obstructive shock as acute obstruction of blood flow associated with presence of systolic BP < 90 mmHg or vasopressors required to achieve SBP ≥ 90 mmHg despite adequate filing status and end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate). [116], [117] PE can be primary (unprovoked) or secondary (provoked) as a result of reduced mobility, prolonged hospitalisation, recent trauma, surgical procedures, hormonal changes in pregnancy, use of oral contraception and hormone replacement therapy (HRT), thrombophilia and malignancy. [118] Annual incidence of PE is ranging from 53 - 162 per 100,000 population. [119], [120] Longitudinal studies have revealed a rising tendency in annual PE incidence rates over time. [121], [122] The diagnosis is often missed. British Lung Foundation reports that the annual incidence of diagnosed pulmonary embolism in the UK is 7– 8 per 10,000 people. Between 2008 and 2012, the number of people who died from pulmonary embolism decreased by 30%. There were 2,300 reported deaths from the condition in 2012 in the UK. Reason for this reduction is the implantation of solid thromboprophylaxis guidelines in high-risk patients admitted to hospitals. [123]

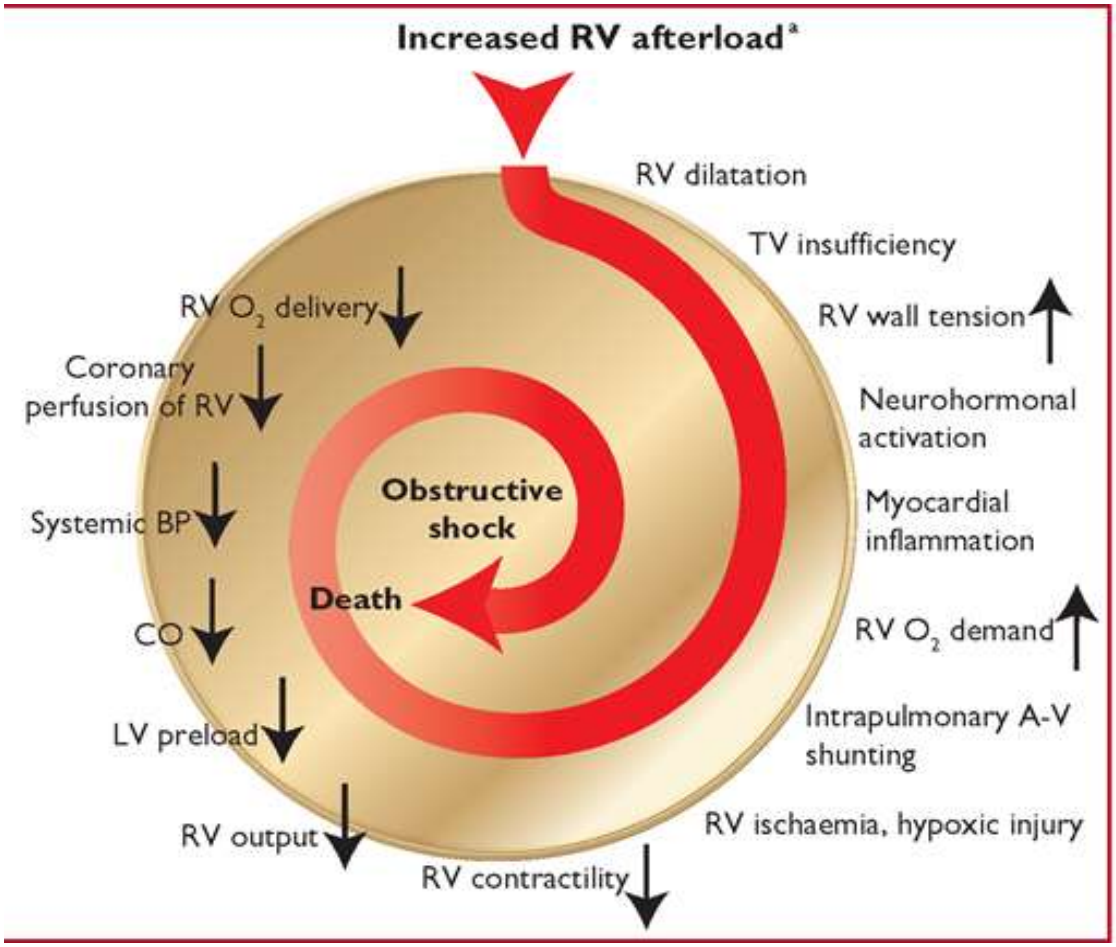


Figure 1.4. Haemodynamic compromise occurs in pulmonary embolism leading to obstructive shock. This is mainly caused by increased right ventricular afterload / strain which in turn affect contractibility and lead to drop in cardiac output**. Abbreviations:** RV: right ventricle, TV: tricuspid valve, LV: left ventricle, CO: cardiac output, A-V: atrio-ventricular. Adopted from ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): *European Heart Journal*.2014; 35(43), 3033 – 80.

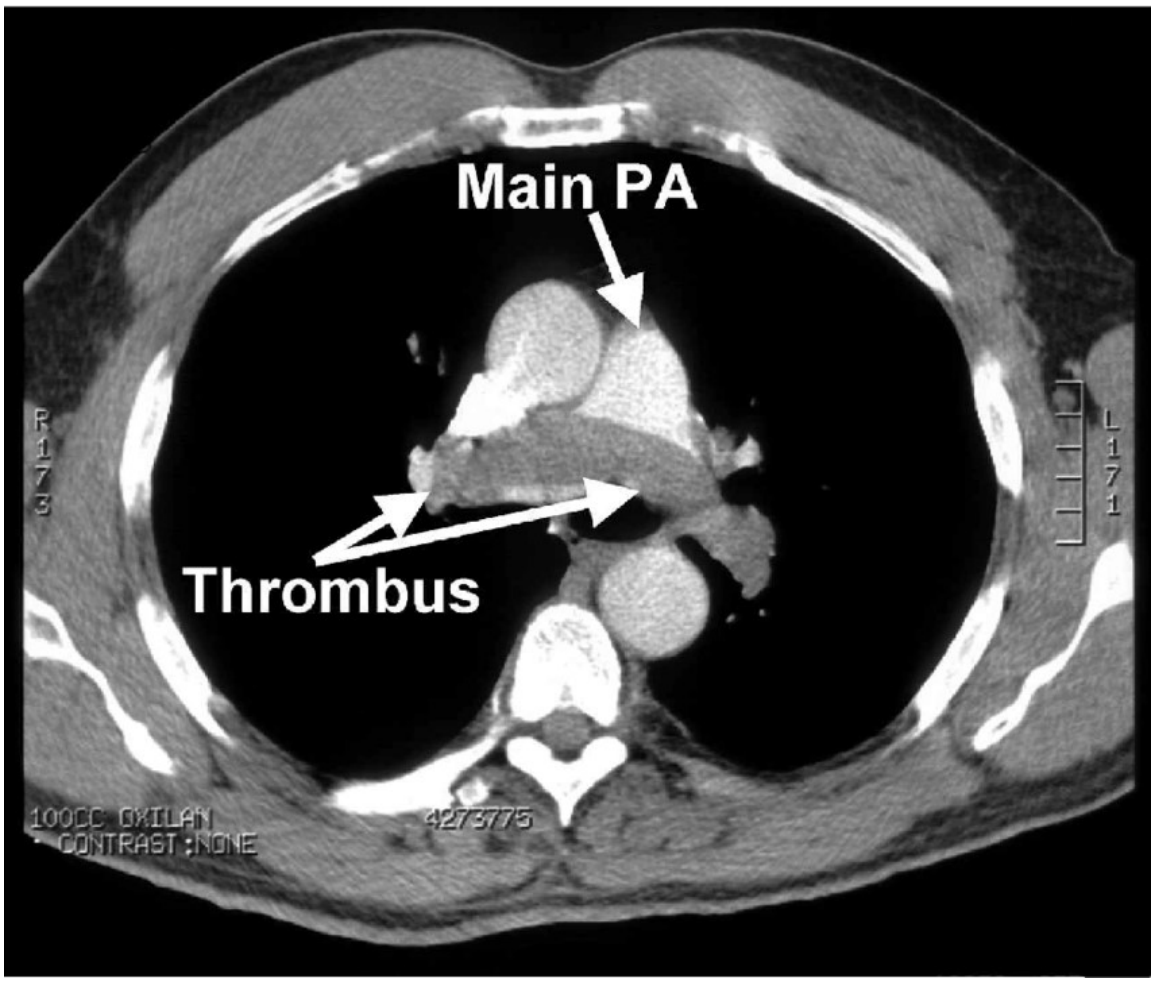


Figure 1.5. Axial CT scan image of massive pulmonary embolism. Large thrombus burden extents from body of main pulmonary artery into bifurcation and both left and right pulmonary arteries. **Abbreviations**: PA: Pulmonary artery. Adopted from Inonu H, Acu B. The value of the computed tomographic obstruction index in the identification of massive pulmonary thromboembolism. Diagn Interv Radiol 2012; 18:255 - 260.

1.4.4.3 Cardiac tamponade

The pericardial sac is non-compliant to even a small amount of fluid around the heart. In chronic pericardial effusion pericardium becomes more adapted and stretches itself to accommodate excess amounts of fluid over time and haemodynamic depression may not happen up to very late stages. [124] In cardiac tamponade increased intrapericardial pressure limits venous return to the heart and causes right ventricular compression. There is a progressive decline in right ventricular end-diastolic volume as diastolic filling lessens, worsening cardiac output similar to how tension pneumothorax leads to decline in cardiac output as a result of decreased ventricular volumes. [125] In progressive cardiac tamponade venous return to compressed right ventricle causes bowing of right ventricle to left and further decrease of cardiac output. Pericardial effusion can happen after pericardial inflammation, currently neoplastic and idiopathic causes are the most common recognised causes. Historically infective pericarditis was the most common cause of pericardial effusion. [125] Other causes include trauma, post pericardiotomy syndrome (post cardiac surgery) [126] and ventricular free wall rupture (VFWR). VFWR is a fatal and dramatic consequence of myocardial infarction and accounts for 15-30% of fatalities post MI. [127] It can cause sudden hemodynamic collapse, electromechanical dissociation, cardiac tamponade, obstructive shock and death. It is the second most common cause of death post MI after left ventricular failure. [127] According to the National Registry of Myocardial Infarction (NRMI), cardiac rupture accounts for a larger percentage of in-hospital mortality in patients undergoing thrombolytic therapy (12.1%) than in patients not receiving thrombolytic therapy (6.1%; *P value* < 0.001). [128] Diagnosis of cardiac tamponade is clinical. In 1988, Claude Beck, a resident and later Professor of Cardiovascular Surgery at Case Western Reserve University, developed a diagnostic criteria for diagnosing cardiac tamponade based on clinical signs. The criteria include presence of hypotension, quiet (“muffled”) heart sounds, and raised jugular venous pressure. [129] Other signs of shock such as dyspnoea, compensatory tachycardia and poor perfusion are normally present. Echocardiography is a well-recognised diagnostic tool to assist diagnosis of cardiac tamponade. The common signs of cardiac tamponade on echocardiogram are early diastolic collapse of the right atrium and ventricle, respiratory variation in Mitral and Tricuspid inflow, dilated, non-collapsing Inferior Vena Cava (IVC) and ventricular interdependence. [130] **(Figure 1.6)**

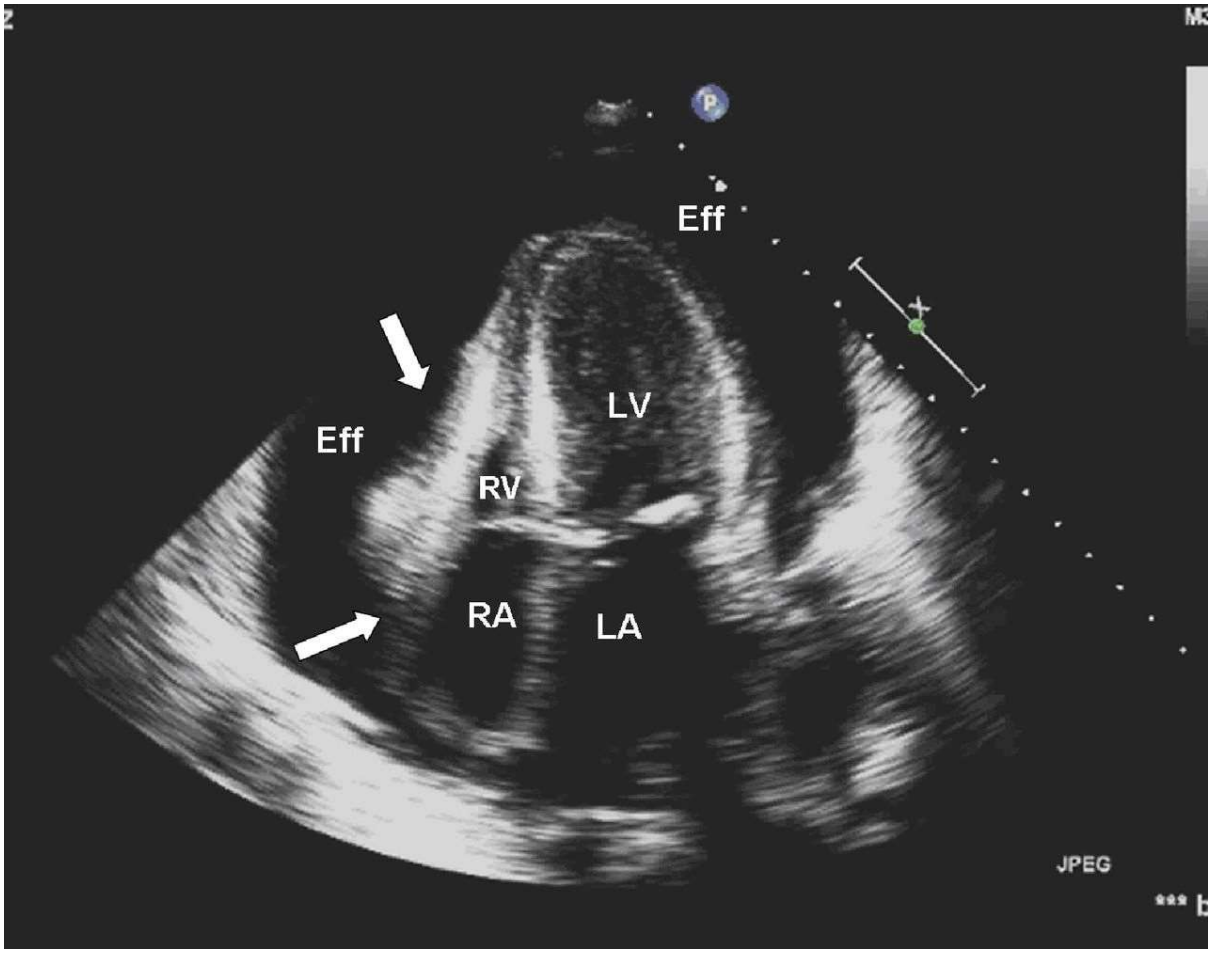


Figure 1.6. Pericardial Tamponade caused by large pericardial effusion which led to right sided chamber collapse on transthoracic echocardiogram, apical four chamber view. **Abbreviations:** Eff: effusion; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle. Adopted from Priscilla Peters, Cooper University Hospital, Camden, New Jersey.

1.5 Importance of diagnosing shock at early stages

Shock is a life-threatening emergency, which requires urgent and rapid assessment, diagnosis, and treatment. [21], [26], [27] Sepsis is the leading cause of in-hospital death, and the mortality of sepsis and septic shock exceeds 40 - 50 %. [131] The longer it takes to establish a diagnosis, the higher the chance of developing a more severe condition. Freitas *et al*, identified a strong relationship between the time required for first record of organ dysfunction and severe sepsis, and mortality associated with it. [132] Risk of death increased by 8.7- fold among patients who were identified 48 hours after organ dysfunction. [133] Several other pieces of evidence have demonstrated the importance of early diagnosis and treatment in reducing mortality among patients with severe sepsis or septic shock. [134], [135], [136] An analysis of the Survival Sepsis Campaign (SSC) impact in 2010 involved 15,022 patients from 165 hospital and revealed continuous and sustained improvements in compliance with early interventions, especially with antibiotic therapy (odds ratio - OR 0.70; *P* value < 0.001), and blood culture requests (OR: 0.78; *P* value < 0.001). This led to a reduction in the mortality rate associated with severe sepsis or septic shock from 30.8% to 27% (*P* value < 0.01). [137] Advanced understanding of shock and protocol-driven care has reduced in-hospital mortality for septic shock from 50% to 10%. [138], [139], [140], [141], [142] However, optimal survival rates are rare, and the rapid evaluation, diagnosis of type, and severity categorisation of shock in critically ill patients in the ED is at best moderate, and often difficult. [143] Although, diagnosis of shock is often obscured during ED evaluation, improved recognition would help practitioners anticipate patients who may require more aggressive interventions or a higher level of care at disposition.

1.6 Shock diagnostic tools and scoring systems / concept of SEPSIS-1, 2, 3

Many factors correlate strongly with the likelihood, severity of shock, and clinical outcomes such as intensive care unit (ICU) admission and early mortality. [143], [144] Hypotension, elevated lactate, [145], Base deficit, [146] acidosis [147] and oxygen delivery [148] all correlate with shock. Many of these biomarkers are readily available in modern EDs. [149], [150], [151], [152] Several methods and diagnostic criteria including Systemic Inflammatory Response Syndrome (SIRS), Early Warning Scores (EWS), National early Warning (NEWS), Modified Early Warning Score (MEWS) and more recently Sequential Organ Failure Assessment (SOFA) and quick Sequential Organ Failure Assessment (qSOFA) have been introduced and used over the years to identify shock at early stages and guide treatment strategies. These scores have been compared retrospectively for detecting clinical deterioration in shocked patients. Here is a summary of diagnostic shock tools and international consensus definitions for sepsis and septic shock.

1.6.1 Systemic Inflammatory Response Syndrome (SIRS); concept of Sepsis-1 and 2

The concept of a systemic inflammatory response syndrome (SIRS) is to describe the complex pathophysiology response to an insult such as infection, trauma, burns, pancreatitis, etc. The earliest sepsis definition, Sepsis-1 came from an American College of Chest Physicians/Society of Critical Care Medicine-sponsored sepsis definitions consensus conference held in Chicago in August 1991. [153] It was clear that there is lack of clarity in the clinical definition of sepsis and there was significant ambiguity in medical literature at the time. [154], [155], [156] Improved understanding of complex physiology and systemic inflammatory response gave birth to the definition of sepsis. Most researchers recognised interruption of inflammatory pathways as a way of improving clinical outcome and mortality. The driving point behind the 1991 consensus was to improve trial design coupled with adding clarity to the existing literature which was full of varied definitions of sepsis and septic shock, by using readily and rapidly available clinical and laboratory parameters. [157] The common early clinical manifestations seen in septic patients such as fever, mental status changes, tachypnoea, tachycardia, hypotension, leukocytosis, thrombocytopenia, and coagulation abnormalities were considered for inclusion in the definition. [158], [159] Based on experience with previous clinical trial design in sepsis four SIRS criteria were defined, namely tachycardia (heart rate > 90 beats/min), tachypnea (respiratory rate > 20 breaths/min), fever or hypothermia (temperature > 38 or < 36 °C), and leukocytosis, leukopenia, or bandemia (white blood cells > 1,200/mm^3, < 4,000/mm^3 or bandemia ≥ 10%). **(Table 1.4)** Patients who met two or more of these criteria fulfilled the definition of **SIRS**, and **Sepsis-1** was defined as infection or suspected infection leading to the onset of SIRS. Sepsis complicated by organ dysfunction was termed **severe sepsis**,

which could progress to **septic shock**, defined as “sepsis-induced hypotension persisting despite adequate fluid resuscitation.” The decision to require 2 of the 4 criteria to identify sepsis was based on an evaluation of the diagnostic sensitivity of using 2, 3, or 4 of the criteria in the acute physiology and chronic health evaluation (APACHE) database to identify those individuals with a clinical diagnosis of sepsis. Using 2 of the 4 criteria produced the highest sensitivity tool for identifying septic patients. SIRS criteria was validated and appeared to function well in large prospective, randomized, double-blind, placebo-controlled clinical trials such as the trial of high-dose methylprednisolone sodium succinate for severe sepsis and septic shock, run by Bone and colleagues. [160] Also in 1995, Rangel-Frausto *et al,* studied 3708 patients admitted to the intensive care unit of University Hospital of Iowa and showed that there is a relation between an increase in number of SIRS criteria that were present as a patient moved along a continuum from sepsis to severe sepsis and to septic shock. There was also an increase in associated mortality rate. [161] The major benefit of SIRS criteria was unity in inclusion and exclusion criteria of clinical trials over a couple of decades. It also improved discussions in literature, medical meetings and daily rounds. However, the international consensus was aware of potential weaknesses of SIRS criteria; firstly, despite high sensitivity it lacked specificity. SIRS includes all potential patients with a pro-inflammatory response. The definition does not differentiate between the normal beneficial host response from a pathologic host response that produces organ dysfunction and there is difficulty determining the role of infection in this inflammatory response. [162] In 2001, Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM) and the American Thoracic Society and the Surgical Infection Society (the ACCP) held the second consensus meeting and updated the criteria for sepsis, recognising the limitations of sepsis-1. [163] They expanded the list of diagnostic criteria, resulting in the introduction of **Sepsis-2**. The documented or suspected infection-specific findings were categorised as general, inflammatory, haemodynamic and organ dysfunction, tissue perfusion variations, biochemical indicators were considered and their roles in early diagnosis were emphasised in the updated document. [163] The conference kept the old diagnostic criteria of sepsis in use but redefined sepsis as a clinical syndrome combined with organ injury. [164] Therefore, in order to be diagnosed with sepsis under the sepsis-2 definition, as with the sepsis-1, an individual must have at least two of SIRS criteria a confirmed or suspected source of infection. [163], [165]

Table 1.4. Systemic inflammatory Response Syndrome (SIRS) criteria.

SIRS is defined when two or more of the following is present:	Temperature > 38 C or < 36 C
	Heart rate > 90 beats per minute (bpm)
	Respiratory rate > 20 breaths per minute or PaCO2 < 4.3 kPa
	White cell counts > 12,000 cells / mm3, < 4,000 cells / mm3
SEPSIS	SIRS plus documented site of infection
SEVERE SEPSIS	SEPSIS associated with organ dysfunction, hypoperfusion or hypotension (SEPTIC SHOCK)

Patients who have two or more of the criteria fulfil the definition of SIRS. Sepsis is defined as SIRS plus documented site of infection and septic is a combination of shock sepsis and organ dysfunction. **Abbreviations**: kPa: kilopascal, mm3: cubic millimeter, PaCO2: Partial pressure of carbon dioxide, SIRS: systemic inflammatory response syndrome. Adopted from Bone C R et al, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. 1992.

1.6.2 (Quick) Sequential Organ Failure Assessment (SOFA, qSOFA); concept of Sepsis 3:

After new advances in sepsis epidemiology and management, in January 2014 an international task force with 19 participants was convened by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) to re-examine the current sepsis and septic shock definitions. Members were selected as per their expertise in sepsis epidemiology and trials. The groups engaged in face-to-face meetings, email correspondence and voting. A systemic literature review and Delphi method *[1] was performed to reach the correct response through consensus. To begin with, the task force recognised that sepsis is a syndrome and there is no unified diagnostic tool. Hence, they decided to use definitions and supportive clinical criteria, which are clear and fulfilled multiple domains of usefulness and validity. As per **Sepsis-3,** sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. [165], [166] The clinical criteria for sepsis include suspected or documented infection and an acute increase in two or more of Sequential Organ Failure Assessment (SOFA) points as a proxy for organ dysfunction. There are multiple scoring systems for assessing organ dysfunction. SOFA score was initially formed in 1994 during a consensus conference organized by the European Society of Intensive Care and Emergency Medicine, to provide a means to objectively assess organ dysfunction in septic patients. [167] It was later understood that it can be used in non-septic patients. The score includes six body systems; respiratory, coagulation, hepatic, cardiovascular, central nervous system, and renal. **(Table 1.5)** The baseline SOFA score should be assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection. Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population. Depending on a patient's baseline level of risk, a SOFA score of 2 or greater identified a 2- to 25-fold increased risk of dying compared with patients with a SOFA score less than 2. [168] Task force aimed to identify best clinical criteria able to identify infected patients with sepsis. Seymour *et al*, tested the predictive validity of SOFA and compared it to SIRS. They studied 1.3 million patients at 12 community and academic hospitals within the University of Pittsburgh Medical Centre health system in southwestern Pennsylvania. Predictive validity of SIRS was compared to SOFA against mortality and ICU admission of three days or longer. For infected patients both inside and outside of the ICU, predictive validity was determined with 2 metrics for each criterion: the area under the receiver operating characteristic curve (AUROC) and the change in outcomes comparing patients with a score of either 2 points or more or fewer than 2 points in the different scoring systems. [167], [169], [170] In ICU patients with suspected infection discrimination for hospital mortality with SOFA (AUROC = 0.74; 95% CI, 0.73 – 0.76) was superior to that with SIRS (AUROC = 0.64; 95% CI, 0.62 – 0.66). The predictive validity of a

* The Delphi method is a forecasting process framework based on the results of multiple rounds of questionnaires sent to a panel of experts. Several rounds of questionnaires are sent out to the group of experts, and the anonymous responses are aggregated and shared with the group after each round. The experts are allowed to adjust their answers in subsequent rounds, based on how they interpret the "group response" that has been provided to them. Since multiple rounds of questions are asked and the panel is told what the group thinks as a whole, the Delphi method seeks to reach the correct response through consensus.

change in SOFA score of 2 or greater was similar (AUROC = 0.72; 95% CI, 0.70 – 0.73). For patients outside the ICU and with suspected infection, discrimination of hospital mortality with SOFA (AUROC = 0.79; 95% CI, 0.78 – 0.80) or change in SOFA score (AUROC = 0.79; 95% CI, 0.78 – 0.79) was similar to that with SIRS (AUROC = 0.76; 95% CI, 0.75 – 0.77). The main disadvantage of SOFA is that its components require advanced laboratory testing and are not promptly available. The score is also not familiar to clinicians outside ICU environments. [169] The task force provided a simple criterion labelled as qSOFA (quick Sequential Organ Assessment Score) with similar predictive validity to SOFA (*P* value*:* 0.55). qSOFA is a simple bedside tool incorporating altered mentation, systolic blood pressure of 100 mmHg or less, and respiratory rate of 22/min or greater, able to identify adult patients with infection. The task force suggested use of qSOFA criteria to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate treatment and to consider referral to critical care. [171] **(Table 1.6)**

In 2001, Levy *et al*, described shock as the state of circulatory failure. [171], [172] A task force led by Shankar-Hari *et al*, in 2016 [172] ran a systematic review and Delphi process to update the septic shock definition. The majority of members voted on considering “hypotension”, “need for vasopressor therapy”, “raised lactate,” and “adequate fluid resuscitation” for inclusion within the new clinical criteria. 14/17; 82.4% of members voted to consider mean arterial pressure (MAP) of less than 65mmHg as hypotension. A majority (11/17; 64.7%) of the task force agreed, whereas 2 (11.8%) disagreed, that an elevated lactate level is reflective of cellular dysfunction in sepsis, albeit recognising that multiple factors, such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance, also contribute. [173] Hyperlactatemia is, however, a reasonable marker of illness severity, with higher levels predictive of higher mortality. [174] Criteria for “adequate fluid resuscitation” or “need for vasopressor therapy” could not be explicitly specified because these are highly user dependent. In order to test validity of selected parameters database from the Surviving Sepsis Campaign’s international multi-centre registry of 28,150 infected patients with at least 2 SIRS criteria and at least 1 organ dysfunction criterion was reviewed. A total of 18,840 patients were identified with hypotension, needing vasopressor therapy with Lactate of more than 2 mmol/L. The results showed that the combination of hypotension, vasopressor use, and lactate level greater than 2 mmol/L (18 mg/dL) identified patients with **mortality rates of 54%** at University of Pittsburgh Medical Centre (n = 315) and **35%** at Kaiser Permanente Northern California (n = 8051). These rates were **higher** than the mortality rates of **25.2%** (n = 147) and **18.8%** (n = 3094) in patients with **hypotension alone, 17.9%** (n = 1978) and **6.8%** (n = 30 209) in patients with **lactate level greater than 2 mmol/L** (18 mg/dL) alone, and **20%** (n = 5984) and **8%** (n = 54,135) in patients with sepsis at University of Pittsburgh Medical Centre and Kaiser Permanente Northern California, respectively. [170] Lactate levels are not easily available in developing countries and this was recognized by task force members. Nonetheless, hypotension and hyperlactatemia were recognised as the criteria for septic shock rather than either alone.

In summary, the 2016 task force summarised the outcome of their research as:

1. Sepsis is a broad syndrome, encompassing clinical symptoms and signs and there is no clinical criterion to identify a septic patient. Hence, pragmatic tools are necessary to emphasis on readily measurable identifiers that could capture sepsis.
2. The retrospective analysis showed that qSOFA could be a useful tool to doctors outside ICU or out of hospital to identify infected patients who are likely to have poor outcome and organ dysfunction at early stages and when laboratory tests are not yet available.
3. Conflicting opinions exist around approaches to hyperlactatemia. As per Kraut JA *et al*, [177] Lactate level is a sensitive, albeit nonspecific, stand-alone indicator of cellular or metabolic stress rather than “shock. Combination of high Lactate and hypotension identifies a separate group of septic shock with high mortality. In settings in which lactate measurement is not available, the use of a working diagnosis of septic shock using hypotension and other criteria consistent with tissue hypoperfusion (eg, delayed capillary refill) may be necessary. [173]
4. Finally, the task force identified the need for similar tools in the pediatric population taking into consideration physiological variations. The process remains a work in progress.

Table 1.5. Sequential Organ Failure Assessment Score (SOFA).

VARIABLES	SCORES				
	0	1	2	3	4
Respiratory	PaO2 / FiO2 >400 SpO2 / FiO2 > 302	PaO2 / FiO2 < 400 SpO2 / FiO2 < 302	PaO2 / FiO2 < 300 SpO2 / FiO2 < 221	PaO2 / FiO2 < 200 SpO2 / FiO2 < 142	PaO2/ FiO2 < 200 SpO2 / FiO2 < 142
Cardiovascular (Doses in mcg/kg/min)	MAP 70 mmHg	MAP ≥ 70 mmHg	Dopamine < + 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (Bilirubin, mg/dL)	< 1.2	1.2 - 1.9	2.0 - 5.9	6.0 - 11.9	> 12
Renal (Creatinine, mg/dL)	< 1.2	1.2 - 1.9	2.0 - 3.4	3.5 -4.9	> 5.0
Coagulation (Platelets x 10^3 / mm^3)	≥ 150	< 150	< 100	< 50	< 20
Neurology (GCS score)	15	13 - 14	10 - 12	6 - 9	< 6

A new increase in SOFA score above the baseline in presence of infection makes the diagnosis of sepsis and increasing SOFA scores is indicative of increased mortality. All catecholamine doses are in presented in uq/kg/min. Organ dysfunction is defined as an increase in SOFA score ≥ 2 points. In patients with no organ dysfunction the assumed score would be zero. **Abbreviations:** GCS: Glasgow Coma Score, FiO2: Fraction of inspired oxygen, MAP: Mean Arterial Pressure, PaO2: Arterial oxygen pressure, SOFA: Sequential Organ Failure (assessment) Score; SpO2: Oxygen saturation. Adopted from Vincent JL, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units. 1998.

Table 1.6. quick Sequential Organ Failure Assessment Score (qSOFA).

Diagnostic criteria	Each diagnostic criterion gets a score of 1
Respiratory	Respiratory Rate (RR) > 22 bpm
Circulation	Systolic Blood Pressure (sBP) < 100 mmHg
Neurology / Mental Status	Altered Glasgow Coma Score (GCS) ≥ 2

Presence of each of these criteria will take a score of 1 and it has been shown that a score of 0 correlates with a mortality of < 1%, score of 1 correlates with mortality of 2-3% and a score of ≥ 2 correlates with a mortality of ≥ 10%. **Abbreviations**: GCS: Glasgow Coma Scale, RR: respiratory rate, sBP: systolic blood pressure. Adopted from Seymour CW, et al. Assessment of clinical criteria for sepsis. 2016.

1.6.3 Early Warning Scores (EWS)

Early warning scores (EWS) are tools used to identify patients with the potential for clinical deterioration or with an established critical illness. An EWS is a derived parameter based on data from physiological readings (e.g., systolic blood pressure, heart rate, respiratory rate, body temperature) and observations (e.g., level of consciousness [AVPU]). Determining an EWS involves assigning a number between 0 and 3 to each of the vital signs and observations, based on how far the parameter value (or observation) is from normal ranges. The sum of the scores of the different parameters yields the patient's total EWS. The higher the EWS, the more serious the patient's condition. [175], [176] Several hundred unique yet similar EWS are in use worldwide. Below is a summary of National Early Warning Score (NEWS) and Modifies Early Warning Score (MEWS).

1.6.3.1 Modified Early Warning Score (MEWS)

In 1997, Morgan *et al*, introduced the EWS score to enable early detection of patient abnormalities using major vital signs prior to deterioration into a critical illness and to secure the timely presence of skilled clinical help by the bedside of those patients exhibiting physiological signs compatible with established or impending critical illness. [177] [178] The original EWS was not presented as a predictor of outcome. In 2000, Stenhouse *et al*, [179] proposed a modified EWS (MEWS) score, which uses modified physiological parameters for scoring, such as temperature, respiratory rate, heart rate, and systolic blood pressure, as well as nursing assessments of mental status or consciousness levels of the patient, and hourly urine output. **(Table 1.7)** The score was evaluated in 206 surgical patients over nine months against the primary outcome of admission to ICU or HDU at West Suffolk Hospital. The sensitivity of the MEWS used with a threshold score of four was 75% for ICU or HDU admission and specificity was 83%. The purpose of the MEWS is to facilitate prompt communication between nursing and medical staff when deterioration in a condition of a ward patient first becomes apparent on the observations chart. The authors intended this system to result in earlier intervention on the ward so that transfer to a critical care facility was either prevented or occurred without unnecessary delay. [179] A number of recent studies have validated the use of MEWS in a variety of patient populations and have indicated that using MEWS as a referral tool can lead to reduced ICU admissions and length of hospitalisation. [180], [181], [182] Evidence also suggests that MEWS is predictive of in-hospital mortality, with higher MEWS values (typically ≥ 4) predictive of increased risk of death. [183] The UK-based Intensive Care Outreach Services found that summarising abnormal physiology into MEWS was a particularly useful tool

in identifying medical patients in need of ICU admission. [184] Burch *et al*, demonstrated the utility of MEWS as a triage tool for medical emergencies seen in emergency department settings where resource and personnel constraints limit the use of more complex triage systems. [185] In addition to general medical and surgical patient populations, MEWS also has been validated in patients with upper gastrointestinal bleeding, [186] cancer, [182] sepsis, [187] and in prehospital patients. [188] In a large prospective study in 2010, Mitchell *et al*, reported that the introduction of a multifaceted intervention to detect clinical deterioration, including MEWS, led to reductions in unplanned ICU admissions (0.5 vs. 1.8%, *P* value = 0.0006) and deaths (0.2 vs. 1.0%, *P* value = 0.03) along with improved vital signs documentation and increased medical reviews. [189]

Table 1.7. Modified Early Warning Score (MEWS).

Physiological Parameters	SCORES						
	3	2	1	0	1	2	3
Respiratory Rate		Less than 8		9 - 14	15 - 20	21 - 29	>30
Heart Rate		Less than 40	40 - 50	51 - 100	101 - 110	111 - 129	>129
Systolic Blood Pressure	Less than 70	71 - 80	81 - 100	101 - 199		>200	
Conscious level (AVPU)	Unresponsive	Response to Pain	Responsive to Voice	Alert	New agitation/ confusion		

MEWS is predictive of in-hospital mortality, with higher MEWS values (typically ≥ 4) predictive of increased risk of death. The scoring system is based on values of respiratory rate, heart rate, systolic blood pressure and conscious level. **Abbreviations:** AVPU: Awake Verbal Pain Unresponsiveness. Adopted from Subbe CP, et al. Validation of Early Warning Score in Medical Admissions. 2001.

1.6.3.2 National early Warning Score; NEWS

In 2007, the Acute Medicine Task Force of the Royal College of Physicians (RCP) recognised a key weakness in current practise which was the lack of standardised EWS scoring across the National Health Service (NHS), having significant implications for patient's safety. This led to publishing recommendations for the development of a National Early Warning Score (NEWS) as a standardised system throughout the NHS at all stages in the acute medicine pathway. Similar to other EWS scores, NEWS was developed to facilitate early detection of deterioration by categorising a patient's severity of illness and prompting nursing staff to request a medical review at specific trigger points. [190] The purpose was to utilise a structured communication tool while following a definitive escalation plan, to standardise the assessment of acute illness, and to enable a more timely response using a common language across acute hospitals nationally. The National Clinical Guideline applies to all adult patients in acute state attending Acute Medical Unit (AMU), all patients attending initial assessment for invasive procedures and in assessments of adult patients out of hospital settings. To establish a NEWS score, it requires allocation of a number between 0 to 3 to each physiological parameter, including respiratory rate, oxygen saturations, temperature, systolic blood pressure, pulse rate and level of consciousness. In addition, a score of 2 should be added for any patient requiring supplemental oxygen (oxygen delivery by mask or nasal cannula) and the sum of scores would represent the patient total NEWS score. The selection of physiological parameters was based on expert opinion and shared information from a previously developed EWS; new paper-based EWS – VitalPAC™ EWS (ViEWS) score. [191] To facilitate standardisation and to provide both visual and numeric prompts to aid identification of abnormal clinical parameters, NHS organisation are now using colour-coded clinical charts to record patient scores. **(Table 1.8)** It provides guidance and recommendations for early assessment and medical attentions to various groups of health-care professionals such as allied health care professionals, nurses, and doctors. NEWS provides a unified approach for the first assessment of acutely ill patients and further monitoring of clinical progress. All NHS staff recording data or responding to NEWS should be trained in how to use NEWS score and how to interpret the total score. As per recommendation by Royal College of Physicians (RCP); a low score is an aggregate NEWS score of 1–4, a medium score is an aggregate score of 5 or more, or a RED score, i.e., an extreme variation in an individual physiological parameter (a score of 3 in any one parameter which is colour-coded RED on the observation chart) and a high score is an aggregate NEW score of 7 or more. **(Table 1.9)** The evaluation of the trigger thresholds for NEWS is based on database analysis of data collected over a period of a year by the Portsmouth Hospitals NHS Trust. This analysis determined the percentage of measurement sets that triggered a response at different aggregate trigger levels for both NEWS and a typical Modified Early Warning Score (MEWS). [191] This analysis was undertaken in acute medical unit (AMU) (81,010 observation sets from 12,476 patients), medical wards (283,288 observation sets from 8,937 patients) and in

surgical wards (197,715 observations set from 7,801 patients). Initially the trigger for medium alert was set as score of 4, in the AMU this would trigger 28% of the time for NEWS and only 10% for MEWS. In the medical wards this would trigger 27% for NEWS and 8% for MEWS, in the surgical wards 16% for NEWS and 3% for MEWS. It was apparent that the NEWS aggregate score was a much more sensitive trigger than most other EWS systems. The NEWS trigger was then set as score of 5 and the results indicated that a NEWS aggregate a score of 5 would trigger for approximately 20% of data sets in AMU or medical wards and 10% in surgical wards. Thus, NEWS triggering at an aggregate **score of 5** was still **more sensitive** than atypical MEWS trigger system currently in use and set to trigger at 4, but crucially also **more specific** at detecting acute clinical deterioration as indicated by the AUROC. The task force then concluded that a NEWS aggregate score of 5 would prompt earlier clinical review of patients with acute illness in hospital. The same analysis indicated that when the trigger for a high-level alert was set at an aggregate **NEW score of 7**, almost 10% of data sets would prompt an alert on AMU or medical wards and roughly 4% on surgical wards. [191] NEWS not only guides recommendation on urgency but also competency of clinical response as well as the most appropriate environment for care of a sick patient. A low score should prompt assessment by a competent registered nurse who should decide if a change to frequency of clinical monitoring or an escalation of clinical care is required. A medium score should prompt an urgent review by a clinician skilled with competencies in the assessment of acute illness, usually a ward-based doctor or acute team nurse, who should consider whether escalation of care to a team with critical-care skills is required such as critical care outreach team. A high score should prompt emergency assessment by a clinical team/critical care outreach team with critical-care competencies and usually transfer of the patient to a higher dependency care area. [190] In 2007, NICE published guidance, recommending a minimum frequency of 12-hourly monitoring. This was considered for the monitoring of small groups of patients, however with more frequent monitoring; 6 hourlies were recommended for patients with acute illness. [192] The task force recognised the need for more frequent monitoring and recommend that for those in the low-score group, the minimum frequency of monitoring should be 12 hourly, increasing to 4–6 hourly for NEWS aggregate scores of 1–4 and a minimum of every hour for those patients with a NEWS aggregate score of 5–6, or a RED score of 3 in a single parameter. Whilst any patient can be considered for continuous monitoring, it is essential for patients with a score of 7 or more. [192] **(Table 1.10)** Further validation of NEWS score is challenging as there is no national or international gold standard EWS system. Furthermore, establishing an outcome measure is difficult because NEWS is used both in initial severity assessment of acutely ill patients and as a track-and-trigger to identify acute clinical deterioration and response. The performance of paper-based EWS – VitalPAC™ EWS (ViEW), introduced by Smith and colleagues at Portsmouth Hospitals NHS Trust, was tested against other EWS scores. The aim was to use it as a template for a national early warning score (NEWS) for the detection of patient deterioration. This data base comprised 198,755 data sets from 35,585 completed and consecutive patient episodes at a medical assessment unit. [191] The primary outcome for the analysis was death within 24 hours of a given observation set. This occurred in 1,999 patients (1% of male and 1% of female patients) and overall, 3,133

of the 35,585 (8.8%) of patient episodes ended in death. The ability of NEWS to discriminate between survivors and non-survivors was assessed using an area under the receiver-operating characteristics (AUROC). Using in-hospital mortality within 24 hours of assessment as the outcome, the AUROC for the NEWS was 0.89 (95% CI: 0.880 –0.895). This was a better performance than most existing EWS systems and consistent with the good performance of ViEWS. [191] A key difference between ViEWS and NEWS is that NEWS allows a trigger RED score of 3 for single extreme values of any physiological parameter, rather than solely based on an aggregate score. Hence, this study can be used as an assessment of strength of NEWS score in predicting deterioration and poor outcome. The decision to trigger on the basis of single extreme values was based on the clinical opinion of the group linked to patient safety and clinical governance.

Summary of recommendations on how to use NEWS score

The news score is not validated to be used in children aged less than 16 years old and pregnant women, whose physiological response to acute illness is different. Furthermore, chronically disturbed physiology in patients with chronic obstructive respiratory disease (COPD) should be considered in interpreting NEWS score. Although NEWS is a guide for clinical assessment but it should not be used as a susbstitute for clinical judgement. For patients whose continuous documentation of NEWS score is not appropriate, such as patients on the end of life pathway, the decision should be discussed with the patient and family and should be clearly documented in clinical notes before use of NEWS chart is discontinued. [190]

Table 1.8. National Early Warning Score (NEWS).

Physiological Parameters	SCORES						
	3	2	1	0	1	2	3
Respiratory Rate (RR)	< 8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturation	<91	92 – 93	94 – 95	≥ 96			
Supplemental Oxygen		YES		NO			
Temperature	≤ 35		35.1 -36	36.1 - 38	38.1 -39	≥ 39	
Systolic Blood pressure (sBP)	< 90	91 – 100	101 - 110	111- 219			≥ 220
Heart rate (HR)	≤ 40		41 - 50	51 - 90	91 - 110	111-130	≥ 130
Level of consciousness				A			V, P or U

Standardized NEWS system across NHS in order to drive the “The step change” required in assessment and response to acute illness. **Abbreviations:** AVPU: The AVPU scale (an acronym from "alert, verbal, pain, unresponsive") is a system by which a health care professional can measure and record a patient's level of consciousness. It is mostly used in emergency medicine protocols. HR: heart rate, RR: respiratory rate, sBP: systolic blood pressure. Adopted from Royal College of Physicians, 2012.

Table 1.9. Interpretation of NEWS score.

NEWS SCORE	RISK
0 – 2	
3 – 5	3: THREAT Patient has acute illness or deterioration of chronic illness
6 – 8	6: SICK Patient is likely to deteriorate rapidly
9	9: NOW Patient has immediate life-threatening illness

Score of 3 - 5 is associated with acute illness or deterioration of chronic illness, score of 6 - 8 is related to likelihood of rapid deterioration and patients with a score of 9 and above are at risk of an immediate life-threatening event. Adopted from NHS early Warning Score Wales, 2013. http://www.1000livesplus.wales.nhs.uk.

Table 1.10. Clinical response to NEWS trigger thresholds.

NEWS score	Frequency of monitoring	Clinical response
0	Minimum 12 hourly	Continue routine NEWS monitoring
1- 4	Minimum 4-6 hourly	- Inform registered nurse to review - Registered nurse to decide on frequency of monitoring and / or escalation if required
≥ 5	Increased frequency to minimum of 1 hourly	- Registered nurse to inform clinical team to review the patient urgently - Urgent review by clinical team who have capacity to manage critically ill patient - Patient to be looked after in environment with monitoring capacity
≥ 7	Continuous monitoring of vital signs	- Registered nurse to inform registrar to review the patient urgently - Emergency review by clinical team who has critical care capacities including advanced airway skills - Consider transfer to critical care; ITU/HDU for level 2, 3 care

NEWS should not replace clinical judgment in deteriorating patients. If a patient is deemed to be unwell despite a low NEWS score, they should be escalated; Examples: cold, clammy patients or those with low urine output. **Abbreviations:** ITU/HDU: intensive care unit / high dependency care unit, NEWS: National early warning score. Adopted from NEWS 2, 2017. National Early Warning Score (NEWS) 2 | RCP London.

1.7 Comparison of different shock tools

A head-to-head comparison of qSOFA and SIRS in predicting mortality

A meta-analysis of 8 studies by Jangi *et al,* included 52,849 patients and showed that a qSOFA score ≥ 2 was associated with a higher risk of mortality in ED patients with infections, with a pooled risk ratio (RR) of 4.55 (95% CI: 3.38 - 6.14) using a random-effects model ($I^2 = 91.1\%$). A SIRS score ≥ 2 was a prognostic marker of mortality in ED patients with infections, with a pooled RR of 2.75 (95% CI: 1.96 - 3.86) using a random-effects model ($I^2 = 89\%$). When comparing the performance of qSOFA and SIRS in predicting mortality, a qSOFA score ≥ 2 was more specific; however, a SIRS score ≥ 2 was more sensitive. The initial qSOFA values were of limited prognostic value in ED patients with infections. The group also stated that qSOFA was a better predictor of mortality than SIRS and recommended using qSOFA ≥ 2 instead of SIRS ≥ 2, to identify infected patients at high risk of death. [193]

A Comparison of qSOFA and SOFA score in predicting mortality in severe sepsis

Akbar Biag *et al*, in a prospective, cohort study of 760 adult patients presented to the emergency department of a middle-income country (Turkey) compared the ability of SOFA vs qSOFA score in predicting in hospital mortality in severe sepsis and septic shock. In patients with severe sepsis, the AUROC of qSOFA for predicting mortality was 0.92 (95%CI; 0.89 – 0.94) with 96% sensitivity and 87% specificity in comparison to the AUROC of SOFA score which was 0.63 (95%CI; 0.55 – 0.70), with 71% sensitivity and 57% specificity. In patients with septic shock, the area under the receiver curve (AUROC) of qSOFA for predicting mortality in subjects was 0.89 (95%CI; 0.85 – 0.92) with 92% sensitivity and 85% specificity in comparison to the AUROC of SOFA score which was 0.63 (95%CI; 0.55 – 0.70 with 70% sensitivity and 59% specificity. This study concluded that qSOFA score is an effective tool in predicting in-hospital mortality in comparison to SOFA score when applied to severe sepsis and septic shock patients. [194]

A Comparison of qSOFA, SIRS and NEWS in predicting in hospital mortality and ICU admissions

In 2018, a retrospective analysis performed at an urban, tertiary care academic centre and enrolled 1818 adults visited ED. This study compared the ability of qSOFA, SIRS and NEWs in predicting mortality and ICU admission. For predicting in hospital mortality, the area under the receiver operating characteristics curve for NEWS (0.65, 95% CI 0.61 - 0.68) was similar to qSOFA (0.62, 95%CI 0.59 - 0.66) and superior to SIRS (*P* value < 0.001), which was not predictive. The sensitivity of NEWS ≥ 5 (74%, 95% CI: 68 - 79%) was similar to SIRS ≥ 2 (80%, 95%CI: 74 - 84%) and higher than qSOFA ≥ 2 (37%, 95% CI: 31- 43%). The specificity of NEWS ≥ 5 (43%, 95%CI 41 - 46%) was higher than SIRS ≥ 2 (21%, 95%CI 19 - 23%) and lower than qSOFA ≥ 2 (79%, 95%CI 77- 81%). Results were similar for the secondary outcome of ICU admission. This study concluded that NEWS has equivalent or superior value for most test characteristics relative to SIRS and qSOFA, calling into question the rationale of adopting qSOFA in institutions where NEWS is already in use. [195]

1.8 Li's Priori Shock (LiPS) tool

In a prospective, observational, cross-sectional, single-centre study in Hong Kong, China, *a priori,* pragmatic, quantitative method for recognising and classifying shock – *Li's Practical Shock* (*LiPS*) tool, was designed by Rainer *et al,* whereby patients admitted to ED were divided into one of the three groups: no shock, possible shock, and shock **(Table 1.11).** The primary outcome was 28-days mortality and secondary outcome was in-hospital mortality or admission to ICU or coronary care unit (CCU). This method was validated against ICU admission and early mortality. In addition, this study tried to identify other variables that might be useful for diagnosing and assessing shock. Group definitions for shock were derived after literature review and by consensus opinion among shock specialists. LiPS tool has sensitivity and specificity of 60% (95%CI: 33 - 83%) and 72% (95%CI: 63 - 81%) respectively for determining in-hospital mortality. [196]

Patients were classified as **'No Shock'** if all of the following criteria were present:

1. There was sign of normal tissue perfusion i.e., normal skin (not mottled);

2. Blood pressure was 'normal', defined as both a systolic blood pressure (SBP) ≥90 mmHg, and a mean arterial pressure (MAP) ≥65 mmHg [3, 20]; and

3. Acid-base status was 'normal' defined as a lactate level <1.5 mmol/L, and a pH >7.3, and a base deficit of 0 to >-3 mEq/L.

Patients were classified as **'Possible Shock'** if there was sign of normal tissue perfusion, as defined above, normal blood pressure defined as both SBP ≥90 mmHg, and a MAP ≥65 mmHg, but some degree of abnormal acid-base status defined as either a lactate level of 1.5 to 4.0 mmol/L, or a pH of 7.1 to 7.3, or a base deficit of -3 to -5 mEq/L

Patients were classified as **'Shock'** if any ONE of the following were present:

1. Evidence of overt sign of tissue hypoperfusion such as mottled skin; or

2. Evidence of an 'abnormal' blood pressure defined as either SBP <90 mmHg, or a MAP <65 mmHg; or

3. Evidence of grossly abnormal acid-base status defined as a lactate level ≥4.0 mmol/L, or a pH ≤7.1, or a base deficit of ≤-5 mEq/L

Table 1.11. Li's Practical Shock (LiPS).

Physiological variables	State of Shock		
	Shock	**Possible Shock**	**No Shock**
	Shock is present if **ANY** one of the followings are found	Shock is possible if **ALL** the **(A+B)** are present and any of C is found	Shock is **NOT** possible if **ALL** the following are found
A: Tissue perfusion (skin mottling)	YES	NO	NO
B: Blood Pressure Systolic blood pressure Mean arterial pressure	< 90 < 65	≥ 90 ≥ 65	≥ 90 ≥ 65
C: Acid Base Status Lactate PH Base deficit	≥ 4.0 ≤ 7.1 ≤ - 5.0	1.5 - < 4.0 7.1 - 7.3 -3.0 - 5.0	< 1.5 > 7.3 > -3.0
D: Skin temperature When present shock classified into cold, normal, and warm			

Shock is present if **ANY** one of: skin mottling, low blood pressure < 90/60 mmHg and markers of hypo perfusion are present. Absence of all is equivalent to no shock and possible shock is when some degree of abnormal acid-base status defined as either a lactate level of 1.5 to 4.0 mmol/L, or a pH of 7.1 to 7.3, or a base deficit of -3 to -5 mEq/L is present. Adopted from Li YL1, Chan CP2, Sin KK3, Chan SS4, Lin PY5, Chen XH6, Smith BE7, Joynt GM8, Graham CA9, Rainer TH. Validating a pragmatic definition of shock in adult patients presenting to the ED. Am J Emerg Med. 2014;32(11):1345-50.

1.9 Refining LiPS

This study had a number of limitations. Firstly, it was a pragmatic study as there was no “gold standard” for shock with which other definitions of shock can be compared to. Secondly, it was a preliminary study, and the sample size was only moderate. Thirdly, it was a single centre study and the generalisability of the data could not be assured. Future studies are required to further validate and refine the definitions and to test them in broader ED populations. Testing against other potential standards of tissue perfusion such as oxygen delivery would also provide further possible factors for inclusion in the shock definition. **In the current study we are aiming to establish a new standard for the diagnosis of shock and aiming to achieve a higher sensitivity and specificity of > 67% and >72% respectively, for determining in-hospital mortality.**

1.10 Treatment of shock

The essence of treating shocked patients is early haemodynamic support in order to prevent organ dysfunction. [197] Whilst, resuscitation is ongoing, search for the cause of shock should continue. The optimal treatment should focus on treatment of the cause. For instance, in cardiogenic shock caused by acute myocardial infarction, percutaneous coronary intervention or thrombolysis should be considered or in septic shock antibiotics should be administered at early stages. [28] In 1969 Weil *et al*, created a useful mnemonic to describe the important components of resuscitation; which is the VIP rule: V; ventilate (oxygen administration), I; infuse (fluid resuscitation), and P; pump (administration of vasoactive agents). [198]

Airway management and ventilation

Oxygen should be administered early to improve tissue perfusion and prevent pulmonary hypertension. [28] Invasive intubation is therefore indicated in all patients with severe dyspnoea, hypoxemia, or persistent or worsening acidaemia (pH, <7.30). [199] Mechanical ventilation delivered by a mask has limited place in intensive resuscitation and failure in technique can lead to potential harm such as worsening of shock and cardiac arrest. [199] Benefit of positive pressure mechanical ventilation via endotracheal tube is increased in intrathoracic cavity pressures which in turn leads to reduced left ventricular afterload, improved cardiac output and arterial pressure. [200] An abrupt decrease in arterial pressures soon after the start of the mechanical ventilation points towards significant hypovolemia. [201]

Fluid resuscitation

The aim of fluid resuscitation is to improve microcirculation and oxygenation. Even in cardiogenic shock patients may benefit from a degree of fluid resuscitation as in significant oedema the intravascular fluid might not be adequate to maintain cell demands. [28] There are three elements which should be considered in fluid replacement:

1) Type of fluid; As described by Myburgh *et al*, the ideal fluid will be the one that produces a predictable and sustained increase in intravascular volume, has a chemical composition as close as possible to that of extracellular fluid, is metabolised and completely excreted without accumulation in tissues and does not produce adverse metabolic or systemic effects. [202] It should be cost-effective, readily available and easy to administer. Currently, there is no such fluid available for clinical use. Crystalloids are freely permeable solutions and contain sodium and chloride. Colloids are suspension of molecules in a carrier solution, incapable of crossing the capillaries membranes. Colloids are able to increase oncotic pressure and expand intravascular volume. Choice of fluid is largely determined by clinician preferences and are affected by regional and institutional protocols, availability, and costs. [203] Colloids such as human Albumin are useful in hypoalbuminemia but are relatively expensive to use, whereas crystalloids such as Normal Saline or Ringer Lactate are easily accessible and cheap. Human Albumin is considered to be the reference colloid. Saline versus Albumin Fluid Evaluation (SAFE) study was conducted in Australia and New Zealand and examined the safety of albumin in 6997 adult patients admitted to ICU. [204] The study assessed the effect of Human Albumin (4%) vs Normal saline in resuscitation and the primary endpoint was defined as death in 28 days. It showed no significant difference between Albumin and saline with respect to the rate of death (relative risk, 0.99; 95%CI, 0.91 - 1.09; *P* value = 0.87) or the development of new organ failure. However, resuscitation with Albumin was associated with a significant increase in the rate of death at 2 years among patients with traumatic brain injury, which could be due to raised intracranial pressure (relative risk, 1.63; 95%CI, 1.17 - 2.26; *P* value = 0.003). Resuscitation with Albumin was associated with a decrease in the adjusted risk of death at 28 days in patients with severe sepsis (odds ratio, 0.71; 95%CI, 0.52 - 0.97; *P* value = 0.03), suggesting a potential, but unsubstantiated, benefit in patients with severe sepsis. [205] In effect the outcome of resuscitation with Albumin and Saline in acute setting is whether a specific group of patients benefit more from Albumin such severely septic patients, requires large, randomised trials. The expense of Albumin led to introduction of semisynthetic colloid solutions. Hydroxyethyl starches (HES) solutions are other types of colloids produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes. Their use, especially when using ones with a high molecular weight, is associated with interference with clotting cascade. [28] In a blinded, randomised, controlled trial involving 800 patients with severe sepsis in the ICU, 30 Scandinavian investigators reported that the use of 6% HES (130/0.42), as compared with Ringer's acetate, was associated with a significant increase in the rate of death at 90 days (relative risk, 1.17; 95% CI, 1.01 - 1.30; *P* value = 0.03) and a significant 35% relative increase in the rate

of renal-replacement therapy. [206] These results are consistent with previous trials of 10% HES (200/0.5) in very similar patient populations. [207] Also, a very recent observational trial raised concerns regarding the increased risk of acute kidney injury in patients treated with gelatin solutions. [208] As with hypertonic crystalloid, colloids are not supposed to replace lots of volume but rather help with fluid shift from one compartment to another. [28] During the early phase of resuscitation following thermal injury, colloid solutions should be avoided for first 12 to 24 hours due to capillary permeability and accumulation of plasma proteins outside the vascular compartment, which contributes to oedema. [209] The reference to crystalloid solutions is Normal Saline, which contains Sodium and Chloride in equal concentrations. Awad *et al*, in an article describing the history of Normal Saline, reported that the 0.9% saline solution is without convincing historical basis, given that the composition of 0.9% sodium chloride is dissimilar to most solutions used in the past, and is in no way 'normal' or 'physiological. [210] Due to this ion difference, excessive resuscitation with Normal Saline can result in hyperchloremic acidosis and renal dysfunction. [211] Linger Lactate or Hartman solution are named as balanced crystalloids and are closer to human body extracellular fluid having lower Sodium concentration and risk of hyperlactatemia, metabolic alkalosis, and hypotonicity (with compounded sodium lactate) and cardiotoxicity (with acetate). [28] Given the concern regarding an excess of sodium and chloride associated with normal saline, balanced salt solutions are increasingly recommended as first-line resuscitation fluids in patients undergoing surgery, [212] patients with trauma, [213] and patients with diabetic ketoacidosis. [214] **(Table 1.12)**

2) Dose of fluid: Aggressive crystalloid resuscitation is not without side effects as it can induce platelet dysfunction and dilution of clotting factors, which may extenuate haemorrhagic situations. As mentioned before, excessive administration of crystalloids may lead to hyperchloremic metabolic acidosis and has been shown to induce pulmonary oedema, cardiovascular dysfunction, abdominal compartment syndrome, and ileus. [215], [216] It is sometimes challenging to define endpoints for fluid resuscitation. Early Goal Directed Therapy (EGDT) recommends a volume of crystalloid to achieve central venous pressure of above 8mmHg. [28] Based on per Frank-Starling physiology the objective is to make cardiac output independent of preload or end diastolic left ventricular volume. [217] In mechanically ventilated patients stroke volume variability (SVV) can be measured by non-invasive methods or pulse-pressure variation by arterial cannulation and can guide fluid responsiveness. [28] The other way of assessing fluid responsiveness is passive leg rising (PLR). Cavallaro and colleagues examined the sensitivity and specificity of PLR in addition to odds ratio and area under the receiver curve (AURC) in PLR-induced cardiac output and pulse pressure changes in 353 patients. [218] With regards to changes in cardiac output, PLR had sensitivity of 89.4% (95%CI 84.1 - 93.4) and specificity of 91.4% (95%CI 85.9 - 95.2). The pooled diagnostic odds ratio was 89.0 (95%CI 40.2 - 197.3) and the AUC was 0.95 (95%CI 0.92 - 0.97) and with it had sensitivity of 59.5% (95%CI 47.4 - 70.7), specificity of 86.2% (95%CI 75.3 - 93.5), pooled diagnostic odds ratio of 10.8 (95% CI 4.4 - 26.1) and the AUC of 0.76 (95% CI 0.67 - 0.86) in assessing

changes in pulse pressure. The authors concluded that passive leg rising (PLR) can predict fluid responsiveness reliably and is not affected by mechanical ventilation and cardiac arrhythmias. [218] Associations between increased cumulative positive fluid balance and long-term adverse outcomes have been reported in patients with sepsis. [219]

3) Rate of fluid administration: Fluids should be infused rapidly to induce a quick response but not so fast that an artificial stress response develops; typically, an infusion of 300 to 500 ml of fluid is administered during a period of 20 to 30 minutes. [220] Special consideration should be taken to account for patients who are already overloaded such as patients with heart failure.

Table 1.12. Common types of fluid used in resuscitation of circulatory shock.

Fluid	Na	Cl	K	Ca	Mg	Buffers	pH	Osmolarity (mOsM/L)
Plasma	140	103	4	5	2	Bicarb (25)	7.4	290
0.9% NaCl	154	154	_	_	_		5.7	308
0.75% NaCl	1,283	1,283	_	_	_		5.7	2,567
Lactated Ringer's	130	109	4	3	_	Lactate (28)	6.4	273
5% Dextrose	_	_	_	_	_		4.0	252
5% Albumin	130-160	130-160	_	_	_	Sodium bicarbonate, hydroxide, or acetic acid	6.4-7.4	309
25% Albumin	130-160	130-160	_	_	_	Sodium bicarbonate, hydroxide, or acetic acid	6.4-7.4	312

Concentration of electrolytes is different per fluid type, which gives raise to different pH and osmolality. **Abbreviations:** NaCl: sodium chloride. Adopted from Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013 Oct31;369 (18):1726-34.

Blood products

The aim of blood transfusion is to improve oxygenation and tissue perfusion. [28] It should be considered when 30% of total blood volume is lost. [221] Most commonly available products include red blood cells (RBC), platelets (PLT) and fresh frozen plasma (FFP). Most hospital across the world established massive blood transfusion protocols to balance infusion ratio of these products to each other. Theses protocols target at least a 1 to 3 ratio of plasma-to-RBC transfusions, and some promote a 1 to 2 ratio. [222], [223] In fact, a strategy of 1 to 1 to 1 involving RBC, FFP, and PLT transfusion has been recently proposed. [224] The Advanced Trauma Life Support (ATLS) resuscitation guidelines recommend early transfusion of RBC in trauma patients with evidence of haemorrhagic shock unresponsive to 2 Litres of crystalloid fluids. [225] The decision to administer RBC transfusion in haemorrhagic shock should not be based on the haemoglobin concentration but rather on clinical presentation, haemodynamic instability, and evidence of ongoing blood loss. Blood transfusion is not risk free. Como *et al,* studied data from a trauma registry of 5645 patients and showed that transfusion of more than 10 units of RBC is associated with increased mortality. [226] Studies also link RBC transfusion to pulmonary oedema, fever, transfusion-related reactions, increased multiple organ failure, decreased immunity, increased rate of infection, citrate toxicity, electrolyte abnormalities, and transfusion-associated lung injury. [227] Adverse effects of FFP have been described as allergic reactions, fever, infection, transfusion-associated overload, and acute lung injury. PLTs have been associated with each of these in addition to thrombosis. [228] Other products such as recombinant factor VIIa (rFVIIa) initiates haemostasis through the formation of a complex between tissue factor and FVIIa. It is mainly used in treatment of bleeding in haemophilia patients with inhibitors to exogenous factors VIII and IX. [229] Boffard and colleagues in a randomised, placebo-controlled, double-blind trial assessed the safety and efficacy of rFVIIa in 301 trauma patients and showed significant reduction in the number of RBC units transfused in first 48 hours. [230] However, off licence of use of rFVIIa is shown to be associated with increased risk of thromboembolism; deep vein thrombus (DVT) and pulmonary embolism (PE). [231]

Pharmacological agents

Vasoactive agents are used when hypotension is severe despite optimal fluid resuscitation. The aim of use is temporary whilst fluid resuscitation is ongoing with aim of discontinuing it when volume depletion is resolved. [28] Adrenergic agonists are the first-line vasopressors because of their rapid onset of action, high potency, and short half-life. [232] The choice of drug is dependent on the required need. For instance, Isoproterenol is a pure β-adrenergic stimulator, and its use is kept for profound bradycardia as its excessive use increases the risk of myocardial ischemia by increasing the risk of tachycardia and subsequent contractibility. On the other hand, Phenylephrine as a pure α-adrenergic agonist can increase vascular tone and blood pressure but can also drop cardiac output and impairs tissue perfusion. [238] Norepinephrine is the vasoactive of choice with predominantly α-adrenergic potential and modest β-adrenergic properties. [233] Administration generally results in a clinically significant increase in mean arterial pressure, with little change in heart rate or cardiac output. The usual dose is 0.1 to 2.0 μg per kilogram of body weight per minute. Dopamine has predominantly β-adrenergic effects at lower doses and α-adrenergic effects at higher doses, but its effects are relatively weak. Dopaminergic effects at very low doses (<3 μg per kilogram per minute, given intravenously) may selectively dilate the hepato-splanchnic and renal circulations, but controlled trials have not shown a protective effect on renal function. [25], [234] Its Dopaminergic effect can suppress Prolactin release which has immunoreactive properties. [239] Hence, its routine use is not recommended. [234] In a multicentre, randomised, double-blind, placebo-controlled trial in Australia and New Zealand the effect of low-dose Dopamine vs placebo was tested in 328 patients admitted to ICU, with at least two criteria for the systemic inflammatory response syndrome (SIRS) and clinical evidence of early renal dysfunction (oliguria or increase in serum creatinine concentration). [235] There was no difference between the Dopamine and placebo groups in peak serum creatinine concentration during treatment (245 vs 249 micromol/L; *P* value = 0.93), in the increase from baseline to highest value during treatment (62 vs 66 μmol/L; *P* value = 0.82), or who required renal replacement therapy (35 vs 40; *P* value = 0.55). [235] Sepsis Occurrence in Acutely ill Patients (SOAP) trial was a large observational multi-central study, looking at data from 108 intensive care units across Europe. SOAP examined the impact of Dopamine vs Norepinephrine on the outcome of shock in 1058 patients. [236] Patients treated with Dopamine had higher ICU and 30-days hospital mortality. The degree of organ dysfunction, as assessed by the maximum and mean SOFA scores during the ICU stay, was similar among patients treated with Dopamine and those who received Norepinephrine. [236] The research group hypothesised increased risk of arrhythmias, reduced release of Prolactin as an immuno-protective hormone and lack of Dopamine efficacy in improving renal perfusion compared to Norepinephrine. [236] Epinephrine with predominantly β-adrenergic effects at low doses, with α-adrenergic effects becomes more clinically significant at higher doses. It can be associated with an increased rate of arrhythmia [237] and a decrease in splanchnic blood flow and can increase blood lactate levels, probably by increasing cellular metabolism. [237] Prospective, randomised studies have not shown any

beneficial effects of Epinephrine over Norepinephrine in septic shock and therefore reserved as second line in severe sepsis. [238], [239] Vasopressins deficiency can happen in certain type of hyperkinetic distributive shock. Russell *et al*, in the Vasopressin and Septic Shock Trial (VASST) found that the addition of low-dose Vasopressin to Norepinephrine in the treatment of patients with septic shock was safe and may associate with a survival benefit for patients with forms of shock that were not severe and for those who also received glucocorticoids. [240] With regards to inotropic agents and increasing cardiac output, Dobutamine will remain the agent of choice. [241] It is less likely to induce tachycardia. [237] An initial dose of just a few micrograms per kilogram per minute may substantially increase cardiac output. Intravenous doses in excess of 20 µg per kilogram per minute usually provide little additional benefit. [242] Phosphodiesterase type III inhibitors, such as Milrinone and Enoximone, combine inotropic and vasodilating properties through decreasing the metabolism of cyclic AMP. They may be useful when β-adrenergic receptors are downregulated or in patients recently treated with beta-blockers. However, they may induce unacceptable adverse effects in patients with hypotension and therefore intermittent, short-term infusions are recommended above continuous infusions. [28] Vasodilators such as Nitryglycerin or Nitroprosside increased cardiac output by reducing ventricular afterload. Their major adverse effect is profound hypotension and tissue hypoperfusion. In study of in-Hospital Mortality in Patients with Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications (ADHER), which was an observational, retrospective study of 65180 patients, who received Nitroglycerin, Nesiritide, Milrinone, or Dobutamine, results showed that in hospital mortality was lower with vasodilators; (4.7% and 7.1% for Nitroglycerin and Nesiritide and 12.3% and 13.9% for patients received Milrinone and Dobutamine). Increased risk of mortality is highly associated with increased risk of arrhythmias related to use of positive inotropic agents; Milrinone and Dobutamine. [243] **(Table 1.13)**

Table 1.13. Pharmacology, dose and therapeutic effect of vasopressors and inotropes.

Drug/Mechanism	Dose/Onset and Duration	Use/Effects
PhenylephrineStronga-1 agonist	Dose: Begin at 100-180 mcg/min; once BP stabilized, decrease rate to 40-60 mcg/min and titrate to MAP. MAX: 9.1 mcg/kg/min or**400 mcg/min. Onset: immediate, half-life: 2-3 hours.	Vasodilatory shock, shock due to aortic stenosis and hypotension, left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Effects: Increase BP, vasoconstriction, increase MAP and SVR
Norepinephrine Stronga-1 and b-1agonists and weakb-2 agonist	Dose: Begin at 2-12 mcg/min and titrate to MAPMAX: 1 mcg/kg/min or**80 mcg/min. Onset: immediate, duration: 1-2 minutes.	Vasodilatory shock (usually drug of choice for sepsis), cardiogenic shock (refractory hypotension with SBP < 70 mmHg). Effects: Increase MAP, vasoconstriction, CO, SVR
Epinephrine Stronga-1, b-1, and b-2 agonists	Dose: Begin at 2-10 mcg/min and titrate to MAPMAX: 0.5 mcg/kg/min or**30 mcg/min Onset: immediate, duration: up to 1 hour	Vasodilatory shock, cardiac arrest, cardiogenic shock, anaphylaxis Effects: Increase in SVR, HR, MAP, CI, and SV
Vasopressin **	Dose: Fixed dose 0.04 units/min; cardiac arrest:40 units IV bolus	Vasodilatory shock, cardiogenic shock, cardiac arrest Effects: Increase in BP, SVR
Dopamine DA, b-1, anda-1 agonist (dose dependent)	Dose: Start at 2.5-5 mcg/kg/min and increase by2.5-5 mcg/kg/min q 10-15 min. Normal dose in grange 2.5-20 mcg/kg/min MAX: 50 mcg/min Onset: 5 min, half-life: 2 minutes	Vasodilatory shock, cardiogenic shock, bradycardia Effects: dose dependent, Increase in HR, CO, BP, and vasoconstriction
DobutamineStrongb-1 and weak b-2 agonist	Dose: 2.5-20 mcg/min; MAX: 40 mcg/kg/min Onset: 1-10 min, half-life: 2 minutes	ADHF, low CO state, cardiogenic shock, septic shock as outlined in early goal directed therapy, bradycardia. Effects: Increase CI, HR, BP, SVR and O2 delivery

Milrinone Phosphodiesterase inhibitor	Dose: 50 mcg/kg IV bolus over 10 minutes (rarely used for ADHF) followed by 0.375-0.75 mcg/kg/min *** Onset: 5-10 hours, half-life: 1-3 hours	

** Ensure adequate volume resuscitation before adding vasopressor or inotropic agents. *** May adjust for impaired renal function to prevent accumulation. **Abbreviations:** ADHF, acute decompensated heart failure; CI, cardiac index; HR, heart rate; BP, blood pressure; SVR, SVR, systemic vascular resistance; PVR, CO, cardiac output. Adopted from Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013 Oct31; 369(18):1726-34.

The following is more specific to different types of shock with an overview on the history of Early Goal Directed Therapy (EGDT) and its use in improving outcome in sepsis and septic shock.

1.11 Early Goal Directed Therapy (EGDT)

Observations of high mortality, fractured, and unstructured care triggered a series of investigations using a system-based approach to identify delays in patient diagnosis and care before hospital admission. Combining system issues with the early pathogenesis and natural progression of sepsis required the development of unique diagnostic and risk stratification criteria to detect patients at risk and most likely to benefit from early diagnosis and treatment. Early Goal Directed therapy (EGDT) was first introduced in early 1990. [244] It comprised of early identification of pathogen and the admiration of appropriate antibiotics followed by early haemodynamic optimisations by measures of preload guided by central venous pressure (CVP) of 8 to 12 mmHg (12-15 mmHg in mechanically ventilated patients), afterload guided by mean arterial pressure (MAP) of more than 65 mmHg, contractibility which guides choice of vasoactive agents and factors related to oxygen delivery for instance; central venous oxygen saturation (ScvO2) of > 70 % or mixed venous oxygen saturation (SvO2) > 65%. **(Figure 1.7)** Due to lack of access to facilities to measure ScvO2, other centres targeted Lactate as a marker of oxygen delivery and it has been shown by Jones *et al*, that lactate clearance of at least 10% was non-inferior to targeting ScvO2**.** [245] Also, one can consider fluid resuscitation or transfusion of RBCs to target a haematocrit > 30% instead of using ScvO2 or SvO2. [221], [246] Resuscitation with crystalloid should be started as soon as possible to achieve CVP of more than 8 mmHg. In patients not responsive to fluid therapy to maintain tissue perfusion and adequate oxygenation vasopressors should be considered with a target MAP of at least 65 mmHg. Norepinephrine or Dopamine should be considered as first inotropes of choice recommended by Surviving Sepsis Campaign guidelines to maintain oxygenation. [247] In patients with evidence of low cardiac output and elevated cardiac filling pressures Dobutamine should be considered. This is in combination with early administration of broad-spectrum antibiotics within the first hour of presentation. In the setting of septic shock, every hour of delay in administration of antimicrobials is associated with a measurable increase in mortality. [221], [248] Between 1997 and 2000, Rivers *et al*, investigated the difference between standard therapy and Early Goal Directed therapy (EGDT) in 263 patients admitted to ED followed by intensive care unit. Patients randomised to standard therapy had significantly higher mortality at 28 days (*P* value of 0.01) and 60 days (*P* value of 0.03) in comparison to patients who received EGDT. The incidence of death due to sudden cardiovascular collapse in the standard-therapy group was approximately double that in the group assigned to early goal-directed therapy, suggesting that an abrupt transition to severe disease is an important cause of early death. It was concluded that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock has significant short-term and long-term benefits. [249] Hence, it became a fundamental component of the sepsis resuscitation bundle for the Surviving Sepsis Campaign (SSC), the National Quality Forum and Centres for Medicare and Medicaid Services. [249]

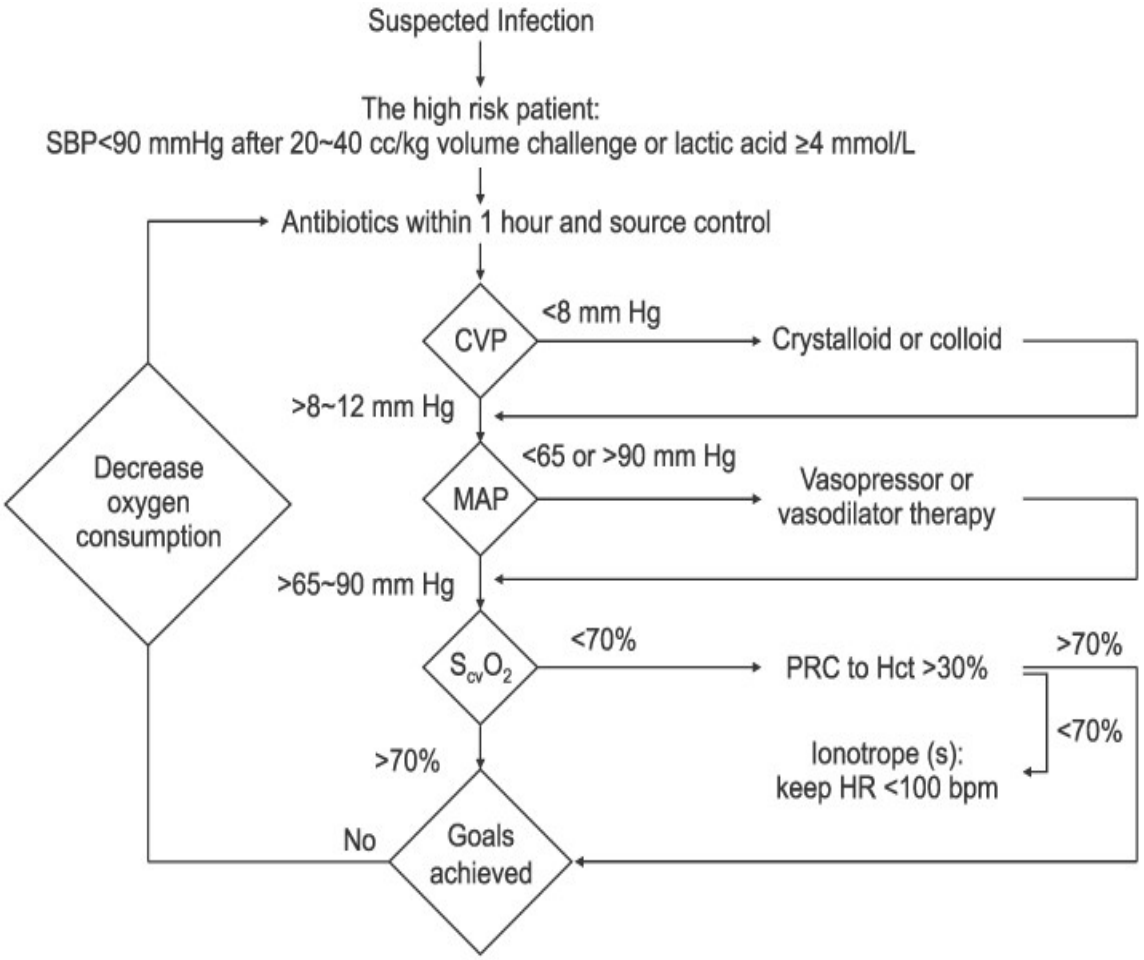


Figure 1.7. Early Goal Directed Therapy (EGDT).

Components of EGDT. **Abbreviations**: EGDT, early goal-directed therapy; CVP, central venous pressure; MAP, mean arterial pressure; ScvO2, central venous oxygen saturation. Adopted from Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 346:1368-77.

1.12 Adjuvant treatments

Other adjuvant therapies such as corticosteroids and recombinant human-activated protein C ([rhAPC] drotrecogin alpha) have been used in the treatment of sepsis and septic shock. Use of corticosteroids remained controversial throughout decades. [21] High dose steroids were not associated with significant mortality benefit. [250] However, smaller dose, e.g., Hydrocortisone dose of 200-300 mg/d is shown to correlate with early reversal of sepsis and reduced mortality. [251] In a multi-centre, randomised, double-blind, placebo-controlled trial; CORTICUS, patients with septic shock were assigned into two different groups; 251 patients received 50 mg of Hydrocortisone and 248 patients received placebo every 6 hours for five days. [252] At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) died (*P* value: 0.51). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock in Hydrocortisone group. [252] Hence, steroids are not recommended for patients with whom early reversal of shock is not needed. There is a role for steroids in patients who are not responsive despite aggressive use of vasopressors, and they are beneficial in patients with chronic steroid insufficiency. [252] Drotrecogin alpha (or rhAPC) has antithrombotic, profibrinolytic, and anti-inflammatory properties like endogenous-activated protein C. It can mediate the procoagulant state and inhibit the systemic inflammatory response in infected patients. The most adverse event associated with use of rhAPC is severe bleeding. Therefore, the current Surviving Sepsis Campaign guidelines suggest considering drotrecogin alpha only for ‘‘adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have an Acute Physiology and Chronic Health Evaluation (APACHE) II [2] score > 25 or multiple organ failure’’ in the absence of contraindications. [23]

[2] Acute Physiology And Chronic Health Evaluation II") is a severity-of-disease classification system (Knaus et al., 1985), one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The first APACHE model was presented by Knaus et al. in 1981.

Cardiogenic shock

Inotrope support of choice is Dobutamine in patients with low cardiac output and Dopamine for patients with symptoms and signs of cardiogenic shock due to its additional vasoconstrictive properties. [28] For patients with refractory hypotension (SBP < 70 mmHg) Norepinephrine should be considered. [253] Backer and colleagues enrolled 1679 patients with cardiogenic shock, of whom 858 were assigned to Dopamine and 821 to Norepinephrine and they showed no difference in primary outcome of 28-days mortality. [25] However, a subgroup analysis of 280 patient showed favoring results with use of Norepinephrine in reducing mortality and tachyarrhythmias. [25] There are many evidence favoring reperfusion strategies and most famously Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, which evaluated treatment strategies in CS caused by acute myocardial infarction (AMI). [88] In this study patient were randomised into two different groups; one being the revascularisation group including patient received emergency coronary artery bypass graft surgery (CABG) or primary percutaneous intervention (PPCI) within 18 hours of presentation and second group being patients who received medical therapy. Patients who received revascularisation met primary endpoint of 30 days mortality by 46.7%, whereas it was met by 56% in the medical therapy group. Additionally, there was a 12.8% absolute risk reduction in 6-month mortality (*P* value: 0.027) and 13.1% absolute risk reduction at 1 year, both favoring revascularization (*P* value: 0.03). [254] Thrombolysis should be considered for patients for whom access to PPCI service is not possible within first 120 minutes of presentation as per European Society of Cardiology Guidelines for management of patient with acute myocardial infarction and ST- segment elevation. [255] The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, evaluated treatment of CS caused by acute MI using different thrombolytic regimens (streptokinase and/or recombinant tissue plasminogen activator (rt-PA)) in addition to standard medical therapy with Aspirin, Heparin, and Atenolol. [256] This study looked at data from 41,021 patients with evolving myocardial infarction across 1081 centres in 15 countries. Patients were randomly assigned to four different thrombolytic strategies, consisting of the use of streptokinase and subcutaneous heparin, streptokinase, and intravenous heparin, accelerated tissue plasminogen activator (t-PA) and intravenous Heparin, or a combination of streptokinase plus t-PA with intravenous Heparin. ("Accelerated" refers to the administration of t-PA over a period of 1-1/2 hours--with two thirds of the dose given in the first 30 minutes--rather than the conventional period of 3 hours.) Primary end-point was defined as 30-days mortality. The results showed 14 percent reduction (95% CI: 5.9 - 21.3%) in mortality for accelerated t-PA as compared with the two streptokinase-only strategies (*P* value: 0.001). The rates of haemorrhagic stroke were 0.49%, 0.54%, 0.72%, and 0.94% in the four groups, respectively, which represented a significant excess of haemorrhagic strokes for accelerated t-PA (*P* value: 0.03) and for the combination strategy (*P* value: < 0.001), as compared with streptokinase only. A combined end point of death or disabling stroke was significantly lower in the accelerated-tPA group than in the streptokinase-only groups (6.9 vs. 7.8%, *P* value: 0.006). The recommendation was that antiplatelet agents including Aspirin and Clopidogrel should be administered for PCI, thrombolysis, or medical management unless contraindicated. [256] Use of Aspirin and clopidogrel is supported by data from multiple trials. [257], [258], [259] There is no data available to support the use of

Prasugrel (a relatively new thienopyridine) as medical management or in conjunction with thrombolytic agents. Additional antiplatelet therapy with a glycoprotein IIb/IIIa inhibitor is commonly used during PCI. There are also multiple anticoagulant options for management of ACS including Heparin, low-molecular-weight heparin, Bivalirudin, and Fondaparinux. [257]

Mechanical circulatory support devices

Use of mechanical circulatory support devices (MCS) such as intra-aortic balloon pump (IABP), left ventricular assist device (LVAD), extracorporeal membrane oxygenation (ECMO), etc has been investigated by various clinical trials. Percutaneous circulatory assist devices provide superior hemodynamic support compared with pharmacologic therapy; this is particularly apparent for the Impella and Tandem-Heart devices. [260] Extracorporeal membrane oxygenation (ECMO) is indicated in patients with poor oxygenation not expected to rapidly improve with alternative temporary mechanical support devices. [261] IABP is recommended as standard therapy in context of cardiogenic shock when medical therapy is not adequate, and patients are awaiting revascularisation. Placement of IABP would help with reducing afterload and consequently offloads the stressed myocardium and improves coronary perfusion. [253] A report from SHOCK trial registry, where 865 patients with cardiogenic shock were evaluated regarding use of thrombolysis therapy and IABP, showed that those selected for IABP had a lower in-hospital mortality than those who did not receive IABP (50 vs. 72%, *P* value: < 0.0001). Patients receiving early IABP (< or = 6 hours after thrombolytic therapy, n = 72) had in-hospital mortality similar to those with late IABP (53 vs. 41%, n = 64, respectively, *P* value: 0.172). [262] In appropriately selected patients not likely to recover from cardiogenic shock without long-term MCS support, a ventricular assist device can be implanted as a bridge to recovery, bridge to bridge, bridge to transplant, or destination therapy. Use of LVAD compared to IABP did not show significant mortality benefit but it has been shown that it can improve haemodynamic parameters such as CO and pulmonary capillary wedge pressure (PCWP). [263], [264], [265], [266]

Treatment of Anaphylaxis

Mainstay of treatment is immediate administration of Epinephrine. [28] It can be administered via trans-muscular (IM), intravenous (IV), sublingual routes and via endotracheal tube. As the main cause of death is airway obstruction, airway management plays a key role in resuscitation of patients with anaphylaxis. [28] In cases of severe laryngeal oedema, cricothyroidotomy or tracheostomy may be performed. Volume expansion should be considered to support circulatory compromise. Glucocorticoids (Methyl prednisone 125 mg IV or Hydrocortisone 500 mg IV) may be administered to prevent relapse of symptoms during severe reactions. However, glucocorticoids have no significant immediate effects. [28] Antihistamines such as H2 antagonists should be given to help with relieving skin manifestations and to shorten the duration of reaction. In patients with regular use of Beta-blockers when other strategies fail, IV Glucagon at initial dose of 1mg IV bolus followed by a continuous infusion of up to 1 mg/h should be considered to maintain inotropic support. [267]

Treatment of neurogenic shock

Fluid resuscitation remains as the first line of therapy followed by vasoactive agents in unresponsive cases. There is lack of evidence in defining blood pressure target and vasopressor of choice. Small trials targeted systolic blood pressure of 85 to 90 mmHg to prevent secondary cord damage. [268], [269] Phenylephrine is often avoided due to its ability to cause marked reflex bradycardia. [28] Atropine can be used for acute, symptomatic bradycardia in doses ranging from 0.4 to 0.6 mcg IV every 4 hours as necessary. It is recommended to have Atropine readily available for patients with spinal cord injuries since bradycardia may occur suddenly especially early after injury. [28] For patients with hypotension and bradycardia, Dopamine or Epinephrine infusions maybe helpful due to their chronotropic effects. In refractory bradycardia or for patients requiring long-term pharmacologic management, Methylxanthines (Aminophylline or Theophylline) and Propantheline have been used as a bridge to pacemaker implantation or for patients who are not candidates for a pacemaker. [270], [271], [272]

1.13 Importance of measuring cardiac output and cardiac power

Several studies have now demonstrated the importance of measuring CO and Cardiac Power (CP). In patients with cardiogenic shock and across a broad spectrum of acute circulatory failure, CP has been shown to be the strongest haemodynamic correlate of mortality, performing well but in decreasing order alongside cardiac power index (CPI), CO, stroke volume (SV), cardiac index (CI), left ventricular ejection fraction (LVEF), systolic blood pressure (sBP), diastolic blood pressure (dBP), mean arterial pressure (MAP), and in direct contrast to heart rate (HR), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressures (PAP), systemic vascular resistance (SVR), SVR index (SVRI) and right ventricular systolic pressure. [273] In assessment of 995 patients with cardiogenic shock in Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I (GUSTO-I) trial, CO and PCWP were shown to have prognostic value. [81] Finke *et al*, analyzed data from SHOCK trial registry, including 541 patients with predominant LV failure, whose hemodynamic measurements were made between 6 h before and up to 12 h after shock diagnosis and CP was calculated as MAP X CO/451 (MAP: mean arterial pressure, CO: cardiac output). They showed that cardiac power and LV work are the only independent hemodynamic correlates of in-hospital mortality, with cardiac power being a stronger correlate than LV work. [273] This study showed that many haemodynamic parameters including MAP, CO, CI, and LV ejection fraction correlate with outcome of cardiogenic shock secondary to LV severe dysfunction. [273] In contrast to findings of GUSTO-I trial, PCWP did not correlate to mortality. The three main reasons for monitoring cardiac function in circulatory shock are for identifying the type of shock, selecting therapeutic interventions, and evaluating the patient's response to therapy. Cardiac output is routinely measured by pulmonary artery catheter (PAC), also known as Swan-Ganz or right heart catheter since its introduction in 1970. This technique is mainly used in critically ill patients and at ICU setting. [274] PAC allows direct, simultaneous measurement of right atrium, right ventricle, pulmonary artery, and filling pressures. Since the mid-1980s, many clinical trials questioned the safety and efficacy of Pulmonary artery catheter. [275], [276] Despite almost 20 years of randomised controlled trials (RCTs), a clear strategy leading to improved survival with the PAC has not been devised. Shah *et al,* performed a large meta-analysis of 13 clinical trials, using data base from MEDLINE (1985-2005), the Cochrane Controlled Trials Registry (1988-2005), the National Institutes of Health ClinicalTrials.gov and the US Food and Drug Administration Web site for RCTs, in which patients were randomly assigned to PAC or no PAC in order to test safety and efficacy of the technique. [277] This study included 5051 patients and a random-effects model was used to estimate the odds ratios (ORs) for death, number of days hospitalized, and use of inotropes and intravenous vasodilators. The combined OR for mortality was 1.04 (95% CI: 0.90 - 1.20; *P* value = 0.59). The difference in the mean number of days hospitalised for PAC minus the mean for no PAC was 0.11 (95% CI, − 0.51 to 0.74, *P* value = 0.73). Use of the PAC was associated with a higher use of inotropes (OR, 1.58; 95%CI: 1.19 - 2.12; *P* value = 0.002) and intravenous vasodilators (OR, 2.35; 95 CI: 1.75 - 3.15; *P* value= 0.001). This study concluded that in critically ill patients, use of the PAC neither increased overall mortality or days in hospital nor conferred benefit. [277] As an invasive method, there is risk of serious complications during or after PAC insertion including arrhythmias, injury to the lung,

thromboembolism, and sepsis. [278], [279], [280] The incidence of direct PAC-related complications may vary with operator level of experience. [286], [279], [281] Overall, the technique is highly invasive and requires a high level of expertise in safe insertion of catheter and interpretation of results. There are other ways of measuring CO such as Doppler, pulse contour analysis and bio-impedance. Each method has its own merits and demerits. **(Table 1.14)** An ideal CO monitor should be minimally invasive or non-invasive, continuous, cost effective, reproducible, reliable during various physiological states and have fast response time. [282] Hence, PCWP did not demonstrate significant beneficial effects on patient outcome, [283], [284] a non-invasive strategy that focuses on measuring haemodynamics affecting CO and CP may be more likely to improve outcome than central venous pressure (CVP) and the pulmonary artery catheter (PAC).

Table 1.14. Different methods of measuring CO, advantages, and disadvantages.

No	Device	Type	Advantages	Disadvantages
1	PAC	Invasive	Gold standard	Catheter related complications
2	Continuous CO by PAC	Invasive	Continuous CO measurement	Catheter related complications Cost
3	LiDCO	Minimally invasive	Only one arterial line Continuous CO measurements Measure SV and SVV	Requires good arterial waveform Requires Calibration Contraindicated in Lithium therapy
4	PiCCO	Minimally invasive	Continuous CO measurement Effective during hemodynamic instability	Requires good arterial waveform Requires calibration
5	FloTrac	Minimally invasive	Continuous CO measurement No calibration	Requires good arterial waveform
6	PRAM	Minimally invasive	No calibration	Still not validated
7	ED	Minimally invasive	Simple to use Reliable Useful in GDT	Measure flow only in descending thoracic aorta Assumptions about aortic size may not be accurate
8	TEE	Minimally invasive	Evaluate cardiac anatomy preload and ventricular function	Cost Skilled personnel
9	Partial non-rebreathing systems	Non-invasive	Ease of use Continuous CO measurement	Affected by changes in dead space or V/Q matching
10	Thoracic	Non	Continuous CO	Affected by electrical noise,
	Bio-impedance	invasive	measurement	movement, temperature, and humidity Requires hemodynamic stability Not useful in dysrhythmias
11	ECOM	Non-invasive	Continuous CO measurement	Coronary blood flow not recorded Electrocautery produces interference

Abbreviations: CO: Cardiac output; ECOM: Endotracheal cardiac output monitor, ED: Esophgeal Doppler, GDT: Goal directed therapy. LiDCO: Lithium dilution CO; PiCCO and FloTrac: Pulse contour analysis, PAC: Pulmonary artery catheter, PRAM: Pressure recording analytic method; SV: Stroke volume, SVV: SV variation, TEE: Transesophgeal echocardiography. Adopted from Mehta Y. Arora D. Newer methods of cardiac output monitoring. World J Cardiol. 2014 Sep 26; 6(9): 1022–1029.

1.14 USCOM and haemodynamics

Ultrasonic Cardiac Output Monitor (USCOM)

In 2001, a device for assessing haemodynamics continuously and non-invasively using Doppler wave ultrasound (the Ultrasonic Cardiac Output Monitor (USCOM Pty Ltd, NSW, Australia), was introduced for clinical use. [285], [286], [287] USCOM uses advanced Doppler haemodynamic to monitor cardiac blood flow. Cardiac output (CO) and stroke volume (SV) monitoring changes the way we diagnose and manage shock, heart failure and hypertension. USCOM has been used in neonatal, paediatric, critical care, emergency, peri-operative, oncological, maternal, and perinatal settings. Previous studies have tested the clinical utility of the USCOM and demonstrated some reliability and reproducibility in measuring haemodyanamics. [288] USCOM provides haemodynamics non-invasively by measuring trans-valvular flow across the aortic or the pulmonary valve. It has been shown to be more accurate and more sensitive to changes than the pulmonary artery catheter (PAC), [289] and is at least as accurate as research quality echocardiography, [274], [290], [291] with a much shorter learning curve. [292], [293], [294], [295] This device is portable, easy to learn, [296] and provides quick, reliable readings at point of care. USCOM is relatively inexpensive and is safer than invasive techniques such as PAC. [297] The accuracy, reliability, and interrater reliability of USCOM to provide haemodynamic measurements such as cardiac output is well proven. [274], [293], [298], [299], [300], [301], [302], [303], [304], [305], [306]

USCOM 1A applications

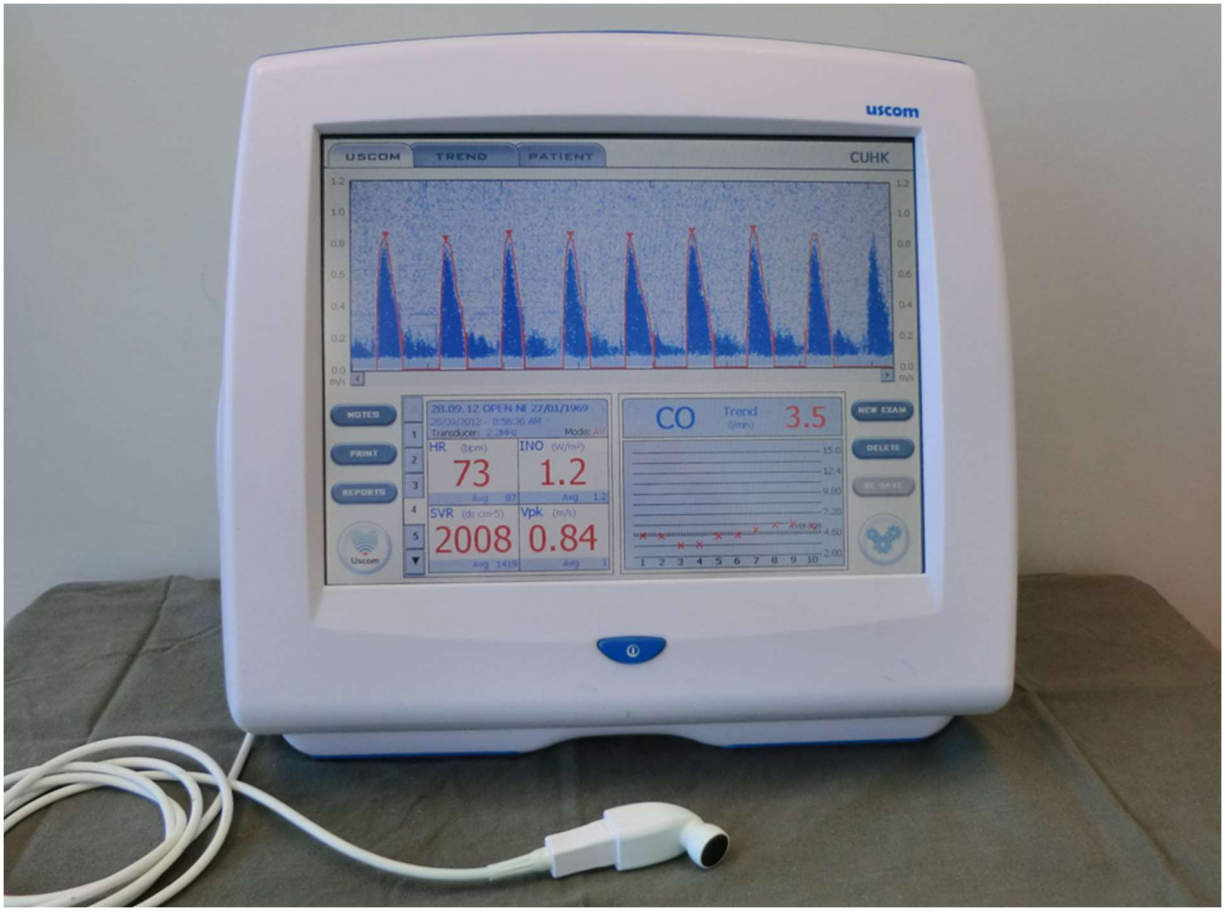
The USCOM provides measured and derived data on 21 haemodynamic variables including oxygen delivery and inotropy which can be applied in following domains:

- **Fluid management** - Assessment of patient fluid status and responsiveness.
- **Shock** - Assessment of haemodyanmic parameters and optimization of them.
- **Cardiac function** - Assessment of cardiac output, systolic function, and response to cardiac resynchronization.
- **Hypotension / hypertension** - Assessment of parameters related to afterload such as systemic vascular resistance.

USCOM features

USCOM uses advanced ultrasonic and data processing technology to measure CO. Reporter software helps in trend analysis and reporting of analyzed data. [289] USCOM 1A monitor provides a touch screen interface which allows instant access to both live and recorded information. USCOM is able to store thousands of patients' files. USCOM is easily portable and only weighs six kilograms. At the time of our study a brand-new device was priced 26,000 Pounds Sterling (GBP) on the international market and a second-hand device was priced roughly around £ 8000. **(Figure 1.8).**

<u>Figure 1.8.</u> Features of Ultrasound Cardiac output Monitor (USCOM 1A).



The above screen shows Doppler tracing and aortic valve Doppler flow. Below numerical readings of haemodynamic parameters are displayed. On the lower right side of the screen, measured cardiac output value and its trending pattern are shown. USCOM has a handheld, pencil probe, which is demonstrated in front of the screen. Using ultrasound gel improves probe's acoustic contact and trace acquisition. Adopted from: https://www.intechopen.com/books/artery-bypass/minimally-invasive-cardiac-output monitoring-.2012).

Transducer

USCOM 1A uses continuous wave Doppler to accurately measure hemodynamic parameters. The technology is most accurate and reproducible with sensitivity to hemodynamic changes of around 2-3%. [289] USCOM uses unique divergent beam acoustics technology. The device transducer operates at a frequency of 2.2 MHZ and utilizes a broad rather than focused ultrasound beam, making it easier to use and less user-dependent than previous Doppler devices. [289], **(Figure 1.9, 1.10, 1.11)**.

Difference between USCOM and echocardiography

Echocardiography has been used for many decades to provide data on both cardiac structures and hemodynamics. Despite its vast usage, echocardiography has never been validated in measuring hemodynamic parameters. Echocardiography uses pulsed wave (PW) Doppler to measure flow velocity and calculate velocity time interval (VTI), which is an essential parameter in measuring stroke volume and cardiac output as will be described in the following sections. USCOM uses continuous wave (CW) Doppler to measure VTI and therefor unlike PW is not reliant on accurate placement of sample volume. The limitation and major source of error in hemodynamic measurements with echocardiography arises from the difficulty in measuring the aortic and pulmonary outflow diameters. [307] USCOM predicts the diameter of aortic and pulmonary valves based on a proprietary algorithm. The algorithm is similar to equations introduced by Nidorf *and* colleagues in 1992. [308] Measurement of VTI is largely automated and enables several ejection wave-forms to be measured, which can then be averaged to provide beat-to-beat hemodynamics. British Society of Echocardiography recommends that an average of a minimum of three measurements should be used for aortic and pulmonary diameters, which takes at least around 5-10 minutes. A typical USCOM examination takes only 3-5 minutes. This is of course less time consuming, more user friendly and has a shorter learning curve in comparison to echocardiography. Lelyveld-Haas *et al*, who measured cardiac output in a total of 1315 critically ill patients, showed that inter-observer variability is significantly lower than echocardiography, ranging from 5.1 to 17%, which indicates less user dependency. [302]

USCOM benefits

USCOM is non-invasive, rapid, and reliable. By being non-invasive it reduces the risk of infection. USCOM can be used in variety of medical fields such as in neonatal, pediatrics, obstetrics and gynecology, geriatrics and critically ill patients in intensive care units and emergency departments. USCOM is relatively light, easily portable and user friendly. It is easily to learn how to use the device and learning curve is short, therefore can be used by nurses and paramedics as well as doctors. USCOM uses left ventricular outflow tract (LVOT) algorithm, which reduces ECHO LVOT diameter variability and exam time. USCOM measurements are reproducible with less intra-operator variability (r: 0.911) [289], [310] USCOM has rapid acquisition time with instantaneous calculation ability of the parameters leading to reduced exam time.

Figure 1.9. USCOM is positioned on suprasternal notch to measure trans-valvular Aortic flow. Adopted from https://imedicimaging.com/uscom-1a/.

1.15 Haemodynamic parameters

USCOM directly measures aortic flow by being placed on suprasternal notch. By placing the probe on parasternal border, USCOM measure pulmonary flow. Operator then can adjust the location and angel of the probe using visual clues from the USCOM 1A display. The USCOM 1A displays 24 haemodynamic parameters of cardiac performance. **(Table 1.15)** Eight of them are user entered values including Central Venous Pressure (CVP), Diastolic Blood pressure (DBP), Systolic Blood Pressure, Oxygen Saturation (SO2), Haemoglobin (Hb), Height and Weight. **(Table 1.16)**

Table1.15. List of haemodynamic parameters measurable by USCOM 1A.

Vpk	Peak Velocity of flow
VTI	Velocity Time Integral
HR	Heart Rate
MD	Minute Distance
ET%	Ejection Time Percent
SV	Stroke Volume
SVI	Stroke Volume Index
SVV	Stroke Volume Variability
CO	Cardiac Output
CI	Cardiac Index
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
Pmn	Mean Pressure Gradient
ET	Flow Time
Etc	Flow Time corrected
SW	Stroke Work
CPO	Cardiac Power
SMII	Inotropy Index
PKR	Potential Kinetic Ratio
OTD	Outflow Tract Diameter

Table 1.16. List of user-entered haemodynamic parameters.

CVP	Central venous pressure
SBP	Systolic BP
DBP	Diastolic BP
MAP	Mean arterial BP
Hb	Haemoglobin
SO2	Oxygen saturation
Hb	Haemoglobin
SO2	Oxygen saturation
Height	Patient's height in cm or inches
Weight	Patient's weight in kg or pounds
BSA	Body surface area

Reference ranges for haemodynamic parameters as measured by USCOM have been established for full-term neonates. [291], [292] Chinese children aged 1 month – 12 years, [303], [311] adolescents aged between 12 – 18 years, [312] adults aged between 18 – 60 years (unpublished data), and the elderly aged 60 – 85 years, [313] all of which are consistent with well-established values.

1.16 The Unmet Need, and the Need for this Study

90-day mortality from severe sepsis and septic shock in Wales and England ranges from 50% to 28%, significantly higher than the ARISE study from Australasia, where mortality was 18%. Hospitals with the most optimal outcomes reach 12% mortality, and some of this success is attributed to the introduction of haemodynamic protocols, which focus on optimising CO, SV, CP and DO2. The Churpek analysis above suggested that the most recent recommended method for detecting shock, i.e., qSOFA, is simply not good enough for assessing clinical deterioration in clinical practice. NEWS and MEWS are potentially better but need validation. **The standard to aim for with any new strategy is a sensitivity and specificity > 67% and >72% respectively for determining in-hospital mortality.** The LiPS study holds potential for being at least as good as MEWS and NEWS but requires further validation and refinement. None of these tools have evaluated advanced haemodynamics and its potential to improve sensitivity and specificity. Part of the difficulty associated with optimising haemodynamics is the inability to measure haemodyanmic parameters such as SVR, CP and DO in the pre-hospital and ED setting in a safe and quick way. The USCOM is a new device that uses standard physiological principles to facilitate the measurement of CO, SVR, CP, DO and central and peripheral pressures and waveforms using safe, accurate and reliable non-invasive means. The USCOM has been available in the UK for 10 years but there has been little research into its value to improve healthcare processes and outcomes. Therefore, it is not currently being used in clinical practice in the UK, although there is increasing interest in Australia and Asia. Establishing the value of these protocols and devices to improve process management and healthcare outcomes would clearly benefit patients in the UK. The limited timescale of this project would allow an initial proof of concept and feasibility study. A larger study may be required to demonstrate the potential generalisability of the findings. Despite the promising results, the single-centre, Australian quality improvement program can only be considered ‘proof of concept’ and it is necessary to establish whether these results are feasible in the UK setting and whether there are trends to support change. The sample size was small (n=80 patients) and single-centre studies often reflect local, and sometimes unique, processes of care. Results of single-centre studies may not be replicated in larger, multi-centre studies and important examples of this have recently been reported within the critical care literature. Both the National Institute for Health and Clinical Excellence (NICE) and the National Patient Safety Agency (NPSA) have recently highlighted the need for a rapid response to acute deterioration of patients in hospital, including those in the ED. [314], [315] The delivery of early, goal directed, protocolled resuscitation may be usefully integrated into such rapid response systems.

1.17 Aims, Hypothesis and Objectives

The aim of this study is to test USCOM ability of identifying shock at early stages of presenting to ED and predicting poor outcome. The main disadvantages in the UK are that only four EDs currently have access to USCOM at point of care – Cardiff, Royal London, Leicester and Newcastle and there is little robust published data on its application in real-world practice. This research aims to fill a major evidence-gap.

Hypothesis

I hypothesised that:

1. There are significant differences in USCOM-derived haemodynamic variables between patients who die/are admitted to ICU with shock and patients who do not die/are not admitted to ICU and do not have shock.

2. There are significant differences in USCOM-derived haemodynamic variables between patients with different types of shock – hypovolemic, restrictive-sepsis, and restrictive-non-sepsis, cardiogenic, obstructive.

This classification is based on proposed hypothesis:

- **Hypovolemic shock is present if**

Either FTc higher than normal range (321 – 415) i.e., > 415 OR SVV is higher than the normal range (>30),

AND

Systemic vascular resistance index is above the mean of the normal range i.e., >2200.

- **Distributive shock is present if:**

Systemic vascular resistance index is <1800 (i.e., below the normal range (1800 – 2400))

- **Cardiogenic shock is present if:**

Inotropy Index is below the normal range i.e., <1.

3. There are significant differences between LiPS definition of shock and clinician gestalt in identification of shock and its relation to mortality.

4. There are significant differences between USCOM-derived haemodynamic and experienced physicians in identification of shock in relation to mortality.

We expect to accept hypotheses 1, 2 and to reject hypothesis 3, 4.

Objectives

1. To investigate whether advanced haemodynamic variables, using USCOM predict 28-day all-cause mortality and ICU admission.

2. To investigate whether advanced haemodynamic variables, using USCOM improve the detection and classification of type of shock.

3. To validate and re-assess diagnostic ability of LiPS tool in internal and external settings.

4. To evaluate clinical gestalt for shock in comparison to LiPS and USCOM-derived shock.

1.18 Novel Aspects of the Study

- Evaluation of haemodynamic variables as predictors of shock, mortality and ICU admission.

There are no published reports for USCOM IA in this area.

- USCOM 1A, as this uses Continuous Wave Doppler (CWD) to measure CO and is not a standard tool in the UK for assessing Haemodynamics.

- Validation of LiPS tool.

- Evaluation of **healthcare worker gestalt** for shock, and severity of illness defined as probability of death or admission to ICU within 28 days.

The study will also inform on the feasibility of future larger RCTs. For example, the study will inform on:

- The infrastructure necessary to perform a future definitive trial, including a Trial Management Group, Trial Steering/Data Management Committee.

- Test the feasibility of the shock studies utilizing USCOM 1A.

- Evaluate and qualitatively explore the collaboration with clinicians in using the USCOM device and algorithms (and reasons for non-compliance) and adherence to interview schedules/focus groups.

- Quantify the number of patients required for a full definitive trial through the estimation of the magnitude of effect and necessary parameters, including the margin of error acceptable to achieve the proposed outcomes.

- Assess the processes of patient recruitment, consent and reasons for non-participation.

- Evaluation of patient acceptability and experience of being evaluated using the USCOM device.

- Assess the quantity and potential patterns of missing data.

- Test the feasibility of collecting the proposed outcome measures for a full trial, including optimal time points, using the electronic case report form.

- Decide whether a fully powered, multi-center randomized trial is indicated by formal assessment of feasibility trial findings.

- If the full definitive impact trial is indicated, then potential research sites across the UK will be contacted for participation and a full trial protocol and funding application to the NIHR will be completed.

Chapter 2

Methods and Materials

In this chapter, I will be writing on essence of haemodynamic parameters, and on how they are measured. Subsequently, I will be writing on the design, setting, recruitment process and conduct of my study. I will be delivering on ethical aspect well as consenting procedure, in line with guidelines of National Institute of Health Research (NIHR).

2.1 How USCOM measures haemodynamic parameters (This section is now moved to chapter 2 from chapter 1)

USCOM measures haemodynamic parameters non-invasively and by using the Doppler ultrasound method.

Essential haemodynamic parameters

Blood pressure

From Ohm's Law, [316] which states that flow (Q) is equal to the pressure gradient (ΔP) divided by resistance (R): Q = ΔP/R, Blood pressure is a product of cardiac output (CO) and systemic vascular resistance (SVR). [317]

BP: CO x SVR

Shock index (SI) is an easy calculable index which is derived from dividing heart rate (HR) by systolic blood pressure (SBP). The normal ranges are 0.5 - 0.7. SI used to predict adverse outcome in haemorrhagic shock, [318], [319] and pulmonary embolism. [320] A systematic review of MEDLINE, EMBASE, Allie and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Open Grey, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (WHO ITRP) in 2016, suggested that elevation of shock index is a moderately accurate predictor of mortality in adult patients with suspected sepsis. An index >= 1 was shown to have low sensitivity and high specificity for mortality prediction. The benefit of shock index is rapid access and simplicity. [321]

Cardiac Output

The cardiac output is the product of the stroke volume (SV) and the heart rate (HR). Therefore, the blood pressure formula can be re-written as:

BP = SV x HR x SVR

Values for cardiac output are usually denoted as L/min. For a healthy person weighing 70 kg, the cardiac output at rest averages about 5 L/min; assuming a heart rate of 70 beats/min, the stroke volume would be approximately 70 ml. Systemic vascular resistance can be calculated from the simple formula:

SVR = BP / CO

USCOM measures cardiac output by first measuring stroke volume, which it does by measuring the ejection velocity time (VTI) of blood flow through the aortic or pulmonary valve. This is achieved by being positioned over the suprasternal notch and the fourth left intercostal space to measure aortic and pulmonary outflow respectively and multiplying this by the cross-sectional area of the orifice **(Figure 1.10, 1.11).** This is based on the continuity equation. This states that the flow in one area must be equal to the flow in a second area if there are no shunts between the two areas. [322] In practical terms, the flow from the left ventricular outflow tract (LVOT) is compared to the flow at the level of the aortic valve. With USCOM the aortic valve area is calculated using the velocity time integral (VTI) which is the most accurate method, preferred and used by echocardiography as well. The flow through the LVOT, or LV Stroke Volume (cm^3), can be calculated by measuring the LVOT diameter (cm), squaring that value, multiplying the value by 0.78540 giving cross sectional area of the LVOT (cm2) and multiplying that value by the LVOT VTI (cm), measured on the spectral Doppler display using pulse-wave Doppler. By calculating the interval between successive pulses, the heart rate can be measured. Multiplying the stroke volume by the heart rate gives us the cardiac output. If we input the patient's blood pressure, then the USCOM can calculate the SVR. [323]

CSA (LVOT) cm2 = 0.785 x LVOT Diameter2

SV = 0.785 x Diameter 2 x VTI (LVOT)

USCOM then displays the stroke volume directly on screen**.** The ejection waveform at the aortic valve approximates a triangle, with a normal velocity range of zero at the base to around 1.4 m/s at the peak. The duration of systole is approximately 350 ms, and diastole around 450 ms, giving a total cycle time of around 800 ms (HR = 75 bpm) denoted by *t*. The mean velocity of ejection can be calculated from the area under the ejection curve by integrating the velocity with respect to time *t*. This is the velocity-time integral or VTI and is known as the stroke distance (SD) as it is the average distance red blood cells travel per heartbeat, normally around 25 cm. (**Figure 1.12, 1.13).**

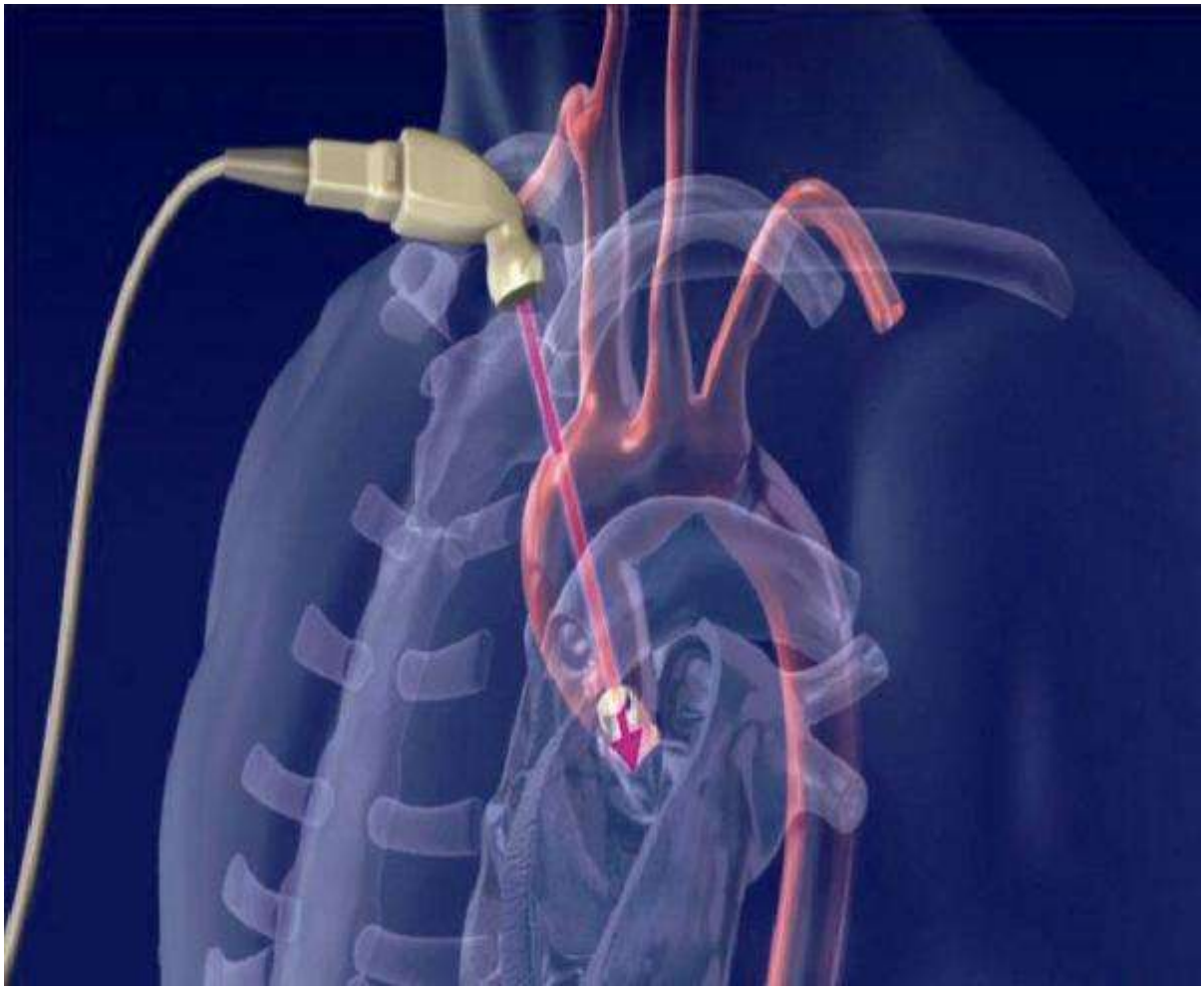


Figure 2.1. How USCOM is positioned to measure trans-valvular Aortic flow: USCOM probe is placed over suprasternal notch to measure trans-aortic flow velocity. Adopted from https://www.slideshare.net/uscom/introduction-to-uscom.

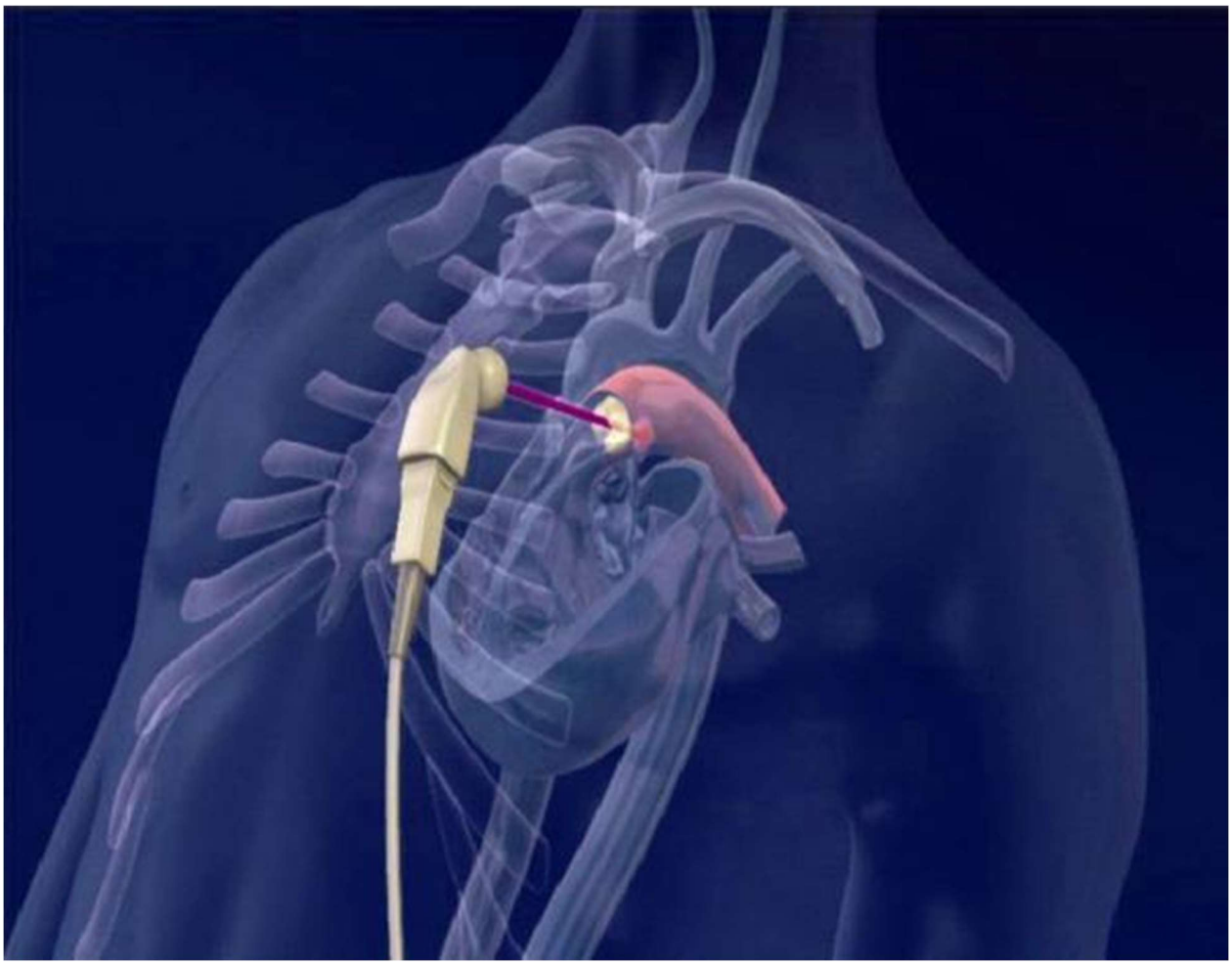


Figure 2.2. How USCOM is positioned to measure trans-valvular Pulmonary flow.
USCOM probe is placed on fourth or fifth left intercostal space to measure trans-pulmonary flow velocity. Adopted from https://www.slideshare.net/uscom/introduction-to-uscom.

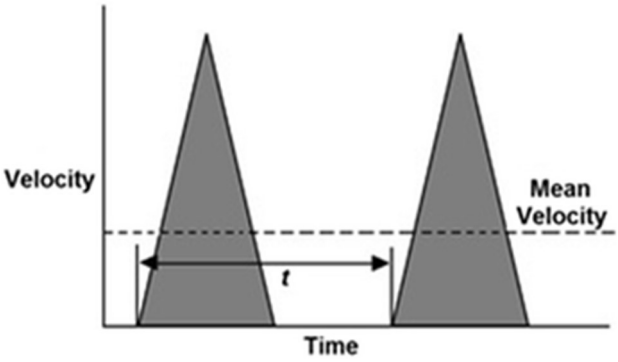


Figure 2.3 Ventriculo-arterial Doppler velocity-time flow profile. The area of the triangle being the mean velocity or velocity-time integral (VTI), and the time between cycles the time or 1/HR. Adopted from Philips R A, et al. Stroke Volume Monitoring: Novel Continuous Wave Doppler Parameters, Algorithms and Advanced Non-invasive Haemodynamic Concepts. 2017.

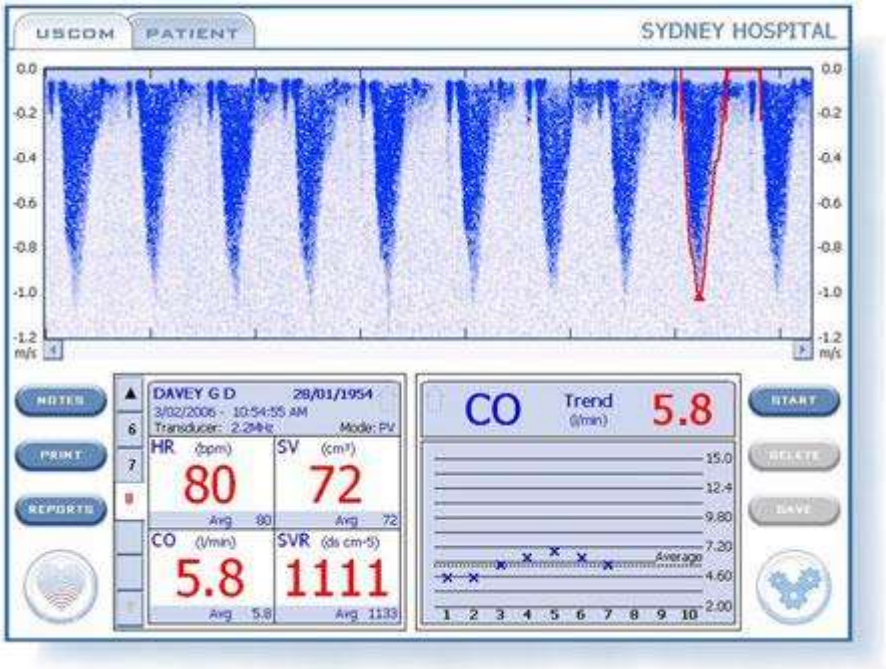


Figure 2.4 Beat to beat quantitative evaluation of haemodynamic parameters. The screen shows Doppler tracing of pulmonary valve Doppler flow. Below numerical readings of haemodynamic parameters are displayed. On the lower right side of the screen, measured cardiac output value and its trending pattern are shown. Adopted from: https://www.intechopen.com/books/artery-bypass/minimally-invasive-cardiac-output monitoring-.2012.

Based on The Frank-Starling law **(Figure 1.14),** cardiac output is synchronized with the venous return, arterial blood supply and humoral length. [323] This is all reliant on right and left ventricular output. Therefore, it is well proven that factors related to preload, afterload and inotropy are well-interlinked.

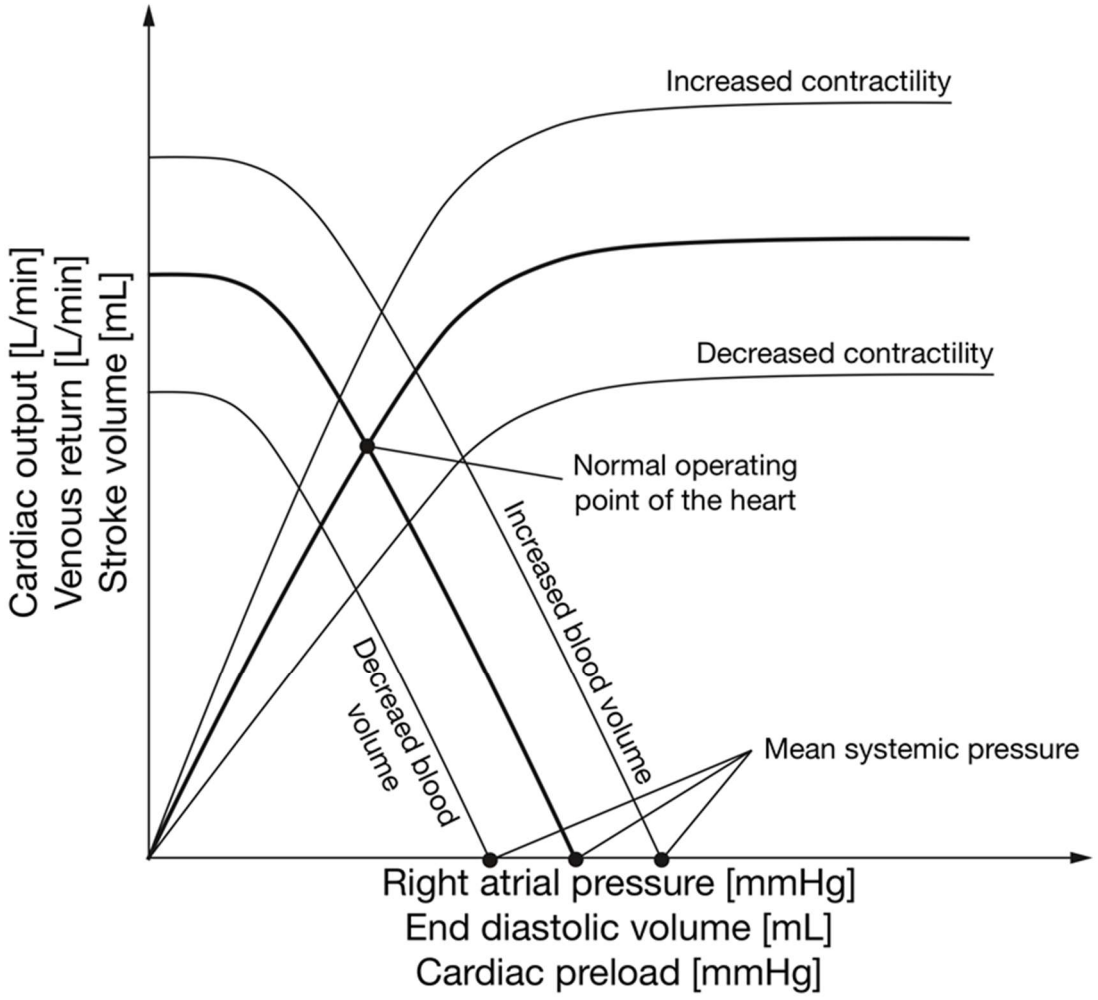


Figure 2.5. The cardiac function curve as predicted by the Frank-Starling law and its coupling with venous return. The intersection of the two curves represents the operating point of the heart. Changes to either the cardiac output or blood volume curve affect how much blood can be circulating and in what way the heart circulates that blood. Adopted from https://belmont.bme.umich.edu/physiology/the-heart.

Venous return (VR) is a product of mean arterial pressure (MAP), right atrium pressure (RAP) and systemic vascular resistance (SVR) as demonstrated in the following formula:

VR: (MAP – RAP) / SVR

Changes in end diastolic volume will directly affect stroke volume and vice versa. This corresponds to the pillars of fluid management in acutely ill patients. Patients who are under-filed will benefit from volume expansion and patients who are overloaded will benefit from vasodilator agents. If appropriate treatment is given, SV and CO will increase, and the same treatment can be continued until they both start falling. By doing a simple leg rising test, if the SV, measured by USCOM, rises as a result of increased blood return to central circulation, this means that the patient is under-filled and if drops it means that patient is already filled.

Preload related haemodynamic parameters

Preload refers to the amount of volume in the ventricle at the end of diastolic phase. In clinical practice the left atrial filling pressure or pulmonary artery wedge pressure (PAWP) are measured as indicators of preload or end diastolic volume by use of invasive techniques such as pulmonary artery catheter, which has its own limitations. [324], (**Table 1.16)**

Table 2.1. Preload related Haemodynamics and units of measurement.

Preload	Units
Flow Time	ms
Flow Time corrected	ms
Stroke volume variability	%

Flow time (FT) / Flow Time corrected (FTc)

Flow time is the duration of time of the flow from the left ventricle during systole. Flow Time corrected (FTc) is Flow Time duration of blood flow in the aorta normalised to 60 beats/min using Bazett's equation. [325] Typically, FTc is one third of the cardiac cycle, equivalent to 0.33 seconds or 333 milliseconds. Thus, typical values for normally hydrated resting healthy individuals are around 330 – 360 milliseconds. [326] Flow time usually correlates to preload. However, if low flow time does not respond to fluid and does not increase SV, high systemic vascular resistance and increased afterload should be considered. Lee *et al,* in a study of twenty neurosurgical patients, evaluated the ability of FTc to predict fluid responsiveness and compared this with the abilities of other preload indices, such as pulse pressure variation (PPV), central venous pressure (CVP), and left ventricular end-diastolic area index (LVEDAI). Haemodynamic parameters were measured before and 12 minutes after fluid loading with 6% hydroxyethyl starch solution (7 ml kg^{-1}). Receiver operating characteristic

(ROC) curves were constructed and compared to evaluate the overall performance of preload related haemodynamic parameters. Areas under ROC curves for FTc were 0.944 (SD: 0.058) and for PPV was 0.909 (0.069) and were significantly greater than those for CVP: 0.540 (0.133), *P* value < 0.001 and LVEDAI: 0.495 (0.133), *P* value < 0.001. This study proved that FTc can predict fluid responsiveness, however, should be used in conjunction with other clinical information. [327]

Stroke volume variability (SVV)

The change in the amount of blood ejected from the left ventricle into the aorta with each heartbeat is called stroke volume variability (SVV). [328] SVV correlates with ventricular filling. It reflects changes of atrial pressures in relation to pattern of respiration. Under normal situations and normal respiration blood pressure drops slightly in inspiration. This is known as pulse paradox. Under positive pressure of mechanical ventilation blood pressure is expected to rise. This is called reverse pulse paradox. Pattern of reverse pulse paradox serves the mechanism of stroke volume variability. [329], **(Figure 1.15)** USCOM calculates SVV as the percentage change between the maximal and minimal stroke volumes (SV) divided by the average of the minimum and maximum. [330], [331]

SVV: SV (max) - SV (min) / SV (mean)

The normal range of SVV under controlled ventilation is less than 10-13%. Currently there are various methods to measure SVV, including *pulse contour analysis, calibrated and non-calibrated pulse power analysis, bioreactance and Doppler ultrasound.* [332] SVV has various clinical applications as a dynamic haemodyanmic parameter reflecting lung and heart interactions and is proven to be an accurate measure of fluid responsiveness. [330] Studies proved that SVV > 10% would indicate fluid response. [333] A systematic review and meta-analysis of clinical trials by Zhang *et el*, investigating the role of SVV in predicting fluid responsiveness, collected data from multiple sources, including MEDLINE, EMBASE, WANFANG, and CENTRAL and included 568 critically ill patients in ICU or operating room. It was shown that SVV measured by PiCCO (Pulse Counter Cardiac Output) has sensitivity of 81% and specificity of 80% in predicting fluid responsiveness (diagnostic Odds Ratio of 18.4). Caution is advised and clinicians need to be aware of the particular ‘cut off’ or ‘grey zone’ threshold values. [334] Some other studies showed that SVV is the only reliable predictor of fluid responsiveness in patients, who are in sinus rhythm, and mechanically ventilated with adequate tidal volumes. [335]

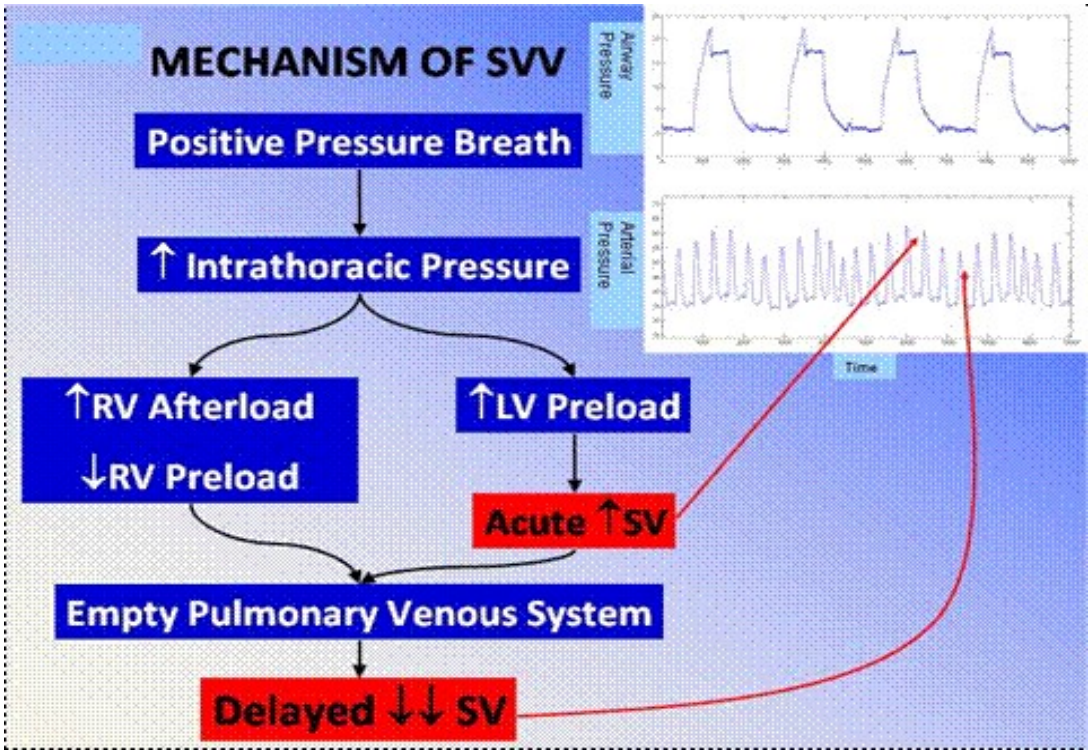


Figure 2.6. Mechanism of stoke volume variability. Under positive pressure of mechanical ventilation blood pressure is expected to rise. This is called reverse pulse paradox. Pattern of reverse pulse paradox serves the mechanism of stroke volume variability. **Abbreviations:** LV: Left ventricle, RV: Right ventricle, SV: stroke volume, SVV: stroke volume variability. Adopted from http://www.scientiacme.org/ccblog.php.

Inotropy related haemodynamic parameters

Inotropy refers to contractile power of the heart and in clinical practice best measured by measuring Inotropy, cardiac output and cardiac power. **(Table 1.17)**

Table 2.2. Inotropy related haemodynamic parameters and units of measurement.

Contractility	Units
Heart Rate (HR)	bpm
Stroke work (SW)	mJ
Cardiac Power	W
Inotropy Index	W/m^2
Peak Velocity	m/s
Mean pressure Gradient	mmHg

Stroke Work (SW)

SW refers to work done by the ventricle to eject the blood out. It is normally product of SV and mean arterial blood pressure:

SW: MAP X SV

SW represents ventricular function during the entire cardiac cycle and incorporates well both with pressure and volume changes. [336] It can be measured separately for the right or left ventricle if invasive catheter guided techniques are used. A retrospective analysis of 115 pre-lung transplant patients between 2005 and 2011 at Presbyterian-Columbia University Medical Center, New York by Hilary and colleagues showed that higher levels of right ventricular stroke work index (RVSWI) are associated with poor outcome and increased mortality, highlighting the significant role of pulmonary hypertension and right ventricular (RV) failure on outcome of lung transplant patients. [337] In this study RVSWI was calculated by the following formula: RVSWI: SVI X (mPAP- mRAP) X 0.0136, where RVSWI is RV stroke volume index, SVI is stroke volume index, mPAP is mean pulmonary artery pressure and mRAP is mean right atrium pressure, measured by Swan- Ganz catheter. [337] Non-invasive techniques free of risks imposed by pulmonary artery catheter, are preferred in order to measure SW.

Cardiac Power (CPO)

Cardiac power (CPO) is an indicator of pumping power of the heart. Tan *et al*, showed that the resting CPO for a hemodynamically stable average sized adult is approximately 1 W. [338] CPO can increase up to 6 W during intense physical activity and can be significantly diminished in patients with chronic heart failure. A report of the Shock trial registry on 541 patients with Left ventricular failure and cardiogenic shock in context of acute myocardial infarction, in which haemodynamics including CO, mean right atrial pressure, pulmonary artery systolic pressure, and pulmonary artery diastolic pressure were measured by PAC and cardiac power output (CPO) (W) was calculated as CPO (W): mean arterial pressure - CO/451, showed that CPO is the strongest independent hemodynamic correlate of outcome. A cut off value of 0.53 was chosen and values of 0.53 W were found to most accurately predict in-hospital mortality (c-statistic: 0.69). The probability of in-hospital mortality with a CPO of 0.53 W was 58% (positive predictive value), whereas the probability of survival given a CPO of 0.53 W was 71% (negative predictive value). [92]

Peak velocity

Peak velocity is an indicator of cardiac contractility and typical values change with age. They are routinely used as diagnostics and to grade valvular stenosis. PV is the highest velocity detected from ultrasound. A study of 28 ICU patients in Fujian Provincial Hospital, China in 2018, showed that the sensitivity and specificity of using peak velocity variations during passive leg rising, measure by ultrasound technique, to predict fluid responsiveness in septic patients were 81.8% and 87.5% respectively, suggesting that peak velocity variation has a role in guiding fluid resuscitation. [339] Low values correlates with high afterload or reduced contractibility. Higher than normal ranges may correlate with the use of inotropic agents and reduced SVR. The following are more detailed approximate values:

20 yrs – 90 -120cm/s
30 yrs – 85 -115cm/s
40 yrs – 80 -110cm/s
50 yrs – 70 -100cm/s
60 yrs – 60 – 90cm/s
70 yrs – 50 – 80cm/s
80 yrs – 40 – 70cm/s
90 yrs – 30 – 60cm/s

Mean pressure gradient

Mean pressure gradient is the average of all the instantaneous pressure gradients throughout ejection. [340] To overcome the problem of stenosis and difference in pressure between the area of stenosis with higher pressures than peak-to-peak pressure, the mean pressure gradient can be calculated by integrating the velocity curve during ejection, and thus the mean gradient. [340] Mean pressure gradient is proven to be a predictor of mortality in severe aortic stenosis. In a large prospective cohort study of 1143 patients with severe aortic stenosis, mean trans-aortic pressure gradient (MTPG) ≥ 60 mmHg had a significantly increased risk of mortality compared with patients with MTPG < 60 mmHg. [341]

Peak Velocity of ventricular ejection (Vpk)

VpK indicates how powerful the ventricle is and can be used as a sensitive global measure of left ventricular performance. It is normally around 1.1 – 1.5 m/s in healthy patients. In patients with cardiac failure or low contractility / inotropy this figure might well be only 0.6 or 0.7 m/s or even less. In a study of 36 patients undergoing diagnostic cardiac catheterisation, peak aortic blood velocity and peak blood acceleration were measured noninvasively by USCOM. Peak velocity and acceleration were measured

at rest just before left ventriculography. In patients with ejection fractions greater than 60%, peak acceleration was 19 +/- 5 m/sec/sec. In patients with ejection fractions of 41% to 60%, peak acceleration was lower, at 12 +/- 2 m/sec/sec (*P* value < 0.001). In patients with ejection fractions of 40% or less, peak acceleration (8 +/- 2 m/sec/sec) was markedly lower than in patients with ejection fractions greater than 60% (*P* value < 0.001). Peak acceleration showed a good linear correlation with ejection fraction (r = 0.90), and a better power fit (r = .93). These results indicate that peak acceleration, measured noninvasively with a continuous-wave Doppler velocity meter, is a useful indicator of global left ventricular performance. [342]

Afterload related Haemodynamic parameters

Afterload refers to resistance or pressure that the ventricles must overcome to eject their blood volumes. In clinical practice this is best measured by measuring systemic vascular resistance (SVR) or pulmonary vascular resistance (PVR). (**Table 1.18)**

Table 2.3. Afterload related haemodynamic parameters and units of measurement.

Afterload	Units
PKR	-
Systemic vascular resistance (SVR)	dynes/seconds/cm^{-5}
Systemic vascular resistance index (SVRI)	dynes/seconds/$cm^{-5/}$ m^2

Systemic vascular resistance (SVR) / Index

Systemic vascular resistance (SVR) refers to the resistance to blood flow offered by all of the systemic vasculature. USCOM calculates SVR by dividing cardiac output measured by calculating SV through VTI and CSA of aortic and pulmonary valves, from blood pressure. USCOM then provides dynamic and beat-to-beat SVR measurements.

SVR (mmHg·min·mL^{-1}): BP (mmHg) / CP (min/ml)

Changes in SVR will grossly impact afterload and guide us in choosing an inotropic agent of choice in managing patients with shock. [23] However, its reliability in adequately assessing left ventricular afterload has been questioned since it is only reflecting peripheral vasomotor tone than ventricular systolic wall force (sigma es), which reflects the combined effects of peripheral loading conditions and left ventricular chamber pressure, dimension, and wall thickness [342] To determine the relationship between SVR and sigma es, Sabbah and colleagues pharmacologically altered left ventricular afterload and contractility in eight dogs instrumented with central aortic microtip and Swan-Ganz catheters. Left ventricular wall thicknesses and dimensions were measured from two-dimensionally targeted M mode echocardiograms. Aortic, right atrial and left ventricular end-systolic pressures as well as cardiac output were recorded. SVR and sigma es were determined under control conditions as well as during infusions of Nitroprusside, Methoxamine, Dobutamine, and Norepinephrine. Control data acquired before each drug infusion were similar. When compared with baseline values, SVR underestimated the magnitude of change in left ventricular sigma es by 22% when afterload alone was decreased (Nitroprusside), 54% when afterload alone was increased (Methoxamine), and 50% when afterload was decreased, and contractility was augmented (Dobutamine). Most importantly, when afterload minimally decreased in association with augmented contractility (Norepinephrine), SVR increased by 21% while sigma es fell by 9%. Thus, discordant changes in the left ventricular afterload (i.e., sigma es) and SVR can occur during pharmacologic interventions, showing unreliability of SVR as a sole indicator of afterload. [342]

Potential to kinetic ratio (PKR)

Potential energy is an indicator of blood pressure and kinetic energy is an indicator of blood flow. The ratio is informative, and the normal ratio is 30/1, showing that more of the ventricular power goes to generating blood pressure rather than flow. In arterial hypertension due to excessive vasoconstriction (as opposed to excessive cardiac output) the PKR is in the range of 60:1 to 150:1. Appropriate therapy with vasodilating medication such as Angiotensin receptor (ACE) inhibitors or calcium channel blockers can reduce the PKR to near normal. Conversely, in hypertension due to excessive cardiac output, the PKR is around 10-15:1. The measure can be used as a method to optimise therapy. [342]

Haemodynamic parameters related to blood flow

Haemodyanmic parameters related to blood flow are those which are not only affected by one but by combination of mechanisms. For instance, minute distance values not only correlate to cardiac contractibility but also to afterload. **(Table 1.19)**

Table 2.4. Blood flow haemodyanamic parameters and units of measurement.

Blood flow	Units
Velocity time integral	m/s
Minute Distance	cm
Ejection Time Percentage	%
Stroke volume (SV)	ml
Stroke volume index (SVI)	ml/m^2
Cardiac Output	ml
Cardiac Index	ml
Stroke volume saturation (SVS)	%

Minute Distance

The minute distance is how far the red blood cells travel in one minute. The area under the velocity-time curve for each heartbeat gave stroke distance, which, when multiplied by heart rate, gave minute distance. The normal flow rate for the aortic minute distance (AMD) is 14 - 22 m/min and for pulmonary artery (PMD) is 10 -16 m/min. MD has a progressive decline with age by 1% per annum of adult life. An aortic flow rate of 10 m/min is too slow and represents hypodynamic circulation. An AMD of 28 m/min is too fast and represents a clearly hyperdynamic circulation. MD correlates well with cardiac output but also can be affected by changes in afterload. In a study of 20 anaesthetised pigs before and during cardiac arrest, esophageal Doppler monitor (EDM, Deltex) was used to measure MD and CO. The study showed that MD correlated well with CO (r^2=0.96) before and during CPR. [343], [344]

Ejection Time percentage (ET%)

Left ventricular ejection time (LVET) measures the period of blood flow across the aortic valve and has a normal value of 0.35 +/- 0.08 second. It is influenced by heart rate, preload, afterload, and contractile state. ET shortens with Mitral valve regurgitation and left ventricular failure. It can increase with compensated aortic stenosis and high cardiac output state. It can be calculated non-invasively by different methods; a) carotid pulse contour (or invasive arterial line), b) M-mode echocardiogram of the aortic valve, and c) Doppler systolic aortic outflow tracing. [345] A study of 1980 middle-aged African Americans, where left ventricular ejection time

(LVET) measured by pulse wave echocardiography, showed that LVET is an independent predictor of incident heart failure (hazard ratio 1.07 (1.02-1.14), *P* value: 0.010 per 10 ms decrease) and provides incremental prognostic information on the risk of future heart failure and death when added to known risk prediction models. [346]

Cardiac Index (CI)

Cardiac output can be indexed by dividing the values of CO by body surface area, allowing direct comparison of these data in patients with different body size and also defining values that will be considered as normal. The unit of measurement is liters per minute per square meter ($l/min/m^2$).

Haemodynamic parameters related to tissue perfusion

Haemodynamic parameters indicating oxygen delivery are measures of shock.

Table 2.5. Perfusion related haemodynamic parameters and units of measurements.

Tissue perfusion	Units
Oxygen delivery	ml/min
Oxygen delivery index	ml/min/ m^2

Oxygen Delivery/ Index (DO2)

Oxygen delivery (DO_2) is the amount of oxygen in the blood delivered to the body's tissues. The ultimate goal of resuscitation is to ensure adequate oxygen delivery (DO_2) to prevent or treat organ dysfunction. Shock is tissue hypoperfusion secondary to reduced oxygen delivery. It can be defined quantitatively by use of haemodynamic parameters:

DO_2 equation (DO_2) = 1.34 x [Hb] (g/L) x CO (L/min) x SpO_2 (%) / 100)

Where DO_2 is oxygen delivery, Hb is haemoglobin, CO is cardiac output, and SpO_2 is oxygen saturation. All these parameters can be easily measured in the ED by USCOM. Shoemaker *et a*l, showed that when the optimal values of cardiac index, DO2, and VO2 used as therapeutic goals were attained in 8 to 12 hours, there was marked and significant reduction in mortality and morbidity rates. [347] This finding was also confirmed in 12 prospective, controlled trials, four of which were randomized.

For each haemodynamic value the normal ranges are different between adults and children and should ideally be indexed as per body surface area in order to give more accurate values and guide management strategies more appropriately.

2.2 Study setting/Context

Our study was held at the University Hospital of Wales (UHW) (Cardiff and Vale University Health Board), which is a university hospital and a tertiary referral center. On average, the ED sees 400 new patients a day of whom 5 to 10 are adults with shock of some description.

2.3 Ethics and Study design

Ethics approval was sought from Wales Research Ethics Committee 2 with the authority to approve projects involving adults who lack capacity to consent. Institutional and Sponsorship approval was obtained from Cardiff University and NHS Research and Development (R&D) approval was sought from Cardiff and Vale UHB to conduct a prospective, single-center, cohort study on adult patients with possible shock associated with an acute illness or injury who presented to the Emergency Department of the University Hospital of Wales, Wales, UK.

2.4 The Approach for Recruitment and Consent

Selection of patients

All patients presenting at the ED were first assessed by the treating ED clinical team and received standard care in accordance with the current best practice. The treating ED clinical team then contacted the dedicated Study Research doctors. Standard care included the following assessments or procedures that are required to evaluate the suitability of patients for the trial:

• In patients with suspected or confirmed infection this should include having arterial or venous blood lactate measurement to assess for the presence of hypoperfusion

Additional investigations and evaluation of the suspected shock occurred as part of standard clinical management. It was also expected that a minimum IV fluid challenge of one-liter fixed bolus within sixty minutes, will be given as part of standard resuscitation for patients with suspected or confirmed infection and evidence of hypotension.

2.4.1 Target Population

Consecutive adult patients presenting to the ED of UHW Wales with a NEWS ≥ 3, requiring a trolley were considered for the study.

Inclusion criteria

Patients must meet all the inclusion criteria to be recruited to the study:

- Adult patients aged ≥18 years
- A NEWS ≥ 3
- Requiring a trolley
- Within one hour of ED arrival

Note that patients were not excluded if they are known or found to be pregnant, have congenital heart disease or aortic stenosis, or post-seizure, or post-exercise but they may have been excluded from analysis.

Exclusion criteria

- Age <18 years

2.4.2 Consent

Previous work on informed consent in critically ill patients, conducted by ICNARC alongside the PAC-Man Study (a randomised controlled trial of 1014 patients in 65 critical care units), indicated that only a minority (2.5%) may be able to provide informed consent. [348] While the proportion of patients able to give informed consent was likely to be considerably higher in this trial, it was essential to have robust plans in place for situations in which informed consent was not possible. Written consent was obtained either from the patient or a relative wherever possible. A waiver of consent was applied to patients who, because of confusion, unconsciousness, or severe disability, were unable to give consent, and when a relative was not present. In these cases, consent was first sought from a second doctor and/or nurse. Thereafter, consent was obtained from the patient or a relative as soon as practically possible. Unless the patient was critically ill the patient or relative were given up to 10 minutes to advise whether to enter the study or not. One of the investigators (either SK or AN), who are NHS staff, approached patients who met the inclusion criteria, if they were deemed well enough to provide consent. Patients were provided with the **DiPS Study Patient Information Leaflet and the DiPS Study Patient Consent Form,** if they were deemed to have capacity to consent and were in a stable condition at the time of consenting. Once eligibility was confirmed and, if the patient was able to give informed consent, then authorised staff described the study, supplementing the oral information with the Patient Information Sheet (PIS). Patients were made aware of the potential risks and benefits. After the doctor or nurse had checked that the PIS and Consent Form were fully understood, the doctor or nurse invited the patient to sign the form and then added their own name and countersigned it. Where an eligible patient was deemed to have capacity to consent but was not in a stable physical condition, one of the study investigators described the study and supplemented the oral information with the **'DiPS Study Patient Information Sheet and Verbal Consent BRIEF'** document. The 'DiPS Study Patient Information Sheet and Verbal Consent BRIEF' document provided the key study information in a very brief and simple manner and allowed for verbal consent to be taken from patients (subject to ethical approval). Any patient provided with the 'DiPS Study Patient Information Sheet and Verbal Consent BRIEF' were re-approached by the study investigators when they were in a stable condition and provided with the '**DiPS Study Patient Information Sheet in RETROSPECT' and the 'DiPS Study Patient Consent Form in RETROSPECT'** documents. The provision of the retrospective PIS and Consent Form allowed the patient to fully consider their participation in the study and they could choose to continue in the study or to cease their involvement and withdraw their data at this point. Where eligible patients were deemed neither to be stable enough nor have the capacity to provide informed consent and a suitable Personal Consultee was available to consider the presumed wishes of the patient, then the Personal Consultee was approached to consider whether the patient would wish to enter the study. The study investigators explained the study to Personal Consultees (see section 2.3.1 for a full definition of a Personal Consultee) and provided them with the **'DiPS Study Consultee Information Sheet' and the 'DiPS Study Consultee Consent Form'.**

Any patient consented via a Personal Consultee was re-approached when they were deemed to be in a stable condition and had adequate capacity to consent and were provided with the **'DiPS Study Patient Information Sheet in RETROSPECT' and the 'DiPS Study Patient Consent Form in RETROSPECT' documents.** The provision of the retrospective PIS and Consent Form allowed the patient to fully consider their participation in the study and they could choose to continue in the study or to cease their involvement and withdraw their data at this point. **Table 2.1** is describing the situations in which each Participant Information Sheet and Consent Form would be used.

Appendix 2.1 provides a summary of different types of patient information sheets and consent forms used in study and provided to patients or waiver of consent.

Proposed action where fully informed consent is not possible

Consultation

If the patient was not competent to give informed consent and there was a Personal **Consultee** present to advice on the presumed wishes on the patient, authorised staff described the study to the patient's Personal Consultee, supplementing the oral information with the DiPS Study **Consultee** Information Sheet and the DiPS Study **Consultee** Consent Form. After the study investigators had verified that the DiPS Study **Consultee** Information Sheet and the DiPS Study **Consultee** Consent Form were understood, the study investigators invited the Personal Consultee to sign the form and then added their own name and countersigned it.

In accordance with the Department of Health's 'Guidance on nominating a consultee for research involving adults who lack capacity to consent' (February 2008), [348] a Personal Consultee may be:

- A family member, (unpaid) carer or friend.
- An attorney acting under a Lasting Power of Attorney.
- A court-appointed deputy, provided that they had a relationship with, or personal knowledge of, the person lacking capacity before their appointment as deputy.

If there was no Personal Consultee present, then the patient was provided with, if in place at the hospital, a suitable Nominated Consultee (Independent Mental Capacity Advocate or member of the NHS team caring for the patient) appointed by the Health Board, if immediately available. The Nominated Consultee was an NHS member of staff with no connection to the study. Informed consent was addressed in the same manner as for the Personal Consultee. Copies of the signed DiPS Study **Consultee** Consent Form were placed in the hospital notes. If a patient or their consultee (Personal or Nominated) refused consent, the patient received usual resuscitation as defined by the clinician responsible for the care of the patient. If there was neither a personal or Nominated Consultee immediately available, then the study investigators proceeded with the study, using the process detailed below under Section 32(9) of the Mental Capacity Act 2005. [349], [350]

Emergency consent

It was likely that, due to the emergency nature of the patients' condition with immediate intervention necessary, there were no legal representatives (Personal or Professional Consultee) available.

The Mental Capacity Act 2005 allows consent through this method when:

a) The research is related to the impairing condition that causes the lack of capacity or to the treatment of those with that condition; or

b) The research cannot be undertaken as effectively with people who do not have the capacity to consent to participate.

Also, the Mental Capacity Act 2005 states that the research:

c) Will be likely to be of benefit to the person lacking capacity, either directly (i.e., by improving her/his personal circumstances) or indirectly (by improving the quality of treatment or care more generally), and that this benefit is in proportion to any burden on that person caused by taking part; or

d) Will serve to increase knowledge of the cause, treatment, or care of people with the same or similar condition and that the risks to participants will be negligible, with no significant interference with their privacy or freedom of action

The Approach for Retrospective or deferred consent

If patient or relative consent has not been possible prior to entering the study, then as soon as possible thereafter, one of the investigators (either SK or AN) approached either the patient, when their condition was more stable, or a relative when they appeared. This process was repeated every 24 hours until consent was obtained. The aim was to continue to seek to obtain consent directly from the patient as soon as possible irrespective of whether a doctor or relative had given prior consent. If the patient recovered and subsequently became able to give consent, then a Retrospective Consent Form was completed. All consent procedures adhered to the Mental Capacity Act 2005. This procedure was the same as if the patient was approached prior to entering the study but using a specific Retrospective Patient Information Sheet. If any patient refused retrospective consent or if any patient or their legal representative (Personal or Nominated Consultee) withdrew consent at any time during the study, then that patient's data was destroyed from the secure, dedicated, study web data entry system and the patient continued to receive usual treatment as defined by the clinician(s) responsible for the care of the patient.

Table 2.6. Brief Summary of the Consenting Process.

	Patient	Relative	Consultee	Patient Information Sheet and Consent Form
	In Emergency Department			
	Has capacity and IS stable	-	-	• DiPS Study Patient Information Sheet v1 20170328 • DiPS Study Patient Consent Form v1 20170328 **OR** • DiPS Study Patient Information Sheet and Verbal Consent BRIEF v1.0 20170328 (Any patient who is provided with the DiPS Study Patient Information Sheet and Verbal Consent BRIEF v1.0 20170328, will be given both the DiPS Study Patient Information Sheet in RETROSPECT v1 20170328 and the DiPS Study Patient Consent Form in RETROSPECT v1 20170328 when they are deemed well enough to provide full consent.)
	Has capacity but is NOT stable	-	-	• DiPS Study Patient Information Sheet and Verbal Consent BRIEF v1.0 20170328 (Any patient who is provided with the DiPS Study Patient Information Sheet and Verbal Consent BRIEF v1.0 20170328, will be given both the DiPS Study Patient Information Sheet in RETROSPECT v1 20170328 and the DiPS Study Patient Consent Form in RETROSPECT v1 20170328 when they are

				deemed well enough to provide full consent.)
	Has NO capacity or is NOT stable	Present	'Personal consultees' (i.e., relatives) if available	• DiPS Study Consultee Information sheet v1.0 20170328 • DiPS Study Consultee Consent Form V1.0 20170328
	Has no capacity or is not stable	Not present	'Nominated consultees' (i.e., professional/ staff consultees)	Medical staff independent of the study team will be approached to consider whether the patient can take part in the study. Any patient entered the study in this manner will be provided with the both the DiPS Study Patient Information Sheet in RETROSPECT v1 20170328 and the DiPS Study Patient Consent Form in RETROSPECT v1 20170328 when they have regained consciousness and are deemed well enough to provide full consent.
	Later			
	Regains capacity and IS stable	-	-	• DiPS Study Patient Information Sheet in RETROSPECT v1 20170328 • DiPS Study Patient Consent Form in RETROSPECT v1 20170328

Patients were divided into two groups; Adult patients with capacity and adult patients who lack capacity either due to learning disabilities or severity of disease. A waiver of consent was applied when the patient was deemed to lack capacity. RETROSPECT consent applies once patients have regained consciousness and are deemed well enough to provide full consent. **Abbreviations**: DiPS; Diagnostic Investigation of Shock.

2.5 Recruitment

We ran a preliminary, pilot study between July to September 2017. We showed that 32% of critically ill patients admitted to resuscitation room of emergency department had shock. 25% of these patients met the primary outcome and were admitted to ICU or died within 28-days. Miss-classification of LiPS was 27%, which is likely explained by failure to utilize the criteria in its full capacity and clinicians' tendency to continue using conventional definition of shock based on blood pressure and heart rate. There was minimal agreement between LiPs and clinical impression of shock however, USCOM and clinicians had acceptable agreement on diagnosis of patients with high likelihood of shock.

During September 2017 to October 2018, a rough, total of 21,600 patients were screened. We undertake a pragmatic recruitment approach, mainly during office hours with availability of at least one of the study doctors. To reduce selection bias and maintain heterogeneity of data, at times we undertook recruitment out of working hours such as in late evenings or during night shifts. Based on inclusion criteria; adult patients aged ≥18 years with NEWS score ≥ 3 and requiring a trolley within one hour of ED arrival**,** 361 patients, equal to calculated sample size, fulfilled the inclusion criteria, consented, and were included in the analysis (Sample size calculation is described at later stage in chapter 3). Only two patients' data were extracted as completion of full USCOM assessment was not possible due to either patient being very unwell or died before assessment took place. To avoid selection bias, we intended to obtain data on patients, who were critically unwell and ED clinicians had to be attending them at all times, from the arrival to ED until death or admission ICU. This meant that study doctors were informed of estimated time of arrival of these patients to ED and were present at the time of arrival, examination, diagnostic work up and treatment. They were performing simultaneous USCOM measurements alongside clinicians in charge of these patient's treatment, who were performing investigations and delivering treatment. In that regards, staff of emergency department of University Hospital of Wales significantly collaborated to the conduct of our study and facilitated data gathering. The strength of this approach was that study doctors were able to measure haemodynamic parameters on arrival before administration of treatment. This was to avoid any delays in approaching patients and measuring observational and haemodynamic values needed for conduct of study. Such delays could potentially affect the accuracy of utilising haemodynamic values in diagnosis and classification of shock. Use of haemodynamic values through administration and after completion of treatment is out of the scope of this research and can be subject to further studies assessing haemodynamic response to treatment. The only weakness to this approach was that sometimes, there were a number of presentations to ED at the same time, who were fulfilling the inclusion criteria. Hence, study doctors were not always able to attend them at earliest possible and including all of them in recruitment process was impossible.

2.6 Measurements / data collection

In my study doctors were members of the NHS care team and had access to patient medical records in their clinical capacity. They used a sophisticated, digital data collection application, which enabled them to collect extensive data on patient demographics including sex, age, ethnicity, height, weight, and data including presenting complaint, past medical, drug and family history. Using automated devices, we measured heart rate, systolic, diastolic, and mean blood pressure (SBP, DBP, MBP), pulse pressure and oxygen saturation. By clinical impression we measured respiratory rate, presence, or absence of a radial pulse and, if present, whether the pulse was bounding, normal or weak; capillary return, peripheral skin temperature (cold, normal, warm), skin color (blue, pink, white, red), mottled skin. Glasgow Coma Score (GCS). Arterial pressure was measured with an appropriately sized cuff using an Oscillometric device (Omron HEM-7200 Automatic Blood Pressure Monitor, Omron Healthcare Co., Ltd, Japan). Pulse pressure (SBP-DBP) was calculated from measured variables. Investigation results such as full blood count, serum creatinine, urea and electrolytes, venous blood gases, PH, lactate, blood glucose, Haemoglobin, Liver function test and C-reactive Protein (CRP), electrocardiographs (ECG), x-rays and other modality scans, all of which are part of the standard care for patients were included. Additionally, they collected data on patient destination and mortality. Haemodynamic parameters were measured by use of USCOM after the clinical assessment was performed by an ED clinician. Note that these readings could be repeated while shocked patients were receiving resuscitation treatment to assess their response. Prior to the study, study doctors (SK and AN) received extensive training on how to use USCOM. The training process was supervised, and their competencies were assessed and approved by Professor Rainer, Professor of Emergency Medicine who recently returned to the UK after 20 years' service in Hong Kong. He has been working on haemodynamics, risk-stratification and USCOM, and has published over 45 articles, abstracts, and letters on this subject in The Lancet and leading specialty journals.

2.7 Medical Assessment

Within 30 minutes of assessing the patient, and with all available data in the emergency room, doctors were asked to state:

- The probability of shock.

- The probability of shock type / diagnosis – restrictive (Septic or Anaphylactic), obstructive (Pulmonary embolism or Pericardial tamponade), hypovolaemic or cardiogenic.

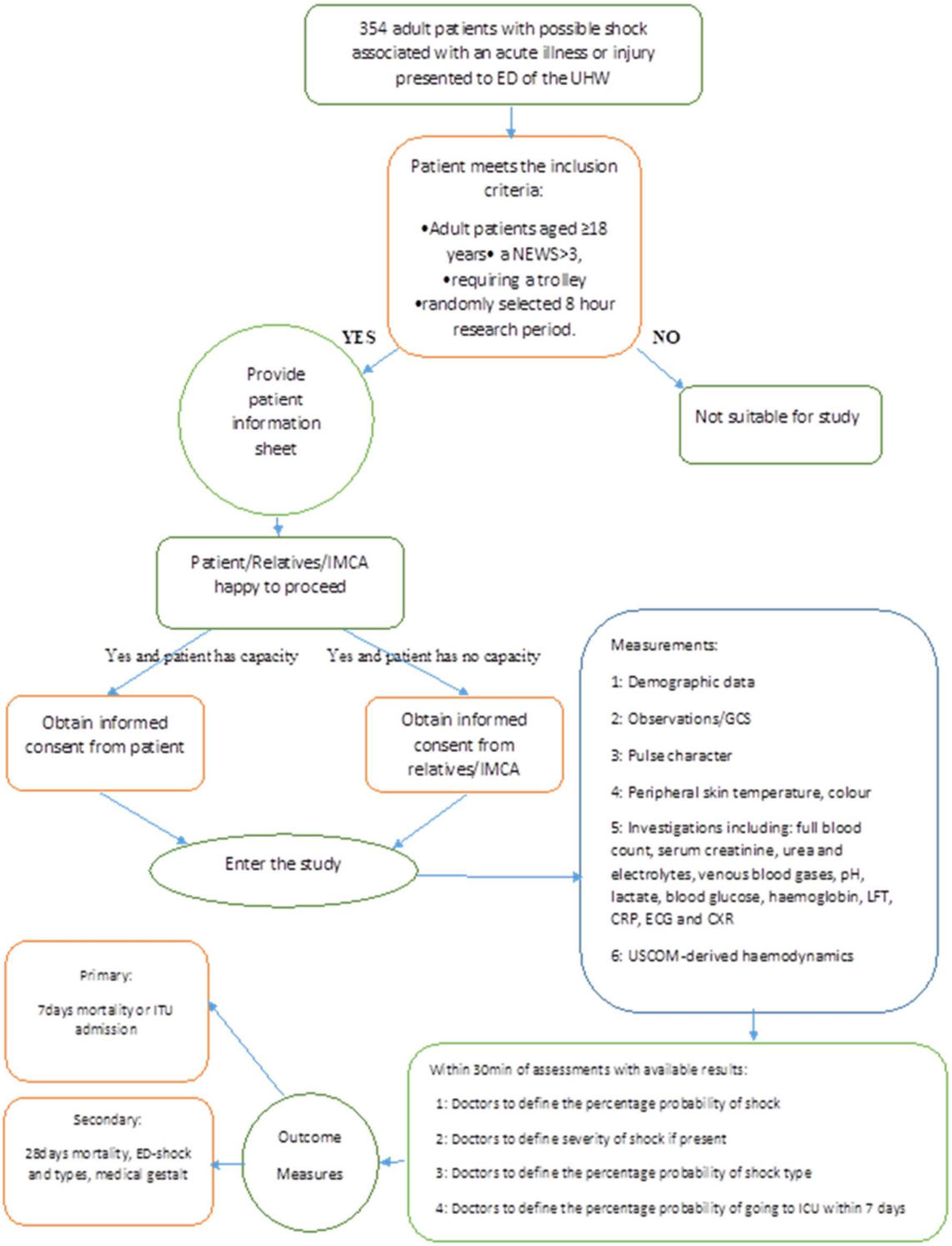
- The severity of shock if present i.e., probability of death within 28 days:

-	Very mild i.e., probability of death	<1%
-	Mild i.e., probability of death	1 – 5%
-	Moderate i.e., probability of death	6 – 25%
-	Severe i.e., probability of death	26 – 50%
-	Very severe i.e., probability of death	51 – 100%

Summary of research Plan, design and theoretical/conceptual framework is outlined in the following diagram.

Diagnostic Investigation of Pragmatic Shock criteria in the Emergency Department (DiPS Study)

Research Plan, Design



LiPs definition

A summary of Li's a priori Shock (LiPS) definitions of shock, possible shock and no shock groups was described previously in Chapter I, is outlined here:

Patients were classified as **'No Shock'** if all the following criteria are present.

1. There are signs of normal tissue perfusion i.e., normal skin (not mottled).

2. Blood pressure is 'normal', defined as both a systolic blood pressure (SBP) ≥90 mmHg, and a mean arterial pressure (MAP) ≥65 mmHg; and

3. Acid-base status is 'normal' defined as a lactate level <1.5 mmol/L, and a pH >7.3, and a base deficit of 0 to >-3 mEq/L.

Patients were classified as **'Possible Shock'** if there is a sign of normal tissue perfusion, as defined above, normal blood pressure defined as both a SBP ≥90 mmHg, and a MAP ≥ 65 mmHg, but some degree of abnormal acid-base status defined as either a lactate level of 1.5 to 4.0 mmol/L, or a pH of 7.1 to 7.3, or a base deficit of -3 to -5 mEq/L.

Patients were classified as **'Shock'** if any ONE of the following were present:

1. Evidence of overt sign of tissue hypoperfusion such as mottled skin; or

2. Evidence of an 'abnormal' blood pressure defined as either a SBP <90 mmHg, or a MAP <65 mmHg; or

3. Evidence of grossly abnormal acid-base status defined as a lactate level ≥4.0 mmol/L, or a pH ≤7.1, or a base deficit of ≤-5 mEq/L.

Urine output was not considered as a criterion for the definition of shock in this study as patient stay in the ED was intended to be short. Hypotension was not necessary for the diagnosis of shock, and acidosis could be variable. However, for the purposes of this study, hypotension was defined as either a SBP < 90 mmHg or a MAP < 65 mmHg. Metabolic acidosis was defined as either a lactate ≥ 4 mmol/L or a base deficit ≤ -5mmol/L. We used the term 'cryptic shock' for those cases with probable global tissue hypoperfusion but with a sBP ≥ 90mmHg. For the purpose of this study, cryptic shock is thus defined as a metabolic acidosis in the presence of a normal blood pressure, in the absence of genetic, pharmacological or renal causes for the acidosis. Refractory hypotension was confirmed either by the presence of a systolic blood

pressure of less than 90 mmHg or a mean arterial pressure of less than 65 mmHg, despite a minimum IV fluid challenge of one-liter fixed bolus within sixty minutes (including IV fluids administered by pre-hospital personnel), or by Hypoperfusion as confirmed by a blood lactate concentration of 4mmol/L or greater.

Refining LiPS

LiPS will be refined to incorporate additional significant variables, which were selected based on logistic regression analysis. We explored the potential for different pragmatic models in the context of ED assessment of patients. The rationale for refining the definition is because there are inaccuracies in the current LiPS, which will be improved by adding other tests. Furthermore, LiPS was developed based on expert opinion and an a priori approach. Objective statistical methods throughout the process, such multivariate logistic regression, produce a more robust model with more stable diagnostic and predictive accuracy.

The acceptable standard

There is no gold standard for the diagnosis, type, and classification of shock against a wide spectrum of patients with undifferentiated illness. Invasive methods may be ideal but are at best impractical in the emergency setting. Therefore, alternative reasonable and pragmatic standards need to be devised and accepted. These may include the need for intensive care, short term-mortality, a composite of both, and correlations against other tools such as APACHE II and MPM score. In this study, validation was sought firstly by demonstrating a significant relationship between classification groups and common individual variables usually available in an ED, and secondly, by demonstrating a “dose-response” relationship between the predicted severity of shock and mortality.

2.8 Follow Up

All patients were followed up at 28-days by visiting their hospital site or searching their electronic patient record (EPR). Study data for patients who have entered or been entered into the study, but who subsequently died during their time in the ED, were retained for the purposes of the study.

2.9 Outcome measures

The primary outcome:

- In-hospital mortality (within 28 days)
- Admission to ICU within 28 days

The secondary outcomes:

- Types of ED-shock
- Validate and refine LiPs
- New gold standard of shock; DiPs

The tertiary outcomes:

- Feasibility variables

The **primary outcome** was defined as admission to either ICU/ CCU within 28 days, or death from any cause within 28 days.

The **primary outcome measure** was the number of patients with either admission to ICU within 28 days or all-cause mortality within 28 days.

The **secondary outcome** of ED shock was defined as probable shock according to LiPS.

The **secondary outcome measure of ED shock** was the number of patients in the ED with probable shock according to LiPS.

The **secondary outcome measure of type of ED shock** was the number of patients in the ED with restrictive, distributive, cardiogenic and obstructive shock.

Tertiary outcomes, for this type of clinical research in the emergency setting, included patient acceptance and experience, medical and nursing acceptance and experience, and evaluation of the infrastructure necessary to perform future definitive randomised controlled trials of this type in an emergency setting, was to inform on sample sizes for future studies, to assess the processes and workload involved in patient recruitment, consent and reasons for non-participation, and assess the potential loss to follow up and impact on analysis and interpretation.

2.10 Data analysis

Data was analysed using the specialist software, MedCalc version 15.8 (MedCalc Software, Mariakerke, bvba, Belgium). The first objective was to investigate whether advanced haemodynamic variables using USCOM, predict 28-day mortality and ICU admission. Normality test was used to define data distribution pattern. Medians and interquartile ranges, means and standard deviations were calculated as appropriate. In a univariate analysis potential factor for determining the primary outcome were identified. T-tests, Mann-Whitney, Chi-squared and Kruskal-Wallis tests were used to compare variables. A *P* value of ≤ 0.05 was considered as significant. We used receiver operating curve (ROC) and assessed sensitivity, specificity, odds ratios, positive predictive value (PPV) and negative predictive value (NPV) for variables. Univariate logistic regression was applied to all independent variables, where 28-day ICU/mortality was the dependent variable. Multivariable Cox proportional hazard regression was used to calculate unadjusted and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Variables with *P* value of < 0.05 were entered a predictive model. Insignificant variables were removed stepwise. We also utilised ROC curves and assessed sensitivity, specificity, odds ratios, positive predictive value (PPV), negative predictive value (NPV), accuracy and prevalence for the model. The second objective was to investigate whether advanced haemodynamic variables using USCOM improve the detection and classification of shock. Patients with high probabilities of shock were assessed for the degree of abnormality of CO, SVR, Inotropy and DO2. CO, SVR, Inotropy and DO2 in patients in the upper quartile of the probability of shock were compared with the same variables in patients in the lower quartile of shock. Differences were compared using the t-test and Mann-Whitney test. The third objective was to validate and refine the LiPS method for detecting and classifying shock. LiPS additive was validated in internal and external settings, using Goodness of fit, Area under Receiver Curve and Linear regression. Different combinations of variables were used in order to develop models, e.g., LiPS

plus other clinical, observational and common blood variables, such as skin temperature, pH and base access, which are not usually evaluated for developing shock. For this model, depending on the selected class of variables, all predictors significant at *P* value of < 0.05 were added simultaneously. Insignificant variables were then removed stepwise leaving only significant variables in the model. The final model provided a pragmatic tool for determining probability of shock. As there is no gold standard for shock, the 'standard' against which the tool was evaluated is 28-day admission to ICU and/or mortality. Although shock, ICU admission and mortality are clearly different outcomes, they are closely related, and constitute the best practical method to assess any proposed 'shock' model. We used ROC curves and assessed sensitivity, specificity, odds ratios, PPV and NPV for the model. The final optimal selected model was named as "Diagnostic Investigation and Predication of Shock (DiPS)". The fourth objective was to evaluate clinical gestalt for shock, or experienced physicians in identification and classification of patients with shock, mortality, and ICU admission. In separate analyses, using Friedman's, McNemar's Test, Kappa and inter-class coefficient, the level of agreement between physician opinion, USCOM-derived shock and LiPS was assessed. Similar analyses to the above were used to address secondary objectives.

2.11 Data management and retention

The patients' identifiable information (name and NHS number) was kept only on NHS computers and were accessible only by the study team with appropriate access rights. The name and NHS number were linked to a study ID number and were stored in an NHS computer. Anonymous data (with study ID numbers but not patients' names and NHS number) were kept on password-protected files on Cardiff University computers. Our university computers were not encrypted at the time, and we are unsure whether it is possible to encrypt single files without encrypting all files. All clinical personnel followed the NHS Code of Confidentiality, and Caldicott Guardian principles. [360] Welsh speaking staff were present on the Units and can provide verbal translation if necessary. The anonymised research data are retained at the end of the study for potential use in future research within the UK and abroad and are stored securely at Cardiff University. Paper data is stored by study group for 15 years and will be destroyed afterwards. Electronic data are retained as it may form the basis of long-term longitudinal follow up and comparative studies. All data will be kept for 15 years. All data will be kept confidential. With consent, anonymised data may be used for future research within the UK and abroad, including use by commercial companies.

Chapter 3

Results

In this chapter, I will be discussing results of data analysis, starting off by sample size calculation, methodology of statistical analysis used for analysis of data and subsequently, results of analysis on each main objective of the study.

3.1 Sample Size

In this study, the primary objective was to investigate whether USCOM derived haemodynamic variables predict outcome of 28-day mortality and/or ICU/CCU admission. The second objective was the ability of USCOM derived haemodynamic parameters in detection and classification of shock and the third objective was to validate and refine a Li Priori diagnostic Shock tool; LiPS. Finally, the fourth objective was to compare clinician gestalt with USCOM-derived shock and LiPS definition of shock.

The study setting was Emergency department of University Hospital of Wales with nearly 400 admissions a day, of which on average five to ten patients are presenting with shock. In pilot study, we showed that 32% of critically ill patients admitted to resuscitation room of emergency department had shock. 25% of these patients met the primary outcome and were admitted to ICU or died within 28-days. Miss-classification of LiPS was 27%. For objective 1, we used rule of thumb to determine the sample size, [350] and Green's formula for conducting regression analysis with larger numbers of independent variables, [351] i.e. $N_2 > 50 + 8$ m; where m is the number of independent variables, and N_2 is the total number of recruited cases. Therefore, the required sample size in this study with 25 independent variables is: $N_2 > 50 + (8 \times 25)$ or $N_2 > 250$. Although we believed that we should have been able to follow up all patients for 28-day outcome, we planned to collect an additional 5% to cover unforeseen circumstances i.e., 260. With regards to objective 2, USCOM has never been used in classification of shock and there is no previous data from which to formulate a sample size calculation, but the information in our study may be useful for future studies and their sample size calculations. In the third objective, I proposed to validate and refine LiPS. Validating LiPS in an external setting, using margin of error of 5%, confidence interval of 95%, population proportion of 32% and LiPS population size of 260, requires at least 147 patients, using n: N*X / (X+N-1) *. [352] As per preliminary study, I aimed for a miss-classification rate of 15%, hence a change from 27% to 15% for predicting 28-day ICU admission or mortality. To achieve this, 354 patients were required to have 80% chance of detecting, as significant at the 5% level, with a decrease in the outcome measure from 27% in the control group to 15% in the

experimental group. [353] The maximum sample size for the study is 354, considering 250 ED patients were required for objective 1, and 354 patients for objective 3. Hence, both objectives could be achieved from the maximum of 354 cases.

3.2 Primary outcome

Primary outcome was defined as admission to ICU/CCU and / OR mortality in 28-days. From 359 patients who met inclusion criteria and were enrolled in the study, 27/359 (7.52%) patients were admitted to intensive care or coronary care units. A difference between percentage of people admitted to ICU in pilot study and actual study was noted, which can be explained by observer bias and tendency to select more sick patients in the piloting process **(Figure 3.1).** From 359 patients who met inclusion criteria and were enrolled in the study, 58/359 (16.2%) of the patients died.

3.3 Demographics

Gender

167/359 (46.5%) of the study population were male and 192/359 (53.5%) were female. From those who were admitted to ICU/CCU, 15/27 (55.6%) were men and 12/27 (44.4%) were women. There was no statistically significant relationship between gender and admission to ICU/CCU (*P* value 0.33). **(Figure 3.1)** From those who died in 28-days, 26/58 (44.8%) were men and 32/58 (55.2%) were female. Patient's gender had no impact on mortality (*P* value: 0.78)

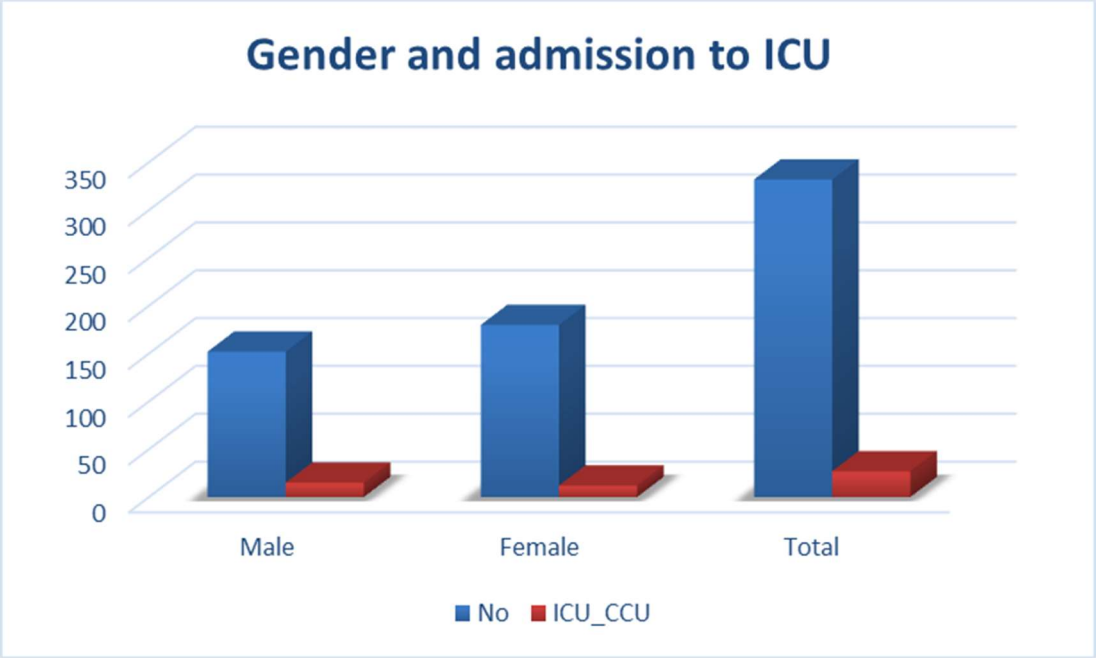


Figure 3.1. Gender and admission to ICU/CCU. Male patients had higher admission rate to ICU/CCU compared to female counterparts; 55.6% vs 44.4%.

Age

Majority of patients were above 70 years old and in age group of 80-89 years. Age group 70-79 had the highest admission rate to intensive care; followed by age groups 60-69, 40-49 and 50-59; 6/27 (22.2%), 5/27(18.5%), 4/27(14.8%) and 4/27(14.8%) respectively. Patients aged 30-39 and above 90 years old, had the lowest ICU admission rate; 1/359 (3.70%) in each group, this is likely due to fitness and lack of comorbidities in first group or old age and lack of suitability for ICU admission in the latter group **(Table 3.1), (Figure 3.2)** Median age for admission to ICU/CCU was 62 (IQR: 57-82) and for admission to wards was 72 (IQR: 47-77). It was shown that age is an independent predictor of ICU admission (*P* value: 0.045). **(Table 3.3)** It was also shown that patients aged 70-79 and above 90 years are more likely to die in 28 days and each group had mortality rate of 15/58 (25.9%). Whereas patients aged between 30 to 49 years old are less likely to die. Overall, the relation between age groups and 28-days mortality was **very highly significant** and well-proven that older patients were more likely to die (*P* value: **0.00002**). **(Table 3.2)** The median age for patients who survived was 70 (IQR: 53-81) and for those who died was 76 (IQR: 67-90). Once again it was shown that age is a very strong predictor of mortality (*P* value: **0.0008**). **(Table 3.3)**

In summary, age is a strong predictor of primary outcome; ICU admission or mortality in 28-days. In contrast, gender did not have any impact on primary outcome.

Table 3.1. Age groups and ICU admission.

Age groups	No	ICU_CCU	Total	*P* value	No %	ICU %	Total %
< 30	24	3	27		7.23	11.1	7.52
30-39 ††	15	1	16		4.52	3.70	4.46
40-49	26	4	30		7.83	14.8	8.36
50-59	30	4	34		9.04	14.8	9.47
60-69	55	5	60		16.6	18.5	16.7
70-79 †	74	6	80		22.3	22.2	22.3
80-89	80	3	83		24.1	11.1	23.1
90 + ††	28	1	29		8.43	3.70	8.08
Total	332	27	359	0.61	100	100	100

Data is presented in group and outcome (%). Mann-Whitney U test is used to established relationship between age group and primary outcome of ICU/CCU admission. †Age group 70-79 had the highest admission rate to intensive care. ††Patients aged 30-39 and above 90 years old, had the lowest ICU admission rate.

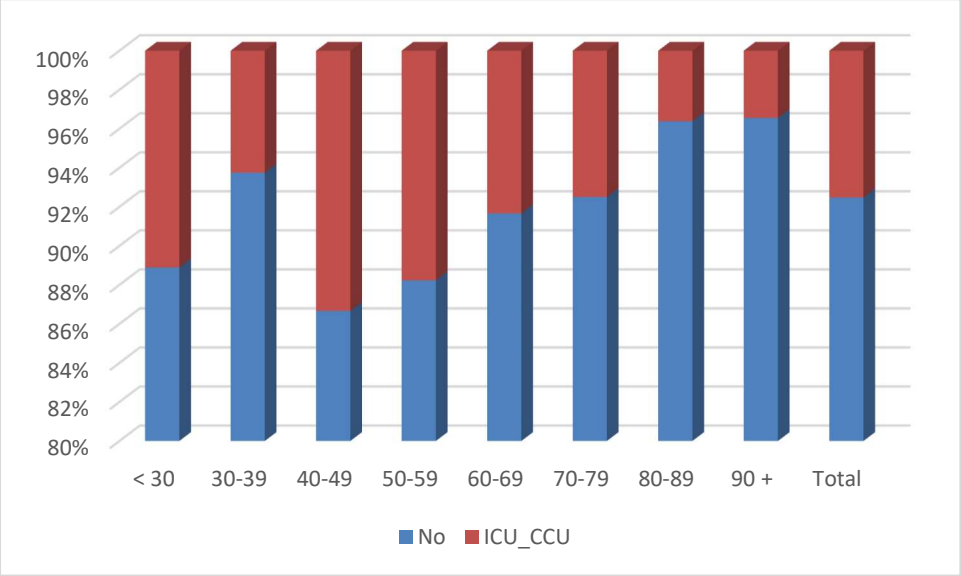


Figure 3.2. Age groups and ICU admission. Majority of patients admitted to ITU were above 70 years old and in age group of 80-89 years. Age group 70-79 had the highest admission rate to intensive care; followed by age groups 60-69, 40-49 and 50-59 respectively.

Table 3.2. Age group and 28-days mortality.

Age groups	Alive	Dead	Total	*P* value	Alive %	Dead %	Total %
< 30	25	2	27		8.31	3.45	7.52
30-39 ††	14	2	16		4.65	3.45	4.46
40-49	29	1	30		9.63	1.72	8.36
50-59	30	4	34		9.97	6.90	9.47
60-69	51	9	60		16.9	15.5	16.7
70-79 †	65	15	80		21.6	25.9	22.3
80-89	73	10	83		24.3	17.2	23.1
90 + †	14	15	29		4.65	25.9	8.08
Total	301	58	359	0.00002	100	100	100

Data is presented in age group and outcome (%). Mann-Whitney U test is used to established relationship between age group and primary outcome of mortality. † Age groups 70-79 and above 90 years old were more likely to die. Mortality rate was lower in patients aged †† 30-39. The relationship between age and mortality is significant. (*P* value: 0.00002)

Table 3.3. Age and primary outcome.

Variable	Median	Inter-quartile range (N:359)	*P*-value
Input Data			
Age			0.045 *
No ICU	72	(47-77)	
ICU/CCU	62	(57- 82)	
Variable	**Median**	**Inter-quartile range (N:359)**	***P*-value**
Input Data			
Age			0.0008 * *
Alive	70	(53-81)	
Dead	76	(67-90)	

Data is presented in median and inter-quartile range. Mann-Whitney U test is used to established relationship between age and primary outcome. The relation between age and primary outcome is significant; *: *P* value: 0.045. In relation to ICU admission and mortality respectively: * * *P* value: 0.0008.

Data on other baseline characteristics such as height, weight, area of assessment and past medical history were collected. Clinical data included respiratory rate, heart rate, systolic and diastolic blood pressure (SBP, DBP), the presence or absence of a radial pulse and, if present, whether the pulse was bounding, normal or weak. We also assessed capillary return, peripheral skin temperature, skin colour, oxygen saturation and Glasgow Coma Score (GCS). Arterial pressure was measured with an appropriately sized cuff using an oscillometric device (Omron HEM-7200 Automatic Blood Pressure Monitor, Omron Healthcare Co., Ltd, Japan). Pulse pressure (SBP-DBP) was calculated from measured variables. Investigations included full blood count, serum creatinine, urea and electrolytes, arterial and venous blood gases, blood glucose, C-reactive protein (CRP), Lactate, electrocardiographs (ECG) and chest x-ray. Not all patients had all baseline characteristics recorded for them. For instance, 324/359 patients had recorded Albumin. This is mainly due to the fact that not all patients admitted to ED had Liver function test. However, study doctors attempted to include as many as possible available data on each patient. Chi-squared and t-test were used to establish relationship between baseline characteristics and combined outcome (28-days mortality and ICU admission). Comparison was made between "28-day combined outcome absent" and "28-day combined outcome present" groups, and *P* value of < 0.05 to be statistically significant. Characteristics including assessment area, skin colour, peripheral pulse, capillary return, body temperature, oxygen supplementation, Glasgow Coma score (GCS), NEWS score, Albumin and assisted ventilation very highly correlated to combined outcome. (*P* values; 0.0023, 0.0078, 0.0041, < 0.000, 0.0028, <0.0001, 0.0015, 0.0001, 0.0026 and 0.0010. respectively). The relation between skin temperature, central cyanosis, venous PH, Bilirubin and Urea with composite outcome was significant (*P* value: 0.0112, 0.0240, 0.0454, 0.0405 and 0.0385 respectively). **(Table 3.4)** The analysis was repeated for grouped baseline characteristics and correlated to outcome. Most parameters which previously had statistical significance in anticipating primary outcome were remained significant, including assessment area, oxygen supplementation, body temperature, GCS, NEWS score, skin temperature, central cyanosis, venous pH, albumin, bilirubin and assisted ventilation. However, when data was grouped, respiratory rate and Lactate had significant relation to primary outcome (*P* value: 0.0022, 0.0497 respectively). **(Table 3.5)**

Table 3.4. Baseline characteristics and combined outcome (N = 359).

Variable	Unit	N	28-day combined outcome absent N=280	28-day combined outcome present N=79	*P* value
Demographics					
Age - mean± SD	Year	359	65.9±19.6	70.5±20.0	0.0702★
Male - n, (%)	-	359	43 (22)	36 (21)	0.8022▲
Old age home resident - n, (%)	-	359	72 (22)	7 (23)	0.8480▲
Weight - mean± SD	kg	359	74.8±19.7	70.2±18.5	0.0565★
Height - mean± SD	cm	359	167.5±12.8	167.8±10.0	0.7792★
BSA - mean± SD	m^2	359	1.9±0.3	1.8±0.3	0.0739★
Assessment Area		359			0.0023▲
Resuscitation Room - n, % High Dependency Area - n, %			113 43	50 13	
Major Trolley - n, %			90	11	
Ambulatory Care - n, %			19	2	
Medical Assessment Unit - n, %			15	3	
Clinical features					
Peripheral skin temperature	-	359			0.0112▲
Normal - n, %			157 (56)	39 (49)	
Cold - n, %			41 (15)	21 (27)	
Warm - n, %			81 (29)	19 (24)	
Skin colour	-	359			0.0078▲
Pale - n, %			27 (10)	18 (23)	
Blue/mottled - n, %			8 (3)	2 3)	
Red - n, %			245 (88)	59 (75)	
Peripheral pulse	-	359			0.0041▲
Strong - n, %			219 (79)	50 (63)	
Weak - n, %			58 (21)	29 (37)	
Central cyanosis		359			0.0240▲
No - n, %			276 (99)	75 (95)	
Yes - n, %			3 (1)	4 (5)	
Capillary return	sec	358			<0.000▲
≤2			80 (29)	6 (8)	
3 – 4			156 (56)	40 (51)	
5 – 6			43 (15)	33 (42)	
Past Medical History					

Cancer - n (%)	-	355	34 (12)	18 (24)	0.0126▲
Diabetes n (%)	-	355	60 (22)	16 (17)	0.2726▲
Stroke n (%)	-	354	27 (10)	3 (4)	0.1103▲
CAD n (%)	-		38 (14)	12 (16)	0.6469▲
CHF n (%)	-		24 (9)	8 (11)	0.6170▲
Hyperlipidemia n (%)	-		56 (20)	10 (13)	0.1702▲
Observations					
Temperature	C	360	37.2±1.1	36.6±1.5	0.0028★
Heart Rate	bpm	361	95.7±23.1	97.0±23.0	0.6577★
Respiratory Rate	rpm	358	21.6±4.4	23.4±6.5	0.0191★
Systolic BP	mmHg	359	122.0±24.8	116.2±24.4	0.0656★
Diastolic BP	mmHg	359	71.3±17.6	67.7±18.4	0.1251★
Mean arterial BP	mmHg	359	88.2±18.0	83.8±18.5	0.0658★
Pulse Pressure	mmHg	359	50.7±20.1	48.5±19.7	0.3820★
Oxygen saturation	%	358	95.6±6.2	95.8±4.1	0.6572★
Oxygen supplement (FiO2)	%	358	28.7±18.8	45.4±32.0	<0.0001★
GCS		361	14.6±1.3	13.5±2.8	0.0015★
Shock index		359	0.8±0.2	0.9±0.3	0.0866★
NEWS		358	4.7±1.9	6.0±2.7	0.0001★
NEWS Groups					<0.0001
3			92 (33)	16 (20)*	
3 – 6			129 (46)	20 (25)*	
7 – 9			46 (16)	23 (29)*	
10 - 13			15 (5)	20 (25)*	
Laboratory results					
Arterial/Venous pH		278	7.38±0.08	7.36±0.10	0.0778★
Venous pH		234	7.39±0.08	7.36±0.10	0.0454★
Arterial/Venous HCO3		237	23.80±3.82	22.76±4.20	0.0942★
Venous HCO3		185	23.81±3.39	23.26±4.00	0.3924★
Arterial/Venous Base deficit		290	0.19±4.91	-2.47±5.43	0.0669★
Venous Base deficit		235	0.4±5.0	-2.3±5.6	0.1184★
WBC (×10^9/L)		360	12.1±5.8	13.4±7.1	0.1414★
Haemoglobin	g/dl	359	12.8±2.2	12.7±2.5	0.6484★
Platelet	x10^9/L	360	264±102	242±101	0.0980★
Sodium (mmol/L)		356	138±4	137±8	0.3245★
Potassium (mmol/L)		258	4.2±0.7	4.2±1.1	0.8350★
Albumin (g/L)		324	33.0±7.3	30.0±7.5	0.0026★
Bilirubin (umol/L)		321	14.7±17.3	26.2±45.4	0.0405★
Urea (mmol/L)		354	7.7±7.0	10.8±12.6	0.0385★
Creatinine (mmol/L)		354	95.9±74.2	109.4±80.6	0.1834★
Lactate (mmol/L)		290	2.0±1.7	2.7±3.1★	0.0419★

Intervention					
Assisted Ventilation - n, (%)			9 (3)	10 (13)	0.0010▲

Data are presented as the mean ± SD or the patient number (%). Combined outcome: Combination of 28-days mortality and ICU admission. ★ t-test, ▲ Chi-squared test, △ Chi-squared test for trend. **Abbreviation:** BSA: Body surface area, CAD: Coronary artery disease, CHF: Congestive heart failure, NEWS: national early warning score, WBC: white cell count.

Table 3.5. Grouped baseline characteristics in relation to combined outcome (N = 359).

Variable	Unit	N	28-day combined outcome absent N=280	28-day combined outcome present N=79	*P* value
Demographics					
Age	Years	359			0.0293
18 – 30 - n, %			24 (9)	4 (5)	
31 – 40 - n, %			19 (7)	3 (4)	
41 – 50 - n, %			20 (7)	6 (8)	
51 – 60 - n, %			26 (9)	7 (9)	
61 – 70 - n, %			49 (17)	13 (17)	
71 – 80 - n, %			68 (24)	18 (23)	
81 – 90 - n, %			64 (23)	15 (19)	
91 – 100 - n, %			12 (4)	13 (17)	
Assessment Area	-	359			0.0023**
Resuscitation Room - n, %			113	50	
High Dependency Area - n, %			43	13	
Major Trolley - n, %			90	11	
Ambulatory Care - n, %			19	2	
Medical Assessment Unit - n, %			15	3	
Observations					
Respiratory Rate	bpm	359			0.0022
≤8 - n, %			0 (0)	0 (0)	
9 – 11 - n, %			0 (100)	0 (0)	
12 – 20 - n, %			129 (46)	31(39)	
21 – 24 - n, %			98 (35)	18 (23)	
≥25 - n, %			55 (20)	30 (38)	
Oxygen saturation (SaO2)	%				0.6729
≥96 - n, %			180 (64)	49 (63)	
94 – 95 - n, %			48 (17)	16 (21)	
92 – 93 - n, %			20 (7)	3 (4)	
≤91- n, %			32 (11)	10 (13)	

Oxygen supplement (FiO2)	%				<0.0001
No - n, %			179 (64)	26 (33)	
Yes - n, %			102 (36)	53(67)	
Temperatur					0.0006
≤35.0 - n (%)			9 (3)	12 (15)	
35.1 – 37.0 - n (%)			174 (64)	47 (60)	
37.1 – 38.0 - n (%)			54 (20)	14 (18)	
≥39.1 - n (%)			35 (13)	5 (6)	
Systolic BP	mmHg	359			0.0628
≤90.0 - n (%)			19 (7)	12 (15)	
91 – 100 - n (%)			38 (14)	9 (12)	
101 – 110 - n (%)			49 (17)	17 (22)	
111 – 219 - n (%)			175 (62)	40 (51)	
≥220 - n (%)			0 (0)	0 (0)	
Heart Rate	bpm				0.5847
≤40.0 - n (%)			0 (0)	0 (0)	
41 – 50 - n (%)			4 (1)	1 (1)	
51 – 90 - n (%)			122 (43)	33 (42)	
91 – 110 - n (%)			85 (30)	18 (23)	
111 – 129 - n (%)			49 (17)	19 (24)	
≥131 - n (%)			21 (8)	7 (9)	
AVPU	-				<0.0001
Alert - n, %			262 (93)	59 (75)	
V, P or U - n, %			20 (7)	20 (25)	
GCS	-				<0.0001
13 – 15			266 (95)	63 (80)*	
9 – 12			13 (5)	8 (10)*	
3 – 8			2 (5)	8 (10)*	
NEWS	-				<0.0001
3			92 (33)	16 (20)*	
4 – 6			129 (46)	20 (25)*	
7 – 9			46 (16)	23 (29)*	
10 - 13			15 (47)	20 (53)*	
Clinical features					
Peripheral skin temperature	-	359			0.0112**
Normal - n, %			157 (56)	39 (49)	
Cold - n, %			41 (15)	21 (27)	
Warm - n, %			81 (29)	19 (24)	
Skin colour	-	359			0.0078**
Pale - n, %			27 (10)	18 (23)	
Blue/mottled - n, %			8 (3)	2 3)	
Red - n, %			245 (88)	59 (75)	
Peripheral pulse	-	359			0.0041**
Strong - n, %			219 (79)	50 (63)	
Weak - n, %			58 (21)	29 (37)	
Central cyanosis		359			0.0240**
No - n, %			276 (99)	75 (95)	

Yes - n, %			3 (1)	4 (5)	
Capillary return	sec	359			<0.0001**
≤2			80 (29)	6 (8)	
3 – 4			156 (56)	40 (51)	
4 – 6 5			43 (15)	33 (42)	
Laboratory results					
Arterial/Venous pH					0.0004
>7.45			26 (9)	12 (17)*	
7.35 – 7.45			201 (72)	32 (45)*	
7.3 – 7.35			23 (8)	7 (10)*	
< 7.3			28 (10)	20 (28)*	
Arterial/Venous HCO3		247			0.0004
>26			41 (22)	10 (17)*	
22 – 26			106 (57)	29 (48)*	
16 – 21.9			33 (18)	17 (28)*	
<16			7 (4)	7 (7)	
Arterial/Venous Base Excess		289			0.0407
>5			16 (7)	5 (7)*	
0 to 5.0			116 (53)	27 (39)*	
-0.1 to -5.0			69 (31)	23 (33)*	
-5.0 -30			19 (9)	14 (20)*	
Platelets	x10^9/ L	359			0.1451
0 – 149			30 (11)	15 (19)	
150 – 400			224 (80)	57 (72)	
>400			26 (9)	21 (9)	
Albumin (g/L)		324			0.0090
<35			140 (56)	54 (73)	
>35			110 (44)	20 (27)	
Bilirubin (umol/L)		324			0.0007
0 – 17			201 (79)	42 (59)	
18 - 34			41 (16)	19 (27)	
>34			11 (4)	10 (14)	
Urea (mmol/L)		354			0.0965
<2.5			9 (3)	2 (3)	
2.5 – 7.1			162 (59)	37 (47)	
7.2 - 14			77 (28)	25 (32)	
>14			27 (10)	15 (19)	
Creatinine (mmol/L)		353			0.1780
<71			97 (35)	30 (38)	
71 - 107			119 (43)	26 (33)	
>108			58 (21)	23 (29)	
Lactate (mmol/L)		290			0.0497
4.1 – 24.0			12 (5)	9 (13)	
2.1 – 4.0			69 (31)	25 (36)	
0 – 2.0			140 (63)	35 (51)	

Intervention					
Assisted Ventilation - n, (%)		356			0.0010
Yes			9 (3)	10 (13)	
No			268 (97)	69 (87)	

Combined outcome: Combination of 28-days mortality and ICU admission. t-test, Chi-squared test been used. **: Statistical significance with *P* value < 0.05. Grouped data is presented as percentage (%). **Note:** Percentages may not sum to 100 because of rounding. **Abbreviation:** BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CHF, congestive heart failure. HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure is SBP minus DBP; CAD, coronary artery disease; CHF, congestive heart failure; SOB, shortness of breath; LOC, loss of consciousness; GCS, Glasgow coma scale; Shock index, pulse divided by systolic blood pressure; WBC, white blood cell; RBC, red blood cell; HCT, Haematocrit; NEU, Neutrophils; eGFR, estimated Glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula.

In summary, the association between characteristics including assessment area, skin colour, peripheral pulse, capillary return, body temperature, oxygen supplementation, Glasgow Coma score (GCS), NEWS score, Albumin and assisted ventilation was very highly significant to combined outcome. Whilst, skin temperature, central cyanosis, venous PH, Bilirubin and Urea, had significant association with composite outcome. However, when data was grouped, respiratory rate and Lactate also had significant relation to outcome.

3.4 Objective 1

To investigate whether advanced haemodynamic variables using USCOM predict 28-day all-cause mortality or ICU admission.

25 haemodynamic parameters were measured by using USCOM. Some variables including oxygen saturation, systolic and diastolic blood pressure, mean arterial pressure and haemoglobin were manually entered into the device in order to help measuring other haemodynamic parameters. **(Table 3.6)** Normality test showed that our data is not symmetrically distributed. Hence, median with its inter-quartile range were given to represent the average data.

Table 3.6. Measurable and non-measurable haemodynamic parameters by USCOM 1A.

Measurable haemodynamic parameters by USCOM 1A.	
Vpk	Peak Velocity of flow
VTI	Velocity Time Integral
HR	Heart Rate
MD	Minute Distance
ET%	Ejection Time Percent
SV	Stroke Volume
SVI	Stroke Volume Index
SVV	Stroke Volume Variability
CO	Cardiac Output
CI	Cardiac Index
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
Pmn	Mean Pressure Gradient
ET	Flow Time
Etc	Flow Time corrected
SW	Stroke Work
CPO	Cardiac Power
SMII	Inotropy Index
PKR	Potential Kinetic Ratio

VP	Velocity peak
SVsat	Stroke volume saturation
DO2	Oxygen delivery
DO2I	Oxygen delivery Index
Non-measurable haemodynamic parameters by USCOM 1A.	
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial blood pressure
SO2	Oxygen
Hb	Haemoglobin

Normality test (Kolmogorov-Smirnov) showed that data on cardiac output (CO) and systemic vascular resistance (SVR) are not normally distributed in relation to ICU/CCU admission (*P* values: 0.09 and 0.034 respectively). Stroke volume variability (SVV) had a skewed distribution in relation to 28-days mortality (*P* value: 0.05).

Figure 3.3. shows skewed distribution of cardiac output (CO) in relation to 28-days ICU/CCU admission. As evident, patients with CO of 4-6 L/min are less likely needing ICU admission.

Figures 3.4. shows skewed distribution of systemic vascular resistance (SVR) in relation to 28-days ICU/CCU admission. Patients with systemic vascular resistance of 1300-1400 dys/ cm5 are more likely to end up in ICU/CCU.

Figure 3.5. shows skewed distribution of stroke volume variability in relation to 28-days mortality. Patients with SVV values of around 65 ml were more likely to die.

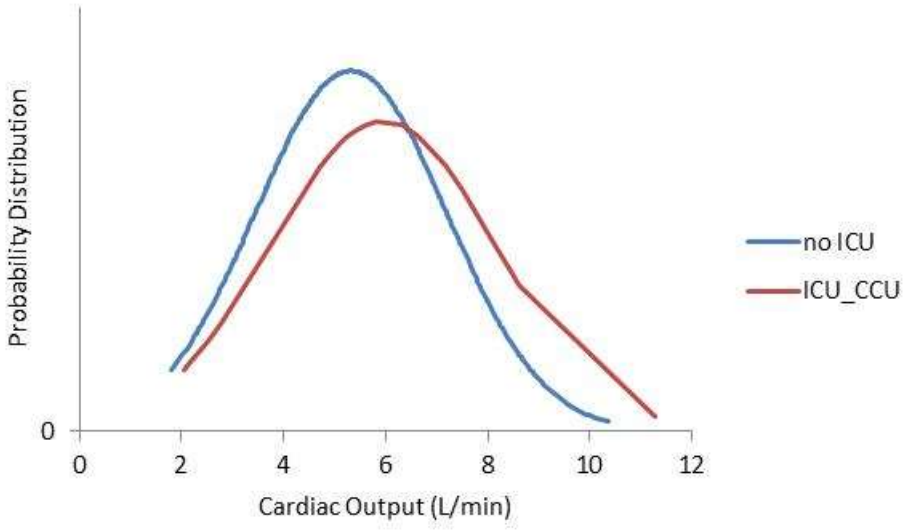


Figure 3.3. Cardiac output (CO) in relation to ICU/CCU admission. Cardiac output has non-normal distribution in relation to ICU admission. It is evident that patients with normal range cardiac output of 4-6 L/min has less admission rate to ICU/CCU. (*P* vale: 0.09)

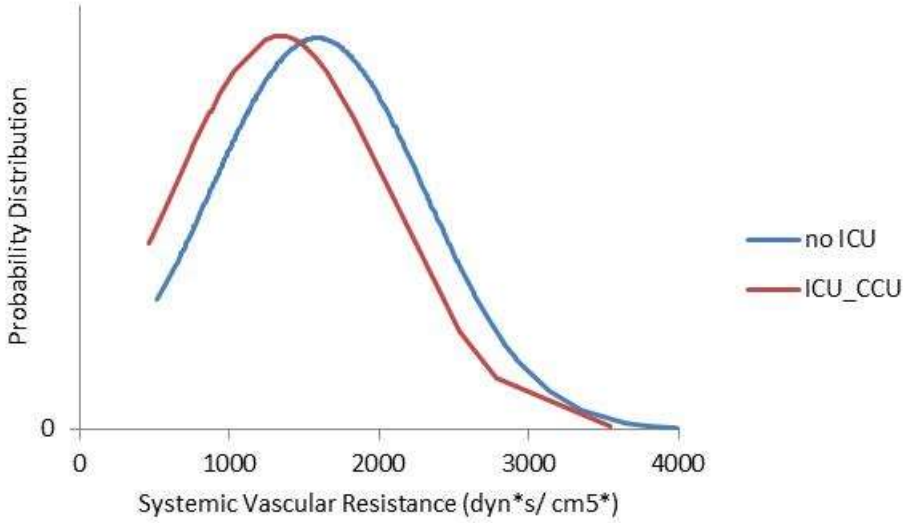
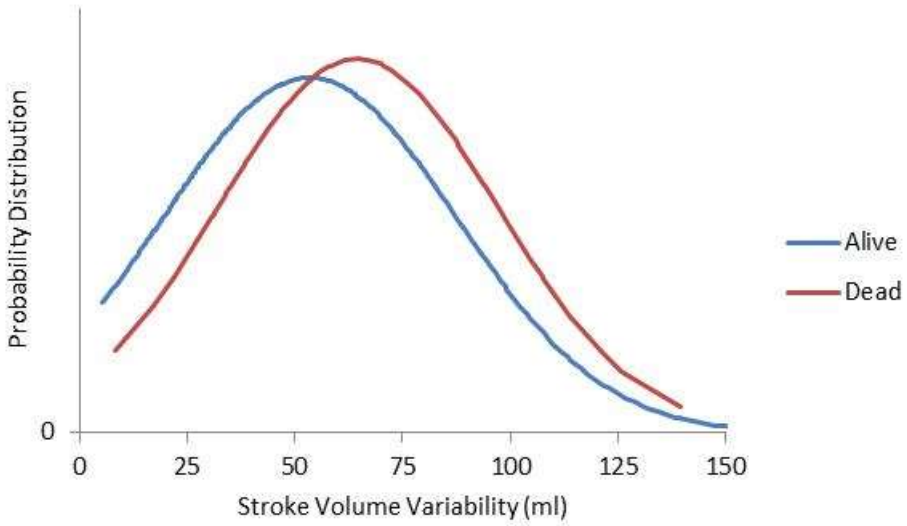


Figure 3.4. Distribution of systemic vascular resistance (SVR) in relation to ICU/CCU admission. Systemic vascular resistance has non-normal distribution in relation to ICU admission. Patients with systemic vascular resistance 1200-1600 dynes s/cm5 are more likely to get admitted to ICU/CCU. (*P* value: 0.034)



<u>Figure 3.5.</u> Distribution of stroke volume variability (SVV) in relation to morality.
Stroke volume variability has non-normal distribution in relation to ICU admission. Stroke volume variability values of 60-70 ml are associated with increased mortality. (*P* value: 0.005)

Haemodynamic parameters and prediction of outcome:

Uni-variant analysis was used to relate each variable to primary outcome. Mann-Whitney test was used, to test the relationship between each non-normally distributed haemodynamic parameter and primary outcome. Whilst t-test were used for normally distributed parameters. Analysis was performed separately for 28-days ICU/CCU admission and mortality.

Admission to ICU/CCU in 28-days:

Amongst measurable haemodynamic parameters systemic vascular resistance (SVR): median: 1297, IQR: (874 - 1534), systemic vascular resistance index (SVRI): median: 2081, IQR: (1559 - 2990) and Potential Kinetic Ratio (PE_KE_Ratio); median: 40, IQR: (23 - 48) had statistical significance in anticipating patient's admission to ICU/CCU within 28-days (*P value*: 0.034, 0.029 and 0.043 respectively). Oxygen saturation (SO2), which was manually entered by the operators to USCOM in order to help measure other haemodynamic parameters, was also capable of predicting primary outcome of ICU admission in 28-days; median: 98, IQR: (96-100), (*P value*: 0.032). **(Table 3.7), (Table 3.8)**

Mortality in 28-days:

Stroke volume variability (SVV) was the only measurable haemodynamic parameter, shown to be a strong predictor of 28-days mortality, median: 58, IQR: (38 - 88), (*P value*: 0.005). **(Table 3.9)** Relation to primary outcomes for parameters with normal distribution including Flow Time (FT) and Haemoglobin (Hb) are outlined separately. **(Table 3.10)**

Table 3.7. Comparison of haemodynamic parameters by primary outcome; 28-days ICU/CCU admission.

Variable	Unit	Median	Inter-quartile range (N:27)	*P* value
Input Data				
Systolic BP	mmHg	111	(86-138)	0.27
Diastolic BP	mmHg	64	(49-86)	0.26
Mean arterial BP	mmHg	84	(64-99)	0.20
Haemoglobin	g/dl	NA	NA	0.31
Oxygen saturation	%	98	(96-100)	0.032*
Output Data				
Preload				
Flow Time	ms	NA	NA	0.54
Flow Time corrected	ms	375	(328-416)	0.89
Stroke volume variability	%	40.7	(31.6-61.1)	0.54
Contractility				
Heart Rate (HR)	bpm	95	(75-119)	0.76
Stroke work (SW)	mJ	625	(411-913)	1.0
Cardiac Power	W	1.06	(0.65-1.43)	0.69
Inotropy Index	W/m^2	1.47	(0.91-1.83)	0.58
Peak Velocity	m/s	1.00	(0.86-1.20)	0.16
Mean pressure Gradient	mmHg	1.87	(1.38-2.57)	0.15
Blood flow				
Velocity time integral (VTI)	m/s	20.0	(12.9-21.8)	0.63
Minute Distance	cm	16.9	(14.2-20.7)	0.28
Ejection Time Percentage, %	%	47	(39-52)	0.90
Stroke volume (SV)	ml	60	(48-76)	0.30
Stroke volume index (SVI)	ml/m^2	32.9	(25.8-40.9)	0.35
Cardiac Output	ml	5.8	(4.8-7.3)	0.09*
Cardiac Index	ml	3.03	(2.51-3.89)	0.15
Stroke volume saturation (SVS)	%	60	(44-73)	0.22
Afterload				
PKR	-	40	(23-48)	0.043*
Systemic vascular resistance (SVR)	dynes/seconds/cm^{-5}	1297	(874-1534)	0.034*
Systemic vascular resistance index (SVRI)	dynes/seconds/$cm^{-5/}$ m^2	2081	(1559-2990)	0.029*
Tissue perfusion				
Oxygen delivery	ml/min	1007	(748-1243)	0.10
Oxygen delivery index	ml/min/ m^2	524	(440-616)	0.11

Data presented using median and Inter-quartile range. t-test, Chi-squared test, Chi-squared test for trend *Statistically significant with *P* value < 0.05. **Abbreviations:** BP: blood pressure, HR: hear rate, PKR: Potential – kinetic ratio, SV: Stroke volume, SVI: Stroke volume index, SVRI: Systemic vascular resistance index, SVS: Stroke volume saturation. VTI: Velocity time integral.

Table 3.8. Comparison of normally distributed haemodynamic parameters by primary outcome; 28- days ICU/CCU admission.

Variable	Unit	Mean	Standard deviation (SD)	*P* value
Input Data				
Haemoglobin	g/dl	132	23.1	0.31
Output Data (Preload)				
Flow Time	ms	289	75	0.54

Data presented using mean ± SD. Statistical significance with *P* value < 0.05. Mean values of Haemoglobin and Flow time were not statistically significant in relation to primary outcome of ICU/CCU admission using t-test. (*P* value > 0.05)

Table 3.9. Comparison of non-normal distributed haemodynamic parameters by primary outcome; 28- mortality.

Variable	Unit	Median	Inter-quartile range (N:58)	*P*-value
Input Data				
Systolic BP	mmHg	111	(104-131)	0.19
Diastolic BP	mmHg	70	(58-79)	0.55
Mean arterial BP	mmHg	85	(73-94)	0.30
Haemoglobin	g/dl	NA	NA	0.13
Oxygen saturation	%	96	(94-99)	0.46
Output Data				
Preload				
Flow Time	ms	NA	NA	0.28
Flow Time corrected	ms	356	(298-398)	0.27
Stroke volume variability	%	58	(38-88)	0.005**
Contractility				
Heart Rate (HR)	bpm	95	(83-115)	0.39
Stroke work (SW)	mJ	584	(419-845)	0.18
Cardiac Power	W	0.86	(0.64-1.22)	0.25
Inotropy Index	W/m^2	1.30	(1.05-1.79)	0.76
Peak Velocity	m/s	0.96	(0.73-1.13)	0.85
Mean pressure Gradient	mmHg	1.67	(0.92-2.49)	0.82
Blood flow				
Velocity time integral	m/s	15.9	(12.8-20.6)	0.14
Minute Distance	cm	14.7	(11.3-18.8)	0.30
Ejection Time Percentage	%	45	(36-51)	0.54
Stroke volume (SV)	ml	55	(39-72)	0.42
Stroke volume index (SVI)	ml/m^2	32	(23-40)	0.97
Cardiac Output	ml	5.00	(3.71-6.48)	0.56
Cardiac Index	ml	2.75	(2.00-3.94)	0.91
Stroke volume saturation (SVS)	%	52	(37-69)	0.44
Afterload				
PKR	-	42	(29-68)	0.52
Systemic vascular resistance (SVR)	dynes/seconds/cm^{-5}	1398	(1122-2040)	0.98
Systemic vascular resistance index (SVRI)	dynes/seconds/$cm^{-5/}m^2$	2481	(1933-3490)	0.56
Tissue perfusion				
Oxygen delivery	ml/min	732	(550-1061)	0.35
Oxygen delivery index	$ml/min/m^2$	429	(296-630)	0.61

Data presented using median and Inter-quartile range. t-test, Chi-squared test, Mann–Whitney U test used. **Statistically significant with *P* value < 0.05. **Abbreviations:** BP: blood pressure, HR: hear rate, PKR: Potential – kinetic ratio, SV: Stroke volume, SVI: Stroke volume index, SVR: Systemic vascular resistance, SVRI: Systemic vascular resistance index, SVS: Stroke volume saturation. SW: Stroke work, VTI: Velocity time integral.

Table 3.10. Comparison of normally distributed haemodynamic parameters by primary outcome; 28-days mortality.

Variable	Unit	Mean	Standard deviation (SD)	*P*-value
Input Data				
Haemoglobin	g/dl	124	24	0.13
Output Data (Preload)				
Flow Time	ms	288	64	0.28

Data presented using mean ± SD. Mean values of Haemoglobin and Flow time were not statistically significant in relation to primary outcome of mortality using t-test.

Chi-squared test was used to test the relationship between haemodynamic variables and combined outcome (28-days mortality and ICU/ CCU admission). SVV is statistically significant in predicting combined primary outcome (*P* value: 0.0303). **(Table 3.11)**

Table 3.11. Comparison of haemodynamic parameters by 28-day combined outcome (N = 359).

Variable	Unit	Normal range	28-day Combined outcome absent N=280	28-day Combined outcome present N=79	OR (95%CI)	P-value
Input Data						
Systolic BP	mmHg					0.0628
≤90.0 - n (%)			19 (7)	12 (15)		
91 – 100 - n (%)			38 (14)	9 (12)		
101 – 110 - n (%)			49 (17)	17 (22)		
111 – 219 - n (%)			175 (62)	40 (51)		
≥220 - n (%)			0 (0)	0 (0)		
Oxygen saturation (SaO2)	%		12 (4)	13 (17)		0.9229
≥96 - n, %			180 (64)	49 (63)		
94 – 95 - n, %			48 (17)	16 (21)		
92 – 93 - n, %			20 (7)	3 (4)		
≤91- n, %			32 (11)	10 (13)		
Output Data						
Preload						
Flow Time corrected	ms					0.8410
0 – 265			27	9		
265 – 320			40	13		
321 – 415		321 – 415	143	39		
415 – 450			38	11		
451 – 675			33	6		
SVV						0.0303†
0 – 30		0 – 30	87 (31%)	11 (14%)		
30.1 – 60			101 (36%)	33 (42%)		
60.1 – 90			47 (17%)	17 (22%)		
>90			46 (16%)	17 (22%)		
Contractility						
HR	bpm					0.2806
0 – 59			9 (3%)	4 (5%)		
60 – 100		60 – 100	164 (58%)	38 (49%)		
>100			108 (38%)	36 (46%)		
Stroke work (SW)	mJ		675±257	650±270		0.4694
Cardiac Power			1.04±0.42	1.04±0.50		0.9325
SMII						0.5296
0 – 0.69			21 (8%)	9 (12%)		
0.7 – 0.99			53 (19%)	11 (14%)		

1 – 1.3		1 – 1.3	69 (25%)	17 (22%)		
1.31 – 1.60			58 (21%)	14 (18%)		
1.61 – 1.90			80 (29%)	27 (35%)		
Peak Velocity	m/s					0.3050
0.3 – 0.5			3 (1%)	2 (3%)		
0.5 – 0.7			40 (14%)	12 (15%)		
0.7 – 0.9			91 (32%)	19 (24%)		
0.9 – 1.3		0.9 – 1.3	122 (43%)	33 (42%)		
>1.3			25 (9%)	12 (15%)		
Mean pressure Gradient						0.1284
0.0 – 1.0			59 (21%)	18 (23%)		
1.0 – 1.6			92 (33%)	16 (21%)		
1.6 – 2.2		1.6 – 2.2	59 (21%)	18 (23%)		
2.2 – 2.8			33 (12%)	9 (12%)		
2.8 – 3.4			19 (7%)	5 (6%)		
>1.3 – 1.5			19 (7%)	12 (15%)		
Blood flow						
Velocity time integral (vti),	m/s		18.1±6.2	17.0±5.4		0.7309
05 – 15			97 (35%)	28 (36%)		
15 – 18			52 (19%)	15 (19%)		
18 – 21			44 (16%)	16 (21%)		
21 – 27		21 – 27	64 (23%)	13 (17%)		
>27			24 (9%)	6 (8%)		
Minute Distance			16.6±5.7	16.2±6.1		0.6062
Ejection Time Percentage, %			45.8±11.1	45.8±10.7		0.4900
Stroke volume (SV), ml			58±20	57±20		0.5052
Stroke volume index (SVI), ml/m²			32±11	32±11		0.8117
Cardiac Output, ml			5.4±1.8	5.4±2.2		0.9037
Cardiac Output, ml			2.9±1.0	3.1±1.3		0.3523
Stroke volume saturation (SVS), %			56.2±19.6	54.2±19.2		0.4404
Afterload						
PKR						0.1357
10 – 25			34 (12%)	17(22%)		
25 – 45		25 – 45	100 (36%)	27 (35%)		
45 – 65			54(19%)	15 (19%)		
>65			93 (33%)	19 (24%)		
Systemic vascular resistance (SVR)		1200-1600				0.5296

<1000			58 (21%)	19 (24%)		
1000 – 1200			35 (13%)	10 (13%)		
1200 – 1600		1200 – 1600	75 (27%)	23 (30%)		
1600 – 1800			31 (11%)	6 (8%)		
1800 – 2000			26 (9%)	3 (4%)		
>2000			56 (20%)	17 (22%)		
Systemic vascular resistance index (SVRI)						0.1009
<1000			3 (1%)	3 (4%)		
1000 – 1400			17 (6%)	6 (8%)		
1400 – 1800			32 (11%)	9 (12%)		
1800 – 2400		1800 – 2400	53 (19%)	22 (28%)		
2400 – 2800			44 (16%)	9 (12%)		
>2800			133 (47%)	29 (37%)		
Tissue perfusion						
Oxygen delivery index						0.2142
0 – 314			69	20		
314 – 590		314 – 590	147	33		
590 – 1211			63	25		

Combined outcome: Combination of 28-days mortality and ICU admission. Grouped data is presented as percentage (%). Chi-squared test was used to establish statistical significance between grouped data and combined outcome. †: Statistical significance with *P* value < 0.05. **Note:** Percentages may not sum to 100 because of rounding. **Abbreviations:** BP: blood pressure, HR: hear rate, PKR: Potential – kinetic ratio, SMII: Smith-Madigan inotropy index. SV: Stroke volume, SVI: Stroke volume index, SVR: Systemic vascular resistance, SVRI: Systemic vascular resistance index, SVS: Stroke volume saturation. SVV: stroke volume variability, SW: Stroke work, VTI: Velocity time integral.

In summary, Stroke volume variability (SVV) is the only haemodynamic parameter, which significantly correlates to mortality outcome as well as composite outcome as demonstrated above.

Here is a summary of sub-analyses highlighting the significance SVV amongst other measurable haemodynamic variables.

Multi-variant logistic regression analysis was used to estimate and quantify the relationship between independent variables and primary outcome of 28-days mortality. A model was created using haemodynamic parameters with lower probability (*P*) value, including Stroke Work (SW), Velocity Time Integral (VTI), Haemoglobin (Hb), Systolic Blood Pressure (SBP) and Stroke Volume Variability (SVV). *P* value of < 0.05 was selected as statistical significance for the model. The regression coefficient and constant were given alongside standard error (SE). Stroke volume variability (SVV) was the strongest predictor of mortality, with the lowest *P* value of 0.08, odds ratio: 1.0 at 95%CI: 1.00-1.02. **(Table 3.12)**

Table 3.12. Regression analysis to quantify the relation between independent variables and 28-days mortality outcome.

Variables	B	S.E.	Wald	*P* value	OR	95% CI
SW	0.0009	0.0011	0.61	0.43	1.00	1.00 - 1.00
VTI	-0.0539	0.0446	1.46	0.23	0.95	0.87 - 1.03
Hb	-0.0098	0.0065	2.25	0.13	0.99	0.98 - 1.00
SBP	-0.0124	0.0082	2.27	0.13	0.99	0.97 - 1.00
SVV	0.0075	0.0042	3.12	0.08	1.01	1.00 - 1.02
Constant	0.9872	1.3854	0.51	0.48	2.68	

A model was created using haemodynamic parameters with lower probability (*P*) value, to quantify relationship between haemodynamic parameters and mortality outcome using regression analysis. *P* value of < 0.05 was selected as statistical significance. Haemoglobin and systolic blood pressure were shown to have lowest *P* value of 0.13. None of the parameters were shown to have a significant statistical relationship to mortality outcome. **Abbreviations:** Hb: Haemoglobin, SBP: systolic blood pressure, SVV: stroke volume variability, SW; stroke work, VTI: Velocity time integral.

The receiver operating curve (ROC) was used to assess diagnostic ability of the model, consistent of the parameters above. Once again Stroke Volume Variability (SVV) had the highest significance with area under receiver curve (AUC) of 0.62, IQR: (0.54 - 0.69), standard Error (SE): 0.375 and *P* value of **0.0046**. This was followed by Haemoglobin (Hb), Velocity Time Integral (VTI), Stroke Work (SW), and systolic blood pressure (*P* values: 0.085, 0.14, 0.18 and 0.19 respectively). **(Table 3.13)**

Table 3.13. Predictive ability of haemodynamic parameters.

AUROC	Area	Std Error	*P* value	IQR range
SBP	0.45	0.0380	0.19	0.37 - 0.52
SW	0.44	0.0417	0.18	0.36 – 0.53
VTI	0.44	0.0400	0.14	0.36 – 0.52
Hb	0.43	0.0420	0.085	0.35 – 0.51
SVV	0.62	0.0375	0.0046‡	0.54 – 0.69

Receiver operating curve (ROC) was used to assess diagnostic ability of the model consist of parameters with low *P* value using area under the receiver curve. Values are shown using Inter-quartile range and Standard error (Std Error). ‡: *P* value of < 0.05 was selected as statistical significance. SVV has the highest predictive ability in relation to outcome (*P* value: 0.0046). **Abbreviations:** AUROC: Area under the receiver operating curve. Hb: Haemoglobin, SBP: systolic blood pressure, SVV: stroke volume variability, SW; stroke work, VTI: Velocity time integral.

In multi-variant regression analysis, stroke volume variability (SVV) was found to be the independent predictor of 28-days mortality, *P* value: 0.024**,** Odds ratio (OR): 1.01 at 95%CI: (1.00-1.02). **(Table 3.14)**

Table 3.14. Stroke Volume Variability (SVV); independent predictor of mortality.

Independent predictor	B	S.E.	Wald	*P* value	OR	95%CI
Stroke_Volume_Variability	0.009	0.004	5.12	0.024 ‡	1.01	1.00 - 1.02
Constant	-2.17	0.286	57.7	0.0000003	0.11	

SVV was found to be the independent predictor of 28-days mortality using Wald Chi-Squared Test. ‡: Statistical significance with *P* value < 0.05.

A best cut-off of 50 mL, equivalent to 30% of values of stroke volume variability was found to have the highest true positive rate together with the lowest false positive rate in prediction of mortality outcome. **(Figure 3.6, 3.7)** A ROC curve, where the true positive rate (sensitivity) was plotted in function of the false positive rate (1-specificity) for different cut-off points of a Stroke Volume Variability (SVV), was created with calculated area under the curve (AUC) of 0.62 with *P* value **of 0.0046**, suggestive of very high statistical significance of SVV values in relation to primary outcome of mortality. **(Figure 3.8)**

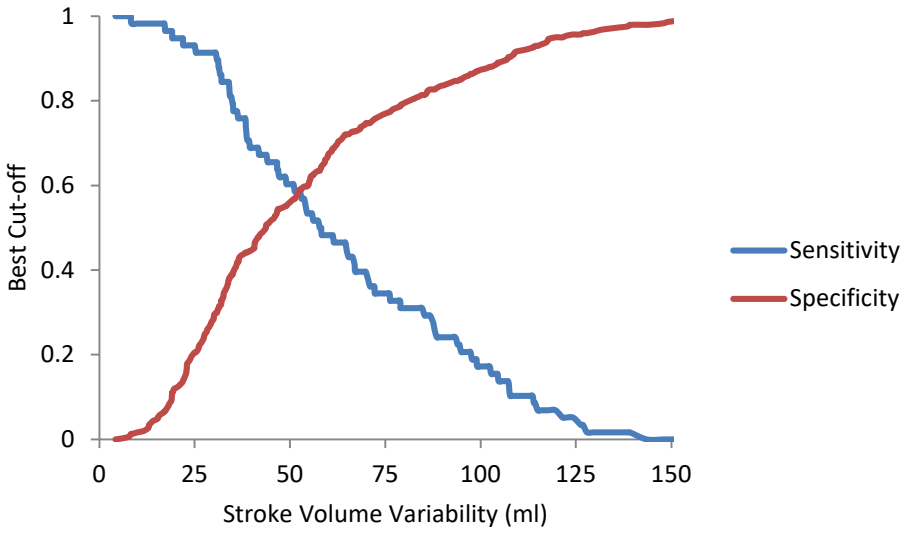


Figure 3.6. Best cut-off value for stroke volume variability. A cut-off of 50 mL, equivalent to 30% of values of stroke volume variability was found to have the highest true positive rate together with the lowest false positive rate in prediction of mortality outcome.

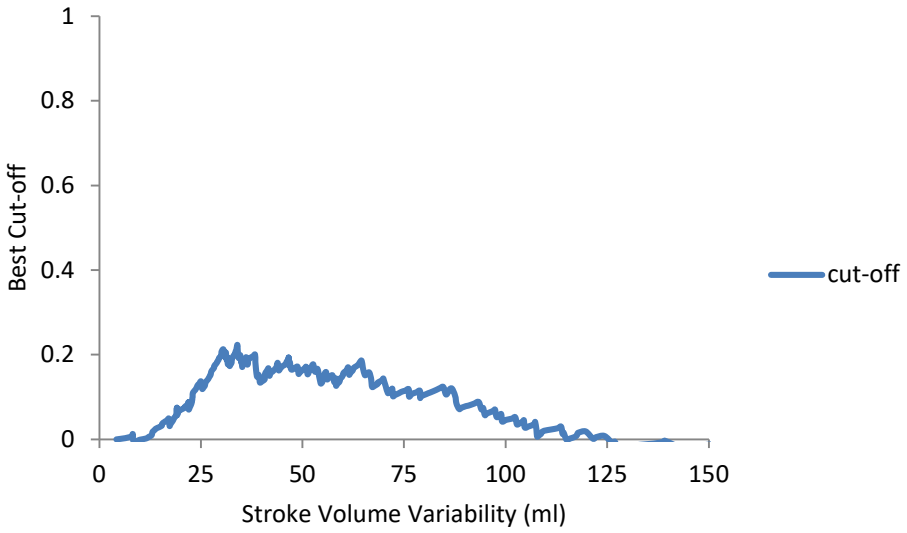


Figure 3.7. Best cut-off for stroke volume variability. A cut-off of 50 mL, of stroke volume variability values is found to have the highest true positive rate together with the lowest false positive rate in prediction of mortality outcome.

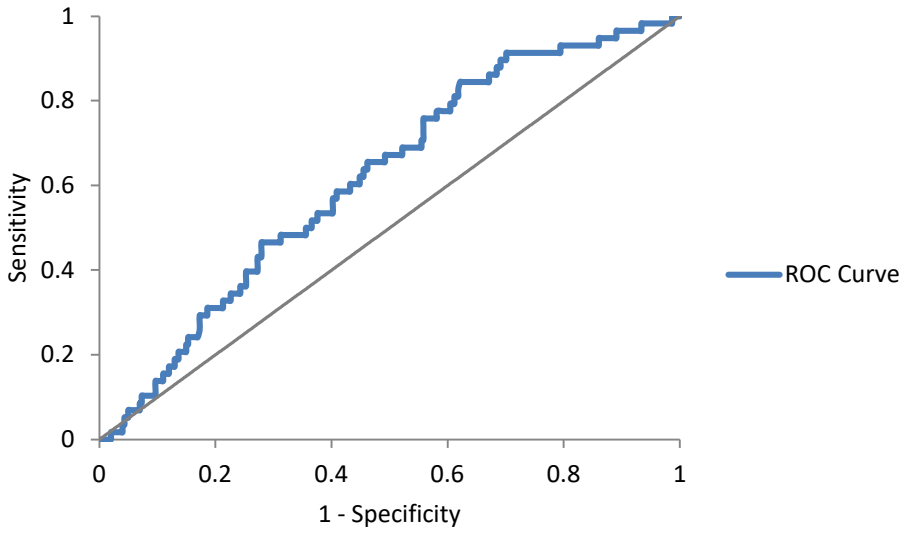


Figure 3.8. Receiver Operating Characteristics Curve for SVV. Stroke Volume Variability (SVV) has the largest area under receiver curve (AUC): 0.62, compared to other haemodynamic parameters in relation to mortality outcome.

Both SVV values; above 50 and below 50 have statistical significance in predication of mortality (*P* value: 0.021). SVV values above 50 are associated with increased mortality rate (35/58, 60.3%). On other hand lower values below 50 are associated with less risk of death (23/85, 39.4%). Similar results apply to SVV % and cut off 30%. **(Table 3.15) (Figure 3.9)**

Table 3.15. SVV values and mortality.

SVV (mL)	Alive	Dead	Total	*P* value	alive %	dead %	Total %
< 50mL	169	23	192		56.1	39.7	53.5
> 50mL	132	35	167		43.9	60.3	46.5
Total	301	58	359	0.021	100	100	100
SVV (%)	**Alive**	**Dead**	**Total**	***P* value**	**alive %**	**dead %**	**Total %**
< 30%	168	23	192		55.8	39.7	53.2
> 30%	133	35	167		44.2	60.3	46.8
Total	301	58	359	0.024	100	100	100

A Cut-off 50 ml stroke volume variability is shown to have statistical significance in predication of mortality using Chi-square test (*P* value: 0.021). Same applies to SVV% when values presented in %. **Abbreviations:** SVV: stroke volume variability.

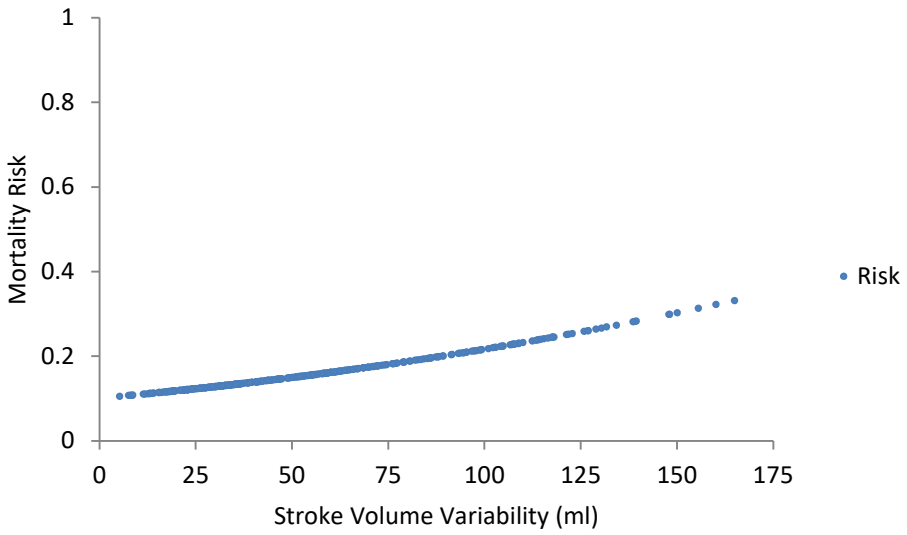


Figure 3.9. Relation between SVV values and mortality risk. Higher values of SVV are related to increased mortality and lower values below 50 ml are associated with less risk of death. Values beyond 100 ml are less likely to be encountered in clinical setting.

In summary

A model using SVV as the strongest and the only independent predictor of poor outcome (28-days mortality) was created (*P* value: **0.021**). AUC was **0.62** with accuracy of **0.57**, likelihood ratio of **1.38**. **(Figure 3.10)** The sensitivity and specificity of the model were calculated as **60%** and **56%** respectively. **(Table 3.16)**

Table 3.16. Characteristics of model using SVV as an independent predictor of mortality outcome.

P value	0.021	LCL	UCL
AUC	0.62	0.54	0.69
Sensitivity	0.60	0.47	0.72
Specificity	0.56	0.50	0.62
False positive rate	0.44	0.38	0.50
False negative rate	0.40	0.28	0.53
Positive predictive value	0.21	0.15	0.28
Negative predictive value	0.88	0.83	0.92
Probability (test+)	0.47	0.41	0.52
Prevalence	0.16	0.13	0.20
Accuracy	0.57	0.52	0.62
Likelihood ratio +ve test	1.38	1.08	1.76
Odds ratio	1.95	1.10	3.46

A model was created using SVV as independent predicator of mortality outcome. Model characteristics are summarized: AUC: 0.62, accuracy: 0.57, likelihood ratio: 1.38. The sensitivity and specificity of the model is 60% and 56% respectively. **Abbreviations:** SVV: stroke volume variability.

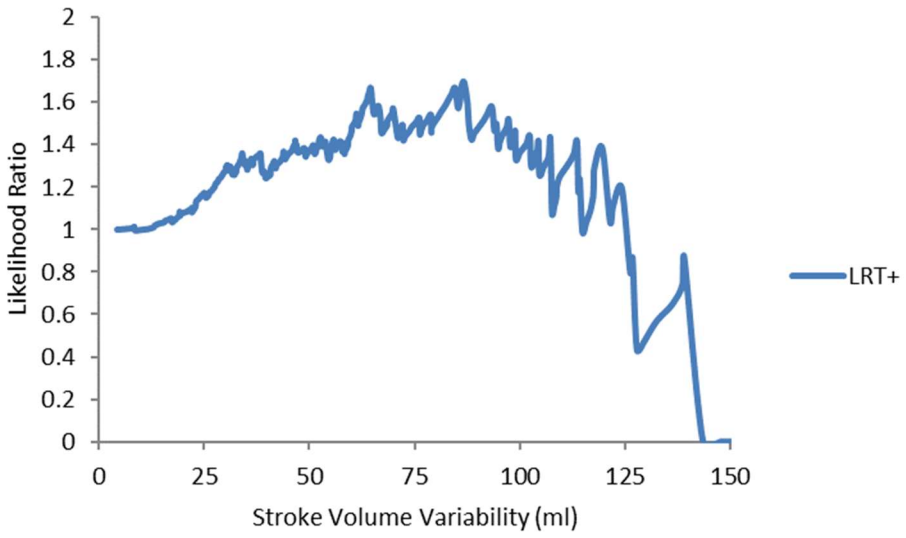


Figure 3.10. Likelihood ratio of a model using SVV as an independent predictor of mortality outcome. SVV values of around 50 ml are associated with higher likelihood ratio of greater than 1.

3.5 Objective 2

To investigate whether advanced haemodynamic variables using USCOM improve the detection and classification of shock.

There is no quantitative definition of shock type, although four distinct types are recognized: distributive, hypovolemic, cardiogenic and obstructive. The type of shock may be determined by clinician gestalt or by haemodynamic parameters measured by USCOM. I hypothesized that shock can be classified using haemodynamic variables. Hence, I categorized patients into different shock categories by using USCOM-derived haemodynamic parameters including Flow Time corrected (FTc), stroke volume variability (SVV), Systemic vascular resistance (SVR) and Inotropy index. I hypothesized:

Hypovolemic shock is present if:

- Either FTc is higher than normal range (321 – 415), i.e., > 415 OR SVV is higher than the normal range (>30).

AND

- Systemic vascular resistance index is > 2200.

Distributive shock is present if:

- Systemic vascular resistance index is <1800 (i.e., below the normal range (1800-2400)).

Cardiogenic shock is present if:

- Inotropy index is below the normal range, i.e., < 1.

Multivariate Logistic analysis was used to assess the relation between USCOM driven shock class as significant predictors of 28-days mortality outcome. From a total of 109, who were not shocked as per above classifications, 93 patients survived, and 16 patients died. When mortality outcome was correlated to shock class, distributive shock had the highest mortality (13/63) with mortality rate of 20.6%. This was followed by hypovolemic and cardiogenetic shock, with mortality rate of 17.2% and 15.9% respectively. Some patients fulfilled two of shock criteria, and were classed as mixed shock, for instance, hypovolemic plus cardiogenic or distributive plus cardiogenic. From 44 patients, who were classed as mix shock, hypovolemic plus cardiogenic, 12.6 % survived, whereas 10.3% died. Only 6 patients were classified as mix distributive plus cardiogenic and there was no mortality reported in this cohort. Overall, analysis of data shows that hypothesized shock classification is unable to predict mortality outcome, (*P* value: 0.77) Another proof to this outcome is that patients, who were classed as no shock by hypothesized classification of shock still have a significant mortality rate of 14.7%, which appears to be unrealistic. **(Table 3.17)**

Table 3.17. Relationship between USCOM-derived shock and 28-day mortality outcome.

Type	Mortality outcome absent (Alive) N: 301	Mortality outcome present (Dead) N: 58	Total	*P* value	Alive %	Dead %	Total%	Mortality rate
Shock grouping								
No shock	93	16	109		30.9	27.6	30.4	14.7
Hypovolemic	77	16	93		25.6	27.6	25.9	17.2
Distributive	50	13	63		16.6	22.4	17.5	20.6
Cardiogenic	37	7	44		12.3	12.1	12.3	15.9
Hypovolemic + Cardiogenic	38	6	44		12.6	10.3	12.3	13.6
Distributive + Cardiogenic	6	0	6		1.99	0.00	1.67	0.00
Total	301	58	359	0.77	100	100	100	16.2

Multivariate Logistic analysis was used to assess the relationship between USCOM derived shock class as significant predictors of 28-days mortality outcome. There was no statistical significance between proposed classification and mortality outcome. (*P* value: 0.77)

Patients were grouped into two distinct groups; those who fulfilled the criteria for one shock class; 1 type and those who fulfilled the criteria for two shock class; 2 types. It was shown that patients with one 1 shock type are more likely to die and had 18.0 % mortality rate, whereas those with 2 shock types are more likely to survive (mortality rate; 12.0%). Chi-squared analysis of grouped data showed that there is no statistically significant association between shock groups and mortality. (*P* value: 0.52) Similar analysis was used to correlate grouped data; Shock and No shock to primary outcome and results showed no significant correlation between these groups and mortality. **(Table 3.18)**

Table 3.18. Grouped shock class and relation to mortality outcome.

MIXED	Alive	Dead	Total	*p* value	Mortality rate%
No shock	93	16	109		14.7
Shock (1 type)	164	36	200		18.0
Shock (2 types)	44	6	50		12.0
Total	301	58	359	0.52	16.2
MIXED	**Alive**	**Dead**	**Total**	***p* value**	**Mortality rate%**
No shock	93	16	109		14.7
Shock	208	42	250		16.8
Total	301	58	359	0.62	16.2

Chi-squared analysis of grouped data showed no statistically significant association between shock groups and mortality outcome. *(P* value > 0.05)

When correlated to demographics, it was well proven that older patients; those aged > 70 years are more likely to have poor outcome. However, age and gender did not associate significantly with mortality outcome when correlated to hypothesized shock class, using USCOM-driven haemodynamic values. **(Table 3.1**

Table 3.19. Relation between patients' demographics, shock class and mortality outcome.

Age	Alive	Dead	Total	*P* value	Alive %	Dead %	Total %	Mortality rate%
< 70	149	18	167		49.5	31.0	46.5	10.8
> 70	152	40	192		50.5	69.0	53.5	20.8
Total	301	58	359	0.0098*	100	100	100	16.2
Age	**< 70**	**> 70**	**Total**	***P* value**	**< 70 %**	**> 70 %**	**Total %**	**> 70 %**
No shock	56	53	109		33.5	27.6	30.4	48.6
Hypovolaemic Shock	40	53	93		24.0	27.6	25.9	57.0
Distributive Shock	31	32	63		18.6	16.7	17.5	50.8
Cardiogenic Shock	20	24	44		12.0	12.5	12.3	54.5
Hypovolemic + Cardiogenic	18	26	44		10.8	13.5	12.3	59.1
Distributive + Cardiogenic	2	4	6		1.20	2.08	1.67	66.7
Total	167	192	359	0.48	100	100	100	53.5
Gender	**Male**	**Female**	**Total**	***P* value**	**M %**	**F %**	**Total %**	**Fem %**
No shock	51	58	109		30.5	30.2	30.4	53.2
Hypovolaemic Shock	49	44	93		29.3	22.9	25.9	47.3
Distributive Shock	31	32	63		18.6	16.7	17.5	50.8
Cardiogenic Shock	16	28	44		9.58	14.6	12.3	63.6
Hypovol + Cardiogenic	18	26	44		10.8	13.5	12.3	59.1
Distribut + Cardiogenic	2	4	6		1.20	2.08	1.67	66.7
Total	167	192	359	0.49	100	100	100	53.5

Data is presented as shock group and % mortality outcome. Hypothetic shock classification as per USCOM derived shock, was correlated to patient demographics including age and gender. No statistical significance was found between the proposed criteria and outcome of shock. Relationship between age and morality outcome however remains significant (*P* value: 0.0098). *: Statistical significance with *P* value <0.05.

3.6 Objective 3

To validate and refine a previously defined diagnostic tool; Li's *a priori* Pragmatic Shock (LiPS), for detection and classification of shock.

As outlined in previous chapters LiPS categorised patients into three distinct categories: No Shock, Possible shock, and Shock. I aimed to reassess LiPS definition of shock in its own and the external setting. Validation was sought by demonstrating a "dose-response" relationship between the severity of shock according to the classification and the final mortality outcome (28-days mortality), which provides face validity to the proposed priori definition. I had permission from LiPS study authors (Li and co-workers) and had access to LiPS data sets. In order to perform accurate validation, I matched my study inclusion criteria with original LiPS study inclusion criteria. Hence, I only used data from patients who were admitted to steaming (High dependency unit) and resuscitation rooms. This corresponds with LiPS study recruitment criteria, where patients are categorized to ED triage categories; 1 (critical), 2 (emergency), or 3 (urgent) out of a 5-point scale. In this categorization, 1 is the most serious and 5 is the least serious. The local target is for category 1 cases to be seen by a doctor immediately in the resuscitation room, category 2 to be seen within 15 minutes, and 90% of category 3 cases to be seen within 30 minutes. The similar approach applies to patients admitted to streaming and resuscitation room at University Hospital of Wales. LiPS study authors provided me with two cohorts; Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong) and Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong). In this analysis, cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff). Firstly, shock status and mortality data, including mortality rate were defined in all three cohorts. **(Table 3.20)**

Table 3.20. Shock status and mortality data in three cohorts.

Shock status	Cohort 1	Cohort 2	Cohort 3	*P value*
No shock	22	51	62	
Possible	53	51	76	
Shock	33	50	81	
Total	108	152	219	0.0000009 *
28-day Mortality	**Cohort 1**	**Cohort 2**	**Cohort 3**	***P* value**
Alive	96	132	175	
Dead	12	20	44	
Total	108	152	219	0.038 *
Mortality Rate%	**Cohort 1**	**Cohort 2**	**Cohort 3**	
Alive	88.9	86.8	79.9	
Dead	11.1	13.2	20.1	
Total %	100	100	100	

Analyzed data using Pearson's chi-squared showed that all three cohorts have statistical significance in relation to shock status and mortality outcome *(P* value: 0.0000009), (*P* value: 0.038) respectively. Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong), Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong) and cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff). *: Statistical significance with *P* value <0.05.

As mentioned in previous chapters, LiPS criteria is consistent of blood pressure, PH, Base excess, Lactate, and skin colour. In order to validate the LiPS definition of shock, an additive score was created to make analysis easier as some of LiPS variables are quantitative and others are qualitative. LiPS additive score was created by adding up physiological variables contributed to formation of LiPS and creating a score of 0 to 7. A score of 7 is presence of skin mottling, SBP < 90 mmHg, MAP < 65 mmHg, Lactate >= 4.0, PH ≤ 7.1 and Base access ≤ -5.0 and a score of 0 is absence of all parameters. LiPS additive score was shown to correlate very well to the shock category as higher scores were correlating to Shock and lower scores were correlating to No shock. **(Table 3.21)** Most patients in all three cohorts had lower LiPS additive score**. (Figure 3.11)**

Table 3.21. Association between LiPS additive score and shock category.

LiPS Additive Score	No shock	Possible	Shock	Total
0	211			211
1		189	20	209
2 +		37	164	201
Total	211	226	184	621
LiPS Additive Score	**No shock**	**Possible**	**Shock**	**Total**
0	211	0	0	211
1	0	189	20	209
2	0	36	57	93
3	0	1	53	54
4	0	0	24	24
5	0	0	16	16
6	0	0	12	12
7	0	0	2	2
Total	211	226	184	621

LiPS additive score was shown to correlate very well to shock category as higher scores were correlating to Shock and lower scores were correlating to No shock. Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong), Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong) and cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff).

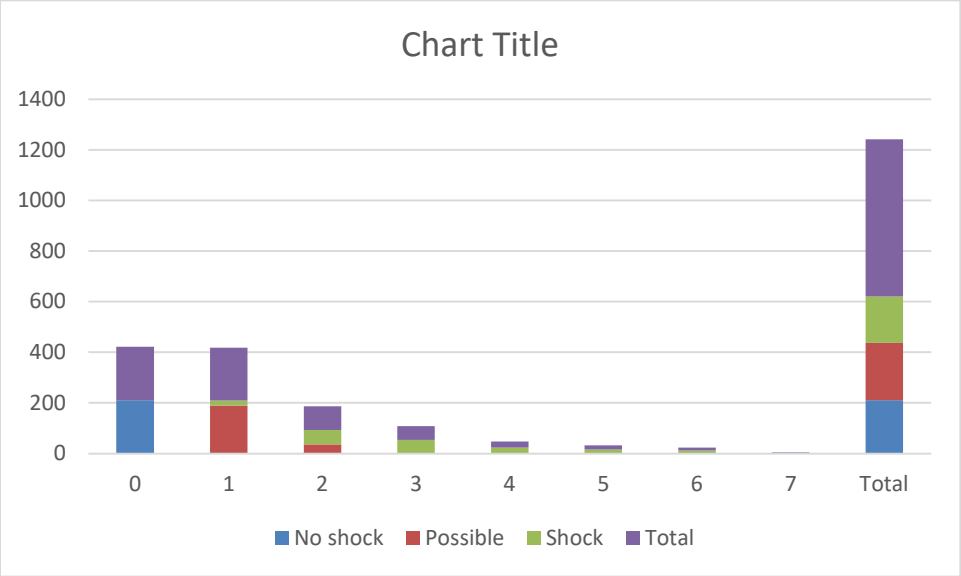


Figure 3.11. Percentage probability shock and LiPS additive scores. LiPS additive score was shown to correlate very well to the shock category as higher scores were mainly correlating to Shock and lower scores were correlating to No shock.

When correlated to mortality, LiPS additive score was shown to have a very highly significant association with primary mortality outcome in all three distinct cohorts (*P* value**: 0.000001**) and higher scores are associated with higher mortality and more diagnosis of shock. **(Table 3.22)**

Table 3.22. LiPS additive score and 28-days mortality in different cohorts.

LIPS Additive Score	Cohort 1	Cohort 2	Cohort 3	*P* value	Total
0	22	51	62		135
1	47	49	68		164
2	20	14	42		76
3	9	18	23		50
4	5	10	9		24
5	2	4	10		16
6	2	6	4		12
7	1	0	1		2
Total	108	152	219	0.000001†	479

LiPS additive score was shown to have a very highly significant association with primary mortality outcome in all three distinct cohorts. Higher scores are associated with higher mortality and diagnosis of shock. (*P* value**:** 0.000001) †: Statistical significance with *P* value < 0.05. Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong), Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong) and cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff).

Goodness of Fit, Linear regression and Area under the Receiver Operating Characteristics (ROC) curve analysis were performed to validate the LiPS criteria, against mortality outcome. Using Liner regression, a very good correlation was shown; *P* value: **0.009** and R2: 0.71. Using ROC Curve to test the diagnostic ability of LiPS additive score, it was shown that score has a very high significance in predicting mortality outcome; AUC: **0.69** and +LR: **2.19**. **(Table 3.23), (Figure 3.12)**

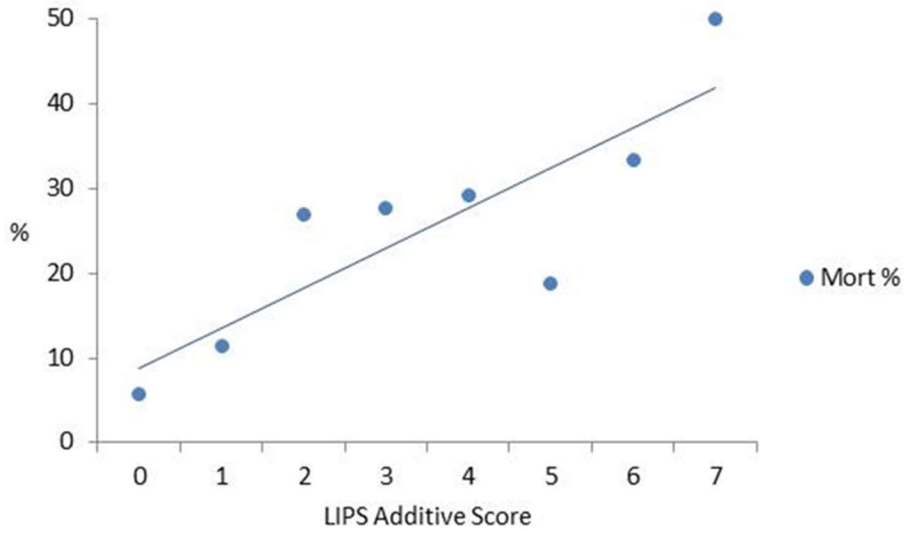
Table 3.23. Relationship between LiPS additive score and mortality using Goodness of Fit.

LiPS Additive Score	Cohort 1	Cohort 2	Cohort 3	Added	o-e	Deaths	Mort %
0	0	0	7	0	0	7	5.19
1	2	6	11	8	1	19	11.6
2	4	3	14	7	7	21	27.6
3	2	6	6	8	1	14	28.0
4	3	1	3	4	0	7	29.2
5	0	1	2	1	1	3	18.8
6	0	3	1	3	1	4	33.3
7	1	0	0	1	1	1	50.0
Total Deaths	12	20	44	32	12	76	15.9
Goodness of Fit					0.09		

LIPS Additive Score and	**R**	**R square**	**F**	**df1**	**df2**	***P* value**	**constant**
Linear Equation	0.84	0.71	14.7	1	6	0.009	8.87

ROC curve	**Area**	**SE**	***P* value**	**LCL**	**UCL**	**cut-off**	**Sensiti.**	**Specif.**	**LRT+**
LiPS Additive Score	0.69	0.029	0.0000007**	0.63	0.75	1.5	0.60	0.72	2.19

Linear regression and Area under the Receiver Operating Characteristics (ROC) curve analysis were performed to validate the LiPS criteria, against mortality outcome. **: Statistical significance with *P* value < 0.05. LiPS additive score was found to have very high statistical significance in predicting mortality outcome of shock; *P* value: 0.0000007, AUC: 0.69 and LR: 2.19. Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong), Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong) and cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff).



R^2 = 0.71 ***P*** **value: 0.009**

Figure 3.12. LiPS additive score and mortality. Coefficient of determination (R^2 = 0.71) is indicative of high level of correlation, between LiPS additive score and mortality outcome.

In summary, LiPS additive score has been validated in three distinct populations (cohorts). A model with scores being categorised into two groups; below 2 and 2 and above was created. The model had good performance ability using regression analysis in all cohorts (*P* value: **0.0006**, **0.0003** and **0.005**, AUC**: 0.77**, **0.71** and **0.62** in cohort 1, 2 and 3 respectively). **(Table 3.24), (Figure 3.13)**

Table 3.24. Characteristics of LiPS additive score model as a predictor of mortality outcome in different cohorts.

	Cohort 1			Cohort 2			Cohort 3		
LiPS Additive Score	**Alive**	**Dead**	**Total**	**Alive**	**Dead**	**Total**	**Alive**	**Dead**	**Total**
< 2	67	2	69	94	6	100	112	18	130
2 +	29	10	39	38	14	52	63	26	89
Total	96	12	108	132	20	152	175	44	219
***P* value**	0.0006*	LCL	UCL	0.0003*	LCL	UCL	0.005*	LCL	UCL
AUC	0.77	0.63	0.90	0.71	0.58	0.83	0.62	0.52	0.71
Sensitivity	0.83	0.55	0.95	0.70	0.48	0.85	0.59	0.44	0.72
Specificity	0.70	0.60	0.78	0.71	0.63	0.78	0.64	0.57	0.71
False Positive Rate	0.30	0.22	0.40	0.29	0.22	0.37	0.36	0.29	0.43
False Negative Rate	0.17	0.05	0.45		0.15	0.52	0.41	0.28	0.56
Positive Predictive P value	0.26	0.15	0.41	0.27	0.17	0.40	0.29	0.21	0.39
Negative Predictive value	0.97	0.90	0.99	0.94	0.88	0.97	0.86	0.79	0.91
Probability (test+)	0.36	0.28	0.46	0.34	0.27	0.42	0.41	0.34	0.47
Prevalence	0.11	0.06	0.18	0.13	0.09	0.19	0.20	0.15	0.26
Accuracy	0.71	0.63	0.80	0.71	0.64	0.79	0.63	0.57	0.70
Likelihood ratio +ve test	2.76	1.86	4.10	2.43	1.64	3.60	1.64	1.20	2.25

Using regression analysis, LiPS additive score was found to have statistical significance in relation to mortality outcome in all three cohorts. AUC for cohort 1: 0.77, followed by 0.71 and 0.62 for cohort 2, 3 respectively. Likelihood ratio was above 2 in all three cohorts. * *P* value < 0.05: Statistical significance. Cohort 1: representing LiPS derivations data, where original population is derived from and where the LiPS criteria was first introduced (Hong Kong), Cohort 2 representing LiPS internal validation data, where the LiPS criteria was first tested and validated internally (Hong Kong) and cohort 3 represents my study population, where the LiPS criteria was re-assessed and validation in an external setting (Cardiff).

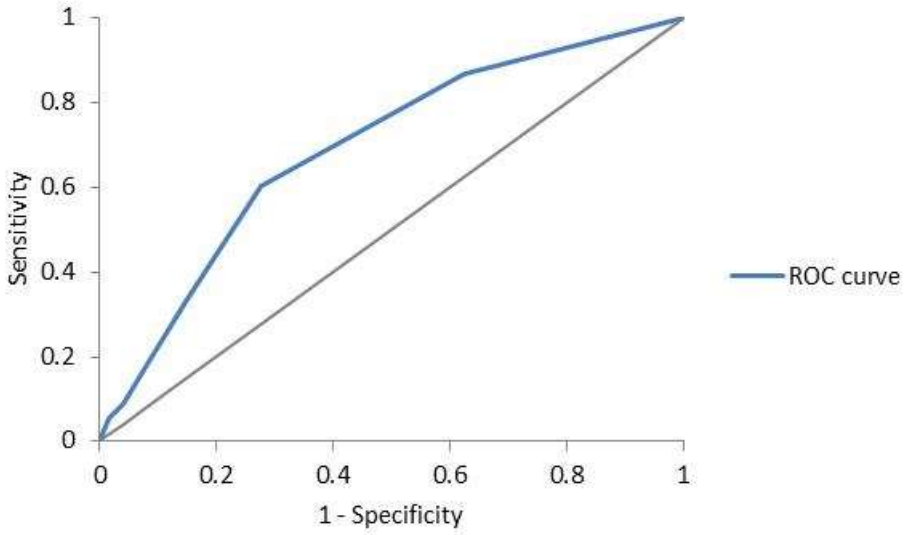


Figure 3.13. ROC curve for LiPS additive score. AUC: 0.71 for LiPS additive score is in keeping with good diagnostic ability of proposed classification in relation to primary outcome.

Diagnostic Investigation and Prediction of Shock (DiPS)

Previously, I showed that baseline characteristics including GCS, Capillary refill time, temperature, Bilirubin, oxygen supplement, respiratory rate, Albumin and systolic blood pressure are predictors of outcome. Some characteristics were sub-grouped into two groups. For instance, GCS was sub-grouped to 3-8 and 9-12 and Capillary refill time to 3-4 and 5-6. All variables were entered a logistic regression model and a calculated score, based on level of significance was allocated to each parameter. Hosmer & Lemeshow test was used as goodness of fit for the model. The model had excellent diagnostic ability in predicting outcome of shock with AUC of **0.813** (95% CI: 0.765 to 0.855), accuracy of **83.3%** and *P* value of < **0.0001**. The model was named as "Diagnostic Investigation and Prediction of Shock, (DiPS)", which can be used as standard quantitative measure of shock with sensitivity of **66.67%** (95% CI: 54.3 - 77.6) and specificity of **80.93%** (95% CI: 75.3 - 85.7). The novelty of the DiPS model is that it included biochemistry values such as Albumin and Bilirubin which were never been used in as values contributing to diagnostic models. (**Table 3.25), (Table 3.26), (Figure 3.14), (Figure 3.15)**

Table 3.25. Multivariate logistic regression for 28-day combined outcome (N = 359).

Variable	Values	Odds ratio	95% CI	Coefficient	*P* Value	Score
GCS	3 - 8	9.1404	1.2046 to 69.3563	2.21270	0.0324	22
	9 - 12	1.3060	0.4034 to 4.2282	0.26695	0.6561	3
Capillary Return	3 - 4	3.7493	1.3483 to 10.4259	1.32157	0.0113	13
	5 - 6	8.7443	2.9269 to 26.1241	2.16840	0.0001	22
Temperature	< 35.1	5.3773	1.7761 to 16.2802	1.68219	0.0029	17
Bilirubin	18 to 34	1.5268	0.7132 to 3.2688	0.42320	0.2759	4
	> 34	4.8743	1.6353 to 14.5284	1.58397	0.0045	16
Oxygen Supplement	Yes	1.8921	0.9793 to 3.6556	0.63769	0.0577	6
Respiratory Rate	> 24	2.5704	1.2959 to 5.0982	0.94406	0.0069	9
Albumin	< 35	1.8593	0.9104 to 3.7971	0.62021	0.0887	6
Systolic Blood Pressure	< 91	1.6702	0.6127 to 4.5528	0.51293	0.3161	5

All 8 variables from table 3.4. were entered into the logistic regression model. AUC = 0.813 (0.765 to 0.855), Cox & Snell R^2 0.215, Accuracy 83.3%, Model *P* value < 0.0001, Hosmer & Lemeshow test: 7.18; Total score = 123.

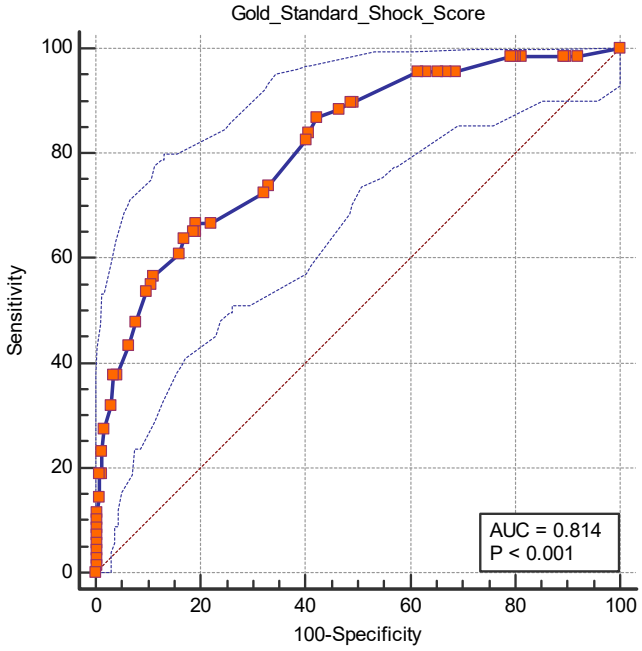


Figure 3.14. ROC of DiPS score and relation to 28-day combined outcome. Area under the receiver operating curve is 0.813 is in keeping with excellent diagnostic ability for the proposed DiPS model. (*P* value <0.001)

DiPS score and prediction of outcome:

Chi-squared test tested a significant difference between DiPS score and combined outcome. In this sub-analysis 305 patients out of total of 359 were included. Patients were sub-grouped to 0-10, 11-30 and 30-77. The lowest DiPS score was associated with less chance of poor outcome and higher scores were associated with more chance of poor outcome, eg, in 91 patients with score of 30 – 77, 46 of them met the 28-days composite outcome, whereas in group of 0-10, only 1 patient met the combined outcome. DiPS score was shown to be very highly significant in predicting outcome. (*P* value < 0.0001) **(Table 3.26)**

Chi-squared test

Classification X	DiPS score group
Classification Y	Combined_Outcome_28_day

Table 3.26: DiPS score of shock and combined outcome.

	DiPS score			
Combined_Outcome_28_day	**0 to 10**	**11 to 30**	**30 to 77**	
No	48	143	45	236 (77.4%)
Yes	1	22	46	69 (22.6%)
Total	49 (16.1%)	165 (54.1%)	91 (29.8%)	305
Chi-squared				60.535
DF				2
Significance level				P < 0.0001
Contingency coefficient				0.407

Chi-squared test was used to analyse the relationship between grouped data combined outcome of shock. *P* value < 0.0001, Contingency coefficient: 0.407. Combined outcome defined as combination of primary outcome of ICU admission and mortality in 28 days.

In summary, DiPS as a novel diagnostic model of shock, using a combination of physiological and laboratory values, has an excellent diagnostic ability in predicting outcome of shock, whilst higher scores are associated with poorer outcome and the lower scores are indicative of better outcome.

3.7 Objective 4

Agreement between LiPS, USCOM and clinical impression of shock

In this section, level of agreement between different diagnostic measures is tested. These diagnostic approaches are including USCOM-derived shock, clinical gestalt of shock and LiPS diagnostic shock tool. Data on clinical impression of shock was collected by asking clinicians about their judgment of patient clinical status; Shock, Possible shock or No shock. A number of statistical tests was used to assess the level of agreement between these methods; firstly, diagnostic ability of LiPS as a pragmatic diagnostic tool and clinical impression of ED clinicians of shock were compared against each other. Inter-rater reliability was measured as percent agreement between LiPS and clinical impression. For which a matrix, in which the columns represented clinical impression and the rows represented LiPS data, was created. It was shown that in 118/359 (32.9%) of the cases both raters agreed that patients do not have shock. In 10/359 (2.79%) of cases both raters agreed on diagnosis of possible shock and finally in 40/359 (11.1%) of cases they agreed on diagnosis of shock. Overall, in 168/352 (46.8%) both raters agreed on potential diagnosis. In 131/359 (36.5%) they nearly agreed and there was no agreement in 60/359 (16.7%) of the cases. It was observed that there is **only 46.8%** agreement between two methods and therefore 54% is representor of incorrect data and misrepresentation of the research data. **(Table 3.27)**

Table 3.27. Percentage agreement between LiPS and clinical impression.

Clinical Impression	LIPS	N	%
No	**No**	118	32.9
No	**Possible**	91	25.3
No	**Shock**	50	**13.9**
Possible	**No**	10	2.79
Possible	**Possible**	10	2.79
Possible	**Shock**	10	2.79
Shock	**No**	10	**2.79**
Shock	**Possible**	20	5.57
Shock	**Shock**	40	11.1
Total		359	100
Agreement between LiPS/Clinical		**N**	**%**
Agreed		168	46.8
Nearly		131	36.5
No		60	16.7
Total		359	100

A table created where columns represent clinical impression and the rows represented LiPS data. Percentage agreement was used to establish level of agreement between two methods. It was observed that there is only 46.8% agreement between two methods and therefore 54% is representor of incorrect data.

Chi-square test (χ^2) were used to measure how expectations compare to actual observed data. It is applied to 2 × 2 contingency tables with a dichotomous trait and matched pairs of data, to determine whether marginal frequencies of LiPS and clinical are equal. χ^2 results are significant (*P* value: 0.00000057), providing sufficient evidence that marginal proportions of LiPS and Clinical data are significantly different from each other. **(Table 3.28), (Table 3.29)**

Table 3.28. Comparison between paired observed and expected agreement between LiPS and Clinical impression.

Shock		Clinical	Clinical	Clinical	
	observed	**no**	**possible**	**yes**	**total**
LIPS	**No**	118	10	10	138
LIPS	**Possible**	91	10	20	121
LIPS	**Yes**	50	10	40	100
	Total	259	30	70	359

Expected	No	Possible	Yes	Total
No	100	11.5	26.9	138
Possible	87.3	10	23.6	121
Yes	72.1	8.4	20	100
Total	259	30	70	359

Contingency table was used with a dichotomous trait and matched pairs of data. Using Chi-square test (χ^2) test, it was shown that marginal proportions of LiPS and Clinical data are significantly different (*P* value: 0.0000005).

Other measures of agreement such as Cohen's kappa coefficient (κ) were used as a more robust measure of inter-rater agreement and was calculated as 0.17 in keeping with no significant agreement between the two methods. Other measures of agreement including Kendall's coefficient of concordance as a non-parametric test or a normalization of Friedman test, with no assumptions regarding the nature of probability distribution, calculated the Kendall's *W* (Kendall's coefficient of concordance) as 0.067. This is also in keeping with above findings. Additionally, I used intra-class correlation coefficient, which is best to be used for grouped rather than paired data but that also showed that LiPS as pragmatic shock tool does not agree with clinical gestalt of shock. The Intraclass correlation coefficient was calculated at 0.5, showing neutral agreement. However as mentioned intraclass correlation coefficient is bets to be used for grouped data. This is like Cronbach's of 0.50, in keeping with poor internal consistency. **(Table 3.29)**

Table 3.29. Summary of agreement tests used to assess level of agreement between LiPS tool and clinical impression of shock.

	Chi-sq	df	*P* value				
McNemar's Test	94.96	3	0.0000005				
Agreement							
Kappa	**Coeffic.**	**std error**	**t**	***P* value**			
	0.17	0.033	5.38	0.0000009			
Cronbach's	**Alpha**	**standard**	**n**				
	0.50	0.50	2				
ANOVA	**Sum**	**df**	**mean**	**Chi-sq**	***P* value**		
Friedman's Test	495	1	32	61.5	0.0000001		
Kendall's	**W**						
coefficient of concordance	0.064						
Intraclass Correlation	**coeffic.**	**LCL**	**UCL**	**F test**	**df1**	**df2**	***P* value**
average	0.50	0.39	0.60	2.01	358	358	0.0000003

Other measures of agreement as more robust measure of inter-rater agreement are in keeping with no significant agreement between LiPS and clinical impression of shock, Cohen's kappa coefficient (κ): 0.17, *P* value: 0.0000009.

To evaluate clinical experience for shock

Statistical methods to test agreement are used to assess whether USCOM derived haemodynamic values can agree with clinical impression. Once again, data on clinical impression of shock was collected by asking clinicians about their judgment of patient clinical status, Shock, Possible shock, or No shock. For categorical data, Kappa coefficient was used to represent level of agreement between the two methods. In 59/359 (16.4%) of the patients both USCOM and clinician agreed that patient is not shocked. In 20/359 (5.57%) both agreed that patient is possibly have shock and in 34/359 (9.47%) they agreed that patient is in shock. Overall, in 113 (31.5%) of the cases both measures agreed on final diagnosis, in 190 (52.9%) USCOM and clinician nearly agreed and in 56 (15.6%) of the cases there was no agreement between USCOM and clinician. The data shows in 84.4% of the cases, clinician and USCOM agreed on diagnosis of shock and possible shock.
(Table 3.30)

Tbale 3.30. Summary of agreement between clinical impression of shock and USCOM.

Clinical	USCOM	N	%
No	**No**	**59**	16.4
No	Possible	152	42.3
No	Shock	48	**13.4**
Possible	no	3	0.84
Possible	**Possible**	**20**	5.57
Possible	Shock	7	1.95
Shock	no	8	**2.23**
Shock	Possible	28	7.80
Shock	**Shock**	**34**	9.47
Total		359	100
Agreed	113		31.5%
Nearly	190		52.9%
No	56		15.6%
Total	359		100%

Percentage agreement was used to establish level of agreement between clinical impression of shock and USCOM derived shock. In 84.4% of the cases, clinician and USCOM agreed on diagnosis of shock and possible shock in keeping with substantial level of agreement between the two methods.

In summary, LiPS diagnostic tool did not agree with clinical impression of shock. However, USCOM and clinicians had acceptable agreement on diagnosis of shock and possible shock.

Chapter 4

Discussion

The main purpose of this study was to investigate the diagnostic ability of a non-invasive method: Ultrasonic Cardiac Output Monitor (USCOM Ltd., Sydney, Australia); as a feasible, continuous-wave Doppler-based technique, providing beat-to-beat right and left haemodynamics, in a fast and cost-effective way in ED. In this chapter, I will be delivering on background of research and what has been found so far in clinical and academic settings in relation to main objectives of this study. I then discuss the key findings of my research and how these two interlink. Additionally, I will be writing on strengths and weaknesses of my work as well as clinical and research implications, future directions and concluding remarks.

4.1 What others have found – previous research and corelation to current study

4.1.1 Cardiac output and its measurement

As emphasized in previous chapters, cardiac output (CO) was shown to act as an independent haemodynamic value, which acts as predictor of outcome in shock. [80] We know that since the introduction of pulmonary artery catheter in 1970, thermodilution cardiac output measurements have been routinely performed as part of assessment of haemodynamics in sick patients in intensive care units. [355], [356], [356] Pulmonary artery catheter (PAC) became the gold standard of cardiac output monitoring for two decades. [355], [356] PAC could assist in collecting information on cardiac pressures, volume status and oxygen saturation. [357], [358] Despite this widespread application over the last 40 years, it remains essentially without validation and clinical outcomes benefit. [359], [360], [361], [362] Additionally, pulmonary artery catheterization involves complications and risks such as infection, arrhythmias and trauma to the artery followed by dissection. [363], [364] Thus, overtime scientific interest has been shifted and clinicians are more interested in using non-invasive methods such ultrasound guided haemodynamic monitors and Doppler technologies. [298], [365] There are several new and non-invasive haemodynamic monitors, which were used across intensive care units and emergency departments and their accuracy in measuring physiological parameters is compared to each other. [286], [287], [365], [366], [367], [368] These methods are ideal for patients out of the window for hemodynamic instability or lack of need for close monitoring such as in emergency department. [301], [369]

4.1.2 USCOM charchteristics

USCOM is repeatedly compared to invasive and non-invasive techniques measuring haemodynamics in various subjects and has been validated in various settings. For instance, USCOM is compared positively with flow probes in animals. [290], [300], [370] Philips and colleagues [298] compared 2D echocardiography and USCOM derived CO measurements in 37 pre-term neonates and obtained 66-paired measures of transpulmonary CO by two techniques, using two tailed t-tests and Bland-Altman analysis to compare results, they showed that mean values of transpulmonary CO were 0.36 ± 0.19 l/min by echocardiography and 0.37 ± 0.14 l/min by USCOM and not significantly different from each other (*P* value < 0.005). The mean difference between measures was 0.00 ± 0.08 l/min, with a mean % error of -3.7% and as a result they concluded that USCOM is as accurate for measurement of neonatal CO as conventional echocardiogram and can make a cost-effective contribution to neonatal haemodynamic management. A comparative study of non-invasive measure of CO with USCOM versus invasive method (PAC) in post cardiac surgery showed a very good agreement between CO and SV measured with USCOM and Swan-Ganz catheter. [368] Showing a bias of 0.18 and limits of agreement of -1.43 to 1.78 between USCOM and PAC in measuring CO in mechanically ventilated patients post cardiac operation, Tan *et al*, showed that USCOM has certainly a place in intensive care unit. [368] In a comparative study of ten patients undergoing liver transplant cardiac output measurements by thermodilution and USCOM at 30-minute intervals throughout the procedure and at 10 specific procedural reference points during the surgery, two hundred ninety paired cardiac output values were measured, and results revealed that the concordance between both methods was excellent in 8 patients and satisfactory in 2. Bland-Altman analysis of all data produced a mean bias of - 0.02 L/minute for USCOM, and the 95% limits of agreement were -1.06 to +1.10 L/minute. [369] Further analysis of the 10 reference time points showed minimal bias and high levels of agreement between two methods. [369] This study concluded that USCOM provides an accurate and non-invasive method for cardiac output measurement during liver transplantation. In 2018, a large meta- analysis of Chinese and English literatures of clinical trials compared using USCOM with thermodilution (TD) in monitoring cardiac function, looked at data from CNKI, Wanfang database, China biomedical literature database, VIP database, China Clinical Trial Registration Centre, PubMed, Embase and Cochrane Library and included a total of 25 studies involving 772 patients. [370] Among all these literatures and extensive pool of data, there were only 5 studies, showing poor level of agreement between the two techniques. Meta-analysis showed that there was no significant difference between the two methods in CO and CI monitoring [CO: mean difference (MD): -0.06, 95%CI: -0.17 - 0.05, *P* value: 0.31; CI: MD: -0.04, 95%CI: -0.13 - 0.05, *P* value: 0.38 respectively]. Subgroup analysis of different TD methods [pulmonary artery catheter (PAC), pulse indicator continuous cardiac output (PiCCO)] and different windows of USCOM ultrasonic probe [aorta (AA), pulmonary artery (PA)] in CO monitoring did not show any significant difference (PAC: MD: -0.07, 95%CI: -0.18 - 0.04, *P* value: 0.23; PiCCO: MD: 0.09, 95%CI: -0.31 - 0.50, *P* value: 0.65; AA windows: MD: -0.14, 95%CI: -0.31 - 0.02, *P* value: 0.09; PA

windows: MD: -0.00, 95%CI: -0.15 to 0.14, *P* value 0.95; AA/PA windows: MD: 0.23, 95%CI: -0.40 to 0.86, *P* value: 0.47). Funnel chart showed that the distribution of CO and CI monitoring were basically symmetrical, indicating that the bias of literature is small. This meta-analysis concluded that USCOM has good consistency with TD method in monitoring the markers of cardiac function including CO and CI, and different windows of ultrasonic probe of USCOM have no significant influence on the monitoring results. [370] Hence, one can conclude that USCOM can be used as a non-invasive alternative to pulmonary artery catheter placement with consequent reduction in patient's risk and morbidity associated with arterial catheterization.

Besides accuracy, there are other desirable characteristics for USCOM monitoring technique: ease of use, a fast response time, reproducibility, operator independency, safety, and cost effectiveness. [295], [366] USCOM is very easy to use and can not only be used by physicians but also by trained nurses. Learning curve is rapid. [295] Freemantle, [370] developed a criteria for acceptance of CO results obtained with the USCOM, and a protocol to optimize inter-assessor reliability of USCOM CO assessments. (Appendix) Using Freemantle training protocol, operator proficiency can be achieved after 20 scans. [371] Stewert *et al*, [372] investigated reproducibility of USCOM and assessed the inter-rater reliability of measurements of cardiac index (CI) and stroke volume index (SVI) in children below the age of eighteen years, who attended ED with infection, trauma, and gastrointestinal problems. They showed significant inter-observer correlation between two raters' measurements of CI and SVI. In this study the two investigators were blinded to each other's measurements. CI (r = 0.76, 95% CI 0.66 - 0.83; *P* value 0.0001) and SVI (r: 0.79; 95% CI: 0.70 - 0.86; *P* value: 0.0001). [372] This study was in line with adult studies such as a prospective study of adult trauma and non-trauma patients in surgical intensive care performed by Jain and colleagues. [294], [373], [374] Their study showed a very high correlation between CI measured by PAC and USCOM in two phases; phase I non-blinded and phase II: blinded; (phase I; r: 0.97, R2: 0.95, *P* value < 0.0001) and phase II; r = 0.93, R2: 0.86, *P* value < 0.0001). [373] The other aspect is safety and tolerability of USCOM. Since, being completely non-invasive and using ultrasound waves, USCOM is deemed to be very safe. In addition, measurements are seemed to be well-tolerated, even in non-sedated patients. [373] Its ease of use and portability make it a practical tool to guide haemodynamic therapy at bedside, not only in the ICU but also in other settings such as emergency department and wards. [274]

4.1.3 USCOM and echocardiography

Using continuous wave Doppler in contrast to echocardiography, which uses pulsed wave Doppler, has two advantages. One ability to obtain more accurate measurements of higher velocities and two is added simplicity from the lack of need to obtain 2D image and subsequent selection of sample area. [375] Echocardiography has been used for many decades to provide data on both cardiac morphology and haemodynamics on clinical grounds. However, it has never been validated in that respect. Echocardiography uses pulsed wave (PW) Doppler to measure flow velocity and calculate velocity time interval (VTI), which is an essential parameter in measuring stroke volume. USCOM uses continuous wave (CW) Doppler to measure VTI and therefore, unlike PW does not require accurate sample volume placement. The major source of error in haemodynamic measurements with echocardiography stems from the difficulty in measuring the aortic and pulmonary outflow diameters. [298] USCOM predicts the diameter of aortic and pulmonary valves based on a proprietary algorithm, which is similar to equations described by Nidorf *and* colleagues in 1992. [308] Measurement of VTI is largely automated and enables several ejection wave-forms to be measured in real time, which can then be averaged to provide beat-to-beat haemodynamics. The British Society of Echocardiography recommends that an average of a minimum of three measurements should be used for aortic and pulmonary diameters, which takes at least around 5 minutes. A full study on average takes about 30 minutes. Whereas a typical USCOM examination takes only 3-5 minutes. Hence, it well understood that USCOM measurements are less time consuming, more user friendly and has a shorter learning curve in comparison to echocardiography. Lelyveld-Haas *et al*, who measured cardiac output in a total of 1315 critically ill patients, using USCOM and echocardiography, showed that inter-observer variability of USCOM is significantly lower than echocardiography, ranging from 5.1 to 17%, which indicates less user dependency. [302] Overall, it is well demonstrated that USCOM has acceptable reproducibility and feasibility in adults and children, [298], [301], [308] and its accuracy allows it to certainly have a role as an alternative to echocardiography in measuring important haemodynamics, related to inotropy such as cardiac output, stroke volume variability and systemic vascular resistance, which can be useful in diagnosing shock and shock types. [288], [375], [376]

4.1.4 Cardiac output, cardiac power, and outcome of shock

Cardiac output and most recently shown cardiac power are strong and independent predictors of outcome, mainly in cardiogenic shock where shock is result of left ventricular dysfunction. [80] Hasdai *et al,* [80] developed a risk assessment prognostic algorithm of 30-day mortality, including clinical and hemodynamic data prospectively collected among patients with cardiogenic shock in the 41,021-patients, participated in Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial, which was later published in Heart journal in 1999. They showed that hemodynamic data derived from physical examination and right heart catheterization (RHC) added valuable information, which increases the ability to predict outcome in high-risk populations. Amongst data obtained from RHC, cardiac output measurements were of greatest prognostic significance. [80] Later in 2004, Finke *et al,* [274] in a valuable article published in journal of American College of Cardiology (JACC) showed that Cardiac power (CPO) is the strongest independent hemodynamic correlate of in-hospital mortality in patients with cardiogenic shock. They enrolled a total of 541 patients with cardiogenic shock, who were originally enrolled in the Should we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial registry. Cardiac power output (CPO) (W) was calculated as mean arterial pressure x cardiac output/451. By multivariate analyses, CPO (odds ratio per 0.20 W: 0.60 [95% CI: 0.44 - 0.83], *P* value 0.002; N: 181) and CPI (odds ratio per 0.10 W/m2: 0.65 [95% CI: 0.48 - 0.87], *P* value: 0.004; N:178) remained the strongest independent hemodynamic correlates of in-hospital mortality after adjusting for age and history of hypertension. In this study the investigators used right heart catheter (RHC) data on CO to calculate CPO in 75% of the patients and for the rest they used CO calculated by echocardiography. [274]

4.1.5 Potential source of error in measuring haemodynamics using USCOM

There are other sources of conflicting data, which question reliability of USCOM and other non-invasive haemodynamic monitors in certain settings. Likewise, any other technique, USCOM has a degree of percentage error. In 1999, Critchely and colleagues ran a MEDLINE* search on studies comparing techniques of cardiac output monitors, dating from 1986, using bias and precision statistics to construct an error-gram and to determine acceptable limits of agreement between various methods including invasive and non-invasive techniques. [370] They showed that using bias, precision, limits of agreement statistics and percentage error, acceptance of a new technique should rely on limits of agreement of up to +/- 30%. [370] In 2010 a meta-analysis by Chong *et al*, [377], [378] on the accuracy and precision of USCOM, showed a wide range of percentage errors (14–56%), across the 10 studies, which compared USCOM with thermodilution in measuring CO in human, using bias and precision statistics similar to Critchelys meta-analysis. [370] Although, this range was also comparable with what was found for other technologies, USCOM did not achieve a percentage error of agreement with bolus thermodilution of ± 30%, suggested by Critchley as a criterion for acceptability of precision. [370] This might be due to that the precision of thermodilution at times of unstable haemodynamics is considerably poorer than previously assumed [361], [364], and can explain the wider percentage errors found for all the minimally invasive methods, including USCOM. [275] The observed agreement of USCOM with thermodilution in the Critchely meta-analysis is consistent with a percentage error for both methods of less than ± 30% relative to the true cardiac output. The negative bias (−0.39 $l.min^{-1}$) found for USCOM in this meta-analysis may indicate a systematic tendency for the technique to underestimate the cardiac output. [370], [377]; [378]

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***MEDLINE** (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online) is a bibliographic **database** of life sciences and biomedical information. It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health.

In a study by Lelyveld-Haas and colleagues, [302] where the values of CO measured by USCOM-1A was compared to PAC in 25 adult patients at a mixed medical and surgical ICU in a major teaching hospital in the Netherlands, results showed that USCOM appeared to underestimate CO compared to the PAC, especially in the higher CO ranges. This systematic difference can be due to failure to capture the peak flow in hyperdynamic patients. On average, USCOM values were 9% below the corresponding cardiac output pulmonary artery catheter (PAC) values (systematic error). [302] In a Doppler-based method, like USCOM, failure to capture the right trace can arise from achievement of a suboptimal angle due to failure of alignment of ultrasound beam to the direction of blood flow in the aorta or pulmonary artery, can lead to underestimation of CO. Other source of error related to USCOM-driven CO measurements is irregularity of heart rate. [379] Because USCOM calculates cardiac output by using one Doppler flow profile and the interpeak distance, irregularity in heart rate will result in beat-to-beat variations in cardiac output estimates. Another source of error is insonation of the wrong vessel instead of aortic or pulmonary artery or the wrong region of the aorta or pulmonary artery, mainly due to a lack of experience. USCOM measures the diameter of the aorta from an estimated nomogram that is based on the subject's height. As mentioned before nomogram is derived from the Nidorf et al, [308] equation, which was rigorously evaluated by one of the authors (RAP) and was found to provide the most reliable estimate of valve dimensions. The 95% confidence intervals on the nomogram represent a ±10%–20% variation in aortic diameters. [308] Even small discrepancies in diameter, can cause quite large systematic errors in the cardiac output measurements. Thus, nomogram-based estimates of the cross-sectional area (CSA) of the aorta are also bound to introduce some systematic error into the measurement of cardiac output in the clinical setting. Another obstacle to accurate measurements of CO, using USCOM is positive-pressure lung ventilation, in which cardiac output fluctuates and is impeded during the inspiratory phase. This not only afffects the unreliability of results but also failure to obtain good traces. In a study by Horster and colleagues, flow detection in mechanically ventilated patients was around 91.7% due presence of sub tissue or gas excess, causing barrier to obtain a good quality ultrasound trace. [365] However, the same study reported 100% flow detection in normally breathing adult subjects. [365] In my study only six subjects (1.67%) were mechanically ventilated. Based on previous work, the overall proportion of failing to obtain an acceptable trace, using USCOM ranges between 5-24%. [286], [297], [302], [366] Other limitations related to evaluation of USCOM derived CO, can be related to failure to obtain quality traces transcutaneously, for instance, in presence of tracheostomy tube and in hyperinflated chest and chronic obstructive lung disease (COPD). Tan et al, [368] reported 21% failure in obtaining acceptable traces in study of adults admitted to intensive care after cardiac surgery.

4.1.6 Haemodynamic paramters and outcome of shock

Paramters related to tissue perfusion

In 2006, consensus of shock defined tissue hypoxia due to inadequate oxygen delivery as a good surrogate of shock, which contributes to the definition of shock. [380] The task force recommended that therapies should be aimed to restore adequate oxygen delivery and organ perfusion. [380] Peripheral tissue oxygen saturation (SO2) has shown promise as an early indicator of tissue hypoperfusion and as a risk stratification tool in various forms of shock. [381] In an observational study by Leichtle *et al*, [382] data from 66 patients, who required ICU admission within 72 hours of initial assessment, 47% of patients requiring ICU had low oxygen saturations below 70%. In this study a 1-point increase in oxygen saturation was associated with a 7% decrease in the odds of requiring ICU admission, and the area under the curve for SO2 was 0.64 (0.51-0.77, *P* value: 0.01). Persistence of low SO_2 levels during the early resuscitation phase of therapy is associated with a more severe organ dysfunction assessed by various SOFA and APACHE II scores. [383] This is supported by many other observations indicating a significant association between clinical abnormal peripheral perfusion and severity of organ dysfunction in patients suffering from shock. [384]

Parmaters related to afterload

Afterload represents all forces opposing left ventricular (LV) fiber shortening during ejection and includes ventricular shape, size, wall thickness, intra-cavity pressure, aortic impedance, blood viscosity, and peripheral resistance. Systemic vascular resistance (SVR) is a frequently used indicator of LV afterload but only represents a static parameter measuring vasomotor tone. [385] In septic shock, hypotension is associated with low systemic vascular resistance. [386] Peripheral vascular failure is usually the dominant hemodynamic feature, and persistent vasodilation, rather than a low cardiac output, is characteristic of non-survivors. [387] Low SVR can be associated with other medical conditions. Melo et al, [386] retrospectively reviewed and analyzed haemodyamic data from patients admitted to intensive care unit over five years and determined that at least a quarter of patients with hypotension and a low SVR have non-septic aetiologies. Although, sepsis and septic shock remained the main aetiology of low SVR, patients with non-septic aetiologies have a similar mortality to septic patients. Clinicians should be aware of the wide spectrum of conditions that induce low SVR such as adrenal insufficiency, anaphylaxis, cirrhosis, hypotension, and pancreatitis.

Several studies showed correlation between low systemic vascular resistance and poor outcome mainly in context of septic shock. Marik *et al*, [388] demonstrated that low SVR beyond 24 hours is a predictor of mortality and the majority in patients (65%), who died of septic shock with a persistently low SVR, while a smaller percentage died of low CO (10%) or of multiple organ failure (25%) after hemodynamic resolution of shock. Wray et al, showed that SVR index (SVRI) > 1529 dyne· sec/cms/ m2 at 24 hours after the onset of shock was associated with survival. [389] To support the idea that patients, who died of septic shock and had a persistent defect in SVR irrespective of CI, in a retrospective study of 42 septic patients by Groeneveld and colleagues, showed that when CI decreases in septic shock, patients with a fatal outcome have less capability to augment vascular resistance than survivors. [390] Hence, they concluded that peripheral vascular failure, even if complicated by inability to maintain an elevated CI, may be a major haemodynamic determinant of mortality in septic shock. [390] SVR can be used as a haemodynamic value, which guides choice of inotropic agent in treatment of shock. [391] In septic and anaphylactic shock, where inappropriate vasodilatation and low systemic vascular resistance are prominent feature, Adrenaline is the drug of choice for patients with anaphylactic shock and various vasopressor agents are preferred in the treatment of septic shock, including dopamine, adrenaline, noradrenaline, and vasopressin. There is increasing evidence that noradrenaline may be the agent of choice for patients with severe septic shock. [392] Oppositely, high afterload caused by elevated SVR is associated with the development of a range of pathologies such as pulmonary hypertension, LV distention, stagnation and pulmonary congestion. Increased cardiac afterload drives pathologic remodeling and predisposes to heart failure. [393]. In cardiogenic shock, where compensatory mechanisms are usually fully activated, systemic vascular resistance is usually high. [394] Cotter et al, previously demonstrated that in patients with exacerbated systolic congestive heart failure, baseline cardiac power index at admission is the strongest predictor of short- and long-term outcome. [395] On the other hand, the main event preceding recurrent worsening heart failure was a steep increase in SVRI. They measured the relationship between changes in CPI and SVRI and showed that SVRI is to be instrumental in the diagnosis of pulmonary oedema. [398]

Parmaters related to inotropy

Potential energy is marker of blood pressure, where kinetic is marker of blood flow. The ratio is very important in balancing haemodynamics with normal ratio being around 30:1. [396] In contrast to SVR, which is a static measure and uses overall cardiac output per minute as if flow is constant, and the average value of MAP as if the arterial tree is passive, potential kinetic ratio (PKR) represents the dynamic relationship between the integrated values for PE and KE during the short period of systolic ejection. [397] Hence, PKR is reliant on factors such as inertance, capacitance and reactance, as well as resistive elements. [396] PKR is an indicative of dynamic

impedance rather than simply passive resistance of the arterial tree. [396] Use of PKR ratio is rarely studied in optimization of haemodynamics and diagnosis or treatment of conditions such as shock and heart failure. Smith and colleagues, [397] developed a formula**, based on haemodynamic theory, to calculate the potential and kinetic energy developed by the ventricle, which results from ventricular inotropy. They then tested the formula, which calculates the effective inotropy Smith-Madigan inotropy index (SMII) against historic haemodynamic data, using a bespoke computer program against stored data for 250 healthy subjects; the control group, and 83 patients known to have acute left ventricular failure (LVF), the LVF group. They compared haemodynamic parameters such as SVR, SV and CI between the two groups. In this study PKR; as measure of arterial impedance, showed a highly significant difference between the groups (*P* value: 0.001), with no patient in the LVF group showing a PKR that approached the highest figure seen in the control group at 86:1 vs 36:1, (*P* value: 0.001). Overall, the LVF group showed a significantly lower SVI, and CI, and significantly higher vascular resistance, and vascular impedance as shown by PKR. The control group showed PKR values 30:1, a much greater proportion of energy going towards arterial pressure than flow, with 96.8% of total energy appearing as pressure against 3.2% for flow. In the LVF group, the CI was significantly lower and the SVR considerably higher than the normal group. Vascular tone is actively increased to maintain MAP in this situation, but this can lead to a vicious circle of declining SV and cardiac output. PKR at 124:1 shows how profoundly the system changes, with 99.2% of the output energy going towards maintaining arterial pressure and only 0.8% towards blood flow. As LVF improves, so PKR trends back towards normal. A very similar situation can occur in patients under anaesthesia with haemorrhage leading to hypotension. This is in contrast with septic shock, where high CO and low SVR are observed, and PKR values are as low as 3:1. The arterial impedance in these situations is too low to allow the CO to generate adequate arterial pressure.

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**SMI = SMI = BP mean x SVol x 10–3 SVol x 10–6 x r x Vmean2 + 7.5 x FT 2 x FT, SMII: SMI / BSA. Where BP mean = (mean arterial pressure–central venous pressure) in mm Hg, SVol=stroke volume in ml, r=density in kg m–3, V mean=mean velocity in m s–1, FT=systolic flow time in ms. The factors 7.5, 10–3 and 10–6 is required to convert milliseconds to seconds, millilitres to cubic metres, and millimetres of mercury to kilopascals (kPa) (1 kPa=7.5 mm Hg), to conform to SI values; see text for explanations. BSA: Body surface area

Parmaters related to preload

Stroke volume variability is the change in the amount of blood ejected from the left ventricle into the aorta with each heartbeat and is reflected by arterial blood pressure changes in relation to the pattern of respiration. [317] Currently, in clinical settings SVV is measured by various techniques including Doppler methods such as USCOM, pulse contour analysis, calibrated and non-calibrated pulse power analysis, and bioreactance. In hypovolemic subjects, a more variable pattern of SVV is observed and conversely, during a state of normovolemia a more stable pattern of arterial changes in response to positive pressure ventilation may be expected to emerge. [398] Berkenstadt *et al,* reported that SVV can be used as a continuous preload variable allowing optimal fluid management. [331] Accuracy of SVV is limited by significant heart or lung disease; particularly arrhythmia, vasodilator therapy and mechanical ventilation using PEEP (Positive End Expiratory Pressure). [399] Cheng *et al*, compared the ability of SVV, flow time corrected (FTc) and central venous pressure (CVP); all as haemodynamic indicators of fluid status, in children post cardiac surgery. [400] They showed that SVV is more reliable method in predicting fluid responsiveness than others (AUC: 0.776) and concluded that CVP and FTc are not as reliable measurements. [400] CVP is currently the most common clinical preload monitoring indicator. In Cheng's study CVP could not predict fluid responsiveness accurately, which is consistent with the finding of Renner *et al,* in a study of infants and neonates undergoing congenital heart surgery. [401] FTc might be useful for predicting fluid responsiveness in children. There are other studies showing that FTc might be a better pre-load parameter than CVP for predicting fluid responsiveness in an accurate manor. [402] The main limitation of CVP is that it is a static measurement and offer minimal information. Instead, SVV is a dynamic indicator for the cardiopulmonary interaction, which can safely be used as a predictor of fluid responsiveness. It has been shown that the incidence of complications, such as pulmonary oedema, would reduce if the goal of fluid therapy is set at an SVV of <10%. [403] Monnet *et al*, showed that in fluid therapy for patients grouped according to cardiac ejection fraction (EF) measured with echocardiography, the AUC of SVV was significantly higher in patients with a high EF than in those with a low EF. [333] Hence, SVV might show better accuracy in patients with good cardiac function than in patients with poor cardiac function. SVV values can be affected by factors such as breathing patterns, tidal volume (Ti), respiratory rate, spontaneous breathing, cardiac arrhythmia, vascular compliance, and abdominal pressure. [404], [405], [406] Normal SVV values are less than 10-15% on controlled mechanical ventilation. [407] Cheng study reported cut off of 17.04%, with a sensitivity and specificity of 84.4% and 60.7% in predicting fluid responsiveness in children [400] Not all current literature supports the use of SVV in patients, who are spontaneously breathing, and the argument is due to the irregular nature of rate and tidal volumes of spontaneous breathing. [408] The haemodynamic effect of spontaneous breathing seems to be diametrically opposed to those that occur during mechanical ventilation. During normal inspiration, the negative intrathoracic pressure increases venous return and right ventricular filling, while reduces left atrial pressure. The effect of spontaneous breathing is more pronounced on venous system

than the arterial one. [408] Hence, venous system as a low-pressure system is more sensitive to small pressure variations. However, excessive respiratory efforts may cause the great veins to collapse, resulting in a reduction in venous return and an increase in the peripheral venous pressure and these effects are similar to those of controlled mechanical ventilation. [408] Importantly, the hemodynamic effects of spontaneous breathing may be variable from one breath to another, as they depend on the respiratory effort, tidal volume, respiratory rate (RR), possible expiratory squeeze that increases intraabdominal pressure. [408] Therefore, not only use of SVV but also use of other dynamic parameters such as systolic pressure variation (SPV), the pulse pressure variation (PPV), and the plethysmographic variability index (PVI) as predictors of fluid responsiveness is limited in spontaneous breathing subjects. Studies are done in spite of the recognized variability of spontaneous breathing and its opposite cardiovascular effects. Most of these studies included a very small number of patients and their results are difficult to interpret. In addition, the spontaneous breathing during these studies was often standardized by instructing the patients to breathe regularly and slowly, [409] or its effects augmented by asking the patients to take a forced inspiration, [410] perform a Valsalva manoeuvre, [411] or by introducing an expiratory resistor. For example, in one study on patients with septic shock the SVV predicted haemodynamic response to fluid challenge, optimal thresholds (>17% or greater) was achieved in spontaneously breathing shocked subjects. [412] This threshold is different from what is found for mechanically ventilated patients. Similar to SVV, a breathing frequency of 6 per min and the addition of an external respiratory resistance were needed to increase the accuracy of SPV and PPV under conditions of progressive central hypovolemia [408]. The PVI was shown to predict hypotension after induction of anaesthesia [413] and after Dexmedetomidine administration [414] in patients with spontaneous breathing. In another study, a threshold PVI value of greater than 19% was a weak predictor of response to PLR in spontaneous breathing volunteers [415]. Perel *et al,* reviewed the physiological basis of dynamic parameters in patients with spontaneous breathing and described their potential clinical utility. [408] They described that the haemodynamic consequences of the spontaneous breathing are greatly dependent on the magnitude of the inspiratory decrease in pleural pressure. These variations may be further exaggerated by the transmission of the negative airway pressure to the aorta and by its effects on the blood volume within the tissue bed of the finger, which may be largely responsible for the fluctuations in the venous trace. [416] Any increase in respiratory resistance or in lung compliance may therefore accentuate the respiratory variations in the SV, can produce higher values of dynamic parameters. High values of dynamic parameters in spontaneously breathing patients should therefore first alert the clinician to the possible presence of a primary respiratory abnormality, and not a hemodynamic one. For instance, increased pressure in venous and arterial wave forms can be a prominent feature of upper airway obstruction. In Perel's study it was noted that increased values of dynamic parameters may also facilitate the detection of breathlessness, which is a common stressful symptom in critically ill patients [408]. It is important to note that an increase in the values of dynamic parameters such as SVV may be an early sign of a decrease in lung compliance because of fluid overload and/or worsening of congestive heart failure. [408] The potential clinical utility of dynamic parameters during

spontaneous breathing that were so far described, are based on sound physiology and a lifetime of clinical observations. Important recommendation by Perel et al, was that clinicians that observe the Pleth dynamic waveform should be vigilant, when using commercially available clinical monitors in ways not envisioned by their manufacturers. Extracting the richness of information contained in the Pleth signal will require sophisticated signal processing skills, combined with innovative physiologic approaches [408].

In summary, one could conclude that continuous dynamic parameters that result from heart–lung interaction are well recognized as predictors of fluid responsiveness only during controlled mechanical ventilation. However, spontaneous breathing may also induce significant haemodynamic changes due to the decrease in the pleural pressure. The dynamic parameters that appear during spontaneous breathing may be used to monitor respiratory rate, and identify PEP, increased respiratory effort, upper airway obstruction, and, to a lesser degree, fluid responsiveness. Dynamic parameters, and especially those that are derived from the widely available plethysmographic waveform, may offer valuable clinical information in spontaneously breathing patients and should not be regarded as artefactual or meaningless. A better understanding of their physiological meaning, combined with future advances in sophisticated signal processing, will increase the clinical utility of these parameters. Thiel *et al*, [417] showed that USCOM-measured SV changes with autologous physiologic challenges have been shown to detect fluid responsiveness with a positive predictive value of 91% in a patient group that included subjects in atrial fibrillation, on and off mechanical ventilation, and on vasopressors.

4.1.7 Classification of shock, using USCOM-derived haemodynamics

Optimization of stroke volume is pivotal in treatment of shock and resuscitation. SV is dependent on preload, afterload and inotropy. Ideally, clinicians should be able to locate their patients on the Starling curve and need be able to know which curve they belong to. If the curve is flat and inotropy is low, SV can be increased significantly in response to fluid challenge. Similarly, a patient with a high inotropy index on a normal curve would increase SV in response to fluids. In conditions such as septic shock, where systemic vascular resistance and afterload are low due to vasodilation, SV and EF can be very high despite low inotropy index. Failure to appreciate this can lead to inappropriate treatments such as inappropriate use of vasoconstrictors to raise afterload with subsequent ventricular failure to handle the increased afterload.

Flow time corrected (FTc) as a proxy for left ventricular ejection time, is studied in several studies looking at the change of FTc (∆FTc) as a potential tool in evaluation of fluid responsiveness. [418] They found that changes in duration of FTc in dehydrated patients, receiving intravenous fluid resuscitation may be helpful in fluid management of hypotensive patients. [419] The benefit of using FTc is that unlike blood pressure or heart rate, it is only affected by very small changes of preload. Not only in volume increase but also in preload reduction, FTc is shown to be able to detect a significant difference in preload reduction with infusion of 0.3 mg of Nitroglycerin (NTG) as a vasodilator in study of Pare and colleagues. [420] As mentioned before, it is proven that FTc functions better than some other measures of fluid responsiveness such as central venous pressure (CVP). [402] This technique has now been validated extensively compared with pulmonary artery catheters and is now widely used in adult anesthesia and intensive care units' practice. The normal FTc is never below 330 ms, as typical flow time is one third of cardiac cycle and when standardized to 60 beats / min, the normal values sit between 330 - 360 ms. [317] The upper limit is mainly depending on clinical scenario. Same principle applies to SVV, as a marker of fluid responsiveness and preload. A cut off point of above 10% was considered to predict fluid responsiveness in mechanically ventilated subjects. [421], [422] Either SVV or FTc being used as preload related haemodynamic variables, it should be in conjunction with systemic vascular resistance (SVR) to accurately anticipate hypovolemic shock and differentiate it from other types of shock. Increase in SVR index (SVRI) beyond upper normal limits (for adults > 2200 dynes/seconds/$cm^{-5/}$ m^2), as a result of direct sympathetic neurohormonal stimulation is commonly seen in hypovolemic shock. [423] SVV or FTC has never been directly correlated to outcome of shock but proven to be valid predictors of fluid responsiveness, which one can argue indirectly correlates to outcome of shock. SVR and its correlation to outcome of shock is more explored in context of septic shock, where due to extensive vasodilatation, it drops below the lower limits of normal. As explained above SVRI values are highly contributing to distributive shock and its outcome. [424]

Inotropy as a measure of myocardial contractibility is rarely used by clinicians as a measurable value. [397] However, the discriminant power of Smith- Medigan Inotropy Index (SMII) can offer valuable diagnostic methods and monitoring tools in anesthesia and critical care medicine as was shown in their study, where significant difference was shown between the values of inotropy index in LVF and the control group. [397] Many methods suggested for an accurate measurement of inotropy. These methods include maximum rate of change of ventricular pressure; dP/dtmax, [425], maximum rate of change of ejection velocity; dV/dtmax, [426], maximum rate of change of flow; dQ/ dtmax, [427] maximum flow acceleration; dV/dt 2 max, [427] end systolic ventricular elastance, [428] the myocardial performance index; MPI (or 'Tei index'), [429] ventricular wall stress and stress rate, [430] fractional shortening of cardiac myofibres, [430] and others. None of these methods achieved clinical adaptation due to sensitivity to changes in preload and afterload. Historically, ejection fraction (EF), calculated by SV divided by left ventricular end diastolic volume (SV/LVEDV), has become a marker of ventricular function. The concept is simple but unfortunately EF is a very poor indicator of inotropy, which is highly sensitive to changes in preload,

afterload, and even heart rate. [397] EF can be severely misleading in low preload conditions such as septic shock, where high levels can be interpreted as high inotropy. Smith-Madigan formula calculates inotropy, taking into consideration the effect of both preload and afterload. [397] Smith's study was the only study, which so far has defined ranges for SMII; for healthy population for all age, mean SMII was 1.78 W/m-2, range 1.35 – 2.24 and for the LVF group, the mean SMII was 0.73 W/m2, range 0.43 – 0.97 W/m2, with significant differences between the two groups (*P* value < 0.001). [397] They established that for a typical normal adult, the value of SMI is around 3 to 5 W, and for SMII around 1.6 to 2.2 W/m2.

4.1.8 Validation and refinement of a previously diagnostic tool; Li's *a priori* Pragmatic Shock (LiPS)

Li Piori definition of shock (LiPS) is a pragmatic, quantitative, priori definition of shock proposed by Li and co-workers; [196] an experienced group of intensivists and emergency medicine doctors in Princess of Wales, Hong Kong, China in 2014. The criteria is based on previously published work and expert opinion. The aim was to define a quick, practical, and easy to use criteria, which uses variables, easily available at point of care, to diagnose shock. Investigators aimed to validate the criteria against 28-days mortality. Task force consensus categorised patients into three distinct categories of Shock, Possible shock, and No shock, where the main components of classification were tissue perfusion, blood pressure, acid base and skin temperature. Furthermore, when shock is present, it could be further sub-classified according to peripheral skin temperature, to cold or warm shock. (Appendix 2) In This study, a total of 111 heterogeneous group (mean age, 67.2 ± 17.1 years; 62% male) of urgent and critical patients, admitted to the resuscitation room or high dependency unit of ED, were recruited. Of all patients, 22 were classified as No shock, 54 as Possible shock, and 35 as Shock. They showed that systolic blood pressure, mean arterial pressure, lactate, and base deficit correlate well with shock classifications (P value < 0.05). Patients who had 3 or more positively defined shock variables had a 100% poor composite outcome; admission to ICU and mortality rate (5 of 5). [196] Patients with 2 shock variables had a 66.7% (4 of 6) poor composite outcome rate. The criteria was validated by the greater percentage of cases with poor composite outcome across the shock classification groups, and also by the greater percentage of cases with poor prognosis for ICU admission alone, CCU admission alone, and mortality alone. Validation was sought firstly by demonstrating a significant relationship between classification groups and individual variables, and secondly, by demonstrating a "dose-response" relationship between the severity of shock according to the classification and the final outcomes, which provides face validity to the proposed a priori definition. [196]

4.1.9 Haemodynamic paramters used by LiPs criteria and prediction of shock outcome

In LiPs study, the authors failed to show significant associations between skin mottling or pH and composite outcome. This might be due to that both mottled skin and low pH are late signs of severe shock, which may have been under-sampled in the original study. Additionally, those patients, who are most severely ill may be unable to provide respiratory compensation in response to metabolic acidosis, whereas patients, who are not so ill may be able to increase their minute ventilation, reduce their arterial carbon dioxide tension, and thereby correct their pH. [431] Studies suggest that pH levels are significantly associated with poor outcome. This is supported by findings of Porter's study, where low pH within the first 24 hours was shown to be one of the most important predictors of mortality in shocked patients. [432] Low pH is an indicator of tissue hypoperfusion and is often observed in multiple organ dysfunction [433] Ross *et al,* showed that a pH of less than 7.1 causes severe impairment of coagulation cascade due to enzyme and protein dysfunction [434]. The common recommendation is to buffer back to a pH above 7.3 so that the coagulation cascade and other physiologic processes can resume function. LiPs study supports the association between Lactate and base excess and poor outcomes. Base excess and Lactate, in contrast to pH, are more rigorously studied in the shock literature. Both tests are easily available during resuscitation of shocked patients. A significant base deficit has shown to be a marker of mortality in many studies [435], [436], [437]. In a study of trauma patients without head injury, a base deficit of 8 mmol/L predicted a 25% mortality rate in patients younger than 55 years old [438]. Furthermore, changes in the base deficit will often precede changes in other hemodynamic parameters in haemorrhagic shock such as pH, urine output and blood pressure. Base excess can be elevated in other conditions, for instance in diabetic ketoacidosis, salicylate overdose, and renal dysfunction and its evaluation can be helpful in establishing disease severity [439]. Lactate is a measure of tissue hypoxia and product of anaerobic metabolism after glycolysis. [440] A recent multi-center study showed that resuscitation based on lactate level changes, improved outcome [441]. Elevated Lactate are predictive of mortality and the time to clear or normalise has been subject of interest in many studies and shown to be predictive of mortality and morbidity [442], [443] A study reported that mortality directly correlates with the time to normalization (or failure to normalize) of lactate levels, with 100% mortality in patients, who failed to achieve normal lactate levels. [438]

LiPS showed that there was not a significant association between skin mottling and poor outcome. Skin mottling is an easily observable way to assess microcirculation and is a classic sign of circulatory shock. It is defined as patchy skin discoloration that usually starts around the knees. It is due to heterogenic small vessel vasoconstriction and is thought to reflect abnormal skin micro-perfusion. More than 40 years ago, Vic-Dupont et al. [444] described clinical patterns of patients with septic shock and noted frequent mottling on the knees (65%). However, it is subject to observer bias and

cannot be used in black patients. [444] It could also be difficult for less experienced doctors to be able to correctly identify skin mottling. In an observational study by Ait-Oufella et al, [445] microcirculation in patients with septic shock admitted to ICU was assessed via blood Lactate, urinary output, and skin mottling. They quantified the extent of mottling on the legs on a 6-degree scale (H6), ranging from 0 to 5; score 0, indicates no mottling and increasing score indicates more vast areas of skin; based on the extension of these purple patches from the patella toward the periphery. Amongst the measured parameters, skin mottling was the strongest predictor of mortality. [445] Fourteen-day mortality according to the H6 mottling score increased from 13% for a score of 0–1 to 70% for a score of 2–3 and 92% for a score of 4–5 (*P* value < 0.001). They also found that death occurred earlier in patients with a higher score (*P* value < 0.0001). This study revealed significant relationship between mottling score and SOFA score; higher the mottling score was, the higher the SOFA score. [445] Also in study of Hariri and co-workers, it was shown that the skin mottling is a good predictive value of the mottling score for mortality at day 28 in patients with sepsis not receiving vasopressors. [446]

The original LiPs study [196] noted a greater degree of anaemia in patients with shock. This is significant as haemoglobin is a crucial factor in tissue oxygen delivery and an essential contributing variable in the DO2 equation, alongside with cardiac output and SpO2 (DO2 = 1.34 × Hb [g/L] × CO [L/min] × Spo2 [%]). In this formula, which measures oxygen delivery to tissues, SO2 is oxygen saturation, CO is cardiac output, Hb is haemoglobin and DO2 is oxygen delivery. In shock, there is an imbalance between DO2 and tissue oxygen consumption (VO2). [447] Conventionally, perfusion status is assessed by whole-body end points such as mental status and standard cardiovascular parameters like heart rate, pulse rate, and systemic blood pressure (SBP). SBP has been the most popular single measure of whole-body perfusion status and been considered in LiPS criteria and correlated to outcome. However, it is difficult to establish agreed values for SBP criterion or cut-off for shock. Furthermore, data from animal models and clinical studies indicate that conventional measures of perfusion status are very poorly correlated with perfusion of specific tissue beds. [448] A systematic evaluation of physical findings in patients with hypovolemia evaluated the diagnostic accuracy for a systolic blood pressure below 95 mmHg in acute blood loss and the effect of model produced a sensitivity of 13% for moderate blood loss and 33% for large blood loss. [403] Hence, a systolic blood pressure below 95 mmHg is not a sensitive measure for ruling out significant blood loss in hypovolemic shock. In septic shock the definition requires the presence of hypotension for the diagnosis of shock. Rivers et al. demonstrated that aggressive and early goal-directed resuscitation can have a significant impact on patient outcomes [137]. This clinical trial evaluated patients with severe sepsis, whose mean systolic blood pressure was above 100 mmHg at baseline, with a blood lactate > 4 mmol/l. Patients in both the control and treatment group had clear evidence of shock as measured by mean saturation of central venous oxygen (ScvO2) of 49% and 48% respectively. [137] The latest definition of shock emerging from this international consensus conference on haemodynamic monitoring and management of shock did not require the presence of

hypotension. [171] Instead, the definition of shock as “failure to deliver and/or utilize adequate amounts of oxygen” is not currently limited to the presence of hypotension. In this manuscript, shock is defined as circulatory and cellular dysfunction, manifested by markers of hypoperfusion such as elevated blood lactate, decreased ScvO2 or SvO2, with or without hypotension. [171]

4.1.10 Haemodynamic parameters led to introduction of DiPs criteria

Serum Albumin is considered as a good prognostic factor in many conditions, mainly in sepsis and septic shock. Viasus and co-workers showed that Albumin value measured at 24 hours after diagnosis of community acquired pneumonia is a predictor of outcome. Decreased albumin levels were also associated with prolonged time to reach clinical stability (*P* value < 0.001), prolonged hospital stay, ICU admission, the need for mechanical ventilation, and 30-day mortality. [449] Hypoalbuminemia is associated with adverse events, such as acute heart failure and cardiogenic shock in acute coronary syndrome. [450] In adult trauma patients, serum Albumin lower than 2.6 g/dL is a significant predictor of mortality and morbidity, advising on consideration of early nutritional support. [451] Holder et al. [452] in a retrospective analysis of septic patients at emergency department showed that the serum albumin <3.5 g/dL and diastolic blood pressure < 52 mmHg independently predicts early progression to severe sepsis or shock. A prospective analysis of 116 mixed surgical and medical ICU patients showed that serum albumin level is a strong predictor of 28-day mortality, and the optimal cut off value maximizing sensitivity and specificity is 29.2 g/L. [453] Patients with lower serum albumin levels more often had abdominal/pelvic sources of infection, acute kidney or liver injury, septic shock, and higher APACHE II and SOFA scores. [453]

Likewise, Albumin, Bilirubin as a marker of liver dysfunction and has shown to act as a good predictor of outcome in septic shock. Bilirubin is the end-product of haem catabolism and is generally considered a lipid-soluble waste product that needs to be excreted. However, growing evidence has suggested that bilirubin at high concentrations can induce inflammation, apoptosis and oxidative stress and can stimulate oxidative stress and decrease cell survival. [454] Hyperbilirubinemia has been associated with overall poor outcomes in critical illness, [455], [456]. Sepsis and bacterial infection account for 20% of jaundice cases in patients of all ages in community hospital settings. [457] With exclusion of primary liver disease, Patel et al. in a study of 251 patients with sepsis, showed that mortality of septic shock increases from 12 to 42% with increasing Bilirubin levels from < 1 to more than 2 mg/dL in seventy-two hours of admission. [458] High serum Bilirubin is associated with development of acute respiratory distress syndrome (ARDS) and mortality in ICU patients. [459]

Skin characteristics, allow clinicians to quickly evaluate the peripheral tissue perfusion with non-invasive bedside parameters such as the skin temperatures and capillary refill time (CRT). Skin temperature is a manifest of microcirculatory perfusion. [460] Backer et al. [461] showed that microcirculatory perfusion alterations predict mortality during serious infections, whereas mean arterial pressure or cardiac output did not. The main pathophysiologic mechanism behind reduced blood flow and low skin temperature is local vasoconstriction mediated by sympathetic neuro-activation. Additional mechanisms could participate to impaired microvascular blood flow are such as local endothelial dysfunction [462], leukocyte adhesion, platelet activation and fibrin deposition [462], which are common is sepsis and septic shock. A moist and cold skin was a factor of worse prognosis in patients with septic shock. [446] Cold hands and feet, and abnormal skin colour are the first clinical signs that developed in meningococcal disease in children [463]. Lima and co-workers proved that in patients with circulatory shock, those who have cold skin had higher incidence of organ failure at 48 hours post resuscitation compared to subjects with normal colour skin. [464] Other scientists showed that temperature gradients between different body parts can be measured and correlate with organ failure and worse outcome. [465]

Capillary refill time (CRT), which is the time required to re-colour the tip of a finger is shown to be a predictor of mortality in septic shock. [169] In unselected paediatric and adult intensive care patients, CRT was related to tissue perfusion and organ dysfunction evaluated by the plasma lactate level and the SOFA score. In paediatric units, index CRT helps to identify the most severely ill children suffering from infectious diseases such as pneumonia, gastroenteritis, and malaria [169] Ait-Oufella et al, [169] in an observational study of ICU patients admitted with septic shock showed that CRT measured at six hours was strongly predictive of 14-day mortality with area under the receiver curve of 84 % (75–94) for the index finger measurement, the AUC of 90 % (83–98) for the knee area. They also showed that CRT correlates well with factors of organ perfusion including arteria lactate. Lara et el. showed that in septic patients admitted to ED, patients with normal CRT required less frequently mechanical ventilation, renal replacement therapy, and ICU admission, and exhibited a lower hospital mortality. [466] Similar to skin mottling where, CRT could not be measured; other clinical signs of peripheral hypoperfusion could be used such as central-to-toe temperature difference. One study showed weak inter-rater variability of CRT in non-trained physicians, [446] however study of Ait- Oufella and colleagues showed good inter-rater concordance by applying a firm pressure lasting 15 sec, enough to remove the blood at the fingertip of patients nail by appearance of a thin white distal crescent (blanching) under the nail. [169] Overall studies show that markers of hypo-perfusion including CRT, skin mottling and temperature can be used as triage tool at the early steps of sepsis management and at admission and after fluid infusion. Recently, a task force of six international experts with extensive bedside experience in treating shock has proposed to integrate peripheral tissue perfusion tools, namely CRT, mottling score and temperature gradients in risk stratification and management of septic patients in resource-limited intensive care units. [467]

Encephalopathy is an early sign of shock. [23] Its usefulness is mainly investigated in context of traumatic brain injury (TBI) and to a lesser extent in sepsis and septic shock. Glasgow Coma Scale Score (GCS) is the most commonly utilized universal tool to assess neurological dysfunction. [468] Data from 35,732 trauma Japanese patients admitted with trauma to ED, showed that a GAP score involving GCS score, patient age and SBP predict mortality better than other scores. [469] In trauma patients with highly likelihood of haemorrhagic or hypovolemic shock, the combination of SBP and GCS is a reliable and equally effective method of assessing physiologic injury severity and trauma outcome. [470] Sepsis often presents early by encephalopathy and/or disturbed consciousness. Altered mental state results from neurological dysfunction secondary to dysregulated host response to infection. [28] The third international consensus definition of sepsis, added the level of consciousness, measured by Glasgow Coma Scale, as an important predictor indicating the development of sepsis in both SOFA and qSOFA. [167] An online review of PubMed and Cochrane Library for studies and review articles assessing the significance of assessment of Glasgow Coma Scale (GCS) for anticipating sepsis or septic shock, by Alalawi and colleagues concluded that lower GCS in patients with sepsis was significantly associated with high mortality rates. [470] Differences in GCS had been associated with different mortality rates; it seemed very low GCS had mortality rates of more than two-thirds of the affected patients. [470]

4.1.11 Clinical gestalt in diagnosing shock

There is increased interest in evaluating the role of clinician experience, otherwise known as gestalt, in assessment of disease or prediction of treatment failure. Some studies concluded that emergency physician gestalt is not sufficiently accurate [471] Thus, there is a need to investigate emergency physician gestalt for diagnosing shock in the ED phase of care. At bedside, doctors usually use information available to them, including history, physical examination, and investigations results such as urine analysis and Lactate to identify and classify shock. Clinical impression is rather holistic but subject to interference. Li and colleagues in an observational study following development of LiPS tool, compared the accuracy of emergency physicians' gestalt with LiPS for diagnosing probably shock, whilst using 30-day mortality as an objective proxy reference. [471] Applying 30-day mortality as a reference standard, emergency physicians identified that 50% of patients (14/30) have probable shock and they were more accurate at identifying patients without shock (147/190), with a specificity which was slightly higher sensitivity than clinical gestalt; (AUROC: 0.722; sensitivity: 0.733, specificity: 0.711, *P* value: 0.0001) was greater than emergency physician gestalt (AUROC: 0.620, sensitivity: 0.467, specificity: 0.774, *P* value: 0.0137) for diagnosing shock [471]. Up to this date this is the only study comparing the diagnostic ability of LiPS tool with clinical impression of shock.

Other studies highlighted that clinical gestalt might not be as accurate as it is thought to be. A study of 458 patients admitted to ED with cardiac sounding chest pain showed that clinical gestalt for diagnosis of acute myocardial infarction (AMI) alone had an area under the receiver operating characteristic curve of 0.76 (95% CI: 0.70 to 0.82). [472] Previous research has shown that general practitioners have only moderate diagnostic accuracy when estimating the likelihood of coronary artery disease. [473] However, this might be reliant on the type of clinical condition as the judgement of the treating physician has been shown to have independent diagnostic value in patients with suspected deep vein thrombosis and pulmonary embolism and is an important component of widely used clinical decision rules for those diagnoses. [474] Balamuth et al. showed that applying an electronic algorithmic approach for identifying pediatric patients with potential sepsis based on abnormal age-based vital signs and at least one high-risk condition, abnormal perfusion, or abnormal mental status has higher sensitivity but lower specificity than sole physician judgment in a cohort of pediatric ED patients with fever or hypothermia. [475] They showed highest observed sensitivity by the combination method. [475] Overall it is assumed that clinician impression brings specificity and reduces unnecessary treatment, including antibiotic overuse, resource utilization, and trauma to patients experiencing unnecessary intensive interventions.

4.2 What we found - Key findings of this study

In current study, I used USCOM as a feasible, continuous-wave Doppler-based method which provides rapid measurements of over twenty haemodynamic parameters. USCOM is repeatedly compared to invasive and non-invasive techniques measuring haemodynamics in various subjects and has been validated in different settings as outlined before. As an accurate, rapid, and reproducible technique, USCOM can be used as a non-invasive alternative to pulmonary artery catheter placement with consequent reduction in patient's risk and morbidity associated with arterial catheterization. Our measurements were made by two study doctors, who received standardised training on how to measure haemodyanmic parameters, using USCOM. The training was provided by an experienced company instructor, who organized multiple hands-on training sessions, after which each operator performed at least 50 sets of measurements. Subsequently, the measured values were comparable with the values measured by the instructor. This process lasted several days until measurements of haemodynamic values were satisfactory and data was reproducible.

Using USCOM derived haemodyanmic paramters, the current study did not show a significant correlation between cardiac output (CO) or cardiac index (CI) and primary outcome of 28-days ICU admission or mortality. However, it showed that other haemodynamic parameters, such as Potential-kinetic ratio (PKR) or systemic vascular resistance (SVR) are significantly associated with risk of ICU admission, whilst Stroke Volume Variability (SVV) was found to be an independent predictor of mortality. We know from previous work that cardiac output and cardiac power corelate well with outcome of shock mainly cardiogenic. The lack of association between cardiac output and outcome of shock in current study could be partly explained by method of use, random and systemic errors likely related to USCOM measurement or can represent a systematic tendency for the technique to underestimate cardiac output as previously been explained. To minimize source of error for example in patients with irregular heart rate (11.9% patients in current study had atrial fibrillation) frequent measurements, over multiple cardiac cycles and averaged data was utilized. To avoid operator related source of error, study was conducted once investigators proficiency was confirmed by professional instructor. The obtained traces were subsequently reviewed, and acceptability was confirmed by Prof T. Rainer, who has over twenty years of experience in field of shock and using USCOM in measuring haemodynamics. Overall, I believe that the allowance of method failure or unsatisfactory traces should be considered, when assessing USCOM reliability and percentage of error. Interpretation of measured CO should be performed alongside all aspects of careful clinical assessment and should be individualised and interpreted in context.

On the other hand, my results show significant association between other haemodynamic parameters such as oxygen saturation, potential/kinetic (PKR) systemic vascular resistance and primary outcome of ICU/CCU admission. Some of which are preload, and some are afterload related haemodynamic variables. I showed that oxygen saturation is a predictor of ICU admission. In current study, PKR values (mean values of 40, IQR: 23-48, *P* value: 0.043), was associated with primary outcome of ICU admissions. We recommend that PKR could, represent a treatment goal in optimisation of haemodynamics along with CO, SV, SMII, and SVR.

When it comes to mortality outcome, stroke volume variability stood out as a strong and independent predictor of death. As mentioned in review of previous literature, stroke volume variability has a well proven place in predication of outcome in mechanically ventilated and little studies up to this date have looked at its potential values in spontaneous breathers. We used SVV in an emergency department setting, where not all patients were ventilated but some of them were receiving biphasic non-invasive ventilation, and a few had intra-tracheal tubes and receiving mechanical ventilation. After performing a sensitivity analysis to obtain an optimal threshold a cut of 50 ml, equivalent to 25% was achieved to be considered as most specific and sensitive value for predicting mortality. (*P* value: 0.021, AUC was 0.62 and sensitivity and specificity of 60% and 56% respectively). As subjects were mainly spontaneous breathers the values should be interpreted in context and higher variation is partly explained by presence of coexisting respiratory disease, increased respiratory effort and presence of arrhythmias.

Other objective of current study was to use USCOM-driven haemodynamic variables in classification of shock into hypovolemic, cardiogenic, and distributive. I recognised that at times some patients had two types of shock in combination, for instance, a mixture of hypovolemic and cardiogenic or distributive and cardiogenic. In proposed classifications, I hypothesised that hypovolemic shock is present if either FTc higher than normal range (321 – 415) i.e., > 415 or SVV is higher than the normal range (>30%) and systemic vascular resistance index is above the mean for normal range i.e., >2200. I have chosen values of 415 as FTc increases beyond upper limits of normal in hypovolemia. I have chosen a cut off 30% in preliminary hypothesis to define hypovolemic shock as my study looks at both mechanically ventilated and spontaneous breathers and higher thresholds are achieved in SVV values as marker of fluid responsiveness in spontaneous breathers. Either SVV or FTc being used as preload related haemodynamic variables, it should be in conjunction with systemic vascular resistance (SVR) to accurately anticipate hypovolemic shock and differentiate it from other types of shock. Increase in SVR index (SVRI) beyond upper normal limits (for adults > 2200 dynes/seconds/$cm^{-5/}$ m^2), is commonly seen in hypovolemic shock. SVV or FTC has never been directly correlated to outcome of shock but proven to be valid predictors of fluid responsiveness, which one can argue indirectly correlates to outcome of shock. SVR and its correlation to outcome of shock is more explored in context of septic shock, where due to extensive vasodilatation, it

drops below the lower limits of normal. For definition of distributive shock, I used values of less than 1800, when normal range is 1800 – 2400 dynes/seconds/$cm^{-5/}$ m^2. To define cardiogenic shock, I used inotropy index, below the normal range i.e., <1. USCOM calculates SMII, using a purpose-written computer program based on the formula given above. We hypothesized that SMII values below 1 W/M2 can be used to classify cardiogenic shock. Nevertheless, I was unable to prove statistically significant association between these classifications and mortality outcome. This could be partly explained by factors related to population characteristics and heterogeneity of data or failure to include very critically ill patients in later or end stages of shock, who are more likely to fulfill the proposed criteria. Up to this date there is no study, which used hypothetic haemodynamic values to categorize shock into different types.

I aimed to reassess LiPS definition of shock in its own as well as in an external setting. I had permission from LiPS study authors and had access to LiPS data sets. In order to perform accurate validation, I matched my study inclusion criteria with original LiPS data as previously been explained in results chapter. Likewise, original study, the greater percentage of cases with poor composite outcome across the shock classification, LiPS definition of shock had highly significant association with outcome across various cohorts. To simplify the criteria, I created the LiPS additive score, by adding up haemodynamic variables used in LiPS original criteria. I showed that higher scores are highly associated with possibility and severity of shock. It was shown that the higher the number of positive shock criteria, the greater the probability of a poor outcome. After running in depth validation analysis, I showed that LiPS additive score correlates very well with mortality outcome and has high diagnostic ability across the different cohorts with different demographics and in both internal and external settings. In summary, my study proved that the LiPS additive tool was able to identify patients at higher risk of poorer outcome with similar, albeit with a slightly lower specificity and specificity, than in the original study.

I noted that there are few discrepancies between results of my study and the original LiPS study with regards to significance of haemodynamic values. In the original study, the authors failed to show significant associations between skin mottling or pH and composite outcome. This as mentioned before is likely due to undersampling or failure to provide respiratory compensation in response to metabolic acidosis in very ill patinets. Despite, in current study, I showed that pH levels are significantly associated with poor outcome, as showin in previous research when PH levels corelated to organ dysfunction and poor outcomes. [433] Both studies supported the association between Lactate and base excess and poor outcomes. In my study, oxygen saturation was not significantly associated with mortality outcome of shock. This finding could be partly explained by that we could not include the sickest patients as they might have died before reaching hospital or before study investigators were able to recruit them into the study and they die due to severe illness. Also, it could be explained by the fact that since sick patients on supplementary oxygen achieved satisfactory saturations, best as measured by pulse oximetry, which one can argue is not the best measure of blood

oxygen and markers such as partial pressure of oxygen (Po2) are more accurate and to be considered. It is interesting to note that, in the original LiPS study, single variables like lactate or base deficit performed better than SBP as a predictor of poor outcome and this finding was duplicated in my study, where the SBP being a marginally poorer predictor of outcome, compared to not only Lactate, base excess but also pH.

In current study, I showed that other values such as levels of albumin, bilirubin, GCS, capillary refill time have significant prognostic value in undifferentiated shock. I used these parameters and proposed a model, based on scoring system. The model was named as “Diagnostic Investigation and Prediction of Shock, (DiPS)”. Using regression analysis and receiver operating characteristic curve, the model had an accuracy of 83.3%8 and AUC of 0.813, indicating good diagnostic ability. These measures are associated with end-organ dysfunction.

The last objective of my research was to compare level of agreement between LiPS definition of shock, USCOM derived shock and clinician’s gestalt. I aimed to determine the accuracy of experienced emergency physician gestalt for detecting and predicting likelihood of shock in the ED compared with LiPS, using 28-day mortality as primary outcome. When assessing patients, emergency physicians gave their opinion, based on all available at emergency department, whether they thought that the patient had shock, and if so, what type of shock they think that patient has. The question asked from ED clinicians was: Do you think that this patient is in shock? If yes, what kind of shock do you think that patient has? According to LiPS, patients were firstly classified into one of three groups: No, Possible and Shock. Our analysis did show poor agreement between LiPS and clinical gestalt (46.8%). I used measures of agreement to assess level of agreement between LiPS with clinical gestalt. Earlier, I showed that LiPS tool has acceptable prognostic value and was validated in different settings. The reason for poor agreement with clinical gestalt can be partly explained by the fact that ED doctors are under work and time pressure to make a diagnostic decision and to correctly manage critically ill patients, and this is often based on a limited amount of material and on clinical experience. Doctors may misunderstand the severity of disease, and may take no account of laboratory results, which have been proven to predict adverse outcome. Secondly a vast majority of clinicians diagnose shock, merely based on evidence of low systolic blood pressure. Whereas normotensive patients can be potentially diagnosed as possible shock by LiPS. My study showed only 57.4% agreement between USCOM and clinical impression. This indicates marginal agreement and up to this date there is no published data on comparison of diagnostic ability of these two methods and other studies are required to assess the difference between these methods. Other reasons for inaccuracy of clinical gestalt in certain conditions such as circulatory shock could be due to poor attention to factors related to micro-perfusion such as skin temperature, CRT, and mottling. As mentioned above, clinicians tend to mainly focus on haemodynamic factors related to macro-perfusion such as systolic blood pressure, core body temperature, urine output and Lactate, which can be misleading under certain circumstances and in certain populations. Most research suggests a joint approach, where clinical data is incorporated with algorithmic or investigation derived information. Hence, I conclude that although my work did not show significant agreement between LiPS and clinical

impression of shock, but I do believe that combination of these methods will enhance accuracy and precision and should be considered as each method has important and valuable abilities, which the other may lack.

4.3 Clinical implications

Shock is a heterogeneous syndrome and not a specific disease. [21] Establishing diagnosis of shock and its sub-types is rather challenging. Using haemodyanmic data will improve diagnostic ability of doctors in ED. [273] The results of current study highlights that haemodynamic data alongside using other parameters and scoring systems such as vital signs, NEWS score and Laboratory values could facilitate the process of establishing diagnosis, severity of illness, and therefore aggressiveness of care. This study shows that USCOM as a safe, non-invasive, and Doppler based technique should be utilized by clinicians in emergency department to measure haemodynamic parameters in a fast and easy way at bedside. Learning curve is steep, hence not only clinicians but also allied health care professionals should be encouraged to learn how to use the device and obtain reliable measurements in a timely fashion.

Haemodynamic guided therapy has been repeatedly used in neonatal, obstetrics, pediatric and ICU populations, although less used in emergency department. [291], [292], [295], [298], [301], [303] We showed that using USCOM in emergency department will enable doctors to have easy access to markers related to severity of illness and outcome of shock such as stroke volume variability, cardiac output, cardiac power, systemic vascular resistance and many other haemodyanmic parameters within a few minutes of clinical evaluation. Use of USCOM should be encouraged in various emergency departments across the United Kingdom. This is without imposing harm and avoiding risks of infection, arrhythmias, or bleeding, which associates with use of invasive measures such as pulmonary artery catheter. [278], [279], [280], [373] This study showed that stroke volume variability and other dynamic parameters such as potential kinetic ratio or flow time corrected could represent a treatment goal in optimization of haemodynamics as well as shock outcome. They should be incorporated to clinical impression of shock and shock severity by clinicians. Using USCOM in clinical setting enables access to continuous, real-time display of measurements and hence allows early recognition of haemodynamic instability or deterioration. It also enables doctors to perform early therapeutic interventions and to recognize their hemodynamic effects. Additionally, USCOM can be used by ED clinicians to titrate therapies to appropriate therapeutic goals.

LiPS is a simple, practical definition of undifferentiated shock, which has been proposed previously and validated in current study. [196] As a pragmatic, quantitative, priori definition of shock, which well correlates with outcome, LiPS criteria should be utilized by ED clinicians when assessing patients with suspected shock. LiPS model will enhance diagnostic ability of clinicians in ED and their anticipation of shock outcome. A combination of LiPS criteria alongside haemodyanmic values measured by USCOM, improves accuracy and precision in establishing the diagnosis of circulatory shock and should be used by ED physicians moving forward.

4.4 Research implications

Continuous research is required to prove and validate findings of the current study and to add to its scientific value by bringing new evidence. Results of this study highlights the need for future research in following aspects:

Accuracy of USCOM as a non-invasive technique remains the most important aspect when evaluating the technology in assessment of haemodynamics. Although this has been extensively studied, [290], [300], [370] but still benefits from further evaluation in various settings and in larger and more heterogeneous populations. Factors such as motion artifact, presence of valve pathology, arrhythmia or restrictive factors related to patients' body habitus, which may limit use of USCOM as a non-invasive technology, should be considered when interpreting the results. The extent of inaccuracy and limitations that these factors impose to USCOM measurements should be further assessed and subjected to future studies. It is important to continue and compare USCOM with other invasive or non-invasive modes of haemodynamic assessments such as pulmonary artery catheter or echocardiography.

This study did not reveal significant correlation between markers of cardiac function such as cardiac output and cardiac power to outcome of shock. Further studies are required to assess USCOM reliability in measurement of such parameters. I showed that stroke volume variability strongly correlates with outcome of shock. Dynamic parameters such as stroke volume variability, potential kinetic ratio, inotropy index should be further examined and correlated to outcome of shock. The values of stroke volume variability should be further defined in anticipation of shock outcome in both ventilated patients and spontaneous breathers. Large meta-analysis is required to establish accurate cut offs in more heterogeneous subjects. There might be great advantage of these measures in highly selected individuals.

DiPs as a proposed model of shock encompasses easily available parameters at bedside, including albumin, bilirubin, GCS, capillary refill time and was shown to have significant prognostic value in undifferentiated shock. Future studies are necessary to validate and refine proposed DiPs model of shock. A head-to-head comparison between DiPS criteria and other well-established and validated tools such as NEWS score, qSOFA and SOFA in larger populations is warranted. Clinical gestalt evaluates the role of clinicians' experience in assessment of a disease and predication of treatment response or failure. There is an unmet need to investigate emergency physician's gestalt in diagnosing shock at point of care. Future research is required to compare diagnostic ability of gestalt with proposed criteria such as LiPS and DiPS. Further testing of a combined technique using diagnostic criteria and haemodynamic data is also advised.

4.5 Strengths

Identifying patients at highest risk of deterioration and death from shock, who derive significant benefit from early interventions is of great interest to ED clinicians. This is the first UK based study, which investigated the role of non-invasive measurement of haemodyanmic parameters In Emergency Department, utilizing USCOM as a feasible, continuous-wave Doppler-based technique, which provides beat-to-beat right and left haemodynamics, in a fast and cost-effective way. Incorporating USCOM derived haemodynamics improves identification and classification of shock. We sampled a heterogeneous population with variety of demographic backgrounds, and comorbidities. In this study, I have showed that stroke volume variability is an important haemodyanmic parameter in anticipating outcome of shock. This parameter was previously studied in context of fluid responsiveness in patients with circulatory shock but never been corelated directly to outcome of shock before. Li Priori definition of shock has shown to have great potentials in diagnosing shock based on access to readily available markers of hypoperfusion at bedside such as PH and Lactate. This study is the first UK based study which re-assessed the diagnostic ability of LiPs criteria in both internal and external settings. In current study, I proposed a novel criterion: DiPS which is shown to have an excellent diagnostic ability in predicting outcome of shock. Overall, the current findings provide information that allows clinicians to make accurate estimates of the probability of shock and survival of patients with shock, so that the likelihood of success can be a factor in decision on aggressiveness of care. Future studies should focus on assessment of haemodyanmic parameters at bedside using USCOM in large and randomized populations, where results can be compared with other non-invasive techniques.

4.6 Limitations

Our study has a number of limitations; Firstly, it is a monocentric study, with moderate sample size and generalizability of the data cannot be assured. Hence, the results need to be confirmed in larger populations. Nevertheless, while the size of this preliminary study was not very large, it was sufficient to highlight significant results and there was a good distribution of cases that would broadly represent the spectrum of severity of diseases in patients presenting to ED. Future studies are required to further validate and refine the definitions and to test them in broader ED populations. Secondly, the results of this study might have been influenced by the working system of the emergency department, availability of study doctors and patient source composition. Future randomized trials with facilities to recruit patients out of hours in larger populations should be considered to tackle selection bias. Thirdly, testing against other potential standards of tissue perfusion such as oxygen delivery was not always possible due to lack of access to parameters required to measure them. Furthermore, not all participants had all the investigations necessary for proposed classifications, such as Venous Blood Gas (VBG), as investigations were at times ordered at discretion of attending physicians. To this, one might argue that patients who had their venous blood gas done were potentially sicker compared to those who did not have venous blood gas, and this has the potential to skew the data and thus affecting the results. However, to overcome this barrier, we attempted to include the equivalents of missing data for instance arterial blood gas when venous gas values were missing.

4.7 Conclusions and future direction

USCOM as a non-invasive, ultrasound technique is previously validated in wide range of animal and human studies. This study is the first UK based analysis, assessing the use of USCOM as an easy to use, safe technique with good reproducibility and operator independency in Emergency Department. USCOM assists non-invasive measurements of haemodynamics in shocked patients, avoiding risks associated to invasive techniques. In this study, I showed that haemodynamic variables such as stroke volume variability, which is proven to be a factor of fluid responsiveness in previous studies, has significantly associated with mortality outcome. Stroke volume variability as a dynamic parameter may offer valuable clinical information in spontaneously breathing patients. I studied wide range of patients, including spontaneous breathers and ventilated subjects and achieved a new cut off for stroke volume values in relation to mortality outcome. Other afterload related values such as Flow time corrected, and potential kinetic ratio is able to act as an important predictors of ICU admission. We recommend that factors such as PKR, which is a dynamic measure of both blood flow and pressure and never been extensively studied in the past, could represent a treatment goal in optimization of haemodynamics along with cardiac output, stroke volume, inotropy index and systemic vascular resistance. Although, the study failed to show association between cardiac output or cardiac power to primary outcome, we concluded that allowance of method failure or unsatisfactory traces should be considered when assessing USCOM reliability and percentage of error. Interpretation of measured CO should be done besides all aspects of careful clinical assessment and should be individualized, and interpreted in context with recognition of USCOM systemic tendency to underestimate cardiac output in hyperdynamic subjects. Using USCOM-derived shock classification, the current study did not show significant association between proposed shock type and primary outcome. Future, large meta-analysis, examining more heterogeneous groups are required to establish more accurate cut offs in various demographics with power to anticipate outcome of shock. Dynamic parameters should be considered rather than static ones and factors of compromise such as presence of dysrhythmias, respiratory variations and technique difficulties should well be taken into considerations, whilst interpreting the results. The current study proved that the LiPS additive tool was able to identify patients at higher risk of poorer outcome with similar, albeit with a slightly lower specificity and specificity, than in the original study. However, the tool was extensively validated in three distinct cohorts with various heterogeneity, more studies are necessary to validate and refine the score to further improve its accuracy. I used easily accessible parameters at point of care in ED and proposed a new definition of shock. DiPS score requires more in-depth assessment and validation in larger adult and pediatric populations. My study did not show significant agreement between different diagnostic measures of shock, including USCOM-derived shock, LiPS and clinical gestalt. However, combination of diagnostic methods such as clinical impression, USCOM derived shock, LiPs and DiPS will enhance accuracy and precision and should be considered moving forward. Future studies should aim to compare these criteria with well established and validated tools such as NEWS score or qSOFA and SOFA.

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Appendix:

2.1.1 Patient information sheet

Patient Information Sheet

Diagnostic Investigation and Prediction of Shock (The DiPS Study)

PARTICIPANT INFORMATION SHEET VERSION 1.0

You are being invited to take part in a research study *led by Cardiff University*. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Thank you for reading this.

1. What is the purpose of this research?

Early recognition of problems in your circulating blood is important in shocked patients. The measurement of how well your blood is being pumped is an essential part in the immediate management of such patients.

We are conducting a study to investigate the usefulness of USCOM (Ultrasonic Cardiac Output Monitor) in patients admitted to the Emergency Department (ED). If you are willing to participate in our research study, it would be greatly appreciated.

Here is a picture of the USCOM:

The “USCOM” is an ultrasound machine similar that used in pregnancy to look at the baby. The difference is that we place an ultrasound probe above or next to the patient’s breastbone and look at the heart valves and blood flow across the valves. The device is completely safe and measures cardiac output without any injections or radiation. The procedure is not painful. The measurements can be helpful for doctors to assess changes in the blood circulation and diagnose the type of shock, so that appropriate treatment can be given promptly. In this research, we aim to investigate how useful it is to apply this device in the ED.

The treatment of your medical condition will not be affected by whether or not you agree to participate in this research. However, if you participate, the findings and measurements may help doctors in guiding treatment for your condition in the future.

We will collect data from the USCOM machine, and also blood pressure, heart rate and other relevant clinical information. All data will be kept for 15 years and will be used only for the purposes of research. All data will be kept confidential.

Participation in this study is entirely voluntary. You may withdraw consent at any time and request us not to use the data.

2. Why have I been invited?

You have been invited because it is possible that your blood is not being pumped as well as it could be. We will use the USCOM device to assess this.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, we will describe the study and ask you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your medical treatment or legal rights.

You are free to withdraw your consent at any time, without giving a reason, even after signing the consent form. Any unused data will be destroyed. Any results that have been used prior to the withdrawal of consent will continue to be used in this study.

4. What will happen to me if I take part?

Sequential ultrasound readings using the USCOM each lasting about 5 minutes will be taken on at least three occasions over the course of your treatment in ED. We aim to take readings just after initial observation recorded by your nurse and within period of treatment. The samples will be collected by one of our doctors using the USCOM.

The doctors treating you will use the USCOM machine to take at least three ultrasound readings (each lasting around 5 minutes) from you on separate occasions during the course of your treatment in the ED. The ultrasound readings will be taken just after the initial observation recorded by your nurse when you were admitted to the ED and during the period of your treatment.

We will use the data in this study to see if we can predict how well you will recover, to evaluate the doctor's treatment, and to inform for future studies. These readings will not be used to guide treatment in this study.

If you want to take part in the study, all data will be kept for 15 years and will be used only for the purposes of research. With your consent, anonymised data may be used for future research within the UK and abroad, including use by commercial companies. All data will be kept confidential.

We will follow your case primarily for 7 days to see how well you do, and will make every effort to try to contact you every day if we have not been able to obtain consent from you. Once consent has been obtained then we will follow your case through electronic records. A secondary purpose of the study is to see how well you do up to 28 days so we will follow your case electronically at 28 days.

Participation in this study is entirely voluntary. You may withdraw consent at any time and request that we don't use your data.

5. Will I be paid anything for taking part?

Any data collected will be treated as a gift to Cardiff University and you will not benefit financially from taking part in this study or in the future should this research lead to the development of a new treatment or medical test.

6. What will my data be used for?

Our research will use the USCOM readings that you provided to improve our understanding of the how well blood is pumped around the body in shocked patients. Your data will be used to help us better understand what is happening during shock and may be available for larger similar studies in the future if they plan to include and combine such information.

7. What are the possible benefits of taking part?

Your contribution will help us understand more about the symptoms, progression, and changes occurring during shock and possibly other medical conditions. The intention in this study is that the information obtained will not immediately alter your care in any way but will help us understand the changes in the circulation during shock. Although, there is no immediate benefit to you from taking part in the trial, if major changes are observed then they may affect your treatment in the future. This will be left to the treating clinician to decide, and the decision that he or she makes is not considered part of this study. The information that we get from this study will help us to improve treatment for patients presenting with shock in the future.

9. What are the possible risks of taking part?

There are no obvious disadvantages to taking part in this study and you won't be exposed to any additional risk during your time in the study. All of the study procedures carried out on you (the USCOM device readings, blood pressure, heart rate monitoring, pulse and oxygen measures) are non-invasive and should not have caused you any additional pain or discomfort. The USCOM device is non-invasive and is not painful, much like having an ultrasound for a baby. The collection of the data will not involve any discomfort and will only take a short amount of time**.** All of the study procedures will be carried out by trained clinical staff.

There are no risks arising from your participation in the study. Your treatment and any risks associated with it will already have been explained to you.

10. Will anyone look at my medical records?

All of your personal data was treated as strictly confidential and only research doctors, who are members of NHS care team, would have access to the medical records in their clinical capacity.

11. Will my GP be told I am taking part in the study?

We will not inform your GP that you are taking part in this study.

12. Will my taking part in this study be kept confidential?

All identifiable information collected about you during the study will be kept strictly confidential in accordance with the Data Protection Act. Your name, address or any other identifying information will not be passed onto anyone and your data will be assigned an anonymous identification code. You will not be identified in any published study results.

Only the Cardiff University research team will have access to the information that can identify you and link you to your data.

14. What will happen to the results of the study?

We hope to use the results from this study to inform larger studies. It is our intention to publish the results of this study in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation.

15. What if there is a problem?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay for it.

If you wish to complain or have grounds for concerns about any aspect of the way you have been approached or treated during the course of this research; the normal National Health complaints procedure is available to you. The Complaints Officer can be contacted on (029) 2074 4095 or concerns@wales.nhs.uk.

Alternatively, you may contact:

Dr J. Mower, Clinical Director,
Emergency Medicine/Emergency Unit
UNIVERSITY HOSPITAL OF WALES
Tel: 029 2074 8004

16. Who is organising and funding this research?

The research is organised by Professors Timothy Rainer and Zaheer Yousef, at the School of Medicine at Cardiff University. This study is being carried out by Professors Timothy Rainer and Zaheer Yousef using their own research funds.

17. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Wales Research Ethical Committee 2.

18. Further information and contact details?

Should you have any questions relating to this study, you may contact us during normal working hours:

Dr Sorayya Kakhi
Cardiology Department
University Hospital of Wales, Cardiff
CF14 4XW
Sorayya.kakhi@wales.nhs.uk

Professor Timothy Rainer
Emergency Department Academic Unit
University Hospital of Wales, Cardiff
CF14 4XW
Tel 029 2074 3653
rainerth@cardiff.ac.uk

Professor Zaheer Yousef
Cardiology Department
University Hospital of Wales, Cardiff
CF14 4XW
Zaheer.yousef@wales.nhs.uk

We would like to thank you for considering taking part in this study. If you decide to participate you will be given a copy of the information sheet and a signed consent form to keep.

2.1.2 Patient information sheet in retrospect

Conformational Patient Information Sheet

Diagnostic Investigation and Prediction of Shock (The DiPS Study)

CONFIRMATIONAL PARTICIPANT INFORMATION SHEET VERSION 1.0

The Emergency Department (ED) you have recently been admitted to is taking part in a research study led by Cardiff University.

When you were unwell, either you agreed to be included in this study or, because you were too unwell to think about it properly, someone else (the person accompanying you at the time of your hospital admission or a member of the medical team responsible for your care) agreed for you to be in the study on your behalf. Now that you are feeling better we would like to ask you whether you want to continue to take part and whether we can use the information that has been collected about you.

Please take time to read the following information carefully and discuss it with others if you wish, before deciding whether you want to stay in the study.

Thank you for reading this.

8. What is the purpose of this research?

Early recognition of problems in your circulating blood is important in shocked patients. The measurement of how well your blood is being pumped is an essential part of the immediate management of such patients.

We are conducting a study to investigate the usefulness of USCOM (Ultrasonic Cardiac Output Monitor) in patients admitted to the Emergency Department (ED). If you are willing to participate in our research study, it would be greatly appreciated.

Here is a picture of the USCOM:

The “USCOM” is an ultrasound machine similar that used in pregnancy to look at the baby. The difference is that we place an ultrasound probe above or next to the patient’s breastbone and look at the heart valves and blood flow across the valves. The device is completely safe and measures cardiac output without any injections or radiation. The procedure is not painful. The measurements can be helpful for doctors to assess changes in the blood circulation and diagnose the type of shock, so that appropriate treatment can be given promptly. In this research, we aim to investigate how useful it is to apply this device in the ED.

The continuing treatment of your medical condition will not be affected by whether or not you agree to participate in this research and you still received the normal standard of care and treatment while you were taking part in the study. However, if you participate, the findings and measurements may help doctors in guiding treatment for your condition in the future.

9. Why was I invited to take part?

You were invited to take part in the study because it is possible that your blood was not being pumped as well as it could be when you were unwell. We used the USCOM device to assess this.

10. What has happened to me in this study so far?

While you were unwell, we collected data from you using the USCOM machine, and also took your blood pressure, heart rate and other relevant clinical information.

The doctors treating you used the USCOM machine to take at least three ultrasound readings (each lasting around 5 minutes) from you on separate occasions during the course of your treatment in the ED. The ultrasound readings were taken just after the initial observation recorded by your nurse when you were admitted to the ED and during the period of your treatment.

We will use the data in this study to see if we can predict how well you will recover, to evaluate the doctor's treatment, and to inform for future studies. These readings will not be used to guide treatment in this study.

Part of this feasibility study is to investigate how the USCOM reading process influences patient care and treatment. However, it is very unlikely that these readings will affect the treatment process as patients will receive their treatment when needed with no delay.

If you want to continue to take part in the study, all data will be kept for 15 years and will be used only for the purposes of research.

Participation in this study is entirely voluntary. You may withdraw consent at any time and request that we don't use your data.

11. What will happen now?

We would like to ask your permission to use the data collected about you during your time in the ED. If you decide that you don't want to be in the study, we will not use any of your information collected about you. If you are happy for us to use your data we will ask you to sign a consent form.

We will follow your case primarily for 7 days to see how well you do, and will make every effort to try to contact you every day if we have not been able to obtain consent from you. Once consent has been obtained then we will follow your case through electronic records. A secondary purpose of the study is to see how well you do up to 28 days so we will follow your case electronically at 28 days.

12. Do I have to take part?

It is up to you to decide whether or not to take part. If you decide that you don't want to be in the study, we will not use any of your information in the study. If you are happy for us to use your data, we will describe the study ask you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your medical treatment or legal rights.

You are free to withdraw your consent at any time, without giving a reason, even after signing the consent form. Any unused data will be destroyed. Any results that have been used prior to the withdrawal of consent will continue to be used in this study.

13. What will my data be used for?

Our research uses the USCOM readings that you have provided to improve our understanding of how well blood is pumped around the body in shocked patients. Your data will be used to help us better understand what happens when a person goes into

shock. Your data will be stored by Cardiff University and may be made available for larger similar studies in the future.

With your consent, your anonymised research data will be retained at the end of this study for use in future research within the UK and abroad. It will be stored securely at Cardiff University. At this stage we do not know what the research will involve. On the consent form you will be given the option to exclude your data from future research. Your data will not be sold for profit.

14. Will I be paid anything for taking part?

Any data collected will be treated as a gift to Cardiff University and you will not benefit financially from taking part in the study or in the future should this research lead to the development of a new treatment or medical test.

15. Will I have benefitted from taking part taking part in this study?

The information we obtained from you will not immediately alter your care in any way but will help us to understand the changes that happen to blood circulation during shock. Although, there is no immediate benefit to you from taking part in the study, if any major changes were observed then they may affect your treatment in the future. This will be up to the treating clinician to decide, and the decision that he or she makes is not considered part of this study. The information that we get from this study will help us to improve treatment for patients presenting with shock in the future. Your contribution will help us understand more about the symptoms, progression, and changes occurring during shock and possibly other medical conditions.

16. Will my taking part in the study have exposed me to any risks?

There are no obvious disadvantages to taking part in this study and you should not have been exposed to any additional risk during your time in the study. All of the study procedures carried out on you (USCOM device readings, blood pressure, heart rate monitoring, pulse and oxygen measures) are non-invasive and should not have caused you any additional pain or discomfort. The USCOM device is non-invasive and is not painful, much like having an ultrasound for a baby. All of the study procedures were carried out by trained clinical staff.

There are no risks arising from your participation in the study. Your treatment and any risks associated with it will already have been explained to you.

17. Who has looked at my medical records?

All of your personal data was treated as strictly confidential and only research doctors, who
are members of NHS care team, would have access to the medical records in their clinical capacity.

18. Will my GP be told I have taken part in the study?

We will not inform your GP that you have taken part in this study**.**

19. Will my taking part in this study be kept confidential?

All identifiable information collected about you during the study will be kept strictly confidential in accordance with the Data Protection Act. Your name, address or any other identifying information will not be passed onto anyone outside of the Cardiff University research team and your data will be assigned an anonymous identification code. You will not be identified in any published study results.

Only the Cardiff University research team will have access to the information that can identify you and link you to your data**.**

20. What will happen to the results of the study?

We hope to use the results from the study to inform larger studies. It is our intention to publish the results of this study in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation.

21. What if there is a problem?

If you were harmed as a result of taking part in this research study, there are no special compensation arrangements. If you were harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay for it.

22. What if I have concerns about my involvement in this study?

If you have any concerns about any aspect of the way you have been approached or treated during the course of this research or if you wish to make a complaint; the

normal National Health complaints procedure is available to you. The Complaints Officer can be contacted on (029) 2074 4095 or concerns@wales.nhs.uk.

Alternatively, you may contact:

Dr J. Mower, Clinical Director,
Emergency Medicine/Emergency Unit
UNIVERSITY HOSPITAL OF WALES
Tel: 029 2074 8004

23. Who is organising and funding this research?

The research is organised by Professors Timothy Rainer and Zaheer Yousef, at the School of Medicine at Cardiff University. This study is being carried out by Professors Timothy Rainer and Zaheer Yousef using their own research funds.

24. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Wales Ethical Committee 2.

25. Further information and contact details.

Should you have any questions relating to this study, you may contact us during normal working hours:

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Professor Timothy Rainer
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rainerth@cardiff.ac.uk

Professor Zaheer Yousef
Cardiology Department
University Hospital of Wales, Cardiff
CF14 4XW
Zaheer.yousef@wales.nhs.uk

We would like to thank you for considering taking part in this study. If you decide to participate you will be given a copy of the information sheet and a signed consent form to keep.

2.1.3 Consultee Patient Information Sheet

Consultee Patient Information Sheet

Diagnostic Investigation and Prediction of Shock (The DiPS Study)

CONSULTEE PARTICIPANT INFORMATION SHEET VERSION 1.0

The Emergency Department (ED) is taking part in a study led by Cardiff University.

We are approaching you because the person you are with could enter the study but they are not well enough at the moment to decide whether they want to. Please read this information sheet and ask any questions you have before deciding whether the person you are with would want to take part in the study. If you don't feel up to looking at this information sheet now, please say so and we can either show you a very brief version or ask the member of staff who has been nominated to help with consent in an emergency what they think.

If you agree that the person you are with should take part in this study, as soon as they are well enough, we will talk to them about the study and see whether they want to stay in the study or not.

Thank you for reading this.

26. What is the purpose of this research?

Early recognition of problems in circulating blood is important in shocked patients. The measurement of how well blood is being pumped is an essential part of the immediate management of such patients.

We are conducting a study to investigate the usefulness of USCOM (Ultrasonic Cardiac Output Monitor) in patients admitted to the Emergency Department (ED). If you think the person, you are with would want to participate in our research study, their involvement would be greatly appreciated.

Here is a picture of the USCOM:

The “USCOM” is an ultrasound machine similar to that used in pregnancy to look at the baby. The difference is that we place an ultrasound probe above or next to the patient’s breastbone and look at the heart valves and blood flow across the valves. The device is completely safe and measures cardiac output without any injections or radiation. The procedure is not painful. The measurements can be helpful for doctors to assess changes in the blood circulation and diagnose the type of shock, so that appropriate treatment can be given promptly. In this research, we aim to investigate how useful it is to apply this device in the ED.

The person you are with will continue to receive the normal standard of care and treatment for the medical condition they have been admitted to the ED with. Their continuing treatment will not be affected by whether or not you agree for them to participate in this study. If you do agree for them to participate, the findings and measurements may help doctors in guiding treatment for others with their condition in the future.

27. Why has the person I’m with been invited to take part?

The person you are with has been invited to take part in the study because it is possible that their blood is not being pumped as well as it could be. If you consent to them taking part in the study, the researchers will use the USCOM device to assess this.

28. **What will happen in this study?**

If you decide that the person you are with would want to take part in this study, we will collect data from them using the USCOM machine, and also take their blood pressure, heart rate and some other relevant clinical information.

The doctors treating them will use the USCOM machine to take at least three ultrasound readings (each lasting around 5 minutes) from them on separate occasions during the course of their treatment in the ED. The ultrasound readings will be taken just after the initial observation recorded by the nurse when they were admitted to the ED and during the period of their treatment while in the ED.

We will use the data in this study to see if we can predict how well the person you are with will recover, to evaluate the doctor's treatment, and to inform future studies. These readings will not be used to guide their medical treatment in this study.

Part of this study is to investigate how the USCOM reading process influences patient care and treatment. However, it is very unlikely that these readings will affect the treatment process as patients will receive their treatment when needed with no delay.

When we think that the person you are with is well enough to make a decision about their participation in the study, we will approach them with full information about the study and will take consent from them. If they decide to continue to take part in the study, their data will be kept for 15 years by Cardiff University and will be used only for the purposes of research. All data will be kept confidential.

Participation in this study is entirely voluntary. You do not have to agree for the person you are with to take part in the study and even if you do, they will be given the option to withdraw their consent and request that we don't use their data, when they are feeling better.

29. What will their data be used for?

Our research will use the USCOM readings provided by the person you are with to improve our understanding of how well blood is pumped around the body in shocked patients. Their data will be used to help us better understand what happens when a person goes into shock. Their data will be stored at Cardiff University and may be made available for larger similar studies in the future.

All the data provided by the person you are with will be anonymised and they won't be identifiable. With their consent, the anonymised research data will be retained at the end of this study for use in future research within the UK and abroad. It will be stored securely at Cardiff University. At this stage we do not know what the research will involve. Their data will not be sold for profit**.** With consent, anonymised data may be used for future research within the UK and abroad, including use by commercial companies.

We will follow their case primarily for 7 days to see how well they do, and will make every effort to try to contact them every day if we have not been able to obtain consent

from them. A secondary purpose of the study is to see how well the person you are with does up to 28 days after their admission to the ED. Once consent has been obtained from the person you are with, we will follow their case through their electronic medical records at 28 days after they have been admitted to the ED.

5. How long will the person I'm with be in the study?

If you agree that the person you are with would want to take part in the study, we will perform the measurements described in section 3 of this Information Sheet while they are in the ED. If the person you are with agrees, we will then follow their case through their electronic medical records for up to 28 days after they have been admitted to the ED.

6. Does the person I'm with have to take part in the study?

No. It is up to you whether or not the person you are with takes part in the study. Deciding not to take part will not affect the standard of care they receive now or in the future. Even if you do decide that they will take part in the study, you can decide to stop their involvement at any time during the study, without giving a reason. If you decide you want them to stop taking part, their medical care or legal rights will not be affected in any way.

When the person you are with is feeling better, we will approach them to give them information about the study, answer any questions they may have and check that they still want their data to be used in the study. They can decide whether they wish to continue with the study or withdraw their consent. If they don't want to continue, we will not use their data in the study.

7. Will I/the person I am with be paid anything for taking part in the study?

Any data collected will be treated as a gift to Cardiff University and you/the person you are with will not benefit financially from taking part in the study or in the future should this research lead to the development of a new treatment or medical test.

8. Are there any benefits to being in the study?

The information we obtain from the person you are with will not immediately alter their care in any way but will help us to understand the changes that happen to blood circulation during shock. There will be no immediate benefit to the person you are with, but if any major changes are observed as a result of them being in the study, then they may affect their treatment in the future. This will be up to the treating clinician

to decide, and the decision that he or she makes is not considered part of this study. The information that we get from this study will help us to improve treatment for patients presenting with shock in the future. Their contribution will help us understand more about the symptoms, progression, and changes occurring during shock and possibly other medical conditions.

9. Are there any risks or discomforts from being in the study?

There are no obvious disadvantages to taking part in this study and the person you are with should not be exposed to any additional risk during their time in the study. All of the study procedures (USCOM device readings, blood pressure, heart rate monitoring, pulse and oxygen measures) are non-invasive and should not cause any additional pain or discomfort. The USCOM device is non-invasive and is not painful, much like having an ultrasound for a baby. All the study procedures will be carried out by trained clinical staff.

The medical treatment the person you are with will receive during their time in the ED and any risks associated with this should already have been explained to you.

10. Will the medical records of the person I'm with be looked at by anyone outside their immediate NHS care team?

If you agree to the person, you're with taking part in the study, relevant sections of their medical notes were treated as strictly confidential and only research doctors, who are members of NHS care team, would have access to the medical records in their clinical capacity.

11. Will their GP be told about their involvement in the study?

We will not inform participant's GPs that they have taken part in this study**.**

12. Will the personal information of the person I'm with be kept confidentially?

Yes. All the information we collect about the person you're with for this study, will be kept in secure databases held at the hospital or Cardiff University. These databases will only be accessed by members of the study team.

All identifiable information collected during the study will be kept strictly confidential in accordance with the Data Protection Act. The name, address or any other identifying information of the person you're with will not be passed onto anyone outside of the

Cardiff University research team and their data will be assigned an anonymous identification code. If they choose to continue with the study, they will not be identified in any published study results.

13. What will happen to the results of the study?

We hope to use the results from the study to inform larger studies. It is our intention to publish the results of this study in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation.

14. What if there is a problem?

If the person you are with is harmed as a result of taking part in this research study, there are no special compensation arrangements. If they are harmed due to someone's negligence, then they may have grounds for legal action, but they may have to pay for it.

15. What if I have concerns about my involvement in this study?

If at any point you or the person you are with is unhappy with any aspect of the study, the normal National Health complaints procedure is available to you. The Complaints Officer can be contacted on (029) 2074 4095 or concerns@wales.nhs.uk.

If you or the person you are with would like to speak to someone independent of the study, you can contact:

Dr J. Mower, Clinical Director,
Emergency Medicine/Emergency Unit
UNIVERSITY HOSPITAL OF WALES
Tel: 029 2074 8004

16. Who is organising and funding this research?

The research is organised by Professors Timothy Rainer and Zaheer Yousef, at the School of Medicine at Cardiff University. This study is being carried out by Professors Timothy Rainer and Zaheer Yousef using their own research funds.

17. Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Wales Ethical Committee 2.

18. Further information and contact details

Should you have any questions relating to this study, you may contact us during normal working hours:

Dr Sorayya Kakhi
Cardiology Department
University Hospital of Wales, Cardiff
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Professor Timothy Rainer
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Tel 029 2074 3653
rainerth@cardiff.ac.uk

Professor Zaheer Yousef
Cardiology Department
University Hospital of Wales, Cardiff
CF14 4XW
Zaheer.yousef@wales.nhs.uk

We would like to thank you for considering taking part in this study. If you decide to participate you will be given a copy of the information sheet and a signed consent form to keep.

2.1.4 Patient consent form

Wales Emergency Unit, Cardiff University

CONSENT FORM

Diagnostic Investigation and Prediction of Shock (The DiPS Study)

Name of Researcher(s): Timothy H Rainer, Zaheer Yousef, Sorayya Kakhi, Huw Williams, Nic Ngua

	Please initial box if you agree and place a cross X if you disagree
I confirm that I have read and understand the information sheet version 2.0. for the above study and have had the opportunity to ask questions and that these have been answered satisfactorily	
I am free to leave the study at any time without giving any reason and without any effect on my medical care or legal rights.	
I agree that information collected about me during the study (including ultrasound data taken from an USCOM machine during my involvement in the study) can be used by the study team.	
I understand that relevant sections of my medical notes and data collected during the study *were looked at and* may *continue to* be looked at by the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I wish to be contacted about any findings that may have important implications for my future health or for the health of my family. [Place a cross X if you do NOT want to be contacted]	
I agree for my data to be used for future use by researchers in the UK and abroad, I understand the research may involve use by the commercial sector and that researchers will not be able to identify me from my data.	
I agree to *continue to* take part in this study	

Name of person giving consent (PRINT) **Date** **Signature**

PATIENT [Note that ONLY the patient should provide confirmatory/retrospective consent

Name of person taking consent (PRINT) **Date** **Signature**

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM FOR YOUR RECORDS

2.1.5 Patient consultee consent form

Wales Emergency Unit, Cardiff University

CONSULTEE CONSENT FORM

Diagnostic Investigation and Prediction of Shock
(The DiPS Study)

Chief Investigator: Professor Timothy Rainer, Emergency Department Academic Unit, School of Medicine, Cardiff University.

Name of Researcher(s): Timothy H Rainer, Zaheer Yousef, Sorayya Kakhi, Huw Williams, Nic Ngua

	Please initial box if you agree
I confirm that I have read and understood the Consultee Participant Information Sheet version 2.0 dated 3d August 2017 for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that the person I am with does not have to take part and is free to leave the study at any time without giving any reason and without any effect on her medical care or legal rights.	
I understand that relevant sections of medical notes and data collected about the person I am with will be looked at by individuals from research team, the regulatory authorities or the NHS Health Board, where it is relevant to their taking part in this research.	
I agree that the person I am with can take part in this study.	

_____	_____	_____
Name of person giving consent (PRINT)	**Date**	**Signature**

CONSULTEE

_____	_____	_____
Name of person taking consent (PRINT)	**Date**	**Signature**

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM FOR YOUR RECORDS

2.1.6 Patient consent form in retrospect

Wales Emergency Unit, Cardiff University

CONFIRMATIONAL CONSENT FORM in RETROSPECT

Diagnostic Investigation and Prediction of Shock
(The DiPS Study)

Name of Researcher(s): Timothy H Rainer, Zaheer Yousef, Sorayya Kakhi, Huw Williams, Nic Ngua

	Please initial box if you agree and place a cross X if you disagree
I confirm that I have read and understand the information sheet version 2.0. for the above study and have had the opportunity to ask questions and that these have been answered satisfactorily	
I understand that it was not possible because of my condition for me to *consent to* participate in this study in a fully informed way prior to accessing critical, time-dependent data. *As I was too unwell to decide to take part, agreement to enter the study was provided by a Consultee on my behalf.* As my condition has improved, I am now able to evaluate the information and consider my participation in the study.	
I understand that I have already been entered into the study but do not have to continue to take part and that I am free to leave the study at any time without giving any reason and without any effect on my medical care or legal rights.	
I agree that information collected about me during the study (including ultrasound data taken from an USCOM machine during my involvement in the study) can be used by the study team.	
I understand that relevant sections of my medical notes and data collected during the study *were looked at and* may *continue to* be looked at by the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I wish to be contacted about any findings that may have important implications for my future health or for the health of my family. [Place a cross X if you do NOT want to be contacted]	
I agree for my data to be used for future use by researchers in the UK and abroad, I understand the research may involve use by the commercial sector and that researchers will not be able to identify me from my data.	
I agree to *continue to* take part in this study	

_____ _____ _____

Name of person giving consent (PRINT) **Date** **Signature**

PATIENT. [Note that ONLY the patient should provide confirmatory/retrospective consent]

_____ _____ _____

Name of person taking consent (PRINT) **Date** **Signature**

THANK YOU FOR PARTICIPATING IN OUR RESEARCH YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM FOR YOUR RECORD

4.1 Fremantle criteria for acoustic image quality assessment

Well-defined image base†	1
Well-defined image peak†	1
Well-defined commencement of flow or heart sound†	1
Well-defined cessation of flow or heart sound†	1
Appropriate scale used on screen‡	1
Minimal acoustic interference§	1
Total	6

- † Must be present on three or more complexes.
- ‡ ‡Scale to maximize image size on screen and in appropriate direction.
- § §Acoustic interference considered significant if it is difficult to differentiate it from the actual cardiac output signal.