Cardiac dysfunction in septic shock
Observational studies on characteristics and outcome

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Le cœur a ses raisons que la raison ne connaît point.
Blaise Pascal (1623–1662)

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ABSTRACT

Background:

Cardiac dysfunction is a well-known complication of sepsis, but its characteristics and consequences, especially on a longer term, remain unclear. The aim of this thesis was to study the characteristics and the implications of cardiac dysfunction for outcome in intensive care unit (ICU) patients with septic shock.

Purpose:

First, to assess the ability of a cardiac biomarker to predict outcome in ICU patients. Second, to characterise cardiac dysfunction in septic shock using speckle tracking echocardiography. Third, to investigate the reliability of echocardiographic methods used to describe cardiac dysfunction in septic shock. Fourth, to study long-term cardiac outcome in severe sepsis and septic shock patients.

Materials and methods:

The cardiac biomarker amino-terminal pro-brain natriuretic peptide (NT-proBNP) was collected in 481 patients on ICU admission and its ability to predict death was assessed. In 50 patients with septic shock, echocardiography was performed on ICU admission and was repeated during and after ICU stay. Measurements of cardiac strain using speckle tracking echocardiography were assessed in relation to other echocardiographic function parameters, NT-proBNP and severity of illness scores, and their change over time was analysed. Echocardiograms from patients with septic shock were independently evaluated by two physicians and the results analysed regarding measurement variability. A nationwide-registry-based open cohort of 9,520 severe sepsis and septic shock ICU patients discharged alive from the ICU was analysed together with a non-septic control group matched for age, sex and severity of illness. In patients who died after ICU discharge, information on causes of death was collected.

Results:

A discriminatory level of significance of NT-proBNP on ICU admission was identified at $\geq 1,380$ ng/L, above which NT-proBNP was an independent predictor of death. With increasing levels of NT-proBNP, patients were more severely ill, had a longer ICU stay and were more often admitted with septic shock. Cardiac strain was frequently impaired in septic shock patients but was not superior to other echocardiographic measurements in detecting cardiac dysfunction. Cardiac strain correlated with other echocardiographic function parameters and with NT-proBNP, and was the least user-dependent echocardiographic parameter in septic shock patients. Cardiac strain remained unchanged over time, did not differ between survivors and non-survivors and could not predict an increased risk of death. During a follow-up of up to nearly 6 years after ICU discharge, 3,954 (42%) of sepsis patients died, 654 (17%) with cardiac failure as the cause of death. With increasing severity of illness on admission, the risk of death with cardiac failure as the cause of death after ICU discharge

increased. In comparison to other ICU patients with similar severity of illness, however, the risk of death due to cardiac was not increased in patients with severe sepsis or septic shock.

Conclusions:

Laboratory or echocardiographic signs of cardiac dysfunction are commonly seen in ICU patients in general and in septic shock patients in particular. The assessment of cardiac dysfunction in patients with septic shock is, however, complicated by pre-existing comorbidities, by treatment given in the ICU and by critical illness in itself. Signs of cardiac dysfunction, and the increasing risk of death related to cardiac failure seen after remission of sepsis, may therefore be reflections of critical illness per se, rather than of sepsis.

LIST OF PAPERS

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

I   **Lina De Geer**, Mats Fredrikson and Anna Oscarsson:
Amino-terminal pro-brain natriuretic peptide as a predictor of outcome in patients admitted to intensive care. A prospective observational study.
European Journal of Anaesthesiology 2012 Jun;29(6):275-9.*

II   **Lina De Geer**, Jan Engvall and Anna Oscarsson:
Strain echocardiography in septic shock – a comparison with systolic and diastolic function parameters, cardiac biomarkers and outcome.
Critical Care 2015 Mar 26;19(1):122.**

III   **Lina De Geer**, Anna Oscarsson and Jan Engvall:
Variability in echocardiographic measurements of left ventricular function in septic shock patients.
Cardiovascular Ultrasound 2015 Apr 15;13(1):19.**

IV   **Lina De Geer**, Anna Oscarsson, Mats Fredrikson and Sten Walther:
Cardiac mortality after ICU discharge in severe sepsis and septic shock patients. A nationwide observational cohort study.
Submitted.

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ABBREVIATIONS

2C	two-chamber view
2D	two-dimensional
4C	four-chamber view
A	late diastolic mitral inflow
a'	late diastolic mitral annular tissue Doppler velocity
AF	atrial fibrillation
ALAX	apical long-axis view
ANOVA	analysis of variance
BNP	brain natriuretic peptide
CI	confidence interval
DT	deceleration time
E	early diastolic mitral inflow
e'	early diastolic mitral annular tissue Doppler velocity
E/e'	E to e' ratio
EF	ejection fraction
GLPS	global longitudinal peak strain
ICD-10	International Classification of Diseases – Tenth Revision
ICU	intensive care unit
IL-1β	interleukin-one beta
IQR	inter-quartile range
κ	Kappa coefficient
LOS	length of stay
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
MAPSE	mitral annular plane systolic excursion
NO	nitric oxide
NT-proBNP	amino-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association Functional Classification of Heart Failure
OR	odds ratio
PEEP	positive end-expiratory pressure
PiCCO	pulse contour continuous cardiac output
proBNP	prohormone of brain natriuretic peptide
PW	pulsed wave Doppler
ROC	receiver operating characteristics curve
Sa	peak systolic mitral annular tissue Doppler velocity
SAPS3	Simplified Acute Physiology Score, third version
SD	standard deviation
SIR	Swedish Intensive Care Registry
SOFA	Sequential Organ Failure Assessment
SVR	systemic vascular resistance

SVRI	systemic vascular resistance index
TNF-α	tumor necrosis factor-alpha
WHO	World Health Organization

CONTENTS

INTRODUCTION

Sepsis

Sepsis is the systemic inflammatory response to infection. The definition of sepsis thus relies on symptoms of global inflammation with evidence, or suspicion, of coexisting infection. Severe sepsis is sepsis causing organ dysfunction, whereas septic shock is a condition of persistent organ dysfunction despite fluid resuscitation (1). The spectrum of disease in sepsis is thereby wide and non-specific, ranging from mild systemic inflammation due to infection, to a global and overpowering immune response and profound organ dysfunction.

The exact incidence of sepsis is unclear but has been estimated to reach 300 cases per 100,000 persons per year (2-4). The incidence of sepsis – more specifically, of severe sepsis or septic shock – is increasing, and represents the largest group of patients in intensive care units (ICU) (2, 5, 6). In Sweden and in other Western countries, approximately 10% of ICU admissions are due to sepsis (5, 7).

The management of sepsis has been subject to much study, and there are now international guidelines regarding its optimum treatment. In principle, the recommended regimen concerns early recognition of the disease, timely support of failing organs and swift control of the underlying infection (1).

Mortality rates in severe sepsis and septic shock are decreasing (5). Nonetheless, the risk of death remains high in comparison to other critically ill patients (8, 9). Furthermore, the risk of death in sepsis is largely dependent on disease severity, i.e. the risk of death from sepsis is related to the number of organs failing in the septic condition (10, 11).

Circulatory compromise is a hallmark of severe sepsis, and even more so in septic shock. The clinical situation can be complicated further by the addition of cardiac dysfunction as a complication of sepsis, i.e. a septic organ dysfunction specifically affecting the heart. There is a general consensus that the addition of septic cardiac dysfunction increases the risk of death in sepsis. Nonetheless, its characteristics and frequency, as well as its long-term consequences, remain unclear.

The heart in sepsis

Cardiac depression in sepsis was first described half a century ago. It was then recognised as the presence of low cardiac output (CO) with a weak pulse pulse and cold skin, i.e. features that would now be interpreted as signs of inadequate perfusion (12, 13). A high or normal CO and low systemic vascular resistance (SVR) were further demonstrated as features of septic shock (14), and the failure of septic patients to increase their CO in response to resuscitation was interpreted as an expression of cardiac depression (15). These reports were the first to recognise septic cardiac dysfunction as the inability of the heart to meet the increasing metabolic demands in sepsis (12).

The function of the heart itself in sepsis was first demonstrated in 1984 using radionuclide cineangiography (16). In a series of 20 patients, an increased left ventricular

(LV) end-diastolic volume, i.e. a dilatation of the LV with a reduced ejection fraction (EF), was demonstrated. Interestingly, survivors showed a more marked LV dilatation and EF reduction, and reversibility over seven to ten days. Non-survivors, in contrast, retained their initial EF, appearing unable to dilate their LV. Not only was this study the first to demonstrate the dynamics of septic cardiac dysfunction, but it was also the first indication of diastolic dysfunction as a prognostic factor in septic shock, although not interpreted as such at that time. Many aspects of septic cardiac dysfunction have, since then, been studied, some of which will be outlined here.

Underlying mechanisms and characteristics of cardiac dysfunction in sepsis

A number of mediators and pathways are associated with cardiac depression in sepsis, but the precise cause remains unclear. A circulating cardiac depressant factor, where potential candidates, among others, include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and nitric oxide (NO), has long been proposed (17-19). Endothelial activation, microcirculatory shunting, metabolic alterations and calcium dysregulation in the myocardium have also been presented as contributors to the pathophysiology (20, 21). Thus, the pathogenesis of septic cardiac dysfunction is now regarded as the result of a complex interaction between systemic factors and molecular, metabolic and structural alterations (20).

The incidence of septic cardiac dysfunction is unclear, but has been described in 20 to 60% of patients with septic shock (22-24). To some extent, this varying incidence is due to the lack of consensus on the definition of septic cardiac dysfunction, with criteria differing between studies. Furthermore, septic cardiac dysfunction may commonly be underestimated. In experimental models using pressure-volume loops, the septic myocardium is characterised by a depressed intrinsic contractility, independent of changes in afterload (25). In vivo, however, the understanding of the situation is complicated by the heart acting in relation to its circulatory context. With septic vasodilation, recognised clinically as low blood pressure or, more correctly, as a reduced SVR, afterload decreases markedly. In this situation CO may, in spite of septic cardiac dysfunction, be normal or even increased (24). The situation is further complicated by the increased oxygen demand inherent to the septic shock situation. Thus, septic cardiac dysfunction can be understood as a situation where the heart, as a consequence of sepsis, fails to meet the global metabolic demands.

Cardiac function imaging in sepsis

Echocardiography is a real-time imaging modality using ultrasound to visualise the movements of the heart, providing information on its anatomy and function. With the introduction of echocardiography in intensive care clinical practice, its diagnostic and prognostic abilities for the assessment of septic cardiac dysfunction have been extensively studied (22, 26-28). Furthermore, echocardiography is increasingly used for haemodynamic monitoring and titration of therapy in septic shock (29-31).

A focused two-dimensional transthoracic echocardiogram with Doppler flow measurements is the most widely used in intensive care (30, 32). The echocardiogram assesses different aspects of the contractile ability as well as of relaxation and filling, i.e.

systolic and diastolic function, of the heart. Numerous studies on septic cardiac dysfunction have described systolic as well as diastolic dysfunction, or a combination of the two, using a variety of different echocardiographic parameters (22, 23, 33). Since a reduced LVEF is the most commonly used definition of septic cardiac dysfunction, echocardiographic studies have mainly concerned the systolic function of the heart. Nonetheless, the diastolic function in sepsis is gaining interest (22, 34). Most studies have assessed cardiac function at or close to ICU admission, and few have studied the echocardiographic characteristics of septic cardiac dysfunction over time (24, 35).

Left ventricular systolic function

The systolic function of the LV is most commonly assessed using LVEF, which is the volume ejected in relation to the end-diastolic volume of the LV (36):

LVEF = LV end-diastolic volume – LV end-systolic volume / LV end-diastolic volume x 100

Quantitative assessment of LV volumes and LVEF using echocardiography relies on the manual tracing of the LV cavity in end-diastole and end-systole in two apical two-dimensional planes, whereafter the end-diastolic and end-systolic volumes of the LV are calculated. This technique, known as the modified biplanar Simpson's method, is the recommended one for echocardiographic assessment of systolic dysfunction, and considered normal if above 50% (36).

From the mathematic formula above follows that LVEF is a function of ventricular size. In a situation with a dilated ventricle, as described in septic shock in the original work by Parker et al. (16), a decreased LVEF does not necessarily imply decreased stroke volumes. Moreover, LVEF is, as outlined above, highly dependent on changes in SVR, and may, as a consequence of septic vasodilation, be misinterpreted (27). In one study, a decreased LVEF was shown in 38% of patients on ICU admission but in 59% on day 3 (24), i.e. with treatment for sepsis, including correction of SVR, septic cardiac dysfunction was unmasked by increasing LV afterload. Thus, LVEF does not necessarily, in the septic situation, reflect the underlying contractility of the heart. The timing of the assessment of LVEF in relation to the course of disease and treatment is therefore paramount for understanding the pathophysiology of septic cardiac dysfunction.

Left ventricular diastolic function

A variety of echocardiographic measurements are used to evaluate the diastolic function of the heart, each reflecting different aspects of LV filling. Pulsed wave (PW) Doppler measurements of inflow velocities at the mitral valve (early mitral inflow, E; late mitral inflow, A; deceleration time from maximum E to baseline, DT; and E to A ratio, E/A) and PW tissue Doppler measurements of tissue velocities at the base of the septum and the LV lateral wall (early diastolic mitral annular tissue Doppler velocity, e'; and late diastolic mitral annular tissue Doppler velocity, a'; Figure 1) are both performed to assess LV diastolic function. In cardiac disease, the ratio of inflow to tissue velocities (E/e') is an accepted surrogate measurement of LV filling pressures and is, together with E, among the most widely used in the assessment of LV diastolic function (37).
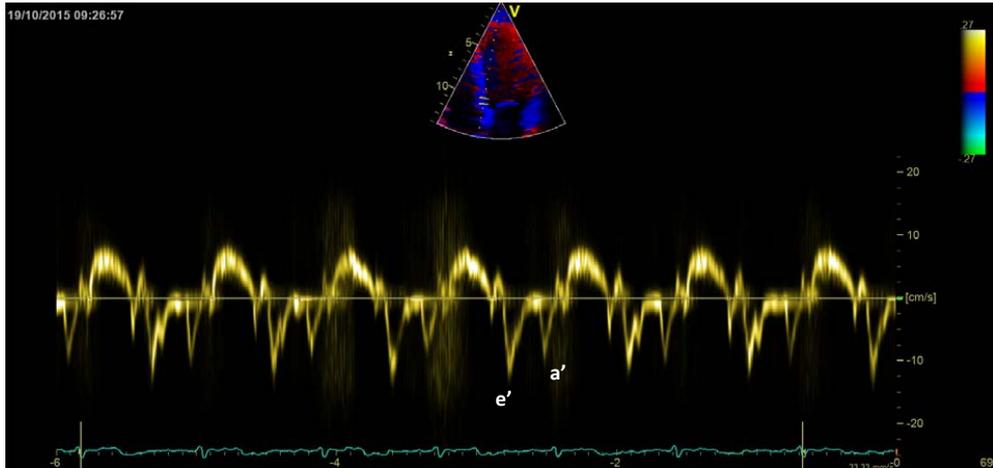
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Figure 1
Tissue velocities at the base of the septum (early diastolic, e'; and late diastolic, a') measured in the apical 4C view using PW tissue Doppler. For abbreviations, see page ix.

The accuracy of Doppler measurements of blood or tissue velocities depends on the ultrasonic angle towards the tissue, and the measured velocities are sensitive to changes in volume loading, ventilator settings and heart rate (37–40). Furthermore, the diastolic function and measurements thereof are affected by age, hypertension, ischaemic heart disease and even diabetes (41), all commonly coexisting with sepsis. The interpretation of diastolic dysfunction is therefore, for a number of reasons, complicated in intensive care patients.

Cardiac strain and speckle tracking

Cardiac strain, or cardiac deformation, is defined as the fractional change in length of a myocardial segment relative to a baseline length (42, 43). The maximum change in length is seen from end-systole to end-diastole, and is expressed as a percentage. During the heartbeat, the cardiac wall segments move in radial, circumferential and longitudinal directions. Deformation – "strain" – can thus be measured in all three directions, longitudinal strain being the most studied (43). Strain can be measured using tissue Doppler imaging or speckle tracking echocardiography, both depending on post-processing of echocardiographic data. Speckle tracking echocardiography has been claimed to be less angle-dependent than tissue Doppler imaging, and also to be relatively independent of pre- and afterload (43). Thus, speckle tracking echocardiography has theoretical advantages in the intensive care setting.

Speckle tracking echocardiography relies on the detection of sonographic features – "speckles" – originating in the reflection of myocardial fibres. These speckles create a pattern that enables tracking of myocardial motion during the cardiac cycle. Since the movement of each speckle is in relation to those surrounding it, local deformation – strain – of the myocardium can be determined (42). Strain in the individual segments of the heart is averaged, producing a global measurement of the strain in the left ventricle. Thus, the

longitudinal strain of the LV as a whole is measured, and referred to as global longitudinal peak strain (GLPS) (42–44).

In cardiology, speckle tracking echocardiography has been shown to be more sensitive in detecting cardiac diseases such as hypertrophic cardiomyopathy, cardiac amyloidosis and chemotherapy–associated cardiac dysfunction, even in asymptomatic patients (45–47). When the studies in this thesis were conducted, speckle tracking had scarcely been described in septic shock. It had been proposed as a more sensitive method in detecting septic cardiac affection, showing changes earlier in the course of disease than other echocardiographic measurements in experimental (48) as well as in clinical settings (33, 49).

Variability of measurements

As outlined above, septic cardiac dysfunction has been described with varying incidence – specifically, impaired systolic or diastolic function has been reported in 20 to 60% of septic ICU patients (22–24). The measurements used for the echocardiographic assessment of cardiac function are manually obtained, and are therefore to some extent inherently subjective. In cardiology, the impact of observer dependence on echocardiographic measurements is well known (50–52). In stress echocardiography especially, a substantial interobserver variability has been described, even among expert observers (50, 51). The intensive care clinical situation often includes tachycardia, high levels of endogenous as well as exogenous catecholamines, and difficulties in image acquisition, not unlike that of stress echocardiography. Furthermore, critically ill patients are often not in steady state. Varying use of vasopressor and inotropic drugs, rapid fluid shifts and positive pressure ventilation are just some of the challenges during image acquisition and interpretation. However, the addition of observer dependency to the interpretation of the echocardiographic findings has been remarkably less studied in intensive care than in cardiology (35). Thus, the extent to which the differing results in the incidence and spectrum of cardiac dysfunction in sepsis is related to the reading of the echocardiograms is unclear.

Cardiac biomarkers in sepsis

Cardiac biomarkers are biological parameters used to evaluate the function of the heart. Originating from the cardiac muscle, they are released as a result of cardiac stress or cell death, and can be detected and quantified, ideally indicating and corresponding to the degree of damage, or dysfunction, in the heart. Cardiac biomarkers were first developed for assisting the diagnosis of cardiac events, but are now extensively used in clinical cardiology not only for diagnostic purposes, but also for stratification and prognostication of cardiac disease. Moreover, cardiac biomarkers have made their way into the intensive care setting, where their use is not confined to cardiac-related areas (53, 54).

Two well-known groups of cardiac biomarkers have been evaluated in septic cardiac dysfunction: the natriuretic peptides and the cardiac troponins. Cardiac troponins have, albeit with conflicting results, been shown to correlate with an increased risk of death in intensive care patients in general (55) as well as in sepsis (56). A correlation to echocardiographic signs of cardiac dysfunction in sepsis has been shown (57), but the

definite role of cardiac troponins in this regard remains to be settled. In this thesis, however, the focus will be on natriuretic peptides.
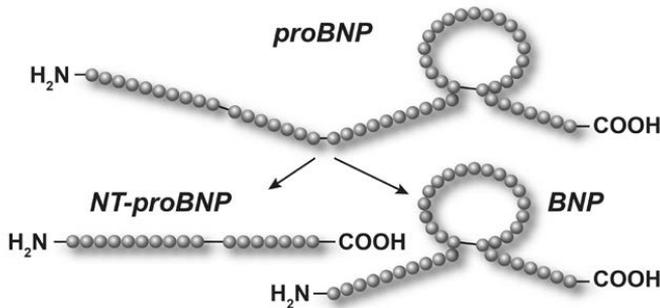

Figure 2
ProBNP is released from cardiac myocytes and cleaved to create the biologically active BNP and, as a byproduct, NT-proBNP. For abbreviations, see page ix.
Illustration by Per Lagman.

Natriuretic peptides

The primary biological function of the natriuretic peptides is to maintain osmotic and circulatory homeostasis (58). A number of natriuretic peptides have been described, all with closely related structures and all initiating similar physiological effects. Among these, the most thoroughly investigated in intensive care are brain natriuretic peptide (BNP) and amino-terminal of brain natriuretic peptide (NT-proBNP) (53).

The BNP prohormone (proBNP) is synthesised in cardiac myocytes and released into the circulation in response to cardiac wall tension. A circulating endoprotease cleaves proBNP into the biologically active BNP and an inactive cometabolite, NT-proBNP (Figure 2). BNP has a half-life of 20 minutes, whereas the half-life of the renally cleared NT-proBNP is 60 to120 minutes, explaining the higher levels and less marked variations of NT-proBNP concentrations (53, 59). NT-proBNP is therefore now the more widely used in clinical practice.

Since natriuretic peptides are released from cardiac myocytes in response to pressure or volume load, increased circulatory levels are found in patients with congestive heart failure (54). In addition, elevated levels of BNP and NT-proBNP are seen in myocardial ischaemia, pulmonary hypertension and renal failure (53). Furthermore, they have been studied for diagnostic purposes in emergency medicine and also in perioperative medicine, where they have been demonstrated as predictors of major cardiac events (60, 61).

In intensive care, the diagnostic abilities of BNP and NT-proBNP have gained much interest. In patients with septic shock, BNP and NT-proBNP are frequently increased, and they have, by comparison to invasive haemodynamic or echocardiographic findings, been proposed as diagnostic markers for septic cardiac dysfunction (22, 62, 63). However, whether increased levels of BNP or NT-proBNP reflect cardiac function in septic shock, or are rather markers of disease severity, is not established. Furthermore, the timing of BNP or NT-proBNP increase in relation to the time-course of cardiac dysfunction in sepsis is unclear. The role of natriuretic peptides in septic cardiac dysfunction thus remains to be settled.

Prognostication and outcome in sepsis

There is much interest in outcome prediction, most commonly for the risk of death, in intensive care. The modalities used for outcome prediction include markers of organ function, such as laboratory data or physiological parameters, and scoring systems.

Cardiac biomarkers and echocardiography in outcome prediction

The risk of death in sepsis increases as more organ systems become affected (10, 11). Markers of specific organ function, or dysfunction, have therefore been assessed for outcome prediction. While the predictive value of natriuretic peptides and echocardiography is well established in cardiology, it is less so in intensive care (22, 64, 65).

The impact of cardiac dysfunction on mortality in septic shock has differed between echocardiographic studies. Nonetheless, in spite of being extensively studied, the effect of systolic dysfunction evaluated using LVEF on the risk of death is increasingly questioned (65). In contrast, a substantial impact of LV diastolic dysfunction on mortality has been demonstrated (22, 34, 66). In cardiology, cardiac strain measured using speckle tracking has been shown to be superior to LVEF in predicting death in heart failure patients (67). In patients with sepsis, the use of speckle tracking in outcome prediction had however, when the studies in this thesis were conducted, not been evaluated.

The predictive abilities of BNP and NT-proBNP have been investigated in specific groups of intensive care patients, such as sepsis (68, 69), as well as in intensive care patients in general (70-72). Irrespective of patient category, higher levels have repeatedly been demonstrated in non-survivors. However, despite its biological plausibility, the predictive ability of elevated levels of natriuretic peptides is unclear.

Thus, while there is widespread consensus that septic cardiac dysfunction increases the risk of death in septic patients, attempts to use biomarkers or specific echocardiographic measures in identifying patients at risk have proven challenging.

Scoring systems in intensive care

Scoring systems for outcome prediction have been used in intensive care since the early 1980s (73). A number of scoring systems are and have been in clinical use, but among the most widely used at present is the third version of the Simplified Acute Physiology Score (SAPS) (74). The construction of SAPS3 was based on data from 19,577 patients in 309 ICUs in 35 different countries, the majority of which in Europe, in 2002. SAPS3 was designed to measure the severity of disease in a patient, as well as to predict the risk of death (75, 76).

SAPS3 includes information on pre-existing comorbidities and other factors regarding the patient's status pre-ICU. Second, it takes into account events surrounding the patient's admission to the ICU, such as admission route, time from hospital to ICU admission, the surgical and infectious status at, and reason for, admission. Third, SAPS3 includes the degree of physiological derangement displayed by the patient ± 1 hour of ICU admission. Thus, SAPS3 provides a severity of illness score, the SAPS3 score, as well as a calculated probability of 30 day mortality, called SAPS3 probability, ranging from 0 to 1.

The Sequential Organ Failure Assessment (SOFA) score rates respiratory, cardiovascular, hepatic, renal, coagulatory and neurological functions, and is used daily to determine the

degree of a patient's organ failure and the rate of deterioration during the ICU stay (77). While primarily designed to describe morbidity, the SOFA score can also be used as a predictor of mortality (10, 11).

The Swedish Intensive Care Registry and the Swedish National Board of Health and Welfare

The Swedish Intensive Care Registry (SIR) is a medical quality register operating to audit and benchmark Swedish intensive care (7). SIR has prospectively collected data since 2001, and in 2015, does so from 77 of the 84 (92%) ICUs in Sweden. SAPS3 has been in use in Swedish ICUs and collected by SIR since 2008. Aside from SAPS3, data reported to SIR include details on individual patients' ICU stay regarding organ support, ICU length of stay (LOS) and diagnoses assigned during the ICU stay. Furthermore, SIR collects data on ICU outcome, and performs a prospective follow-up on vital status. Collected data is validated internally, and in cases of inconsistencies or logical defects returned to the local, submitting ICU, for correction.

The Swedish National Board of Health and Welfare is a government agency serving to collect information, develop standards and undertake official duties in the medical field in Sweden (78). Its roles include the collection and registration of causes of death assigned by physicians in all deceased persons in Sweden. Information on causes of death in specific patients can therefore be sought in the Swedish National Board of Health and Welfare's Death Register.

Patients admitted to Swedish ICUs and thereby registered in SIR can thus, if they have died after ICU discharge, be identified in the Swedish National Board of Health and Welfare's Death Register, and information on their causes of death collected.

ICU outcome and follow-up

The risk of death is high in sepsis patients not only in the ICU. Even after ICU discharge, sepsis patients have a higher ongoing morbidity and mortality than the general public and other categories of ICU patients (79-81). The long-term consequences of septic organ dysfunction and the major causes of death after intensive care are, however, unclear. Whether the cardiac effects of sepsis persist, or more specifically, whether septic cardiac dysfunction may cause long-term cardiac failure severe enough to contribute to mortality, is unknown.

The optimal duration of follow-up for the determination of the risk of death after ICU is uncertain, but measurement of mortality at 30 days or at hospital discharge is the most widely used time-frame (82). However, as many as one-third of ICU patients may still be in hospital at 30 days, and a substantial proportion of deaths occur soon after hospital discharge (83, 84). There are also indications of an increasing number of ICU patients being discharged from hospital not to home, but to other care facilities (5). The value of a longer follow-up time has therefore been proposed (82, 85). However, this may raise difficulties in distinguishing between the effects of critical illness and of those from underlying age and comorbidities, both of which increase the risk of death in the ICU as well as after discharge (86, 87). The ideal period of follow-up would be up to a time point at which the effects of

critical illness remain the principal determinants of outcome, and before age, comorbidities and other pre-existing factors can have a marked and confounding impact on survival. Such an ideal follow-up time has not been established, and would likely differ according to the population and the outcome studied. The optimum follow-up time after severe sepsis or septic shock, and more specifically, the ideal time to identify any cardiac consequences of sepsis, is unknown.

In summary

Cardiac dysfunction in septic shock is a situation where the heart, as a consequence of sepsis, fails to meet the systemic demands. Such cardiac dysfunction is easily masked by coexisting circulatory changes, and its characteristics regarding echocardiographic findings and cardiac biomarkers are unclear. Furthermore, its impact on mortality, especially on a longer term, remains unknown.

HYPOTHESIS AND AIM

The hypothesis underlying this thesis was that cardiac dysfunction is underestimated in intensive care patients with septic shock and that it increases the risk of death, even on a longer term. The specific hypotheses of the individual studies were as follows:

    I   That the cardiac biomarker NT-proBNP can be used as a prognostic marker for death in ICU patients

    II   That measurements of cardiac strain using speckle tracking echocardiography are superior to other echocardiographic measurements used for detecting cardiac dysfunction in patients with septic shock

    III   That there is an observer-related influence on the assessment of cardiac function in septic shock patients

    IV   That even after remission of severe sepsis or septic shock, patients are at an increased risk of death from cardiac failure

The aim of this thesis was hence to study the characteristics and the implications for outcome of cardiac dysfunction in intensive care patients with septic shock. The specific objectives of the individual studies were as follows:

    I   To assess the ability of the cardiac biomarker NT-proBNP to predict outcome in intensive care patients

    II   To characterise cardiac dysfunction in septic shock using speckle tracking echocardiography

    III   To investigate the reliability of echocardiographic methods used to describe cardiac dysfunction in septic shock

    IV   To study long-term cardiac outcome in severe sepsis and septic shock patients

MATERIALS AND METHODS

All studies in this thesis were performed at Linköping University Hospital, using data collected at the Intensive Care Unit of the hospital (studies I – III) or from the Swedish Intensive Care Registry and the Swedish National Board of Health and Welfare (study IV).

Ethical aspects

All studies were approved by the Regional Ethical Review Board in Linköping, Sweden. The specific ethical aspects of the individual studies were addressed as follows:

In **study I** (Dnr 2010/222-31), all clinical and laboratory data collected were part of routine registration of patients admitted to the unit, and informed consent was not required.

For **studies II and III** (Dnr 2012/233-31), informed consent was sought from patients at inclusion. The observational nature of the studies allowed us to assume consent in patients incapacitated by acute illness. In these cases informed consent was, when possible, obtained from included patients after recovery. Patients who were not expected to survive longer than 24 hours, in whom intensive care treatment was partly withheld from admission and who due to language barriers or mental inability were not expected to be able to give consent even after recovery, were not included.

Study IV (Dnr 2014/31-31) regards data from medical registers, and the requirement for informed consent was waived.

Study designs, populations, data sets and methods used

Study I is a prospective observational study on survival after ICU admission in general ICU patients. **Study II** is a prospective observational study on echocardiographic characteristics in ICU patients with septic shock. **Study III** is a quantitative reliability analysis of echocardiographic measurements in septic shock. **Study IV** is a prospective observational study on survival in severe sepsis and septic shock patients in ICUs in Sweden.

Patients and settings

For study I, the study cohort consisted of 481 patients admitted to the mixed, non-cardiothoracic, tertiary general ICU of Linköping University Hospital, from June 2009 to November 2010. Studies II and III regard 50 patients admitted to the ICU of Linköping University Hospital, presenting with septic shock and with an expected ICU stay of 24 hours or longer. Patients were included from October 2012 to September 2014. For study IV, a cohort of 9,520 severe sepsis and septic shock patients admitted to Swedish ICUs from January 2008 to August 2013, collected from SIR, was used. In addition, a control group of 4,577 patients individually matched to the study cohort regarding age, sex, severity of

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illness and ICU length of stay was collected. The relative size and relations of the different cohorts is illustrated in Figure 3, and the patient selection process for study IV in Figure 4.
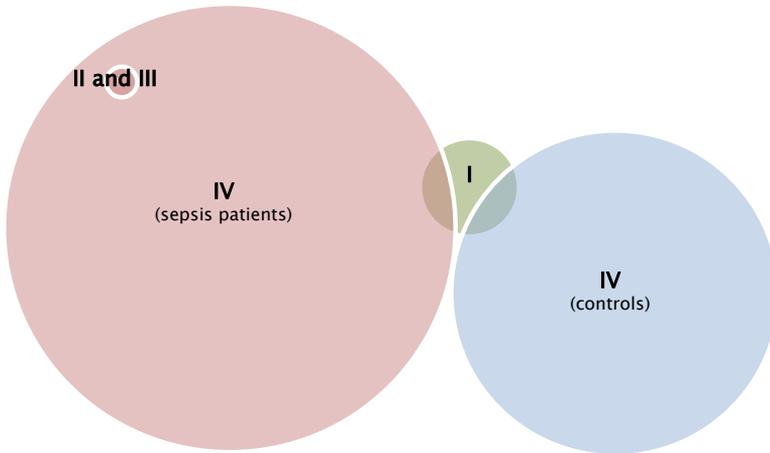

Figure 3
The relative size, illustrated as areals, and relations of the patient cohorts underlying the studies in this thesis. The patients included in studies II and III were also included in the cohort underlying study IV. Study IV also included some of the patients in study I, both sepsis patients and controls.
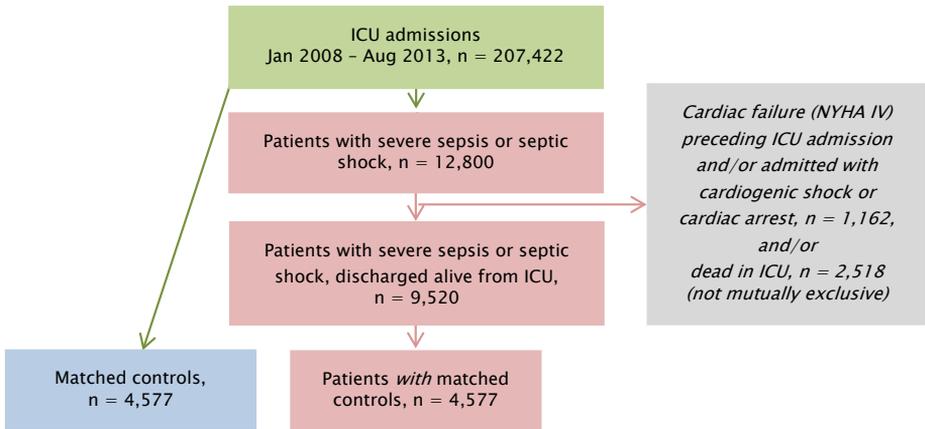

Figure 4
Patient selection flowchart for study IV. For abbreviations, see page ix.

Definitions

Severe sepsis and septic shock were defined according to the following criteria (1): (i) evidence or clinical suspicion of infection; (ii) two or more signs of systemic inflammatory response syndrome: (a) temperature >38 or <36 °C; (b) pulse >90 beats per minute; (c)

respiratory rate >20 breaths per minute or mechanical ventilation; (d) white blood cells >12,000 μL⁻¹ or <4,000 μL⁻¹ or >10% bands; (iii) at least one organ dysfunction; and, for septic shock, (iv) systolic blood pressure <90 mm Hg despite fluid therapy and requiring vasopressor therapy.

Patients in studies II and III were considered to have a history of cardiac disease if they had prior or current ischaemic heart disease, cardiac surgery, and hypertension or cardiac failure. Information on pre-existing cardiac disease was sought from patients, family and from medical charts. In study IV, information on whether patients were in severe cardiac failure preceding ICU admission was collected. Severe cardiac failure was considered according to the New York Heart Association (NYHA) functional classification of cardiac failure class IV, i.e. patients with symptoms even at rest who are unable to carry on any physical activity without discomfort (88).

For study IV, diagnoses registered as major or contributing causes of death according to the World Health Organization International Statistical Classification of Diseases and Related Health Problems – Tenth Revision (ICD-10) were collected (89). The specific ICD-10 codes were those corresponding to cardiac failure, i.e. I50.1 (left ventricular failure), I50.2 (systolic cardiac failure), I50.3 (diastolic cardiac failure), I50.4 (combined systolic and diastolic cardiac failure) and I50.9 (cardiac failure, unspecified).

Laboratory and clinical data

The cardiac biomarker NT-proBNP was collected on ICU admission for study I. For study II, NT-proBNP was collected on admission and daily thereafter during the first week of intensive care. Plasma concentrations were analysed using ELECSYS 2010® immunoassays (Roche Diagnostics, Mannheim, Germany).

Data on physiological variables was collected prospectively for studies I and II. In addition, for study II, data from invasive haemodynamic monitoring by means of transpulmonary thermodilution (PiCCO®, Pulsion Medical, Munich, Germany) was collected. Data on cardiac index and systemic vascular resistance index (SVRI) from continuous measurements were collected when echocardiography was performed. In all studies, data on comorbidities and treatment given in the ICU as well as on ICU length of stay and outcome were assembled prospectively. SAPS3 and SOFA score (page 8) were calculated to assess severity of illness. For studies I – III such data were collected in the ward, whereas for study IV, they were obtained from SIR.

Echocardiography

For studies II and III transthoracic echocardiography was performed as early as possible on the day of admission. For study II, echocardiography was also performed on day 3 or 4, and in survivors, also 8 to 30 days after inclusion. A Vivid E9 ultrasound scanner (GE Healthcare, Horten, Norway) was used, acquiring two-dimensional (2D) apical two-chamber, four-chamber and long axis views (2C, 4C and ALAX) of the left ventricle (LV) at a frame rate of >40 frames/second. All analyses were performed offline (EchoPac version 112, GE Healthcare, Horten, Norway) by two observers, independently and blinded. Global longitudinal peak strain (GLPS) was calculated as the average speckle tracking strain from

each of the 18 LV segments from the 2C, 4C and ALAX views (six segments per view, base–mid–apex, in three views) (Figure 5).
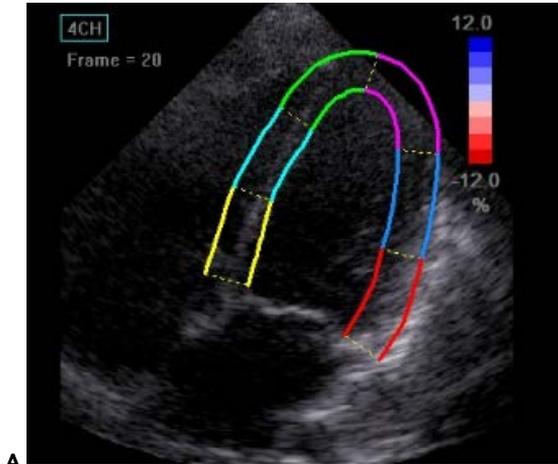

Figure 5
The global longitudinal peak strain (GLPS) of the LV was calculated as the average of the longitudinal peak strain in 18 segments of the LV, i.e. in six segments per view in three different views.
A: The six segments used for strain measurements in the 4C view.
B: The longitudinal segmental strain of the myocardium during the cardiac cycle in the same view and on the same occasion.
For abbreviations, see page ix.
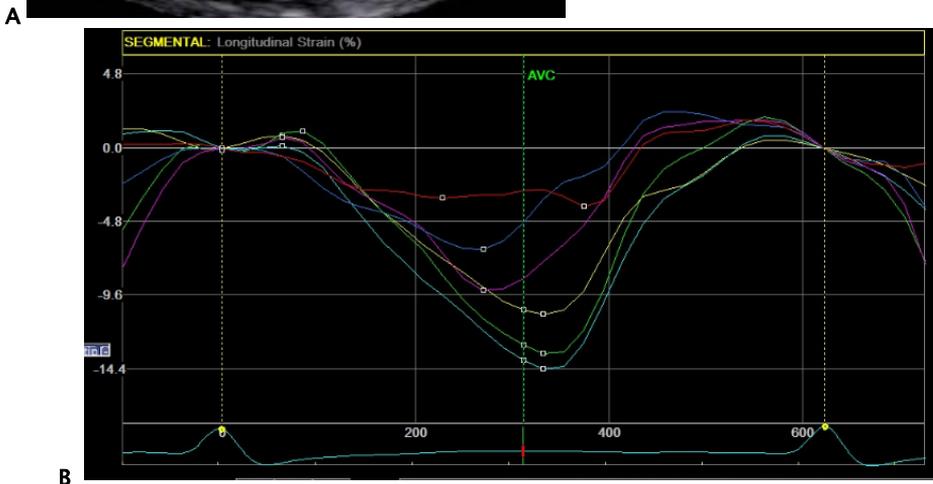
LV volumes and LVEF were calculated using the modified biplanar Simpson's method. E velocity was measured using pulsed wave (PW) Doppler in the mitral inflow at the tip of the valve. Early diastolic tissue velocity of the base of the septum (e'; page 4; Figure 1) was measured in the apical 4C view using PW tissue Doppler, and E/e' ratios were calculated. All echocardiographic studies were recorded over three consecutive cardiac cycles, independently of breathing cycles, and averaged. In patients with non-sinus rhythm, measurements were collected and averaged over 5 to 10 heartbeats. GLPS was considered decreased when >–15% (44). Systolic dysfunction was defined as LVEF <50% (36), and diastolic dysfunction as E/e' >15 and/or e' <0.08 m/s (37).

Registry data

For study IV, registry data on age, sex, ICU admission details, ICU length of stay, treatment given in the ICU, diagnoses assigned at discharge and data on outcome, were collected from SIR. The dataset also contained data on severity of illness on ICU admission according to SAPS3 and corresponding estimated mortality rates, i.e. SAPS3 probability. From SAPS3, data was collected regarding the presence of severe cardiac failure preceding ICU admission. In analyses on outcome after intensive care, patients admitted after cardiac arrest or with cardiogenic shock, and who in SAPS3 were categorised as having severe cardiac failure preceding admission to intensive care, were excluded. Furthermore, between-groups comparisons regarding severe sepsis or septic shock patients and matched controls were based on individually matched pairs (page 14; Figure 4).

The individual patients' personal identity number (90) was used to identify the same individuals in the Swedish National Board of Health and Welfare's Death Register. There, diagnoses considered as causes of death are registered according to ICD-10 (89). For all patients in the cohort who could be identified in the Swedish National Death Registry, ICD-10 codes registered as causes of death were collected. After cross-linking, personal identity numbers were replaced by a running number, anonymising the database. Cross-linking and anonymisation was performed by the Swedish National Board of Health and Welfare, in order to ensure patient integrity.

Statistical methods

In all studies, descriptive statistics were used to determine the data distribution. Data were largely found to have non-Gaussian distributions, and are thus presented as medians with interquartile ranges (IQR), numbers (percentages) and proportions with 95% confidence intervals (CI) as appropriate. Where applicable, data are shown as means with standard deviations (SD). Accordingly, the Mann-Whitney U-test, χ^2-test, Kruskal-Wallis test and, where applicable, t-test, were used for comparison between groups. All probability values were two-tailed and the level of significance was set at $p < 0.05$.

For **study I**, a receiver-operating characteristic (ROC) curve and a log-rank test were used to identify a discriminatory level of significance and a Kaplan-Meier analysis to assess survival. Spearman's rank correlation test was used to analyse the correlation between laboratory and clinical data, a univariate logistic regression to identify predictors of death and a stepwise logistic regression analysis to test the independence of the predictors. Odds ratios (OR) were calculated and are presented with 95% CI.

In **study II**, the correlation between variables was explored using Spearman's rank correlation test, and for temporal changes, a repeated-measures analysis of variance (ANOVA) was applied. Univariate linear regression analyses were used to explore the explanatory value of variables, and a logistic regression model to determine their ability to predict mortality.

In **study III**, the inter-observer variability of parameters was determined by the intra-class correlation coefficient, Pearson's correlation coefficient and Bland-Altman plots (91). Reliability analyses using kappa statistics were performed in order to determine the consistency between observers. The kappa coefficient for agreement was interpreted as

follows: poor <0.20, fair, 0.21 – 0.40; moderate, 0.41 – 0.60; good, 0.61 – 0.80; and very good, 0.81 – 1.0 (92). Intra-observer repeatability was calculated using the intra-class correlation coefficient (ICC).

For **study IV**, Kaplan-Meier analyses with log-rank tests were used to assess survival. Conditional and unadjusted Cox proportional hazards regressions were used to analyse the risk of death within groups, and hazard ratios (HR) were calculated and are presented with 95% CI. The risk of death was expected to be highest early after ICU discharge, and HR were computed for the first 30 days after ICU discharge as well as for the whole follow-up period.

All statistical analyses were performed using STATA v11.1 (Stata Corp LP, College Station, TX, USA; studies I, II and IV) and IBM SPSS v22.0 (IBM Corp, Armonk, NY, USA; studies II, III and IV).

RESULTS

The detailed results of the papers included in this thesis are presented in the original communications, and are therefore merely summarised here.

Paper I

Four hundred and eighty-one patients were included in the study (Table 1). NT-proBNP concentrations were collected on ICU admission and were markedly elevated in non-survivors compared to survivors. The level of NT-proBNP that best predicted death within 30 days, which was the primary outcome measure of the study, was identified at $\geq$1,380 ng/L. Interestingly, this level of NT-proBNP, $\geq$1,380 ng/L, also best predicted death in the ICU.

	All patients (n = 481)	Patients with NT-proBNP <1,380 ng/L on admission (n = 267)	Patients with NT-proBNP ≥1,380 ng/L on admission (n = 214)	p
Age, years	64 (47 – 73)	58 (39 – 67)	69 (60 – 76)	< 0.001
SAPS3	58 (47 – 69)	51 (41 – 62)	66 (55 – 75)	< 0.001
Severe sepsis or septic shock	71 (15)	13 (5)	58 (27)	< 0.001
ICU LOS, hours	57 (25 – 137)	44 (22 – 114)	71 (28 – 178)	< 0.001
Dead in ICU	40 (8)	12 (4)	28 (13)	0.001
Dead within 30 days	110 (24)	29 (15)	71 (33)	< 0.001

Table 1
Patients included in study I; baseline demographic data and comparison between groups of patients with NT-proBNP above and below the discriminatory threshold. Medians (IQR) and numbers (%), as appropriate. For abbreviations, see page ix.

Patients with NT-proBNP above the discriminatory threshold were more severely ill on admission and the reason for admission was more often severe sepsis or septic shock. Furthermore, they were older, had higher organ failure scores, stayed longer in the ICU and had a markedly higher risk of death than in those below the threshold (Table 1). In a stepwise logistic regression analysis including age, ICU LOS, SOFA and renal failure (i.e. creatinine >170 µmol/L on ICU admission), NT-proBNP $\geq$1,380 ng/L was found to independently predict an increased risk of death. Figure 6 (page 20) shows the Kaplan-Meier survival estimates in groups of patients above and below this level.
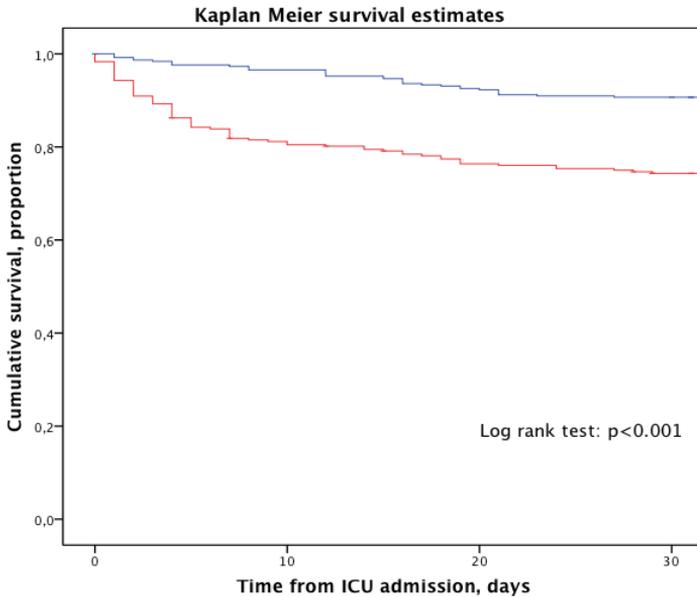
Figure 6
Kaplan–Meier survival estimates over 30 days after admission in patients above and below the discriminatory level of NT–proBNP (blue: NT–proBNP <1,380 ng/L; red: NT–proBNP ≥1,380 ng/L). For abbreviations, see page ix.

The risk associated with elevated levels of NT–proBNP was further evaluated by dividing the cohort into quartiles according to NT–proBNP level. With increasing levels of NT–proBNP, patients were more severely ill and were more often in severe sepsis or septic shock – indeed, in the highest quartile 33% of patients were diagnosed with severe sepsis or septic shock, whereas there was none in the lowest quartile. Figure 7 shows the increasing mortality seen with increasing levels of NT–proBNP on admission (30–day mortality 36%; OR 3.9 (95% CI 2.0 – 7.3, p <0.001) in the highest quartile compared to the lowest).
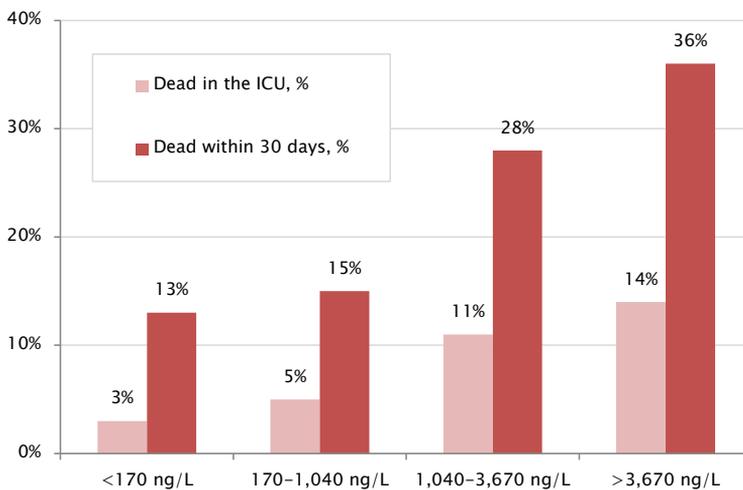

Figure 7
ICU and 30–day mortality in patients grouped in quartiles according to their level of NT–proBNP on ICU admission. For abbreviations, see page ix.

20

Paper II

Fifty patients admitted to the ICU with septic shock were included in study II. The characteristics of studied patients are displayed in Table 2. The first echocardiographic examination was performed as early as possible after admission, and always on day 1. Two patients died before the echocardiogram was undertaken; in three, image quality was inadequate; and in one patient, images were lost in the storage process. Thus, in 44 patients, echocardiographic images could be analysed. In 26 of the patients, a second echocardiogram was performed after initial clinical stabilisation. In eight patients, a follow-up echocardiogram was performed after ICU discharge.

	All patients (n = 50)	Survivors at 90 days (n = 33)	Non-survivors at 90 days (n = 17)	p
Age, years	65 (58 – 74)	64 (54 – 71)	72 (65 – 79)	0.02
SAPS3	73 (45 – 84)	68 (59 – 76)	81 (70 – 88)	0.01
ICU LOS, days	5 (2 – 11)	7 (3 – 12)	3 (1 – 6)	0.02
Cardiac comorbidities	24 (48)	14 (42)	10 (59)	0.17
NT-proBNP, ng/L	4,635 (2,342 – 14,325)	4,070 (1,400 – 8,510)	10,500 (2,860 – 30,700)	0.03
e', m/s	0.11 (0.08 – 0.16)	0.11 (0.08 – 0.16)	0.11 (0.08 – 0.16)	0.95
E/e'	7.4 (5.8 – 10.9)	7.4 (6.0 – 11.7)	7.4 (5.7 – 9.0)	0.60
LVEF, %	50 (40 – 57)	50 (44 – 58)	47 (36 – 56)	0.47
GLPS, %	−17 (−20 – (−13))	−17 (−21 – (−14))	−15 (−19 – (−11))	0.11

Table 2
Baseline characteristics of patients included in study II and a between-groups comparison according to survival at 90 days. Medians (IQR) and numbers (%), as appropriate. For abbreviations, see page ix.

Thirty-one patients (70%) had LV dysfunction on the first examination, and there was marked overlap with systolic and diastolic dysfunction, as seen in Figure 8 (page 22). Only two of the nine patients who had decreased LVEF, and showed signs of diastolic dysfunction as well as impaired GLPS on the first examination, died within 30 days. Of those examined a second time, i.e. alive but not yet discharged, there was LV dysfunction in 16 patients (62%), and all of these had decreased GLPS in combination with other echocardiographic signs of cardiac dysfunction.

GLPS correlated with LVEF (r = −0.70, p <0.001), e' (r = −0.59, p <0.001) and NT-proBNP (r = 0.54, p <0.001) on day 1, whereas on the second examination, the correlation was weaker (Paper II). GLPS did not correlate with SVRI or vasopressor dose as measures of afterload, nor with cardiac index, respiratory pressures, volume of fluids given or fluid balance, or with SOFA score. In all echocardiographic parameters there was a large range in measurement values from day 1 to follow-up. LVEF and e' showed a significant change over time, whereas GLPS and E/e' did not. Laboratory and clinical parameters, with SOFA score, NT-proBNP, volume load administered and positive end-expiratory pressure (PEEP), were all collected daily up to day 7, and all showed significant changes over time. Furthermore, NT-proBNP correlated with LVEF (r = 0.50, p = 0.001) but less so with diastolic function parameters e' (r = 0.36, p = 0.02) or E/e' (r = 0.31, p = 0.05). NT-proBNP did not correlate with respiratory pressures, volume load and fluid balance, nor with cardiac index, SVRI, vasopressor dose or SOFA score.
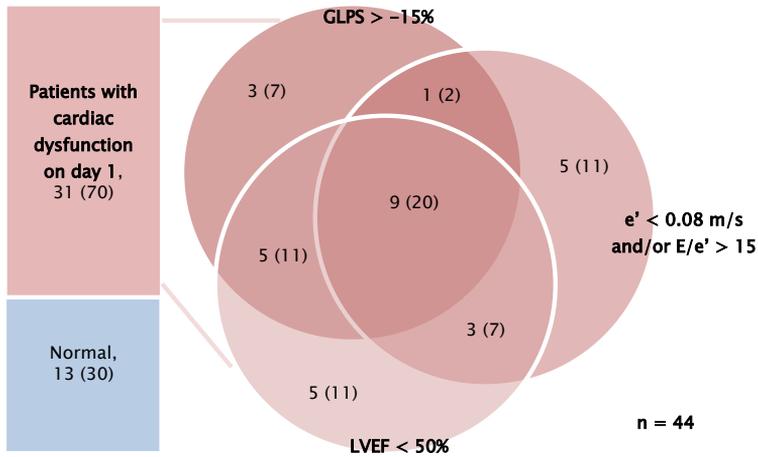
Figure 8

Venn diagram illustrating the distribution and overlap of systolic and diastolic dysfunction in the patients where cardiac dysfunction was seen on day 1. In 6 of the 50 included patients, no images could be analysed. Areals are approximate. Data are presented as numbers (percentages). For abbreviations, see page ix.

Of the 50 patients included, 13 (26%) died in the ICU. Another two patients died within 30 days, and within 90 days, 17 patients (34%) had died (page 21; Table 2). NT–proBNP was significantly higher in non–survivors than in survivors, but none of the echocardiographic parameters measured differed significantly according to survival. A logistic regression model showed that GLPS >–15 gave an odds ratio for death at 90 days of 2.5, but the result was not statistically significant (95% CI 0.66 – 9.46, p = 0.17). No predictive value was gained by using a multivariable model with LVEF, e' and NT–proBNP in addition to GLPS. Thus, GLPS could not be used to predict mortality.

Paper III

Echocardiograms from the day of ICU admission were available in 47 of the 50 patients included in study II. These 47 patients represent the group studied in paper III. In 44 (94%) of the examinations, image quality was sufficient for analysis of diastolic (e' and E/e') and systolic (EF and GLPS) function parameters. In these 44 examinations, echocardiographic measurements were performed by two independent observers.

The agreement between the two observers was moderate (kappa (κ) = 0.60 for e', κ = 0.50 for E/e' and κ = 0.60 for EF) to good (κ = 0.71 for GLPS). The correlation coefficient was 0.76 for e', 0.85 for E/e', 0.78 for EF and 0.84 for GLPS (p <0.001 for all four). The ICC between observers for e' was very good (0.85, 95% CI 0.73 – 0.92), good for E/e' (0.70, 95% CI 0.45 – 0.84), very good for EF (0.87, 95% CI 0.77 – 0.93) and excellent for GLPS (0.91, 95% CI 0.74 – 0.95; p <0.001 in all four). Systematic bias was assessed using a Bland–Altman

analysis, where mean differences and 95% limits of agreement for e', E/e', EF and GLPS were −0.01 (−0.07 – 0.04), 2.0 (−14.2 – 18.1), 0.86 (−16 – 14.3) and 0.04 (−5.05 – 5.12), respectively.

Ten randomly selected examinations were re-analysed by one of the observers in order to assess the repeatability of measurements performed by the same person on different occasions. Thus, ICC was 0.91 (95% CI 0.58 – 0.98), 0.95 (95% CI 0.80 – 0.99), 0.84 (95% CI 0.75 – 0.90) and 0.89 (95% CI 0.55 – 0.97; p <0.01 in all four) for e', E/e', EF and GLPS, respectively. An example of inter- and intraobserver differences in the measurement of cardiac strain is shown in Figure 9.
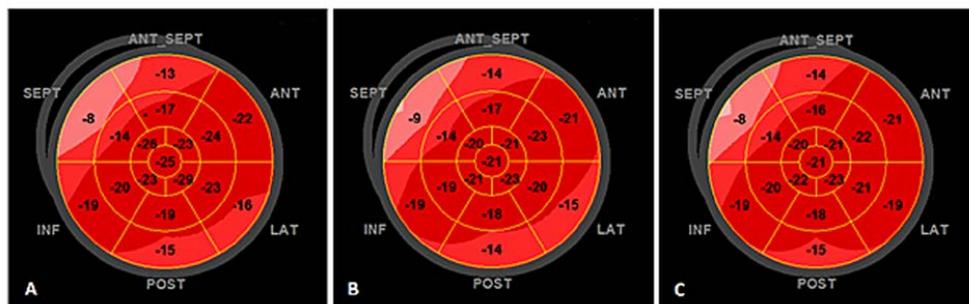

Figure 9
Segmental strain of the left ventricle illustrating the variability of measurements. **A**. Measurements performed by observer 1; **B**. Measurements performed by observer 2; and **C**. Measurements re-assessed by observer 2.

Thirteen patients (28%) had atrial fibrillation (AF) when the echocardiogram was performed. Excluding these from the analyses did not, however, markedly alter the results.

The results of study III thus indicate moderate observer-related differences in the assessment of LV dysfunction in septic shock patients. GLPS is the least user-dependent and most reproducible measurement of LV dysfunction in patients with septic shock.

Paper IV

For study IV, data on 12,800 individual patients admitted to Swedish ICUs and diagnosed with severe sepsis or septic shock was collected from SIR. Patients who were categorised as having severe cardiac failure preceding ICU admission (n = 1,010) and those who were admitted with cardiogenic shock or cardiac arrest (n = 205) were excluded from the statistical analysis, as well as those who died in the ICU (n = 2,518; 20%). Thus, the cohort used for the study consisted of patients without pre-existing severe cardiac failure (NYHA IV) and not presenting with cardiogenic shock or cardiac arrest on admission, who were all alive at ICU discharge (n = 9,520). The selection of patients is displayed in Figure 4 (page 14) and the characteristics of included patients are shown in Table 3 (page 24).

During a follow-up time of 17,693 person-years (median 583 days/person, maximum 5.7 years), 3,954 (42%) patients died, 654 (17%) with cardiac failure as the major or as a contributing cause (page 24; Table 3). The median time from ICU discharge to death was 94 days (IQR 12 – 449) for all-cause death and 86 days (IQR 13 – 404) for death related to cardiac failure.

The association of increasing severity of illness in severe sepsis or septic shock and death with cardiac failure as cause of death post-ICU was assessed by dividing the sepsis cohort into quartiles according to SAPS3 on admission (Table 3).

	All patients (n = 9,520)	Quartile 1 SAPS3 27–57 (n = 2,446)	Quartile 2 SAPS3 58–64 (n = 2,607)	Quartile 3 SAPS3 65–73 (n = 2,337)	Quartile 4 SAPS3 74–124 (n = 2,130)	p
Age, years	68 (58 – 77)	58 (42 – 67)	68 (59 – 76)	72 (64 – 80)	73 (65 – 80)	<0.001
SAPS3	63 (55 – 72)	–	–	–	–	–
ICU LOS, hours	48 (24–120)	24 (0–72)	48 (24–120)	48 (24–120)	72 (24–168)	<0.001
Death after ICU discharge	3,954 (42)	440 (18)	973 (37)	1,208 (52)	1,333 (63)	<0.001
Cardiac failure registered as cause of death	654 (17)	67 (15)	188 (19)	202 (17)	197 (15)	<0.001

Table 3
Characteristics and outcome of severe sepsis and septic shock patients discharged alive from the ICU. The table also displays the characteristics and outcome of patients grouped in quartiles according to SAPS3 on admission, and a between-groups comparison of the quartiles (quartile 1-quartile 4). Data are presented as medians (IQR) and numbers (percentages) as appropriate. For abbreviations, see page ix.

The post-ICU mortality rates in general increased markedly with increasing severity of illness. The proportion of deaths related to cardiac failure did not, however, increase linearly. However, when applying a Cox proportional hazard model and thereby taking into account the time to death, the death rate with cardiac failure as major or contributing cause of death increased (HR 1.58 (95% CI 1.19 – 2.09) comparing hazard rates in the highest quartile to the lowest, p = 0.001). The survival characteristics in the quartiles are further illustrated in Paper IV.

In order to further assess cardiac outcome after severe sepsis and septic shock, a control group was created, consisting of patients requiring intensive care for reasons other than sepsis, but matched as described (page 14; Figure 4). Matches were identified for 4,577 patients, both groups consisting of patients without severe cardiac failure (NYHA IV), cardiogenic shock or cardiac arrest on admission, and all discharged alive from the ICU.

While all patients in the sepsis group were diagnosed with severe sepsis or septic shock, the most commonly assigned diagnoses in the control group were chronic obstructive pulmonary disease (n = 757; 17%), respiratory insufficiency (n = 737; 16%), acute renal failure (n = 628; 14%), bacterial pneumonia (n = 597; 13%), gastrointestinal bleeding (n = 524; 11%), intoxications (n = 358; 8%), cerebrovascular incidents (n = 221; 5%) and multiple trauma (n = 192; 4%). The between-groups comparison was based on a follow up-time of 10,719 person-years (median 575 days/person, maximum 5.7 years) in severe sepsis and septic or septic shock patients and 9,740 person-years (median 543 days/person, maximum 5.7 years) in controls. The number of deaths in general was lower in patients with severe sepsis or septic shock than in controls, but the proportion of death with cardiac failure as cause of death was higher in severe sepsis or septic shock patients (Paper IV). Also, the survival estimates regarding all-cause death was higher in severe sepsis or septic shock patients than in controls, wheras the survival estimates regarding death with cardiac failure as cause of death did not differ between groups (page 25; Figure 10).

The hazard rate for all-cause death was lower in severe sepsis and septic shock patients compared to controls (HR over the whole study period 0.90, 95% CI 0.84 – 0.96, p <0.001), even when analysing only the first 30 days after ICU discharge (HR day 0 – 30 0.89 (95% CI 0.83 – 0.96, p = 0.002). The hazard rate for death with cardiac failure as a major or contributing cause, however, did not differ between groups (HR over the whole study period 0.97 (95% CI 0.88 – 1.10, p = 0.62); HR day 0 – 30 0.98 (95% CI 0.82 – 1.17, p = 0.67)).

Kaplan Meier survival estimates, death from cardiac failure
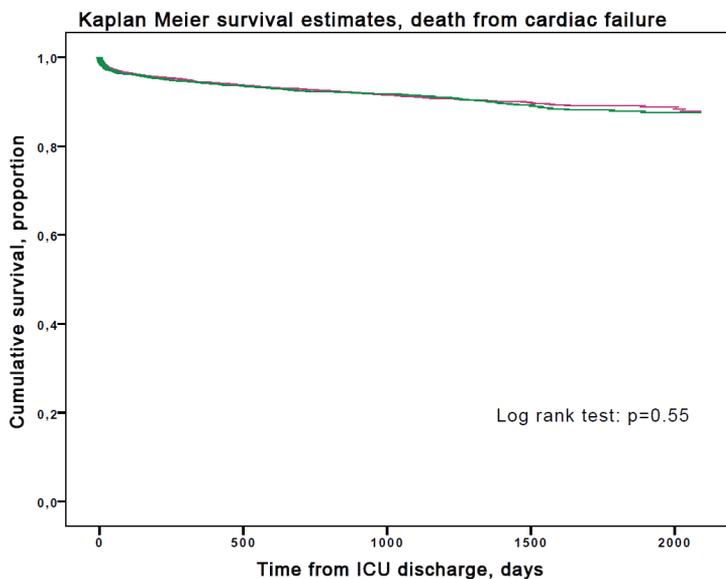
Figure 10
Kaplan-Meier survival estimates of cardiac failure-related death after ICU discharge in severe sepsis and septic shock patients (purple) and matched controls (green), all without pre-existing cardiac failure (NYHA IV), none presenting with cardiogenic shock or cardiac arrest on admission and all discharged alive from the ICU (n = 4,577 in each group on day 0, which denotes discharge from ICU). For abbreviations, see page ix.

DISCUSSION

The aim of this thesis was to study the characteristics and the implications on outcome of cardiac dysfunction in intensive care patients with septic shock. The thesis adds to the understanding of the dynamic nature of cardiac dysfunction in septic shock by illustrating its characteristics during the acute phase of the disease, and by demonstrating its dynamics and longer-term outcome.

Patient selection and settings (papers I – IV)

The studies included in this thesis are all based on adult intensive care patient cohorts, all collected from mixed, non-cardiothoracic ICUs.

Study I is based on a group of patients representing a typical general ICU population, of different ages and referred to the ICU for different reasons. In such an unselected ICU population, the clinical spectrum is wide and nonspecific. In other studies on the use of natriuretic peptides in intensive care, focus has been on specific groups of patients (60, 63, 68, 93), and studies on NT-proBNP in general ICU populations preceding study I have been more limited in size (70-72, 94). Although direct comparison between studies is complicated by differences in patient selection, the results of study I are in the same range as in preceding studies. Indeed, the inclusion of patients irrespective of cause enables the study to demonstrate the value of NT-proBNP as a marker of disease severity, rather than a diagnostic tool.

The patients included in **studies II and III** were all admitted to the ICU with septic shock. Patients presenting with severe sepsis or those who developed sepsis while in the ICU for other reasons were not included, in an attempt to acquire some uniformity in the limited-size cohort. In other studies on cardiac dysfunction in sepsis, patients with severe sepsis have been included alongside those with septic shock (22, 33, 34, 95), which widens the range of disease, and also complicates direct comparison between studies. In contrast, we excluded the most severely ill patients, i.e. those expected to survive for less than 24 hours, for research ethical reasons. How these most severely ill patients have been handled in other studies has rarely been described.

In **study IV**, patients with severe sepsis were included alongside those with septic shock, since SIR does not discriminate between the two. Also, not only those presenting with severe sepsis or septic shock on admission were included, but all those being diagnosed with either of the two conditions during ICU stay. Thereby a larger cohort and additional statistical strength was obtained, but also a wider range of disease severity.

In studies I, II and III, patients with pre-existing cardiac disease were included. These patients were logically more vulnerable in cardiac health, but their specific impact on the results of the studies was not investigated. In study II especially, the large proportion of patients with pre-existing cardiac disease may explain the differences seen in comparison to other studies on GLPS in septic shock, wherein patients with pre-existing cardiac disease

were not included (48, 49, 95). Nonetheless, the aim was to evaluate GLPS in study II, and NT-proBNP in study I, in conditions as similar as possible to those encountered clinically. In study IV, in contrast, we excluded patients with pre-existing severe cardiac failure and with admission diagnoses that could be linked to cardiac disease, and a substantial proportion of patients in the cohort were thereby omitted from analysis. The inclusion of these patients in studies I, II and III, and exclusion in study IV, may have implications for the external validity of the findings.

A control group of non-septic ICU patients was collected for study IV. In other studies, the long-term survival of severe sepsis and septic shock patients has been assessed by comparison to the general public (79, 80, 96, 97) or to other groups of ICU patients (98–100). The control group in study IV was selected using a different approach than in previous studies, by matching sepsis patients and controls regarding severity of illness, age and ICU LOS. The underlying rationale was to identify any specific septic effect on the heart, while excluding the impact of differing ages and disease severity in the between-groups comparison. The register-based design furthermore enabled the selection of a cohort which was generally larger than previous studies (79).

Aspects on assessing cardiac function in septic shock (papers I – III)

Different aspects of cardiac function in the acute phase of critical illness and soon thereafter were assessed in general intensive care patients in **study I** and in septic shock patients in **studies II and III**.

Laboratory and clinical data

The interpretation of an elevated NT-proBNP in the intensive care setting is complicated. In study I, we saw frequently and markedly increased levels of NT-proBNP, but their correlation to echocardiography or to any other measure of cardiac function was not investigated. In contrast to observations on patients with acute respiratory failure (93), no relation was seen between increased levels of NT-proBNP and mechanical ventilation. Study II showed no correlation of NT-proBNP with ventilator pressures, volume load or fluid balance, in contrast to the underlying physiological principle of NT-proBNP being increased in response to volume and pressure load. Other studies have presented varying results in this regard (68, 93), possibly explained by varying sampling times, as well as by differences in patient selection and range of disease severity.

The correlation of the level of NT-proBNP to cardiac function in intensive care patients is unclear. NT-proBNP levels comparable to those in heart failure patients have been demonstrated in sepsis patients, but with a wider variability (63). This complicates the interpretation of absolute values in an individual patient, as well as the comparison between studies. There are also conflicting results regarding the correlation of NT-proBNP with echocardiographic data (22, 101). Nonetheless, NT-proBNP and BNP have been proposed as screening tools especially for identifying diastolic dysfunction in general ICU populations, as well as in sepsis (69, 101). Study II, in contrast, showed a much weaker correlation of NT-

proBNP with diastolic function parameters than with LVEF and GLPS, and no correlaton with invasive measurements of cardiac function.

Thus, the use of NT-proBNP as a marker of cardiac function in intensive care patients is still unclear. NT-proBNP does not seem to exclusively reflect cardiac failure, and the results presented here cannot provide support for such use. This thesis instead suggests a primary role of NT-proBNP in general ICU patients (study I) as well as in septic shock (study II) as a marker of disease severity.

Echocardiography

The assessment of cardiac depression in patients with septic shock is challenged by the septic pathophysiology itself. As outlined previously in this thesis, cardiac dysfunction in sepsis can be masked by a concurrent low SVR and elevated CO, complicating the interpretation of parameters used for monitoring of LV function (24, 27, 65).

The landmark study first describing cardiac dysfunction in septic shock showed systolic impairment in ten of 20 patients during the first 48 hours of ICU admission (16). Echocardiographic studies have reported similar results with a reduced global systolic function in 30 to 60% of septic shock patients (23, 35) and reversibility in survivors (26, 28, 102). The definition of systolic dysfunction has varied (LVEF 45 to 55%) and comparison between studies is therefore complicated. In study II, the generally recommended LVEF of <50% was used as the cut-off (36), and in line with previous results, a reduced LVEF was seen in 50% of patients.

With the introduction of tissue Doppler in clinical practice, the diastolic function of the heart in sepsis has gained interest. Several studies have shown decreased e' and increased E/e' in septic patients, with a prevalence varying from 20 to just under 60% (22, 34, 101, 103). When we in study II used the same definitions as in these studies (E/e' >15 and/or e' <0.08 m/s), a prevalence of 50% was found. In contrast to previous longitudinal studies (22, 34, 103), and possibly reflecting pre-existing cardiac disease in studied patients, no improvement over time was seen.

The nature of cardiac dysfunction in sepsis has been further investigated by using other echocardiographic techniques to assess cardiac function. For example, tissue Doppler measurement of the peak systolic velocity at the mitral annulus (Sa) has showed a linear association with LVEF in septic shock (23, 104). Also, a correlation of the mitral annular plane systolic excursion (MAPSE) has been demonstrated with LVEF as well as with e' and E/e' (104, 105), and MAPSE is therefore thought to reflect systolic as well as diastolic function. GLPS, used in study II, is regarded as a measure of contractility. However, we found not only an association of GLPS with LVEF but also with e' and E/e', indicating a marked overlap of, or interaction between, systolic and diastolic dysfunction. Thus, while GLPS is regarded as a measure of systolic function, systolic dysfunction commonly coincides with diastolic dysfunction in patients with septic shock.

When study II was conducted, speckle tracking had been only sparsely evaluated in intensive care, despite its theoretical advantages. It had been studied clinically in paediatric septic shock (49), and later, in adult severe sepsis and septic shock patients (33) as well as in experimental porcine septic shock (48). These studies suggested that speckle tracking, and measurements of GLPS, was able to identify an impaired LV function in more patients

than LVEF. Also, in line with the findings in cardiology settings, where GLPS is regarded as a more sensitive measurement of systolic cardiac function than LVEF (45–47), changes in GLPS were seen earlier in the course of sepsis than changes in LVEF (48). Study II, in contrast, could not demonstrate any superiority of GLPS to LVEF in detecting LV dysfunction. The differences may, in line with the results seen regarding diastolic function measurements, be related to the higher prevalence of cardiac disease in study II than in other studies, in experimental and paediatric studies especially. This is further highlighted by a later study on GLPS in adult severe sepsis and septic shock patients where those with previous cardiac disease were excluded (95). There, impaired GLPS was seen early in the course of disease, and despite preserved LVEF.

Speckle tracking echocardiography shows cardiac motion and deformation, but does not measure pressures. Changes in underlying conditions affecting the contractile state of the myocardium are therefore, in themselves, invisible. The deformation observed is nonetheless a product of the contraction of the myocardium and of its modulation by pre- and afterload. GLPS therefore does not only reflect myocardial contractility, but must be interpreted in the context of loading conditions: in the septic situation primarily volume state, ventilator pressures and SVR. Novel cardiac function parameters such as afterload-related cardiac performance, where CO is seen in relation to SVR, have therefore been presented (106), but have not yet come into clinical practise. However, in contrast to the underlying link between cardiac function and afterload, no correlation was seen with SVRI or vasopressor doses in study II. The sample size may have been too limited to show such an interaction, which is nonetheless physiologically likely to have been present.

The value of serial measurements rather than isolated values has been illustrated by the unmasking of septic cardiac dysfunction by vasopressor treatment given in order to restore SVR (24). Study II showed a significant improvement over time in LVEF, whereas GLPS, e' and E/e' remained close to normal values at all measurement time-points. This too may be a reflection of the treatment of septic shock in studied patients as well as of the septic pathophysiology.

Thus, the understanding of whether laboratory or echocardiographic signs of cardiac dysfunction are the consequences of the acute illness or rather markers of decompensated underlying disease, or of the septic pathophysiology itself, remains challenging. This highlights the need for a better understanding of how to use echocardiography and cardiac biomarkers in evaluating the heart in the critically ill patient. An integration of clinical parameters and biomarkers with echocardiographic measures is possibly a more comprehensive measure to understand cardiac dysfunction in septic shock (107).

Reliability and variability

The observer-related variability in echocardiography has been scantily studied in the intensive care context (35, 38–40). Study III showed moderate observer-related differences, especially in diastolic, and to a lesser extent, in systolic function parameters in septic shock patients. This variability may thus have contributed to the differing results reported regarding cardiac dysfunction, and its impact on mortality, in these patients (22, 65, 101).

In cardiology, substantial observer-related differences in echocardiography are well-known and extensively described. (51, 108–110). Although the clinical situation in septic

shock differs from that in cardiology, the results of study III indicate similar difficulties in septic shock patients as those encountered in cardiology. In stress echocardiography especially, where there are phyisiological and clinical similarities to the intensive care situation, a high degree of variability has been described even among expert observers (50). A markedly improved reproducibility has been seen in the interpretation of dobutamine stress echocardiography with the use of GLPS (52). In line with this, our findings indicate a good reproducibility of GLPS in septic shock. Furthermore, the superior reproducibility of GLPS in stress echocardiography, in study III also in septic shock, illustrates the advantage of semi-automated techniques, with less manual processing (111).

Since echocardiography is increasingly used not only for diagnosing cardiac dysfunction, but also for monitoring and for titrating therapy in septic shock, the results of study III may have clinical implications (29, 31). The observer-related differences in the assessment of diastolic function suggest the need for some caution in this regard. However, much of the haemodynamic support in septic shock targets the systolic function of the heart (1). While echocardiographic data should be interpreted in relation to the clinical picture as a whole in the individual patient, the good reproducibility in LVEF seen in study III and in previous reports (35) encourages the use of echocardiography as a monitoring tool. Moreover, the increasing interest in GLPS in septic shock (33, 95) is further supported by study III.

On predicting cardiac outcome in ICU patients (papers I - IV)

Different aspects on cardiac outcome was assessed in all the cohorts studied in this thesis.

Study I was, when it was published, the largest study assessing the predictive ability of NT-proBNP in a mixed ICU population. We found that NT-proBNP levels close to the thresholds used clinically, and reported in other studies (70, 71, 94), could predict death in general intensive care patients. Statistically, the predictive ability of NT-proBNP was independent of age, ICU LOS and the presence of sepsis. Furthermore, its predictive ability was comparable to SAPS3 and SOFA in a pattern similar to other studies, but where the predictive ability of NT-proBNP had been compared to other severity of illness scores (70, 112). While demonstrating a predictive value of NT-proBNP in general ICU patients, this thesis does not support the use of NT-proBNP as a replacement for other prognostic markers, laboratory or clinical variables and scoring systems alike, in intensive care clinical practice. NT-proBNP may instead be an aid in identifying the most severely ill with the highest risk of death, irrespective of cause (68, 70, 71, 94). As outlined previously in this discussion, an elevated NT-proBNP does not necessarily reflect cardiac failure in intensive care patients, but may rather be a marker of disease severity. Thus, it is reasonable to assume that the predictive value of NT-proBNP lies in its relation to the risk of all-cause death rather than to death from cardiac causes specifically.

In **study II**, there was no difference regarding echocardiographic parameters between survivors and non-survivors. When septic cardiac dysfunction was first described, LVEF was paradoxically reduced in survivors, compared with non-survivors (16). Some studies have confirmed this finding (24), whereas in other studies, and in study II in this thesis, no difference in LVEF between survivors and non-survivors was seen (23, 101). Indeed, the use

of LVEF for outcome prediction is now increasingly questioned (65, 66). Diastolic dysfunction, in contrast, is thought to have a substantial impact on the risk of death in septic shock (22, 34, 66, 101). Is is however unclear to what extent this is a reflection of the septic pathophysiology (39), or to the increased risk of death associated with underlying comorbidities (113). Thus, the impact of diastolic dysfunction on mortality does not necessarily reflect cardiac dysfunction caused by sepsis. Moreover, the results from **study III** in this thesis imply that observer-related differences may have had an influence on the reports regarding outcome in relation to echocardiographic parameters, diastolic function parameters in particular. Furthermore, an association of decreased right ventricular strain with mortality in septic shock has been shown (33). No relation of LV strain – GLPS – to outcome in septic shock has previously been demonstrated, and in study II, no such predictive ability of GLPS was seen. Thus, this thesis cannot identify any specific echocardiographic sign or parameter that independently predicts adverse outcome.

Study IV was conducted in an attempt to identify any specific septic long-term effect on the heart. This was done by assessing death with cardiac failure as the major or as a contributing cause of death after ICU discharge in patients with severe sepsis and septic shock. An increasing risk of death after ICU discharge, in general and with cardiac failure as cause of death particular, was seen with increasing severity of illness on admission. The result is in line with the description of sepsis and of severity of illness as major determinants of death after intensive care (10, 96, 100). The finding does not, however, provide evidence that sepsis in itself is the cause of this increased risk of death.

Previous comparisons between ICU patients in general and sepsis patients in particular have shown a higher post-ICU mortality risk than in the general public (79–81, 96), and a higher risk of death post-ICU in sepsis patients in than in other patient categories (83, 98, 100). However, it is unclear to what extent this increased risk of death is related to sepsis itself, or to the severity of illness during the acute phase, irrespective of the underlying cause.

The specific causes of death post-ICU have been scantily studied. Most studies have reported causes of death in the ICU or while still in hospital, and have been limited in size (114, 115). In patients with bacteraemia, an increased risk of myocardial infarction has been shown in comparison to hospitalized non-bacteraemic and general-population controls (116). However, since only a subgroup of these patients was in intensive care and focus was on ischaemic heart disease, direct comparison to our study is complicated.

The result of the comparison in study IV of sepsis patients to matched controls differs to some extent depending on the statistical method used. Overall, in contrast to previous studies, and contradicting the original hypothesis of study IV, sepsis patients do not appear to be at an increased risk of death, in general or with cardiac failure as cause of death, when compared to non-sepsis patients with equal severity of illness. As outlined above, sepsis patients were closely matched to controls, possibly to an extent where the differences in outcome may have been eliminated. If the impact of severity of illness, age and ICU LOS itself was greater than that of sepsis, the relation of exposure to outcome – in study IV the relation of sepsis to death from cardiac failure – could be obscured (117–119). One cannot exclude whether such overmatching may in part explain the lack of difference in results between the groups.

Follow-up time

The follow-up time in interventional as well as observational studies in intensive care varies. While ICU-, 30-day- and in-hospital-mortality are the most commonly used, there is an increasing interest in longer follow-up (82, 85, 86, 96). In this thesis, a progressively longer follow-up time was used in the different study cohorts. Specifically, follow-up was 30 days in study I and 30 as well as 90 days in study II. In study IV, we used a large open cohort with follow-up time varying from directly after ICU discharge up to more than five years.

NT-proBNP was associated with adverse outcome at 30 days in study I. Other authors have investigated NT-proBNP in relation to death in the ICU as well as 28-, 30-, 90-day or even 1-year mortality (68, 70, 71, 120, 121). Results have differed, reflecting differences in study design and focus, but also the previously discussed uncertain clinical implication of an elevated NT-proBNP as other than a marker of severity of illness.

The follow-up time in echocardiographic studies on septic shock patients has also varied from ICU mortality up to 1-year mortality (22, 34, 120). Results have differed with respect to the echocardiographic parameters used as outlined above, but there is little to support that the differences reported are related to differences in follow-up time.

The most appropriate follow-up time as well as the best starting point for follow-up in studies on long-term mortality after ICU is a subject of ongoing debate (82, 83). Mortality after ICU discharge has been described to reach a plateau after 90 days (85) and few studies have followed patients beyond six months (84, 122). Others have demonstrated an increased rate of death for at least two to three years (79, 83, 96) or even five years (80, 81) in ICU patients. Moreover, some studies on post-ICU outcome have begun at hospital discharge (83), and others have excluded the directly ICU-related mortality by excluding deaths during the first week after ICU discharge (10). Furthermore, the relative impact of different factors affecting long-term outcome appear to vary with progressively longer follow-up (84). In study IV, follow-up began at ICU discharge, since the focus of the study was on the impact of cardiac failure originating in the septic episode. Moreover, the study was based on an open cohort where the follow-up time differs between the patients in the cohort. Risk factors unrelated to the septic episode, such as increasing age and other newly introduced diseases, may thereby have been introduced. Nonetheless, study IV highlights the need for future studies on what is the optimum follow-up time in septic shock patients (85, 96).

Limitations

In this thesis, there are limitations that must be considered. For **studies I, II and III**, all data were collected from the same centre, where local management routines may have influenced patient selection as well as treatment and outcome. Furthermore, the hospital is a tertiary care centre, to which some patients are referred from other hospitals. Intensive care may thus have started before admission, and inclusion into the studies thereby relatively late in the individual patients' courses of disease. This may have influenced the results regarding laboratory as well as echocardiographic and clinical data, in study I as well as study II. In **study IV**, data was provided from a large number of ICUs, where local management routines may have influenced the decision whether to admit a patient to the ICU or not, as well as the reporting to the registries.

Secondly, clinicians were not blinded to the laboratory, clinical and echocardiographic data collected for studies I, II and III. Clinical decision-making and the results of the studies may thereby have been affected. However, our intention was purely observational, and we wanted clinical decisions to be based on the best available data. A further major limitation of studies I, II and III is the use of cardiac biomarkers and echocardiographic parameters whose use is best described in cardiology settings rather than in intensive care, along with the limited size of the studies.

In study IV, data was collected from medical registers, and the accuracy of diagnoses and other data collected and used for analysis was not monitored. Furthermore, the diagnoses recorded as causes of death are largely reported on a clinical basis. The accuracy of death certificates in delineating the causes of death is debated (123, 124), and data collected on this basis is therefore subject to some uncertainty. Thus, the main limitation of study IV concerns the uncertainties related to its register-based design.

The strength of study I is the broad inclusion of patients with subsequent systematic analysis of the prognostic ability of NT-proBNP. In studies II and III, the major strength lies in the parallel use of echocardiographic measurements, biomarkers and clinical data, and the repeated analysis of the same throughout the most unstable period, using observer blinded measurements. Further strength is found in all echocardiograms used for analysis being collected by the same expert-level echocardiographer, thus providing the best possible image quality for analysis. The major strength of study IV is the design offering a possibility to address the question of long-term cardiac outcome after severe sepsis and septic shock in a large population. The principal strength of this thesis as a whole is the multifaceted and systematic approach to describing the different aspects of cardiac dysfunction in septic shock.

CONCLUSIONS

The studies included in this thesis have led to the following conclusions:

    I   The cardiac biomarker NT-proBNP is markedly elevated in a mixed critically ill patient population, increases with severity of illness, and predicts an increased risk of death. However, NT-proBNP is probably not exclusively a marker of cardiac failure in intensive care patients, but rather one of severity of illness.

    II   The global longitudinal peak strain of the left ventricle is commonly affected in patients with septic shock. It remains unchanged over time, despite clinical remission and normalising LVEF and NT-proBNP, but cannot predict an increased risk of death.

    III   The global longitudinal peak strain is the least user-dependent and most reproducible echocardiographic parameter indicating left ventricular dysfunction in septic shock. It is not more sensitive in detecting cardiac dysfunction in septic shock patients than other echocardiographic parameters.

    IV   The risk of death due to cardiac failure after severe sepsis and septic shock increases with increasing severity of illness, even after ICU discharge. However, in ICU patients with and without severe sepsis and septic shock, the risk of death related to cardiac failure was comparable.

The final conclusion of this thesis is that signs of cardiac dysfunction are common in ICU patients, but that its assessment in patients with septic shock is complicated by pre-existing comorbidities, by treatment given in the ICU and by critical illness itself. The signs of cardiac dysfunction and the increasing risk of death seen after remission of sepsis may therefore be reflections of critical illness per se, rather than of sepsis.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Allmän blodförgiftning, sepsis, är ett mycket allvarligt tillstånd, där kroppens alla organsystem påverkas. Vid sepsis utvecklas ibland hjärtsvikt som en del av förloppet, och sjukdomstillståndet förvärras då ytterligare.

Hjärtsvikt kan under den akuta sjukdomsfasen döljas av att sepsis, och även den behandling som samtidigt ges inom intensivvården, framkallar andra akuta förändringar i cirkulationen. Vid sepsis är hjärtfunktionen därför svårbedömd, och tolkningen av de metoder, som används för att påvisa nedsatt hjärtfunktion, är komplicerad. Vidare är det oklart huruvida sepsis ger negativa effekter på hjärtfunktionen på längre sikt. Det är känt att patienter med sepsis, jämfört med befolkningen i allmänhet och även jämfört med intensivvårdspatienter som inte drabbats av sepsis, har en försämrad överlevnad under lång tid efter den akuta sjukdomsfasen. Vad som orsakar denna ökade risk är inte klarlagt, och inte heller i vilken mån det beror på hjärtsvikt med upprinnelse i den akuta fasen av sepsissjukdomen. Denna avhandling fokuserar på olika sätt att identifiera hjärtsvikt hos intensivvårdspatienter, i synnerhet hos dem med sepsis, och på långtidseffekterna på hjärtat av sepsis.

Avhandlingen undersöker NT-proBNP – en biologisk markör, som frisätts från hjärtmuskeln vid hjärtsvikt – och om nivån av NT-proBNP kan användas för att indikera försämrad prognos hos intensivvårdspatienter. Avhandlingen studerar också en metod där man med hjärtultraljud mäter hjärtmuskelns förmåga till sammandragning, och förkortning under hjärtslaget, för att tidigt kunna påvisa nedsatt hjärtfunktion hos svårt sjuka intensivvårdspatienter med sepsis. Likaledes undersöks hur hjärtfunktionen förändras under sepsisförloppet, samt hur mätningar av hjärtmuskelns sammandragning förhåller sig till andra hjärtfunktionsmätningar med hjärtultraljud. Slutligen studeras överlevnaden efter sepsis på lång sikt, med avseende på sepsispatienters risk att avlida i hjärtsvikt.

Avhandlingen visar, att intensivvårdspatienter med förhöjda nivåer av NT-proBNP har klart försämrad överlevnad. Avhandlingen visar också, att hjärtfunktionen hos patienter med sepsis ofta är nedsatt under den akuta fasen av sjukdomstillståndet. Mätning av hjärtmuskelns sammandragningsförmåga är mindre användarberoende än andra hjärtultraljudsmetoder, men är i jämförelse med andra metoder inte känsligare när det gäller att påvisa nedsatt hjärtfunktion vid sepsis. Försämrad sammandragningsförmåga i hjärtmuskeln under akutfasen av sepsistillståndet kan inte heller indikera försämrad överlevnad efter avslutad intensivvård. Slutligen ses att risken för att avlida i hjärtsvikt efter den akuta sjukdomsfasen ökar med ökande svårighetsgrad i sepsissjukdomen, och att risken kvarstår under avsevärd tid efter att patienterna skrivits ut från intensivvården. För att undersöka om denna risk är relaterad till sepsissjukdomen i sig, eller till svår sjukdom oavsett orsak, görs i avhandlingen en jämförelse med andra mycket svårt sjuka patienter, som intensivvårdats av annat skäl än sepsis. Denna jämförelse visar, att risken att avlida i

hjärtsvikt efter intensivvård är lika hög bland de patienter som intensivvårdats av något annat skäl än sepsis.

Sammanfattningsvis visar denna avhandling att tecken till hjärtsvikt, påvisad med såväl blodprov som hjärtultraljud, är vanligt förekommande hos intensivvårdspatienter. Tecken till hjärtsvikt under den akuta sjukdomsfasen, och den med sjukdomsgraden ökande risken för att avlida i hjärtsvikt efter intensivvård, tolkas dock som en effekt av svår sjukdom i allmänhet, snarare än av sepsistillståndet som sådant. Fortsatta studier behövs för att belysa hur hjärtat påverkas under svår sjukdom och de långtidseffekter på hjärtfunktionen, som följer därefter.

ERRATA

The following errata have been identified in the original papers included in this thesis:

Paper	Page; section	Original	Corrected
Paper I European Jornal of Anaesthesia 2012;29:6	Page 276; Table 1	Table 1	Table 1, page 19 in thesis
	Page 277; Figure 1	Figure 1	Figure 6, page 20 in thesis
Paper II Critical Care 2015;19:122	Throughout	é; á	e'; a'
	Page 4; Results; line 16	Positive end–espiratory pressure PEEP	Positive end–espiratory pressure (PEEP)
	Page 4; Results; line 28	hazards ratio	odds ratio; page 22 in thesis
	Page 7; Table 3	ICU length of stay, days, median (IQR)	ICU length of stay, hours, median (IQR)
	Page 7; Table 3	SVRI: 1310 (1066 to 1582)	SVRI: 1,310 (1,066 to 1,582)
		NT–proBNP, ng/L: 4230 (1210 to 10400); 7940 (2780 to 26400)	NT–proBNP, ng/L: 4,230 (1,210 to 10,400); 7,940 (2,780 to 26,400)
		GLPS, %: −17.2 (−20.0 to (−13.0)); −15.0 (−19.7 to (−11.0))	GLPS, %: −17.2 (−20.0 to −13.0); −15.0 (−19.7 to −11.0); Table 2, page 21 in thesis
		é, m/s: 0.12 (0.83 to 0.16)	e', m/s: 0.12 (0.08 to 0.16)
Paper III Cardiovascular Ultrasound 2015;13:19	Page 1; Abstract	Mean difference and 95% limits of agreement for é: −0.01 (0.04 – 0.07)	Mean difference and 95% limits of agreement for e': −0.01 (−0.07 – 0.04); Page 23 in thesis
	Page 7; References; number 13.	De Geer L, Engvall J, Oscarsson A. Crit Care 2015;19:857	De Geer L, Engvall J, Oscarsson A. Crit Care 2015;19:122

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REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39: 165–228.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29: 1303–1310.
3. Wilhelms SB, Huss FR, Granath G, Sjoberg F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: difficulties with methods and interpretation of results. *Crit Care Med* 2010; 38: 1442–1449.
4. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348: 1546–1554.
5. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014; 311: 1308–1316.
6. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D, Sepsis Occurrence in Acutely Ill Patients I. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; 34: 344–353.
7. The Swedish Intensive Care Registry. [cited 2015, 20th of August]. Available from: http://www.icuregswe.org.
8. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013; 41: 1167–1174.
9. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B, Network CU-R. Current epidemiology of septic shock: the CUB-Rea Network. *Am J Respir Crit Care Med* 2003; 168: 165–172.
10. Sakr Y, Vincent JL, Ruokonen E, Pizzamiglio M, Installe E, Reinhart K, Moreno R, Sepsis Occurrence in Acutely Ill Patients I. Sepsis and organ system failure are major determinants of post-intensive care unit mortality. *J Crit Care* 2008; 23: 475–483.
11. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015; 372: 1629–1638.
12. MacLean LD, Mulligan WG, McLean AP, Duff JH. Patterns of septic shock in man--a detailed study of 56 patients. *Ann Surg* 1967; 166: 543–562.
13. Clowes GH, Jr., Vucinic M, Weidner MG. Circulatory and metabolic alterations associated with survival or death in peritonitis: clinical analysis of 25 cases. *Ann Surg* 1966; 163: 866–885.
14. Wilson RF, Sarver EJ, Rizzo J. Hemodynamic changes, treatment, and prognosis in clinical shock. *Arch Surg* 1971; 102: 21–24.
15. Weisel RD, Vito L, Dennis RC, Valeri CR, Hechtman HB. Myocardial depression during sepsis. *American journal of surgery* 1977; 133: 512–521.
16. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE. Profound but reversible myocardial depression in patients with septic shock. *Annals of internal medicine* 1984; 100: 483–490.
17. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced

ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. *J Clin Invest* 1985; 76: 1539–1553.

18. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. *The Journal of experimental medicine* 1996; 183: 949–958.

19. Kumar A, Brar R, Wang P, Dee L, Skorupa G, Khadour F, Schulz R, Parrillo JE. Role of nitric oxide and cGMP in human septic serum-induced depression of cardiac myocyte contractility. *The American journal of physiology* 1999; 276: R265–276.

20. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. *Crit Care Med* 2007; 35: 1599–1608.

21. Chew MS, Shekar K, Brand BA, Norin C, Barnett AG. Depletion of myocardial glucose is observed during endotoxemic but not hemorrhagic shock in a porcine model. *Crit Care* 2013; 17: R164.

22. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, Avidan A, Beeri R, Weissman C, Jaffe AS, Sprung CL. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J* 2012; 33: 895–903.

23. Weng L, Liu YT, Du B, Zhou JF, Guo XX, Peng JM, Hu XY, Zhang SY, Fang Q, Zhu WL. The prognostic value of left ventricular systolic function measured by tissue Doppler imaging in septic shock. *Crit Care* 2012; 16: R71.

24. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 2008; 36: 1701–1706.

25. Barraud D, Faivre V, Damy T, Welschbillig S, Gayat E, Heymes C, Payen D, Shah AM, Mebazaa A. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: comparison with dobutamine and milrinone. *Crit Care Med* 2007; 35: 1376–1382.

26. Jardin F, Brun-Ney D, Auvert B, Beauchet A, Bourdarias JP. Sepsis-related cardiogenic shock. *Crit Care Med* 1990; 18: 1055–1060.

27. Jardin F, Fourme T, Page B, Loubieres Y, Vieillard-Baron A, Beauchet A, Bourdarias JP. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. *Chest* 1999; 116: 1354–1359.

28. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Feger F, Rouby JJ. Acute left ventricular dilatation and shock-induced myocardial dysfunction. *Crit Care Med* 2009; 37: 441–447.

29. Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, Pinsky MR, Hofer CK, Teboul JL, de Boode WP, Scolletta S, Vieillard-Baron A, De Backer D, Walley KR, Maggiorini M, Singer M. Clinical review: Update on hemodynamic monitoring—a consensus of 16. *Crit Care* 2011; 15: 229.

30. Au SM, Vieillard-Baron A. Bedside echocardiography in critically ill patients: a true hemodynamic monitoring tool. *Journal of clinical monitoring and computing* 2012; 26: 355–360.

31. Porter TR, Shillcutt SK, Adams MS, Desjardins G, Glas KE, Olson JJ, Troughton RW. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2015; 28: 40–56.

32. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128: 1810–1852.

33. Orde SR, Pulido JN, Masaki M, Gillespie S, Spoon JN, Kane GC, Oh JK. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. *Crit Care* 2014; 18: R149.

34. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, Brown DR, Oh JK. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. *Mayo Clinic proceedings Mayo Clinic* 2012; 87: 620-628.

35. Bergenzaun L, Gudmundsson P, Ohlin H, During J, Ersson A, Ihrman L, Willenheimer R, Chew MS. Assessing left ventricular systolic function in shock: evaluation of echocardiographic parameters in intensive care. *Crit Care* 2011; 15: R200.

36. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1-39 e14.

37. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2009; 10: 165-193.

38. Juhl-Olsen P, Hermansen JF, Frederiksen CA, Rasmussen LA, Jakobsen CJ, Sloth E. Positive end-expiratory pressure influences echocardiographic measures of diastolic function: a randomized, crossover study in cardiac surgery patients. *Anesthesiology* 2013; 119: 1078-1086.

39. Mahjoub Y, Benoit-Fallet H, Airapetian N, Lorne E, Levrard M, Seydi AA, Amennouche N, Slama M, Dupont H. Improvement of left ventricular relaxation as assessed by tissue Doppler imaging in fluid-responsive critically ill septic patients. *Intensive Care Med* 2012; 38: 1461-1470.

40. Quintard H, Muller L, Philip I, Lena P, Ichai C. Influence of acute preload changes on mitral annulus velocity measured by tissue Doppler echocardiography in critically ill patients. *Journal of clinical ultrasound : JCU* 2012; 40: 419-423.

41. Blomstrand P, Engvall M, Festin K, Lindstrom T, Lanne T, Maret E, Nystrom FH, Maret-Ouda J, Ostgren CJ, Engvall J. Left ventricular diastolic function, assessed by echocardiography and tissue Doppler imaging, is a strong predictor of cardiovascular events, superior to global left ventricular longitudinal strain, in patients with type 2 diabetes. *European heart journal cardiovascular Imaging* 2015; 16: 1000-1007.

42. Bohs LN, Trahey GE. A novel method for angle independent ultrasonic imaging of blood flow and tissue motion. *IEEE transactions on bio-medical engineering* 1991; 38: 280-286.

43. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, Nesser HJ, Khandheria B, Narula J, Sengupta PP. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010; 23: 351-369.

44. Dalen H, Thorstensen A, Aase SA, Ingul CB, Torp H, Vatten LJ, Stoylen A. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2010; 11: 176-183.

45. Ho E, Brown A, Barrett P, Morgan RB, King G, Kennedy MJ, Murphy RT. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. *Heart* 2010; 96: 701-707.

46. Yajima R, Kataoka A, Takahashi A, Uehara M, Saito M, Yamaguchi C, Lee K, Komuro I, Funabashi N. Distinguishing focal fibrotic lesions and non-fibrotic lesions in hypertrophic cardiomyopathy by assessment of regional myocardial strain using two-dimensional speckle tracking echocardiography: comparison with multislice CT. *International journal of cardiology* 2012; 158: 423-432.

47. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation* 2003; 107: 2446-2452.

48. Hestenes SM, Halvorsen PS, Skulstad H, Remme EW, Espinoza A, Hyler S, Bugge JF, Fosse E, Nielsen EW, Edvardsen T. Advantages of strain echocardiography in assessment of myocardial function in severe sepsis: an experimental study. *Crit Care Med* 2014; 42: e432-440.

49. Basu S, Frank LH, Fenton KE, Sable CA, Levy RJ, Berger JT. Two-dimensional speckle tracking imaging detects impaired myocardial performance in children with septic shock, not recognized by conventional echocardiography. *Pediatr Crit Care Med* 2012; 13: 259-264.

50. Hoffmann R, Lethen H, Marwick T, Arnese M, Fioretti P, Pingitore A, Picano E, Buck T, Erbel R, Flachskampf FA, Hanrath P. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. *J Am Coll Cardiol* 1996; 27: 330-336.

51. Unzek S, Popovic ZB, Marwick TH, Diastolic Guidelines Concordance I. Effect of recommendations on interobserver consistency of diastolic function evaluation. *JACC Cardiovascular imaging* 2011; 4: 460-467.

52. Yamada A, Luis SA, Sathianathan D, Khandheria BK, Cafaro J, Hamilton-Craig CR, Platts DG, Haseler L, Burstow D, Chan J. Reproducibility of regional and global longitudinal strains derived from two-dimensional speckle-tracking and doppler tissue imaging between expert and novice readers during quantitative dobutamine stress echocardiography. *J Am Soc Echocardiogr* 2014; 27: 880-887.

53. McLean AS, Huang SJ. Cardiac biomarkers in the intensive care unit. *Annals of intensive care* 2012; 2: 8.

54. Cowie MR. BNP: soon to become a routine measure in the care of patients with heart failure? *Heart* 2000; 83: 617-618.

55. Markou N, Gregorakos L, Myrianthefs P. Increased blood troponin levels in ICU patients. *Curr Opin Crit Care* 2011; 17: 454-463.

56. Bessiere F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. *Intensive Care Med* 2013; 39: 1181-1189.

57. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, Beeri R, Weissman C, Sprung CL, Landesberg A. Troponin elevation in severe sepsis and septic shock: the role of left ventricular diastolic dysfunction and right ventricular dilatation*. *Crit Care Med* 2014; 42: 790-800.

58. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. *Nature* 1988; 332: 78-81.

59. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail* 2005; 11: S81-83.

60. Januzzi JL, Jr., Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005; 95: 948-954.

61. Oscarsson A, Fredrikson M, Sorliden M, Anskar S, Eintrei C. N-terminal fragment of pro-B-type natriuretic peptide is a predictor of cardiac events in high-risk patients undergoing acute hip fracture surgery. *Br J Anaesth* 2009; 103: 206-212.

62. Sturgess DJ, Parmar D, Dulhunty JM, Hedge R, Jarrett P, Udy A. A preliminary evaluation of plasma b-type natriuretic peptide as a screening test for left ventricular diastolic dysfunction in non-cardiac intensive care. *Anaesth Intensive Care* 2013; 41: 591-595.

63. Rudiger A, Gasser S, Fischler M, Hornemann T, von Eckardstein A, Maggiorini M. Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. *Crit Care Med* 2006; 34: 2140-2144.

64. Christenson RH. What is the value of B-type natriuretic peptide testing for diagnosis, prognosis or monitoring of critically ill adult patients in intensive care? *Clinical chemistry and laboratory medicine : CCLM / FESCC* 2008; 46: 1524-1532.

65. Sevilla Berrios RA, O'Horo JC, Velagapudi V, Pulido JN. Correlation of left ventricular systolic dysfunction determined by low ejection fraction and 30-day mortality in patients with severe sepsis and septic shock: a systematic review and meta-analysis. *J Crit Care* 2014; 29: 495-499.

66. Sanfilippo F, Corredor C, Fletcher N, Landesberg G, Benedetto U, Foex P, Cecconi M. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. *Intensive Care Med* 2015; 41: 1004-1013.

67. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circulation Cardiovascular imaging* 2009; 2: 356-364.

68. Varpula M, Pulkki K, Karlsson S, Ruokonen E, Pettila V, Group FS. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. *Crit Care Med* 2007; 35: 1277-1283.

69. McLean AS, Huang SJ, Hyams S, Poh G, Nalos M, Pandit R, Balik M, Tang B, Seppelt I. Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. *Crit Care Med* 2007; 35: 1019-1026.

70. Kotanidou A, Karsaliakos P, Tzanela M, Mavrou I, Kopterides P, Papadomichelakis E, Theodorakopoulou M, Botoula E, Tsangaris I, Lignos M, Ikonomidis I, Ilias I, Armaganidis A, Orfanos SE, Dimopoulou I. Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. *Shock* 2009; 31: 342-347.

71. Almog Y, Novack V, Megralishvili R, Kobal S, Barski L, King D, Zahger D. Plasma level of N terminal pro-brain natriuretic peptide as a prognostic marker in critically ill patients. *Anesthesia and analgesia* 2006; 102: 1809-1815.

72. Meyer B, Huelsmann M, Wexberg P, Delle Karth G, Berger R, Moertl D, Szekeres T, Pacher R, Heinz G. N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. *Crit Care Med* 2007; 35: 2268-2273.

73. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818-829.

74. Breslow MJ, Badawi O. Severity scoring in the critically ill: part 1--interpretation and accuracy of outcome prediction scoring systems. *Chest* 2012; 141: 245-252.

75. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR, Investigators S. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med* 2005; 31: 1336-1344.

76. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR, Investigators S. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; 31: 1345-1355.

77. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26: 1793-1800.

78. The National Board of Health and Welfare. [cited 2015, 20th of August]. Available from: http://www.socialstyrelsen.se/english.

79. Niskanen M, Kari A, Halonen P. Five-year survival after intensive care--comparison of 12,180 patients with the general population. Finnish ICU Study Group. *Crit Care Med* 1996; 24: 1962-1967.

80. Cuthbertson BH, Elders A, Hall S, Taylor J, Maclennan G, Mackirdy F, Mackenzie SJ. Mortality and quality of life in the five years after severe sepsis. *Crit Care* 2013; 17: R70.

81. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA* 1997; 277: 1058-1063.

82. Ranzani OT, Zampieri FG, Park M, Salluh JI. Long-term mortality after critical care: what is the starting point? *Crit Care* 2013; 17: 191.

83. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. *Crit Care Med* 2013; 41: 1229-1236.

84. Ranzani OT, Zampieri FG, Besen BA, Azevedo LC, Park M. One-year survival and resource use after critical illness: impact of organ failure and residual organ dysfunction in a cohort study in Brazil. *Crit Care* 2015; 19: 269.

85. Taori G, Ho KM, George C, Bellomo R, Webb SA, Hart GK, Bailey MJ. Landmark survival as an end-point for trials in critically ill patients--comparison of alternative durations of follow-up: an exploratory analysis. *Crit Care* 2009; 13: R128.

86. Williams TA, Dobb GJ, Finn JC, Webb SA. Long-term survival from intensive care: a review. *Intensive Care Med* 2005; 31: 1306-1315.

87. Williams TA, Dobb GJ, Finn JC, Knuiman MW, Geelhoed E, Lee KY, Webb SA. Determinants of long-term survival after intensive care. *Crit Care Med* 2008; 36: 1523-1530.

88. The New York Heart Association Functional Classification of Heart Failure. The New York Heart Association Functional Classification of Heart Failure. 2015. 2015 [cited 2015, 17th of August]. Available from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp.

89. The World Health Organization International Classification of Diseases – Tenth Edition. The World Health Organization International Classification of Diseases – Tenth Edition. 2015. 2015 [cited 2015, 20th of July]. Available from: http://www.who.int/classifications/icd/en/.

90. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology* 2009; 24: 659-667.

91. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-310.

92. Altman DG. Practical statistics for medical research. London, UK: Chapman & Hall; 1991.

93. Okkonen M, Varpula M, Linko R, Perttila J, Varpula T, Pettila V, Group FS. N-terminal-pro-BNP in critically ill patients with acute respiratory failure: a prospective cohort study. *Acta anaesthesiologica Scandinavica* 2011; 55: 749-757.

94. Cuthbertson BH, Patel RR, Croal BL, Barclay J, Hillis GS. B-type natriuretic peptide and the prediction of outcome in patients admitted to intensive care. *Anaesthesia* 2005; 60: 16-21.

95. Dalla K, Hallman C, Bech-Hanssen O, Haney M, Ricksten SE. Strain echocardiography identifies impaired longitudinal systolic function in patients with septic shock and preserved ejection fraction. *Cardiovasc Ultrasound* 2015; 13: 30.

96. Wright JC, Plenderleith L, Ridley SA. Long-term survival following intensive care: subgroup analysis and comparison with the general population. *Anaesthesia* 2003; 58: 637-642.

97. Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Teparrukkul P, Chaowarat S, Day NP, Graves N, Cooper BS. Long-term survival after intensive care unit discharge in Thailand: a retrospective study. *Crit Care* 2013; 17: R219.

98. Korosec Jagodic H, Jagodic K, Podbregar M. Long-term outcome and quality of life of patients treated in surgical intensive care: a comparison between sepsis and trauma. *Crit Care* 2006; 10: R134.

99. Meynaar IA, Van Den Boogaard M, Tangkau PL, Dawson L, Sleeswijk Visser S, Bakker J. Long-term survival after ICU treatment. *Minerva Anestesiol* 2012; 78: 1324-1332.

100. Kaufmann PA, Smolle KH, Krejs GJ. Short- and long-term survival of nonsurgical intensive care patients and its relation to diagnosis, severity of disease, age and comorbidities. *Current aging science* 2009; 2: 240-248.

101. Sturgess DJ, Marwick TH, Joyce C, Jenkins C, Jones M, Masci P, Stewart D, Venkatesh B. Prediction of hospital outcome in septic shock: a prospective comparison of tissue Doppler and cardiac biomarkers. *Crit Care* 2010; 14: R44.

102. Vieillard Baron A, Schmitt JM, Beauchet A, Augarde R, Prin S, Page B, Jardin F. Early preload adaptation in septic shock? A transesophageal echocardiographic study. *Anesthesiology* 2001; 94: 400-406.

103. Etchecopar-Chevreuil C, Francois B, Clavel M, Pichon N, Gastinne H, Vignon P. Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. *Intensive Care Med* 2008; 34: 250-256.

104. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation* 2002; 105: 1195-1201.

105. Bergenzaun L, Ohlin H, Gudmundsson P, Willenheimer R, Chew MS. Mitral annular plane systolic excursion (MAPSE) in shock: a valuable echocardiographic parameter in intensive care patients. *Cardiovasc Ultrasound* 2013; 11: 16.

106. Werdan K, Oelke A, Hettwer S, Nuding S, Bubel S, Hoke R, Russ M, Lautenschlager C, Mueller-Werdan U, Ebelt H. Septic cardiomyopathy: hemodynamic quantification, occurrence, and prognostic implications. *Clinical research in cardiology : official journal of the German Cardiac Society* 2011; 100: 661-668.

107. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J* 2015.

108. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004; 90: 511-517.

109. Li C, Zhang J, Zhou C, Huang L, Tang H, Rao L. Will simultaneous measurement of E/e' index facilitate the non-invasive assessment of left ventricular filling pressure in patients with non-valvular atrial fibrillation? *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2010; 11: 296-301.

110. Yamamoto K, Nishimura RA, Chaliki HP, Appleton CP, Holmes DR, Jr., Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: critical role of left ventricular systolic function. *J Am Coll Cardiol* 1997; 30: 1819-1826.

111. Maret E, Brudin L, Lindstrom L, Nylander E, Ohlsson JL, Engvall JE. Computer-assisted determination of left ventricular endocardial borders reduces variability in the echocardiographic assessment of ejection fraction. *Cardiovasc Ultrasound* 2008; 6: 55.

112. Shah KB, Nolan MM, Rao K, Wang DJ, Christenson RH, Shanholtz CB, Mehra MR, Gottlieb SS. The characteristics and prognostic importance of NT-ProBNP concentrations in critically ill patients. *The American journal of medicine* 2007; 120: 1071-1077.

113. Esper AM, Martin GS. The impact of comorbid conditions on critical illness. *Crit Care Med* 2011; 39: 2728-2735.

114. Mayr VD, Dunser MW, Greil V, Jochberger S, Luckner G, Ulmer H, Friesenecker BE, Takala J, Hasibeder WR. Causes of death and determinants of outcome in critically ill patients. *Crit Care* 2006; 10: R154.
115. Braber A, van Zanten AR. Unravelling post-ICU mortality: predictors and causes of death. *Eur J Anaesthesiol* 2010; 27: 486-490.
116. Dalager-Pedersen M, Sogaard M, Schonheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: a 20-year population-based cohort study. *Circulation* 2014; 129: 1387-1396.
117. Marsh JL, Hutton JL, Binks K. Removal of radiation dose response effects: an example of over-matching. *BMJ* 2002; 325: 327-330.
118. Greenland S, Morgenstern H. Matching and efficiency in cohort studies. *American journal of epidemiology* 1990; 131: 151-159.
119. Mansournia MA, Hernan MA, Greenland S. Matched designs and causal diagrams. *International journal of epidemiology* 2013; 42: 860-869.
120. Bergenzaun L, Ohlin H, Gudmundsson P, During J, Willenheimer R, Chew MS. High-sensitive cardiac Troponin T is superior to echocardiography in predicting 1-year mortality in patients with SIRS and shock in intensive care. *BMC anesthesiology* 2012; 12: 25.
121. Rhee CK, Lim SY, Koh SO, Choi WI, Lee YJ, Chon GR, Kim JH, Kim JY, Lim J, Park S, Kim HC, Lee JH, Lee JH, Park J, Koh Y, Suh GY, Kim SC. Usefulness of N-terminal pro-B-type natriuretic peptide in patients admitted to the intensive care unit: a multicenter prospective observational study. *BMC anesthesiology* 2014; 14: 16.
122. Nesseler N, Defontaine A, Launey Y, Morcet J, Malledant Y, Seguin P. Long-term mortality and quality of life after septic shock: a follow-up observational study. *Intensive Care Med* 2013; 39: 881-888.
123. Nielsen GP, Bjornsson J, Jonasson JG. The accuracy of death certificates. Implications for health statistics. *Virchows Archiv A, Pathological anatomy and histopathology* 1991; 419: 143-146.
124. Snyder ML, Love SA, Sorlie PD, Rosamond WD, Antini C, Metcalf PA, Hardy S, Suchindran CM, Shahar E, Heiss G. Redistribution of heart failure as the cause of death: the Atherosclerosis Risk in Communities Study. *Population health metrics* 2014; 12: 10.

APPENDIX (PAPERS I – IV)

Papers

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