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HEMODYNAMICS IN THE CRITICALLY ILL

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Academic dissertation

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To Tommy, Lukas, Linus and Isak

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ABSTRACT

BACKGROUND

Adequate blood circulation is necessary for tissue perfusion and oxygen supply. Derangements in perfusion due to circulatory failure may lead to end-organ failure without prompt and accurate restoration of circulation and perfusion, which is performed by targeting sufficient levels of preload, afterload, and cardiac contractility. Current international guidelines recommend early vigorous fluid resuscitation, restoration of mean arterial pressure (MAP) to ≥60-65 mmHg, when necessary by using vasopre ssor agents, and restoration of depressed cardiac contractility and output by inotrope treatment to improve survival and avoid end-organ failure. However, evidence for the beneficial impact of inotrope use in septic shock, hemodynamic targets for resuscitation in severe acute pancreatitis (SAP), or optimal blood pressure for prevention of septic acute kidney injury is rather limited. Furthermore, feasible means of assessing fluid responsiveness to prevent excessive fluid resuscitation are warranted. The objective of this study was to evaluate different hemodynamic variables in addition to vasopressor and inotrope treatment during the early phases of severe sepsis, septic shock, and SAP and their association with development of end-organ failure and outcome. We also sought to find relevant hemodynamic parameters for assessing fluid responsiveness during early resuscitation of septic shock.

PATIENTS

A total of 1022 patients, 440 with septic shock, 159 with SAP, and 423 with severe sepsis, were included in the study. All patients were treated in the ICUs of Helsinki University Hospital during 2005-2012, except for the 423 patients with severe sepsis, who were treated in 13 different Finnish ICUs during 2011-2012.

MAIN RESULTS

Of patients with septic shock, 44.3% received inotrope treatment during the first 24 hours in the ICU, the majority of these patients receiving dobutamine (90.3%). The mortality of inotrope receivers was significantly higher than that of non-receivers (42.5% vs. 23.9%). Patients who received inotropes were generally more severely ill and received higher doses of norepinephrine. The use of inotropes in these patients was independently associated with worse outcome, also after adjustment with propensity score. In patients with severe sepsis and SAP, the use of inotropes was less frequent, 16.0% and 16.4%, respectively. Vasopressors, most often norepinephrine, were administered to the majority of patients with severe sepsis, SAP, and septic shock. The highest dose of norepinephrine during the first day in ICU was associated with worse outcome.

Lower MAP, higher central venous pressure (CVP), and lower cardiac index (CI), but not higher heart rate (HR), were associated with 90-day mortality in patients with SAP.

Decreases in MAP and systolic arterial pressure were the best predictors of fluid responsiveness in 20 mechanically ventilated patients with septic shock during a temporary elevation of positive end-expiratory pressure (PEEP) from 10 to 20 cm H_2O. A decrease of less than 8% ruled out fluid responsiveness, with a negative predictive value of 100%.

The time-adjusted MAP during the first 24 hours in the ICU of patients developing acute kidney injury (AKI) during the first five days in the ICU was significantly lower than that of patients not developing AKI (74.4 mmHg vs. 78.6 mmHg). The best cut-off value for time-adjusted MAP was 72.7 mmHg. Lower time-adjusted MAP or alternatively time-adjusted MAP below 73 mmHg was independently associated with progression of AKI.

CONCLUSIONS

Inotropes are frequently used in patients with septic shock. In severe sepsis and SAP, inotrope use is less frequent. The vast majority of patients received vasopressor treatment. Norepinephrine was the vasopressor of choice in nearly all patients. Use of inotropes and the highest vasopressor dose during the first day in ICU were significantly associated with 90-day mortality.
Although inotropes may have beneficial effects in patients with septic shock, by increasing cardiac output and perfusion, they might also have adverse effects that eventually lead to higher mortality. Although vigorous fluid resuscitation is advocated in the early treatment of SAP to maintain sufficient tissue perfusion, our study showed that overzealous resuscitation might be harmful, reflected by the association of higher CVP with worse outcome. To avoid overhydration during fluid resuscitation of patients with septic shock, a lack of a decrease in MAP during elevation of PEEP from 10 to 20 cm H_2O may be used as an accessory means of assessing fluid responsiveness. Lower time-adjusted MAP in patients with severe sepsis is associated with progression of AKI. Higher targets of MAP may be indicated for ensuring adequate perfusion of the kidney in this patient group.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals (I–IV):

I Wilkman E, Kaukonen K-M, Pettilä V, Kuitunen A, Varpula M. *Association between inotrope treatment and 90-day mortality in patients with septic shock*. Acta Anaesthesiol Scand 2013; 57(4):431–42.

II Wilkman E, Kaukonen K-M, Pettilä V, Kuitunen A, Varpula M. *Early hemodynamic variables and outcome in severe acute pancreatitis. A retrospective single-center cohort study*. Pancreas 2013;42(2): 272-8.

III Wilkman E, Kuitunen A, Pettilä V, Varpula M. *Fluid responsiveness predicted by elevation of PEEP in patients with septic shock*. Acta Anaesthesiol Scand 2014; 58(1): 27-35

IV Meri Poukkanen*, Erika Wilkman*, Suvi T Vaara, Ville Pettilä, Kirsi-Maija Kaukonen, Anna-Maija Korhonen, Ari Uusaro, Seppo Hovilehto, Outi Inkinen, Raili Laru-Sompa, Raku Hautamäki, Anne Kuitunen, Sari Karlsson, the FINNAKI Study Group. *Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study*. Crit Care 2013; 17(6): R295
*equal contribution

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ABBREVIATIONS

AKI	Acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Adult respiratory distress syndrome
CI	Cardiac index
CO	Cardiac output
CPR	Cardiopulmonary resuscitation
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
DO_2	Oxygen supply
HES	Hydroxy ethyl starch
HR	Heart rate
IABP	Intra-aortic balloon pump
IAP	Intra-abdominal pressure
ICD-10	International Classification of Diseases, tenth revision
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible nitric oxide synthetase
KDIGO	Kidney Disease: Improving Global Outcomes
LV	Left ventricle
LVEDA	Left ventricular end-diastolic area
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MDRD	Modification in Diet in Renal Disease (equation)
MMDS	Microcirculatory and mitochondrial dysfunction syndrome
MOD	Multiple organ dysfunction
MPAP	Mean pulmonary artery pressure
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
O_2	Oxygen
OPS	Orthogonal polarization spectral imaging
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
PLR	Passive leg raising
PPV	Pulse pressure variation
RRT	Renal replacement therapy
SAE	Sepsis-associated encephalopathy
SAP	Severe acute pancreatitis
ΔSAP	Change in systolic arterial pressure
SAPS	Simplified Acute Physiology Score
SCr	Serum creatinine
$ScVO_2$	Central venous oxygen saturation
SDF	Sidestream dark field imaging

SOFA	Sequential Organ Failure Assessment
STEMI	ST-elevation myocardial infarction
SV	Stroke volume
SVO_2	Mixed venous oxygen saturation
SVV	Stroke volume variation
TEE	Transesophageal echocardiography
TM	Thrombomodulin
TNF	Tumor necrosis factor
TTE	Transthoracic echocardiography
VO_2	Oxygen supply
VTI_{Ao}	Aortic velocity time integral

1. INTRODUCTION

Human hemodynamics has intrigued medical practitioners, philosophers, and scientists for over two thousand years. We have come a long way in our understanding of hemodynamics since the Galenic era, which dominated medical practice for over 1600 years. Galen of Pergamon (129-200 AD), who gained fame as a surgeon to the gladiators, was convinced that hemorrhage was one of the conditions that benefited from bloodletting. He was also convinced that blood flowed outwards in both veins and arteries from the liver, where it was constantly formed. The erroneous notions were not corrected until 1543, when Andreas Vesalius published "De Humanis Corporis Fabrica".[1] A lesser known fact is that Leonardo da Vinci (1452-1519) spent his last years of life studying the anatomy of the cardiovascular system, depicting the vessels and the function of cardiac valves with surprising accuracy.[2]

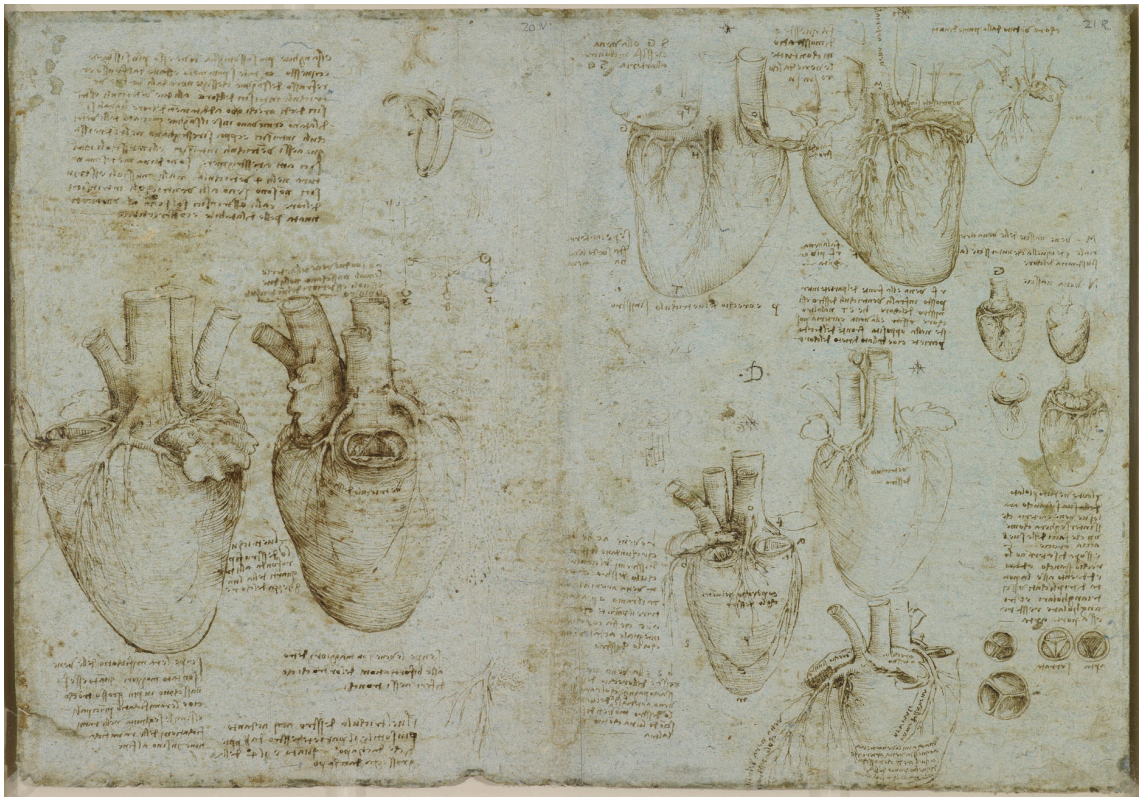


Figure 1. Leonardo da Vinci's study of an ox's heart c. 1511-1513

Royal Collection Trust / © Her Majesty Queen Elizabeth II 2013

The English physiologist William Harvey (1578-1657) made two seminal discoveries without which modern understanding of hemodynamics and shock would not be possible. Firstly, he noted that blood circulated from the heart in the arteries and to the heart in the veins. Secondly, based on his calculations of cardiac output, he also

determined that blood could not be formed in the liver, but was in constant circulation. The term "shock" was first used in a translation of Henri-Francois Le Dran's article describing gun shot wounds in the 1740s. The word was, however, rarely used in this context for the following century. Moreover, it was exclusively used for gunshot wounds until the American Civil War, when Dr. Samuel Gross published a manual for military surgeons in 1861. He realized that shock was a physiologic response to many forms of injury and focused on the neurologic findings of this physiologic state. By the end of World War I, "wound shock" or "traumatic shock" was thought to be a two-stage phenomenon. Primary shock was considered a neurologic entity and secondary shock was presumably caused by toxins that led to hypotension by pooling of the blood in the capillaries. [1]

Alfred Blalock first described the importance of blood volume in the development of shock in the 1920s. Blalock proposed a classification of shock based on the four principal underlying mechanisms; his classification is highly similar to the one still in use today. Blalock produced 44 scientific articles during 1927-1942, shedding more light on this enigmatic phenomenon than anyone before him. [1]

During the Crimean war in the 1850s Florence Nightingale created separate care areas for the most severely injured soldiers. This has been cited as the beginning of intensive care. Modern intensive care began evolving during the 1950s, triggered by the Danish poliomyelitis epidemy and the need for respiratory support. In the mid 20th century, dialysis machines were already used for renal failure, and hemodynamic and cardiac care developed as alternating current defibrillators and patient monitors were introduced to the market. The founders of the two first American Intensive Care Units, M.H. Weil and P. Safar together with W.C. Shoemaker, founder of the first trauma center in Chicago, were pioneers in the field of critical care medicine throughout the 20th century. [3,4] *In addition to their vast clinical work, they produced more than 1300 scientific articles establishing much of the foundations of intensive care as we know it today.*

In the non-cardiac ICU, severe sepsis and septic shock are among the leading causes of death.[5] Sepsis, severe sepsis, and septic shock have for many years been on the list of the 10 leading causes of death in the United States. [6] Published in-hospital mortality rates of severe sepsis and septic shock have varied from 25% to 70%. [7] In a recent large study of nationwide inpatient data, the incidence of severe sepsis increased from 200 to 300/100 000 in the total American population during 2003-2007.[8] These results closely agree with those of earlier studies. [5,9]

Severe sepsis accounts for about 6-15% of all ICU admissions, a proportion showing remarkable consistency across studies. [10-14] In the FINNSEPSIS study, severe sepsis accounted for 11% of Finnish ICU admissions, and 28% of these patients died in hospital. [10] The proportion varies slightly according to local or national ICU resources and the proportion of beds reserved for the most critically ill. [12] Although mortality rates seem to decrease, along with ICU lengths of stay and mean cost per case, this effect is attenuated by the rising incidence of severe sepsis, resulting in a continuous increase in treatment

costs. [8] There is also evidence that the proportion of patients with severe sepsis and multiple organ failures is increasing, while the proportion of patients with single organ failure is declining. [8]

Severe sepsis is defined as a systemic inflammatory response to infection complicated by organ dysfunction, hypoperfusion, or sepsis-induced hypotension, while septic shock is characterized by evidence of hypotension or hypoperfusion, which is not resolved by adequate fluid resuscitation. [15] A more profound hemodynamic compromise has been associated with more severe organ dysfunction and worse outcome, and early hemodynamic optimization has become the mainstay of treatment of these conditions. [12,16]

In severe acute pancreatitis, the microcirculation of the pancreas is deranged [17] and the decrease in systemic vascular resistance along with the cytokine and inflammatory mediator profiles are comparable to changes occurring in severe sepsis and septic shock. [18] Although aggressive and vigorous fluid therapy is currently advocated for the treatment of patients with severe acute pancreatitis,[17] there is remarkable lack of knowledge regarding its administration and optimal hemodynamic targets. [19,20] Insufficient data also exist on the association of early hemodynamic function with later progress and outcome of the disease.

The incidence of acute pancreatitis has also been shown to increase.[21] In the United States, acute pancreatitis accounts for about 200 000 hospital admissions each year. [17] In the Finnish population, acute pancreatitis leads to 70 hospitalizations /100 000 population, indicating an annual total of nearly 4000 hospital admissions.[21] Mortality due to acute pancreatitis has decreased only slightly over the last decades. [17] For severe acute pancreatitis, which develops in one-fifth of all cases, mortality rates of 20-30% have been reported. [22-24]

Although inotrope treatment is included in current sepsis treatment guidelines,[16] insufficient evidence of a beneficial effect in terms of outcome exists. These recommendations are mainly based on expert opinion and on incorporation of inotropes into treatment bundles that have been shown to improve survival.[16,25] However, growing evidence has emerged that catecholamine inotropes are associated with increased mortality in patients with heart failure. [26-28] Moreover, no benefit was seen in terms of improved survival when inotropes were administered in order to increase oxygen delivery to a supranormal level in critically ill patients. [29] Evidence indicates several adverse effects of inotropes, including increased myocardial oxygen consumption and an elevated risk of both arrhythmias and myocardial ischemia. [30-32] Inotropes may also cause metabolic disturbances and increased bacterial growth.[33] Some evidence also suggests that dobutamine may have pro-inflammatory effects. [34]

There is little debate today of whether fluid resuscitation is an essential part of early hemodynamic optimization of patients with septic shock. [35] At the same time, increasing evidence is emerging in support of an association between higher fluid load and worse outcome. There is broad agreement that invasive (static) filling pressures, such as central

venous pressure and pulmonary occlusion pressure, are poor markers of preload and ill suited for prediction of fluid responsiveness in these patients. [36,37] In recent years, the focus has been on the dynamic indices of preload and functional hemodynamic monitoring. By utilizing cardiorespiratory interactions and their impact on venous return and cardiac output, fluid responsiveness may be predicted at bedside.[38] Though superior to static measurements, there are several limitations to the clinical use of dynamic indices, of which the lack of suitable monitoring devices is merely one. Easy and feasible means of assessing fluid responsiveness for everyday use by ICU clinicians are required.

Acute kidney injury (AKI) occurs frequently in patients with severe sepsis, septic shock, and severe acute pancreatitis. [39,40] In severe sepsis, AKI develops in approximately half of the patients. Severe sepsis and septic shock are the primary etiological factors for AKI in nearly half of all critically ill patients. [40] Septic patients with AKI have worse outcome than those with preserved renal function, which is also true for patients with severe acute pancreatitis. [40,41] Septic AKI is not only the consequence of alterations in kidney perfusion due to hemodynamic failure. However, hemodynamics plays a role in the development and progression of this condition. Autoregulation is altered during severe sepsis and septic shock, rendering kidney perfusion vulnerable to hemodynamic changes and more dependent on blood pressure levels and cardiac output. Some studies have reported that maintaining higher levels of blood pressure in patients with septic shock than those currently recommended (≥ 65 mmHg) would be beneficial for preservation of kidney function.[42,43] Evidence also suggests that administration of norepinephrine to patients in septic shock improves kidney perfusion and glomerular filtration rate. [44] However, raising blood pressure using catecholamine vasopressors is also associated with potential harm. [45]

Despite numerous advances in the field of hemodynamic treatment of severe sepsis, septic shock, and severe acute pancreatitis, much remains to be done. This study was prompted by the lack of evidence of beneficial effects of inotropes in septic shock and insufficient knowledge of how to optimally resuscitate a patient with severe acute pancreatitis. Moreover, there is a demand for feasible ways of assessing fluid responsiveness to avoid excess fluid with deleterious effects. Lastly, optimization of kidney perfusion and blood flow is still one of the only means to prevent the progression of septic AKI. While studies of the underlying pathophysiology of septic AKI are underway, clinicians are left with few specific means of improving the outcome of these patients. Knowledge of the association of hemodynamic variables and vasoactive support with progression of AKI may, by way of further randomized studies, lead to better outcomes of these patients in the future.

2. REVIEW OF THE LITERATURE

2.1 DEFINITION OF HEMODYNAMICS

Circulation of blood through the cardiovascular system is essential for the transport of oxygen and metabolites to the cells of all tissues of the body.
The term hemodynamics is used to describe the forces that the heart must generate to circulate blood through the cardiovascular system. This system is made up of the heart and the network of arteries, veins, and capillaries that transports the blood to, through, and from the tissues.

Adequate hemodynamics can also be defined in terms of bioenergetics. Adequate hemodynamics prevails when the transport of oxygen and metabolites to the cells and the subsequent clearing of waste products meet the tissues' needs. [46]

2.1.1 DEFINITION OF HEMODYNAMIC INSTABILITY OR FAILURE

In 1862, the American academic trauma surgeon Samuel D. Gross described hemodynamic failure as the "rude unhinging of the machinery of life". [47] "Machinery of life" eloquently describes cell metabolism, oxygen supply, and consumption as we understand it today.

The term hemodynamic instability may be used to describe the clinical situation in which perfusion failure manifests as features of circulatory shock or advanced cardiac failure, or it may be used to describe less severe conditions where one or more measurements are not in the normal range, but are not clearly pathological. In the literature, other synonyms for hemodynamic instability, such as hemodynamic or circulatory failure, or simply shock, are also frequently used to describe the same phenomenon. Shock is defined as hemodynamic instability leading to hypoperfusion and a decrease in oxygen supply to the tissues. [48]

The physical findings of hemodynamic failure include hypotension, abnormal heart rate, changes in mentation or consciousness, cold extremities, skin mottling, and cyanotic periphery, in addition to oliguria or anuria. [46,49,50] These clinical manifestations reflect perfusion failure, in other words, the imbalance between the needs of the tissues and the supply of oxygen and energy that they receive. [46] Hemodynamic failure is usually a systemic complication of an underlying disease. In everyday clinical practice, this emphasizes the importance of the clinical examination and careful history taking. Treatment of hemodynamic failure is usually not fully successful without knowledge of the underlying condition. [46,49]

In clinical practice, physicians define hemodynamic failure by a combination of clinical findings, as mentioned above. The common denominator for these signs is the

deterioration of systemic and microvascular blood flow, but the underlying hemodynamic mechanism differs according to which part of the circulatory system is most severely afflicted. These differing mechanisms create the basis for the classification of types of hemodynamic failure. [46,49]

During recent years the focus of hemodynamic failure has turned to the insufficiency and dysfunction of the microcirculation and the subsequent or concomitant malfunction of cells and organelles responsible for energy production. The microcirculation is now considered the battlefield of shock pathophysiology. It has become apparent that an improvement of macrocirculatory parameters alone, without restoring the microcirculation, is insufficient in the battle against circulatory shock and the end-organ damage and high mortality that it causes in critically ill patients. [51]

2.1.2 CARDIOVASCULAR SYSTEM

In a simplified model, the hemodynamic system constitutes the pump, represented by the heart, the plumbing, represented by the vasculature, and the fluid being pumped, represented by the blood in the vessels.

The human heart works as a double pump surrounded by a common lining, the pericardium. It comprises four separate chambers, namely the left atrium and ventricle and the right atrium and ventricle. Systole stands for the phase of contraction of the ventricles, while diastole stands for the phase of filling of the ventricles, during which the atria contract to enhance ventricular filling.[52] The pericardium renders the different chambers of the heart dependent on each other; the filling of the right ventricle impedes the filling of the left ventricle and vice versa. Moreover, the left ventricle receives the blood that the right ventricle has ejected a few heartbeats earlier, defined as series interdependence of the ventricles (parallel and series interventricular interdependence).[53-55]

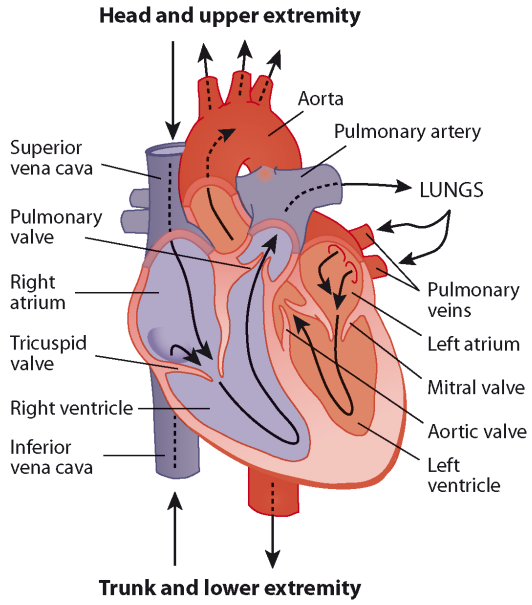


Figure 2. Structure and blood flow of the heart. Modified from Hall JE, Guyton AC. Guyton and Hall Textbook of Medical Physiology, 2011, with permission by Elsevier. [52]

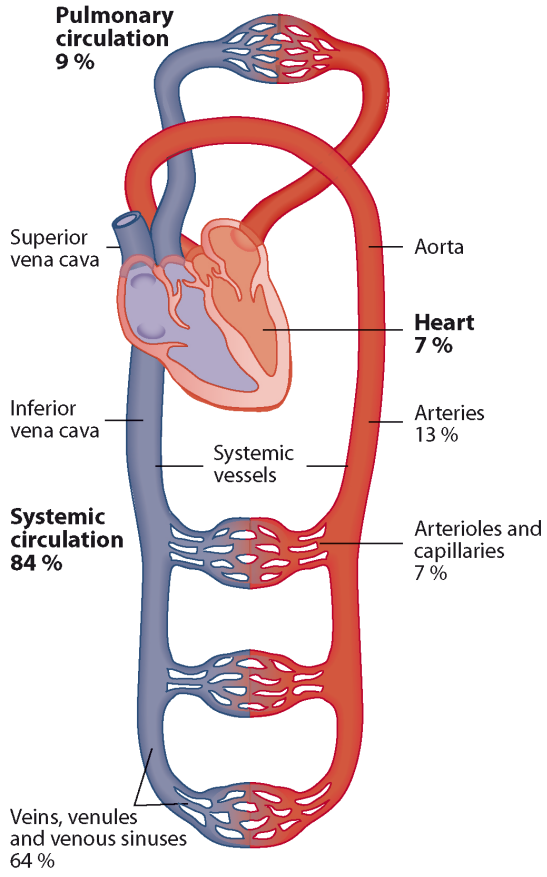


Figure 3. Distribution of blood in different parts of the circulatory system. Modified from Hall JE, Guyton AC. Guyton and Hall Textbook of Medical Physiology, 2011, with permission by Elsevier. [52]

The systemic and pulmonary circulation can be described in a simplified manner as follows: The left atrium receives oxygenated blood from the lungs through the pulmonary veins. The blood then enters the left ventricle, from where it is ejected into the aorta, and from there it is further directed into the arteries of the systemic circulation. The arteries then gradually branch and narrow into smaller arteries, or arterioles, as they further branch into the capillary system. The capillaries, which are the smallest vessels in the body, are responsible for the microcirculation and the perfusion of the tissues. After perfusion of the tissues, the capillaries join to form venules, which further join into larger veins. Finally, the veins join the inferior or superior vena cava, which transports the deoxygenated blood into the right atrium. From the right atrium, the blood is transported into the right ventricle, from where it is ejected into the pulmonary arteries of the lungs. In the lungs, the blood is re-oxygenated during its passage through the alveolar vessels and then returned to the left atrium. [52]

2.1.3 MACROVASCULAR HEMODYNAMICS – PHYSIOLOGY OF VENOUS RETURN AND CARDIAC FUNCTION

In terms of physiology, the mechanism of the left ventricle can be depicted by the cardiac function curve, which describes the amount of blood ejected by the left ventricle into the systemic circulation (cardiac output) relative to the amount of blood it has received from the venous flow in terms of right atrial pressure (preload). [52,55] It is loosely related to the Frank-Starling law of the heart, which states that: ”in normal hearts, diastolic volume is the principal force that governs the strength of ventricular contraction”. Cardiac output (CO) is the term used to describe the amount of blood that the heart pumps into the vasculature during one minute. The slope of the cardiac function curve may vary according to the contractile function of the left ventricle. The cardiac function curve of a heart with depressed contractility is less steep than that of the normal heart. For every increase in preload, there is a lesser increase in cardiac output than for the normal heart. [52,53,55]

Likewise, the return of the deoxygenated blood to the right atrium may be described by the *venous return curve*. The venous return curve depicts the flow of venous return in relation to the pressure in the right atrium. The slope of the venous return curve is also affected by the resistance to venous return. Over time the cardiac output must equal the venous return and vice versa, as the heart can only eject what it receives. [53,55-57] The driving force of the venous return is the mean systemic filling pressure, which is the pressure measured in the vessels of the cardiovascular system when pumping of the blood by the heart has ceased and there is no flow through the vessels. The mean systemic filling pressure cannot therefore normally be measured at bedside. The venous system has a high compliance and capacitance (distensibility) compared with the arterial system. Approximately 70% of the blood volume is located in the venous system. Most of the blood forms the unstressed volume, which is defined as the blood volume that fills the veins, without causing tension to the vessel walls. The stressed volume is the part of the blood volume that resides in the veins, causing wall tension and thus building up the mean circulatory filling pressure driving the venous return towards the heart, as shown in

Figure 4 a. [53,55] The combination of the cardiac function curve and the venous return curve can be used to describe the physiology of the cardiovascular system. The cross-section of the two curves indicates the operating point for the cardiovascular system (Figure 4 b). [55]

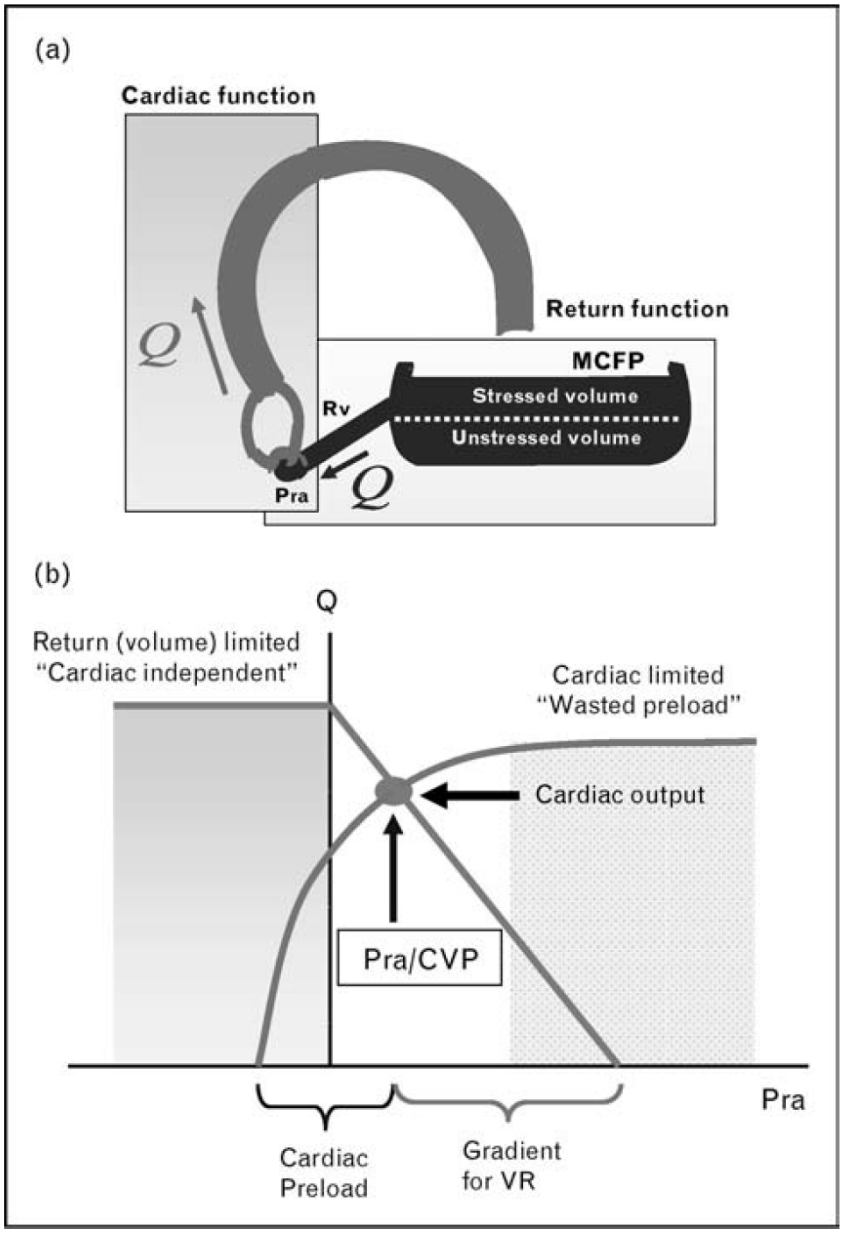


Figure 4. Venous return function and cardiac function. Q: flow, Rv: resistance to venous return, Pra: right atrial pressure, MCFP: mean circulatory filling pressure, VR= venous return. Permission granted by Wolters Kluwer Health. S.Magder, Fluid status and fluid responsiveness, Current Opinion in Critical Care, 16:4, p. 290, 2010. [60]

2.1.4. MICROVASCULAR FUNCTION AND TISSUE PERFUSION

The task of the microcirculation is to perform the final steps of the transport of oxygen from the vessels to the cells. The microcirculation is strategically placed at the interface between the circulatory system (supplier) and the parenchymal cells (consumers). The microvessels, or the capillaries, are the narrowest and most distal of the vessels in the cardiovascular system. Each cell of the parenchymal tissues is situated in close vicinity to at least one capillary, so that passive diffusion can ensure an efficient supply of oxygen to the cell. Due to high permeability of arteriolar walls to oxygen, arterioles also represent a major source of oxygen to tissues of low blood flow. [58]

Ultimately, the oxygen is transported into the cells, and further into the mitochondria, located in the nuclei of the cells, where it is consumed in energy production processes. Integrity of this chain of events is essential for normal function of the tissues. When energy requests of the cells are not met, energy failure follows. Cells may then attempt to adapt to the situation, but if adaptation fails, apoptosis or necrosis of the cells will follow, resulting in end-organ damage. [46,59]

2.2 CLASSIFICATION OF HEMODYNAMIC FAILURE

The definition of hemodynamic failure is based on the mechanism or the specific part of the cardiovascular system that is most severely affected. The basis for the classification of types of hemodynamic failure, or more commonly, types of shock, was first proposed by Weil and Shubin in 1968 and further developed and abbreviated by Weil and Shubin in 1971. [46,61,62] The four categorical states of shock are *1) hypovolemic shock, 2) cardiogenic shock, 3) obstructive shock, and 4) distributive shock*. Clinically, hemodynamic failure may possess features of more than one of the four main types. [49] Patients with distributive shock caused by sepsis may also have depressed myocardial contractility, which is characteristic of cardiogenic shock, or they may have intravascular fluid loss, which is associated with hypovolemic shock. [49,63]

For better understanding of the classification of shock types, the mechanisms responsible for the instability of the cardiovascular system can be divided into eight main mechanisms or sites of dysfunction as proposed by Weil: [49,62,63]

1) Preload or venous return
2) Cardiac function, contractility, and rhythm
3) Afterload or arteriolar resistance to flow
4) Capillary exchange, substrate exchange, and fluid shifts
5) Venular resistance control of capillary hydrostatic pressure
6) Arteriovenous shunt
7) Venous capacitance
8) Mainstream patency

2.2.1. HYPOVOLEMIC SHOCK

Hypovolemic shock is probably the most frequent type of hemodynamic failure caused by a decrease in venous return. [64] Hypovolemic shock is caused by a critical reduction of the intravascular volume by blood loss (hemorrhage) or other fluid losses such as losses from the gastrointestinal tract due to diarrhea or vomiting, or inflammatory fluid losses into bodily cavities due to trauma or infection. It may also be caused by surface fluid losses due to burns, by failure of fluid intake, or by endocrinological disturbances such as diabetes insipidus. [49,65]

Hypovolemia causes shock by decreasing primarily the stressed, but eventually also the unstressed volume, leading to a decrease in venous return. The decrease in venous return subsequently decreases cardiac output, as a consequence of the decrease in cardiac preload. [57]

Fluid losses activate the sympathetic system, which increases the release of catecholamines. This may temporarily compensate for lesser volume losses by causing venoconstriction and thus increasing the stressed blood volume and venous return. However, when losses exceed 40% of the blood volume, most patients will develop hypotension. When the compensatory threshold is reached, the decrease in venous return and cardiac output will lead to manifestations of frank shock. [57,64]

2.2.2. CARDIOGENIC SHOCK

In cardiogenic shock, cardiac failure causes end-organ hypoperfusion. [66] Cardiogenic shock may be caused by a variety of cardiac mechanisms that lead to the fairly rapid deterioration of the pumping function of the heart, ultimately resulting in a decrease in cardiac output and shock. [64,65] Microcirculatory, neurohumoral, and cytokine factors are also involved in the development of this entity of shock. [66]

The most common cause of cardiogenic shock is myocardial ischemia or infarction, usually within 24 hours of the primary insult. [67] The loss of approximately 40% or more of the ventricular muscle mass due to infarction frequently leads to cardiogenic shock.[65,68] Cardiogenic shock may also be caused by a variety of mechanical complications of myocardial infarction such as rupture of the ventricular free wall, septum, or papillary muscles. [66] Other causes of myocardial dysfunction and cardiogenic shock include acute myopericarditis, tako-tsubo cardiomyopathy, or hypertrophic cardiomyopathy. [66]

Valvular dysfunction may cause cardiogenic shock either by impeding the ejection of the ventricle (stenosis) or by regurgitation due to valvular insufficiency. Most frequently, the cause of valvular cardiogenic shock is acute mitral valve regurgitation due to rupture or malfunction of the chordae tendinae or papillary muscles as a complication of myocardial infarction. [64-66]

Tachyarrhythmias or bradyarrythmias may also cause cardiogenic shock. These dysrhythmias, of which tachyarrythmias of ventricular origin are the most ominous, may often be consequences of underlying systemic or cardiac causes. A thorough clinical examination is essential for detecting possible underlying causes such as myocardial ischemia and metabolic disturbances. [69] Anti-arrythmogenic therapy often fails if the underlying cause is left untreated. [64]

Finally, cardiogenic shock may also be due to deterioration of left ventricular diastolic function. Diastolic dysfunction is more difficult to assess than systolic function. Derangements in relaxation and compliance likely contribute to many if not all cases of cardiogenic shock. Diastolic dysfunction may lead to shock through failure to receive and consequently eject the required cardiac output. [66]

2.2.3 OBSTRUCTIVE SHOCK

Obstructive shock is characterized by a mainstream obstruction to flow, which leads to a reduction of cardiac output. [49,63,64] Cardiac tamponade, pneumothorax, and massive pulmonary embolism cause obstruction to venous return by increasing right atrial pressure or right ventricular afterload. [57,70] Obstructive shock may also be caused by a thrombus of a artificial heart valve or dissection of the aorta by obstructing outflow from the (left) ventricle. In the early phases, obstructive shock may be difficult to distinguish from cardiogenic shock. Some of the subtypes of obstructive shock may also possess features of obstructive as well as cardiogenic shock (cardiac tamponade). [64]

2.2.4 DISTRIBUTIVE SHOCK

Distributive shock can be defined as any physiological condition that results in maldistribution of blood flow (arterial, capillary, and venous) in the absence of primary cardiac dysfunction. [64] Distributive shock accounts for an array of different conditions, all of which lead to a common hemodynamic picture. The classical hemodynamic pattern in distributive shock is that of high cardiac output and systemic hypotension. [64,65] Although septic shock is the most common type of distributive shock, a similar hemodynamic profile may be caused by non-infectious conditions, such as anaphylaxis, spinal cord injury, drug-induced expansion of the venous capacitance beds, or decreased arteriolar resistance, and by severe forms of liver dysfunction. [46,65] It may also be caused by rare systemic diseases such as capillary leak syndrome. [71] Contrary to the three other forms of shock, distributive shock is usually, especially in the early stages, characterized by normal or increased cardiac output. [65]

Neurogenic shock results from upper thoracic spinal cord injury and subsequent loss of sympathetic vascular tone. It manifests as hypotension and bradycardia, with warm dry skin. Patients with neurogenic shock show symptoms of hypovolemia as a result of vasodilation, while actually being euvolemic. [65]

Anaphylactic shock is a form of distributive shock in which vasodilation, hypotension, and redistribution of blood flow is caused mainly by the liberation of histamine in response to medication, insect bites and stings, blood products, or food allergies. [64] As a reaction to allergens, through mechanisms of antigen-antibody binding, mast cells liberate cytotoxic substances, such as histamine and leukotrienes, which affect the heart, circulation, and peripheral tissues. The permeability of the endothelium is markedly increased, leading to extravasation of fluid and proteins to the extravascular space. In rare cases, anaphylactic reactions also lead to depression of cardiac contractility. [64,65,72]

Septic shock is defined as hypotension induced by sepsis, which persists despite adequate fluid resuscitation. [73] It is one of the major challenges for physicians working in the ICU because of its complexity, high incidence, and high mortality. Though great advances have been made during recent years in elucidating the complex nature and

pathophysiology of septic shock, many questions remain unanswered. [74] In septic shock, inflammatory mediators, including cytokines, cause vasodilation, but also concomitant vasoconstriction. Some mediators cause myocardial depression, but despite this effect, cardiac output is usually increased. Activated leukocytes and platelets cause obstruction of the microvasculature, which leads to loss of autoregulatory functions of peripheral tissues and a mismatch between oxygen supply and demand. [63] It has been stated that the main pathophysiologic feature of septic shock is the maldistribution of blood flow and shunting of oxygen supply to the tissues. [64,75]

2.3 PATHOPHYSIOLOGY OF CIRCULATORY SHOCK

Derangements in one or many of the components of the circulatory system may ultimately lead to the development of shock. The division of shock types into the four main types is performed based on the principal underlying mechanisms for development of shock. [49,62,76,77]

The intravascular volume, the heart, and the resistance circuit constitute three important mechanisms in which alterations may lead to the development of circulatory shock. The intravascular circulating volume is essential for regulation of blood pressure and venous return. The heart regulates cardiac output by changes in contractility, heart rate, and loading conditions. The resistance circuit is responsible for increases and decreases in vascular resistance, alterations in cardiac load conditions, blood pressure, and distribution of blood flow. Heterogeneity of arteriolar tone between different organs causes maldistribution of blood flow and local mismatch between oxygen demand and supply. [49,62,76] The fourth and fifth components are the capillaries and the venules. Alterations in the permeability or cross-section of the capillaries may cause severe impairment of tissue oxygenation. Bypass of capillaries by opening of arteriovenous shunts contributes to tissue hypoxia during shock. [49,76] The venules are most prone to occlusion during changes in rheology. Increases in venular tone may then lead to increased extravasation in the capillary network. [49,76] The venous capacitance circuit, in which 70–80% of the total blood volume resides, is the sixth component. A decrease in venous tone leads to impairment of venous return, while an increase in venous tone leads to enhancement of venous return. Mainstream patency forms the last component. Obstruction to both arterial and venous blood flow causes impediments to either ventricular ejection or venous return. [54,76]

In circulatory shock, the underlying diseases or causes may vary widely. [64] Derangements in any of the components of the circulatory system may lead to circulatory failure, which if its allowed to proceed without timely intervention, ultimately will lead to the common picture of shock. Changes in macrohemodynamics may lead to impaired microcirculatory perfusion of the tissues. [78] In certain types of shock, microvascular derangements seem to precede macrovascular alterations. [79] Derangements on the

microcirculatory level may persist despite stabilization of the macrocirculation. [80] Hence, changes in the microcirculation seem to be of even greater importance in the development of failure of tissue oxygenation than changes in the macrocirculation. [51]

For a more detailed description of the different underlying pathophysiologies, the four main categorical types of shock may be further divided into two categories, hypodynamic shock (cardiogenic, obstructive, and hypovolemic) and hyperdynamic shock, due to pathophysiological similarities. [76] Vasodilatory shock is a final common pathway of long-lasting and severe shock of many causes. [81]

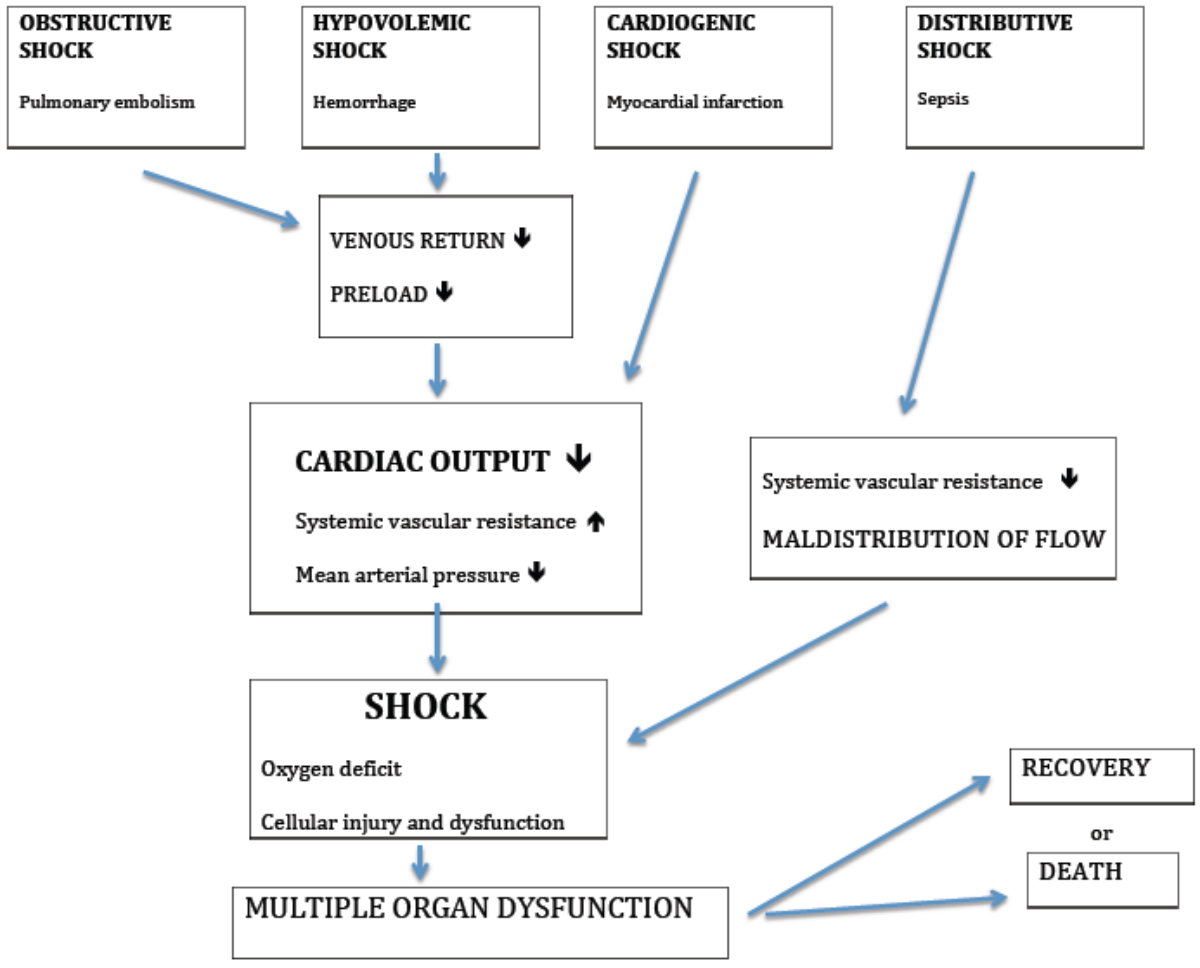


Figure 5. Common pathway of shock.

2.3.1. PATHOPHYSIOLOGY OF HYPODYNAMIC SHOCK

The central features of hypodynamic shock are low cardiac output and vasoconstriction.

When tissue perfusion is reduced to a critical level because of a reduction in cardiac output due to loss of blood volume, loss of pump function, or obstructed flow, a set of compensatory reflexes is elicited. The sympathetic system is activated to compensate for the reduced tissue perfusion, increasing heart rate and contractility. As a result, catecholamines, angiotensin, vasopressin, and endothelins are released. [76,82] These substances cause vasoconstriction, shifting the blood from the capacitance circuit (unstressed volume) to the central circulation (stressed volume), thereby causing a (temporary) compensatory increase in venous return. [76] Blood flow is directed away from muscles and the splanchnic area towards the brain and the heart. Water and sodium retention is enhanced by release of vasopressin and activation of the renin-angiotensin system.

As the shock state worsens, blood pressure decreases further and coronary perfusion is impeded, compromising cardiac function. As vasoconstriction increases further, the weakened myocardium encounters yet another increase in afterload, further impairing cardiac function. The terminal phases of shock are characterized by an increase in microvascular permeability due to changes in capillary hydrostatic pressure. Leukocytes adhere to the endothelial walls and concomitant changes in red blood cell rheology facilitate platelet adhesion. This chain of events ultimately leads to the blocking of capillary beds and progression of tissue hypoxemia. The process is accelerated by the release of systemic mediators of inflammation. Upon progression of the cascade of shock to this point of “no-reflow” and end-organ damage, irreversible hypoperfusion, hypotension, and death will inevitably follow. [64,76,82]

2.3.2 PATHOPHYSIOLOGY OF HYPERDYNAMIC SHOCK

The central features of hyperdynamic shock are high cardiac output (CO) and vasodilation, with derangements in microcirculation and oxygen utilization.

Hyperdynamic shock, particularly septic shock, is characterized by the release of inflammatory mediators in the bloodstream in reaction to exogenous agents. This profoundly complex pro-inflammatory cascade is triggered by severe microbial infection or extensive tissue damage. Activation of the complement system and hyperactivation of the cellular innate immune system lead to an excessive inflammatory response. Neutrophils and macrophages then react to the initial inflammatory stimuli of released cytokines, such as interleukin-1β, interleukin-6, tumor necrosis factor- α (TNF-α), interferon-γ, chemokines, and complement activation products, resulting in the release of secondary mediators (lipid factors and reactive oxygen species). [76,83,84] This complex cascade leads to arterial and venous vasodilation and a concomitant increase in cardiac output. The influence of vasodilatory substances, such as nitric oxide (NO), predominates

over endogenous and exogenous vasopressor agents. Vasodilation may also be enhanced by inappropriately low levels of vasopressin or cortisol, producing vascular hyporesponsiveness to catecholamines. [81,85] Limitations of nutrient flow develop as a result of blocking of the capillaries due to adhesion of activated leukocytes and platelets to the endothelium, in interplay with the activated coagulation cascade. The terminal phase of hyperdynamic shock is characterized by refractory hypotension, worsening tissue hypoperfusion, acidosis, and hypodynamic circulation. [76]

2.3.3 PATHOGENESIS OF VASODILATORY SHOCK

In septic shock, as well as in prolonged and severe hypotension caused by cardiogenic or hemorrhagic shock, the clinical picture is dominated by excess vasodilation. [81]

Despite differences in the mechanisms of vasodilation depending on the underlying condition, some important common mechanisms exist. Vasoconstriction requires the binding of a ligand, such as angiotensin or norepinephrine, to the surface receptors of the vascular smooth muscle cell. [76,81,82] Through actions of second messengers, calcium is released from intracellular stores and the calcium level in the cytosol is increased. Calcium then binds to calmodulin, which activates a kinase that phosphorylates myosin. This enables activation of myosin ATPase by actin and subsequent contraction of the smooth muscle. Vasodilators, such as nitric oxide (NO), lead to the dephosphorylation of myosin, thus preventing contraction. [81]

The membrane potential and more specifically the ion transporters and channels of the plasma membrane of the muscle cells also play a crucial role in vasodilation and vasoconstriction. Hyperpolarization of the plasma membrane prevents calcium influx and constriction. The K_{ATP}-channels allow efflux of potassium, thus depolarizing the membrane. Pharmacologic activation of these channels therefore inhibits vasoconstriction. These channels are activated by low cellular energy levels (ATP) and high levels of H^+ and lactate under physiological conditions, thus connecting metabolism with vasodilation and blood flow. [81]

Increased synthesis of NO contributes to vasodilation and hyporesponsiveness to vasopressors in vasodilatory shock. In septic and decompensated hemorrhagic shock, the production of NO is increased due to inducible nitric oxide synthases (iNOS). The vasodilating effect of NO is probably mainly mediated through the activation of myosin light-chain phosphatase. Resistance to vasopressor agents is mostly a consequence of NO-induced activation of calcium-sensitive potassium channels, leading to hyperpolarization of the plasma membrane in smooth muscle cells. [81,86]

Vasopressin levels rise in septic and hemorrhagic shock as a consequence of baroreflex activation. Normally vasopressin plays only a minor role in arterial pressure regulation, but during hypotension and shock it is released from the neurohypophysis. As shock worsens, vasopressin levels decrease, however, probably due to depletion of vasopressin

stores in reaction to massive stimulation. Correction of these inappropriately low levels of vasopressin raises blood pressure in patients with hemorrhagic and septic shock, as well as in organ donors and patients who have suffered from cardiac arrest and are refractory to vasopressor treatment. [81,87]

2.3.4 MICROCIRCULATORY CHANGES DURING SHOCK

The main prerequisite for adequate tissue oxygenation and end-organ function is preserved microcirculatory function. [79,88] The microcirculation consists of the smallest blood vessels in the body, with a diameter of 100 μm or less, and its main purpose is to transport oxygen and nutrients to the cells. The microcirculation is regulated by myogenic, metabolic, and neurohumoral mechanisms. During sepsis severe derangements of these regulatory mechanisms occur. [79,88]

A main feature of the pathogenesis of distributive shock is shunting of oxygen transport to the tissues. [79] Septic microcirculatory dysfunction is characterized by a heterogeneity of capillary blood flow. Some capillaries are underperfused, while others are normoperfused. [89] Vulnerable microcirculatory units become hypoxic, and the partial pressure of oxygen drops below the level of venous blood. This gap in oxygen tension is more severe in sepsis than in hemorrhagic shock and cannot be measured by monitoring parameters of systemic hemodynamics. [79] In sepsis and distributive shock, signal transduction pathways are deranged. Incapability of endothelial cells to perform regulatory function follows. In addition, nitric oxide (NO) is produced by inducible nitric oxide synthases (iNOS), further aggravating the microvascular dysfunction by increased shunting of blood flow. Some areas express less iNOS, which renders these areas prone to hypoperfusion. [75] Abnormalities in the nitric oxide system are one of the key features of distributive shock. [90]

In addition to these changes, alterations in both erythrocytes and leukocytes occur. Erythrocytes become more rigid and undeformable, increasing the likelihood of aggregation. Leukocytes induce an array of inflammatory mechanisms by which they alter cellular interactions and coagulation as well as disrupt structures of microcirculation, ultimately leading to tissue edema. [79,88]

While the microcirculation seems to be the driving force in septic shock, experimental data reveal that in hemorrhagic shock microcirculation follows macrocirculation. [78] In hemorrhagic shock, microcirculatory variables were closely related to macrocirculatory parameters also during the resuscitation phase. Moreover, the microcirculation of the gut was found to be far more susceptible to blood loss than the heart. [78] In septic shock, parameters describing microcirculation have not been shown to improve despite successful restoration of macrocirculation. [80]

2.3.5 CHANGES IN OXIDATIVE METABOLISM DURING SHOCK

When global distribution of blood flow is decreased or there is regional maldistribution of blood flow at the macrovascular or microvascular level, impairment of oxidative metabolism follows. Though oxygen consumption may be increased in the initial phases of shock, all types of shock eventually lead to a decrease in oxygen consumption. Data from experimental studies, some of which were conducted nearly half a century ago, show that adverse outcome was directly related to the degree of total accumulated oxygen debt. [76,91]

In normal circumstances, oxygen consumption (VO_2) is independent of oxygen delivery (DO_2). During a decrease in cardiac output a compensatory increase in oxygen extraction from a normal level of 25% to a maximum level of 80% takes place and oxygen consumption remains unaltered. When oxygen extraction is maximized, a critical level of DO_2 is reached, below which VO_2 is totally dependent on DO_2. Further decreases in DO_2 lead to decreases in VO_2 and a need for anaerobic metabolism. [76,92] In critical illness, alterations caused by medication or septic changes in vasomotor reflexes lead to critical tissue hypoxia at lower levels than during normal physiological conditions. [76]

During tissue hypoxia there is a deficit of oxygen, which is mandatory for oxidative phosphorylation in the mitochondria. In anaerobic conditions, cells have to manage on two molecules of adenosine triphosphate (ATP) per molecule of glucose generated during glycolysis in the cytoplasm, in contrast to the 38 molecules of ATP generated under aerobic conditions. Also under anaerobic conditions, pyruvate cannot enter the citric acid cycle. Instead it is turned into lactate, which cumulates as a sign of deficits in cellular energy metabolism. [46,76]

In addition to the mechanisms elicited by decreases in blood flow, other mechanisms are responsible for worsening of oxidative metabolism. Several inflammatory mediators, such as NO, endotoxin, oxygen radicals, and tumor necrosis factor-α (TNF-α), impair mitochondrial function, as shown in animal studies of septic shock and reperfusion injury. [93] Serum from patients with septic shock has been demonstrated to inhibit mitochondrial respiration in experimental studies. [94] Secondary to a period of cellular dysoxia due to microvascular derangements, mitochondrial function becomes impaired. It is not clear whether this phenomenon is reversible, but if so it is assumed that the reversibility is time-dependent. This impairment of both the microcirculatory and mitochondrial functions has been defined as the microcirculatory and mitochondrial dysfunction syndrome (MMDS). [79]

2.4 EPIDEMIOLOGY AND INCIDENCE OF HEMODYNAMIC FAILURE IN CRITICAL ILLNESS

2.4.1 EPIDEMIOLOGY AND INCIDENCE OF HEMODYNAMIC FAILURE IN THE CRITICALLY ILL

Hemodynamic failure is frequently encountered in critically ill patients. [48] Few studies have, however, assessed the overall incidence of hemodynamic failure in critically ill patients. The overall incidence of shock was 33.6% in a large study comprising 198 European intensive care units (ICUs). [95] Of these patients, 80% received norepinephrine for hemodynamic support. In this large European multicenter study (SOAP), 36% of patients without sepsis and 63% with sepsis had hemodynamic failure. In 8% versus 14% of these patients hemodynamic failure presented as a single, isolated organ failure. Of a total of 3147 patients, 462 (15%) were diagnosed with septic shock. [95,96]
In the large multicenter prospective study by Vincent and collaborators exploring the usefulness of SOFA score for assessing organ dysfunction and failure, the association between organ dysfunction and outcome was evaluated. The study was conducted in 40 ICUs located in 13 European countries, in addition to Brazil, Canada, and Australia in the late 1990s. For a total of 1449 patients with a variety of indications for admission, including elective surgery, the subscore for cardiovascular organ dysfunction was assessed as part of the total SOFA score. The cardiovascular subscore was elevated, indicating some degree of hemodynamic failure at the time of admission of 29% of the patients. [97]

2.4.2 EPIDEMIOLOGY AND INCIDENCE OF SEPTIC SHOCK

In previous epidemiological studies of sepsis, severe sepsis, and septic shock, the occurrence of septic shock in patients diagnosed with severe sepsis has ranged from 46% to 77%. [98,99] In the Finnsepsis study, which was conducted in 24 Finnish ICUs during four months in 2005, the total incidence of severe sepsis was 0.38/1000 in the adult Finnish population. During the study period 470 patients of a total of 4500 consecutive ICU admissions had severe sepsis and 77% of these developed septic shock. [10,100] In a prospective observational study comprising 24 Italian ICUs, the incidence of septic shock was 33% in patients with sepsis and approximately 4% in the total ICU patient population. [98] In these studies, the main sources of infection were the lungs, abdomen, skin or soft tissue, and the urinary tract. [10,98]

2.4.3 EPIDEMIOLOGY AND INCIDENCE OF OTHER TYPES OF SHOCK IN THE CRITICALLY ILL

Hemorrhagic shock continues to be a leading cause of mortality, accounting for 30-40% of trauma-related deaths. Trauma is the leading cause of death in patients younger than 45 years in the USA. [101] Of all deaths caused by injury, 50% occur at the site of the accident, 30% during the first 24 hours, and 20% later due to multiple organ dysfunction (MOD). [101] Exact data on the incidence of hemorrhagic shock in patients admitted to hospital due to hemorrhage are, however, scarce. In a study from a trauma center in San Diego, hypovolemic shock was present in 13.1% of the 466 patients who had not received cardiopulmonary resuscitation prior to hospital admission. [102] Even after initial survival, patients suffering from hypotension due to hemorrhagic shock are at risk for acidosis, sepsis, and multi-organ dysfunction. [103]

The incidence of cardiogenic shock in Finland has not been studied. [104] The incidence of cardiogenic shock in the United States is approximately 40 000 to 50 000 cases per year. [66] Cardiogenic shock complicates approximately 5-8% of ST-elevation myocardial infarctions (STEMI), which are the leading cause for cardiogenic shock. In recent years, the prevalence has decreased due to early intervention and reperfusion therapies. [66,105]

In a Chinese study assessing the incidence of organ failure associated with severe acute pancreatitis (SAP), cardiovascular failure as a single organ failure or as part of a multiple organ failure was reported in 18% of the patients. [39] In the Finnish study by Halonen and collaborators, 80% of SAP patients managed in ICUs showed at least some degree of hemodynamic compromise, deduced from elevated cardiovascular SOFA scores during their ICU stay. [106]

2.5 ORGAN MANIFESTATIONS IN SHOCK

Hemodynamic failure or shock itself is often defined as an organ failure. Several of the severity scoring systems that are utilized in critical care have a subscore for describing cardiovascular function. [97,107,108] Higher scores have been associated with worse outcome in ICU patients. [97,108-110] The development of organ failure in association with hemodynamic failure has been most extensively studied in hemorrhagic and septic shock. The association of hypoperfusion with organ failure or postoperative complications has also been assessed. [111,112]

2.5.1 KIDNEY

When assessing a patient in shock, urine output provides a means of looking at the circulation. [63] Persisting but not transient oliguria is predictive of development of new acute kidney failure, especially in the face of increasing vasopressor requirements and hemodynamic instability. [113] The pathophysiology of AKI during shock is, however, somewhat unclear. The mechanisms leading to injury have mainly been studied in experimental animal models or through indirect evaluation of kidney function, as repetitive renal biopsies of critically ill patients would not be ethically justifiable. [114] Studies of hypodynamic shock (hypovolemic, hemorrhagic, and cardogenic shock) have suggested that a deterioration of renal perfusion, leading to ischemia and subsequent re-perfusion injury, is the main pathophysiological mechanism responsible for the development of AKI during hemodynamic failure.[114,115] This also holds true for postoperative AKI, which predominantly is considered to be a consequence of transient or persisting renal ischemia. [116] Complete renal ischemia and re-perfusion have clearly been associated with AKI in clinical and experimental studies.[115] Somewhat contradictorily, temporary occlusion of the renal artery or global ischemia caused by cardiac arrest has only been shown to cause transient changes in renal function. [117,118]

Acute kidney injury due to septic shock seems to evolve in a slightly different setting. Results from experimental studies concerning renal blood flow during septic shock have been inconsistent. In a systematic review of 160 experimental studies of AKI in sepsis, renal blood flow was increased in about 30% of the studies, and the only predictor of low renal flow was low cardiac output. [119] Evidence exists that auto-regulation of renal blood flow is impaired in critical illness before and during AKI, rendering renal blood flow dependent on cardiac output. During hyperdynamic sepsis AKI may develop in a setting of high renal blood flow. [119,120] In an experimental study of conscious sheep, Langenberg and coworkers showed that the development of AKI during septic shock is associated with an increase in renal blood flow and a decrease in vascular resistance, which subsequently leads to a marked decrease in glomerular filtration and an increase in serum creatinine. [121] Data from another experimental study implied that renal recovery was associated with a decrease in cardiac output, an increase in vascular resistance, and a decrease in renal blood flow. [122] Based on experimental data, it seems that AKI associated with septic shock may be of hyperemic origin. [114,121,122] Dilation of afferent arterioles and a more pronounced

dilation of efferent arterioles of the kidney lead to an increase in blood flow, with a concomitant decrease in glomerular filtration rate. [114]

Recent evidence suggests, however, that the development of AKI during shock is not only a question of blood flow and perfusion. Some evidence has emerged that AKI develops due to inflammatory derangements in the microcirculation, with subsequent capillary leak and intrarenal shunting, and that pro-inflammatory cytokines and NO play an important role in this process. [115,123,124] The decrease in blood flow and renal perfusion may not be a prerequisite for but rather the consequence of a complex cascade of inflammatory and microvascular events taking place during the early phases of AKI. [115]
To further complicate the issue of hemodynamics and AKI, treatment and prevention of this frequent phenomenon in the critically ill still rely on optimal restoration of macrohemodynamics and accurate fluid restoration. [115,125] Evidence exists that an increase in systemic blood pressure increases glomerular filtration. [44] There is also some evidence from studies of septic AKI that lower blood pressure levels are associated with development or progression of AKI. [126,127]

2.5.2 BRAIN

Several neuropathological alterations take place during shock. [128,129] Changes in consciousness and mentation are common clinical findings in all types of shock. These changes provide the clinician with another means of looking at the circulation. [63] Cerebral oxygen function accounts for approximately 20% of total resting body oxygen consumption. The high metabolic demand must be met, and as the brain is unable to store energy, high blood flow is required. Cerebral blood flow accounts for about 20% of the total cardiac output, of which 90% is needed for brain function and 10% for cell viability.[129] Under physiological circumstances, the mechanisms of cerebral autoregulation are able to maintain a relatively constant cerebral blood flow within a range of mean arterial pressure (MAP) from 60 to 150 mmHg. [129] There is evidence, however, that critical illness and sympathetic activation impair autoregulation, and cerebral blood flow becomes dependent on systemic blood flow also within the normal ranges of autoregulation. In an experimental model of anaphylactic shock in rats, Davidson and collaborators found that cerebral blood flow decreased linearly with a decrease in MAP, thus impeding cerebral oxygenation. The decrease in cerebral flow was moreover not fully corrected by volume expansion. In an experimental study in sheep with septic shock, the findings were similar, indicating severe impairment of cerebral blood flow and microcirculatory derangement, especially in the early stages of shock. [130] The findings of two earlier experimental animal studies of hemorrhagic and cardiogenic shock, on the other hand, indicated preserved cerebral perfusion under these conditions.[131,132]

The differences in preservation of cerebral flow may be accounted for by the different inflammatory profiles of the different shock types. [133] In a canine experimental study of cardiac arrest, the microcirculation was severely altered after restoration of spontaneous circulation and did not correlate with macrohemodynamic measurements. [134] There are

also data from studies in patients with septic shock that vasomotor reactivity is disturbed during septic shock, causing detrimental changes in microcirculation and perfusion. [135] These alterations in cerebral blood flow and microcirculation have been proposed to be attributable to septic encephalopathy (SAE), a diffuse form of cerebral dysfunction, often encountered in critically ill patients.[128,135] The neuropathological correlates of septic encephalopathy have not been extensively investigated. [136] In a study by Sharshar and coworkers focusing on the neuropathology of patients who had died of septic shock, signs of ischemia were present in all patients. It was more pronounced in autonomic centers in patients with septic shock than in patients who had died of other causes and was more often associated with apoptosis. Also, in these patients, levels of intravascular iNOS were significantly higher than in other patients, while levels of TNF-α did not differ. [136,137] In a recent study, magnetic resonance imaging revealed high incidences of leukoencephalopathy and ischemia in patients with septic shock. These findings were associated with adverse outcome. [138]

2.5.3 GUT, LIVER, AND PANCREAS

"Shock bowel", or "hypoperfusion complex", is a term used to describe findings in abdominal computed tomography scans of patients in severe hypovolemic shock, often due to trauma and hemorrhage.[139] The "hypoperfusion complex" entails abnormally intense contrast enhancement of the bowel wall, mesentery, kidneys, and pancreas; decreased caliber of the abdominal aorta and inferior vena cava; and moderate to large peritoneal fluid collections. This entity was first presented by Taylor and collaborators in the late 1980s and was associated with poor outcome. [140] The intestinal mucosa is affected during hemorrhagic shock, resulting in significant local inflammation, damage of the enterocytes and the gut barrier function, and translocation of mediators and pathogens from the gut lumen to the surrounding tissues. [103] The intestine has been suggested to play a central role in the development of shock by being a primary source of inflammatory mediators. [141] An experimental animal study revealed that inflammatory mediators are secreted into the gut lumen during hemorrhagic shock, where they interact with the endothelial cells in a paracrine fashion. [103] During ischemia or reduced integrity of the gut wall pancreatic enzymes may penetrate the gut and become systemic, triggering circulatory shock. [142]

In an animal study of intestinal microcirculation during hemorrhage, microcirculatory flow decreased proportionly to the decrease in systemic flow in the gastric and colon mucosa as well as in the liver and the kidney. However, the pancreatic flow decreased more than the systemic blood flow, implying that the pancreas is particularly susceptible to hemodynamic failure. [143] Earlier studies indicate that splanchnic hypoperfusion during shock, or hypoperfusion during cardiac bypass operations, may lead to pancreatitis. Pancreatitis is then further aggravated if hypoperfusion persists, as is the situation during postoperative low cardiac output. There is also evidence that temporary ischemia renders the pancreas more vulnerable to digestive enzymes.[18] If pancreatitis follows, hemodynamic failure may be further aggravated due to the release of inflammatory mediators. [144]

Ischemia during or after hemorrhagic shock may cause hepatic injury. The ischemic stress is plausibly mediated by an array of inflammatory mediators, leading to microcirculatory dysfunction, leukocyte infiltration, cell membrane damage, impaired biliary flow, and fibrosis. [145] Strong evidence indicates that cardiogenic shock or cardiac failure may cause hepatic injury through mechanisms of hypoperfusion. [146] Septic shock is also one of the most common etiologies for hepatocellular injury in the ICU. [147]

2.5.4 COAGULATION

In the pathogenesis of sepsis, inflammation and coagulation play crucial roles. Increasing evidence indicates that inflammation activates coagulation, and coagulation reciprocally affects inflammation. [148] The majority of critically ill patients with systemic inflammatory response have coagulation abnormalities, ranging from subtle, hardly detectable ones to fulminant disseminated intravascular coagulation (DIC). [148] During sepsis and septic shock several mechanisms contribute to alterations in coagulation. The most important underlying mechanism is thrombin formation mediated by tissue factor. [148,149] When the integrity of vessel walls is disrupted, or when circulating cells or endothelial cells are exposed to cytokines, most importantly IL-6, expression of tissue factor follows. Tissue factor then comes into contact with blood, leading to activation of the coagulation cascade. [148] During inflammation-induced activation of coagulation the three most important anticoagulant pathways may also be impaired. First, during severe inflammatory response, the antithrombin (AT) levels are markedly decreased, partly due to impaired synthesis. Second, the protein C system malfunctions at all levels. Third, the function of tissue factor pathway inhibitor (TFPI) seems to be impaired during severe inflammation, further aggravating the imbalance between coagulation and anticoagulation. [148,149]

In hemorrhagic shock, coagulopathy is closely linked to the underlying trauma and the trauma mechanism, and to the degree of blood loss and the subsequent fluid resuscitation. Tissue factor plays an important role also in activating coagulation due to trauma and blood loss by binding to factor VII, and thus, initiating the coagulation cascade. During hemorrhage, DIC may be caused by excessive formation of thrombin and fibrin concomitant with excessive consumption of platelets and coagulation factors. [150] It appears that hypoperfusion is essential for the development of coagulopathy during trauma and hemorrhage. Tissue injury induces thrombin formation, which in combination with shock-induced hypoperfusion results in increased activation of thrombomodulin (TM), leading to development of coagulopathy. The protein C system seems to play a role also in the development of coagulopathy during hemorrhagic shock by causing both impaired clot formation and enhanced lysis of the formed clot. [151] In traumatized patients with hemorrhagic shock, coagulopathy may also arise at a later stage. Factors that have been associated with coagulopathy at this later stage include acidosis, hypothermia, and excessive hemodilution. [150]

2.5.5 LUNG

In adult respiratory distress syndrome (ARDS) of inflammatory origin, the vascular endothelial cells play a pivotal role. These cells constitute a multifunctional monolayer of cells, which play an important part in regulating vascular tone, coagulation, and immune responses. In extrapulmonary injury, such as sepsis, trauma, and hemorrhage, activation of the endothelial cells leads to generation of reactive oxygen species and release of an array of inflammatory mediators, which cause increased vascular permeability and sequestration of neutrophils, ultimately leading to ARDS. [152]

There is now increasing evidence of the association of ARDS and multi-organ dysfunction (MOD) with the mesenteric lymphatic route during hemorrhagic shock. Patients who have been resuscitated from severe hemorrhagic shock often develop systemic inflammatory response syndrome (SIRS). These patients may develop ARDS and MOD, which may lead to death. Evidence now exists that the mesenteric lymphatic route is essential for the transport of factors that lead to distant organ injuries. Animal studies have shown that ligation of the mesenteric lymphatic duct can abrogate the progression of the organ injuries normally seen in post-hemorrhagic animals. [153,154]

2.5.6 HEART

In cardiogenic shock, failing pump function is a prerequisite for circulatory failure. [66,105,155] Cardiac function is often altered secondary to circulatory failure also in shock types of other origin.
Established hemorrhagic shock ultimately leads to anaerobic metabolism, ischemia, and frequently cardiac failure. [156] In hemorrhagic shock, the ischemic disorder is induced by impaired perfusion of organs due to hypovolemia. The disorder may be further aggravated by reperfusion injury as a consequence of blood transfusion and fluid therapy.[157] Organ injury is thought to be mediated by cytotoxic cytokines, lysosomal enzymes, and free radicals, which are released during prolonged ischemia and reperfusion. In addition, direct deleterious effects of lysosomal enzymes cause mitochondrial dysfunction, further impairing cardiac function. [157]

Increasing evidence is emerging for the gut playing a crucial role in the pathogenesis of SIRS and MOD following shock. Previously, bacterial translocation was considered essential for this process. Recently, however, it has been shown that non-bacterial factors from the intestine egress into the mesenteric lymph, leading to the development of post-shock organ failure. [154] The underlying mechanisms seem to involve the interaction of pancreatic enzymes with the ischemic gut. Interestingly, mesenteric lymph generated during burn injury causes changes in myocardial contractility. Astonishingly, cardiac contractile dysfunction was prevented by mesenteric lymph duct ligation in rats subjected to hemorrhagic shock. [154]

One of the key findings of myocardial dysfunction in septic shock came from the group of Parrillo in 1984. [158] The classic study by Parker and coworkers showed that 15 of 20

patients with septic shock had depression of the left ventricle in terms of left ventricular ejection fraction (LVEF) during the first two days. All 20 patients had high CO and low systemic vascular resistance (SVR). The most interesting finding was that survivors had low LVEF for four days, after which it slowly returned to normal by days 7-10. The low LVEF was combined with reversible left ventricular dilatation, also normalizing in 7-10 days. [158,159] These findings of evident systolic deterioration, being worst on day 2 and recovering after day 3-4, finally reaching normal values in a week have been confirmed in many studies. [158] In a prospective echocardiographic study by Vieillard-Baron and coworkers, the incidence of left ventricular (LV) systolic function in patients with septic shock was 60%, as defined by LVEF < 45%.[160] Patients with septic shock also have depressed response to volume expansion, as shown by Ognibene and collaborators. [161] During the last decade there has been increasing interest in diastolic dysfunction during septic shock. In a recent fairly large prospective study of patients with severe sepsis or septic shock, the incidence of isolated LV systolic dysfunction was 9%, combined systolic and diastolic dysfunction 14%, and isolated LV diastolic dysfunction 38%. In this study, diastolic dysfunction was the strongest predictive factor for mortality, also after adjustment for confounding factors. [162] Similar results have been demonstrated earlier by the groups of Sturgess and Ikonomidis. [163,164]

As for the underlying mechanisms of myocardial dysfunction during septic shock, it was believed for decades that reduced coronary blood flow was the primus motor of septic myocardial dysfunction. This was, however, proved incorrect in direct studies of blood flow and metabolism in the 1980s. [158] A decade earlier, Wangensteen and coworkers suggested that myocardial depression was due to a circulating myocardial depressant factor. Parillo later showed that serum obtained from patients suffering from septic shock actually caused changes in cardiomyocytes in vitro, an effect most likely caused by circulating cytokines. Nonetheless, myocardial depression lasts longer than the “cytokine storm”, and currently cytokines are thought to participate in the initial events leading to prolonged septic cardiomyopathy. [158] This prolonged phase of myocardial dysfunction is believed to be further aggravated by several intrinsic mechanisms of the myocardium, including alterations in the beta-adrenergic pathway, decreased response of myofilaments to calcium, production of NO and peroxynitrite, and cell death and apoptosis. [158] Scmittinger and coworkers recently conducted a post-mortem study of hearts of patients who had died of septic shock. One-fifth of the patients had non-occlusive cardiac ischemia, a typical finding in patients suffering from an imbalance in supply and consumption of oxygen, which is frequently seen in states of high sympathetic tone. Nearly all patients had contraction band necrosis, which is caused by irreversible hypercontraction of the myocytes. This finding, which is the hallmark of pheochromocytoma, is also frequently referred to as catecholamine necrosis and can be caused experimentally by infusion of catecholamines. This recent finding emphasizes the importance of stress-induced changes in shocked hearts.[165]

2.6. HEMODYNAMIC MONITORING

Hemodynamic assessment and monitoring play a fundamental role in the management of the critically ill patient with hemodynamic failure.[166-168] Monitoring of critically ill patients usually entails use of several monitoring methods, including clinical assessment of vital signs. Hemodynamic monitoring is used in the ICU to identify cardiovascular failure or insufficiency by assessing isolated values as well as trends of values over time. Hemodynamic monitoring also provides information needed to identify the probable cause and is equally important in assessing response to therapy. [169]

The ultimate aim of hemodynamic monitoring is to measure whether the circulation provides sufficient and adequate oxygen supply to meet the prevailing oxygen demand. [170] It must be emphasized that no means of monitoring or the monitoring device itself can improve outcome, unless accompanied by effective treatment. [169] Conducting studies for comparative evaluation of different methods of hemodynamic monitoring with outcome endpoints is challenging, as outcome depends not only on monitoring, but also on the treatment provided. [168] Furthermore, interpretation of values achieved relies on the skills and experience of the attending physician. During the past 50 years hemodynamic monitoring has developed rapidly. There is now a wide range of available methods for hemodynamic evaluation, from highly invasive methods to mini-invasive or completely non-invasive ones. The focus has turned from static measures to dynamic ones, but despite this development and the numerous experimental and clinical studies, it is still unclear whether the choice of hemodynamic monitoring matters. [168] Traditionally, hemodynamic monitoring has focused on macrohemodynamic indices. Lately, monitoring of the microcirculation has attracted much interest, as its importance in the development and pathophysiology of shock has been established.[171]

2.6.1 MEAN ARTERIAL PRESSURE

Basic monitoring of the critically ill patient has included invasive measurement of blood pressure, particularly mean arterial pressure (MAP). Although hypotension is not an absolute requirement for identifying shock according to some of the definitions provided,[172] it frequently accompanies shock and is a prerequisite for the current definition of septic shock. [173] MAP is an important parameter for assessing adequacy of macro hemodynamics and response to fluid and vasopressor therapy. Monitoring and targeting values for MAP constitute an essential part of current treatment guidelines for septic shock. [35,174,175] Results from previous studies indicate that maintaining MAP at 60-65 mmHg has beneficial effects on outcome. [176] Sufficient perfusion pressure of end organs is pursued by preserving adequate blood pressure. MAP, in addition to other hemodynamic parameters, such as heart rate, cardiac output, central venous pressure, and pulmonary artery occlusion pressure (PAOP), can also be used for differentiating types of shock. [169]

2.6.2 STATIC PRELOAD MEASURES, MIXED VENOUS OXYGEN SATURATION, AND CARDIAC OUTPUT

Central venous pressure (CVP) and PAOP are static indices of preload, meaning that they measure the pressure within a chamber in relation to the atmosphere. For five centuries, CVP has been frequently monitored and utilized in the ICU to describe the pressure of the right atrium and indirectly the cardiac filling pressure and preload status. [177-179] CVP accurately describes the pressure in the right atrium when no obstruction of the venae cavae exists. [177] CVP is, however, dependent on cardiac function, and a specific or isolated value of CVP has little predictive value for fluid responsiveness. [37,180] In a systematic review of 24 studies, Marik and coworkers found that there was no association between CVP and the circulating blood volume, and that CVP could not predict fluid responsiveness. [179] However, CVP may provide important information and aid the clinician in decision-making and hemodynamic profile analysis [169] once the basic principles and the restrictions for its use are understood. [178]

The pulmonary artery catheter (PAC) provides the clinician with right (CVP) and left side (PAOP) filling pressures as well as with pulmonary artery pressures. In addition, it provides a means of cardiac output (CO) measurement through thermodilution and the possibility to continuously measure mixed venous oxygen saturation (SVO_2). The introduction of the balloon-tipped catheter in 1970 [181] brought a powerful tool for semi-continuous hemodynamic monitoring to the ICU and provided data that previously was available only in catheterization laboratories. [171,182] In clinical studies, the filling pressures obtained by use of PACs have not been found to predict fluid responsiveness, and thus, the PAC is not optimal for assessing preload status.[37] Many studies have assessed potential advantages and disadvantages of the PAC in different patient populations[182] since the first large retrospective study by Connors and coworkers that indicated higher mortality and higher costs of treatment. [183] Based on a multitude of retrospective and prospective clinical trials, however, the use of the PAC is not associated with any change in mortality and morbidity.[182,184] Due to its invasiveness, lack of unquestionable superiority, and the continuing development of other less invasive, but equally accurate means of hemodynamic measurement, the popularity of PACs has declined in recent years. [185] Nevertheless, the PAC may still provide invaluable information in diagnosis and assessment of response to treatment in cardiac conditions and refractory shock, and although not indicated for the general ICU population, it should not be forgotten. [185-187]

CO measurement by thermodilution using the PAC is still considered the “gold standard” and continues to serve as a reference for newer less invasive methods of cardiac output monitoring. [188] Measurement of CO is not currently advocated in the treatment of all patients with shock, but it is recommended in the treatment of patients with evidence of ventricular failure or refractory shock. [172] Although several mini-invasive and entirely non-invasive methods have been presented in recent years showing feasibility and fairly good accuracy, [189,190] clinical validation studies assessing impact on treatment are warranted. [191]

Mixed venous oxygen saturation describes the oxygen saturation of mixed venous blood and can only be obtained using a PAC. This hemodynamic parameter is the only one that actually describes the relationship between systemic oxygen supply (DO_2) and demand (VO_2). A decrease in SVO_2 indicates an imbalance in these two parameters, either through a decrease in DO_2 or an increase in VO_2. During an increase in VO_2, also under physiological conditions, O_2 extraction and CO increase. A decrease in SVO_2 is therefore not synonymous with tissue hypoxia, but it indicates the extent to which the oxygen reserves are stressed.[192] During microcirculatory derangements and shunting of the capillaries, such as during distributive shock, SVO_2 may be normal, or high, despite local tissue hypoxia. Under such circumstances, other means of assessing sufficient global and tissue perfusion, such as measurement of CO and lactate values, are needed. [193]

2.6.3 DYNAMIC PRELOAD MEASURES AND CONCEPT OF FLUID RESPONSIVENESS

Assessment of preload status in the hemodynamically unstable patient in the ICU is a difficult task. The question is will this patient increase cardiac output and thus oxygen supply with further fluid resuscitation. Only about 50% of patients with hemodynamic failure in the ICU will respond to fluid loading by an increase in CO. [194] Fluid responsiveness is the term used to describe the ability to increase CO in reaction to volume expansion. In several studies, positive fluid response has been defined as an increase of either SV or CO by 15% or more. [195] The gold standard for assessing fluid responsiveness has long been "the fluid challenge" accompanied by repeated CO monitoring. [196] According to the Frank-Starling curve, there is a curvilinear relationship between preload and SV, and hence, CO. An increase in preload will increase CO significantly, but only as long as the ventricle operates on the steep part (ascending portion) of the curve. If the ventricle is operating on the flat part of the curve, an increase in preload will only result in a marginal increase in CO, while simultaneously exposing the patient to possible deleterious effects of hypervolemia such as edema formation. [197] There is also increasing evidence that greater fluid loads are associated with worse outcome. [198-202] Static filling pressures have proven unreliable in assessing preload status, having the adequacy of coin tossing, and repetitive unnecessary fluid boluses may indeed cause harmful overhydration. [37,179]

In normal individuals with spontaneous breathing, blood pressure decreases during inspiration. Usually, in healthy individuals, it does not decrease by more than 5 mmHg. Nevertheless, in certain conditions, such as in constrictive pericarditis, this phenomenon is exaggerated, causing greater swings in blood pressure and the complete disappearance of the radial pulse during inspiration. This has been termed Kussmaul's sign, first presented by Adolf Kussmaul in 1873. [203] A reversed phenomenon occurs during positive pressure ventilation. This has been called reversed pulsus paradoxus, systolic pressure variation, and respirator paradox, among others. [204] Morgan and coworkers first reported that mechanical ventilation causes cyclic changes in blood flow of the vena cava,

pulmonary arteries, and aorta. [205] Later, Rick and Burke described an association between volume status and systolic pressure variation in critically ill patients. [204,206]

During positive pressure inspiration intrathoracic pressure increases, which concomitantly increases the opposing pressure for venous return, thus impeding filling of the right atrium and ventricle. This, after a phase lag of a few heartbeats, usually during expiration, leads to a decrease in left ventricular preload and stroke volume. The swing phenomenon is further augmented by an increase in right ventricular afterload through an increase in pulmonary vascular resistance during inspiration and an increase in left ventricular preload through squeezing of the pulmonary vascular beds and a decrease in left ventricular afterload during inspiration. This results in an increase in stroke volume and systolic blood pressure during mechanical inspiration and a decrease of both during mechanical expiration. [195]

During spontaneous breathing the opposite occurs. Hypovolemia amplifies these findings, while hypervolemia diminishes the variation by counteracting the underlying mechanisms.[195] The decrease in systolic blood pressure during expiration from the systolic pressure reference line measured during an end-expiratory pause, ΔDown, has been found to accurately reflect volemic conditions and to also be associated with responsiveness in both animal [207-209] and clinical studies. [210-212] A multitude of studies have assessed the capability of changes in arterial waveform, stroke volume variation (SVV), and pulse pressure variation (PPV) during mechanical ventilation to accurately predict fluid responsiveness. Michard and coworkers noted that changes in pulse pressure reliably predicted fluid responsiveness in patients with acute circulatory failure over 20 years ago. [213] Since then, different dynamic indices, such as PPV or SVV during positive pressure ventilation, have been shown to be superior indicators of fluid responsiveness compared with static preload indices, and different monitoring appliances have been developed. [214,215] However, because of their dependence on blood pressure or SVV induced by respiration, they may be unreliable in clinical practice due to arrhythmias or spontaneous breathing efforts. [216,217]

Passive leg raising (PLR) is, as the term implies, a maneuver during which the legs of the patient are passively lifted. Usually, it is performed in the ICU by tilting the bed. This has been described as a means of assessing fluid responsiveness, as it mobilizes about 200-400 ml of blood from the lower extremities to the venous return, thereby increasing preload. If the patient is fluid-responsive, the maneuver will transiently increase SV and CO, as assessed by some means of continuous CO monitoring device or echocardiography. Unlike the classic fluid challenge, PLR will not increase the total fluid load. The use of PLR requires a means of real-time assessment of hemodynamic changes, preferably Doppler assessment of aortic flow.[218-222] PLR has adequately predicted fluid responsiveness during spontaneous breathing and extra-corporeal life support, but evidence indicates that it is not reliable during increased intra-abdominal pressure. [223-225]

2.6.4 ECHOCARDIOGRAPHY FOR HEMODYNAMIC MONITORING

Echocardiography is of great importance in the assessment of cardiogenic shock. The evaluation of local or global akinesia or hypokinesia and identification of mechanical complications of myocardial infarction are important in setting a diagnosis, as is the assessment of valvular function. [226-228] Echocardiography has also become increasingly important in the ICU in assessing other patient groups with hemodynamic failure. [226,229,230] The advantage of echocardiography over catheter-derived parameters lies in its ability to visualize the heart and to reveal obvious underlying pathology for hemodynamic failure, e.g. cardiac tamponade. [166] Due to improvement of ultrasound appliances and image acquisition, transthoracic echocardiography (TTE) instead of transesophageal echocardiography (TEE) should be the primary method in the ICU because of its safety and lack of invasiveness. [228,230] Evidence exists that echocardiographic methods are accurate for assessing fluid responsiveness. [231-234] Respiratory changes in the inferior vena cava assessed by TTE have predicted fluid responsiveness in two separate clinical studies of septic patients with circulatory shock. [233,234] Using TEE, Feissel and coworkers found that the variation of aortic maximum velocity was a good predictor of fluid responsiveness in patients with septic shock. [231] Also using TEE, the group of Viellard-Baron assessed the collapsibility of the superior vena cava for prediction of fluid responsiveness. [232] A collapsibility index of over 36% was associated with an increase in CO to subsequent volume expansion. [232] In addition, data from an experimental animal study indicate the potential usefulness of variation of the aortic time velocity integral to predict fluid responsiveness. [235] Echocardiography may also be used for the assessment of cardiac filling pressures in the ICU setting. [236] Moreover, echocardiography is also useful for diagnosing systolic and diastolic dysfunction, thus enabling optimal hemodynamic support. [160,163,237] However, it must be kept in mind that TTE has been validated against thermodilution-derived CO measurements, which currently are considered to be the gold standard in a minority of the conducted studies. [238]

2.6.5 MONITORING OF MICROCIRCULATION

There is evidence that hemodynamic resuscitation targeting certain macrohemodynamic target values is not always sufficient to adequately restore tissue oxygenation and prevent development of organ dysfunction. [29,239,240] In recent years, the focus has turned to the microcirculation and its restoration. As a result, there is growing interest in monitoring the microcirculatory function. [170]

Mixed venous oxygen saturation describes the relationship between oxygen supply and demand, but it cannot recognize a local mismatch, particularly of organs in which the perfusion may be compromised before others.[170] Lactate, which cumulates during hypoxia, may also be used as a marker of tissue hypoxia, but is also not sensitive for local changes and is somewhat non-specific. [241-247] The use of the lactate-to-pyruvate ratio for assessment of microcirculatory function was described by Weil and Afifi in a clinical study over 40 years ago. [241] Tissue carbon dioxide concentrations (tCO_2) have also been shown

to correlate with derangements in tissue perfusion. Tissue hypercarbia may be assessed by sublingual or buccal capnometers, which are not, however, widely used in clinical practice today. [49,248]

Near-infrared resonance spectroscopy (NIRS), which measures the oxygen saturation from the fractions of oxyhemoglobin and deoxyhemoglobin, may be used for assessment of tissue oxygen saturation (StO_2). The technique of combining measurement of thenar StO_2 and a brief episode of forearm ischemia shows promise for quantification of microvascular dysfunction. [249] Microvideoscopic techniques, such as orthogonal polarization spectral imaging (OPS) and sidestream dark field imaging (SDF), visualize the microcirculation and enable the clinician to assess the heterogeneity of the capillaries, the proportion of perfused versus non-perfused capillaries. These techniques are mainly used in research. [170,249]

2.7. TREATMENT OF HEMODYNAMIC FAILURE

Until the end of the 1960s, treatment of shock was symptomatic. The Trendelenburg, or the head-down position, was widely used for hemodynamic optimization. Blankets or heating devices were used to conserve body heat. In addition, blood pressure was raised with drugs. Due to advances in shock research during the 1960s, Weil and Shubin were able to propose a novel approach to shock treatment in 1969, the "VIP approach". [250] *The focus was now on early and efficient treatment with a systematic approach, allowing the physician to gain diagnostic insights while treating the patient. The VIP approach consisted of three therapeutic-diagnostic maneuvers: ventilation, infusion, and pumping. A postscript, PS, was added to describe the importance of pharmacological and surgical treatment, when needed.* [250]

Despite numerous advances and a myriad of studies in the field, VIP still depicts the essence of shock treatment today. In current guidelines, fluid and vasopressor therapies are advocated to reach certain hemodynamic targets, primarily a MAP ≥65 mmHg and CVP of 8-12 mmHg. Although there has been much debate as to the correct targets and the adequacy of CVP as an indicator of fluid status, these targets are still the mainstay of current guidelines. [35]

2.7.1 FLUID TREATMENT

The history of intravenous fluid therapy allegedly began during the European cholera epidemic in 1831. The young Irish physician William Brooke O'Shaughnessy proposed water and salt repletion as supportive care for cholera patients. There was little progress until Ringer and Schwartz revived the research in intravenous fluid therapy in the 1880s, but still intravenous fluid was only given to extremely ill patients. During World War II blood transfusions were widely given to wounded soldiers. [251] *A new enthusiasm for crystalloid infusions began in the 1960s, and the importance of fluid repletion in shock became apparent later that decade.* [250,251] *In the following decades, attention was directed to oxygen supply and consumption, targeting supranormal levels of oxygen supply, but this regime later turned out to be a disappointment.* [29,240,252,253] *The importance of timely, early goal-directed therapy (EGDT) of shock became apparent with the study by Rivers in 2001.* [25]

The key factors in the EGDT treatment algorithm were early recognition of septic patents and prompt initiation of treatment, which included fluid resuscitation, packed red blood cell transfusions, and inotrope treatment. [25] In 2004, the treatment guidelines of septic shock in the "Surviving Sepsis Campaign" emphasized the importance of an acute resuscitation bundle with timely fluid resuscitation. [174] Prompt and vigorous fluid resuscitation was also highlighted in the two following versions of the sepsis guidelines targeting hemodynamic goals of resuscitation. [35,175]

The initial step in optimization of hemodynamics in circulatory failure is fluid resuscitation. [254] Fluid resuscitation in shock aims at restoring intravascular volume, hemodynamics, tissue perfusion, and ultimately cellular metabolism to an adequate level, primarily by increasing CO. [35,254] Restoration is ideally performed during hemodynamic monitoring for assessment of treatment response and should be performed early to avoid development of end-organ failure[254] The choice of fluid has been the subject of several studies. [255-258] Resuscitation with fluids containing albumin was assessed in the SAFE study. Patients with septic shock showed a trend of reduction in mortality when resuscitated with albumin solution, but there was an increased mortality in patients with severe brain injury who were allocated to albumin treatment. [255] Albumin is recommended in current treatment guidelines for sepsis in patients needing high amounts of crystalloids during resuscitation. [35] Synthetic colloids, such as hydroxyl ethyl starches (HES) and gelatine, have been largely used in fluid resuscitation due to their alleged superiority in replacing intravascular volume, despite their higher costs and the lack of randomized controlled trials showing a clear benefit. [258,259] They have been associated with an increase in allergic reactions, derangements in hemostasis, pruritus, and kidney injury. [258] Although newer HES solution with lower molecular weights and reduced substitution may have less impact on coagulation, [260] shock was reversed with no more delay using crystalloids in a prospective study. [261] Furthermore, the volume requirements were only marginally lower using HES than crystalloids. [261] During recent years an increasing amount of data has indicated that the use of HES is associated with serious adverse effects, such as an increase in AKI and greater mortality. [256,257] In a Cochrane review of 42 studies, the incidence of AKI and the need for renal replacement therapy (RRT) was higher in patients treated with HES. [262,263] The use of HES solutions is not currently advocated in the treatment of patients with sepsis. [264]

Theoretically, the use of hypertonic saline may have advantages for resuscitation. Although some evidence exists of a benefit in certain circumstances, overall the data for use in humans are not convincing. Hypertonic saline has been shown to effectively reduce elevated intracranial pressure, but this treatment has not improved clinical outcome in randomized trials. [258] There is also some evidence of deleterious effects of normal saline for fluid treatment. [265] In the trauma setting, evidence also exists for an outcome benefit of a restrictive, hypovolemic resuscitation regime prior to surgery to treat sites of blood loss. [266]

The general consensus is that fluid therapy should be initiated as early as possible. However, the optimal amount of fluid to be administered remains obscure. [258] The adverse effects of aggressive fluid therapy are well known. [267] In recent years, evolving data have raised concern of the deleterious effects on outcome of liberal fluid replacement regimens compared with restrictive ones in several critically ill patient groups. [200,201,268-270] The retrospective studies could not answer the question of whether adverse outcome was due to fluid overload or differences in severity of illness. A prospective study clearly showed a benefit of a restricted fluid strategy in terms of ventilator-free days and length of stay in the ICU, despite a lack of differences in mortality. [201] These recent advances emphasize the importance of prediction of fluid responsiveness in order to avoid excess fluid therapy. [198]

2.7.2 VASOPRESSORS

Vasopressors have been used in the treatment of shock since the early 1940s. Interestingly, the different impacts of norepinephrine (and metaraminol) on renal blood flow and glomerular filtration in healthy subjects, and in those with vasodilatory or hemodynamic shock, were assessed as early as in 1955. [271] *The influence of acidosis on vascular responsiveness to catecholamines was also elucidated in the late 1950s.* [272]

The use of vasopressors is recommended in the current guidelines when fluid repletion alone cannot restore hemodynamic stability and sufficient perfusion. Vasopressor therapy is also frequently required to sustain life and maintain perfusion, even though hypovolemia has not yet been completely resolved. [35]

The vasopressors used in the ICU are mainly catecholamines, with different profiles as to effects on α- receptors and β-receptors, with some also acting on dopamine receptors. Vasopressin is a peptide hormone, with entirely different mechanisms of action than the catecholamines. [273] Vasopressors mainly induce vasoconstriction of the arterioles, thus counteracting excess vasodilation and increasing venous return. Through β-receptor-mediated mechanisms, they may also exert direct actions on myocardial contractility and heart rate. [273] Until recently, no consensus has existed regarding the superiority of any particular vasopressor. However, prospective randomized studies reveal the most beneficial profile to be possessed by norepinephrine, a potent α-adrenergic agonist, with less potent β-receptor action, in treating patients with hemodynamic failure. [274,275] Norepinephrine and dopamine, the natural precursor of norepinephrine and epinephrine, have until now been considered equal first-line vasopressors for treatment of shock, [175] although some evidence from a large retrospective study has suggested that dopamine was associated with worse outcome. [95,175] Data from earlier studies also indicated that norepinephrine was more efficient in achieving targets of blood pressure and plausibly had a more beneficial effect on splanchnic circulation. [276,277] However, evidence based on several prospective randomized studies of septic shock now shows that dopamine treatment is associated with other adverse effects such as arrhythmia and tachycardia. [274,278,279] In two recent systematic reviews and a meta-analysis, treatment with norepinephrine was superior to dopamine also in terms of lower mortality. [278,280] Consequently, norepinephrine is now considered the primary vasopressor in septic shock. [35]

The renal effects of norepinephrine and particularly dopamine have been the subject of much debate. Due to dopaminergic mechanisms, dopamine vasodilates renal and mesenteric beds at low doses. Previously, this effect was considered beneficial for maintaining renal function. [273,281] However, a large randomized study showed no benefit, and subsequently, the use of “renal dopamine” has not been advocated. [281] The effects of norepinephrine on renal blood flow appear different between normal subjects and patients in shock. [271,282] Although norepinephrine may cause harmful vasoconstriction during physiological circumstances, it seems to be beneficial in terms of glomerular filtration and creatinine clearance in patients with shock, at least when raising blood pressure from levels below the lower range of autoregulation. [44,282] Nevertheless, a higher

total catecholamine load has been associated with worse outcome in patients with septic shock. [45]

Other catecholamines have also been studied in the treatment of shock. [283-286] Phenylephrine, a synthetic, selective α_1-agonist, increases blood pressure through vasoconstricton. There is, however, concern that it may decrease cardiac output and impair splanchnic blood flow, based on animal and clinical studies. [275,283,286-288] Therefore, it is not recommended as a primary vasopressor in shock. The use of epinephrine, an α- and β-adrenergic catecholamine, has also been subject to controversy. Epinephrine increases cardiac oxygen delivery, but concomitantly it increases myocardial oxygen consumption. It has been shown to induce hyperlactatemia and acidosis through direct metabolic effects, but this may be difficult to differentiate from changes caused by tissue hypoxia. [286] Concerns have been raised regarding impaired splanchnic perfusion. [273,286] Two large prospective randomized studies comparing epinephrine to norepinephrine (with addition of dobutamine) found no differences in mortality. [273,285,286,289] In the epinephrine group, lactate levels were higher and acidosis was more common, but the incidence of serious adverse effects in terms of arrhythmias was similar. [285,289] Epinephrine is recommended as a second-line vasopressor in the current guidelines. [35]

Vasopressin is normally synthesized in the hypothalamus, is stored in the pituitary gland, and acts in a completely different manner to catecholamines. Under normal physiological conditions, vasopressin has little effect on blood pressure. It is released in response to hypovolemia and increases with plasma osmolality. It causes vasoconstriction via V1 receptors and increases responsiveness to catecholamines. [273,290] Vasopressin levels increase in hemorrhagic shock, but the response seems abnormally low in septic shock,[291] possibly due to depletion of pituitary stores. [292] Its use has been associated with ischemic skin and tongue lesions, and concern has been raised as to its possible deleterious effects on splanchnic circulation. [286]

Two small randomized trials comparing vasopressin with norepinephrine showed a decrease in catecholamine requirements in the vasopressin group. [293,294] A large randomized trial revealed no difference in outcome between patients with septic shock receiving vasopressin and those receiving norepinephrine, but patients who were less severely ill seemed to benefit from vasopressin therapy. [295] A post hoc analysis of the same trial showed that patients at risk of AKI had a lower incidence of AKI progression and lower mortality rates when treated with vasopressin. [296] In another post hoc study of the same trial, the combination of vasopressin and corticosteroids was associated with a decrease in incidence of organ dysfunction and mortality. [297] Two recent systematic reviews and meta-analyses assessed vasopressin as treatment for vasodilatory shock. The conclusions differed somewhat, but neither review found vasopressin to be associated with worse outcome than catecholamines. [298,299] The use of vasopressin is currently advocated only in combination with norepinephrine at low doses [35] as repletion therapy, although some data show good response also at higher doses. [300]

2.7.3 INOTROPES

The use of inotropes is indicated in shock when fluid therapy and vasopressor therapy are inadequate for restoring tissue perfusion and oxygen supply. They are administered to increase force and rate of myocardial contractility, and thus, CO and oxygen delivery. [301]

In the 1960s, the focus shifted to the balance between oxygen delivery (DO_2) and consumption (VO_2), as measurement of CO and oxygen content in blood became possible at bedside. The concept of pathologic oxygen supply dependence, a linear relationship between DO_2 and VO_2, was postulated. The rationale was that an increase in DO_2 would be beneficial for patients in shock, as oxygen debt and energy deficit had been found to be associated with poor outcome in clinical studies. [302] Targeting supra-normal levels of DO_2 as part of "supra-normal" resuscitation by using inotropes, fluids, and blood transfusions seemed beneficial in early studies of high-risk surgical patients. [252,303,304] The results from two prospective randomized studies showed either no improvement [240] or increases in mortality, [29] consistent with several other studies, [35,302] and supra-normal resuscitation has not been advocated since.

The use of inotropes as part of treatment of shock today relies on scant evidence of their beneficial effects. The study by Rivers and coworkers in 2001 showed a marked outcome benefit for the treatment arm in which dobutamine was included for achieving targets of $ScVO_2$. [305] Similar results have been shown by Jones and coworkers in 2010. [306] Several studies are currently being conducted to assess the benefit of the treatment algorithm presented by Rivers relative to current clinical practices. [307] In patients with chronic cardiac failure, inotropes, particularly catecholamines, have been clearly associated with adverse effects and worse outcomes. [26-28]

In septic shock, CO is often increased. Nevertheless, in a substantial proportion of patients, septic cardiomyopathy is present, evidenced by impairment of systolic or diastolic function, or both, without structural changes. [308,309] In these patients, based on measured or suspected low CO, and high filling pressures or adequate fluid status, in addition to adequate blood pressure level, inotropic treatment is currently recommended, guided by trends in clinical data of hypoperfusion. [35,308] Dobutamine, a synthetic catecholamine available as a racemic mixture, with mixed β-receptor and modest α-receptor effects, is the primary inotrope recommended for these purposes, despite little evidence of an outcome benefit. [35,301] Dobutamine has also been used to treat cardiogenic shock, and as it increases myocardial oxygen demand, it is used as a stressor in cardiac assessment. [301] However, in a recent meta-analysis it was associated with worse outcome in terms of mortality in severe heart failure. [310] It causes an increase in cardiac output, stroke volume, and heart rate, but it may cause malignant ventricular arrhythmias at any dose. [311,312] There is also evidence of improvement of microcirculation with the use of dobutamine, but as yet, no clear evidence has emerged of less end-organ failure. [302]

During the last twenty years there has been increasing interest in levosimendan, a calcium-sensitizing inodilator. It has a dual mechanism of action, including both calcium sensitization, which enhances contractility, and opening of ATP-dependent potassium

channels, which induces vasodilatation.[312] Some results have indicated that levosimendan may improve survival in surgical and cardiologic settings.[313] However, evidence of beneficial effects in septic shock is scarce, although some prospective studies have shown promising results.[314-316]

Currently, neither levosimendan, milrinone, nor other phosphodiesterase inhibitors are recommended in the treatment of septic shock.[35,317] A small study assessing the potential role of milrinone and enteral β-blockers in shock,[35,318] demonstrated that such a treatment regime is feasible and also potentially beneficial in terms of improvement of hemodynamic parameters.[318,319]

2.7.4 ADJUVANT THERAPIES

Treatment of shock does not merely consist of administration of fluids and vasoactive substances. The underlying cause needs to be addressed promptly and accurately. In cardiogenic shock, early revascularization and mechanical support by intra-aortic balloon pump (IABP) counterpulsation are currently recommended, in addition to fluid and vasoactive therapy,[67] although recent data suggest that counterpulsation is associated with neither short-term nor long-term survival benefit.[67,320,321] In septic shock, the early administration of effective antimicrobial treatment has proven beneficial in terms of outcome in several studies.[35,322] In addition, early and adequate source control of the infection is also advocated, preferably within 12 hours of diagnosis.[35] For patients suffering from hemorrhagic shock, source control, i.e. stopping the source of bleeding, is essential for obvious reasons in addition to restoration of blood volume.[323]

2.8 OUTCOME IN HEMODYNAMIC FAILURE OR CIRCULATORY SHOCK

A Finnish study, conducted in the late 1990s, assessed the association between resolution of circulatory failure and outcome. Altogether 83 patients with circulatory failure were evaluated. The overall hospital mortality was 39.8% and the ICU mortality 33.7%. Sepsis was diagnosed in 20% of the patients. [239] In a large European study conducted in 24 countries in 2002, the mortality of all patients with shock was 38%, while it was 47.4% for patients with septic shock. The mortality for patients with hemodynamic failure without sepsis was 34%. The mortality for patients with sepsis and any degree of hemodynamic failure was significantly higher, 42%. [95,96]

In the Finnsepsis study conducted in 24 Finnish ICUs in 2004-2005, the overall ICU, in-hospital, and 1-year mortalities were 16%, 28%, and 41%, respectively. The mortality for patients with cardiovascular failure (SOFA subscore ≥ 3, without other organ dysfunctions) was 33%. The mortality rose to 69% in patients with SOFA subscores of at least 3 points in all organ groups. [10] The mortality rates rise with advancing age. In a recent substudy of the European SOAP II study, the mortalities for patients with hemodynamic failure aged under 75 years, 75-84 years, and over 85 years were assessed. The 6-month mortality for these three age groups was 59%, 79%, and 92%, respectively. The cause of death in the age groups was shock in 20%, 24%, and 26%, respectively. [324]

Mortality rates for cardiac shock previously ranged from 50% to 80%. [105], but have now declined due to early intervention therapies. [66] In an American study, comprising data from 775 US hospitals during 1995-2004, the hospital mortality in cardiogenic shock at the beginning of the study was 60%, but had decreased to 48% by the year 2004. [67] In Finland, the current hospital mortality due to cardiogenic shock is 46-48%. [104]

According to previous studies, anaphylactic shock leads to lethal outcome in 3-10% of cases. [325] The mortality rates in hemorrhagic shock vary widely based on the underlying trauma mechanisms, but in recent studies mortality rates ranging from 15% to 40% have been reported.[323]

3. AIMS OF THE STUDY

The objective of this study was to assess the relevance of early hemodynamics and hemodynamic treatment for outcome and development of end-organ injury in patients with severe sepsis, septic shock, and severe acute pancreatitis. In addition, methods for evaluating fluid responsiveness at bedside in patients with septic shock were sought.

Specific aims of the study were as follows:

1. To assess the association of inotrope treatment and early hemodynamic variables with outcome in patients with septic shock, with a subgroup analysis of patients monitored by a pulmonary artery catheter.

2. To assess the association of early hemodynamic variables and vasoactive treatment with outcome in patients with severe acute pancreatitis, with a subgroup analysis of patients with circulatory shock.

3. To evaluate whether elevation of PEEP from 10 to 20 cm H_2O induces hemodynamic changes in mean arterial pressure, systolic arterial pressure, or pulse pressure or changes in parameters derived by transesophageal echocardiography that would predict fluid responsiveness in patients with septic shock.

4. To assess the association of early hemodynamic variables, with special reference to time-adjusted mean arterial pressure, and vasoactive treatment with the development of acute kidney injury during the five first days in the intensive care unit in patients with severe sepsis.

4. PATIENTS AND METHODS

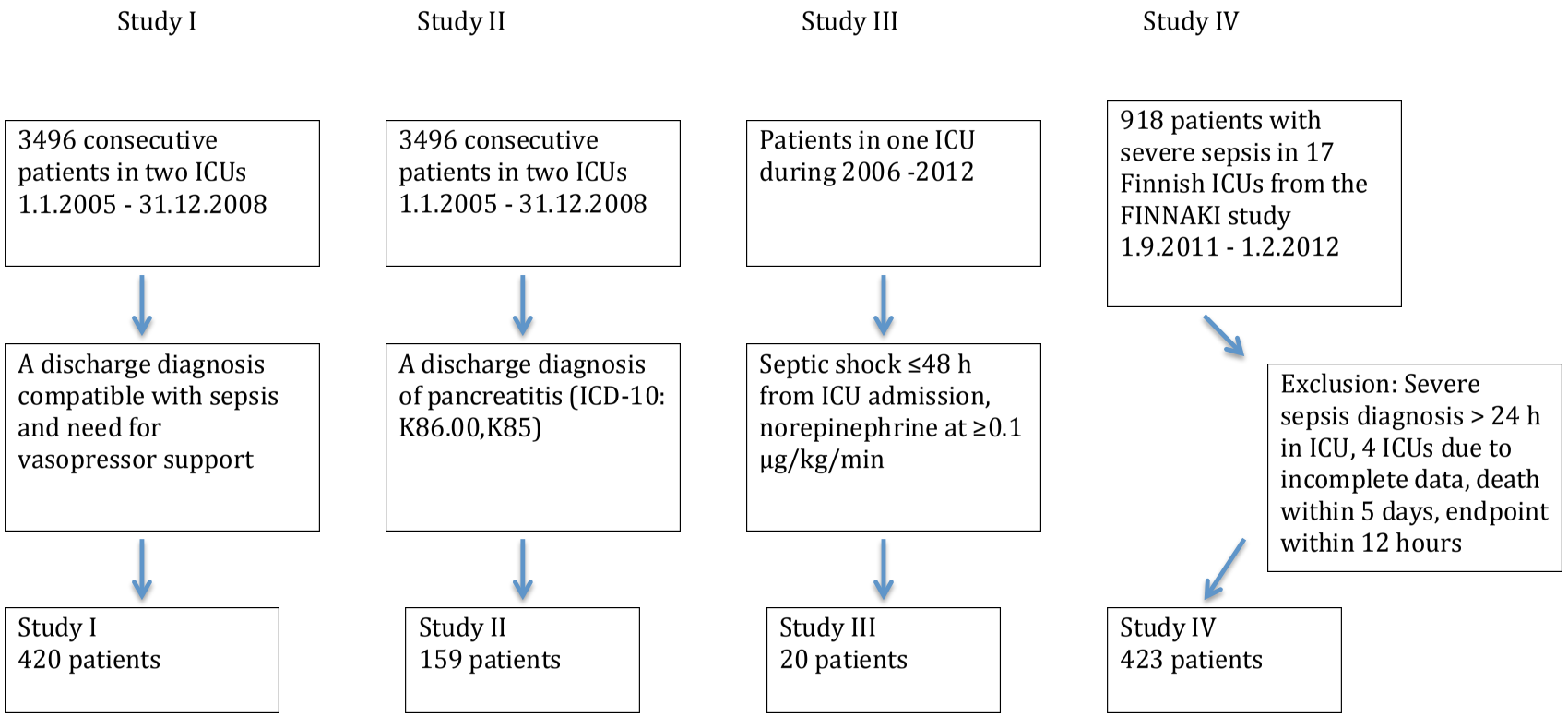
4.1 PATIENTS

We included 1022 patients in Studies I to IV. Studies I to III were conducted at Helsinki University Central Hospital, and Study IV was a Finnish multicenter study conducted in 17 Finnish ICUs. The flowchart of inclusion of patients into the studies is presented in Figure 6. The demographic data of the patients of Studies I to IV are shown in Table 1. The Ethics Committee of Helsinki University Central Hospital approved all study protocols. In Studies III and IV, written informed consent was given by the patient or a proxy. Written consent was waived by the Ethics Committee for Studies I and II.

Study I was a retrospective cohort study conducted in two ICUs (9-bed mixed and 10-bed surgical ICU) at Helsinki University Central Hospital. All 3496 consecutive patients in the ICUs during the period from 1.1.2005 to 31.12.2008 were considered eligible for the study. We identified 526 patients with a diagnosis compatible with sepsis registered on admission and later confirmed on discharge (pneumonia, urosepsis, intra-abdominal sepsis, CNS infection, or sepsis). The 420 patients included in the study had a diagnosis compatible with sepsis and need for vasopressor support during the first 24 hours in the ICU. A subgroup analysis was also performed on the 252 patients monitored by a pulmonary artery catheter.

Study II was a retrospective cohort study conducted in the same two ICUs at Helsinki University Central Hospital. All 3496 consecutive patients treated in the ICUs between 1.1.2005 and 31.12.2008 were assessed for eligibility. The 159 patients of the study were retrospectively identified based on the International Classification of Diseases (ICD-10) diagnoses “acute pancreatitis” (ICD-10: K85) or “ acute alcohol pancreatitis” (ICD-10: K86.00). In addition, a subgroup of 73 patients with circulatory shock, defined as need of hemodynamic support by use of norepinephrine at a dose exceeding 0.1 μg/kg/min for one hour, was identified.

Study III was a prospective study conducted in one ICU at Helsinki University Central Hospital during 2006-2012. All patients with septic shock defined by the APCCP/SCCM Consensus Conference criteria, an inserted pulmonary artery catheter, age over 18 years, sinus rhythm, mechanical ventilation and sedation, pulmonary artery occlusion pressure (PAOP) ≤ 18 mmHg, and use of norepinephrine at a dose of at least 0.1 μg /kg/min for hemodynamic support were considered eligible for the study. The 20 patients of the study fulfilled the inclusion criteria and met none of the exclusion criteria (contraindication to elevation of PEEP or performing TEE, heart valve insufficiency, or stenosis).



Altogether 1022 patients were included in Studies I-IV, of which 8 patients were included in both Studies I and III.

Figure 6. Inclusion of patients into Studies I to IV.

Study IV was a predefined substudy of the prospective observational FINNAKI study that was conducted in 17 Finnish ICUs from 1.9.2011 to 1.2.2012. All 918 patients of the FINNAKI study filling the APCCP/SCCM Consensus Conference criteria of severe sepsis were assessed for eligibility. Patients from 4 ICUs were excluded due to incomplete hemodynamic data. Moreover, patients who fulfilled the criteria of severe sepsis later than 24 hours, or fulfilled the endpoint (development or progression of AKI) within 12 hours of admission to the ICU, or died within 5 days of admission to the ICU were excluded. The final study population consisted of 423 patients with severe sepsis from 13 Finnish ICUs.

Table 1. Demographic data of Studies I to IV.

	Study I	Study II	Study III	Study IV
Number of patients	420	159	20	423
Age	58.0 (46.0-69.0)	48.0 (40.0 -56.0)	56.5 (53.3-69.3)	63.0 (51.0-64.0)
Gender (male)	264 (62.9)	130 (81.8)	13 (65.0)	276 (65.2)
SOFA on day 1	9.0 (7.0-11.0)	7.0 (4.0-9.0)	10.0 (8.0-14.3)	8.0 (6.0-10.0)
APACHE II	20.0 (15.0-26.0)	15.0 (12.0- 22.0)	*	22.0 (17.0-26.0)
SAPS II	41.5 (32.0-50.0)	31.0 (22.0-42.0)	*	40.0 (32.0-49.0)
Highest dose of norepinephrine (24 h)	0.31 (0.14-0.70)	0.07 (0.0-0.24)	0.51 (0.30-0.62) #	0.09 (0.0-0.22)
Inotrope treatment (24 h)	186 (44.3)	26 (16.4)	10 (50.0)	47 (11.1)
MAP	74.7 (70.8-79.1)	82.5 (77.0-96.1)	75.5 (68.0-83.5)#	76.6 (71.2-83.7)
Highest lactate value	2.7 (1.7-5.0)	1.5 (1.0-2.4)	*	1.9 (1.3-3.3)
ICU length of stay	5.0 (2.0-9.0)	6.0 (2.0-14.0)	*	4.0 (2.0-8.0)
ICU mortality	73 (17.4)	14 (8.8)	*	21 (5.0)
90-day mortality	135 (32.1)	24 (15.1)	*	101 (23.9)

*Not assessed in the study
#Before intervention

Data are presented as median (interquartile range, IQR) or number (percentage), as appropriate

Table 2. Summary of Studies I to IV.

	Design	Aims	Patients	Main variables	Other variables	Endpoints
Study I	Retrospective	To assess the association of inotrope treatment in addition to vasopessor treatment and hemodynamic variables with 90-day mortality	420 consecutive patients with septic shock (sepsis and need for vasopressors), subgroup of 252 patients with pulmonary artery catheter in two ICUs	Use and doses of inotropes and vasopressors	SOFA score, APACHE II score, lactate, MAP, SV, CI, CVP, SVO2, urine output, creatinine	90-day mortality
Study II	Retrospective	To assess the association of early hemodynamic variables (and early hemodynamic treatment) with 90-day mortality	159 consecutive patients with severe acute pancreatitis, subgroup with circulatory shock (need for norepinephrine > 0.1 mcg/kg/min for ≥ 1 hour) in two ICUs	MAP, HR, CVP, lactate, urine output	SOFA score, APACHE II score, etiology of pancreatitis, CI, SV, SVO2	90-day mortality
Study III	Prospective interventional	To assess whether hemodynamic changes induced by elevation of PEEP predict fluid responsiveness	20 patients with septic shock (need for norepinephrine > 0.1 mcg/kg/min for ≥ 1 hour) within 48 hours of admission to ICU in one ICU	MAP, SAP, PP (ΔMAP, ΔSAP, ΔPP) and LVEDA and VTI_{ao} (ΔLVEDA, ΔVTI_{ao} by TEE)	CO, SV, HR, CVP, SVR, DO2, PaO2/FiO2	Fluid response defined as an increase in CO by ≥15%
Study IV	Prospective observational	To assess the association of early hemodynamic variables with development and progression of AKI during days 1-5 in ICU	423 patients with severe sepsis from 13 Finnish ICUs	Time-adjusted MAP, area and aggregate time below MAP thresholds (55, 60,65,70,75,80,85 mmHg), use and doses of vasoactive agents	SOFA score, SAPS II score, lactate, BE, pH, fluid balance, use of colloids and radio-contrast dye, comorbidities	Development or progression of AKI during days 1-5 in ICU, secondary endpoint:LOS in ICU, 90-day mortality

4.2 STUDY DESIGNS AND PROTOCOLS

Study I was a retrospective study in which we assessed the effect of use of inotrope treatment on 90-day mortality and examined factors associated with the initiation of inotrope treatment in patients with septic shock. Patient data were retrospectively collected from the clinical data management system (PICIS, Wakefield, MA, USA, and Dräger Medical, Lübeck, Germany) and from the Finnish Intensive Care Consortium database (Tieto Oy, Helsinki, Finland). Mortality data were obtained from the Finnish Intensive Care Consortium database and from the Population Register Center in Helsinki, Finland. Demographic and continuously measured hemodynamic data as well as data of vasopressor and inotrope use and other medications for hemodynamic support were collected and statistically analyzed. We assessed the association of demographic data, disease severity scores (APACHE II and SOFA for day I), hemodynamic variables, vasopressor treatment, blood lactate levels, and indicators of renal function (serum creatinine and urine output) with the initiation of inotrope treatment. Most importantly, the association between inotrope treatment during the first 24 hours in the ICU and outcome was assessed. The primary endpoint was 90-day mortality, but hospital mortality, ICU and hospital lengths of stay, and 1-year mortality were also assessed. A subgroup of patients monitored by using a pulmonary artery catheter was evaluated for PAC-derived hemodynamic parameters associated with use of inotropes and outcome. In this group of patients, the ability to respond to inotrope treatment by an increase in SV and CI was assessed. The changes in hemodynamic parameters induced by inotrope treatment and their association with outcome were also evaluated. To reduce the selection bias of more severely ill patients receiving inotropes with a higher propensity, adjustment with propensity scoring based on observed variables was performed in both the general study population and the subgroup monitored by PAC. Due to the retrospective design of the study, patients were treated according to current international and local guidelines at the discretion of the attending physician.

Study II was a retrospective cohort study in which the association of early hemodynamic variables (first 24 hours in the ICU) with outcome was assessed in critically ill patients with severe acute pancreatitis. Demographic data, disease severity scores, continuously measured hemodynamic variables, data of renal function and data of vasopressor and inotrope therapy were collected as described for Study I. The association of hemodynamic variables and hemodynamic support of the general study population and those of the subgroup with circulatory shock with 90-day mortality, which was the primary endpoint, was assessed. The associations of hemodynamic variables with early mortality (within 14 days of ICU admission) and ICU and hospital lengths of stay were also assessed.

In Study III, an interventional prospective study, the predictive values of changes in hemodynamic parameters during elevation of PEEP from 10 to 20 cm H_2O were evaluated. The study algorithm is shown in Figure 7. Upon inclusion of the patient into the study, PEEP was set at 10 cm H_2O. At PEEP 10 cm H_2O, baseline catheter-derived measurements and TEE were performed. PEEP was then temporarily elevated to 20 cm

H_2O, during which measurements and TEE were performed again during an end-expiratory pause. PEEP was then returned to baseline. A volume expansion with plasma expander was then conducted, after which the measurements and TEE were re-performed for assessment of response to fluid. All patients were mechanically ventilated, sedated, and paralyzed during the study. The changes in catheter-derived hemodynamic values and in left ventricular end-diastolic area (LVEDA) and aortic velocity time integral (VTI_{Ao}) assessed by TEE were statistically evaluated for their ability to predict fluid responsiveness. The changes in respiratory parameters, blood gas analysis, and DO_2 induced by elevation of PEEP and volume expansion were also assessed.

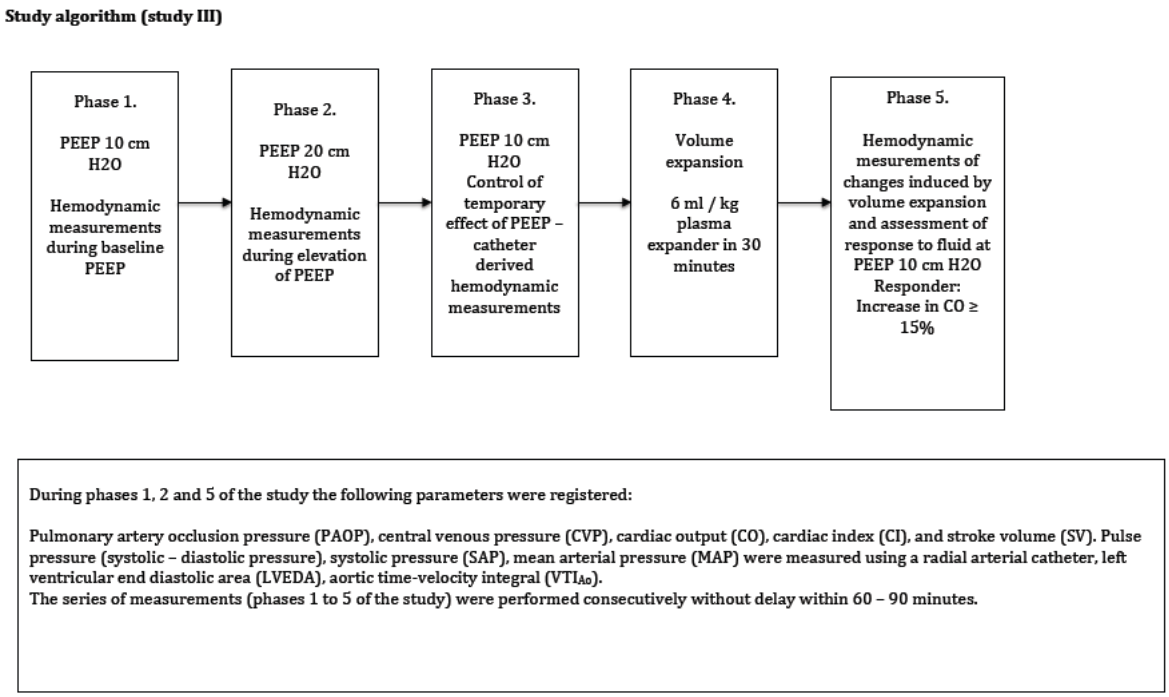


Figure 7. Study algorithm for Study III

Study IV was a predefined prospective observational substudy of the multicenter FINNAKI study. Its aim was to evaluate the association of early hemodynamics with development and progression of AKI during the first five days in the ICU. Special emphasis was put on MAP and vasoactive treatment during the first 24 hours in the ICU. Routine data (demographics, diagnoses, disease severity scores, outcome measures) were collected from the Finnish Intensive Care Consortium database. A standardized case report form (CRF) for registration of data on chronic and present health information, risk factors for AKI, infections and antimicrobial treatment, organ dysfunction, fluid balance, and information on renal replacement therapy (RRT) was filled at admission and daily during days one to five in the ICU, and at ICU and hospital discharge. KDIGO criteria[326] for AKI were assessed continuously based on urine output and measured creatinine values. The last serum creatinine (SCr) value from the preceding year, excluding the week before admission, was used as the baseline. If no baseline values were available, the

Modification in Diet in Renal Disease (MDRD) equation was used. The time-adjusted MAP was calculated based on each median value during the first 24 hours or until endpoint was reached and assessed for an association with development of AKI, as shown in Figure 8. The areas and aggregate times below MAP threshold values from 55 to 85 mmHg were calculated and were also assessed for an association with development of AKI. Moreover, the associations between vasoactive treatment and factors previously known to be associated with AKI, such as comorbidities, fluid balance, fluid therapy, and radio-contrast dye, were assessed.

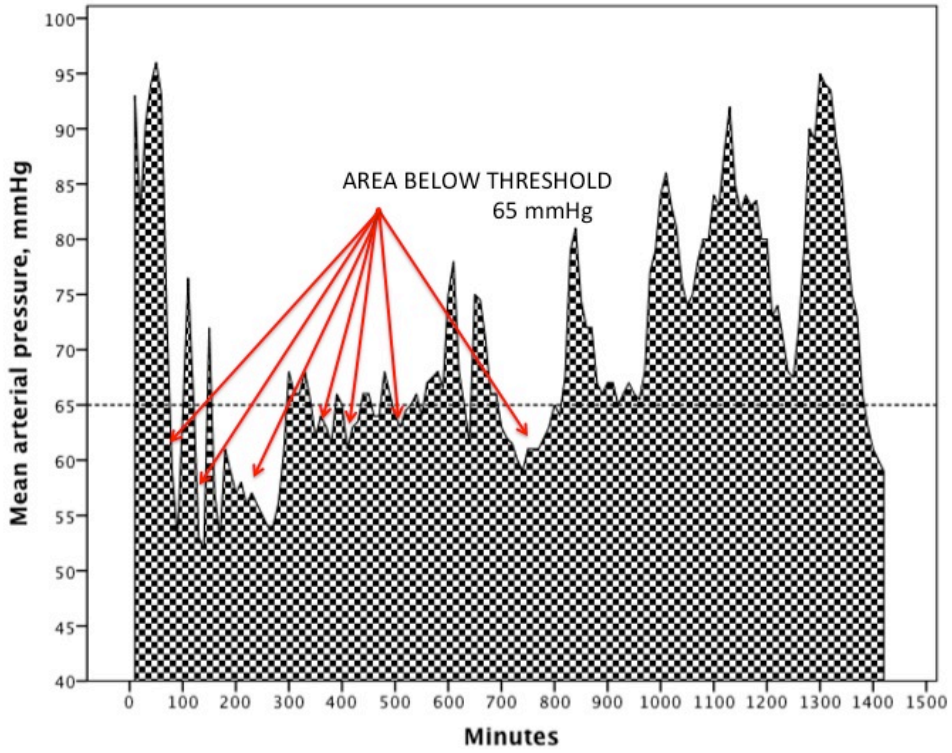


Figure 8. MAP during the first 24 hours for a patient with severe sepsis. The reference line is set at 65 mmHg and the arrows indicate (significant) areas below this line

4.3 CLINICAL DATA

For Studies I, II, and III, intensive care data were retrieved from the Finnish Intensive Care Consortium database (Intensium ®, Tieto Oy, Helsinki, Finland), which collects data from Finnish ICUs for benchmarking purposes. These data comprise information on admission and discharge from ICU and hospital, outcome measures, severity scoring [Acute Physiology and Chronic Health evaluation (APACHE II), [327] Sequential Organ Failure Assessment score (SOFA), [328] and Simplified Acute Physiology Score (SAPS II) [329]], diagnosis according to the International Classification of Diseases (ICD-10) classification, and basic demographic data such as age and gender. Patients were included into Studies I and II based on ICD-10 and APACHE III diagnoses. In these studies, data from the Finnish Intensive Care Consortium database were combined with data from the clinical data management system (PICIS, Wakefield, MA, USA, and Dräger Medical, Lübeck, Germany). Clinical data included continuously measured hemodynamic data and information on administration of vasopressors and inotropes and corticosteroid treatment. Continuous hemodynamic data (MAP, HR, SVO_2, mean pulmonary artery pressure (MPAP)) were collected as 5-minute median values. These values were manually validated and further filtered to 1-hour median values. Central venous pressure, CI, SV, and PAOP were registered every 1 to 6 hours upon measurement. Obvious outliers were manually removed from all hemodynamic measurements. Clinical data also included hourly urine output and routine blood sample parameters such as blood lactate and serum creatinine. Patients were identified based on individual admission numbers, and social security numbers were used for identification and retrieval of outcome data from the Population Register Center (Helsinki, Finland). For Study I, admission and discharge data from the emergency department clinical data system (Centricity, Clinisoft, GE, Fairfield, CT, USA) were collected. For Study II, additional data on surgical treatment was collected from the Operation Room Clinical Database (PICIS, Wakefield, MA, USA). In Study III, clinical and demographic data were collected prospectively onto a standardized CRF, as were data from hemodynamic measurements and blood samples. The results from the TEE were recorded onto the hard disk of ultrasound devices (Vivid I, GE, Fairfield, CT, USA), from where data were later retrieved for analyses.

In Study IV, data from the Finnish Intensive Care Consortium database (Intensium ®, Tieto Oy, Helsinki, Finland) were combined with prospectively collected data on the standardized CRF of the FINNAKI study. In addition, data on MAP and other hemodynamic variables, such as CVP, CO, and intra-abdominal pressure (IAP), were prospectively collected into the database. The CRF was used for daily registration of data on chronic and present health information, risk factors for AKI, sepsis, infections and antimicrobial treatment, organ dysfunction, fluid balance, and information on RRT. The CRF was first filled on admission, then daily through days 1-5, on discharge from the ICU, and finally on discharge from the hospital. Mean arterial pressure was prospectively collected in the local database as 2- or 5-minute medians, these values were then manually validated for the first 24 hours for eradication of erroneous values before conversion into 10-minute medians for analysis.

4.4 HEMODYNAMIC MEASUREMENTS

In Studies I, II, III, and IV, invasive measurement of blood pressure was performed continuously on all patients, generally by use of a radial arterial catheter as part of routine patient care. In some instances, for technical reasons, other anatomic sites for the catheter, such as the femoral artery, were preferred. In Studies I and II, CVP was monitored by either a central venous catheter or a pulmonary artery catheter. In Study I, 252 patients (60%) had a pulmonary artery catheter and 156 patients (37%) had some other means (central venous catheter) for measurement of central venous pressure; 22 patients (5.2%) had neither type of catheter inserted within 24 hours of ICU admission. In Study II, 64 patients (40%) had a PAC, 155 patients (97%) had another means of CVP measurement (central venous catheter), and only 4 patients had neither catheter type inserted within 24 hours of admission. In Study III, all patients had a PAC inserted, as this was one of the inclusion criteria of the study. In Studies I and II, CI, SV, CO, PAOP, SVO_2, and MPAP were all measured by use of a PAC, as other means of performing these measurements were not available in the ICUs at the time of the study. In all studies, SVO_2 was measured continuously using a fiberoptic catheter by reflection spectrophotometry. In Studies I, II, and III, CO measurements were generally performed by using the thermodilution method, ideally by use of 10 ml of ice-cold fluid (+0 - +6 degrees centigrade). The mean of three consecutive measurements was generally registered. Heart rate was recorded from the continuous EKG registration or alternatively from the arterial pressure wave registration. In Study III, the researchers performed thermodilution measurements of CO and measurement of PAOP as part of the study protocol during an end-expiratory pause.

4.5 TRANSESOPHAGEAL ULTRASOUND

Transesophageal ultrasound examinations were performed as part of the study protocol in Study III. Ultrasound devices with esophageal probes (Vivid I, GE, Fairfield, CT, USA) were used.Prior to the first ultrasound examinations at baseline, the adequacy of sedation was confirmed, after which the patients were paralyzed by administration of rocuronium (0.5 mg / kg) intravenously, and the probe was placed in the esophagus. Transesophageal ultrasound, during which left ventricular end-diastolic area and aortic velocity time integral (LVEDA and $VTI_{Ao)}$ were registered, was performed at baseline (PEEP set at 10 cm H_2O), during elevation of PEEP to 20 cm H_2O, and after volume expansion. LVEDA and VTI_{Ao} were registered and recorded from the transgastric view. LVEDA was measured by planimetry from the leading edge of the left ventricular endocardial border, and VTI_{Ao} was measured by pulse-wave Doppler at the level of the aortic valve. Before commencing the study, TTE and TEE were performed to ensure the absence of heart valve pathologies.

4.6 BLOOD SAMPLES

For Studies I, II, and IV, routine blood samples were drawn during normal clinical practice and follow-up. Routine laboratory tests comprised blood gas analyses, including lactate measurement, SCr, urea concentration, bilirubin concentration, hemoglobin and hematocrit, leukocyte and platelet count blood samples for daily assessment of disease and organ failure scores. In Study III, blood gas samples were drawn according to the study algorithm at baseline and after the volume expansion.
A laboratory sample protocol was also used for Study IV, but these samples were not used in this substudy.

4.7 INTERVENTIONS

In Study III, TEE was performed as described in Section 4.5. Moreover, a fluid challenge was conducted according to the protocol outlined in Figure 7. The fluid challenge consisted of 6 ml/kg plasma expander (Gelofusine, B.Braun Medical, Melsungen, Germany) and was given in 30 minutes. Moreover, blood samples were drawn at baseline and at the end of the study. Patients in all studies were otherwise managed according to local and international guidelines, at the discretion of the attending physicians.

4.8. DISEASE SEVERITY SCORES AND END-ORGAN FAILURE

In Studies I to IV, disease severity and organ failure scoring were part of normal clinical practice and follow-up. These were routinely registered in the Finnish Intensive Care Consortium database (Intensium ®, Tieto Oy, Helsinki, Finland), from where they were retrieved for the studies. Assessment of organ failures was performed daily in all ICUs using the SOFA score.[328] The severity of disease at baseline was also assessed using APACHE II [327] and SAPS II[329] scores after 24 hours in the ICU.

In Study IV, AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[326] We defined and staged AKI according to changes in serum creatinine (SCr) and urine output. The last SCr value from the previous year (excluding the week before the ICU admission) was used as the baseline SCr, and for those without a baseline value (n=292) we estimated it by using the Modification in Diet in Renal Disease (MDRD) equation], assuming a glomerular filtration rate of 75 ml/min/1.73 m2. The endpoint in Study IV was defined as new onset or progression of AKI (KDIGO stages I, II, or III or initiation of RRT) during days 1 to 5 in the ICU.

4.9 GENERAL POLICY IN THE MANAGEMENT OF PATIENTS IN THE INTENSIVE CARE UNIT

In Studies I to IV, patients were managed in the ICU according to current international and local guidelines,[330] at the discretion of the attending physician. Vasopressor treatment (mainly norepinephrine) was advocated when fluid treatment alone was inadequate to restore targets of MAP, generally a level of at least 65 mmHg. Inotropes were recommended when cardiac output or tissue perfusion achieved by fluid resuscitation and vasopressor treatment was insufficient, as defined by low CI, low SVO_2 (below 65%), or such clinical signs as cool mottled skin. Insufficient perfusion could also be suspected based on high lactate values and low urine output, which did not respond to volume expansion. The use of a PAC was recommended in the ICUs when the need for vasopressor support (norepinephrine) exceeded 0.1 μg/kg/min in Studies I and II. The management of patients with SAP in Study II followed widely accepted international [331,332] as well as local guidelines. Fluid treatment of these patients also followed current guidelines of treatment of sepsis, septic shock, and pancreatitis. [330,332,333] In Study II, prophylactic antibiotic therapy was initiated according to local guidelines. Surgical treatment was performed early only in cases of abdominal compartment syndrome, when conservative means of treatment were futile. Pancreatectomy or pancreatic necrosectomy was performed preferentially no earlier than at 3 weeks of illness. Endoscopic retrograde cholangiopancreatography was performed if required.

4.10 OUTCOME MEASURES

The ICU, hospital, and 90-mortality data for Studies I, II, and IV were acquired from the Finnish Intensive Care Consortium database and the Population Register Center in Helsinki, Finland. Long-term mortality data for Study I was acquired from the Population Register Center, Helsinki, Finland. In Study IV, new onset or progression of AKI was the primary endpoint (see Section 4.8).

4.11 STATISTICAL METHODS

STATISTICAL ANALYSES

The statistical analyses in Studies I and II were performed using SPSS 16.0 and 17.0 software (SPSS Inc., Chicago, IL, USA). In Studies III and IV, statistical analyses were performed using IBM SPSS Statistics 19.0 and 20.0 software (IBM, Armonk, NY, USA). For analysis and calculations of the MAP data of Study IV, NCSS 8 software (Kaysville, UT, USA) was used.

PRESENTATION OF DATA

In Studies I to IV, data are presented as absolute numbers and percentages, as median values with interquartile ranges (IQR, 25^{th} and 75^{th} percentiles), or as means and standard deviations (SD).

STATISTICAL SIGNIFICANCE

In all studies (I-IV), $p<0.05$ was considered significant.

MANN-WHITNEY U-TEST

This test was used for comparison of continuous variables between independent groups. It was used for hemodynamic, laboratory, and demographic data in Studies I to IV for independent groups such as inotrope receivers and non-receivers, survivors and non-survivors, fluid responders and non-responders, and patients with AKI or without AKI.

PEARSON'S CHI-SQUARE OR FISHER'S EXACT TEST

These tests were used as appropriate for the comparison of categorical data in Studies I to IV. Generally, Fisher's exact test was used when the number of cases in a sample was less than five.

KAPLAN-MEIER SURVIVAL CURVES

Kaplan-Meier survival curves were constructed for 90-day mortality differences between inotrope receivers and non-receivers in Study I.

MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

This analysis was used to test the independent effect of variables on outcome.

PROPENSITY SCORING

Propensity scoring was used to reduce selection bias and the influence of confounders in Study I. It was calculated based on variables found to be associated with initiation of inotrope treatment; outcome measures were not included in the calculation. The propensity score for inotrope treatment achieved by multivariable logistic regression was then added to the final regression analyses as a covariate.

RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE

ROC analysis, with the calculation of areas under the curve (AUC), was used in Study III to evaluate the prognostic value of changes in hemodynamic variables for prediction of fluid responsiveness. The best cut-off values were identified using the Youden Index method (sensitivity +specificity -1). [334,335] The best cut-off value for clinical purposes was identified in Study III as the value at which specificity and negative predictive value were highest (100%).

In Study IV, ROC analysis was used to evaluate the prognostic value of time-adjusted MAP and highest norepinephrine doses in the development and progression of AKI. As in Study III, the best cut-off values were identified as the values of highest Youden Index.

AREAS UNDER THE ROC CURVE (AUC)

AUCs were used to determine the accuracy of hemodynamic variables for prediction of fluid responsiveness in Study III and the predictive value of time-adjusted MAP and highest doses of norepinephrine in development and progression of AKI in Study IV. The AUC was calculated with 95% confidence intervals.

AREA UNDER CURVE (TRAPEZOIDAL RULE)

For the calculation of time-adjusted MAP in Study IV, the AUC of 10-minute median MAP values on the Y-axis and time as minutes on the X-axis was computed by the trapezoidal rule using NCSS 8 software. The time-adjusted MAP was calculated as the AUC divided by the aggregate time of MAP follow-up until reaching an endpoint or up to 24 hours. In Study IV, the area of MAP x time (minutes) below MAP thresholds (55-85 mmHg) and the aggregate time spent below these thresholds were also calculated

SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES

		CONDITION (Fluid response) Positive (Responder)	Negative (Non-responder)	
TEST OUTCOME (ΔMAP)	Positive	A=true POSITIVE	C=false POSITIVE	A+C
	Negative	B=false NEGATIVE	D=true NEGATIVE	B+D
		A+B	C+D	

Sensitivity, specificity, positive predictive value, and negative predictive value were used in Study III and were calculated as follows:

Sensitivity = true positives/ true positives + false negatives = A / (A+B)
Specificity = true negatives/ (true negatives + false positives) = D/ (C+D)
Positive predictive value = true positives / (true positives + false positives)= A/ (A+C)
Negative predictive value = true negatives / (true negatives + false negatives)= D/ B+D)

5. ETHICAL ASPECTS

The Ethics Committee of Helsinki University Central Hospital approved all study protocols (I-IV). Due to the retrospective design and lack of intervention in Studies I and II, informed consent was waived.

Informed consent was obtained from all subjects or next of kin in Study III before inclusion in the study. In Study IV, written consent was obtained from all subjects or next of kin with a deferred consent policy.

6. RESULTS

6.1 FACTORS ASSOCIATED WITH INOTROPE TREATMENT AND THE ASSOCIATION BETWEEN TREATMENT AND OUTCOME IN SEPTIC SHOCK (I)

The results showed that inotropes were used rather frequently in patients with septic shock in the two ICUs included in the study. Of the 420 patients, 186 (44.3%) received inotrope treatment. Patients who were treated with inotropes were generally more severely ill, as defined by higher APACHE II scores [24.0 (18.0-29.0) vs. 18.0 (14.0-23.0)], higher SAPS II scores [45.5 (37.0 - 58.0) vs. 38.0 (29.8-46.0)], and higher SOFA score for day 1 [10.0 (8.0-13.0) vs. 8.0 (6.0-10.0)] ($p<0.001$ for all). The patients who received inotropes had higher heart rate, lower MAP, and higher CVP during the first 24 hours in ICU ($p<0.001$ for all). These patients also received higher doses of norepinephrine and vasopressin, and they more often received sepsis hydrocortisone, all indicating a more severe degree of hemodynamic compromise. In addition, the lactate levels in inotrope receivers were significantly higher than in non-receivers [4.1 (2.2-6.7) mmol/l vs. 2.1 (1.5-3.3) mmol/l, $p<0.001$]. Higher CVP, higher dose of norepinephrine, and higher lactate values were independently associated with inotrope treatment. Of all inotropic substances, dobutamine was used most frequently (90.3% of all inotrope administrations). In 147 patients (79%), a single inotrope was used. The mortality of patients receiving at least two different inotropes was significantly higher than that of those receiving only one (64.1% vs. 36.7%).

When analyzing factors associated with outcome, the results of the multivariable regression analysis revealed that use of inotrope treatment [OR 2.29 (1.33-3.94)], higher APACHE II score, and advanced age were independently associated with 90-day mortality. In a second regression model, in which inotropic substances were analyzed separately, dobutamine [OR 2.34 (1.36-4.02)] was associated with 90-day mortality. The results remained unchanged when adjusted for propensity to receive inotropes. The hospital and 90-day mortalities were significantly higher for inotrope receivers than for non-receivers (33.9% vs. 17.1%, $p<0.001$ and 42.5% vs. 23.9% $p<0.001$ respectively).

In the subgroup of 252 patients monitored by a PAC, an even higher proportion received inotrope treatment (160/252, 63.5%). In this subgroup of patients, a higher lactate level and lower SVO_2 and CI values were independently associated with inotrope treatment. Also in this subgroup, ICU, hospital, and 90-day mortalities were significantly higher among inotrope receivers than among non-receivers (28.1% vs. 14.1%, 33.8% vs. 18.5%, and 41.9% vs. 19.6% respectively) ($p<0.02$ for all).

In the multivariable diagnosis, lower MAP, higher APACHE II score, higher age, male gender, inotrope treatment [OR 2.36 (1.01-5.52)], and a modest increase in SV were

independently associated with 90-day mortality. After adjustment with propensity to receive inotropes, the results were unchanged, except for inotrope treatment, which was no longer significant. We also found that in inotrope receivers the ability to increase SV in response to inotrope treatment was associated with survival at 90 days (p=0.003).

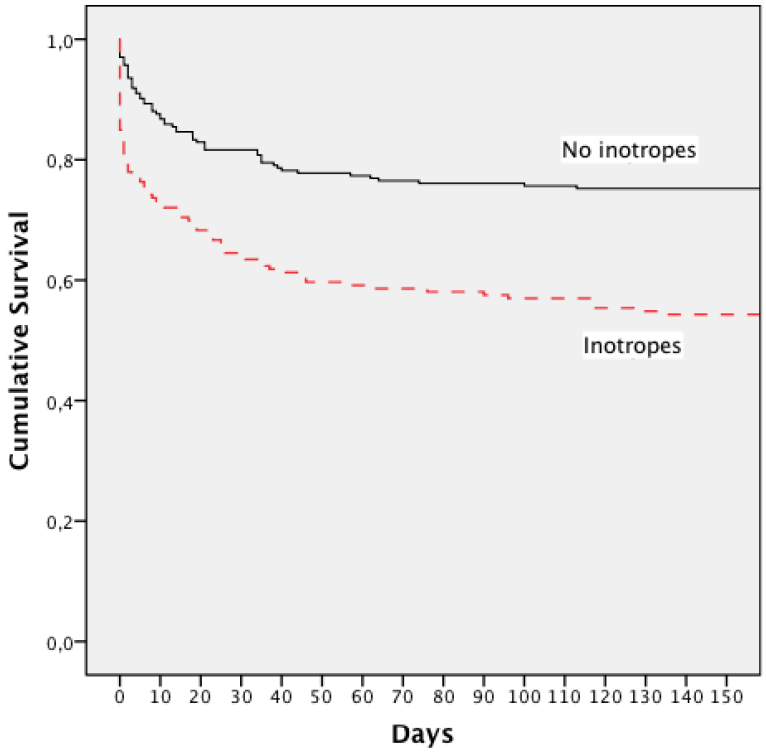


Figure 9. Kaplan Meier survival plot of inotrope receivers and non-receivers in Study I.

6.2 EARLY HEMODYNAMIC VARIABLES AND OUTCOME IN SEVERE ACUTE PANCREATITIS (II)

Of the 159 patients with SAP in Study II, the majority (64.2%) received vasopressors during the first 24 hours. In 73 patients, the norepinephrine dose exceeded 0.1 μg/kg/min for at least one hour. These patients constituted the subgroup of patients with circulatory shock. Inotropes were administered to 26 patients (16.4%); nearly all of these patients (25/26) received dobutamine. A minority of the patients (15.1%) also received hydrocortisone for hemodynamic support. A total of 38 patients (23.9%) underwent abdominal surgery during their ICU stay. In 19 patients (11.9%), primary surgery was performed within 24 hours of ICU admission.

The 90-day mortality for all patients with SAP was 15.1%. Early mortality (within 14 days) accounted for half of the deaths. In the subgroup of 73 patients with circulatory failure, 90-day mortality was significantly higher, 26.0%.

Age ($p=0.001$), but not gender or etiology of pancreatitis, was associated with 90-day mortality. Time spent in hospital before referral to the ICU had no association with outcome. More severe illness, in terms of higher APACHE II and day 1 SOFA scores, was also associated with 90-day mortality ($p\leq0.001$). The use of inotropes per se, higher doses of norepinephrine, and higher lactate values, all indicating hemodynamic failure within the first 24 hours, were also associated with 90-day outcome. Patients who succumbed to the disease had lower minimum values of MAP [66.1 (61.0 -70.6) vs. 71.1 (64.3-80.0) mmHg, $p=0.002$]. Indicators of impairment of renal function, such as lower hourly urine output, higher SCr values, and higher renal SOFA subscore were also associated with death at 90 days ($p<0.002$ for all). Patients who underwent surgery at any time during their ICU stay had significantly higher 90-day mortality than those who did not (26.3% vs. 11.6%, $p=0.006$).

For the whole study group, advanced age, higher serum creatinine, and lower MAP were independently associated with 90-day mortality. In the subgroup of patients with circulatory shock, higher APACHE II score, lower CI, and higher CVP predicted 90-day mortality.

6.3 PREDICTION OF FLUID RESPONSIVENESS BY CHANGES IN HEMODYNAMIC VARIABLES DURING ELEVATION OF PEEP IN SEPTIC SHOCK (III)

Of the 20 patients studied, 30% were fluid responders, as defined by an increase in CO by at least 15% subsequent to a fluid challenge. In fluid responders, DO_2 increased as a result of the fluid challenge, while in non-responders it decreased.

The best predictors of fluid responsiveness were PEEP-induced decreases in MAP and systolic arterial pressure (ΔMAP and ΔSAP). We found no association of changes in echocardiographic measurements, LVEDA, and VTI_{A_0} induced by elevated PEEP (from 10 to 20 cm H_2O) with fluid responsiveness. The catheter-derived filling pressures CVP or PAOP were not able to predict fluid responsiveness either at baseline or during elevation of PEEP. The differences in decrease in CO or VTI_{A_0} were not statistically significant between responders and non-responders.

In the ROC analysis, the AUC for the change in MAP (ΔMAP) and the change in systolic arterial pressure (ΔSAP) induced by elevated PEEP (CI 95%) were 0.91 (0.77-1.0) and 0.82 (0.64-1.0), respectively.

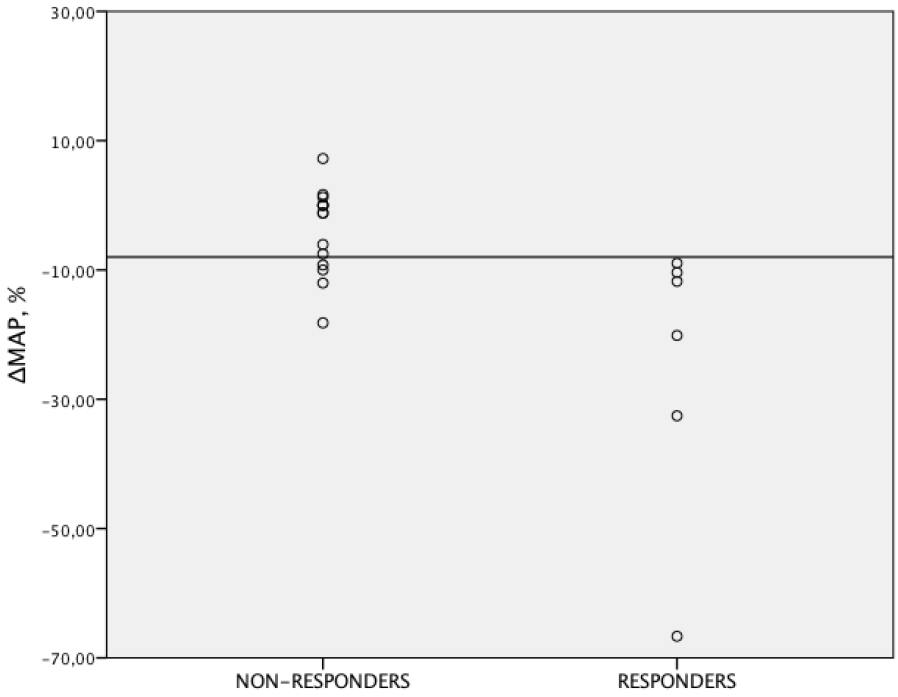


Figure 10. Change in MAP during elevation of PEEP from 10 to 20 cm H_2O in fluid non-responders and fluid responders. Reference line is set at Δ MAP -8%.

By the Youden Index, the best cut-off for ΔMAP was -10.2, sensitivity 83% (95% CI 0.44-0.97), but the best cut-off for clinical purposes was a decrease in MAP by at least 8%, with a sensitivity and an NPV of 100%.

6.4 ASSOCIATION BETWEEN EARLY HEMODYNAMICS AND PROGRESSION OF AKI IN SEVERE SEPSIS (IV)

Of the 423 patients with severe sepsis, 153 (36.2%) developed AKI during the first five days in the ICU. In 51 patients (12.1%), AKI progressed further during days 1 to 5, and 34 patients (8.0%) received RRT. The patients who developed AKI more often suffered from septic shock (87.6% vs. 68.5%, $p<0.001$). Patients who developed AKI more often had diabetes (type I or II) and chronic kidney disease (CKD), but not hypertension, as comorbidities prior to ICU admission. A greater portion of patients who developed AKI had also been subject to radiocontrast dye and colloids preceding ICU admission.

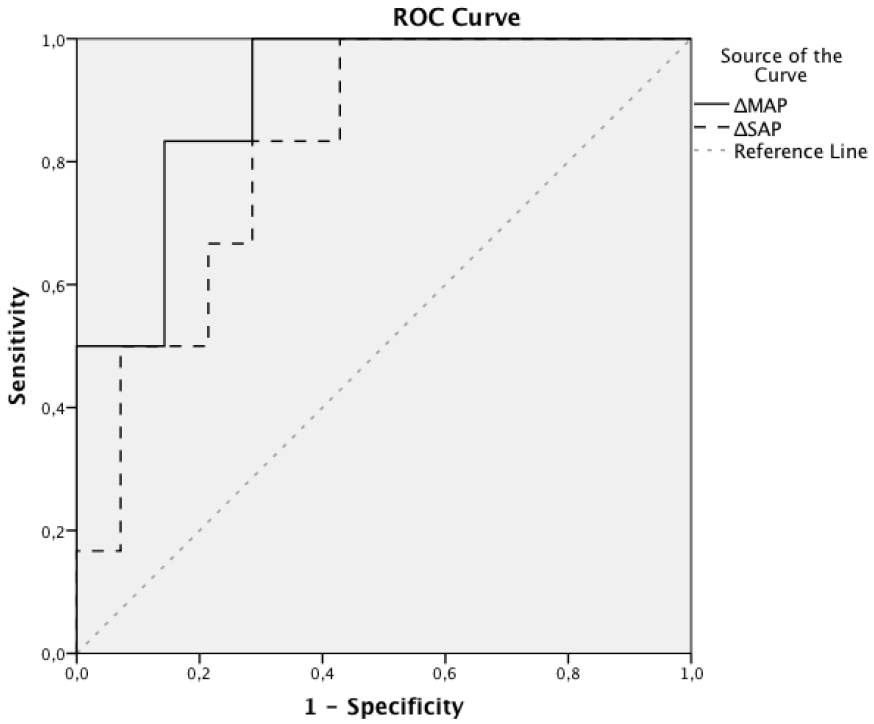


Figure 11. AUCs of ΔMAP and ΔSAP in ROC analysis of Study III.

Generally, patients who developed AKI appeared more severely hemodynamically compromised in terms of requirements for vasopressor and inotrope support, in addition to lower blood pressure levels, during the first 24 hours in ICU. The time-adjusted MAP was significantly lower in patients who developed AKI than in those who did not [74.4 (68.3-80.8) vs. 78.6 (72.9-85.4) mmHg]. Patients developing AKI also spent significantly longer periods of time at values of MAP lower than 70 mmHg (55-70 mmHg) ($p<0.05$). These patients received norepinephrine more often and at higher doses, both during the first 24 hours and throughout the study period ($p<0.001$ for all). A substantially greater portion of patients with AKI also received inotrope treatment (26.1% vs. 7.1%, $p<0.001$).

In the ROC analysis, by use of the Youden Method, the best cut-off for time-adjusted MAP for the first 24 hours was 72.7 mmHg for prediction of progression of AKI. As for dose of norepinephrine, the best cut-off was 0.19 µg/kg/min.

In the multivariable regression analysis, highest lactate during 24 hours, CKD, daily dose of intravenous furosemide, and time-adjusted MAP per mmHg [odds ratio (OR) 0.96; 95% CI 0.94 to 0.99] were independent predictors of progression of AKI. In the second model to which time-adjusted MAP of 73 mmHg was added as a categorical variable, highest lactate, CKD, daily dose of intravenous furosemide, dobutamine treatment, and time-adjusted MAP below 73 mmHg were independent predictors of progression of AKI.

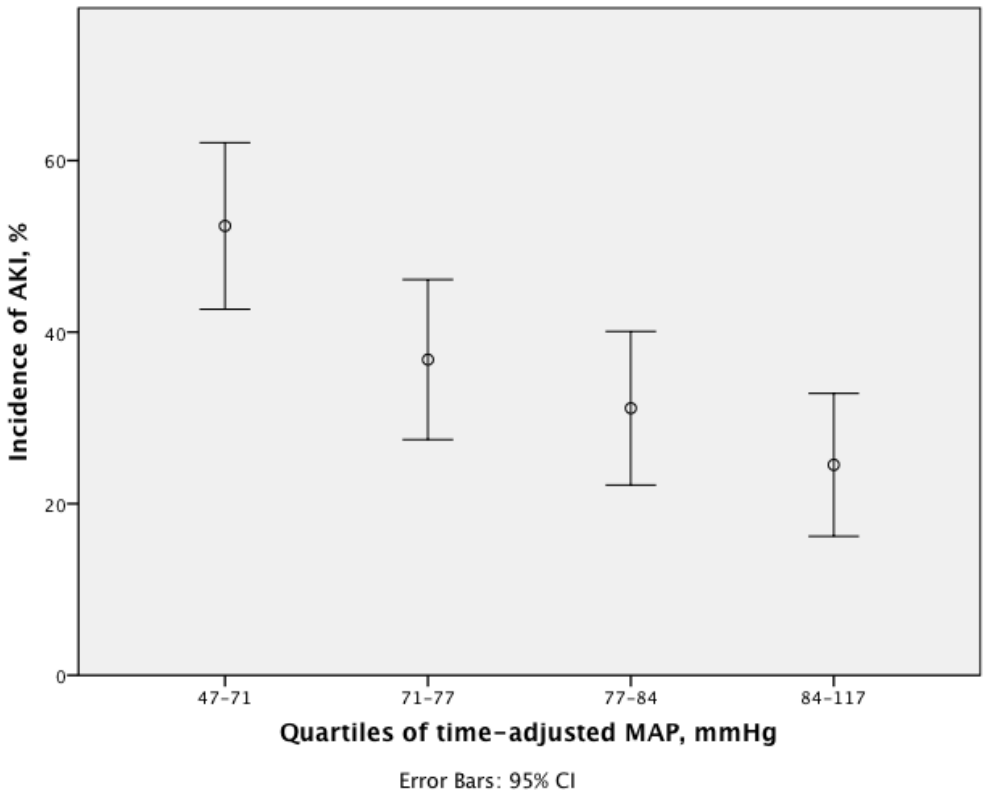


Figure 12. Incidence of AKI by quartiles of time-adjusted MAP during the first 24 hours in the ICU (Study IV).

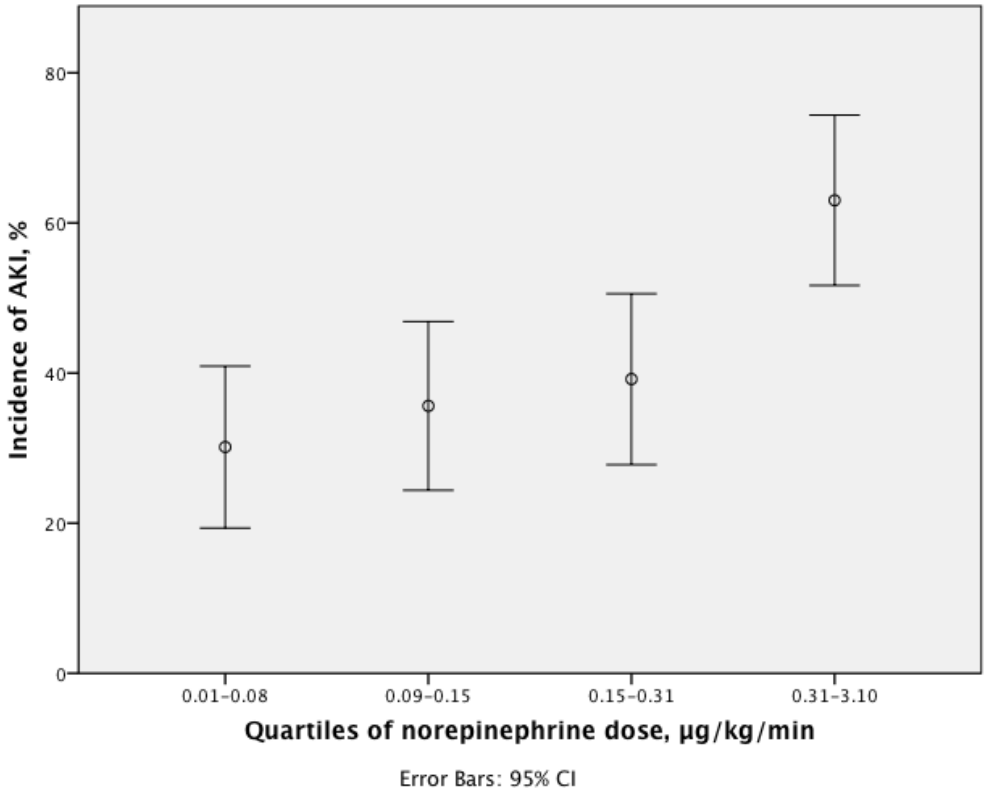


Figure 13. Incidence of AKI by quartiles of maximal dose of norepinephrine during the first 24 hours in the ICU (Study IV).

6.5 VASOACTIVE TREATMENT OF CRITICALLY ILL PATIENTS WITH SEPSIS AND SEVERE ACUTE PANCREATITIS (I, II, and IV)

In the two retrospective studies of septic shock and SAP, the maximum doses of norepinephrine infusions were 0.31 (0.14-0.69) and 0.07 (0.0-0.23) μg/kg/min, respectively. In the study of patients with septic shock, norepinephrine treatment was a prerequisite for inclusion in the study. Inotropes were received by 44.3% of patients with septic shock and by 16.4% of patients with SAP. In these two studies, patients who received inotropes received significantly higher doses of vasopressors [0.56 μg/kg/min (0.25 – 1.14) vs. 0.20 μg/kg/min (0.10-0.39) for patients with septic shock, and 0.32 μg/kg/min (0.13-0.55) vs. 0.029 (0.0-0.18) for patients with SAP]. In both studies, the maximum dose of norepinephrine administered during the first 24 hours and the use of inotropes per se were associated with 90-day mortality. In patients with SAP, the highest norepinephrine dose and the use of inotrope treatment were also associated with early death (≤ 14 days).

In the prospective study of patients with severe sepsis, the maximum dose of norepinephrine was 0.19 μg/kg/min (0.07-0.47) for patients who developed AKI and 0.08 μg/kg/min (0.00-0.19) for those who did not. In this study, the dose of norepinephrine was associated not only with progression of AKI ($p<0.001$) but also with 90-day mortality ($p=0.037$), despite the fact that all patients who died within the first five days were excluded from the study. The use of inotropic substances was associated with development of AKI, but not with 90-day mortality.

Vasopressin was used in only one patient in the SAP study. In patients with septic shock, it was administered to 16 patients (3.8%). Both the use of ($p=0.001$) and the dose of vasopressin ($p=0.012$) were associated with 90-day mortality in this group of patients. In patients with severe sepsis, vasopressin was used in only 5 patients, 4 of whom developed AKI. The difference did not reach statistical significance ($p=0.06$) regarding AKI or 90-day mortality ($p=1.0$).

In patients with septic shock, sepsis corticosteroid treatment was initiated in 60.2% as hemodynamic support. Sepsis corticosteroids were administered to 15.1% of patients with SAP. In both studies, hydrocortisone treatment was significantly associated with 90-day mortality ($p<0.001$). In the prospective study of patients with severe sepsis, 23.9% received sepsis corticosteroids. In the subgroup of patients who received norepinephrine during the first 24 hours, the proportion was 31.5%. Consistent with the two retrospective studies, corticosteroid treatment was associated with both progression of AKI ($p<0.001$) and death at 90 days ($p=0.01$) also in this prospective study.

6.6 OUTCOME OF SEVERE SEPSIS, SEPTIC SHOCK, AND SEVERE ACUTE PANCREATITIS (I, II, and IV)

In Study I, the mortality in the two ICUs for patients with septic shock was 17.4%, the hospital mortality was 24.5%, and the 90-day mortality was 32.1%. In patients with severe acute pancreatitis, the mortality rates were substantially lower: the ICU mortality was 8.8%, the hospital mortality 13.2%, and the 90-day mortality 15.1%.
When the 70 excluded patients in the severe sepsis group who had died within days 1 to 5 were included in the mortality rates, the ICU mortality in 13 Finnish ICUs was 18.5% and the 90-day mortality 34.7%.

7. DISCUSSION

STRENGTHS AND WEAKNESSES OF THE STUDY

In Studies I and II, the study populations were large and a considerable portion of the patients were monitored by a PAC, providing detailed hemodynamic data of patients with septic shock. Despite being retrospective studies, the hemodynamic data and data on vasoactive treatment were prospectively registered into the clinical patient data system, improving the quality of these data. The adjustment with propensity to receive inotropes also reduced some bias in this retrospective study. The incorporation of TEE and PAC-derived variables into Study III contributed to a large set of assessed hemodynamic variables, allowing a more focused approach in future studies. The large and prospective multicenter data of Study IV, in addition to the highly detailed MAP data, add strength to this study. Moreover, a large set of data of factors associated with development of AKI was prospectively collected, also providing strength to the study. Lastly, 90-day mortality was used as an outcome measure; this is more informative than 28-day or 30-day mortalities, which have mostly been used previously. Critically ill patients often require ICU and hospital care for long periods of time, sometimes with additional weeks of rehabilitation in primary care facilities.

There are some limitations to the study. First and foremost, the retrospective design of Studies I and II must be noted. Due to their retrospective design, the results of these studies may only generate hypotheses and serve as a platform for future prospective studies. These studies were also conducted in a single hospital, which may decrease the general applicability of the results. Inclusion in these studies was based on diagnoses registered in the database, which may have led to erroneous inclusions. The high number of patients monitored by PAC may also be considered a limitation, as it does not reflect current European ICU practices. Important clinical data, demographic data, and laboratory data as well as data on comorbidities were not retrieved in these studies. The addition of these variables to the propensity score adjustment in Study I would have increased the strength of the model. The lack of data of IAP in Study II also needs to be emphasized due to its impact on abdominal perfusion pressure data.

The limited sample size of Study III calls for validation in a larger study population. The study was conducted in sedated and mechanically ventilated patients with septic shock, with sinus rhythm and no serious comorbidities. Therefore, the results may not apply to other groups of patients. Moreover, the changes in hemodynamic variables observed in this study may not be observed using other baseline values and increments of PEEP. Lastly, the study was not designed for elucidation of the underlying mechanisms of hemodynamic changes during elevation of PEEP.

Although prospective, the design of Study IV was observational without randomization regarding hemodynamic support. Possibly, therefore, the hemodynamic changes observed between patients who did and did not develop AKI were caused by

differences in severity of illness. The decision to exclude patients who died during the five days of the study in an attempt to decrease the impact of competing risks may be considered flawed, as it may have caused selection bias through exclusion of the most severely ill patients. Information on abdominal perfusion pressure could not be assessed in the study. Information of IAP was registered only in patients in whom elevated IAP was suspected, and inclusion of the registered values would thus have led to an increase in bias. The relationship between cardiac output and AKI could not be assessed due to lack of data on cardiac output. Lastly, although the results indicated an association of use of colloids with progression of AKI, we could not deduce the type of colloid used in the ICU, which would have been of further interest.

METHODOLOGICAL CONSIDERATIONS

Due to the retrospective nature of Studies I and II and the observational nature of Study IV, any conclusions about causality cannot be drawn. In addition, some other methodological factors must be considered. The retrospective identification of patients with septic shock and severe acute pancreatitis based on APACHE III and ICD-10 diagnoses (and need for vasopressor support during the first 24 hours) may have affected the composition of the final study population. It may have led to incorrect inclusions and exclusions, rendering the study population different or even incomparable to populations with septic shock of other studies. On the other hand, retrospective inclusion may lead to a more varied admixture of patients through inclusion of patients with varying comorbidities, who possibly would have been excluded from a prospective study. One might argue that a retrospective study at its best provides a more realistic study population that is closer to clinical practice. By adjusting for propensity to receive inotropes, the selection bias was likely diminished. However, propensity scores can only adjust for measured variables, and we recognize that many potentially important variables affecting initiation of inotrope treatment or outcome were not included in the model.
Data were collected over a four-year period, during which changes in the treatment of critically ill patients may have occurred, potentially affecting the results. In addition, some provider-dependent differences in the care of patients may persist despite the different ICUs being included in the propensity score to reduce any bias.

While Study III was being performed, many advances were made in assessment of fluid responsiveness and bedside echocardiography. At the time of planning the study, TEE was widely preferred to TTE in ICU patients. Had the study commenced today, transthoracic parameters would probably have been chosen, mainly due to their lack of invasiveness and fewer contraindications for use. Numerous methods and appliances for assessing fluid responsiveness and CO based on pulse pressure or stroke volume variation have been validated in recent years and are now widely used in the ICU. For less invasive monitoring, some of these methods could also have been used for assessing the response to fluid. However, at the time of the study, the PAC was considered the gold standard for CO assessment.

The prospective design of Study IV was appropriate for assessing the association between hemodynamic factors and progression of AKI. However, the inclusion of patients over a six-month period was performed during the autumn and winter months, which may have had an impact on the occurrence of severe sepsis due to seasonal variation. The geographical coverage of the 17 ICUs was good. The choice of patients with severe sepsis for the analysis could have been supplemented by a substudy of patients with septic shock, as these patients seem to be at greatest risk of developing AKI. Furthermore, as evidenced by earlier studies, [126] hemodynamic variables and vasoactive treatment seem to matter most in this group of patients, in which derangements of autoregulation of end-organ blood flow plausibly are most severe. As for the multivariable regression analyses of Studies I, II, and IV, the choice of variables in the models may be debated. We aimed at including variables lacking interrelationships, but as several hemodynamic variables and a given treatment may be correlated, the variables chosen may not always be fully independent.

ASSOCIATION OF INOTROPE TREATMENT WITH OUTCOME IN SEPTIC SHOCK

This study showed that higher CVP, higher doses of norepinephrine, and higher lactate values during the first 24 hours in the ICU were associated with inotrope treatment. Moreover, inotrope treatment, higher APACHE II score, and higher age were independently associated with 90-day mortality. Dobutamine was used in 90% of inotrope receivers.

This is one of the first studies assessing the association of inotrope treatment with outcome in patients with septic shock. Current guidelines recommend the use of dobutamine for raising CO and tissue perfusion in patients with septic shock when the response to fluid and vasopressors is inadequate. [35] The evidence supporting the use of dobutamine is nevertheless rather weak. Evidence exists that dobutamine may increase CO and venous oxygen saturation and may possibly be advantageous for splanchnic circulation. [336,337] However, a recent study failed to show any benefit of dobutamine treatment in terms of tissue perfusion, despite an increase in CO. [336]

In a recent large retrospective study, the use of inotropes was associated with higher mortality and development of AKI, even after adjustment for propensity to receive inotropes. [338] Dobutamine, milrinone, and epinephrine were defined as inotropes; levosimendan was not used in their patient group. In patients with heart failure, dobutamine may be associated with worse outcome, also in terms of mortality, when compared with control treatment or placebo. [310] Levosimendan seems to reduce mortality in cardiac surgery and cardiology settings. Insufficient data exist of its use in patients with septic shock. [313]

The adverse effects of catecholamine inotropes, such as arrhythmias, increased myocardial oxygen consumption, and elevated risk of myocardial ischemia, are fairly well known. Furthermore, and perhaps more interestingly, dobutamine has been shown to affect innate immunity in a pro-inflammatory manner, as opposed to norepinephrine.[34] Evidence also exists that catecholamines, in addition to being enhancers of biofilm formation, may be potent stimulators of bacterial growth by participating in bacterial iron metabolism.[339,340]

In the current study, higher lactate values, higher norepinephrine values, and higher CVP were associated with inotrope treatment. This finding is not surprising since all of these parameters may reflect a more severe hemodynamic compromise. A higher CVP value may partly reflect futile attempts to stabilize the patient by vigorous fluid resuscitation, but it may also be explained by an inability to adapt to the increase in volume, in other words, being the price paid for volume expansion.[161,250] Higher doses of norepinephrine in this study were probably required in more severely ill patients with more profound vascular hyporesponsiveness.[341]

Higher lactate values are most probably explained by impaired tissue perfusion and anaerobic metabolism, thus serving as an indication for initiation of inotropes.[342,343] However, a decision to initiate inotrope treatment is not always based on correct indications. High lactate levels might not be caused by insufficient CO, but instead by aerobic glycolysis and mitochondrial disturbances, and therefore, should not be corrected by inotropes.[344-346]

Inability to respond to dobutamine by an increase in SV has earlier been shown to be associated with poor outcome in septic shock.[347] This finding was also confirmed in our study. In patients receiving inotropes, the ability to increase SV was associated with better outcome. In patients not receiving inotropes, the change in SV had no bearing on outcome. This phenomenon may be explained by a cardiovascular or preload reserve in inotrope responders, which is associated with a more favorable outcome.[29,348] Lately, diastolic dysfunction has been found to be associated with poor outcome in septic shock.[163,164,349] Catecholamine inotropes may not be the ideal treatment for these patients, as they may induce increased myocardial stiffness.[350-352]

Although inotropes may be beneficial in short-term use for patients with septic shock, the beneficial effects may be outweighed by deleterious ones over time, ultimately leading to worse long-term outcomes. Moreover, some patients, particularly those who do not respond favorably to dobutamine by elevation of SV, possibly will not benefit from the treatment, but are merely exposed to different adverse effects. Based on the retrospective design of this study, no definite conclusions can be drawn. However, evidence from this and other studies suggest that the use of inotropes may indeed be associated with worse outcome in patients with septic shock. Therefore, randomized prospective studies to scrutinize the causality of this observed association are justified.

ASSOCIATION OF EARLY HEMODYNAMIC VARIABLES WITH OUTCOME IN SEVERE ACUTE PANCREATITIS

Few studies have assessed the association between hemodynamics and outcome in SAP. [353]Although fluid treatment is advocated in all current guidelines for severe pancreatitis, there is great uncertainty regarding hemodynamic targets for resuscitation and details of fluid resuscitation to optimize outcome are scant. [19,354] Although SAP has several similarities with septic shock [355], current guidelines for management of septic shock may not be optimal for management of SAP.

Advanced age, higher serum creatinine, and lower MAP were independent risk factors for 90-day mortality in patients with SAP in this study. In the subgroup of patients with circulatory shock, higher APACHE II score, higher CVP, and lower CI were independently associated with 90-day mortality.

Previously, results from a small retrospective study by Malcynski and coworkers showed that high blood lactate values, low arterial blood pressure, and high heart rate were associated with adverse outcome in this group of patients, all being indicators of a more profound circulatory failure, as was the use of vasopressors and inotropes. [353] In the present study, these findings were confirmed, except for heart rate, which had no association with outcome.

The theoretical basis for aggressive fluid resuscitation is that rapid restoration of the microcirculation will prevent further local damage and prevent escalation of the disease and ultimately the development of organ failure. [356] Early mortality in SAP has been attributed mainly to cardiopulmonary failure and early multi-organ dysfunction. Late mortality is predominantly caused by infectious complications and consequent organ dysfunction. Although infectious complication may lead to organ failure, there is also some evidence of an opposite causal relationship. Multiple organ dysfunction (MOD) has been shown to precede infectious complications by an average of two weeks. MOD is thus thought to cause deterioration of the immune response, facilitating bacterial translocation and development of uncontrolled infection. [357] Be that as it may, early hemodynamics and resuscitation have considerable importance for both early and late outcome measures.

Nonetheless, overzealous rehydration does not appear to be the solution to the problem of how to optimally manage hemodynamics. As in other groups of critically ill patients, [200,358] there is now some evidence that excessive fluid load is associated with worse outcome in patients with SAP. [359] We found that in patients with SAP and circulatory shock, a higher CVP and a lower CI were associated with 90-day mortality. Higher CVP has also been associated with poor outcome in patients with septic shock [200] and in patients with SAP. [360] Due to the design of our study, the underlying cause for this association could not be determined. We can only hypothesize that it may be due to either excess fluid resuscitation or impaired myocardial function with a concomitant inability to adjust and benefit from the volume expansion, [161,250] or plausibly both. The hypothesis of impaired cardiac contractility is supported by the fact that low CI also was associated with poor outcome.

Over the last decades, concerning many patient groups in the ICU, the pendulum has swung from restrictive fluid administration to liberal fluids, and back again. Some of this change may be the result of temporal fluctuations in current perceptions of what is right according to the rule of art. Nevertheless, acknowledging that fluids are drugs with an optimal dosage and potential side-effects makes sense, especially in the face of recent data pointing to important adverse effects. [256,257]

In addition to optimal fluid resuscitation, information regarding appropriate targets for hemodynamic management is urgently needed. The current study showed that low blood pressure is associated with worse outcome, but this may be explained by both more severe disease and suboptimal management. Furthermore, as this study could not analyze the association of IAP or abdominal perfusion pressure with outcome, an important piece in the hemodynamic puzzle is regrettably missing. As shown by two recent meta-analyses of hemodynamic treatment and fluid resuscitation of patients with SAP, large prospective randomized studies for assessing optimal hemodynamic management of early SAP are clearly warranted. [19,20]

PREDICTION OF FLUID RESPONSIVENESS BY ELEVATION OF PEEP IN PATIENTS WITH SEPTIC SHOCK

In the current study, a decrease in SAP and MAP during elevation of PEEP from 10 to 20 cm H_2O predicted fluid responsiveness in mechanically ventilated patients with septic shock. In the ROC analyses, the AUC for the changes in MAP and SAP was 0.91 and 0.82, respectively. These predictive values are comparable with those of PPV and SVV. [38] For clinical use, the most important result was that MAP decreased by 8% or more during elevation of PEEP in all patients who responded favorably to fluid challenge. The results indicate that the current method could be used for ruling out fluid responsiveness in this group of patients, using only the ventilator and an arterial pressure line.

During the time period that this study was conducted many dynamic means of assessing fluid responsiveness were assessed and validated. [38,361] Nonetheless, the issue of predicting fluid response continues to puzzle clinicians. The translation of methods proven reliable in experimental or clinical studies into everyday practice is not always easy and straightforward. Accurate methods may not even be reliable when transferred from bench to bedside, a problem that has been stressed in recent studies [362,363] Moreover, only a few echocardiographic methods have been validated against the gold standard, namely CO assessment by thermodilution. [238] Due to individual ventilator settings based on differences in pulmonary function and consciousness, arrhythmias, and occasional contra-indications to the use of particular means of assessing fluid responsiveness, one method of assessing fluid responsiveness will not fit all patients at all times.

The most important and challenging part of predicting fluid responsiveness is the determination of which patients will not benefit at all from further fluid, as given fluid cannot be easily removed. In the current study, the calculated oxygen supply decreased in

non-responders subsequent to the volume expansion, while it increased in responders, further emphasizing the importance of knowing when to give fluid and when to stop.

Somewhat surprisingly, neither LVEDA nor VTI_{Ao} at baselineor during PEEP were associated with a positive response to fluid in this study. Earlier results regarding the predictive value of LVEDA for assessment of fluid responsiveness in critically ill patients have been controversial. [364] As for $VTI_{Ao,}$ we may only hypothesize that squeezing of pulmonary beds may counteract the decrease in venous return induced by PEEP or that changes in the dimensions of the aortic root may attenuate the change in VTI_{Ao}. The decrease in CO during elevation of PEEP measured by thermodilution was not predictive of fluid responsiveness. CO decreased significantly in all patients during PEEP, without significant differences between the groups.

The study group being rather small and the patients being mechanically ventilated and sedated prevent direct application of these findings to other study groups. In addition, the results need validation in a larger population.

EARLY HEMODYNAMIC VARIABLES AND DEVELOPMENT OF ACUTE KIDNEY INJURY IN SEVERE SEPSIS

This study demonstrated that time-adjusted MAP during the first 24 hours in ICU was independently associated with the progression of AKI. Other factors associated with progression of AKI were higher lactate levels, CKD, dose of intravenous furosemide, and use of dobutamine. Patients who developed AKI had significantly lower time-adjusted MAP over the first 24 hours and they also spent a significantly longer period of aggregate time below MAP threshold levels of 75 mmHg. The best cut-off level of MAP for prediction of development of AKI was 73 mmHg. These results suggest that maintaining MAP over 73 mmHg and minimizing time spent at MAP below 75 mmHg would protect the kidney and prevent progression of AKI.

There is some evidence also from earlier studies that MAP higher than the currently recommended level of ≥ 65 mmHg is needed for protecting kidney function of patients with severe sepsis. In the prospective study by Badin and coworkers, a level of over 72 mmHg seemed to protect patients with septic shock from progressing to AKI. In patients with shock for other reasons, no association between MAP and AKI was found. [126] Similar results were demonstrated by Dünser and coworkers in a retrospective study. Hourly blood pressure time integrals were associated with initiation of RRT, serum creatinine, and urine output, but not with parameters describing liver function. [43]

The finding that higher blood pressure levels may protect the kidney appears reasonable in light of previous evidence. Data from two recent studies of limited size demonstrated that in shock patients an increase in MAP from 65 to 75 mmHg leads to improvements in glomerular filtration and urine output. [44,365] Several earlier studies have shown similar results. [282,366,367]

Nonetheless, two recent rather small prospective studies failed to show any benefit in renal function with an increase in MAP. However, in the work by Bourgoin and coworkers, MAP was raised from 65 mmHg to 85 mmHg in the intervention group. This level might be too high for beneficial effects, as proposed by Badin and coworkers. [126] Furthermore, evidence exists that any increment in MAP over 70 mmHg in patients with septic shock via an increase in vasopressor load [45] is associated with worse outcome. In the study by LeDoux and coworkers, MAP was elevated by use of norepinephrine to 75 mmHg and subsequently to 85 mmHg. In this study, there was an increase in urine output when increasing MAP from 65 mmHg to 75 mmHg, but a decrease to below baseline value when MAP was further elevated via norepinephrine to 85 mmHg. There was also a trend of higher lactate values when targeting MAP values over 85 mmHg, in addition to a less favorable SVO_2. To achieve the MAP target of 85 mmHg, a more than two-fold dose of norepinephrine was needed relative to the requirements at a baseline MAP of 65 mmHg. [368] The results of these two studies are therefore not comparable with the more recent studies targeting a MAP of 75 mmHg.

The current study also demonstrated that higher doses of norepinephrine were associated with, but were not an independent predictor for, progression of AKI. This finding is plausibly explained by an increase in adverse affects of catecholamines with increasing doses. [45] It is possible that excessive use of norepinephrine causes harmful vasoconstriction of regional vascular beds, resulting in deterioration in renal perfusion and renal function. [369] The relationship between vasopressor requirements and progression of AKI may also be explained by patients with more severe disease requiring higher vasopressor doses, which consequently leads to higher incidences of end-organ failure. [85]

The study also showed that a higher fluid load and use of colloids were associated with progression of AKI and worse outcome. Earlier data imply that fluid load is associated with impaired renal recovery and generally worse outcomes in critically ill patients. [268] The adverse effects of hydroxyethyl starches on renal function and outcome have also been highlighted in recent studies. [256,257]

The clinical problem is how to balance between excessively high and low levels of MAP to protect the kidney. There is also the consideration of optimal dosage of norepinephrine for best possible outcome. Lastly, one cannot overlook the importance of optimal fluid resuscitation for kidney function as well as for optimizing outcome. The balance between too little and too much is further complicated by differences in disease severity and comorbidities of critically ill patients.

OUTCOME IN SEVERE SEPSIS, SEPTIC SHOCK, AND SEVERE ACUTE PANCREATITIS

In this study, the mortality of severe sepsis and septic shock was consistent with that of the earlier Finnish multicenter FINNSEPSIS study [10] and also with international studies.[7] The mortality of patients with SAP was comparable with or slightly lower than in previous studies. [22-24] Interestingly, early deaths accounted for half of the deaths, as has been noted elsewhere. [24] Although information on the incidence of AKI in severe sepsis using the new KDIGO criteria is lacking, the incidence of AKI in this study is largely consistent with data from earlier studies. [3,7,0] The incidence of AKI in severe sepsis was slightly lower than in the previously presented FINNAKI study, plausibly due to differences in the inclusion criteria, excluding patients who died during days 1-5 in the ICU and those with onset of AKI later than 5 days. [3,6,9]

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The results of this study may serve as a platform for further randomized controlled trials aimed at determining the impact of inotrope use in critically ill patients, the hemodynamic targets for fluid resuscitation in SAP, the predictive value of a decrease in blood pressure during elevation of PEEP, and the impact of higher MAP on the progression of AKI. While anticipating the results of such studies, these findings provide food for thought for clinicians concerning everyday ICU practice. While only hypothesis generating, our results indicate that inotrope treatment in patients with septic shock may be associated with adverse outcome, and the benefits and harms of such treatment should always be carefully considered. In addition, our results suggest that no or only a modest decrease in MAP during elevation of PEEP in patients with septic shock is indicative of lack of positive fluid response to a fluid challenge. This straightforward and swift method may help clinicians to avoid harmful overhydration. Furthermore, our results imply that maintaining MAP over 75 mmHg in patients with severe sepsis may prevent onset and progression of AKI.

In many fields, such as in the hemodynamic support of patients with SAP, there is a paucity of elementary information on optimal management and targets for resuscitation. In such fields, large randomized studies are urgently needed. This also applies to the hemodynamic management of patients with severe sepsis or septic shock. To prevent the development or progression of AKI, which is responsible for a substantial increase in the morbidity and mortality of these patients, a large prospective randomized study is justified. Due to the vast number of confounding factors, such a study would have to be standardized not only by severity of illness but also by hemodynamic support provided. The predictive value of a decrease in MAP for assessing fluid responsiveness also needs to be validated in a larger population before definite conclusions can be made of its usefulness in clinical practice. Furthermore, based on our results and those of a recent crossover study evaluating the effects of dobutamine infusion, there is reason to doubt that inotropes are exclusively beneficial for patients with septic shock. The impact of inotropes on outcome should be assessed in a large randomized prospective study.

The development of intensive care appears to have reached a crossroads. In many aspects, results and outcomes have improved markedly over the last decades. However, only marginal further improvements can be achieved by general guidelines for the whole population of shock patients or patients with SAP or, for that matter, the entire population of critically ill patients.

For instance, inotrope administration may not be universally beneficial for all septic patients with low cardiac output. There may, however, be a specific subgroup of patients who would benefit, and this group should be identified. Prospective randomized studies will eventually shed some light on enigmas such as this, but we also need further information of the genomics and individual properties of each patient to be able to provide optimal tailored treatment for patients admitted to the ICU.

8. CONCLUSIONS

Based on the results of this study, the following conclusions can be drawn:

1. Inotrope treatment was independently associated with 90-day mortality for all patients with septic shock. The results remained unchanged after adjustment with propensity score. In the subgroup of patients monitored with PAC, failure to increase in SV, but not inotrope use per se, was associated with 90-day mortality.

2. Advanced age, higher serum creatinine, and lower MAP were independently associated with 90-day mortality in patients with SAP. In patients with SAP and circulatory shock, higher CVP and lower CI were independent predictors for 90-day mortality.

3. A decrease in MAP during elevation of PEEP from 10 to 20 cm H_2O predicted fluid responsiveness in patients with septic shock. A decrease in MAP of less than 8% during elevation of PEEP excluded a positive response to a subsequent fluid challenge, with a NPV of 100%.

4. Time-adjusted MAP was significantly lower and independently associated with progression of AKI in patients with severe sepsis. In addition, chronic kidney disease, lactate level, dose of intravenous furosemide, and use of dobutamine were independent predictors of progression of AKI. The results suggest that avoiding hypotensive episodes below 73 mmHg may prevent progression of AKI.

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