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HEMODYNAMICS AND OUTCOME OF SEPTIC SHOCK

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Academic Dissertation

To be presented with the permission of the Medical Faculty of the University of Helsinki,
for public examination in Auditorium 2 of the Biomedicum, Haartmaninkatu 8.
On December 8th, 2007, at 10 a.m.

Helsinki 2007

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ISBN 978-952-92-2966-6 (paperback)
ISBN 978-952-10-4347-5 (PDF)
http://ethesis.helsinki.fi

Layout Lifeteam Oy

Helsinki University Printing House
Helsinki 2007

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals. The publications are reprinted with the kind permission of the copyright holders.

I Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettila V. Hemodynamic variables related to outcome in septic shock. *Intensive Care Medicine* 2005; 31: 1066–71.

II Varpula M, Karlsson S, Ruokonen E, Pettila V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Medicine* 2006; 32: 1336–43.

III Varpula M, Pulkki K, Karlsson S, Ruokonen E, Pettila V, for FINNSEPSIS Study Group. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. *Critical Care Medicine* 2007; 35: 1277–83.

IV Varpula M, Karlsson S, Parviainen I, Ruokonen E, Pettila V. Community acquired septic shock: Early management and outcome in a nationwide study in Finland. *Acta Anesthesilogica Scandinavica* 2007; 51:1320–1326.

ABBREVIATIONS

ACCP	American Collage of Chest Physicians
ACTH	Adrenocorticotropic hormone
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
AUC	Area under the curve
BNP	Brain natriuretic peptide
DO_2	Oxygen delivery
cGMP	Cyclic guanosine monophosphate
CVP	Central venous pressure
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CI	Cardiac index
CO	Cardiac output
CO_2	Carbon dioxide
CCO	Continuous cardiac output
Dobu	Dobutamine
ED	Emergency department
EF	Ejection fraction
EGDT	Early goal-directed therapy
ESICM	European society of intensive care medicine
HES	Hydroxyethylstarch
HR-QoL	Health-related quality of life
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible form of nitric oxide synthase
ICD	The International Statistical Classification of Diseases and Related Health Problems
ISF	International Sepsis Forum
K_{ATP}	ATP-sensitive potassium channels
LA	Left Atrium
L/P-ratio	lactate/pyryvate ratio
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MDS	Myocardial depressant substance
MMDS	Microcirculatory and mitochondrial distress syndrome
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
NEP	neutral endopeptidase
NO	Nitric oxide
NOS	Nitric oxide synthase
NP	Natriuretic peptide
NT-proBNP	Amino-terminal pro-brain natriuretic peptide
O_2ER	Oxygen extraction ratio
OPS	Orthogonal polarisation spectral imaging
PA	Pulmonary artery
PAC	Pulmonary artery catheter
$PaCO_2$	Arterial partial pressure of carbon dioxide

Paop	Pulmonary artery occlusion pressure
$PgCO_2$	Gastric intramucosal partial pressure of carbon dioxide
$PslCO_2$	Sublingual tissue PCO2
PVR	Pulmonary vascular resistance
PEEP	Positive end expiratory pressure
RA	Right atrium
rhAPC	Recombinant human activated protein C
ROC	Receiver operating characteristic curve
RV	Right ventricle
SAFE	Saline versus Albumin Fluid Evaluation
SaO_2	Arterial oxygen saturation
SAPS II	Simplified Acute Physiology Score II
SCCM	Society of Critical Care Medicine
$ScvO_2$	Central venous oxygen saturation
SMR	Standardised mortality ratio
SOAP	Sepsis Occurrence in Acutely Ill Patients
SPSS	Statistical Package for the Social Sciences, a computer statistics program
SV	Stroke volume
SVC	Superior vena cavae
SIRS	Systemic inflamma tory response syndrome
SOFA	Sequential Organ Failure Assessment
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
TNF-α	Tumour necrosis factor-α
VASST	Vasopressin and Septic Shock Trial
V1-receptor	Vasopressin1-receptor
VO_2	Oxygen consumption

ABSTRACT

Background Septic shock is the common killer in non-coronary intensive care units (ICUs). The most crucial issue concerning the outcome of septic shock is the early and aggressive start of treatment aimed at normalization of hemodynamics and early start of antibiotics during the very first hours. The optimal targets of hemodynamic treatment or impact of hemodynamic treatment on survival after that are less known.

The objective of this study was to evaluate different aspects of the hemodynamic pattern in septic shock with special attention to prediction of outcome. In particular components of early treatment and monitoring in the ICU were assessed.

Patients A total of 410 patients, 218 with septic shock and 192 with severe sepsis or septic shock were included in the study. The patients were treated in several Finnish ICUs during 1999–2005.

Main results In septic shock the most important basic hemodynamic variables concerning the outcome were the mean of mean arterial pressure (MAP) and lactate during first six hours in ICU and the mean MAP, area of mixed venous oxygen saturation (SvO_2) under 70 %, and mean central venous pressure (CVP) during first 48 hours. The MAP levels under 65 mmHg and SvO_2 below 70 % were the best predictive thresholds.

The mean SvO_2 was below the mean $ScvO_2$ during early sepsis. Bias of difference was 4.2 % (95 % limits of agreement –8.1 % to 16.5 %) by Bland-Altman analysis. The difference between saturation values correlated significantly to cardiac index (CI) and oxygen delivery (DO_2).

The NT-proBNP levels at admission to ICU and 72 hours later were significantly higher in hospital nonsurvivors. The NT-proBNP values 72 hrs after inclusion were independent predictors of hospital mortality.

The compliance of early treatment according to the international guidelines was poor in Finnish hospitals and this was reflected in mortality. A delayed initiation of antimicrobial agents was especially associated with unfavorable outcome.

Conclusions This study showed that the hemodynamic profile; MAP under 65 mmHg, SvO_2 under 70 %, and a high CVP may help to distinguish patients with an increased risk of death in septic shock. NT-proBNP on third day may improve the risk assessment further.

$ScvO_2$ can not be used as a substitute of SvO_2 in hemodynamic monitoring in ICU. No clear evidence, however, of the value of neither $ScvO_2$ nor SvO_2 as a treatment target in ICUs exists.

Early treatment in septic shock is not optimal in Finland. The failure to rapidly diagnose and start appropriate treatment increases the mortality. With education, local protocol implementation, and follow-up the prognosis in septic shock can be improved.

1 INTRODUCTION

"Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

Sir William Osler – 1904

The body's response to an infection is a complex cascade of events that start when pathogenic micro-organisms activate the expression of various pro- and anti-inflammatory cytokines and apoptotic biomarkers leading to humoral, cellular, neuroendocrinological, circulatory, and coagulation involvement (Cinel and Dellinger 2007; Annane et al. 2005). The first clinical signs of sepsis include the unspecific symptoms of systemic inflammatory response (SIRS); fever, tachycardia, tachypnea, or elevation of the peripheral leukocyte count. When the host response to sepsis proceeds further, the clinical signs of organ failure including renal insufficiency, respiratory failure, hepatic involvement, septic encephalopathia, coagulation abnormalities, and circulatory collapse develop. Severe sepsis is characterised by concomitant organ dysfunction and septic shock results when blood pressures fall despite adequate fluid resuscitation.

Severe sepsis and septic shock are leading causes of death in non-coronary ICUs in developed countries (Martin et al. 2003; Sands et al. 1997). Severe sepsis or septic shock accounts for as many deaths as acute myocardial infarction in hospitals (Angus et al. 2001). In Finland, 11 % of ICU admissions are due to sepsis, 28 % of these patients die during the hospital stay and 40 % within the next year (Karlsson et al. 2007). The incidence of severe sepsis and septic shock is continuously increasing and although the mortality has decreased during the last few decades, the total number of deaths is growing (Angus et al. 2001; Friedman et al. 1998; Martin et al 2003).

Septic shock is characterised by hemodynamic disturbances that need correction with vasopressor treatment. The typical hemodynamic profile in early sepsis is the peripheral vasodilatation, which along with increased vessel permeability leads to hypovolemia and hypotension. Even after the correction of the volemic status, the hypotension persists because of decreased vascular resistance and disturbances in myocardial contraction.

The transition from sepsis to septic shock may occur fast and the time window for interventions is short. Treatment must promptly control the source of infection and restore hemodynamic homeostasis. Early targeted hemodynamic treatment has improved the outcome for severe sepsis (Rivers et al. 2001), while no benefit has been observed with the start of hemodynamic treatment after the development of organ failure (Kern et al. 2002).

A variety of biomarkers have been studied for their ability to help in earlier diagnosis, treatment decisions, or assessment of prognosis in sepsis. The biomarkers procalcitonin, C-reactive protein (CRP), interleukin 6, the TREM-1 receptor (triggering receptor expressed on myeloid cells-1), and lipoprotein binding protein may improve early diagnosis of a bacterial infection. While natriuretic peptides cardiac troponins, neutrophil CD64 expression, serum interleukin-8 endogenous protein C, neopterin, S-100β protein, neuron-specific enolase (NSE), plasma DNA, and several other cytokines and regulators of inflammation have been studied as prognostic indicators (Gibot et al. 2004; Meisner 2005; Ngyuen et al. 2006; Livaditi et al. 2006; Rhodes et al. 2006). At present their use is limited because of insufficient accuracy, prognostic capability, and timeliness. Combining information from several markers improved diagnostic accuracy for detection of the bacterial infection in a recent study (Kofoed et al. 2007).

The ultimate target of hemodynamic treatment is the adequacy of oxygen delivery in

respect to metabolic needs. The cornerstone of hemodynamic treatment is fluid resuscitation. The choice of optimum fluid or optimal targets of fluid resuscitation, however, are less clear. After adequate intravascular volume repletion, vasopressor treatment is started for provision of sufficient perfusion pressure to organs. Norepinehrine is the drug of choice in septic shock but vasopressin has showed promising results as an additive agent (Dellinger et al. 2004; Farand et al. 2006; Lauzier et al 2006). Myocardial dysfunction is common in septic shock. Different guidelines for indications of inotropic support are inadequacy of global perfusion, low cardiac output, or severely decreased myocardial function (Dellinger 2003; Dellinger et al. 2004). The early treatment protocol in which global perfusion was enhanced with red blood cells and dobutamine, according to central venous oxygen saturation ($ScvO_2$) values in the emergency department (ED), lead to improved survival (Rivers et al 2001). Besides vasoactive medications, several other treatment options may have an effect on the hemodynamics of patients. These include for example low-dose steroid treatment, activated protein C, and renal replacement therapy.

The above mentioned landmark study of Rivers et al. was one trigger for our study. Rivers' study showed that the outcome can be improved with a special hemodynamic treatment. We wanted to clarify some of the hemodynamic aspects that are faced in everyday clinical practice in ICUs and in treatment of septic patients. Despite several treatment protocols that have been introduced, the hemodynamic targets had mostly been based on theoretical backgrounds. We investigated the optimal thresholds of commonly used hemodynamic variables in respect to the outcome of septic shock Because of the increasing interest in the use of central venous oxygen saturation instead of mixed venous oxygen saturation, we also assessed the correlation and agreement of these parameters on reference to the international guidelines concerning treatment of septic shock . Inspired by the excellent results of early goal directed therapy, we wanted to find out how the patients with septic shock are treated in Finland and how the early treatment affects the outcome. We also hypothesized that a simple hemodynamic biomarker, NT-proBNP, could be of help in recognizing those prone to adverse outcome.

2 REVIEW OF THE LITERATURE

2.1 DEFINITIONS OF SEPSIS

The current definition of sepsis was produced in 1992 by a panel of experts at the Consensus Conference of American Collage of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) (Bone et al. 1992) (Figure1).

According to these definitions sepsis is the state where the patient is having an infection, based on clinical or microbiologic findings, and signs of systemic inflammation (systemic inflammatory response syndrome, SIRS). The term "severe sepsis" requires the presence of organ dysfunction and septic shock requires systemic hypotension refractory to fluid administration.

Current sepsis criteria are shown in table 1.

The introduction of consistent criteria has improved the conduct and interpretation of clinical trials. Although even after 1992 much variation in the selection criteria in studies in the field of sepsis has occurred. In some retrospective studies ICD-codes from hospital registers are used instead of the above mentioned sepsis criteria, and in some studies a positive blood culture (bacteraemia) is required for inclusion. Detection of infection has also varied from the clinical suspicion to a proven microbiological diagnosis.

Current consensus criteria have gained much criticism. The SIRS criteria are common and unspecific. Actually the outcome of patients with sepsis (infection and SIRS criteria) do not differ from the outcome of patients with

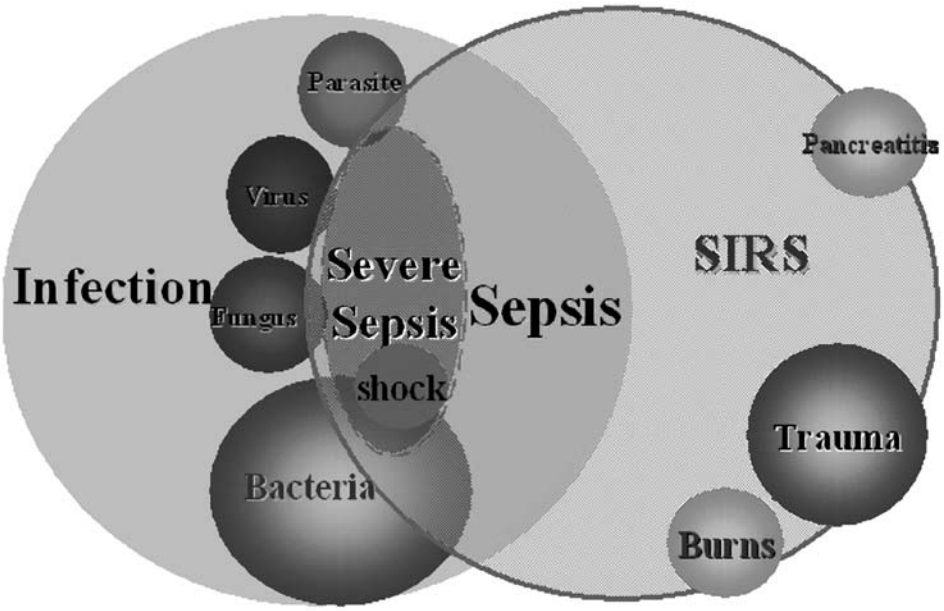

Figure 1. The interrelationship between systemic inflammatory response syndrome, infection and sepsis. Modified from Bone at al 1992.

infection but not fullfilling the SIRS criteria (Alberti et al. 2003).

In 2001, a consensus conference re-evaluated the 1992 sepsis definitions. The list of signs and symptoms of sepsis were expanded for clinical use, but the official definitions of sepsis were kept unchanged (Levy et al. 2003). The same conference presented a new staging system, PIRO, which takes into account four domains: predisposition (P), insult (I), response (R), and organ dysfunction (O). The PIRO model, however, has so far not gained wide acceptance in clinical use.

In 2005, definitions of the common infections associated with sepsis were described. These definitions were made for improving the quality and comparability of clinical trials of sepsis. Consensus definitions were developed for the six most frequent causes of infections in septic patients: pneumonia, bloodstream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections (Calandra et al. 2005).

2.1.1 Definitions of septic shock

In the physiological sense, shock is a medical condition in which the tissue perfusion is insufficient to meet the metabolic demand for oxygen and nutrients. In 1992, the ACCP/SCCM Consensus Conference Committee defined septic shock as follows: "patient is having a sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may included, but are not limited to, lactic acidosis, oliguria, or in acute alteration in mental status" (Bone et al. 1992). In clinical practice, however, the connection between infection and hypotension or organ failure is not always easy to prove. The patient might be hypotensive because of sedation and organ failures might exist because of comorbidity. For improving the patient selection, modified criteria have been used in many trials.

The Prowess criteria, created by Bernand et al., define cardiovascular instability as follows: systolic blood pressure of 90 mmHg or less or

Table 1.Definitions and criteria of sepsis (Bone et al. 1992).

Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Bacteremia	The presence of viable bacteria in the blood.
Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: 1. temperature > 38 °C or < 36 °C 2. heart rate > 90 beats per minute respiratory rate >20 breaths per minute or $PaCO_2$ < 4,3 kPa 3. white blood cell count > 12 $10^6/mm^3$ or < 4 000/mm^3 or >10 % immature (band) forms
Sepsis	The systemic response to infection, manifested by two or more of the SIRS criteria.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

mean arterial pressure (MAP) of 70 mmHg or less for at least 1 hour, despite adequate fluid resuscitation, adequate intravascular volume, or use of vasopressors (Bernard et al. 2001). In a review by Annane et al. the definition of septic shock included an even more exact hemodynamic characterisation with a minimum dose of vasopressor needed. According to Annanes definition, a patient is having septic shock if he or she fulfilled the criteria of severe sepsis and has a MAP less than 60 mmHg (less than 80 mmHg if previous hypertension) after 20–30 mL/kg of starch, 40–60 mL/kg of saline or pulmonary capillary wedge pressure 12–20 mmHg. Or patient needs dopamine over 5 μg/kg/min or norepinephrine or epinephrine a maximum of 0.25 μg/kg/min to maintain MAP over 60 mmHg (80 mmHg). Refractory septic shock was defined as a need for dopamine over 15 μg/kg/min, norepinephrine or epinephrine over 0.25 μg/kg/min (Annane et al. 2005). In many trials a predefined minimum needed dose of vasopressor treatment has been added to the inclusion criteria of septic shock.

An international consensus conference about hemodynamic monitoring in shock was held in April 2006. One of the recommendations was that hypotension should not be required to define shock. Instead, the shock is defined as circulatory and cellular dysfunction, manifested by markers of hypoperfusion such as elevated blood lactate or decreased central venous ($ScvO_2$) or mixed venous (SvO_2) oxygen saturation with or without hypotension (Antonelli et al. 2007).

2.2 INCIDENCE OF SEPTIC SHOCK

The incidence of sepsis has continues to increase in developed countries (Martin et al. 2003). A study of hospital discharge data in the United States from 1979 to 2000 found an increase in incidence from 83 per 100 000 to 240 per 100 000, about 9 % annually (Martin et al. 2003). Similarly, in a cohort study conducted in 206 French intensive care units (ICUs), 14.6 % of patients experienced severe sepsis or septic shock, compared with 8.4 % of ICU patients a decade earlier (Brun-Buisson et al 2004). Reasons for this constant increasing are thought to be the better recognition of sepsis, more patients with compromised immune status, aged populations, and a growing number of resistant microbes.

The incidence of severe sepsis in epidemiological studies has varied from 0.38 per 1000 to 3 per 1000 population and from 6.3 % to 27.1 % of all ICU admissions. The incidence of critical care admissions with severe sepsis has been increasing over time (Brun-Buisson et al. 2004; Harrison et al. 2006). The reported incidence of septic shock has varied between 7 % to 88 % of all sepsis patients and 6.3 % to 14.7 % of all ICU admissions (Antonelli et al. 2007). The large ranges are not explainable by true differences, but by a variation in sepsis definitions and, for most, the sampling frame in the studies. The prevalence of cardiovascular dysfunction (septic shock) in the hospital discharge data based study was 7 % of all sepsis patients (Martin et al. 2003). In an observational study 20–27 % of all septic patients in general wards and ICUs combined had septic shock, but in studies that screened only ICU patients the incidence of septic shock have been up to 88 % (table 2). According to a Finnish single centre study, severe sepsis or septic shock is more common in those ICU patients who have community acquired infections instead of patients with hospital acquired infections on admission (Ylipalosaari et al. 2006).

All patient with sepsis are not treated in ICUs. In a study regarding emergency department visits, most visits for sepsis resulted in admission to non-critical units. Only 12 % of all sepsis patients were admitted to the ICU while the overall hospital admission rate of sepsis patients was 87 % (Strehlow et al. 2006). In an observational cohort study of severe sepsis, based on hospital discharge data, 51 % of patients with severe sepsis received intensive care (Angus et al. 2001). Sands et al found that severe sepsis accounted for 2.0 % of all hospitalizations and that 59 % of patients with severe sepsis required ICU care (Sands et al. 1997).

Most epidemiological studies have only included patients already admitted to the ICUs which depends on ICU bed availibility and admission policies, effecting the observed in-

Table 2. The criteria, incidence, and mortality of septic shock patients in epidemiological studies.

Reference	Country	Design*	Definition	Time frame	Screened populaition	No. of patients screened	No. of sepsis cases	% of all ICU adm.	Pop. incid. / 1000	Hospital mortality (%)	Septic shock % of all sepsis cases	Hospital mortality of septic shock
Salvo 1995	Italy	P	Consensus criteria	4/1993 – 3/1994	First 3 cases each month in 99 ICUs	1101	106 sepsis, severe sepsis or septic shock	9.6%	NA	52.2	21.7	82 %
Brun-Buisson 1995	France	P	Consensus criteria	1.2.1993	All cases in 170 medical ICUs	11 828	1052 severe sepsis	8.9%	NA	59	71	NA
Rangel-Frausto 1995	USA	P	Consensus criteria	8/1992 – 4/1993	All cases in 3 ICUs and 3 floors in one hospital	3708	11 226 sepsis, severe sepsis or septic shock	12.6%	NA	16 sepsis 20 severe sepsis	9	46
Sands 1997	USA	P	Consensus criteria	1/1993 – 4/1994	All ICU patients and all floor patients with blood cultures at 8 hospitals	12 759	1166 sepsis syndrome	NA	NA	34 (28-day)	25	NA
Angus 2001	USA	R	ICD-9codes	1995	All cases at all hospitals (n = 936) in 7 US states	6 621 559	192 980 severe sepsis	11.2%	3 severe sepsis	28.6	24.4	32.4
Padkin 2003	UK	R	"Prowess criteria"	12/1995–2/2000	All cases on day 1 in 91 ICUs in national registry	56 673	15 362 severe sepsis	27.1%	0.51 severe sepsis	47.3	88	50.2
Teres 2002	USA	R	Consensus criteria	1998–1999	All cases on day 1 in 50 ICUs	21 480	2434 severe sepsis	11.3%	NA	36.3	11.3	48
Alberti 2002	8 countries	P	Consensus criteria	5/1997 – 5/1998	All cases in 28 ICUs	14 364 8 353 >24h	3239 sepsis, severe sepsis or septic shock	21 %	NA	13.2–66.8 in subgroups	36	38.8-66.8
Martin 2003	USA	R	ICD-9 codes	1979–2000	1% subset of all US hospital admissions	750 Milj	10.3 Milj sepsis	NA	0.83-2.40 sepsis	27.8–17.9	7	NA
Brun-Buisson 2004	France	P	Consensus criteria	11.12.2001	All cases in 206 ICUs	3738	546 severe sepsis	14.6%	NA	35 (30-d)	56	NA
Finfer 2004	Australia/NZ	P	Consensus criteria	5.8.1999	All cases in 23 ICUs	5878	691 severe sepsis	11.8%	0.77	37.5	NA	NA
van Gestel 2004	Netherlands	P	Consensus criteria	24h 12/2001	All cases in 47 ICUs	455	134 severe sepsis	31 %	0.54	NA	37	NA
Flaatten 2004	Norway	R	ICD-10-CM codes	1999	All cases in all Norwegian hospitals	700 107	6665 sepsis	NA	0.47 severe sepsis,1.5 sepsis	27	23.5	29.3
Silva 2004	Brazil	P	Consensus criteria	5/2001 – 1/2002	All cases in 5 ICUs	1383	415 sepsis (214 severe sepsis)	17.4%	NA	46.9	49	52.2
Karlsson 2007	Finland	P	Consensus criteria	11/2004 - 2/2005	All cases in 24 ICUs	4500	470 severe sepsis	10.4%	0.38 severe sepsis	28.3	77	38.5
Vincent 2006	24 European countries	P	Consensus criteria	2wk 5/2002	All cases in 198 ICUs	3174	1177 sepsis	37 %	NA	32.2	39	54.1
Engel 2007	Germany	P	Consensus criteria		All cases on one day 402 ICUs	3877	415 sepsis or septic shock	10.7%	0.76-1.1 severe sepsis	55.2	NA	62.4
Harrison 2006	UK	R	"Prowess criteria"	12/1995-1/2005	All cases on one day in 172 ICUs	343 860	92 672 severe sepsis	27.0%	0.46-0.66	30.8-34.3	NA	NA

*P=prospective, R= retrospective

cidence of severe sepsis and septic shock. Thus, in some studies the incidence is not the true incidence of severe sepsis or septic shock, but the incidence of ICU treated cases of sepsis patients. The higher incidence of sepsis in ICUs may be due to ICU bed shortage when only the most critically ill patients are treated in ICU. In a prospective, multi-center, observational study of ICU treated sepsis in 24 European countries, the incidence of severe sepsis of all ICU admissions ranged from 10 % in Switzerland to 64 % in Portugal (Vincent et al. 2006).

The criteria, incidence, and mortality of septic shock patients in epidemiological studies are shown in table 2

2.3 HEMODYNAMIC ALTERATIONS IN SEPTIC SHOCK

2.3.1 Historical perspectives

The gram-negative bacteraemia shock syndrome was described in 1960 as follows:

'Before shock became established in the patients with bacteraemia the skin was invariably warm and dry, the pulses were full, yet all were confused and disorientated ... as shock progressed the skin invariably became cold, grey and clammy and the pulse rapid, weak, and thready'.

A temporal connection between the 'warm' and 'cold' shock was already understood in the 1950´s although the knowledge about pathophysiologic mechanisms was lacking. At that time the common impression was that hyperdynamic warm shock was the initial phase of septic shock and hypodynamic cold shock was a premorbid phase of shock and mainly resulted from myocardial depression. Since monitoring techniques with a pulmonary artery catheter have developed, the understanding about hemodynamics of septic shock has increased. During the 1970´s it was generally agreed that hypodynamic phase was mostly related to inadequate volume resuscitation and hypovolemia.

Although myocardial depression in sepsis was incorrectly blamed for the hypodynamic phase of shock in 1950`s, in 1984 Parrillo and Parker et al. showed, using radionuclide cardiac imaging and the pulmonary artery thermodilution technique, that left ventricular ejection fraction (LVEF) is commonly decreased in early sepsis despite elevated cardiac output (CO).

2.3.2 Characteristics

The hemodynamic pattern of septic shock is characterized by an early hypercirculatory phase with increased CO and decreased systemic vascular resistance (SVR). The clinical signs include tachycardia, tachypnea, and warm extremities. Vasodilatation and increased permeability lead to both absolute and relative hypovolemia. Most patients also show some degree of myocardial depression if it is assessed. Despite a compensatory increase of CO, the elevated SVR, hypovolemia, and myocardial depression induce a hypotension, which, by definition, is a distinctive mark of septic shock (Figure 2). Without aggressive fluid resuscitation in this phase, a profound hypotension and progressive acidosis develop leading to irreversible shock, multiple organ failure, and death. In adequately volume resuscitated patients during early shock, the global blood flow to vital organs (i.e.heart, gut, and kidney) is commonly increased, but multiple organ failure may develop anyway demonstrating that the pathophysiology behind organ failure in sepsis is much more complex than just circulation (Di Giantomasso et al. 2003). While global hemodynamics correlate well to organ hypoperfusion in other shock modes, this is not true in septic shock. Increasing evidence suggest a pivotal role of microcirculation over measurable macrocirculation as a cause of organ dysfunction in septic shock and severe sepsis.

2.3.3 Vasodilatation

The pathological vasodilatation in sepsis is due to inappropriate activation of vasodilator mechanisms of smooth muscles and the failure of vasoconstrictor mechanisms despite an activation of renin-angiotensin-aldosterone

system and high plasma concentrations of catecholamines. The three main mechanisms behind vasodilatation are activation of ATP-sensitive potassium (K_{ATP}) channels in the plasma membranes of vascular smooth muscles, activation of the inducible form of nitric oxide synthase (iNOS), and deficiency of the hormone vasopressin (Landry 2001).

Several cytokines and endotoxins can induce the expression of iNOS in vascular endothelial and smooth muscle cells resulting in a massive release of nitric oxide (NO) and profound vasodilatation via cyclic guanosine monophosphate (cGMP) lowering intracellular calcium levels. The intracellular calcium is eventually responsible for a vasoconstriction of the smooth muscle cells. Nitric oxide (NO) also decreases the response to catecholamines, which may be partly due to activation of K_{ATP} channels by NO. Besides unwanted effects to the vascular system, however, NO has pro- and antiinflammatory, as well as oxidant and antioxidant properties, which may have an important role in sepsis (Hauser et al. 2005).

The decrease in cellular ATP concentration, acidosis, and lactatemia promotes the activation of K_{ATP} channels. Also neurohormonal activation, like atrial natriuretic peptide and adenosine, which are both increased in septic shock (Martin et al. 2000; Witthaut et al. 2003), may activate K_{ATP} channels. The activation of K_{ATP} channels produce membrane hyperpolarisation of smooth muscles, which closes voltage-dependent Ca^{2+} channels and leads to reduction in intracellular Ca^{2+} and thus to vasodilation.

Vasopressin is a hormone released from neurohypophysis. In normal conditions, vaso-

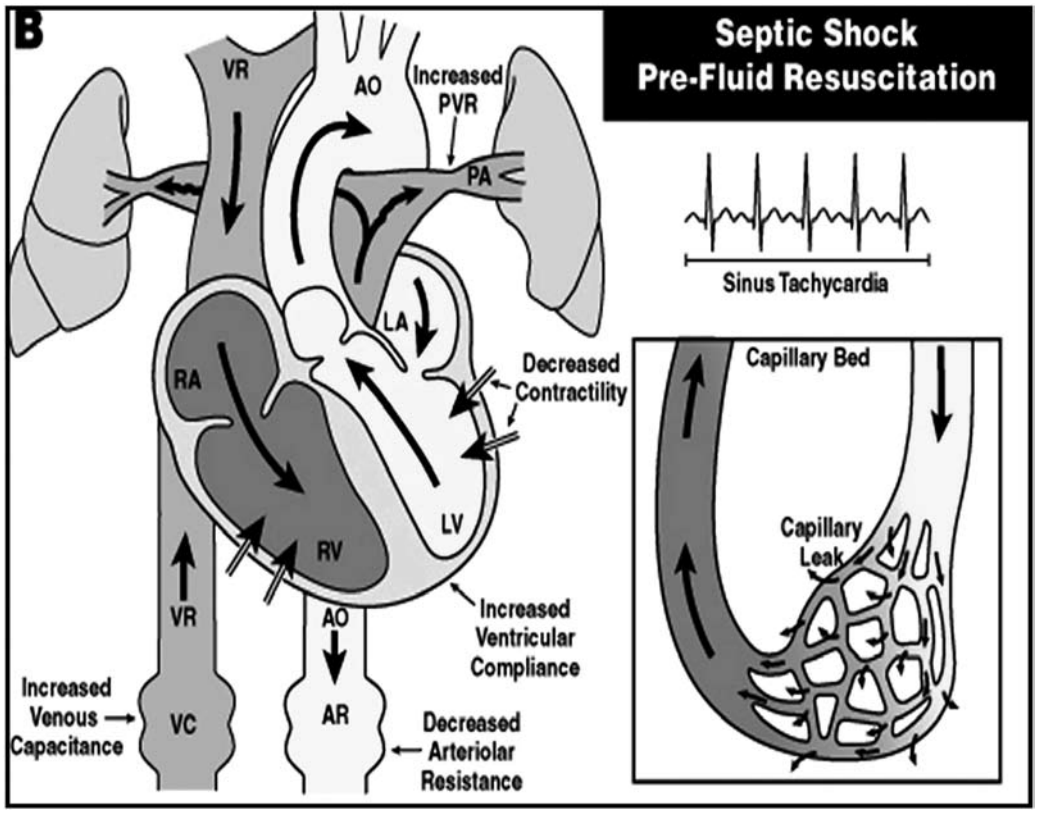

Figure 2. Hemodynamic alterations in early septic shock. Depending on the disease itself, phase of the sepsis, and treatments the patient may have features of vasodilatative shock, cardiogenic shock, hypovolemic shock, as well as obstructive shock with a rise in pulmonary vascular resistance. Adapted from (Dellinger 2003) with permission.

pressin regulates the water homeostasis of the body. In response to hypotension, however, an early approximately ten-fold increase in plasma vasopressin occurs and vasopressin contributes to the maintenance of adequate blood pressure in early shock. When shock persists, the plasma concentrations of vasopressin decrease back toward baseline. Inappropriately low hormone levels during septic shock may be caused by the depletion of neurohypophyseal stores or inhibition of synthesis or release (Barrett et al. 2007). The vasopressor mechanism of vasopressin is complex. It potentiates the vasoconstrictor effect of norepinephrine, inactivates K_{ATP} channels in smooth muscles, decreases the synthesis of iNOS, stimulates adrenocorticotropic hormone and hence cortisol secretion, blunts the increase in cGMP in cytosol and activate vascular smooth muscle V_1 receptors (Landry 2001; Barrett et al. 2007). Contrary to other vasoconstrictors, vasopressin can also cause vasodilation in some vascular beds (Okamura et al. 1999), but the significance of this in sepsis is not clear.

Chances of cortisol level or vascular responsiveness to the cortisol are well known in sepsis. Glucocorticoids are required for normal cardiovascular reactivity to angiotensin II, epinephrine, and norepinephrine. The effect of cortisol on hemodynamics is mediated partly by the increased transcription and expression of the receptors for these hormones. Cortisol has an effect on cardiac contractility, vascular tone, and blood pressure. Glucocorticoids are also required for the synthesis of N+, K+-ATPase, and catecholamines (Marik 2007).

2.3.4 Myocardial depression

It has been proposed that myocardial depression contributes to septic shock in at least 50 % of the patients (Charpentier et al. 2004; Rabuel et al. 2006). Only some of these patients, however, show inappropriate low oxygen delivery and thus need an inotropic treatment for myocardial depression. In Finnish sepsis study (Finnsepsis), 25 % (118 of 470) of patients was treated with dobutamine during the first day in ICU. Myocardial depression is a reversible phenomenon that subsided in 7–10 days if the patient survived (Court et al. 2002).

The characteristics of myocardial depression in septic shock are reduced ventricular ejection fraction and biventricular dilatation, although the marked dilatation has not been confirmed in some echocardiographic studies (Poelaert et al. 1997; Jardin et al. 1999; Charpentier et al. 2004). In septic myocardial depression the response of left ventricular work to volume load is diminished, resulting in a flattened Frank-Starling curve (Ognibene et al. 1988). Diastolic dysfunction is not as clearly defined, but there is evidence from animal and human studies that impaired compliance may contribute to septic myocardial depression (Court et al. 2002; Krishnagopalan et al. 2002). Poelart et al. demonstrated using tranesophageal echocardiography, that cardiac dysfunction in septic shock is a continuum from isolated diastolic dysfunction to both diastolic and systolic ventricular failure (Poelaert et al. 1997). Right ventricular dysfunction closely parallels the left ventricular dysfunction in sepsis showing a dilatation of the ventricle and a reduced ejection fraction (EF).

The evaluation of myocardial function is always affected by the loading condition that might fluctuate rapidly in sepsis and this has to be taken into account when myocardial function is evaluated. Left ventricular afterload is typically very low in early sepsis, unless not affected with vasoactive treatment. Fluid resuscitation changes the loading condition rapidly and a decreased EF might emerge only when hypovolemia has been corrected. The right ventricle is very vulnerable to an acute increase in afterload and severe right ventricular dysfunction or acute cor pulmonale may be produced by an increase in pulmonary vascular resistance (PVR) due to an acute lung injury, high PEEP, or high airway pressures during ventilator treatment. Hypercapnia or metabolic acidosis may also increase PVR and thus contribute to the occurrence of right ventricular failure in sepsis.

The etiology of myocardial depression in sepsis was first thought to be a decreased perfusion of the heart. Studies, however, have shown that coronary blood flow is normal or

even elevated in septic shock (Dhainaut et al. 1987). The most important mechanism in initiation of myocardial depression is most possibly the different circulating myocardial depressant substances (MDS) related to the pathogenesis of sepsis. The list of all potential MDS is extensive, but cytokines, like tumor necrosis factor-α (TNF-α) and interleukin-1β seem to be of particular importance. The depressant action is mediated at least partly by production of NO (Kumar et al. 2001). The exact mechanisms behind septic myocardial dysfunction are complex, however, and remain unclear. The underlying mechanisms may include down-regulation of β-adrenergic receptors, depressed postreceptor signaling pathways, impaired calcium liberation from the sarcoplasmic reticulum, impaired electromechanical coupling and mitochondrial dysfunction of the cardiomyocytes (Rudiger and Singer 2007).

Besides the septic myocardial depression, multiple factors associated with critical illness, including hypoxia, acidosis, electrolyte disturbances, along with vasoactive medications and neurohormonal changes, may affect the cardiac function during treatment of septic shock.

The impact of septic myocardial dysfunction on the outcome has been controversial. Some studies have found an initially lower LVEF and more dilated LV in patients who survived (Parker et al. 1984; Jardin et al. 1999), while some have noticed decreased cardiac function in non-survivors (Vincent et al. 1992; Poelaert et al. 1997). Different mechanisms in evaluation of cardiac function and fluctuation of the loading conditions probably explain these differences. In theory, the failure to increase ventricular compliance results in the inability to maintain stroke volume and hence cardiac output which explains the better survival of those with early LV dilatation (Price et al. 1999). Right ventricular dilatation and acute cor pulmonale was associated with adverse outcomes in acute respiratory distress syndrome (ARDS) (Jardin et al. 1994; Jardin and Vieillard-Baron 2007) but current treatment guidelines with lower tidal volumes and lower inspiratory pressures have improved a prognosis of ARDS related cor pulmonale (Vieillard-Baron et al. 2001).

2.3.5 Vascular permeability

One main problem in septic shock is increased vascular permeability (Dellinger 2003). The pathophysiology of this, however, is not completely understood in human septic shock. In general the movement of fluids between extra- and intravascular compartments depends on the hydrostatic, osmotic, and colloid-oncotic pressures. In an intact vasculature, the endothelium forms a continuous, semipermeable barrier that controls fluid movement between intra- and extravascular spaces. The barrier integrity differs between organs and even within vascular segments of the same organ. Water can diffuse freely through all endothelial pores, and so for example the decrease in serum osmolality by the administration of hypo-osmolar fluids results in edema formation. Macromolecules, like albumin, only pass through the capillary membrane via larger pores that are 10–30×103 times less common than small pores. The movement of macromolecules through these pores by convection depends solely on transcapillary hydrostatic pressure and total pore area. Even a minute increase in total area of the large pores may cause a substantial loss of macromolecules (Mehta and Malik 2006; Stewens et al. 2000).

In sepsis, an inflammatory stimulus leads to increased permeability and the loss of barrier function of the endothelium, resulting in a shift of water, and macromolecules, and proteins into the extravascular space (Holbeck 2003; Lehr et al. 2000).

Several plasma mediators, like TNF-α, IL-1β, IL-6, IL-8, interferon-δ, leptin, complement and vascular endothelial growth factor (VEGF), increase vascular permeability in sepsis (Nooteboom et al. 2002, van Eijk et al. 2006, Pickkers et al. 2005; Dvorak 2006). High infusion rates of exogenous catecholamines, like norepinephrine, can also induce lung edema by increasing filtration and microvascular pressure. In theory, the massive fluid loading also leads to the increase of hydrostatic pressure and vascular fluid leaks, but on the other hand pre-treatment with saline or albumin before experimental septic shock reduces vascular permeability in rats (Anning et al.

2004). Although vascular permeability is not a therapeutic target in sepsis, some therapies may improve the endothelial barrier function. For example simvastatin, sphingosine 1-phosphate, adrenomedullin, and activated protein C have been studied for this purpose (Looney and Matthay 2006; Temmesfeld et al. 2007).

2.3.6 Cardiac biomarkers

Troponins

Cardiac troponins are intracellular proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consist of three sub-units: troponin T (cTnT), troponin I (cTnI) and troponin C. Cardiac troponins are not normally detectable in plasma, but the elevation of troponin T or troponin I is highly sensitive for detecting myocardial cell damage. Cardiac troponins are commonly used as diagnostic markers in acute coronary syndrome, but these can be also elevated in many other clinical conditions even in the absence of overt ischemia. Elevation of troponins can be seen in about half of the patients with severe sepsis. In septic shock, a relationship between elevated cTnI or cTnT levels and left ventricular dysfunction, assessed either by echocardiography or a pulmonary artery catheter (PAC), have been reported (Favory 2006; Maeder et al. 2006). The elevation of troponins is associated with a poorer prognosis in sepsis.

While coronary circulation is commonly increased in sepsis, several factors may contribute to the microinjury and minimal myocardial cell damage in septic shock. A possible direct cardiac myocytotoxic effect of endotoxins, cytokines, or reactive oxygen radicals has been postulated. Also microvascular thrombotic injury or myocardial ischemia due to sepsis induced hypotension, vasopressor agents, anemia or hypoxia may contribute to elevation. TnT is also increased in renal failure, which is common in septic shock (Favory 2006; Maeder et al. 2006).

Natriuretic peptides

Atrial natriuretic peptides (ANP) and brain natriuretic peptides (BNP) are polypeptide neurohormones, which are produced and secreted by cardiomyocytes. Natriuretic peptides (NP) induce vasodilatation, increase diuresis, and inhibit renin and aldosterone production. Thus these hormones are important regulators of the fluid and electrolyte homeostasis of the body. The NPs may also play a role in inflammatory processes, endothelial dysfunction, vascular remodelling, counteract the hypertrophy and fibrosis of the myocardium, inhibit the sympathetic activation and vasopressin response, and release of endothelin, cytokines, and growth factors (Levin, Gardner and Samson 1998; Ruskoaho 2003; Clerico et al 2006).

The main stimuli for synthesis and release of BNP are myocardial wall stress and increased intravascular volume. The BNP is mainly produced in cardiac ventricles but to lesser extend also in the atriums. It is secreted into the blood as a prohormone, where it is cleaved into active BNP and inactive metabolite N-terminal pro-brain natriuretic peptide (NT-proBNP). The BNP and NT-proBNP are secreted in equimolar amounts, but are removed from the circulation by different mechanisms, making the plasma concentrations unequal (Levin et al. 1998; Ruskoaho 2003). Only small amounts of BNP are stored in granules and the activation of the BNP gene is needed for BNP production. This activation, however, can occur rapidly (Hall 2004).

Renal excretion is regarded as the main clearance mechanism of NT-proBNP, whereas BNP is cleared by specific clearance receptors and enzyme neutral endopeptidase. NT-proBNP has a longer half-life than BNP (120 min vs. 22 min)

Both BNP and NT-proBNP are diagnostic markers in heart failure and also predictive markers of prognosis in several cardiovascular diseases (Doust et al. 2004). The use of both markers is considered equivalent for diagnosis of heart failure (Mueller et al. 2004; Mueller et al. 2005) and outcome prediction after myocardial infarction (Richards et al. 2003). They are also used in different diagnosis in acute dyspnea. These can also be used in follow-up, evaluating the adequacy of diuretics and other unloading treatment in chronic heart failure patients. Synthetic recombinant human BNP

(nesiritide) has been approved for the treatment of acutely decompensated congestive heart failure.

In recent years, several studies have found elevated levels of NPs in sepsis and evidence that NPs could predict mortality in severe sepsis and septic shock also exists (Brueckmann et al. 2005; Castillo et al. 2004; Charpentier et al. 2004; Hoffmann et al. 2005; Roch et al. 2005), although this is not confirmed in all studies (McLean et al. 2007; Rudiger et al. 2006).

The elevation of NPs in sepsis is probably multifactorial and there might be variations in etiology if BNP or NT-proBNP is used. Elevation has been associated with septic myocardial depression, assessed with echocardiography or a pulmonary artery catheter, and increased troponin levels also correlate with elevated NPs in sepsis (Charpentier et al. 2004; Brueckmann et al. 2005; Hoffmann et al. 2005; Roch et al. 2005). Other factors, relevant in sepsis, may also enhance the production of NPs like IL-1b, TNF-α, IL-6, lipopolysaccharides from Gram-negative bacteria, angiotensin II, endothelin-1, α-1-adrenergic stimulation, and hypoxia (Clerico et al. 2006; Hanford et al.1994; Harada et al 1999; Ma et al. 2005; Tanaka et al. 2004; Tomaru et al. 2002). Renal failure seems to increase the level of both BNP and NT-proBNP, although the influence on NT-proBNP might be more pronounced because of its renal clearance (Jason et al.2005).

2.3.7 Microcircular dysfunction

The microcirculatory unit, which comprised of the arteriole, capillary bed, and postcapillary venule, is the final destination from where oxygen and nutrients are transported to tissues and waste products are removed. Alterations of microcirculation in sepsis contribute to the development of MODS (Vincent and De Backer 2005). In sepsis, several derangements in microcirculation have been reported: reduction of the number of perfused capillaries, reduced red blood cell deformability, endothelian cell dysfunction with increased permeability and apoptosis, altered vasomotor tone, an increased number of activated neutrophils, and activation of the clotting cascade with fibrin deposition (Vincent and De Backer 2005). These microcirculatory derangements can occur despite preserved arterial pressure and on the other hand the treatment with vasoactive medication for preserving MAP may indeed decrease the microvascular blood flow despite increase in perfusion pressure (Krejci et al. 2006, Hiltebrand et al. 2007). In an experimental study with a fecal peritonitis model, administration of norepinephrine, epinephrine, or phenylephrine increased perfusion pressure, but both norepinephrine and epinephrine decreased microcirculatory flow in the intestine while phenylephrine had no effect on regional blood flow (Krejci et al. 2006). Both experimental and human studies have shown that microvascular alterations associate with poor outcome in sepsis (Sakr et al. 2004, Trzeciak et al. 2007). Microcirculation and its role as a therapeutic target are under wide investigation in septic shock. Vasodilatators, like prostacyclin and nitroglycerine or other NO donors, have showed promising results for the improvement of microcirculatory perfusion in sepsis (Siegemund et al. 2007; Spronk et al. 2002)

Besides impaired microcirculation, septic shock may also induce changes in oxygen utilisation at a mitochondrial level leading to "cytopathic hypoxia" or "microcirculatory and mitochondria distress syndrome" (MMDS) (Spronk et al. 2005).

2.4 MONITORING OF HEMODYNAMICS IN SEPTIC SHOCK

"Not everything that counts can be counted, and not everything that can be counted counts."

Albert Einstein

2.4.1 Basic monitoring

Monitoring of the hemodynamics should be a diagnostic aid that helps in treatment decisions. The ultimate purpose of hemodynamic monitoring in septic shock is to determine if the circulation is consistent with the metabolic needs of the tissues, and to determine which

components of the hemodynamic profile need to be adjusted for adequate consumption-demand balance for avoiding, or correcting, tissue hypoxia. Although hemodynamic monitoring is considered essential in circulatory shock, its targets and benefit are poorly documented.

With standard monitoring techniques it is not possible to reliably assess tissue hypoxia and thus monitoring of optimal consumption-demand balance is always somewhat extrapolative. Clinical, as well as laboratory signs of hypoperfusion, have to be taken into account together with hemodynamic monitoring in the treatment of the patient. The fact that the pathophysiology of tissue hypoxia is more complex than just the derangements in circulation must be remembered.

For the last four decades, the pulmonary artery catheter (PAC) has been used for hemodynamic monitoring of critically ill. The benefits of PAC have been questioned in recent years. Three recent studies and two meta-analysis showed that the complication or mortality rates are not increased with PAC, although no benefit could be shown either (Rhodes et al. 2002; Richard et al. 2003; Shah et al. 2005; Harvey et al. 2005; Harvey et al. 2006). Richard et al. conducted a multicenter randomised controlled study on the effects of PAC on the outcome in patients with shock or ARDS. In 676 patient, from which 452 had septic shock, morbidity or mortality benefits could not be observed, but the authors concluded that the PAC remains a safe procedure for the management of patients with shock or ARDS. It has since been argued that the lack of the benefit in those studies could be caused by their lack of goal-oriented treatment protocol. It is also unclear as to what the real differences between the monitoring of the patients was, because some of the patients had some alternative method of cardiac output monitoring and some had a PAC without a continuous SvO_2 measurement. In the study of Richard et al., 64 % in the PAC group and 78 % in the control group had echocardiography performed for the assessment of hemodynamics. Actually, so far no study demonstrated that any other monitoring techniques could improve the outcome of the patients.

Mean arterial pressure (MAP) is the driving perfusion pressure of the tissues. MAP is commonly monitored invasively and continuously via the radial or femoral artery. Oscillometric blood pressure measurement is not a reliable substitute for intra-arterial blood pressure measurement in a critically ill patient (Cohn 1967; Bur et al. 2003).

Central venous pressure (CVP) reflects the right atrial pressure and is commonly used as a marker of preload. It can be measured with a CVP- catheter or with PAC.

Pulmonary artery occlusion pressure (Paop), or wedge pressure, is measured with PAC while the balloon on the distal tip located in a West zone 3 in the lungs is inflated, i.e. wedged. In the West zone 3 the pulmonary arterial and venous pressure exceed the alveolar pressure, so the wedged balloon measure the backpressure of left atrium. West zone 3 conditions exist at the bottom region of the lungs. Paop is thought to be a reflection of the left ventricular end-diastolic pressure (LVEDP) and it is commonly used as a preload measurement. Several studies, however, have shown that CVP or Paop are not reliable methods to assess the patients' ability to increase the cardiac output for a fluid challenge (Tavernier et al. 1998; Michard et al. 2000; Kumar et al. 2004).

The cardiac output, cardiac index and stroke volume (CO, CI, SV) can be measured with a thermodilution method with PAC. In that method the fixed volume of cool fluid is injected through a proximal port of the PAC and the change of temperature is registered by a thermometer at the tip of PAC. The CO is calculated using temperature-time decay curves by Stewart-Hamilton equation. Cardiac output can be measured continuously (CCO) with special PAC catheters with a thermofilament.

Cardiac output can also be assessed with echocardiography using doppler techniques, pulse contour analyses from the arterial pressure waveform of a peripheral artery, esophageal doppler, transpulmonary thermodilution, thoracic electrical bioimpedance, or partial

CO_2 rebreathing technique based on the indirect Fick method. Different techniques have mostly been compared in patients without shock. Although the mean bias have been clinically acceptable, the deviations have been wide in some studies. Continuous and automatic monitoring are advantages of the new methods. The measurement of CO or targeting to some predefined CO, however, have not shown any impact on outcome in septic shock.

2.4.2 Monitoring of global perfusion

2.4.2.1 SvO_2

Mixed venous (SvO_2) saturation reflects the balance between oxygen requirement and oxygen delivery, and thus may be used to assess the adequacy of tissue oxygenation.

Oxygen delivery (DO_2) depends on hemoglobin concentration, cardiac output, and arterial oxygenation ($DO_2 = CO \times Hb \times 1.31 \times SaO_2 + (0.003 \times PaO_2)$) In normal conditions only about 25 % of arterial oxygen are used for metabolic needs and thus the normal SvO_2 is about 75 %. If DO_2 falls relative to oxygen consumption (VO_2) or oxygen demand increase, the tissues begin to extract more oxygen (oxygen extraction ratio, $O_2ER = VO_2 / DO_2$) and SvO_2 falls. When the mismatch between DO_2 and VO_2 can not be compensated by an increased O_2ER, anaerobic metabolism and lactic acidosis occur. It have to be remembered, however, that SvO_2 is a flow-weighted average of venous oxygen content of all different organs, and thus may not accurately reflect tissue hypoxia of an individual organ (Huang 2005).

The SvO_2 is measured from the pulmonary artery blood samples obtained from a PAC distal port. By using infrared oximetry, which is based on reflection spectrophotometry, SvO_2 can be monitored continuously. SvO_2 predicts mortality in sepsis (Heiselman et al.1986; Krafft et al. 1993), but no clear evidence of its value as a treatment target is available. Maintaining $SvO_2 \geq 70$ % failed to improve the outcome in a large study of intensive care unit patients (Gattinoni et al. 1995).

2.4.2.2 $ScvO_2$

Central venous oxygen saturation ($ScvO_2$) is a mixture of venous blood from the upper body, while SvO_2 reflects the flow-weighted oxygen balance of the whole body. The $ScvO_2$ reflects changes in oxygen delivery, or changes in consumption in the upper body and brain. $ScvO_2$ is measured in blood samples taken from central venous catheter or continuously by using a fiberoptic central venous line. The sampling site is important for the right interpretation of values, because saturation values are different in the right atrium, in the inferior vena cava, and in the superior vena cava when blood from the lower body and coronary sinus has been mixed (Lee et al 1972; Edwards and Mayall 1998).

Normally $ScvO_2$ is lower than SvO_2, but for patients in shock a consistent reversal of this relationship occurs and $ScvO_2$ may overestimate the true SvO_2 under shock conditions. Individual values in shock may differ up to 18 % to 22 % (Lee et al. 1972; Faber 1995; Edwards and Mayall 1998; Turnaoglu et al. 2001; Reinhart et al. 2004). The reason for this difference is understood when considering that SvO_2 is a mixture of saturation of the superior vena cava ($ScvO_2$), the inferior vena cava, and the coronary sinus, which are all blended according to the proportion of blood flow. The distribution of blood flow in a low-flow condition away from renal, splanchnic, and mesenteric circulation toward cerebral and myocardial perfusions, including a more desaturated blood from the coronary sinus and less well saturated blood from renal circulation, contribute to this difference. During sedation decreased oxygen consumption by brain and hypoperfusion within the hepatosplanchnic region leading to a highly depressed hepatic and splanchnic venous saturation may also explain the difference between $ScvO_2$ and SvO_2.

Early goal-directed therapy (EGDT), aimed at a $ScvO_2$ over 70 % during the first six hours, has been shown to reduce mortality among patients with severe sepsis and septic shock (Rivers et al. 2001). The use of $ScvO_2$ in initial resuscitation has been applied to the sepsis guidelines (Dellinger et al. 2004). $ScvO_2$, like

SvO_2, is an excellent measurement in detecting decreased DO_2. $ScvO_2$ reflects hypovolemia and acute cardiac failure more accurately than conventional hemodynamic measurements (Goldman et al. 1968; Ander et al. 1998; Madsen et al.1993; Rady et al. 1992; Scalea et al. 1990). After a resuscitation period, however, $ScvO_2$ is mostly normal (Reinhart et al. 2004). At the time of unplanned admission to a multidisciplinary ICU about 20 % of patients have a $ScvO_2$ below 60 % and these patients have a higher mortality than patients with a higher $ScvO_2$ (Bracht et al. 2007).

2.4.2.3 Lactate

When oxygen delivery fails to meet tissue oxygen demand a compensatory increase in oxygen extraction occurs. If this compensatory response is exhausted, tissue hypoxia leads to anaerobic metabolism, and lactate production as the end product of anaerobic glycolysis.

Under basal conditions about 0.8–1.0 mmol/kg/h lactate is produced continuously mainly by the skeletal muscle, skin, brain, red blood cells, intestine, and renal medulla. This lactate is utilized predominantly by the liver (Cori cycle), kidneys and heart muscle. Lactate clearance rate may exceed a level of 320mmol/L/h. If the production exceeds the clearance capability, hyperlactatemia will develop.

In the normal situation glucose is metabolised mainly via an aerobic pathway, in which pyryvate enters into tricarboxylic acid cycle (krebs cycle). Energy production of this aerobic metabolism is 36 ATP molecules. If pyryvate molecule is metabolized to lactate only 2 ATP molecules is yielded (Figure 3) (Fall and Szerlip 2005; Levy 2006). The important reason for lactatemia in septic shock is the hypoperfusion and lactate represent a useful and clinically obtainable surrogate marker of tissue hypoxia. Other explanations also exist, however, for the high lactate values in sepsis. Pyruvate dehydrogenase dysfunction or exhaustion, liver failure, use of epinephrine, and increased protein catabolism may increase lactate in sepsis. Actually, the hyperlactatemia in sepsis is not necessarily associated with the elevation of the lactate to pyruvate ratio (L/P ratio), which also suggests other mechanism than hypoperfusion alone behind lactatemia (Suistomaa et al. 2000). Recent studies have speculated that the increased lactate production, mostly by muscles could be beneficial extra fuel for organs in sepsis (Levy 2006).

Whatever the reason, hyperlactataemia remains an excellent prognostic marker in sepsis. The initial lactate level, peak lactate level, duration of lactatemia, and lactate clearance during the first six hours have been shown to predict survival in sepsis (Bakker et al. 1991; Nguyen et al. 2004).

A venous lactate level greater than 4 mmol/l, measured in the emergency department (ED), is highly specific for recognition of poor hospital outcome of patients with signs and symptoms suggestive to infection (Shapiro et al. 2005;Tretzjak et al.2007).

Septic patients with preserved autonomic compensatory responses, like young people, may have elevated lactate levels as a sign of global tissue hypoperfusion despite stable hemodynamic parameters. The outcome of these patients, without proper therapy, might be even worse than of those with clinical shock. In a subgroup analysis from the Rivers et al. pivotal EGDT study, patients with a raised lactate but normal blood pressure in the standard therapy group had a 60-day mortality of almost 70 % while it was 46.5 % for the whole standard therapy group (Bennet 2005; Trzeciak and Rivers 2005).

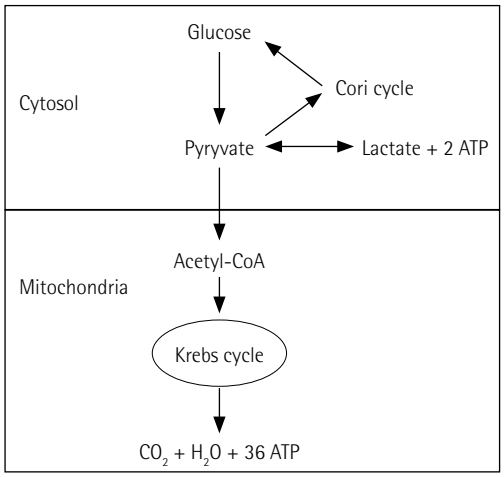

Figure 3. A simplified chart of glycolysis

2.4.3 Monitoring of regional perfusion

Blood flow in a single organ may be severely impaired despite sufficient global hemodynamic parameters (Ruokonen et al. 1993). Insufficient hepatosplanchnic blood flow may contribute to the pathogenesis of multiple organ dysfunction (Ackland et al.2000). Impaired microcirculation is associated to mortality in sepsis (Sakr et al. 2004; Trzeciak et al. 2007). Poeze et al. showed that after a resuscitation period of sepsis, regional variables, like gastric mucosal pH, mucosal PCO_2 gap, and indocyanine green blood clearance were better outcome predictors than global hemodynamic variables (Poeze et al. 2005).

The methods for measuring regional organ perfusion or microcirculation have been under wide investigation. Gastric tonometry is a method for providing information about the circulation of the stomach and the rest of the splanchnic bed. The monitoring of gastric intramucosal pH (pHi) was initially used to assess dysoxia. The calculation of the pHi, however, involves a number of uncertainties and instead of pHi the PCO_2 gap, defined as a difference between the gastric mucosal PCO_2 and the arterial PCO_2 ($PgCO_2$), may more specifically reflect the adequacy of gastric mucosal blood flow.

Several studies have demonstrated the prognostic value of gastric tonometry in septic shock (Maynard et al. 1993; Poeze et al. 2005), but the treatment aimed at increasing pHi has not improved outcome in trials (Gomersall et al. 2000). Evidence also exists that gastric PCO_2 is not a reliable marker of hepatosplanchnic perfusion in sepsis (Creteur et al.1999). The reliability of measurements are prone to a number of technical limitations. In clinical use the enteral feeding and gastric ulcer profylaxis may have an effect on the values of gastric tonometry (Creteur 2006). Sublingual capnometry is a simple, noninvasive method for the assessment of increased sublingual CO_2 tension, although a commercially available sublingual capnometry device is currently lacking. Sublingual PCO_2 ($PslCO_2$) correlates with gastric tonometry (Creteur 2006; Creteur et al. 2006) and it was a better predictor of outcome than traditional markers of tissue hypoxia, like lactate and SvO_2 in 54 hemodynamically unstable critically ill patients (21 with septic shock) (Marik and Bankov 2003).

Orthogonal polarisation spectral imaging (OPS) is a new technique for imaging microcirculation in clinical studies. The improvement of microcirculatory alterations, assessed sublingually with an OPS, predict survival in septic shock while persistent microcirculatory alterations are associated with multiple organ failure (MOF) and death (Sakr et al. 2004).

Several techniques for monitoring the regional perfusion and microcirculation have been used in experimental settings, but no clinically useful and reliable methods are available. In addition, regional perfusion measurements have not showed outcome benefit as an endpoint to guide the therapy. Routine assessment of regional perfusion or microcirculation is not yet recommended for shock (Antonelli et al. 2007).

2.4.4 Role of echocardiography in monitoring

The use of echocardiography in the monitoring of critically ill patients has increased during the last few years. It provides a real-time two-dimensional structural and functional imaging of the heart, along with doppler techniques making it possible to assess data on dynamic circulation, loading conditions, and cardiac output.

In septic shock echocardiography may give additional information to the conventional monitoring of the volemic status, systolic or diastolic dysfunction of the left ventricle, right heart failure, and fluid-responsiveness. With echocardiography it is possible to rule out some structural problems like pericarditis or endocarditis, which may be present in sepsis. It is also possible to follow the short-term influence of the hemodynamic treatment on cardiac function (Barbier et al. 2004; Jardin and Vieillard-Baron 2005; Jardin et al. 1999; Vieillard-Baron et al. 2004)

Echocardiography is not a continuous monitoring method and the use of that requires a

high degree of user expertize. Echocardiography based monitoring has not been studied in goal oriented trials and its benefit over some other monitoring techniques has not been assessed. An example of echocardiography based monitoring strategy in septic shock is shown in Figure 4.

2.5 TREATMENT OF HEMODYNAMIC ALTERATIONS IN SEPTIC SHOCK

2.5.1 Antimicrobial treatment

The cornerstone of the treatment of septic shock is the early and adequate eradication of infection with antimicrobial agents or surgical source control. The antibiotic treatment can also be seen as a part of the hemodynamic treatment. The animal data has shown that in early septic shock both antibiotics and cardiovascular support alone are relatively ineffective in the treatment. When combined, however, these two therapies provide a significantly better chance of survival (Natanson et al 1990).

In an animal model of sepsis, a critical time point for first the antibiotic dose, concerning outcome, seems to be the onset of clinical shock (Kumar et al 2006). In a murine model of Escherichia coli septic shock, a persistent increase of serum lactate, TNF- alpha, IL-6 levels, and remarkably increased mortality was found, if antibiotic treatment was initiated more than 12 hours after implantation of a bacteremic clot when clinical signs of shock had already developed (Kumar et al 2006). Kumar et al. also showed that the timing of antibiotic treatment is relevant even after symptoms of clinical shock have developed. In a retrospective analysis of over 2500 patients with septic shock, the mortality increased for every single hour that the adequate antimicrobial treatment was delayed after the beginning of hypotension (Kumar et al 2006).

Antimicrobial agents may also have other effects than antimicrobe eradication. Azole antifungal agents have been shown to interfere with neutrophils and lymphocyte function and

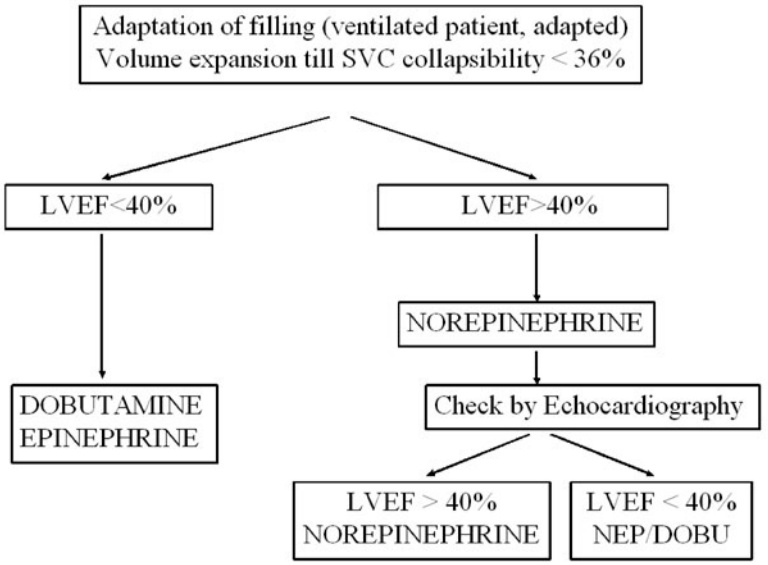

Figure 4. An example of echocardiography guided hemodynamic monitoring and treatment of septic shock. Adopted from (http://www.pifo.uvsq.fr/hebergement/webrea/index.php?option=com_content&task=view&id=14&Itemid=66) with permission.

SVC Superior Vena Cava, LVEF Left ventricular ejection fraction, NEP Norepinephrine.

ketoconazole may inhibit thromboxane A2 synthetase, which have a direct role in cardiopulmonary dysfunction and pulmonary edema in sepsis. Intravenous fluconazole reduced the development of organ failure and mortality in intra-abdominal sepsis in small prospective placebo-controlled trial (Jacobs et al. 2003)

2.5.2 Early Goal Directed Therapy (EGDT)

In 2001, Rivers et al. published a study about Early Goal Directed Therapy (EGDT) in severe sepsis. In that study the early recognition and early aggressive treatment starting already in the ED, showed a 16 % absolute mortality reduction compared to more conservative treatment. Thereafter, the concept of EGDT has been accepted into sepsis treatment guidelines.

The protocol of the EGDT study is shown in Figure 5. The main differences between the EGDT and standard group in that study were the amount of fluids, inotropes, and red blood cell transfusions during the first six hours of treatment. After three days, however, the amount of fluids and inotropes did not differed between the groups. The most important issue in the EGDT concept was the earlier timing of the aggressive treatment. A recent analysis shows that early hemodynamic optimisation decreases several biomarkers in septic shock and this decrease is associated with the severity of global tissue hypoxia. Significant decrease with EGDT therapy can be seen as soon as three hours after the start of treatment for interleukin-1 receptor antagonist (IL-1ra) and intercellular adhesion molecule-1 (ICAM-1), after six hours for tumor necrosis factor-α (TNF-α) and caspase-3, and after 12 hours for interleukin-8 (IL-8) (Rivers et al. 2007).

The EGDT study was the first ever to show a mortality reduction with a specific hemodynamic treatment in septic shock. Earlier studies, which have targeted supranormal oxygen delivery, had showed inconsistent results in critically ill, mostly postoperative patients. The concept of supranormal oxygen delivery was originally based on observational studies of critically ill patients, which have showed this kind of hemodynamic pattern in survivors vs. nonsurvivors. The meta-analysis of the studies on goal directed hemodynamic optimisation in high-risk patients, however, showed that actually the only important issue concerning mortality in these had been the timing. If the treatment had been

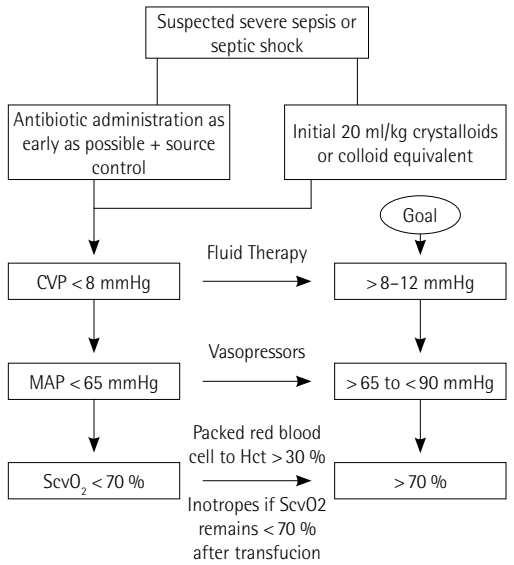

Figure 5. EGDT protocol. Modified from (Rivers et al. 2001).

started before development of organ failure, the mortality was reduced with goal directed treatment (Kern and Shoemaker 2002).

The EGDT protocol has been widely adopted and several reports have reported the reduced mortality in individual hospitals after implementation of EGDT in clinical reality (Sebat et al. 2005; Gao et al. 2005; Kortgen et al. 2006; Micek et al. 2006; Nguyen et al. 2006; Otero et al. 2006; Shapiro et al. 2006; Trzeciak and Rivers 2003). Nguyen et al reported that even after the active implementation process only a minority of patients is treated exactly according to the guidelines, however, but those who are most actively treated have a better outcome (Nguyen et al. 2007).

2.5.3 Fluids

Target of treatment

The vasodilatation in the early phase of the septic shock along with the disturbances in vessel permeability lead to hypovolemia, which always needs a rapid correction with volume resuscitation. Although the fluid therapy in early sepsis is a necessity, the optimum target in monitoring and the choice of the fluid are less clear.

The theoretical target of volume expansion is the increase in cardiac output and hence the global perfusion. The minimum goal in fluid resuscitation according to the EGDT study (Rivers et al 2001) and the Surviving Sepsis guidelines (Dellinger et al. 2004) is CVP over 8 mmHg or over 12 mmHg in mechanically ventilated patients. Some reviews have suggested a left heart filling pressure of 8–12 mmHg or 12–15 mmHg (Hollenberg et al. 2004; Ruokonen et al. 2002; Zanotti et al. 2006), based on an older small study by Packman et al. in whick the fluid resuscitation over this point did not result in a further increase in SV or CI (Packman et al. 1983). Plenty of evidence exists, however, that CVP or Paop are poor indicators of preload (Kumar et al. 2004; Magder 2005; Osman et al. 2007) and several factors, like elevated intrathoracic pressure or intra-abdominal pressure, hamper the interpretation of intrathoracic pressure measurements. Also it is noteworthy, that preload as such, does not correspond to a patient's ability to increase cardiac output with a fluid challenge, to fluid responsiveness (Kumar et al. 2004; Michard et al. 2000; Tavernier et al. 1998).

According to the Frank-Starling curve, the relationship between preload and cardiac output is not linear and the response to the volume expansion is seen only in the steep part of the pressure-volume curve. In the flatter part of curve the volume expansion will not increase the stroke volume and the overt fluid therapy may only lead to adverse effects, like lung edema, tissue edema, elevated intra-abdominal pressure, hyperchloremic acidosis (Scheingraber et al. 1999), dilutional anemia, and eventually to decreased perfusion and even to increased mortality. Positive fluid balance was an independent predictor of mortality in the large observational SOAP study (The Sepsis Occurrence in Acutely Ill Patients) (Vincent et al. 2006). The conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care of patient with acute lung injury in a randomised study (Wiedemann et al. 2006).

The assessment of fluid responsiveness may help with the achievement of optimal volume status. The fluid responsiveness can be assessed with several dynamic measures based on intrapleural pressure swings during ventilation. For example systolic pressure variation, pulse pressure variation, a decrease in systolic pressure from baseline (dDown), stroke volume variation, changes in aortic blood flow velocity, and aortic velocity-time integral seen with a pulse-doppler echocardiography, and collapsibility of the superior or inferior vena cava seen with echocardiography have been introduced for this purpose (Preisman et al. 2005; Kramer et al. 2004; Tavernier et al. 1998; Reuter et al. 2003; Slama et al. 2004; Slama et al. 2002; Feissel et al. 2001; Vieillard-Baron et al. 2004; Barbier et al. 2004; Feissel et al. 2004). The hemodynamic response to passive lag raising also predicts the patient fluid responsiveness (Lafanechere et al. 2006, Monnet et al. 2006). Several limitations in dynamic measurements also exists and routine use of these is not recommended in shock

although some selected patients may have an advantage with these (Antonelli et al. 2007).

Volume treatment in early septic shock is mandatory, but it has to be individually tapered and carefully monitored with the clear targets to increase the global or regional perfusion.

Choice of fluid

According to the recent guidelines both colloids and crystalloid are equally suggested for volume resuscitation in sepsis (Vincent and Gerlach 2004) based mostly on the meta-analyses and systematic reviews concerning patient with critical illness in general, mostly surgical or non-septic. Results of these studies can not be directly extrapolated to the patients with sepsis and even septic patients may need different consideration in volume replacement therapy in early and later phases of sepsis.

Colloids and crystalloids have several different properties, which may have an influence on the course of sepsis. The similar elevation of filling pressures can be achieved with both types of fluid but approximately three to four times more volume of crystalloid than colloid is required for this and this is accompanied with a higher incidence of pulmonary edema (Rackow et al. 1983). In an experimental study, early volume resuscitation with albumin and HES resulted in higher CO and DO_2 and lower lactate levels than gelatin or Ringer's lactate in septic shock, but the choice of fluid did not affect the outcome (Su et al. 2007). It seems that hydroxyethylstarch (HES) administration, at least 10 % HES 200/0.5 and 6 % HES 200/0.6–0.66, may be a risk factor for acute renal failure in patients with severe sepsis or septic shock (Schortgen et al. 2001; VISEP trial, preliminary data). But other synthetic colloids may also have adverse effects to renal function (Davidson 2006). Use of colloids can decrease the platelet aggregation and modify the inflammation but whether this is unfavourable in sepsis is not known. The choice of a specific fluid may influence to the development of intra-abdominal hypertension or cerebral edema (O'Mara et al. 2005). Controlled studies on these issues in sepsis are lacking, however, and the contribution of these characteristics on mortality is unresolved.

The use of albumin in volume resuscitation was studied in the large SAFE study (Saline versus Albumin Fluid Evaluation) with almost 7000 critically ill patients. Although no significant difference in mortality in the whole study group could be detected, a non-significant trend to better survival was observed in a non-randomised subgroup of over 1200 patients with severe sepsis (Finfer et al. 2004). Systematic reviews and meta-analyses have come to different conclusions concerning the safety or advantages of the use of albumin in critically ill patients and so far its use is not recommended for volume resuscitation of septic patient (Anonymous 1998; Wilkes and Navickis 2001; Alderson et al. 2007).

2.5.4 Vasopressors

Target of treatment

By definition, every patient in septic shock needs a vasopressor treatment for adequate perfusion pressure. Minimal data exist on an optimal blood pressure target to guide the vasopressor treatment. A MAP 60 mmHg to 65 mmHg has been traditionally chosen because of the physiological autoregulation range. Autoregulation is a manifestation of local blood flow regulation. It is defined as the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. Autoregulation operates especially well in vital organs like in the renal, cerebral, and coronary circulation. A MAP of about 60 mmHg to 65 mmHg is considered as a threshold and below that the autoregulation of blood flow to vital organs ceases, resulting in pressure dependent regional blood flow, exposing organs to tissue hypoxia and organ dysfunction.

Animal data show that the elevation of the normotensive MAP with norepinephrine does not increase regional perfusion in porcine sepsis if the MAP is within its autoregulatory range (Krouzecky et al. 2006). Two small human studies have also suggested that the elevation of MAP from 65 mmHg to 85 mmHg, with norepinephrine, neither affects metabolic variables nor improves renal function or regional perfusion (Bourgoin et al. 2005;

LeDoux et al. 2000). It is unclear, however, if moderate hypotension even below 65 mmHg would be better than the aggressive use of vasopressor agents. No difference on survival was demonstrated when vasopressor agents versus placebo were administered to sustain arterial pressure in the course of experimental peritonitis in the murine model of septic shock (Tang et al. 1996). Also treatment with a selective NO-inhibitor incresed mortality despite the elevation of blood pressure (Bakker et al. 2004; Lopez et al. 2004).

A recent consensus conference recommended a target MAP over 65 mmHg for septic shock patients (Antonelli et al. 2007).

Vasopressor agents

Catecholamines, like dopamine, norepinephrine, epinephrine, and sometimes phenylephrine are used as a vasopressor agent in septic shock. In recent years vasopressin, an endogenous hormone, and terlipressin, a synthetic analogue of vasopressin, have also been eagerly studied. Current guidelines suggest the use of dopamine or norepinephrine as a first line agent (Dellinger et al. 2004).

According to the recent Cochran systematic review, the current data do not support the use of any particular vasopressors in terms of reducing overall mortality in septic shock (Mullner et al. 2007). In observational cross-sectional European cohort study (SOAP), the use of dopamine and epinephrine were associated with an increased mortality in sepsis (Vincent et al. 2006). Martin et al. reported a better survival with norepinephrine over other vasopressors (dopamine, epinephrine) in their prospective observational study with a logistic regression analysis (Martin et al. 2000) and norepinephrine was more effective than dopamine in correcting sepsis induced hypotension in a non-randomized study (Martin et al. 1993). When dopamine alone is sufficient to restore the blood pressure, however, the outcome is generally favourable (Levy et al. 2005).

Vasopressin has been effective in increasing the blood pressure of patients refractory to conventional vasopressor treatment. Vasopressin in addition to norepinephrine leads to a significant reduction in vasopressor requirement (Patel et al. 2002; Micek et al. 2007) although it alone may not be sufficient to restore blood pressure (Micek et al. 2007). The potential adverse effects to regional circulation and cardiac function have reduced its clinical use. In an experimental study, high doses of vasopressin lead to a decrease in mesenteric and renal blood flows (Malay et al. 2004). It seems that the safe dose range for exogenous vasopressin in septic shock is narrow. The overall effect of low-dose vasopressin and norepinephrine to blood flow of the intestine or kidneys in septic shock has been mostly favorable, however, along with the increasing perfusion pressure (De Backer et al. 2003; Farand et al. 2006).

The effect of vasopressin on mortality in septic shock was studied in a large prospective controlled trial (VASST, Vasopressin and Septic Shock Trial). The preliminary results (published in 28th International Congress of Critical Care and Emergency Medicine, Brysel, 2007) showed that contrary to the hypothesis, low-dose vasopressin reduced mortality compared to norepinephrine in a subgroup of patients with less severe sepsis (lower need for vasopressors) but had no advantage for patients with a high norepinephrine dose. In that study, low-dose vasopressin had no more significant side effects than norepinephrine. In a retrospective study by Luckner et al. the dose of NE before start of vasopressin was an independent predictor of mortality. The mortality rapidly increased if NE dosages exceeded 0.6 μg/kg/min before AVP infusion had been implemented (Luckner et al. 2005)

In few small trials terlipressin, a synthetic analogue of vasopressin, with a longer half life and a stronger affinity to vasopressin-1 receptors, have been studied in catecholamine refractory septic shock. Its effect on blood pressure has been favorable, but possible side effects to cardiac function have been alarming (Albanese et al. 2005).

2.5.5 Inotropic medication

Target of treatment

In the 1980's and 1990's there was much enthusiasm to increase CO and DO_2 to supranormal

values, thus mimicking the hemodynamic profile of survivors of sepsis (Edwards et al 1989; Shoemaker et al. 1993). The studies aimed at some supranormal cardiac output, however, have failed to show benefit in mixed critically ill patients (Hayes et al. 1994; Gattinoni et al. 1995). Later it was observed that increase in DO_2 does not lead to an increase in VO_2 in nonsurvivors (Hayes et al 1997), which may be a sign of cytopathic disturbances, mitochondrial dysfynction and microcirculatory failure in septic shock. The ability of patients to increase VO_2 to a dobutamine infusion is associated with a good outcome. This implies that patients whose cells are functioning in a normal manner do well and patients whose cells are no longer able to function normally have a poor outcome (Rhodes et al. 1999).

Cardiac function is often impaired in septic shock when assessed with echocardiography or with radionuclide techniques. Current guidelines suggest the use of dobutamine as an inotropic medication in patients with a measured low cardiac output despite fluid resuscitation (Dellinger et al. 2004). According the EGDT protocol, inotropic medication should be introduced according to the signs of insufficient perfusion, measured with $ScvO_2$ (Rivers et al. 2001). Some have proposed that inotropic medication should be started if the left ventricular ejection fraction is less than 40 % measured with echocardiography (Figure 4).

Inotropic agents

Dobutamine is generally considered as a treatment of choice for sepsis-related myocardial depression (Dellinger et al. 2004). Dobutamine increases the cardiac index and stroke volume, although the heart rate also increase in most patients. Dobutamine increases regional blood flow in sepsis and has shown beneficial effects when used as a combination with vasopressor agents. No study has shown improved outcome with the use of dobutamine, however, and evidence exists that high doses may have an adverse effects to outcome (Hayes et al. 1994). Morelli et al. investigated the effects of levosimendan on systemic and regional hemodynamics in dobutamine resistant septic myocardial depression. They found that levosimendan improves systemic hemodynamics and regional perfusion in sepsis and is a safe and efficacious alternative to dobutamine (Morelli and Teboul 2006). Levosimendan may improve right ventricular performance and global perfusion in ARDS associated with septic shock (Morelli et al. 2006).

2.5.6 Adjuvant therapies

Corticosteroids

Cortisol is essential in regulating the impaired vasomotor tone of the vasculature. Cortisol decreases the NO mediated vasodilatation, sensitizes the receptors to catecholamines, and affects the distribution of body fluids by improving the endothelial barrier function (Marik and Zaloga 2002; Prigent et al. 2004; Rhen and Cidlowski 2005). The use of low dose corticosteroids improves the shock resolution in septic shock, although the effect on mortality has been controversial (Annane et al. 2004; Keh and Sprung 2004). In a recent Corticus trial low dose corticosteroids resulted in earlier resolution of shock, but the recurrence of shock or new infections occurred more often in the treatment group and corticosteroids showed no benefit in mortality (unpublished). The improvement of hemodynamics is not predicted by the results of an adrenocorticotropin (ACTH) stimulation test (Morel et al. 2006).

Activated protein C

Recombinant human activated protein C (rhAPC) improved the outcome of adult patients with severe sepsis and septic shock (Bernard et al. 2001). The positive effect was most pronounced in those with more severe sepsis. In one retrospective study rhAPC decreased the norepinephrine dose required to maintain arterial pressure (Monnet et al. 2005). The possible beneficial effects of rhAPC on hemodynamics are likely multifactorial. In experimental models rhAPC decrease nitric oxide synthase (NOS) activity and TNF-α production, but no significant effect on cytokines has been detected in human studies (Sennoun et al. 2007). Some in vivo and in vitro studies have shown that RhAPC may improve endothelial

barrier function and thus decrease the vascular permeability in sepsis (Looney and Matthay 2006).

Others

The nitric oxide synthase inhibitor, NG-methyl-L-arginine hydrochloride, promoted the resolution of shock in a multicentered, randomised, placebo-controlled study (Bakker et al. 2004). The phase III trial was prematurely terminated, however, because of increased mortality (Lopez et al. 2004). Methylene blue, an inhibitor of nitric oxide, increases the mean arterial pressure and systemic vascular resistance in septic shock and vasopressor requirements decrease. Studies on the influence on outcome are lacking (Kirov et al. 2001; Kwok and Howes 2006). The inhibition of K_{ATP} channels with sulfonylureas has restored MAP in experimental endotoxemic shock (Lange et al. 2006). One study investigated the inhibition of K_{ATP} channels with glibenclamide in human septic shock, but failed to achieve a reduction in norepinephrine (Warrillow et al. 2006). Outside the vasculature, K_{ATP} channels may also represent a protective mechanism against cellular damage. (Buckley et al. 2006).

Different modalities of high-volume or isovolume hemofiltration have improved hemodynamics in septic shock patients with multiple organ dysfunction (Joannes-Boyau et al. 2004; Ratanarat et al. 2005; Haase et al. 2007), but the indications in septic shock without renal failure are not clear (Cole et al. 2002).

2.6 OUTCOME OF SEPTIC SHOCK

The mortality rate is sepsis increases with the severity of the sepsis. Rangel-Frausto et al. prospectively evaluated the mortality rate in relation to the sepsis criteria of 3708 patients. Mortality increased with the number of criteria for systemic inflammatory response syndrome (SIRS) or if the clinical sepsis severity increased. The mortality rate without SIRS criteria was 3 %, while it was 7 % with two, 10 % with three, and 17 % with four SIRS criteria. Mortality rate was 20 % in severe sepsis and 46 % in septic shock (Rangel-Frausto et al. 1995). Alberti et al found no difference in hospital mortality rate between patients with infection and with sepsis (i.e. infection and SIRS criteria) without organ dysfunction, while presence of organ dysfunction or shock had a strong prognostic significance (Alberti et al. 2003).

The hospital mortality rate of septic shock in epidemiological studies has varied from 29 % to 82 % (table 2) and in placebo arms of randomized trials, hospital mortality has varied from 30 % to 87 % (Dellinger 2003). The wide variations in observed mortality depend partly on the different selection of patients in studies. Differences in ICU admission policy and differences in critical care organisations in different countries may also have influenced results when only patients inside ICU are evaluated. Shortage of ICU beds leads to tight admission criteria with only the most critical patients being admitted, hence the mortality rate is probably higher.

The outcome of septic shock has improved over time. When 131 studies from 1958 to 1997 with over 10 500 patients were evaluated, evidence existed of a small improvement in the survival rate from septic shock over the last few decades (Friedman et al.1998). Important studies that have reported a signifigant mortality benefit and that have changed the treatment in sepsis have been published in the 21st century. Rivers et al. demonstrated a 16 % decrease in absolute 28-day mortality with EGDT (Rivers et al. 2001). RhAPC reduced absolute mortality by 6 % in severe sepsis Bernard et al. 2001) and low-dose steroid replacement decreased mortality by 10 % for those septic shock patients, who did not respond to adrenocorticotropin test (Annane et al. 2002). In addition, the control of glucose balance with insulin infusion showed a 3.7 % mortality reduction in critically ill ICU patients and lung-protective ventilatory treatment has reduced mortality in acute respiratory distress syndrome, which occurs commonly in septic shock. Based on these results, the European Society of Intensive Care Medicine (ESICM), International Sepsis Forum (ISF), and Society of Critical Care Medicine (SCCM) started the world-wide Surviving Sepsis Campaign (SSC) with the target of achieving a 25 % reduction in

sepsis mortality by 2009. The SSC aims to reach this target with a multipoint strategy; building awareness of sepsis, improving diagnosis, increasing the use of appropriate treatments, educating healthcare professionals, improving post-ICU care, developing guidelines and facilitating data collection for audit and feedback (www.survivingsepsis.com).

Long-term outcome data after treatment of septic shock is sparse. In the Finnsepsis Study one-year mortality after ICU-treated severe sepsis or septic shock was 40.9 % (Karlsson et al. 2007). Jagodic et al. found that the two-year mortality of severe sepsis or septic shock after treatment in surgical ICU was 67 %, which was higher than after trauma (43 %)(Jagodic et al. 2006). In the PROWESS trial, one-year survival of patients with severe sepsis or septic shock was 53 % for the treatment group and 49 % for the placebo group (Angus et al. 2004). In a prospective study of patients with sepsis syndrome in the ED, the overall one-year mortality was 22 %. The presence of SIRS criteria alone had no prognostic value, but each additional organ dysfunction increased the adjusted one-year mortality hazard by 82 % (Shapiro et al. 2006). The one-year mortality after bloodstream infection associated sepsis without shock was 36 % and with shock 61 %. Surgical diagnosis and increasing age were independently associated with late mortality (Laupland et al. 2005). Weycker et al. obtained data from the U.S. health insurance database for the study on the long-term outcome of over 16 000 patients that were hospitalized because of severe sepsis in 1991–2000. He found an one-year mortality of 51.4 % and five-year mortality of 74.2 %. Advanced age, comorbidities, organ dysfunction, and hospital discharge to another facility were associated with a higher mortality (Weycker et al. 2003). Quartin et al. reported that among 30-day sepsis survivors, sepsis reduced the remaining mean life span from a predicted 8.0yrs to 4.1yrs (Quartin et al.1997)

The 28-day, or hospital mortality, is generally used as an end-point in clinical trials. The mortality of septic shock, however, increased constantly even after first month or first hospitalization period. Exact reasons for this late mortality are not clear, although the risk is increasing with advanced age, co-morbidities, and disease severity at the beginning. Longer follow-up and studies on the reasons for late deaths are warranted in future trials (Vincent 2004).

Sepsis survivors may suffer from residual organ dysfunction. Patients may have lose their extremities or have severe impairments of muscle function. Persistent symptoms such as dyspnea, fatigue, depression, and impaired functional status may lead to reduced quality of life. The long-term health-related quality of life (HR-QoL) of survivors of sepsis is lower than that of the general population (Heyland et al. 2000), but it might not differ from other patients who had survived critical illness not involving sepsis (Granja 2004; Jagodic et al. 2006).

3 AIMS OF THE STUDY

The objective of this study was to evaluate different aspects of hemodynamic patterns in septic shock, especially components of early treatment and monitoring. The specific aims were:

1. To assess the impact of hemodynamic variables on the outcome of patients with septic shock and to identify the optimal threshold values related to outcome with special reference to continuously monitored mean arterial pressure (MAP) and mixed venous oxygen saturation (SvO_2). (I)

2. To assess the correlation and agreement of central venous oxygen saturation ($ScvO_2$) and mixed venous oxygen saturation (SvO_2) and to compare $ScvO_2$–SvO_2 difference to lactate, oxygen-derived, and hemodynamic parameters in early septic shock. (II)

3. To evaluate the predictive value of NT-proBNP on mortality in a large unselected patient population with severe sepsis and septic shock. (III)

4. To determine, how the early treatment guidelines were adopted and what was the impact of early treatment on mortality in septic shock patients in Finland. (IV)

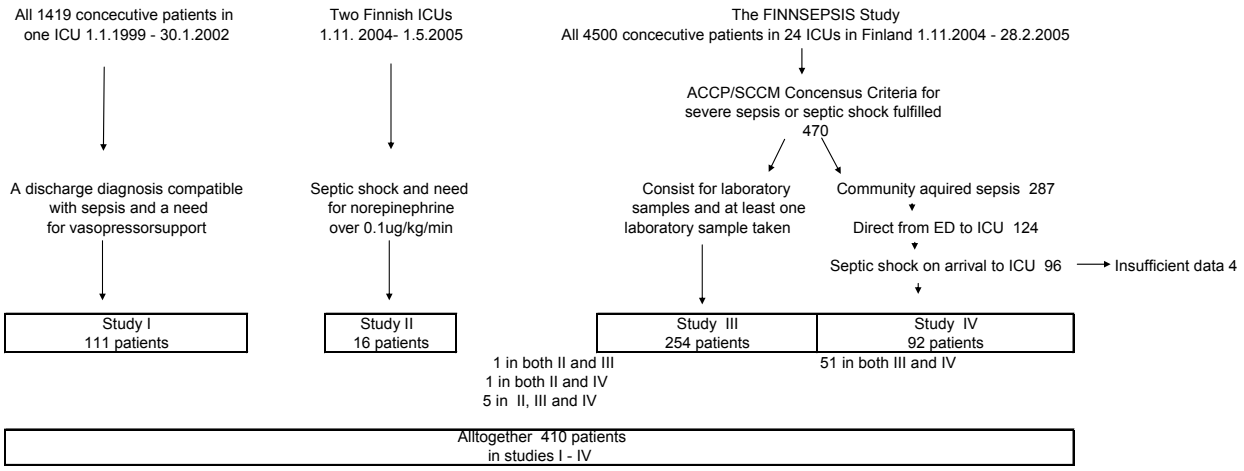

Figure 6. The flowchart of inclusion in studies I–IV

4 PATIENTS AND METHODS

4.1 PATIENTS

Altogether 410 patients were included in studies I-IV. The flowchart of inclusion is presented in Figure 5. The demographics of the study patients are presented in Table 3.

Study I was a retrospective cohort study which was conducted in one nine-bed medical-surgical intensive care unit (ICU) at the Helsinki University Hospital. All 1419 consecutive patients that were admitted to the ICU between January 1, 1999 and January 30, 2002 were considered eligible. The 111 patients with a discharge diagnosis compatible with sepsis (sepsis, pneumonia, meningitis, or peritonitis) and a need for vasopressor support during the first 48 h constituted the final study population with septic shock.

Study II was a prospective study conducted in two Finnish ICUs from November 2004 to June 2005. Sixteen patients with septic shock fulfilling the criteria set by the APCCP/SCCM Consensus Conference were included. In addition a norepinephrine dose over 0.1 μg/kg/min for maintaining mean arterial blood pressure over 65 mmHg was required for inclusion in addition.

Studies III and IV were substudies of a prospective observational cohort study on the incidence and prognosis of sepsis in Finland (the Finnsepsis study). The Finnsepsis study was conducted over a four-month period (from November 1, 2004 to February 28, 2005) in 24 ICUs in Finland. All adult patients (≥ 18 years) that were admitted in the participating ICUs during the study period were screened daily for the criteria of severe sepsis and septic shock proposed by ACCP/SCCM. All patients filling these criteria; known or suspected infection, with two or more criteria of the systemic inflammatory response syndrome, and at least one sepsis-induced, new organ failure were included to the Finnsepsis study. A patient was included to study III, if the consent for blood tests was obtained from the patient or their legal representatives. Study IV included patients who had community-acquired sepsis, were admitted directly from the ED to ICU, and fulfilled the criteria of septic shock according to the attending physicians. A total of 55 patients were included in both studies III and IV.

Comparison of demographics and characteristics of patients are shown in Table 3.

4.2 STUDY DESIGNS

Summary of the study designs is shown in Table 4.

Study I

In the study I we analyzed the common hemodynamic variables as outcome indicators in septic shock during the first six and 48 hours separately. In addition we evaluated, whether the time or area under critical MAP or the SvO_2 level would be a better predictor of survival than the mean values of these or the other hemodynamic variables and which threshold level is the best discriminative level between survivors and non-survivors. An example of this method is shown in Figure 6. Both MAP and SvO_2 were recorded from the database every 10 mins (each value was considered representative of the values within the previous 10 mins). Ppao, CVP, CI, and SV were recorded every one to six hours. Serum lactate was recorded upon arrival and on day two. If the patient expired within the 48-h monitoring period, the last hours data were excluded. A 30-day mortality rate was assessed.

Table 3.Demographics of the patients in Studies I - IV

	Study I	Study II	Study III	Study IV
Number of patients	111	16	254	92
Age	52 (39-63)	51 (44-62)	60 (49-72)	57 (49-62)
Male sex	62 (56%)	13 (81%)	175 (69%)	67 (73%)
Apache II	17 (11-22)**	23 (18-29)	23.5 (18-29)	26 (20-33)
SOFA on 1.day	8 (6-12)	10 (9-12)	8 (6-11)	10 (7.25-12)
ICU mortality	33 (30%)	NA	34 (13%)	20 (22%)
Hospital mortality*	36 (33%)*	6 (38%)	67 (26%)	30 (36%)
Norepinephrine medication on day 1	93 (84%)	16 (100%)	178 (70%)	79 (86%)
Maximal dose of norepinephrine (ug/kg/min)	0.15 (0.05-0.46)	0.26 (0.16-0.36)	0.18 (0.08-0.34)	0.35 (0.10-0.43)
Ventilator treatment	104 (94%)	16 (100%)	153 (60%)	68 (74%)
Positive blood culture	61 (55%)	5 (31%)	72 (28%)	42 (46%)
Primary site of infection				
Lung	47 (42%)	6 (38%)	106 (42%)	45 (49%)
Intra-abdominal	15 (14%)	6 (38%)	81 (32%)	15 (16%)
Central nervous system	8 (7%)	1 (6%)	6 (2%)	2 (2%)

*30-day mortality in Study I

** Data available from 66 patients

Data are expressed as number (percentage) or median (25-75 percentiles)

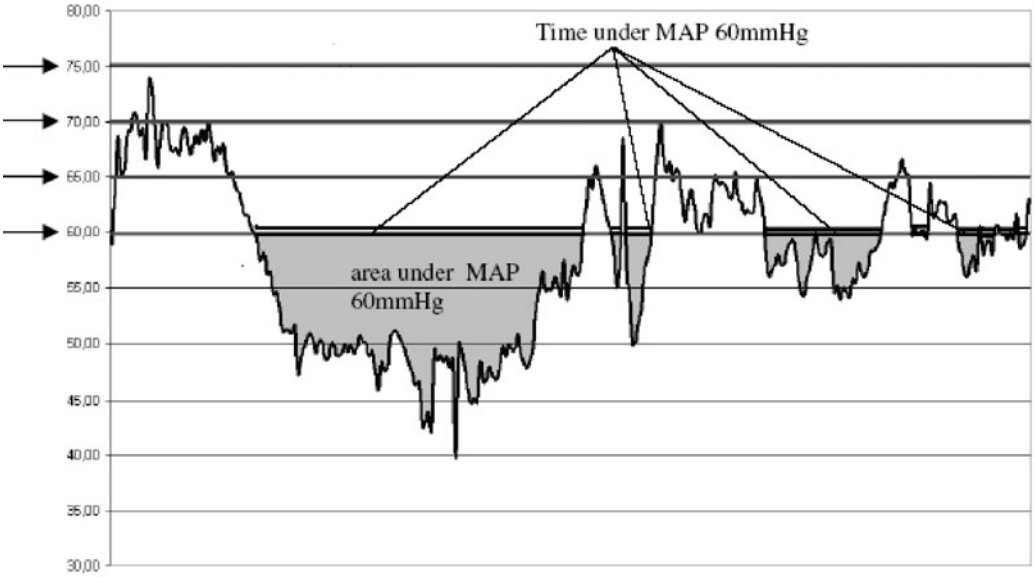

Figure 7. An example of recording the mean arterial pressure during the first 48h in the ICU in Study I.. Arrows are the threshold values used in calculations. The hypotension area/time is calculated as the total area/time of MAP values lower than the threshold, divided by the duration of the monitoring time. Hypotension area under 60 mmHg is shown in grey. Black line indicates the hypotension time under 60 mmHg

Study II

In this study we evaluated the correlation and the agreement of $ScvO_2$ and SvO_2 and also compared the $ScvO_2$–SvO_2 difference to lactate, oxygen derived and hemodynamic parameters during early severe septic shock in ICU. Simultaneous blood samples were drawn slowly from the distal port of the unwedged PAC for SvO_2 and from the side port of the introducer for $ScvO_2$ immediately after the patient inclusion and every six hours thereafter up to 24 h. Arterial samples were drawn from the arterial catheter. Hemodynamic measurements and measurements of arterial plasma lactate level were performed immediately after blood sampling.

Table 4: Summary of Studies I–IV

	Desing	Aims	Patients	Main Variables	Other variables	Endpoint
Study I	Retrospective	To evaluate the predictive value of common hemodynamic variables especially MAP and SvO2 and to assess the most predictive threshold levels regarding mortality.	111patients with sepsis and need for vasopressors (septic shock) in one ICU	Hypotension time and hypotension area: Time and area under MAP less than 60, 65, 70 and 75 mmHg Hypoperfusion time and hypoperfusion area: Time and area SvO2 less than 60%, 65% 70% during first 6 and 48 hours in ICU	Ppao, CVP, CI, SV, lactate during first 6 and 48 hours in ICU APACHE II, SOFA, Demograprics, Use and doses of vasopressor agents, Pao2/Fio2, PEEP	30-day mortality
Study II	Prospective	To assess the correlation and agreement of ScvO2 and SvO2 and to compare ScvO2-SvO2 difference to lactate, oxygen-derived and hemodynamic parameters in early septic shock in ICU after initial resuscitation period.	16 patients with septic shock and dose of norepinephrine over 0.1ug/kg/min in two ICUs	SvO_2 and $ScvO_2$	Demographics,Lactate, CI , Paop, CVP , SVR ,MAP DO2 , VO2 , O2er, B-Hb, Body temperature Doses of vasoactive medication APACHE II, SOFA	Agreement and correlation
Study III	Prospective	To evaluate the predictive value of NT-proBNP regarding hospital mortality in severe sepsis and clinical characteristics of patients with elevated NT-proBNP	254 patients with severe sepsis or septic shock in 24 ICUs	NT-proBNP	APACHE II, SAPS II, SOFA, Demographics Use and doses of vasopressor agents, platelet count, plasma creatinine concentration, estimated creatinine clearance, bilirubin, CVP Paop, MAP, P-lactate, positive blood culture, fluids	Hospital mortality One-year mortality
Study IV	Prospective	To determine the success of early treatment, the impact of early treatment on mortality and the impact of separate early treatment targets in septic shock patients in Finland.	92 patient with septic shock, community aquired sepsis and came from ED to ICU in 24 ICUs	Early treatment targets: Measurement of lactate during the first six hours from admission to ED; Obtaining the blood cultures before start of the antibiotics; Starting the antibiotics within three hours from admission to the ED; Reaching the mean arterial pressure over 65 mmHg, central venous pressure over 8 mmHg, SvO2 >65% or ScvO2>70% during first six hours	Demographic data, basic hemodynamic data, basic laboratory data, need for vasoactive drugs, ventilator treatment, fluids and blood products. APACHE II, SOFA.	Hospital mortality One-year mortality

Study III
In this study we evaluated the predictive value of NT-proBNP regarding hospital mortality in severe sepsis and septic shock in a large, unselected, representative patient population. We also assessed the clinical characteristics of patients with elevated NT-proBNP. Blood samples for NT-proBNP analyses were obtained from an indwelling arterial catheter or by venapuncture at inclusion and 72 hours thereafter. Both ICU and hospital mortality was recorded. One-year mortality data was obtained from Statistics Finland.

Study IV
In this prospective substudy of the epidemiological cohort study, we evaluated the success of the early sepsis treatment in 24 Finnish ICUs.

Patients were divided into two groups according to the number of achieved targets.

The group ≥ 4 consisted of patients who reached four or more treatment targets and the group ≤ 3 of those with three or less targets. Also the impact of separate treatment targets concerning the outcome was evaluated.

The ICU and hospital mortality was recorded from hospital records and one-year mortality data from Statistics Finland.

4.3 LABORATORY MEASUREMENTS

Plasma N-terminal pro-brain natriuretic peptide (III)
Blood samples were obtained from an indwelling arterial catheter or by venapuncture into Li-heparin containing tubes. The plasma fraction was separated and samples were stored at −20 °C or colder at the enrolling site before being sent to the Helsinki University Hospital, where samples were stored at −80 °C. Samples were analysed 9–13 months later in batches after a single thaw. The plasma concentration of NTproBNP was determined using a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany) on an Elecsys 2010 automatic analyzer (Roche Diagnostics). All laboratory analysis was performed in a single acredited laboratory (Helsinki University Central Hospital Laboratory, HUSLAB).

Plasma lactate (I–IV))
Plasma lactate levels were measured from an indwelling arterial catheter by a photometric method. Although the measurement of lactate was not included in the study protocol in studies III and IV, it was measured as a routine clinical measurement and the evaluation of lactate values was prospectively defined.

Other
Although no specified laboratory sample protocol was chosen, routine tests were taken daily as a part of patient follow-up and for organ failure and disease severity scores. These tests included blood gas analyses, serum creatinine, urea and bilirubin concentrations, hemoglobin and hematocrit, white blood cell count and platelets. In study III the estimated creatinine clearance was calculated using the Cockcroft and Gault formula:
(140 – Age) × weight (kg) × F} / (Plasma Creatinine × 48.816). Where F = 1 if male, and 0.85 if female (Cockcroft and Gault 1976).

4.4 HEMODYNAMIC MONITORING AND MEASUREMENTS

Pulmonary artery catheter (PAC) or central venous catheter (I–IV)
Only study II included PAC insertion in the study protocol, but PAC derived data was used in studies I and III when available. In these studies pulmonary artery catheterization or central venous catheterization was performed if the local intensivist deemed it necessary. Commonly the use of a pulmonary arterial catheter was considered appropriate if norepinephrine was used. In study I, 100 of the 111 (90 %) patients had PAC, in study II all 16 patients and in study III 121 (48 %) patients had a pulmonary artery catheter and an additional 95 patients (38 %) had central venous catheter inserted. In study II a four-lumen pulmonary artery catheter (PAC) with introducer (7.5 F Paceport Oximetry TD Catheter with AMC Thromboshield 780HF75, Edwards Lifesciences LCC, Irvine,

CA, USA) was inserted. A typical wedge pressure tracing with the balloon inflated and chest X-ray confirmed the correct placement of the catheter in the West zone 3 position.

The cardiac output (CO) was determined with the thermodilution method via PAC by injecting 10 mL of isotonic saline through the proximal port of PAC. The CI was computed by dividing CO by the patient's body surface area. Three to five measurements were obtained and averaged.

SvO_2 (I, II, IV) and $ScvO_2$ (II, IV)
In study I, SvO_2 was continuously measured with a fiberoptic catheter by reflectance oximetry.

In study II, the SvO_2 samples were drawn slowly from the distal port of the unwedged PAC and $ScvO_2$ samples from the side port of the introducer. Oxygen saturation was determined photospectrometrically with a co-oximetry (Ciba-Corning 850 and 855, Medfield, MA, USA).

In study IV, SvO_2 (or $ScvO_2$) was measured either with the fiberoptic method or with co-oximetry using separate samples.

4.5 INTERVENTIONS

Besides laboratory analyses (I, II, III) and oximetric and hemodynamic measurements (II), patients were treated according to the discretion of attending physicians without special treatment protocols and without therapeutic interventions.

4.6 DATA COLLECTION

During the inclusion period of study I, our unit used an ICU clinical data management system (CareVue, Hewlett-Packard, Boston, MA, USA) which automatically stored all physiologic data displayed in the database of the monitors (DatexAS3, Datex-Ohmed, Helsinki, Finland) at a five-minute sampling frequency as well as all laboratory and medication data. The requisite data was extracted retrospectively from the database.

Studies III and IV included patients from 24 ICUs from 21 hospitals. All data were collected daily by local study nurses or investigators (Appendix). Data was stored through an internet-based Finnish intensive care quality consortion (Intensium Ltd.Kuopio, Finland).

4.7 OUTCOME MEASURES

Mortality
The 30-day mortality (Study I), hospital mortality (Study III and IV), and one-year mortality (Study III and IV) data were acquired from the hospital records and Central Population Registry of Finland.

The standardized mortality ratio (SMR)
The standardized mortality ratio (SMR) was calculated as the ratio of observed hospital mortality over the predicted hospital mortality (Study IV). Probability of hospital death was calculated using the Simplified Acute Physiology Score (SAPS) II.

Disease severity scores
SOFA (Sequential Organ Failure Assessment (Vincent et al 1998)
SOFA score evaluate status of the following organ systems separately: Respiration, coagulation, hepatic, cardiovascular, renal, and central nervous system. The SOFA score were calculated for days one and two (Study I), for day one (study II and IV) or for day one and three (Study III).

Acute Physiology and Chronic Health Evaluation (APACHE) II score (Knaus et al 1985) and Simplified Acute Physiology Score (SAPS) II (Le Gall, Lemeshow and Saulnier 1993)
To evaluate the severity of illness APACHE II and SAPS II scores were calculated for the first 24 hours in the ICU (Study I–IV)

4.8 STATISTICAL ANALYSES

Statistical significance: The level of $p<0.05$ was considered statistically significant

in all tests. The analyses were performed using the SPSS 10.1.3 (I) or 13.0 (II–IV) software (SPSS,Chicago,Ill.).

The Kolmogorow-Smirnov test was used for testing the normality of continuous variables (II, III).

Mann-Whitney U test was used for the comparison of continuous variables of two samples of observations like demographic, hemodynamic or laboratory data between survivors and non-survivors (I–III) or patients in different groups (IV).

Chi-Square or Fisher's exact tests were used for testing the difference between two samples of categorical variables. Fisher's exact was used if the number of cases in a sample was below five (I–IV).

Spearman's rank correlation test was used for determining the relationship between two continuous variables, which were not normally distributed like comparison of NT-proBNP and physiological and laboratory variables or SvO_2–$ScvO_2$ difference and hemodynamic or perfusion variables (I–III).

Linear regression analysis was used to find the potential confounding factors that would best predict the value of the dependent variable (NT-proBNP). The variables that first yielded significance in the univariate model, were tested with a linear regression analysis using log-transformed NT-proBNP, because values of NT-proBNP were not normally distributed (III).

Bland-Altman analysis is a statistical method, which assess the agreement between two methods of clinical measurement. It can be used for comparison of a new method with an established one to see whether they agree sufficiently for the new one to replace the old. The Bland-Altman graph plots the difference between two measurements against their averages. The Bland-Altman analysis was used to evaluate the agreement between $ScvO_2$ and SvO_2 in study II.

Intraclass correlation (ICC) was used to measure the statistical significance of correlation between $ScvO_2$ and SvO_2 measurements of patients at different time-points (II). The ICC was used instead of the Pearson correlation, because of repeated measurements of a single patient at five separate time-points, which made the data intracorrelated and not totally independent.

Friedman test is a nonparametric test for several related samples. It was used to detect the differences between $ScvO_2$ and SvO_2 measurements across different time-points and also across different levels of $ScvO_2$ (II).

Kruskal-Wallis test is a non-parametric method for comparing the medians between two or more samples to determine if these have come from different populations. The Kruskal-Wallis test was used in study III where the study population was divided to groups according to quartiles of APACHE II, SAPS II, and SOFA scores and the differences of NT-proBNP between groups was assessed (III).

Kaplan-Meier test was used to evaluate one-year mortality differences in studies III and IV.

Multivariate forward logistic regression analysis was used to test the independent effect of the variable on the outcome (I, III, IV).

Receiver operating characteristic curve (ROC) analysis was used in study III for finding the best predictive cut-off values of NT-proBNP for predicting mortality. The best cut-off values are defined as the threshold values that maximized the sum of the sensitivity and specificity.

Areas under the ROC curve (AUC) were used for determining the predictive accuracy of variables. AUCs were calculated for mortality prediction using all MAP and SvO_2 derived parameters as predictive variables in study I, and NT-proBNP in both time points as predictive variables in study III.

Diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of NT-proBNP for mortality prediction was assessed as follows:

		Condition		
		Dead	Alive	
Test outcome	Positive*	A=true Positive	C=fase Positive	A+C
	Negative**	B=false Negative	D=true Negative	B+D
		A+B	C+D	

**NT-proBNP values above cut-off*
***NT-proBNP values below cut-off*

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

5 ETHICAL ASPECTS

The Ethics Committee approved the study protocols. Informed consent was obtained from patient or next of kin before blood tests in studies II, III, and IV.

The study was partly supported by EVO grant TYH 6235 from Helsinki University Hospital and a grant from Päiviki and Sakari Sohlberg foundation. N-terminal pro-brain nartiuretic peptide assays were provided free of charge by Roche Diagnostic.

The authors of the studies have not disclosed any potential conflicts of interest.

6 RESULTS

6.1 PREDICTION OF MORTALITY ACCORDING TO HEMODYNAMIC VARIABLES (I)

The study showed that in septic shock during first six hours in ICU the most important variables concerning mortality were the mean MAP (p=0.001) and lactate upon arrival (p=0.02). When a patient was followed for up 48 hours the mean MAP, the mean CVP, and a hypoperfusion area (SvO_2) under 70 % were independently associated with mortality by a logistic regression analysis. Receiver operation curves regarding the 30-day mortality were plotted for allthe MAP and SvO_2 derived variables. The highest AUC values were found for the hypotension area under 65 mmHg (AUC 0.853, 95 % CI 0.772–0.934) and for the hypoperfusion time under 70 % (AUC 0.747, 95 % CI 0.618–0.876). According to these the best discriminative threshold value concerning mortality is 65 mmHg for MAP and 70 % for SvO_2.

6.2 SVO_2 VERSUS $SCVO_2$ IN SEPTIC SHOCK (II)

In early severe septic shock, simultaneous values of $ScvO_2$ and SvO_2 correlated significantly (intraclass correlation coefficient 0.89, 95 %CI 0.82–0.93, p<0.001). The mean SvO2 was below the mean ScvO2 at all time points during the first 24 hours. When simultaneous measurements were evaluated with the method proposed by Bland and Altman, the agreement of $ScvO_2$ and SvO_2 was not adequate.

The agreement between $ScvO_2$ and SvO_2 by the Bland–Altman plot showed that the bias of difference was 4.2 % (95 % limits of agreement from –8.1 % to 16.5 %). We found that the difference between simultaneous ScvO2 and SvO_2 (Δ[ScvO2–SvO_2]) inversely correlate to CI (p = 0.036) and to DO_2 (p = 0.007), but detected no correlation to other measured variables or to the dose of norepinephrine. We concluded that for clinical use the agreement of $ScvO_2$ and SvO_2 is not adequate and that SvO_2 is not estimated on the basis of $ScvO_2$ in septic shock.

6.3 NT-PROBNP AS A PROGNOSTIC FACTOR IN SEVERE SEPSIS AND SEPTIC SHOCK (III)

The NT-proBNP values upon admission varied from 55 pg/mL to 146 592 pg/mL (median 4396 pg/mL), and at 72 hours from 39 pg/mL to 247 812 pg/mL (median 2889 pg/mL). The NT-proBNP levels upon admission were significantly lower in hospital survivors (median 3479 pg/mL; 25^{th} and 75^{th} percentiles 1102 pg/mL and 9970 pg/mL) than non-survivors (median 7908 pg/mL; 25^{th} and 75^{th} percentiles 2658 pg/mL and 20855 pg/mL; p = 0.002). This difference persisted at 72 hours (median 2354 pg/mL; 25^{th} and 75^{th} percentiles 631 pg/mL and 6362 pg/mL vs. 5688 pg/mL; 25^{th} and 75^{th} percentiles 1479 pg/mL and 17972 pg/mL; p = 0.002) (Figure 8). In ROC analysis the area under the curve (AUC) of NT.proBNP for hospital mortality upon admission was 0.631 (95 % Cl 0.549–0.712, p = 0.002) and at 72-hour 0.648 (95 % Cl 0.554–0.741, p = 0.002).

The best cut-off value of NT-proBNP upon admission for hospital mortality was 7090 pg/mL with a sensitivity of 58 % (95 % Cl 45–69 %), a specificity of 66 % (95 % Cl 59–73 %), a positive predictive value of 38 % (95 % Cl 29–48 %), a negative predictive value of 81 % (95 % Cl 74–87 %), and an accuracy of 64 %. The best cut-off value of NT-proBNP after 72 hours was 8948 pg/mL with a sensitivity of 45 % (95 % Cl 30–60 %), a specificity of 81 % (95 % Cl 74–86 %), a positive predictive value

of 40 % (95 % Cl 27–54 %), a negative predictive value of 84 % (95 % Cl 77–89 %), and an accuracy of 73 %. The Kaplan-Maier curves for one-year mortality according the best cut-off limits are shown in Figure 9.

In the univariate logistic regression analysis the significant predictors ($p < 0.05$) for hospital mortality were age, SAPS score, APACHE II score, SOFA score, lowest MAP, maximal dose of norepinephrine and epinephrine, and plasma lactate. These and NT-proBNP values were entered into a multiple forward stepwise logistic regression model. Independent predictors of hospital mortality were the SAPS II score ($p < 0.001$) and 72-hour NT-proBNP ($p = 0.014$).

The NT-proBNP upon admission significantly correlated to the highest Paop ($p < 0.001$), eCrCl ($p = 0.002$), lowest platelet count on the first day ($p = 0.03$), and positive

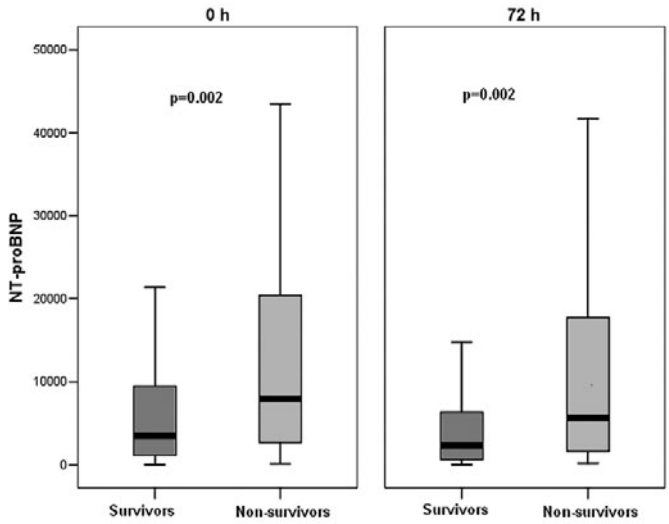

Figure 8. N-terminal pro- brain natriuretic peptide (NT-proBNP) levels of hospital survivors and nonsurvivors at admission and 72 hrs thereafter. Data are presented as median values (line) with 25th and 75th percentiles (boxes) and 5th and 95th percentiles (whiskers).

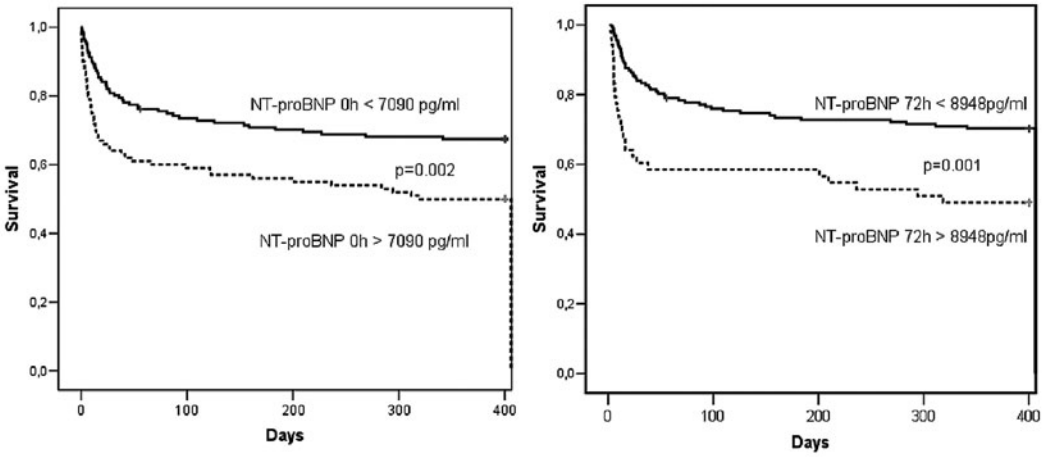

Figure 9. Kaplan-Meier survival curves according to N-terminal pro–brain natriuretic peptide (NT-proBNP) levels at admission (A) and at 72 hrs (B). Cut-off limits are best cut-off limits that predict hospital mortality. From Study III.

blood culture (p = 0.04) according to a linear regression analysis. After 72 hours the linear regression analysis showed that only eCrCl (p < 0.001) had an independent effect on the NT-proBNP value.

6.4 LACTATE AS A PROGNOSTIC FACTOR IN SEPTIC SHOCK (I, III, IV)

According to Study I, serum lactate upon arrival to ICU was significantly associated with mortality (p = 0.02) when only the first six hours hemodynamic variables were assessed with the logistic regression analyses. When the first 48 hours were evaluated, however, the admission lactate was not significant anymore.

In Study III and IV, the first lactate value and the highest value during the first 24 hours in ICU were recorded. According to the ROC analysis, in Study III, which also included patients without septic shock, the AUC of the first lactate value was 0.665 (95 % CI 0.586–0.744) and 0.686 (95 % CI 0.606–0.766) for hospital mortality. In Study IV the corresponding AUCs were 0.794 (95 %CI 0.674–0.913) of the first lactate and 0.761 (95 % CI 0.626–0.897) of the first day maximal lactate (p < 0.001 for all)

6.5 EARLY TREATMENT OF SEPTIC SHOCK IN FINLAND (IV)

All predefined end-points of early treatment concept were completed for 6 of 92 patients (6.5 %). When single targets were analysed separately, blood cultures were obtained most often (79 of 92, 86 %). The $ScvO_2$/SvO_2 target was measured in time for 18 patients, but the goal was achieved for only 10 patients (11 %). The CVP was measured during the first six hours for 34 patients and the goal of over 8 mmHg was achieved for 29 patients (32 %). Lactate was measured during the first 6 six hours in 53 (58 %), a MAP of over 65 mmHg was achieved in 68 (74 %) and antibiotics were started during the first three hours in 49 (53 %) patients. The serum lactate value was measured in the ED before ICU transfer for 20 of the 92 patients (22 %). CVP was measured in the ED for two patients and neither $ScvO_2$ nor SvO_2 was measured in the ED or the ICU for 35 (38 %) patients. Antibiotics were started before ICU admission for 46 (50 %) patients.

In an univariate analysis of separate treatment targets, the delay in the start of antimicrobic treatment within three hours from ED admission was significantly associated with hospital mortality (p = 0.04). In a forward logistic regression analysis, the delay on the start of the antibiotics within three hours was an independent predictor of mortality when all separate targets were used as independent variables (p = 0.04). When APC treatment, low-dose steroid treatment, APACHE II, and SOFA scores were added to the analysis, only the APACHE II score (p < 0.001) was an independent predictor of hospital mortality.

When the one-year mortality was analyzed, the start of antibiotics within three hours (p = 0.001) and the APACHE II value (p = 0.001) were independent predictors of mortality in a logistic regression analysis. If antibiotic treatment was started within three hours, one-year mortality was 33 % (16 of 49 [95 % CI 21–47 %]), while it was 72 % (31 of 43 [95 % CI 57–83 %]) if the treatment was delayed.

The Kaplan-Maier curve of mortality, according to the start of the antibiotics within three hours, is shown in Figure 10.

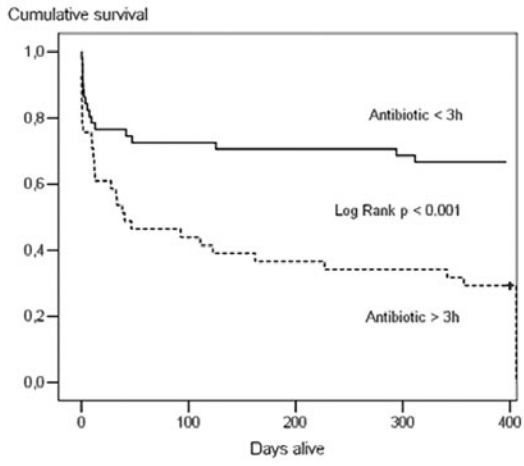

Figure 10. The Kaplan-Maier curve about mortality according the start of the antibiotics within three hours. From Study IV.

The hospital mortality of those 33 patients who reached four to six treatment targets (group ≥ 4) was 24 % (8 of 33 [95 % CI 13–41 %]) compared to 42 % (25 of 59 [95 % CI 31–55 %]) of those 59 patients who reached three targets or less (group ≤ 3) (p = 0.08). The median delay from hospital admission to ICU transfer was 1.6 hours (0.7, 2.1) in group ≥ 4 and 3.5 hours (2.0, 8.9) in group ≤ 3. The severity of disease assessed with the APACHE II or SOFA score had no influence on the early treatment success.

6.6 MORTALITY (I, III–IV)

According to the combined results of Studies I and IV, the ICU mortality rate of septic shock was 26 % (53 of 203 patients): 33/111(30 %) in Study I and 20/92 (22 %) in Study IV. The hospital mortality rate in Study IV in the overall population of septic shock patients was 36 % (33/92), and the 30-day mortality in Study I was 33 % (36/111). In Study III, which included the patients with severe sepsis and septic shock, the ICU and hospital mortality rates of the study patients were 13 % (34 of 254) and 26 % (67 of 254) (Table 3, page 36).

The one-year mortality was assessed in Studies III and IV. It was 51 % (47/92) according to Study IV in septic shock patients and 40 % (102 of 254) according to Study III in severe sepsis and septic shock.

7 DISCUSSION

Strengths and weaknesses of the study

The results of this study offer an aid for clinicians in their every-day work. We showed the importance of adequate MAP and SvO_2 as well as the optimal thresholds concerning the outcome with a huge amount of hemodynamic measurements. The predictive value of NT-proBNP was shown prospectively with representative and large patient population. We proved the disagreement of $ScvO_2$ and SvO_2 measurements in septic shock during the ICU treatment, which might affect on monitoring methods in ICUs. Furthermore, we showed the reality of an early treatment of septic shock nationwide in Finland, which might help us to improve the treatment of septic patients. Although the number of patient was quite small, this does not impair the generalization of the results to all patients with community aquired septic shock.

Some limitations of the studies can be addressed. First the optimal time point to assess the mortality after septic shock is not clear although the hospital mortality is the most used time point. Many patients suffering sepsis are transferred from the hospital to rehabilitation centers or to nursing homes where they will probably die and never actually return home. Hospital mortality rate does not tell the true mortality concerning this issue. The 28-day or 30-day mortality is not good either, because hospital length of stay after sepsis is very long. We used the 30-day mortality in Study I and hospital mortality in Study III and IV. In addition, one-year mortality was evaluated in Studies III and IV.

The retrospective nature is a limitation of Study I. Although the data were collected online with the data management system, we cannot exclude the possibility of some false recordings related to patient care, movement, or signal artefacts. All data was checked before analysis and outliers were eliminated and bias seems unlikely because of the substantial number of recorded values. In addition we did not record the fluid balance, which could have been informative concerning CVP.

A limitation of Study II is the small sample size. The patient group, however, was homogeneous with regard to the severity and timing of septic shock. In the correlation analysis, samples of one patient are pooled from several time points, which may have affected the results.

Limitations of the Study III were that we were able to include only part of the Finnsepsis study patients. These patients, however, did not differ from patients without consent for blood samples. Because of the nature of the study, we were not able to control the hemodynamic treatment, and we did not have any load independent measurements about cardiac function during sepsis. In addition, the amount of volume resuscitation before blood samples is not definite and is missing for part of the patients.

The sample in Study IV was relatively small, but with the tight inclusion criteria the study group is a uniform group of patients who most probably would have had a benefit of aggressive early treatment. As a limitation, we did not assess the patient's status on arrival to the ED and, therefore, timing of some relevant treatments, such as fluids, were not recorded exactly during the ED stay. In addition, we only included patients that had been admitted to the ICU because of septic shock and it is possible that some patients that had avoided ICU admission, because of proper EGDT therapy in the ED, may not have been included. We did not assess the clinical situation in the ED, which may have affected treatment decisions.

Hemodynamic variables in outcome prediction and as treatment targets in septic shock

Our results suggest that during standard treatment the most important hemodynamic vari-

ables predicting the 30-day outcome in septic shock are MAP and lactate for the first six hours and MAP, SvO_2, and CVP for the first 48 hours. The best predictive threshold level for mortality was MAP of 65 mmHg and SvO_2 of 70 % supporting the current guidelines.

Poeze et al. studied regional and global hemodynamic variables as an outcome indicator in 28 patients with septic shock (Poeze et al. 2005). They found that upon admission no variable was superior to others as a predictor of outcome, but after stabilization the variables of splanchnic function were better predictors, than common pressure- or volume- related variables. They used only single MAP, CVP, and Paop measurements before and after resuscitation treatment, however, and they did not measured SvO_2 at all. Most studies report hemodynamic variables as a single measurement or as a mean of a couple of values. In septic shock this approach may be misleading since rapid changes in hemodynamics occur due to the disease and the treatment. We used parameters derived from the continuous monitoring of MAP and SvO_2, allowing better exploration of these parameters cumulatively over time. We also took into account both the duration and severity of hypotension and hypoperfusion. We did not find hypotension time or area more informative than the mean MAP over six hours or 48 hours, although the highest AUC value was found for hypotension area under 65 mmHg (AUC 0.853, 95 % CI 0.772–0.934). The hyperperfusion area of SvO_2 under 70 % was more predictive than the mean value of the continuous SvO_2 measurements over 48 h.

One interesting finding was the predictive impact of high CVP. One reason for high CVP could be a volume over-loading. A recent observational pan-European study reported that a positive fluid balance was among the strongest prognostic factors for death (Vincent et al. 2006). In a prospective randomised study of ARDS the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care stay patients (Wiedemann et al. 2006).

Based on our data, however, it is not possible to assess whether more aggressive treatment targeting to higher MAP and SvO_2 improves survival. In septic shock observational studies have shown a higher CI, higher SvO_2, and higher oxygen delivery and consumption in survivors. Several goal-directed studies targeting at survivors' supranormal hemodynamic pattern have failed to show benefit in sepsis. Those who actually reach the targets had a better outcome, however, indicating the crucial importance of hemodynamic response on survival. This favorable response may only be a marker of a less severe disease itself, not of benefit of treatment. We did not find that dose of norepinephrine predict survival independently which support the importance of disease severity over treatment. The MAP was a predictive sign irrespective of NA dose. Several opposite findings exist, however. Nitric oxide synthase inhibitor, NG-methyl-L-arginine hydrochloride, increased mortality although the perfusion pressure was better maintained with the treatment (Lopez et al. 2004).

The trial by Rivers et al. found that the early goal-directed therapy targeting to MAP over 65 mmHg, CVP 8 to 12 mmHg and $ScvO_2$ over 70 % during the first six hours in the emergency department resulted in a significant reduction in mortality in septic patients (Rivers et al. 2001). The meta-analysis on trials that describe the hemodynamic goals in acute, critically ill patients revealed statistically significant mortality reductions when patients with acute critical illness were treated early to achieve optimal goals before the development of organ failure (Kern and Shoemaker 2002). It seems that the time course of sepsis is of outstanding importance when the hemodynamics of the patient and hemodynamic treatment is evaluated.

Clinical importance of NT-proBNP in outcome prediction of septic shock

NT-proBNP is commonly elevated in patients with severe sepsis and septic shock. NT-proBNP at 72 hrs in the ICU was an independent predictor of hospital and ICU mortality. According to our results, the acute cardiac load contributes to the NTproBNP values at admission, but renal failure is the main confounding factor later.

Few studies, with a relatively small number

of patients and selected populations, have investigated the predictive power of NPs in severe sepsis (Brueckmann et al. 2005; Charpentier et al. 2004;Hoffmann et al. 2005; Roch et al. 2005). In agreement with our results, these earlier studies also found significantly elevated levels of NPs in non-survivors compared to survivors. A very recent study could not verify the prognostic value of BNP in 40 patients with severe sepsis and septic shock, but there was an inadequately low number of non-survivors for mortality analysis (McLean et al. 2007).

Factors that increase the wall stress of myocardium lead to increased production of natriuretic peptides. In our patients these factors could be septic myocardial depression, volume overloading, or excessive use of vasopressors. Several studies have found a correlation between septic myocardial depression and natriuretic peptides (Charpentier et al. 2004, Roch et al. 2005). We did not found any association between CI and NT-proBNP. This is not surprising because CI is a load-dependent measurement and after fluid loading elevated CI is commonly seen in septic shock despite of the myocardial depression. The low CI as well may be a sign of hypovolemia, not myocardial depression. The dose of NE correlated to the NT-proBNP values in univariate analysis but this was not seen in linear regression analysis any more. Elevated Paop had an independent effect on NT-proBNP levels on the first day. The reasons for this could be the volume loading, myocardial depression, or both, Unfortunately we were not able to register the amount of volume loading trustworthly. In addition, patients with septic myocardial depression generally need much volume loading for hemodynamic support (Charpentier at al. 2004).

We showed that NT-proBNP predicts mortality in severe sepsis and septic shock. Its usage as a biomarker in sepsis is promising. More studies, however, are needed on the physiologic implications of NPs, influence of treatment on NPs, confounding factors, optimal time of analysis, optimal cut-off points in different assay preparations, and activation of the neuroendocrine system in sepsis as a whole, before we are able to use these data for treatment decisions or for outcome prediction.

Agreement of SvO_2 and $ScvO_2$

Study II demonstrated that during the first day in ICU, the average difference between $ScvO_2$ and SvO_2 values was 4 %, but the individual differences varied from 8 % to 17 % and thus $ScvO_2$ and SvO_2 are neither equal nor interchangeable.

The clinical utility of $ScvO_2$ is documented in the early setting of septic shock and whether it equals SvO_2 in this phase is less relevant. It is more relevant to understand the pathophysiological differences of these two measurements later in the ICU settings and the fact that the results about treatment of early sepsis can not be extrapolated to patients who are treated after the resuscitation period in the ICUs.

In study I we showed that SvO_2 values below 70 % increased the risk of mortality in septic shock. According to the data from Study II, 16 % of SvO_2 values were below 70 %, while $ScvO_2$ was above 70 %. If we then assume that SvO_2 over 65 % and $ScvO_2$ over 70 % are clinically acceptable, treatment decisions would still have been different after 14 % of the measurements (either SvO_2 below 65 % while $ScvO_2$ over 70 % or SvO_2 over 65 % while $ScvO_2$ below 70 %).

In the study conducted by Reinhart et al., evaluating critically ill patients during an average of 56 hours with the continuous measurement of $ScvO_2$, over 87 % of the values of nonsurvivors and 95 % of those of survivors were over 70 % (Reinhart et al. 2004). This may suggest that a $ScvO_2$ of 70 % as a treatment goal in septic shock after the resuscitation period is insensitive for the detection of tissue oxygen demand. In addition, nearly 20 % of abrupt changes over 10 % of SvO_2 cannot be detected with $ScvO_2$ in severe sepsis or septic shock (Martin et al. 1992)

Role of early treatment in septic shock in Finland

The adoption of the EGDT concept and Sepsis Resuscitation Bundle was unsatisfactory in Finnish hospitals in 2004–2005. Moreover, the failure in rapid diagnosis and start of appropriate treatment reflected on mortality. Delayed start of antibiotics was the most significant separate early treatment variable influencing

the excess of deaths.

Study IV was conducted without any local protocol implementation and before national guidelines were published in Finland. Mortality rates of the compliant and non-compliant group in our study were comparable to the mortality reduction that has been reported in studies comparing outcomes before and after sepsis protocol implementation (Micek et al. 2006; Otero et al. 2006; Shapiro et al. 2006; Trzeciak et al. 2006). These before and after comparisons have all been done in single hospitals mostly using retrospective control patients and different protocols. In real life, even after active an protocol implementation process, patients are treated differently. A recent work by Ngyen et al. showed that during the two years follow-up, along with the active protocol implementation, only 77 of 330 eligible patients completed the early treatment bundle, although compliance increased with time. The hospital mortality of the compliant and non-compliant group was 21 % and 40 %, which was comparable to our results.

Only a few studies besides ours have evaluated which separate components are most important for a better outcome. In a prospective study by Mizek et al. (Micek et al. 2006), not achieving 20 mL/kg intravenous fluid administration before vasopressors in the ED, was independently associated with hospital mortality. In a study by Ngyen et al., the start of antibiotics within four hours, monitoring of lactate clearance and completing the whole EGDT or bundle protocol were associated with the better outcome. In our study the delay in antimicrobial therapy was associated with a worse outcome. Kumar et al. showed that after detection of hypotension, the mortality increased for every single hour that the adequate antimicrobial treatment was delayed (Kumar et al. 2006). Also, in a prospective study, by Garnacho-Montero et al., of 224 patients with sepsis (of which 114 in septic shock), a risk for in-hospital mortality increased by 9 % for every hour of delay of the administration of the correct antibiotic (Garnacho-Montero et al. 2006).

We also found that EGDT procedures were only seldom performed in the ED and thus the early treatment was more often unsatisfactory when the transfer was delayed from the ED to the ICU.

Clinical implications and future perspectives

The most relevant finding concerning everyday clinical practice was the reality of the early treatment of septic shock in Finland and especially the importance of the early start of antimicrobial treatment in septic shock. The importance of time delay is well understood in the treatment of myocardial infarction or stroke, but based on our results, is still underestimated in septic shock. International guidelines and clinical studies are not enough for adequate implication of new treatment protocol especially when multidiscipline skills are needed. The national guidelines and organized local protocol implementation and education across the clinical boundaries may be mandatory for a better outcome in severe sepsis and septic shock. While the whole protocol may be difficult to realize, even small changes like the earlier start of antibiotic treatment may lead to better results.

Another implication for clinical practice is that $ScvO_2$ can not be used as a substitute for SvO_2 in septic shock as estimation of global perfusion. The $ScvO_2$ and SvO_2 vary highly even with comparable vasoactive treatment and thus SvO_2 is not estimated on the basis of $ScvO_2$. The usefulness of SvO_2 itself in guiding the treatment in septic shock, however, needs to be re-evaluated in a randomized trial using goal-oriented therapy and continuous measurements.

In septic shock during the first two days, the routinely monitored variables MAP, SvO_2, CVP, and lactate on arrival associate with mortality. Our results support the recent guidelines aiming at aMAP over 65 mmHg and SvO_2 over 70 %, although we did not study hemodynamic parameters as treatment targets.

The implication of the clinical use of NT-proBNP in outcome prediction is a still controversial issue. We should know more about the etiology of NT-proBNP elevation in septic shock, whether the disease itself or aggressive treatment leads to the excessive elevation. Also the impact of the elevation of BNP or ANP on

the hemodynamic course of shock needs further studies.

Severe sepsis and septic shock still carries a high mortality even though studies in 20th century have shown that reduction in mortality is possible. Sepsis has been studied extensively in recent years. One of the most important issues that has been understood, is the relevance of timing concerning the outcome. The timing should be taken into account in future trials because it is obvious that the whole pathophysiologic entity in septic shock is different in early sepsis, before resuscitation treatment, and later if the shock persists. One major problem concerning the outcome studies is the highly complicated course of illness when all confounders can hardly be controlled, even though the single treatment strategy could be of benefit. Extremely large study populations would be needed to prove the benefit. On the other hand the heterogenity of patients make the interpretation of the results difficult in the large study populations. For example, the efficacy of drotrecogin alfa or corticosteroids depends on the severity of the illness even if all patients have septic shock by definition (Annane et al.2002, Bernard et al. 2001, Abraham et al. 2005). Some treatment that does not show a significant benefit in trials may still help a small subgroup of patients with special characteristics (Deans et al. 2007). That denotes that the results of the studies about a mixed critical illness population should be interpretated with caution.

The clinical picture vary a lot in septic shock. Some may have a refractory shock unresponsive to vasopressors, some an extremely increased permeability and pulmonary oedema, and some may show a fulminant myocardial depression. More individually targeted treatment for special hemodynamic characteristics might be needed in septic shock in future. The one of the most important study subjects in future is the microcirculation. The ongoing disturbations of microcirculation after the first resuscitation are of great importance concerning for both mortality and morbidity. While systemic hemodynamics can be maintained at the expense of impaired microcirculatory perfusion, it would be extremely important to develop new biomarkers or monitoring methods about microcirculation for everyday clinical use.

In the near future, the role of vasopressin and its derivatives in extreme vasodilatation will hopefully become clearer and the studies focusing on the tretment options for extreme vessel permeability would be of great interest. The unsolved problem of optimal volume replacement therapy and optimal monitoring of volume replacement needs further studies. Interesting issues are, if the treatment of septic myocardial dysfunction with inotropes improve the outcome, even in the absence of a global perfusion deficit, and what is the optimal trigger for starting the inotropic treatment.

The one intriguing question is, which are the most important hemodynamic treatment targets and can the outcome be improved with a specific goal-directed hemodynamic treatment even after resuscitation period. It might be a delusion, however, to imagine that a similarly targeted hemodynamic treatment would ever be a solution in a complex and highly variable hemodynamic course in septic shock.

At this time no a quick and accurate serologic tests or biomarkers for clinical use exist. Hopefully some marker in future will provide a simple bedside test that will help in earlier diagnosis and treatment decisions in sepsis. Our findings on NT-proBNP might inspire new studies on the role of natriuretic peptides in treatment decisions concerning inotropes or volume loading. It would be exciting to know, if the extreme elevation of NPs is already seen from the first beginning of septic shock or is it atleast partly induced by aggressive treatment and what is the relevance of NPs in septic vasodilatation.

A new century had shed light on the devastating course of septic shock. While the active investigation of the complex pathogenesis and development of new innovative therapies continue, there is a one thing, which we allready know. That is the importance of the early treatment. If the first golden hours, the window of opportunity, are missed, the salvation of the patient is much more difficult. We can not ignore that.

8 CONCLUSIONS

Based on the results of these studies the following conclusions can be drawn:

1. Low average mean arterial pressure, mixed oxygen saturation values below 70 % and high average central venous pressure during the first 48 hours of treatment, are associated with mortality in septic shock. The best discriminative threshold values are 65 mmHg for MAP and 70 % for SvO_2.

2. Central venous oxygen saturation and mixed oxygen saturation are not equal or interchangeable in hemodynamic evaluation of patient with septic shock in the ICU.

3. The N-terminal pro-brain natriuretic peptide is commonly elevated in severe sepsis or septic shock and it is an independent predictor of survival in day three in the ICU.

4. Inappropriate early treatment of septic shock and especially the delay in the start of antibiotics impair the prognosis of septic shock. Early treatment of septic shock is not optimal in Finland.

9 ACKNOWLEDGEMENTS

This study was carried out in the Intensive Care Unit, Department of Anaesthesiology and in the High Dependency Unit, Department of Medicine, Helsinki University Hospital during the years 2003–2007.

I am thankful to Professor Per Rosenberg and Professor Oll Kirvelä for an opportunity to work and accomplish this study in Department of Anesthesiology. I am also deeply thankful to Professor Markku S. Nieminen for his positive attitude to my choices to specialize in intensive care and for help and support in several projects during the years.

First of all I want to thank my supervisor Docent Ville Pettilä. Your talent to push someone towards the goal is extraordinary. Sometimes irritating but mostly constructive criticism from you, way to tell things straight out, help with statistics, and also your clinical skills and knowledge, have been essential for this dissertation as well as for my work as a critical care doctor.

I thank the official reviewers Professor Tero Ala-Kokko and Professor Else Tonnesen for their supportive comments and constructive criticism and suggestions to improve the dissertation. I thank Shannon Kuismanen MSc. for editing the language and Jari Simonen for layout of this dissertation.

I express my warm gratitude to study nurses Maiju Salovaara, Sari Sutinen, Pekka Leinonen and Leena Pettilä. Your help with data management, messy papers, and blood samples has been invaluable. Especially the moments at (and in) the freezer has been unforgettable. I remember with gratitude Marja Pere, study nurse, who expired tragically in tsunami on December 2004.

My most sincere gratitude is expressed to Finnish ICU collaboration, to all those great colleagues and study nurses from 24 ICUs across the Finland. Your valuable effort during Finnsepsis study made this thesis possible.

I express my warm thanks to all co-authors, above all to Sari Karlsson, MD. the lady Finnsepsis herself. Your energy and spirit were essential for the success of Finnsepsis. I wish all good luck for your own dissertation. Remember that a new pair of shoes may help when reviewers are nasty. I thank Docent Esko Ruokonen, the wise man from east, for his supportive, friendly and always beneficial comments. I also thank Docent Ilkka Parviainen, Minna Tallgren PhD. Docent Kari Pulkki, Katri Saukkonen MD, for their efforts for this study.

I want to express my special thankfulness to Docent Liisa-Maria Voipio-Pulkki. I owe to you that I am working among critical medicine. Your support and confidence on fresh specialist was an important step on my way from internist to intensivist.

I want to express my special thanks to my ”boss” Docent Anne Kuitunen. This project would have been much harder without your positive support and a pleasant atmosphere at everyday work, not to mention the fat-bike tours and inspiring work with Elsa. I also want thank the personnel of Meilahti Intensive Care Unit 23 who are always ready to help with study patients without complaining. It is always a pleasure to work with you.

I thank all those colleagues and friends at work who have cheered up the busy days and sleepless nights with humor (sometimes quite black) and with discussions about matters of life and death. This work is really much more than a way to earn money.

I thank my sisters Heli and Tuija, my sister-in-law Sari and her husband Juha and all my friends who keep on reminding me that life is really outside the hospital. I thank my mother, Irma, for support and for relaxing moments in fascinating and peaceful Inari where I too seldom have opportunity to visit. I also thank Liisa and Matti, my parents-in-law for caring of our children during busy times.

And finally I thank my family for enormous support, tolerance and patience though kitchen table is drowning under paper piles and home is sometimes like after explosion. Tero, your experiences of study projects of your own have been helpful. And last but certainly not least Anni, Salla and Ville: You have grown up the real survivors of life during this project.

Financial support from the Helsinki University Hospital Research fund is gratefully acknowledgement.

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ORIGINAL PUBLICATIONS

APPENDIX

Participating hospitals, investigators (Inv.), and Study Nurses (SN) in the FINNSEPSIS-study:

Satakunta Central Hospital Hospital, Dr. Vesa Lund (Inv.), Marika Vettenranta, Päivi Tuominen (SN); East Savo Central Hospital, Dr. Markku Suvela (Inv.), Sari Hirvonen, Anne- Marja (SN); Central Finland Central Hospital, Dr. Raili Laru-Sompa (Inv.), Tiina Kirkhope (SN); South Savo Central Hospital, Dr. Heikki Laine (Inv.), Aki Savinen, Pekka Kettunen (SN); North Carelia Central Hospital, Dr. Sari Karlsson (Inv.), Jaana Kallinen, Vesa Parviainen (SN); Seinäjoki Central Hospital, Dr. Kari Saarinen (Inv.), Johanna Kristola, Niina Tuominen (SN); South Carelia Central Hospital, Dr. Seppo Hovilehto (Inv.), Sari Melto, Marjut Repo (SN); Päijät-Häme Central Hospital, Dr. Pekka Loisa (Inv.), Merja Esselström, Riitta Hallikainen (SN); Kainuu Central Hospital, Dr. Tuula Korhonen (Inv.), Ulla Koponen, Kirsti Pomell (SN); Vaasa Central Hospital, Dr. Pentti Kairi (Inv.), Marianne Ström (SN); Kanta-Häme Central Hospital, Dr. Ari Alaspää (Inv.), Elina Helminen (SN); Lappi Central Hospital, Dr. Outi Kiviniemi (Inv.), Tarja Laurila (SN); Keski-Pohjanmaa Central Hospital, Dr. Tadeusz Kaminski (Inv.), Tea Verronen (SN); Kymenlaakso Central Hospital, Dr. Jussi Pentti, Dr. Seija Alila (Inv.); Helsinki University Hospital, Dr. Ville Pettilä, Dr. Marjut Varpula, Dr. Marja Hynninen (Inv.), Marja Pere, Maiju Salovaara (SN); Helsinki University Hospital (Jorvi), Dr. Tero Varpula (Inv.), Mirja Vauramo (SN); Helsinki University Hospital (Peijas), Dr. Rita Linko (Inv.), Kimmo Kuusisto (SN); Tampere University Hospital, Dr. Esko Ruokonen, Dr. Pertti Arvola (Inv.), Minna-Liisa Peltola, Anna-Liina, Korkala, Jani Heinilä (SN); Kuopio University Hospital, Dr. Ilkka Parviainen (Inv.), Seija Laitinen, Elina Halonen, Mirja Tiainen, Heikki Ahonen (SN); Oulu University Hospital, Dr. Tero Ala-Kokko (Inv.), Tarja Lamberg, Sinikka Sälkiö (SN); Länsi-Pohja Central Hospital, Dr. Jorma Heikkinen (Inv.), Kirsi Heinonen (SN).