Strain echocardiography in the critically ill patient

Studies in patients with septic shock and subarachnoid haemorrhage

Keti Dalla

Department of Anaesthesiology and
Intensive Care Medicine,
Institute of Clinical Sciences at
Sahlgrenska Academy
University of Gothenburg

Gothenburg, Sweden, 2019

UNIVERSITY OF
GOTHENBURG

Cover illustration by Art Décor “The Marble Heart”

Strain echocardiography in the critically ill patient
– Studies in patients with septic shock and subarachnoid haemorrhage

keti.dalla@vgregion.se

ISBN 978-91-783-3386-8 (PRINT)
ISBN978-91-7833-387-5 (PDF)
http://hdl.handle.net/2077/59054

Printed in Gothenburg, Sweden 2019
Printed by BrandFactory

To Elias, Georgios, Alexander and Maria-Isabella

"Ούκ ἔνι ἰατρικὴν εἰδέναι, ὅστις μὴ οἶδεν ὅ τι ἐστὶν ἄνθρωπος"

"No-one can know medicine without knowing what it is to be human"

Hippocrates, 460-377 BC

Abstract

In this thesis, strain echocardiography by two-dimensional speckle tracking imaging (2D-STI), was used for the evaluation of left ventricular (LV) and right ventricular (RV) function in critically ill patients with septic shock and subarachnoid haemorrhage.

The aims were to: 1) investigate the value of strain echocardiography for the early detection of LV and RV dysfunction not diagnosed with conventional echocardiography in severe sepsis and septic shock, 2) to study the effects of norepinephrine on RV systolic function and pulmonary hemodynamics in patients with norepinephrine-dependent septic shock 3) evaluate the use of strain echocardiography for detection of myocardial injury in patients with subarachnoid haemorrhage (SAH) and 4) study the impact of general anaesthesia and positive pressure ventilation (PPV) on RV and LV myocardial longitudinal strain.

The main findings were that LV and RV systolic performances, as detected by 2D-STI, were impaired to a greater extent in septic patients with preserved ejection fraction, when compared to critically ill, non-septic patients with preserved ejection fraction (PEF). In septic shock, norepinephrine-induced increases in mean arterial pressure (MAP), improves RV performance without affecting pulmonary vascular resistance (PVR). The diagnostic performance of global LV strain and regional LV strain to detect myocardial injury in patients with subarachnoid haemorrhage is not superior to that of conventional echocardiography. Finally, general anaesthesia with PPV decreases absolute values of LV and RV longitudinal strain in patients with no heart disease.

In conclusion, strain imaging is useful in the early detection of myocardial dysfunction in sepsis and evaluation of the vasopressor therapy. It does not have better diagnostic performance in detecting global or regional systolic dysfunction in patients with SAH than conventional echocardiography. The impact of anaesthesia and PPV should be taken into consideration when strain imaging is used in ICU patients.

Keywords: Strain echocardiography, left ventricle, right ventricle, septic shock, subarachnoid haemorrhage, norepinephrine

Sammanfattning på svenska

Svår sepsis (blodförgiftning) och septisk chock är starkt associerade med hög sjuklighet och dödlighet hos intensivvårdspatienter. Septisk chock definieras som en kombination av infektion, organdysfunktion och lågt blodtryck trots vätskebehandling. Vid septisk chock orsakar systemisk inflammation ett ihållande lågt blodtryck på grund av att blodkärlen är patologiskt utvidgade och/eller att hjärtats prestation har försämrats. För att höja blodtrycket, används i första hand kontinuerlig tillförsel av kärlsammandragande och hjärtstimulerande läkemedel, oftast noradrenalin.

Subarachnoidalblödning (SAH) är en annan allvarlig typ av sjuklighet hos intensivvårdspatienter som beror på att en kärlmissbildning i hjärnan brister. SAH drabbar relativt unga personer, medelåldern vid insjuknade är c: a 50 år. En fjärdedel av dessa patienter utvecklar hjärtkomplikationer pga ett kraftigt stresspåslag, så kallad stressutlöst hjärtsvikt.

Ekokardiografi används för att bedöma hjärtfunktionen och kontraktionsförmågan mäts med ejektionsfraktionen (EF), vilket är ett grovt mått för bedömning av hjärtats kontraktilitet. Myokardiell strain är en annan relativt ny ekokardiografisk metod för bedömning av hjärtats systoliska funktion. Med strain mäts hjärtmuskelns procentuella förkortning. Strain är en mer känslig parameter än EF för att identifiera hjärtsvikt.

I delarbete I visades att hos patienter med allvarlig sepsis/septisk chock, diagnosticerades systolisk hjärtdysfunktion i större utsträckning med strain ekokardiografi än med konventionell ekokardiografi. I delarbete II, studerades effekten av noradrenalin på högerkammarens (HK) funktion och lungkärlsmotståndet (PVR). Noradrenalin förbättrade HK funktionen mätt med strain ekokardiografi utan att påverka PVR. I delarbete III visades att strain ekokardiografi inte är bättre än konventionella ekokardiografi för att upptäcka myokardiell skada hos patienter med subarachnoidalblödning. I delarbete IV, påvisades att anestesi med mekanisk ventilation minskar de absoluta värden av myokardiell strain.

Avhandlingen visat att strain ekokardiografi är användbar för tidig upptäckt och för utvärdering av behandling av hjärtdysfunktion hos patienter med septisk chock. Strain:s förmåga att upptäcka hjärtskada hos patienter med SAH är inte jämförbar med konventionell teknik

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Keti Dalla, Caroline Hallman, Odd Bech-Hanssen, Michael Haney, Sven-Erik Ricksten

Strain echocardiography identifies impaired longitudinal systolic function in patients with septic shock and preserved ejection fraction.

Cardiovascular Ultrasound 2015; 13: 30

II. Keti Dalla, Odd Bech-Hanssen, Sven-Erik Ricksten.

Impact of norepinephrine on the afterload and function of the right ventricle in septic shock - a strain echocardiography study.

Submitted

III. Keti Dalla, Odd Bech-Hanssen, Jonatan Oras, Silvana Naredi, Sven-Erik Ricksten.

Speckle tracking-vs conventional echocardiography for the detection of myocardial injury - A study on patients with subarachnoid haemorrhage.

Acta Anaesthesiologica Scandinavica 2018; 63: 365-372

IV. Keti Dalla, Odd Bech-Hanssen, Sven-Erik Ricksten

General anaesthesia and positive pressure ventilation suppress left and right ventricular myocardial shortening in patients without myocardial disease - a strain echocardiography study.

Submitted

Contents

Abbreviations

A-max	maximum flow velocity during late LV filling
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
Ch	chamber
CI	cardiac index
CO	cardiac output
CT	computed tomography
CVP	central venous pressure
DAP	diastolic arterial pressure
DPAP	diastolic pulmonary arterial pressure
E-dec time	peak early LV diastolic flow deceleration time
E-max	maximum flow velocity during early LV diastolic filling
Echo	echocardiography
EF	ejection fraction
FAC	fractional area of change
FiO_2	fraction of inspired oxygen
GLS	global longitudinal strain
HR	heart rate
ICU	intensive care unit
IVRT	isovolumetric relaxation time
LV	left ventricle
LVEF	left ventricular ejection fracti
LVEDV	left ventricular end-diastolic volume
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVESVI	left ventricular end-systolic volume
LVOT	left ventricular outflow track
LVSWI	left ventricular stroke work index
MAP	mean arterial pressure
MPAP	mean pulmonary arterial pressure
NA	not applicable

NE	norepinephrine
PAOP	pulmonary occlusion pressure
PEEP	positive end expiratory pressure
PEF	preserved ejection fraction
PPV	positive pressure ventilation
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
RR	respiratory rate
RV	right ventricle
RVEDAI	right ventricular end-diastolic area index
RVESAI	right ventricular end-systolic area index
RVSWI	right ventricular stroke work index
S`	peak systolic velocity of the tricuspid annulus
SAP	systolic arterial pressure
SAPS III	simplified Acute Physiology Score
SD	standard deviation
SC	septic cardiomyopathy
SOFA	sepsis-related Organ Failure Assessment score
SPAP	systolic pulmonary arterial pressure
SV	stroke volume
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TAPSE	tricuspid annular plane systolic excursion

Introduction

Septic cardiomyopathy

Severe sepsis and septic shock are the most important causes of morbidity and mortality in patients admitted to the intensive care unit [1,2]. Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The organ dysfunction can be represented by an increase in the Sequential Organ Failure Assessment (SOFA) score [3] of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia [4].

Myocardial depression in sepsis has been recognized for over 40 years. The earliest studies using pulmonary artery catheter thermodilution technique showed a common LV depression and sometimes LV dilatation with a potential reversibility within 7-10 days [5,6] . Right ventricular dysfunction has also been reported since 1983 using gated cardiac scintigraphy [7] and later pulmonary artery catheter [8]. Nowadays the myocardial depression in sepsis is denoted as septic cardiomyopathy (SC). It is seen in up to 50% of patients [9] and is characterized by decreases contractility, impaired ventricular response to fluid therapy and in some cases LV and/or RV dilatation [10,11].

In SC, the myocardium is functionally and structurally injured. Endotoxins cause diffuse myocardial edema [12]. Increasing levels of inflammatory cytokines, mitochondrial dysfunction and enhanced nitric oxide (NO) production has been described leading to myocardial cell depression [13-15]. NO is believed to act in the heart by inducing mitochondrial dysfunction [16,17] decreasing the myocyte response to calcium, and downregulating β-adrenergic receptors and thus, resistance to endogenous catecholamines [18]. Thus, the dysregulation of the normal immune response can lead to sepsis-induced cardiomyopathy and multiorgan failure [19].

Septic shock is classified as a type of distributive shock due to peripheral vasodilatation and increased capillary permeability. Fluid treatment to augment cardiac preload has been the primary intervention for severe sepsis/septic shock [10,20] and the ability to restore cardiac output depends on the functional state of the heart. On the other hand, changes in afterload with low systemic vascular resistance (SVR) can improve myocardial systolic function, explaining why a heart with impaired contractility, due to sepsis, may be able to generate normal, or even high cardiac output [21]. Therefore, the early diagnosis of SC is essential for the management of sepsis with fluids, vasopressors and/or inotropic therapy.

Left ventricular ejection fraction (LVEF, stroke volume/left ventricular end-diastolic volume) is the first described parameter for the assessment of SC [5,22]. For more than three decades, 2D- echocardiography has been used to study myocardial dysfunction in severe sepsis, demonstrating impaired LV function in septic shock and a high incidence of global LV hypokinesia with LV dilatation as well as, in some patients, isolated impairment of LV relaxation [11,23-25]. In recent years, the use of deformation analysis of the myocardium (strain echocardiography) have shown that the incidence of RV and LV dysfunction in

septic shock seems to be higher compared to conventional techniques [26,27]. The major limitation of these ICU-trials was the lack of a control group with non-septic critically ill patients, as their cut-off values to define RV and LV dysfunction were based on normal subjects at their institutions.

As it is known, patients admitted to ICU often require sedation and positive-pressure ventilation which may potentially change the LV and RV loading conditions and myocardial contractility. Furthermore, little is known about the combined effects of anesthesia/sedation, positive pressure ventilation and the transition from spontaneous breathing to positive pressure breathing on LV and RV myocardial strain in patients with normal cardiac function. Study I was designed to evaluate the myocardial function in patients with early severe sepsis or septic shock compared to that of another cohort of critically ill trauma non-septic patients using strain echocardiography. The objective of study IV was to gain more information about the influence of general anaesthesia and PPV, per se, on myocardial longitudinal strain values in patients with normal heart function.

Norepinephrine and right ventricular haemodynamics in septic shock

Septic shock is defined as a subset of sepsis, characterized by, after adequate volume resuscitation, the need of vasopressors in order to maintain a normal MAP ≥ 65 mmHg. Norepinephrine (NE) administration increases arterial pressure due to its vasoconstrictor effect and is recommended as the first-choice vasopressor in this group of patients. Concerns have been raised regarding a potentially negative effect of norepinephrine

on myocardial function due to a norepinephrine-induced increase in LV afterload. The RV afterload is frequently elevated in sepsis due to increased PVR particularly in septic patients with associated acute lung injury requiring mechanical ventilation. Norepinephrine has the potential to further increase RV afterload by an alpha-mediated pulmonary vasoconstriction in septic patients. Schreuder et al [28] investigated the effects of catecholamines on RV function using thermodilution technique and concluded that norepinephrine increases the RV afterload by 26% while RV ejection fraction (RVEF) remained unchanged. The study from Martin et al [29], 1994 showed also that NE increase RV afterload without significant alterations on RVEF, while more recent studies have shown that norepinephrine does not increase PVR in norepinephrine-dependent septic or vasodilatory shock [30-32].

To gain more information on the effects of norepinephrine on RV performance in patients with septic shock, study II was designed to investigate the immediate effects of changes in NE infusion rates/MAP levels on RV systolic function and RV afterload by the combined use of strain echocardiography and a pulmonary artery thermodilution catheter.

Subarachnoid aneurysmal haemorrhage and stress-induced cardiomyopathy

Subarachnoid haemorrhage (SAH) is a form of stroke characterized by extravasation of blood into the subarachnoid space. SAH is, in 80 % of all cases, caused by rupture of an intracranial arterial aneurysm. The cerebral aneurysms develop during the course of life indicating that SAH is more of a chronic disease [33,34] with a lot of risk factors affecting the appearance of aneurysms and SAH. It represents approximately 5% of all

strokes with a relative low age of onset, 50-60 years. During the last three decades the mortality has declined, and now nearly 65% of SAH-patients survive the acute phase [34].

Acute cardiac dysfunction is commonly seen in SAH [35,36] ranging from benign electrocardiographic (ECG) abnormalities[37], mild elevation of cardiac biomarkers [38] to severe heart failure [39,40]. The cardiac dysfunction in SAH, also denoted as stress-induced cardiomyopathy (SIC), is characterized by transient regional LV systolic dysfunction, caused by both excessive circulating levels of catecholamines and substantial local release of norepinephrine.

Acute cerebrovascular injury leads to increased intracranial pressure and autonomic disturbance [41 42]. The massive release of catecholamines into the circulatory system, and also locally, at the myocardial sympathetic nerve terminals leads to: 1) A continuous stimulation of the adrenergic receptors followed by excessive calcium release and a prolonged actin-myosin interaction [43,44]. This results in an inability of cardiac muscle fibers to relax leading to myocardial cell injury and death [45]. 2) A negative inotropic response due to β2-adrenoceptor mediated Gi protein pathway activation by the excessive levels of epinephrine. Normally epinephrine binds to β2-adrenoceptors and activates Gs proteins. The switch between the Gs and Gi protein signaling pathway, at excessive levels of epinephrine, is termed stimulus trafficking [46]. This mechanism is theoretically supported by the study of Dujardin at al 2001, where the autopsy of patient with SIC after brain damage showed poor correlation between areas of LV hypokinesia and areas of cardiac necrosis [47].

The appearance of cardiac dysfunction in SAH, has been reported to be associated with poor neurological outcome[48]. Early release of cardiac

biomarkers is associated with increased risk of cardiopulmonary complications, delayed cerebral ischemia, or poor functional outcome at discharge [49]. The reported frequency of elevated cardiac troponin at admission is 20%-40% [50,51] and the reported prevalence of LV dysfunction ranges from 8% to 27% in SIC [52]. Conventional two-dimensional (2D) echocardiography has been the method of choice for the evaluation of global and regional LV function in this group of patients. However, assessment of regional wall motion abnormalities (RWMA) requires extensive experience and there is a substantial inter-observer variation [53]. Myocardial deformation, strain echocardiography, has been introduced for the detection of LV dysfunction in the recent years. The value of myocardial strain, however, has not been evaluate in this group of patients.

Strain echocardiography

Strain echocardiography by speckle-tracking is a relatively new and promising method for assessment of myocardial systolic function, as it can differentiate between active and passive (scar) movement of myocardial segments. Speckle-tracking echocardiography measures the relative movement of myocardial gray-scale alterations (speckle patterns) and can thereby quantify systolic deformation, strain, describing percentage changes in myocardial segment length. Myocardial strain is defined as a fractional change in length between 2 time points, end-diastole ($L0$) and end-systole (L) and calculated as: $\varepsilon = (L-L0)/L$ or $\Delta L/L0$. Strain in echocardiography describes deformation: lengthening, shortening

or thickening. Subsequently, strains are calculated from each LV segment in circumferential, longitudinal, or radial directions [54,55] (Fig.1). The most frequently used strain variable is global longitudinal strain (GLS), which has been introduced for the detection of LV dysfunction not appreciated by conventional echocardiography [56,57]. Negative values of longitudinal strain indicate myocardial contraction.

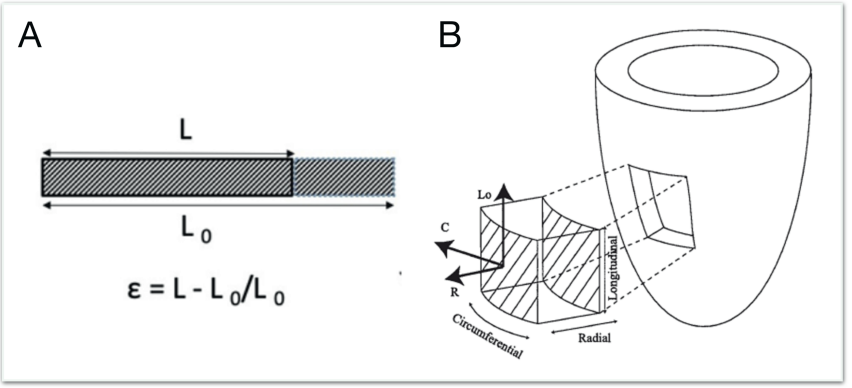

Fig. 1 *A: The equation for the calculation of stain. B: The three types of strain, radial, circumferential and longitudinal according to the heart coordinate system (from Ref. 55)*

In this thesis the RV free wall strain is presented as the mean of the three segments of the RV free wall (basal, mid wall, apical) using the four-chamber view (Fig.2). The peak longitudinal LV strain is determined using the three apical projections and presented as the mean of the 18 segments (Fig.3).

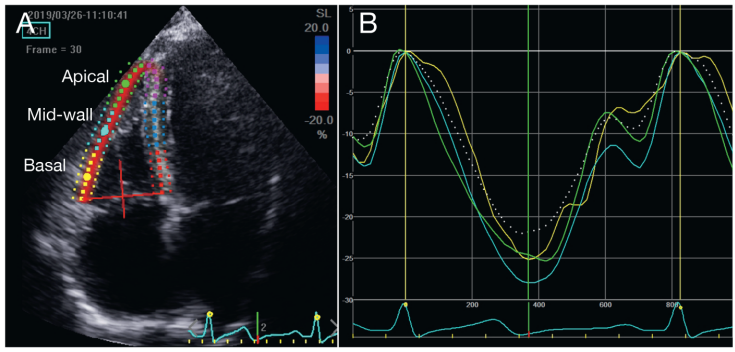

Fig. 2 *Strain analysis of RV free wall*

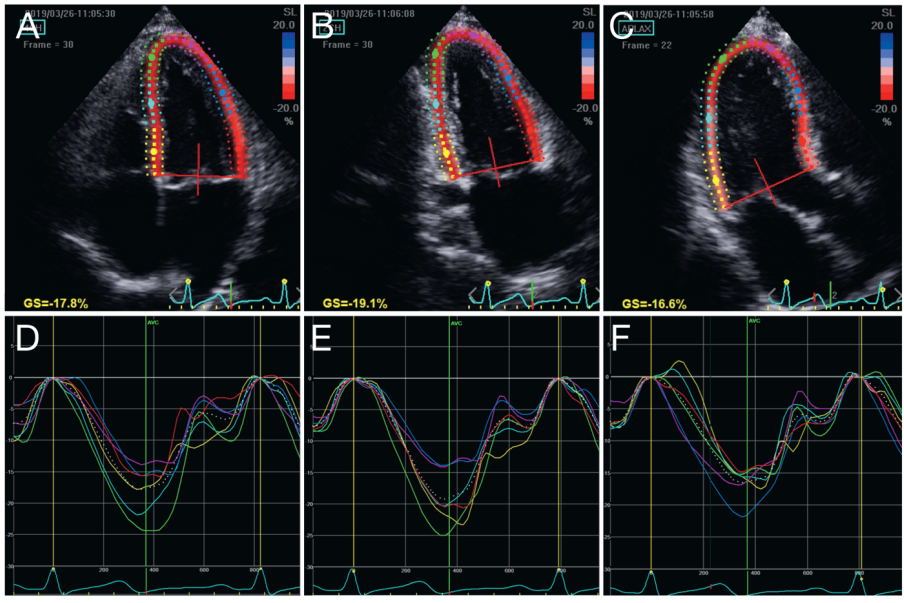

Fig. 3 *Strain analysis of LV using three apical projections.*

What was known before this thesis?

Paper I Speckle tracking imaging (STE) detected impaired ventricular performance in children with sepsis. (Basu et al. Pediatr Crit Care Med 2012)

STE may unmask systolic dysfunction not seen with conventional echocardiography. RV dysfunction, especially when severe, was associated with high mortality in patients with severe sepsis or septic shock. (Orde et al. Critical Care 2014)

Lack of a control group of ICU patients with on-going multimodal intensive care treatment.

Paper II Norepinephrine may improve the RV oxygen supply/demand ratio and RV ejection fraction with a concomitant increase in PVR. (Schreuder et at . Chest 1989)

Norepinephrine exerted a favorable effect on right ventricular function depside the increase in PVR in septic shock. (Martin et al. Intensive Care Med 1994)

In septic shock norepinephrine infusion to MAP 65-75 mmHg increased significantly pulmonary and systemic vascular resistance index (PVRI, SVRI), left ventricular stroke work index (LVSWI) and right ventricular stroke work index (RVSWI). (Albanèse at al. Crit Care Med 2005)

Data from studies where the renal function was investigated in septic and vasodilatory shock by increasing mean arterial pressure with norepinephrine did not show significant changes in PVRI. (Bourgoin et al. Crit Care Med 2005, Redfors et al. Crit Care Med 2011)

Controversial results regarding the impact of NE on RV afterload.

Paper III GLS allows a more sensitive detection of LV systolic impairment in SAH patients with preserved EF.(Cinotti et al Intensive Care med 2016)

The diagnostic performance of GLS and regional longitudinal strain (RLS) to detect myocardial injury in SAH was not investigated.

Paper IV Mechanical ventilation with increasing levels of PEEP in ICU patients causes a decrease in RV strain. (Franchi et al. Biomed Res Int 2013)

No data on the effects of general anaesthesia and PPV on LV, RV strain values in non-ICU patients with normal cardiac function.

Aims

Paper I

To evaluate left ventricular global longitudinal myocardial function in patients with early severe sepsis or septic shock compared to that of trauma non-septic patients using 2D speckle tracking strain echocardiography

Paper II

To investigate the immediate effects of norepinephrine on right ventricular systolic function and afterload by the combined use of strain echocardiography and a pulmonary artery thermodilution catheter in patients with norepinephrine-dependent septic shock.

Paper III

To compare the diagnostic performance of conventional- vs 2D-speckle tracking echocardiography in patients with subarachnoid haemorrhage for the detection of myocardial injury.

Paper IV

To study the influence of general anaesthesia and positive pressure ventilation on left and right ventricular longitudinal strain in patients without myocardial disease.

Methods

Patients

In this thesis, using myocardial deformation imaging, we studied the heart function of patients with severe sepsis and septic shock (I, II), patients with subarachnoid haemorrhage (III) and patients receiving general anaesthesia and PPV for non-cardiac surgery (IV).

Paper I, II

In study I we retrospectively performed a myocardial deformation analysis of echocardiograms from 48 adult patients with early, severe sepsis/septic shock and compared the systolic myocardial strain with the myocardial strain of 24 ICU patients with major trauma. The inclusion criteria were: a) age ≥18 years b) all patients from the sepsis group fulfilled criteria for severe sepsis and septic shock c) no previous history of cardiac disease d) the echocardiograms were obtained within 48 h after the arrival to the ICU in all patients e) the echocardiographic image quality was acceptable for off-line strain analysis. Additionally, a reference group with normal echocardiograms were obtained from the institutional echocardiographic database. The trauma group and healthy controls were matched by gender and age to the septic patients.

Study II is a prospective cross-over study were 11 patients with early septic shock have been included. The inclusion criteria were: a) age ≥ 18 years b) verified infection and SOFA score > 2 c) need of norepinephrine to maintain MAP > 65 mmHg d) adequate fluid resuscitation to achieve a

stroke volume variation < 12% before the inclusion e) serum lactate > 2 mmol/l, f) all patients were in need of mechanical ventilation and sedated with fentanyl and Propofol infusion. The exclusion criteria were: 1) severe circulatory instability refractory to treatment and/or need of inotropic agent 2) poor quality of echocardiographic images and 3) patients having a pacemaker, premorbid heart disease, previous cardiac surgery, severe tricuspid or mitral regurgitation.

Paper III

Seventy-one patients with verified SAH were included. The inclusion criteria were aneurysmal SAH and age ≥ 18 years. Diagnosis of aneurysmal SAH was made with brain computed tomography (CT) scan and confirmation of aneurysmal SAH with CT angiography or digital subtraction angiography (DSA).

Exclusion criteria were 1) patients in whom aneurysmal SAH diagnosis was not confirmed, 2) patients with a previous SAH, stroke, traumatic brain injury and other intracerebral processes 3) patients with pacemaker, coronary artery disease, heart failure or previous cardiac surgery 4) patients with imminent clinical signs of brain death and 5) patients with poor-quality of echocardiographic images for strain analysis.

Paper IV

Twenty-one patients, ASA I-II (American Society of Anesthesiologists physical status classification system,1941), scheduled for non-cardiac surgery under total intravenous anesthesia were included. The exclusion criteria were 1) history or signs of cardiac, pulmonary or systemic disease, 2) any cardiac or antihypertensive medication and 3) age < 18 year

and 4) a body mass index ≥ 30 kg m^{-2}. We performed echocardiographic examination before and 10- 15 minutes after induction of anesthesia, intubation and start of PPV. General anaesthesia was induced and maintained by continuous infusion of Propofol and Remifentanil.

Haemodynamic measurements

Arterial blood pressure

In study I, haemodynamic variables were obtained from the patient' s intensive care chart at the time of the echocardiographic examination. In studies I, II, and III, systolic, mean and diastolic arterial blood pressure were measured invasively by a catheter in the radial artery. In study IV, arterial blood pressure was measured non-invasively using an occluding upper-arm cuff of suitable size in the supine position.

Pulmonary and systemic haemodynamics

In study II, each patient underwent a catheterization with a 7.5 F pulmonary artery catheter (Baxter Healthcare, Irvine CA). Cardiac output (CO) and stroke volume were measured by thermodilution technique (mean of three 10-ml ice-cold saline injections) and indexed to the body surface area to receive cardiac index (CI) and stroke volume index (SVI). Heart rate, arterial blood pressure, systolic and mean pulmonary arterial pressure (MPAP) and central venous pressure (CVP) were continuously measured. Pulmonary arterial occlusion pressure (PAOP) was measured intermittently. The transducers were referenced to the midaxillary line. Pulmonary. SVRI, PVRI, RVSWI and LVSWI were calculated according to standard formulas.

$PVR = [(MPAP - CVP)/CO] x\ 80$

$SVR = [(MAP - PCWP)/CO] x\ 80$

$RVSWI = SV \times (MPAP - CVP) \times 0.0136 / BSA$

$LVSWI = SV \times (MAP - PCWP) \times 0.0136 / BSA$

Arterial elastance

In studies II, IV, effective arterial elastance (E_a), as a measure of total left ventricular afterload, defined as the ratio of left ventricular (LV) end-systolic pressure and stroke volume [58,59], was calculated as:

$Ea = 0.9\ x\ SAP / SV$

In study II, effective pulmonary arterial elastance (Epa), as a measure of total right ventricular afterload, reflecting both resistive and pulsatile components [60] of pulmonary arterial circulation was calculated as:

$Epa = (MPAP - PCWP) / SV$

Echocardiographic measurements

Conventional echocardiography

Transthoracic 2D echocardiographic examination was performed in all study patients. In study I, echocardiograms were obtained using one of three different ultrasound machines (Vivid E9, GE Healthcare, USA, iE33, Philips Healthcare, Netherlands and X300, Siemens, Germany). In II, III, IV the ultrasound scanner system used was Vivid E9, General Electric Medical System, Horten Norway with a 5-MH transducer.

The following echocardiographic loops were recorded with a frame rate > 50 frames /sec: left parasternal long- and short axis, apical two-, three- and four-chamber views. Standard measurements of LV systolic function included LV volumes, LVEF by the modified Simpson's rule, time velocity integral in the LV outflow tract (TVI-LVOT) and stroke volume (π x LVOT radius^2 x TVI-LVOT). Mitral, aortic and pulmonary vein Doppler flow profiles were recorded for measurements of LV isovolumetric relaxation time, peak early LV diastolic flow deceleration time (E-deceleration time), maximum flow velocity during LV early (E) and late (A) diastolic filling and pulmonary vein peak systolic (S) and peak diastolic (D) flow velocities. The ratios of E/A and S/D were calculated. Impaired LV function was defined as a LVEF < 50%. The presence of RWMA in study III was identified [61] by an experienced investigator in echocardiography, who was blinded to the information of plasma levels of hsTnT.

Strain echocardiography

Strain measurements were performed off-line in the four-chamber, three- and two-chamber views. In study I, the stored images were analyzed in an offline system (Syngo Velocity Imaging System, Siemens, Germany), in II, III and IV the EchoPAC workstation version 201, (GE Medical Systems, Milwaukee, Wisconsin, USA) was used.

Myocardial strain (S) is presented as fractional change (%) in length between two time points, end-diastole (L_0) and end-systole (L) and calculated as: $(L - L_0)/L_0 \times 100$. Negative values of strain indicate myocardial shortening. From four-chamber, three- and two-chamber views we determined LV GLS and from four-chamber views the RV-free wall strain.

Experimental protocols

Paper I

In this retrospective study, standard echocardiographic examinations of ICU-patients with severe sepsis or septic shock and ICU-patients with major trauma as well as healthy controls were retrospectively identified and then reanalysed for assessment of myocardial strain using speckle-tracking echocardiography.

Paper II

In this prospective cross-over study on mechanically ventilated patients with septic shock, the RV function and pulmonary hemodynamics were studied at three different target levels of MAP applied in random order: 60 mmHg, 75 mmHg and 90 mmHg, using pulmonary artery catheter, conventional and strain echocardiography.

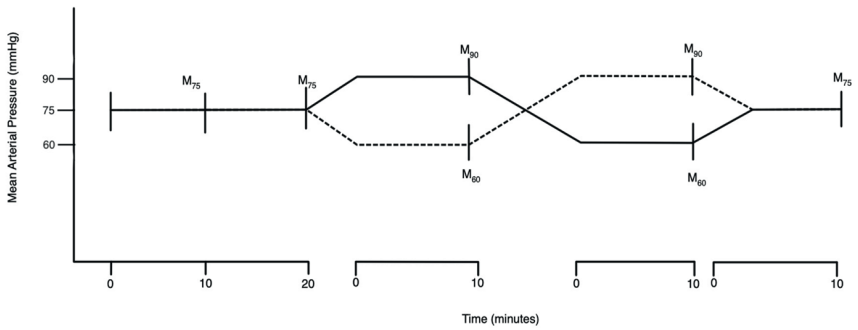

Fig. 4 *Experimental protocol study II*

Paper III

In this observational study, strain and conventional echocardiography was used for detection of myocardial injury within 48 hours from the ICU arrival in 71 unselected patients with verified SAH. Myocardial injury was defined as a peak hsTnT 90 ng/l 62. A reduced LV GLS was defined as GLS -15%. Two cut-off levels were used for the definition of regional longitudinal strain (RLS), ie when segmental strain was > -15% (liberal) or > -11% (conservative) in ≥ 2 adjacent segments.

Paper IV

Conventional and strain echocardiography was performed approximately 60 minutes before and 10-15 min after the induction of anaesthesia in patients with no cardiac medication scheduled for a non-cardiac surgical procedure. General anaesthesia was induced and maintained by propofol and remifentanil. The examinations included apical four-, three- and two-chamber projections, mitral and aortic Doppler flow velocities and tissue Doppler velocities of tricuspid annulus. LV end-systolic elastance (Ees) and aortic elastance were determined (Ea).

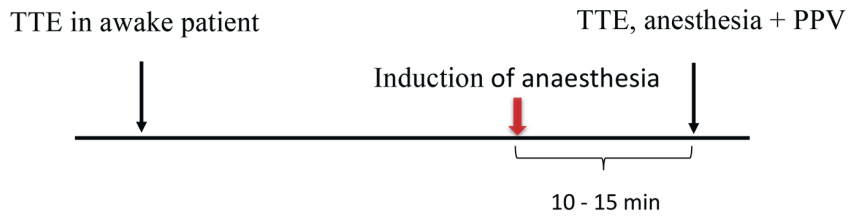

Fig. 5 *Experimental protocol study IV*

Statistics

In study I, independent Student' s t-test was used to compare differences between septic and trauma patients. Categorical data were compared using Fisher' s exact test. Linear regression analysis was applied to quantify the strength of the relationship between global LV systolic strain and LV ejection fraction for septic and trauma patients.

In study II, an analysis of variance (ANOVA) for repeated measurements was used to evaluate the haemodynamic and echocardiographic effects of norepinephrine-induced variations in mean arterial pressure.

In study III, tests of sensitivity, specificity, positive (sensitivity/(1-specificity)) and negative likelihood ratios ((1-sensitivity)/specificity) for LVEF, GLS, RWMA, and RLS, were assessed to detect myocardial dysfunction, defined as hsTNT ≥ 90 ng/l. Interobserver agreement for the detection of RWMA:s was assessed by calculation of Cohen's kappa coefficient

In study IV, paired Student's t-test was used to compare the means before and after induction of anaesthesia.

Results

Paper I

In this study there were no significant differences between the sepsis and the trauma group with respect to gender, body weight, need for mechanical ventilation or ICU length of stay. Sepsis patients were older and sicker with a higher SAPS II score and a more frequent use of vasopressor therapy. Pneumonia was the most common cause of sepsis, followed by abdominal sepsis, necrotizing fasciitis, and urosepsis.

Haemodynamic variables

The heart rate was higher while systolic and mean arterial pressures and SVR were significantly lower in the sepsis group compared to the trauma group. CVP was significantly higher in the sepsis group compared to the trauma group, while CVP did not differ significantly comparing patients from the two groups with preserved ejection fraction (PEF), sepsis-PEF and trauma-PEF. There was no difference in right ventricular systolic pressure between groups.

Echocardiographic variables

Conventional echocardiographic data showed that in septic patients LV ejection fraction was significantly lower whereas the stroke volume, cardiac output and variables for diastolic function did not differ. There were no differences in conventional echocardiographic variables between the sepsis-PEF and trauma-PEF group.

Myocardial deformation analysis showed that the LV global longitudinal strain was 8% lower in the septic groups (all) compared to trauma group (all). In the sepsis-PEF group, LV global strain was 14% lower than the trauma-PEF group. In septic patients with preserved LVEF 50 % had a depressed LV global longitudinal function compared to 8.7 % in the respective trauma group (Fig. 6). RV strain was also lower (21%) in the septic (all) compared to the trauma group (all) as well as in the sepsis-PEF (17%) compared to the trauma-PEF.

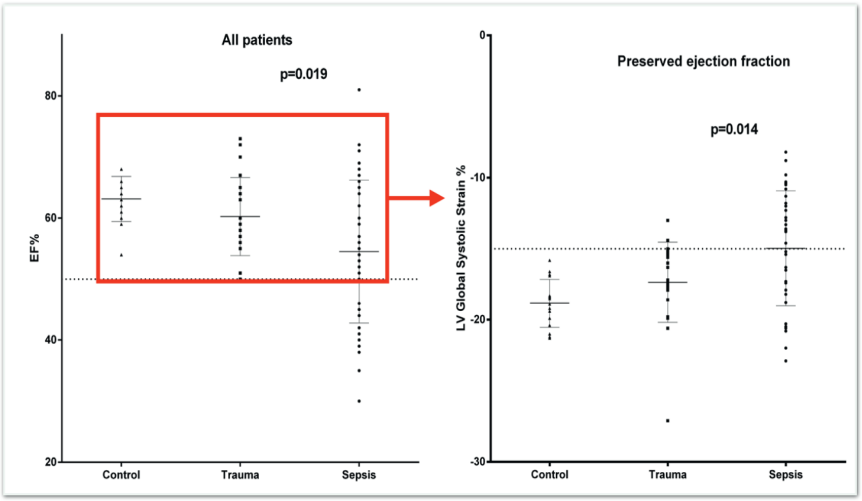

Fig. 6 *Shows that 50% of septic patients with preserved LVEF had a depressed LV global longitudinal function according to the strain analysis compared to 8.7 % in the respective trauma group*

Paper II

Haemodynamic variables

ANOVA for repeated measurements of haemodynamic variables showed

that higher infusion rates of norepinephrine were accompanied by higher SVI, MPAP, PCWP, CVP, SVR, LVSWI and RVSWI, and lower PVR/SVR ratio. PVRI and heart rate were not affected by norepinephrine. There was a trend for higher CO and CI at higher doses of norepinephrine. Ea increased by 36%, while Epa was not significantly affected (Fig.8).

Echocardiographic variables

Impaired RV function, defined as a RV free wall strain > -24%, was seen in 64% of patients at baseline (MAP 75). Higher infusion rates of norepinephrine were accompanied by improved RV function as reflected by an increase in RV free wall strain (Fig.7), increase in TAPSE and increase of tricuspid annular systolic velocity S´. SVI increased with norepinephrine. There was a trend for higher CO, CI and LVEDV at higher doses of norepinephrine, while LV ejection fraction and variables of diastolic function, were not affected. CVP and RVEDAI as measures of RV preload increases with higher infusion rates of norepinephrine.

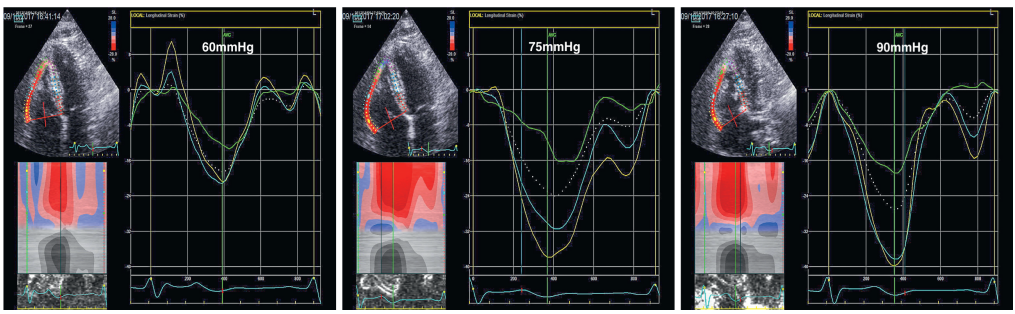

Fig. 7 *Norepinephrine infusion improved RV systolic function as assessed by the RV free wall longitudinal strain.*

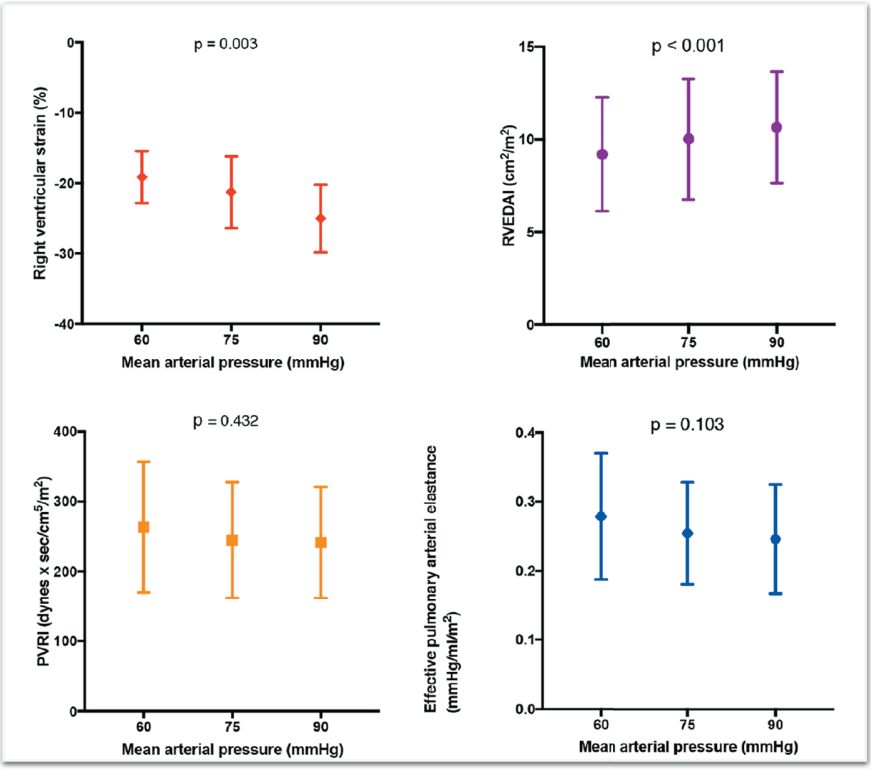

Fig. 8 *Shows the significant increase of the absolute value of RV-strain and right ventricular end-diastolic area index (RVEDAI) with increased doses of norepinephrine. Pulmonary vascular resistance index (PVRI) and effective pulmonary arterial elastance were not significantly affected by higher doses of norepinephrine.*

Paper III

Patients with subarachnoid haemorrhage and myocardial injury (hsTnT ≥ 90 ng/L) were mostly females needed mechanical ventilation and use of vasopressors. They also had a higher World Federation of Neurological Surgeons (WFNS) for SAH grading score on arrival and higher levels of NTpro BNP compared with patients with low levels of hsTnT.

Echocardiographic variables

Patients with increased hsTnT had a higher incidence of impaired LVEF, stroke volume and hypokinesia (RWMA). A number of 1212 segments were judged as having normal contractility and 66 as impaired contractility. Among patients with elevated hsTnT, 12 patients had RWMA, while none of the patients with low hsTnT < 90 ng/L had RWMA (Fig 9). The distribution of $RWMA_s$ in the basal, mid-ventricular and apical segments were: 3%, 67% and 30%, respectively.

Patients with subarachnoid haemorrhage and myocardial injury had lower LV GLS compared to those with hsTnT < 90 ng/L. Ten patients with elevated hsTnT (56%) had low LV GLS compared to two patients (4%) from the group without myocardial injury, hsTnT < 90 ng/L (Table 1). The specificity and sensitivity of GLS was comparable to that of LVEF and RWMA (Table 2).

Speckle tracking analysis of 1253 segments identified 288 segments with impaired longitudinal systolic strain. The specificity and sensitivity of regional longitudinal strain to detect myocardial injury were 54% and 94%, respectively (Table 2). The intra- and inter-observer variability for assessment of RLS were 20.2% and 22.3%.

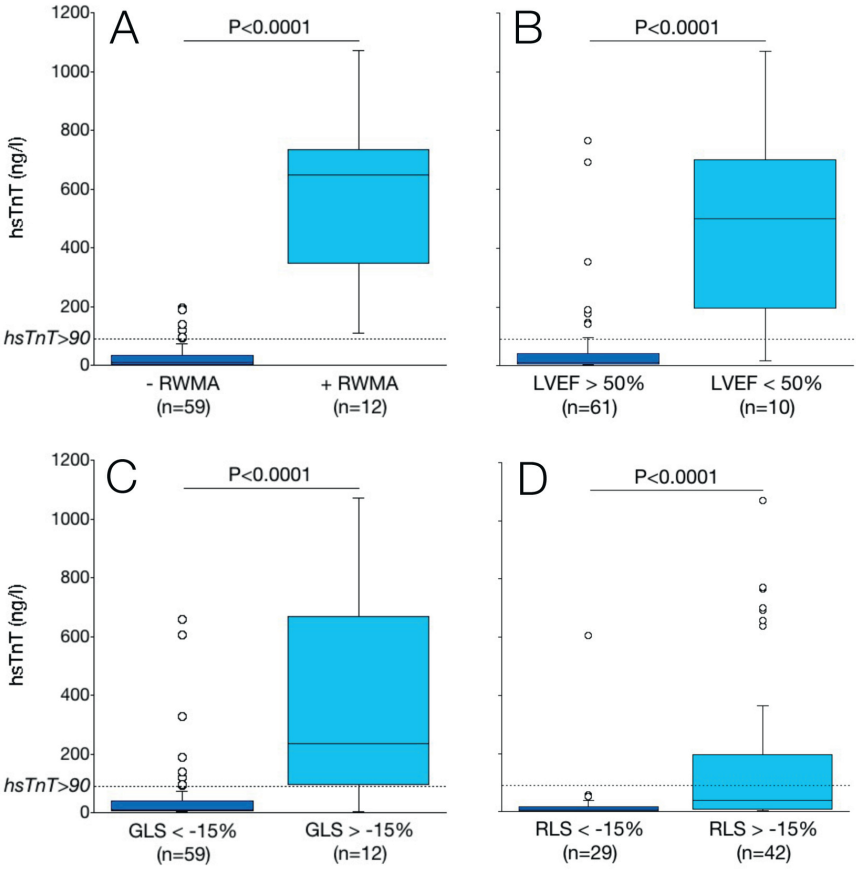

Fig. 9 *Shows how the distribution of high sensitive troponin T (hsTnT) related to the presence of regional wall abnormalities (RWMA), reduced left ventricular ejection fraction (LVEF), global longitudinal strain (GLS) and regional longitudinal strain (RLS).*

Table 1. Systolic LV function according to conventional and strain echocardiography values

	All patients n =71	Low hsTnT n = 53	High hsTnT n = 18	p-value Low- vs high hsTnT
LV ejection fraction (EF %)	61.2 ± 10	64 ± 6	52 ± 13	0.003
EF <50 % (n, %)	10 (14%)	1 (2 %)	9 (50%)	<0.001
Stroke volume (ml)	76 ± 21	80 ± 20	65 ± 21	0.010
Cardiac output (l/min)	5.0 ±1.4	5.1 ± 1.4	4.5 ± 1.3	0.112
Cardiac index	2.7 ± 0.8	2.8 ± 0.8	2.5 ± 0.7	0.223
RWMA (n, %)	12 (17 %)	0	12 (67 %)	<0.001
LV global longitudinal strain (%)		20.1 ± 2.4	14.3 ± 4.4	<0.001
LV global longitudinal strain > -15% (n, %)	12 (17 %)	2 (4 %)	10 (56 %)	<0.001
Regional longitudinal strain > -15% (n, %)	42 (59 %)	25 (47 %)	17 (94 %)	<0.001
Regional longitudinal strain ≥ -11% (n, %)	20 (28 %)	10 (19 %)	10 (56 %)	0.007

Table 2. Diagnostic performance of conventional and strain echocardiography for the detection of myocardial injury (hsTnT ≥ 90 ng/l)

	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
EF <50%	50% (30 - 70)	98% (90 – 100)	26 (4 – 195)	0.50 (0.3 - 0.8)
GLS> -15%	56% (30 - 70)	96% (90 – 100)	15 (4 - 61)	0.46 (0.3 – 0.8)
RWMA	67% (40 - 80)	100% (90 – 100)	*	0.33 (0.2 – 0.6)
RLS> -15%	94% (70 – 100)	54% (40 – 60)	2.0 (1.5 – 2.7)	0.1 (0.01 - 0.7)
RLS ≥ -11%	55% (30 - 70)	81% (70 – 100)	2.9 (1.5 – 5.9)	0.54 (0.3 – 0.9)

Paper IV

Haemodynamic variables

Total intravenous anaesthesia with positive pressure ventilation was associated with a significant reduction of arterial blood pressure. The fall in arterial blood pressure was accompanied by a decrease in stroke volume, cardiac output and heart rate. Systemic vascular resistance and end-systolic arterial elastance were not significantly affected.

Echocardiographic variables

Left ventricular systolic function as assessed by GLS decreased, while LVEF was not significantly affected. Preload indices such as RV end-diastolic area index, LV end-diastolic volume index, E-max and A-max decreased after induction of anaesthesia with PPV.

Right ventricular systolic function assessed by RV free wall strain, tricuspid annular peak systolic velocity, tricuspid annular plane systolic excursion S` and RV fractional area change decreased after induction anaesthesia.

At the baseline echocardiographic examination, LVEF was decreased (< 50%) in 4 of 21 patient, GLS (> -16%) was impaired in 1 patient and RV free wall strain (> -24%) in 3patents. The general anaesthesia and PPV increased the number of patients with impaired GLS and RV free wall strain to 6 and 8 patients respectively.

Table 3 The effect of anaesthesia and PPV on MAP and systolic function of left and right ventricle

	MAP (mmHg)	HR (bpm)	SVI (ml/m2)	CI (L/min/m^2)	GLS	RV free wall strain
Baseline	91 ± 14	72 ± 16	37 ± 11	2.6 ± 0.7	-19.1 ± 2.3	-26.8 ± 3.9
During anaesthesia	65 ± 8	67 ± 14	32 ± 9	2.0 ± 0.7	-17.3 ± 2.9	-24.1 ± 4.2
Mean difference, SD	26 ± 15	5 ± 11	6 ± 5	0.6 ± 0.5	1.7 ± 2.0	2.6 ± 3.2
p-value	<0.001	0.038	<0.001	<0.001	<0.001	0.001

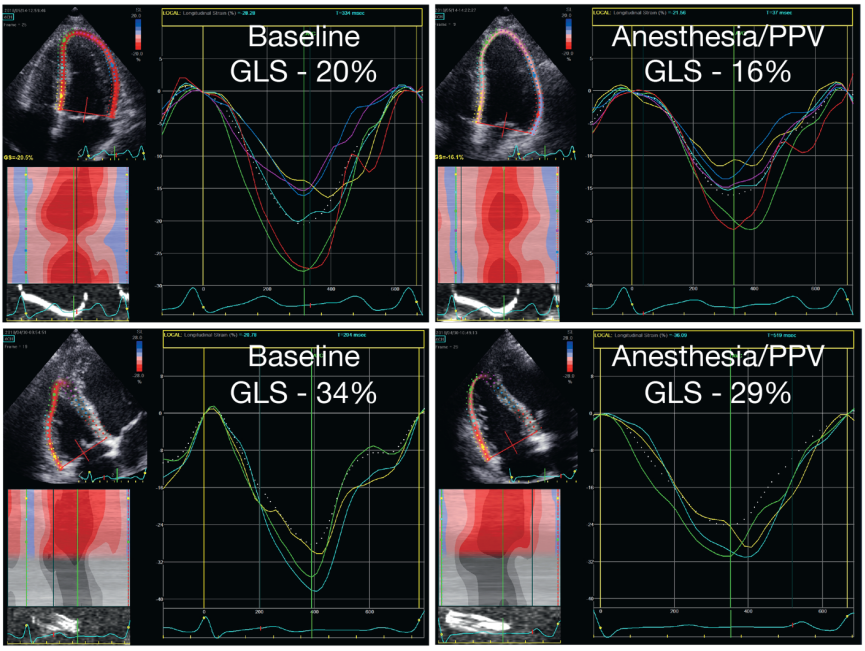

Fig. 10 *Shows the reduced LV GLS and RV-free wall strain after induction of general anaesthesia and PPV*

Discussion

Assessment of LV systolic function by conventional echocardiography.

Left ventricle is the pressure generator for the blood supply to the body with a thick-walled chamber, which does not match easily measurable geometric shape. In a healthy heart, the LV chamber consists of a cylindrical and an ellipsoid part. In diseased states, this shape may change globally or regionally, and this is the primary reason for the difficulty in measuring its dimensions and volumes during different phases of cardiac cycle using echocardiography. Global LV function can be assessed using changes in the LV dimensions and volumes between LV diastole and systole. The recommended calculations for assessment of global LV systolic function are: fractional shortening (FS), fractional area of change (FAC), ejection fraction (LVEF) and stroke volume (SV) or cardiac output (CO).

Fractional shortening of LV is calculated by the following equation: FS = LVIDd – LVIDs/LVIDd × 100%. Where, LVIDd is LV internal diameter at end diastole and LVIDs is LV internal diameter at end systole. The FS has limited clinical use as it a) measures myocardial function in just one plane and describes only the contractility of inferior and anterior walls, b) does not represent global LV shortening in the presence of regional wall motion abnormalities (RWMA), c) overestimates the overall LV function because the measurements of LV diameter are made at basal segments and as it is known these segments often contract adequately even in the presence of a significant LV systolic dysfunction and d)

measurements are greatly influenced by preload and afterload of LV.
FAC is calculated using LV's end diastolic and end systolic area from the planimetry of short axis views according to the following formula: FAC = LVEDA − LVEDS/LVEDA × 100%. Normal value is considered at FAC > 35% and severe LV systolic dysfunction at FAC < 15% [63]. It is a simple measurement and easy to obtain. It has been shown that there is a good correlation with LVEF measured using radionuclide angiography and scintigraphy, especially when EF is < 45% [64]. It is very commonly used for assessing LV preload by TEE [65]. The use of the method is limited by the fact that it is highly preload and afterload-dependent, its asses contractility in one plane and at one level, usually the mid-papillary level and that the presence of severe RWMA in the apical or basal segments would severely overestimate LVEF.

LVEF is a measure in echocardiography, which has become the most important metric of LV systolic function utilized by clinicians. Clinical decision-making and patient management in a number of cardiovascular conditions largely rely on LVEF [66-68]. In patients with heart failure with reduced LVEF, ejection fraction has proved to be an important predictor of clinical outcome [66,69,70]. However, the discriminatory value of LVEF in predicting morbidity and mortality was limited in LVEF values over 45% [69]. LVEF is measured indirectly from estimations of LV volume. Volumetric measurements are based on tracings of the interface between the endocardium and the LV cavity in the apical four- and two chamber views. The calculation of LVEF is highly dependent on the optimal acquisition and quality of the echocardiographic image. It is also a time-consuming process due to the manual tracing of the endocardium. Furthermore, it is also highly preload and afterload-dependent with relatively high inter- and intra-observer variability [71,72].

Assessment of systolic LV function by myocardial strain

Myocardial fiber architecture of the LV consists of longitudinal fibers, and mid-myocardial layers formed by circumferential fibers [73] (Fig.11). In systole, the shortening of longitudinal fibers causes the displacement of the LV basal plane towards the apex, while the shortening of circumferential fibers induces an inward deformation of the LV myocardium. The most frequently used strain variable, global longitudinal strain (GLS), measures the contractile function of longitudinally oriented subendocardial myocardial fibers. In various clinical conditions impairment of longitudinal function precedes the reduction in circumferential indices, giving rise to subclinical impairment of LV systolic function [74]. The function of circumferential layer can, to a certain extent, compensate for the initial reduction in longitudinal function, as both LVEF and fractional shortening are often normal despite the fact that longitudinal function can be significantly impaired [75] (Fig 12). However, conventional variables, such as LVEF or fractional shortening, reflect the geometric change of LV rather than the contractile function of the myocardium. Furthermore, LVEF is a volumetric technique which indirect reflects the function of both longitudinal and circumferential LV fibers, without the ability to distinguish functional impairment of one of these components.

A recent study [72] tested the variability of GLS by speckle-tracking obtained by different vendors using different ultrasound machines and software packages. The study showed that the reproducibility of GLS was good and in many cases superior to the reproducibility of LVEF. However, the variation between vendors was statistically significant.

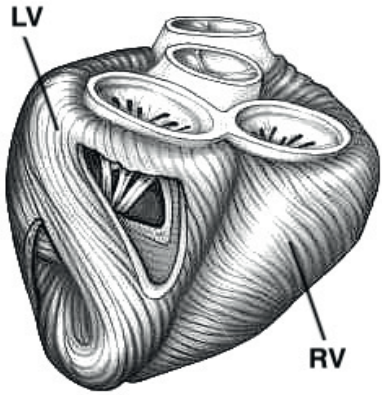

Fig.11 *Left ventricular myocardial fiber architecture, posterior view.*

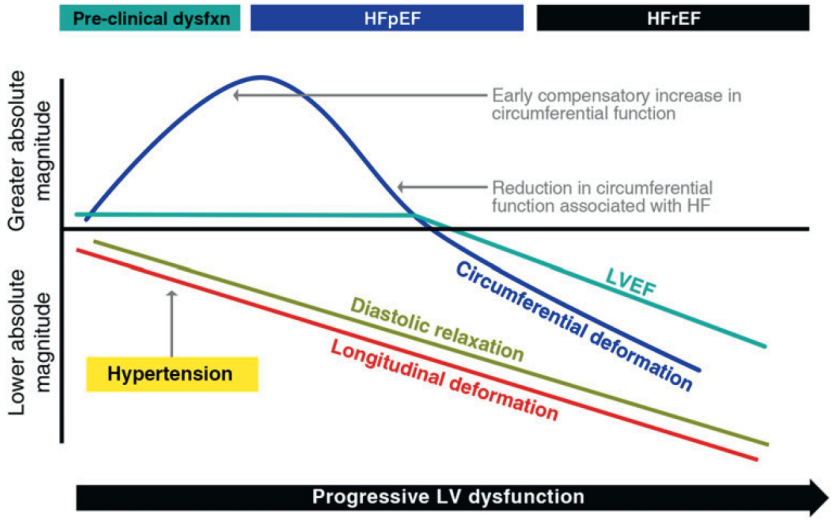

Fig. 12 *Shows the transition from heart failure with preserved ejection fraction (HFpEF) to heart failure with reduced ejection fraction (HFrEF) in arterial hypertension. The progressive changes in left ventricular function are seen as reduced longitudinal shortening with compensatory increased circumferential shortening while the LVEF is preserved. Impairment of circumferential deformation, and of LVEF occurs, inducing the transition from HFpEF to HFrEF (from Ref. 75)*

Assessment of systolic RV function by echocardiography

The right ventricle in the normal heart is the most anteriorly situated cardiac chamber with thinner wall than the LV myocardium. Normal RV contraction is a peristaltic wave directed from RV inflow tract to infundibulum (Fig.13). Longitudinal shortening is the major contributor to overall RV performance.

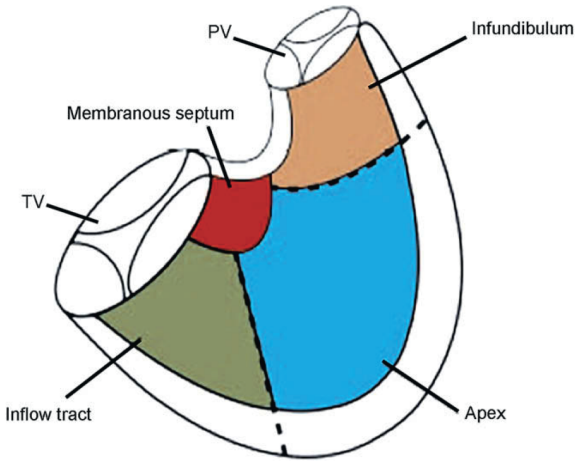

Fig. 13 *The right ventricle with 3 major chamber components; inflow tract, infundibulum (outflow tract), and apex.*

Among available imaging techniques, 2D echocardiography remains the most widely used tool for RV assessment [61,76]. A quantitative method using M-mode echocardiography in order to assess longitudinal RV function is the measurement of the tricuspid annular plane systolic excursion (TAPSE), which estimates the level of the systolic excursion of the lateral tricuspid valve annulus toward the apex in the four-chamber view. This echo-parameter has demonstrated an excellent correlation with radionuclide ventriculography-derived RV EF ($r = 0.92$)[77] and proved to be o

good predictor of prognosis in heart failure [78]. Limitation of the method is that the cursor should be optimally aligned along the direction of movement of the tricuspid lateral annulus in the apical four-chamber view. Values <17 mm are highly suggestive of RV systolic dysfunction.

RV FAC estimates global RV systolic function by tracing the RV area in end-diastole and end-systole. Values < 35% indicates RV systolic dysfunction. A right ventricular-focused view is needed to ensure that the entire RV is visualized in the image sector.

DTI-derived tricuspid lateral annular systolic velocity (S`) is easy to measure and reproducible. It has been shown to correlate well with other measures of global RV systolic function. Age-related cut-off values have been reported in a large sample of healthy subjects[79]. Like TAPSE, S` can be influenced by the overall cardiac motion. A good alignment of the Doppler cursor is necessary to avoid velocity underestimation. S′ < 9.5 cm/sec indicates RV systolic dysfunction [61].

More recently, it has been shown that myocardial deformation imaging techniques are able to better describe regional contractility of the right ventricle diminishing the influence of the overall cardiac motion [80,81]. Strain measurement may prove useful as an early indicator of RV dysfunction in the course of pulmonary arterial hypertension[82]. It can also detect early alterations of RV function in patients with systemic sclerosis and normal pulmonary pressures [83]. RV strain correlates well with radionuclide RV EF. A cut-off point of systolic RV strain of 25% can predict a lower than 50% EF of the RV with a sensitivity and specificity of 81% and 82% respectively [84].

RV strain is influenced by; image quality, the placement of the basal reference points (the atrial side of the tricuspid annulus should be avoided), the width of the region of interest which should be limited to

the myocardium excluding the pericardium, and finally, RV loading conditions.

Echocardiographic assessment of cardiac dysfunction in severe sepsis and septic shock

In recent years, echocardiography is a commonly used noninvasive method for assessing cardiac performance in ICU. The LVEF is the most frequently used echo parameter familiar to all clinicians with somewhat limited utility in sepsis due to: the load-dependency of the method, the lack of ability to distinguish impairment in radial, longitudinal or circumferential directions and therefore difficulties to recognize subtle changes in ventricular performance. The method fails to accurately identify all patients with septic cardiomyopathy [85]. Furthermore, the prognostic value of LVEF is doubtful as several follow-up studies found no difference in LVEF between survivors and non-survivors in sepsis [86,87].

In paper I we compared the systolic myocardial function of critically ill adult patients with early severe sepsis or septic shock to that of non-septic patients with major trauma using LVEF, FS, CO, GLS, RV FAC and RV free wall strain. The main findings were that LV and RV systolic performances, as detected by GLS, were impaired to a greater extent in septic patients with preserved ejection fraction, when compared to critically ill trauma patients with preserved ejection fraction, suggesting that strain imaging may be useful in the early detection of myocardial dysfunction in sepsis. The lower GLS, despite lower systolic blood pressure and lower systemic vascular resistance, as well as a more frequent use of catecholamines, strongly suggests that LV systolic function was impaired in the septic patients.

RV free wall systolic strain was also clearly lower in the septic patients compared to the trauma patients. The lower RV strain could theoretically be explained by a higher RV afterload, as more patients in this group were mechanically ventilated with higher airway pressure and with more pronounced lung injury compared to the trauma patients. RV systolic pressure, as a measurement of afterload, did however not differ between septic and trauma groups. The most likely explanation for the lower RV strain in the septic group is that the septic process itself causes myocardial depression involving both LV and RV. In study II, 64% of the patients had a RV free wall strain > -24 %, at a baseline MAP of 75 mmHg, suggesting that RV function was compromised, confirming the results of study I and previous strain echocardiographic studies on patients with severe sepsis or septic shock [88]. The other conventional echo parameters for assessment of systolic function in study I as, LV FAC, and RV FAC showed a trend for lower values in the septic compared to the trauma group.

The major limitation of study I was its retrospective nature and the relatively small sample sizes. Another limitation was that three different ultrasound machines were used for the echocardiographic examinations. However, the same software for analysis of strain was used by an experienced operator, who performed all the primary end-point measurements. Furthermore, the observer was blinded to the diagnoses and the intra-observer coefficient of variation was acceptably low. Another limitation was the lack of repeated echo examinations. Thus, a further deterioration of myocardial function could have been detected by standard echocardiography later in the course of sepsis.

The impact of norepinephrine-induced increases in MAP on RV performance and haemodynamics in septic shock

Norepinephrine administration increases arterial pressure due to its vasoconstrictor effect and is recommended as the first-choice vasopressor in septic shock [89]. In paper II the cardiac effects of norepinephrine with focus on the RV function of patients with septic shock were investigated. The main findings were that RV function was improved by increasing doses of norepinephrine, as assessed by both strain and conventional echocardiography. Interestingly, PVRI and Epa, indices of RV afterload, were not affected. In contrast, norepinephrine infusion induced a pronounced increase in SVRI and Ea.

The norepinephrine-induced improvement in RV performance was most likely explained by an increase in RV preload and improvement of RV contractility, by ß-1 receptor stimulation, in combination with a lack of effect on RV afterload (Fig. 14). RV preload was assessed by measuring CVP and RVEDAI, and both showed a significant increase with higher infusion rates of norepinephrine. CVP is a poor predictor of preload status in ICU patients requiring mechanical ventilation and PEEP [90,91] but it remains, however, the most frequently used variable to guide fluid resuscitation in critically ill patients [92]. In this study we were focused on the CVP-trend, during alterations of MAP-levels, rather than on single CVP values. RVEDA has been proven to be a reliable predictor of preload-recruitable increases in CI, especially in patients receiving higher levels of PEEP where PAOP is difficult to interpret [93]. In paper II, RVEDAI was used as a substitute for RVEDVI as we didn't use 3D-echocardiography. Furthermore, the focus was not on absolute volume measurements, but rather on the relative changes in RV end-diastolic dimensions at various infusion rates of norepinephrine.

In the present study, RV free wall strain, TAPSE end S` indicate that norepinephrine exerts a positive inotropic effect on the right ventricle but, as it is known, these parameters are influenced by loading conditions. To draw conclusions about the direct inotropic effects on RV pressure-volume loops should be obtained to determine RV end-systolic pressure volume relationship (end-systolic elastance) or the preload recruitable stroke work as load-independent indices of RV contractility.

Studies on the effects of norepinephrine on the pulmonary vascular bed are scarce and contradictory. Some studies have shown that increasing doses of norepinephrine induces increases in PVRI in patients with septic shock [28,29,94], while more recent studies have shown that norepinephrine does not increase PVRI in norepinephrine-dependent septic or vasodilatory shock [30,31]. In paper II, RV afterload, measured as pulmonary vascular resistance and effective pulmonary arterial elastance, was not affected. Possible explanatory mechanisms could be the initial aadrenergic receptor-mediated contractile response which is followed by ß-adrenergic receptor-mediated relaxation, at higher norepinephrine doses [95]. Another explanation could be the increased endogenous release of vascular endothelial nitric oxide (NO) by a flow-dependent increase of vascular endothelial shear stress [96,97] due to norepinephrine-induced increase in pulmonary blood flow .

The major limitation of study II was the low number of included patients. Another limitation was that we only studied the acute effects of norepinephrine, within 24 hours, on systolic RV function and pulmonary haemodynamics and can, therefore, not draw conclusions about the potential long-term effects of norepinephrine on these variables in this group of patients.

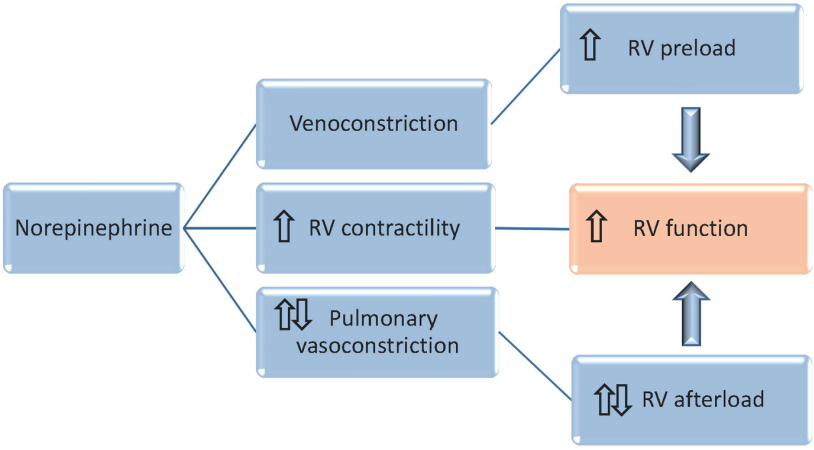

Fig. 14 *The norepinephrine-induced improvement in RV performance in septic shock is explained by an increase in RV preload and improvement of RV contractility, by ß-1 receptor stimulation, in combination with a lack of effect on RV afterload.*

The impact of general anaesthesia and PPV on strain measurements

In paper IV, general anaesthesia with PPV, induced a significant reduction of LV GLS and RV free wall strain, SVI and CI. According to our data, anaesthesia and PPV caused a decrease of preload as assessed by RVEDAI, LVEDVI, E- and A-velocities. In contrast LV afterload, measured by the calculation of SVRI and Ea, was not significantly altered. The fall in LV GLS and RV free wall strain induced by anaesthesia and PPV can be explained to some extent by the preload-reduction and, theoretically, by a propofol-induced negative intropic

effect on myocardium.

As it is known, all conventional- and strain-echocardiographic measurements of systolic function are load-dependent. To distinguish the impact of preload from the pure effects of anaesthesia on myocardial contractile function, pressure-volume loops will be needed to obtain. Previous experimental [79-82] and clinical studies [83,84] using end-systolic pressure-volume relationship have demonstrated that propofol impairs myocardial contractility. We suggested that the reduction of CO, MAP and echo-measurements of systolic function after induction of anaesthesia were explained by 1) a direct propofol-induced dilatation of venous capacitance vessels, causing reduced venous return and 2) probably direct negative inotropic effects of propofol on myocardium.

What are the effects of PPV on cardiac filling and thereby strain and conventional systolic echo measurement? In critically ill patients it is known that PPV increases intra-thoracic pressure that can reduce severely the venous return and CO [85]. Furthermore, it has been shown that the application of PPV with PEEP in mechanically ventilated patients decreases intra-thoracic blood volume [86] and LV and RV end-diastolic volume as assessed by conventional echocardiography [87-89]. Franchi et al have investigated the effects of mechanical ventilation with PEEP on myocardial strain in ICU patients and showed that increasing levels of PEEP causes a decrease in RV strain [90]. It is therefore not unlikely that the fall of RV and LV preload in study IV may to some extent be caused by the transition from spontaneous breathing to PPV and one limitation of this study was that we could not distinguish the effects of anaesthesia from PPV on RV and LV longitudinal strain.

General anaesthesia combined with PPV was associated with a signifi-cant reduction of GLS and RV strain. This reduction of GLS and RV strain reaches values considered pathological in a substantial proportion of patients without myocardial disease and should be taken into consideration when strain imaging is used in mechanically ventilated and sedated ICU patients.

Echocardiographic assessment of stress-induced cardiomyopathy in patients with subarachnoid haemorrhage

The rationale for the present observational methodological trial was to evaluate whether the new diagnostic imaging technique, speckle tracking echocardiography (STE), was superior to conventional echocardiography for detection of myocardial injury in SAH patients. The main finding of this study was that the diagnostic performance of GLS was comparable but not better than that of RWMA and LVEF. Furthermore, RLS could not reliably detect regional myocardial injury due to unacceptably low reproducibilityand specificity. Our data are in conflict with Cinotti et al [110], who suggested that GLS allows a more sensitive detection of LV systolic impairment in SAH patients with preserved EF. The major limitation of their study was that they have not reported the proportion of patients with preserved LVEF how had impaired LV GLS and have not assessed the diagnostic performance of GLS to detect myocardial injury. Furthermore, they assessed regional wall motion using RLS, without presenting data on the diagnostic performance and intra-/ inter-observer variability of RLS.

The distribution of RWMAs in this study showed that two-thirds of all segments with hypokinesia/akinesia were localized in the mid-ventricular portion followed by 30% in the apical and only 3% in the basal portion of the LV. Previous studies [111] found that RWMA were frequent both in the basal and mid-ventricular segments particularly in the anterior and antero-septal region. This variation between studies can be ascribed to the density and distribution of ß-adrenergic receptors and sympathetic nerve endings, which may differ among individuals [52,112].

For the clinical application of speckle tracking echocardiography, the definition of normal values of LV strain is of crucial importance [113]. Despite promising data using GLS and RV strain for evaluation of LV and RV function, quantitative assessment of the magnitude of regional LV deformation has been questioned because of lack of reference values with low dispersion, suboptimal reproducibility, and considerable inter-vendor measurement variability [61,114]. However, in a recent meta-analysis, the normal range of GLS, obtained by conventional echocardiography, was found to be −15.9% to -22.1% [115]. We therefore used a cut-off value of -15% in the present study, supported by the findings in a group of healthy controls obtained by our own laboratory of clinical physiology and by the meta-analysis of Yingchoncharoen et al.

As there are no reference values for RLS in current recommendations, we arbitrarily set the cut-off for abnormal RLS to ≥ -15% or ≥ -11%. The latter cut-off value we used, was supported by the report of Kusunose et al [116] who demostrated, in patients with cardiac infarction, that the best cut-off value for RLS by STE to detect RWMA was ≥ -11%. To take a more conservative approach and to avoid overestimation of the number of segments with pathologic RLS, we decided to accept as pathological

only segments from examinations which showed that ≥ 2 adjacent segments had impaired systolic strain (≥ -15% or ≥ -11%) . In spite of that, we found that the diagnostic performance of RLS was poor. The major limitation of this study was that, in this population of SAH patients, 44% required sedation, fluid treatment and mechanical ventilation with various degrees of PEEP. In addition, 42% were treated with norepinephrine. This multimodal intensive care therapy would probably affect our data on global and regional LV performance, as assessed by STE, in addition to the disease process itself.

Conclusions

Paper I: Left ventricular (LV) and right ventricular (RV) systolic function is impaired in critically ill patients with early septic shock. Up to 50% of septic patients with preserved LVEF had impaired LV function as detected by speckle-tracking 2D-echocardiography. Strain imaging may be useful in the early detection of myocardial dysfunction in sepsis.

Paper II: In patients with septic shock, increasing doses of norepinephrine improves RV systolic function, as assessed both by strain- and conventional echocardiography. This was explained by an increase on RV preload and that norepinephrine affects neither pulmonary vascular resistance nor effective pulmonary arterial elastance (RV afterload).

Paper III: The diagnostic performance of LV global longitudinal strain is not superior to standard echocardiography for the detection of myocardial injury in subarachnoid haemorrhage. LV regional longitudinal strain could not reliably detect regional myocardial injury in this group of patients.

Paper IV: General anaesthesia and positive pressure ventilation (PPV) reduces systolic LV and RV function to levels considered indicating dysfunction in a substantial proportion of patients without myocardial disease. These effects should be taken into account when evaluating heart function in surgical or critically ill patients subjected to anaesthesia /sedation and PPV.

Acknowledgement

Foremost, I would like to express my sincere gratitude to my supervisor Prof. ***Sven-Erik Ricksten*** for the continuous support during my Ph.D. study and research, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my Ph.D. study!

Besides my advisor, I would like to thank my co-supervisor Assoc. Prof. ***Odd Bech-Hansen*** for the contribution, sharp echo-knowledge, insightful comments, and hard questions. Without his contribution, the completion of this thesis would be impossible!

Many thanks to my co-supervisor Assoc. Prof. ***Sylvana Naredi*** for the encouragement and generous help with the SAH-study.

My sincere thanks also go to the head of the Department of Anesthesia in my hospital, Dr. ***Peter Dahm*** and to the section chief Dr. ***Karin Löwhagen*** for giving me the time I needed in order to complete this thesis. I would also like to thank all former heads of the Department of Anesthesia and ICU at Sahlgrenska University Hospital for their support.

I thank my colleagues and all the nurses at the Central Intensive Care and Neurocritical Care Unit, the staff in the operative theaters as well as the personal of Department of Clinical Physiology at Sahlgrenska University Hospital for their continuous contribution and unlimited help during the inclusion process and preparation of the material for this research.

Last but not the least, I would like to thank my family for supporting me throughout the course of my research and for the endless love they show me.

References

1. Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2014;2:380-6.
2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med 2016;193:259-72.
3. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.
4. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
5. Weisel RD, Vito L, Dennis RC, Valeri CR, Hechtman HB. Myocardial depression during sepsis. The American Journal of Surgery 1977;133:512-21.
6. PARKER MM, SHELHAMER JH, BACHARACH SL, et al. Profound but reversible myocardial depression in patients with septic shock. Annals of internal medicine 1984;100:483-90.
7. Hoffman MJ, Greenfield LJ, Sugerman HJ, Tatum JL. Unsuspected right ventricular dysfunction in shock and sepsis. Ann Surg 1983;198:307-19.
8. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. CHEST Journal 1990;97:126-31.
9. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997;23:553-60.
10. Jardin F, Fourme T, Page B, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. Chest 1999;116:1354-9.
11. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Critical care medicine 2008;36:1701-6.
12. Cunnion RE, Parrillo JE. Myocardial dysfunction in sepsis. Crit Care Clin 1989;5:99-118.

13. Flesch M, Kilter H, Cremers B, et al. Effects of endotoxin on human myocardial contractility involvement of nitric oxide and peroxynitrite. J Am Coll Cardiol 1999;33:1062-70.
14. Natanson C, Eichenholz PW, Danner RL, et al. Endotoxin and tumor necrosis factor challenges in dogs simulate the cardiovascular profile of human septic shock. J Exp Med 1989;169:823-32.
15. 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. J Exp Med 1996;183:949-58.
16. Exline MC, Crouser ED. Mitochondrial mechanisms of sepsis-induced organ failure. Front Biosci 2008;13:5030-41.
17. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 2002;360:219-23.
18. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med 2007;35:1599-608.
19. Fink MP. Cytopathic hypoxia in sepsis: a true problem? Minerva Anestesiol 2001;67:290-1.
20. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
21. Boissier F, Razazi K, Seemann A, et al. Left ventricular systolic dysfunction during septic shock: the role of loading conditions. Intensive Care Med 2017;43:633-42.
22. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100:483-90.
23. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, Rouby J-J. Isolated and reversible impairment of ventricular relaxation in patients with septic shock*. Critical care medicine 2008;36:766-74.
24. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, Rouby J-J. Acute left ventricular dilatation and shock-induced myocardial dysfunction*. Critical care medicine 2009;37:441-7.
25. Jardin F, Fourme T, Page B, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. CHEST Journal 1999;116:1354-9.
26. 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*. Pediatric Critical Care Medicine 2012;13:259-64.
27. Orde SR, Pulido JN, Masaki M, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. Crit Care 2014;18:R149.
28. Schreuder WO, Schneider AJ, Groeneveld AB, Thijs LG. Effect of dopamine vs norepinephrine on hemodynamics in septic shock. Emphasis on right ventricular performance. Chest 1989;95:1282-8.

29. Martin C, Perrin G, Saux P, Papazian L, Gouin F. Effects of norepinephrine on right ventricular function in septic shock patients. Intensive Care Med 1994;20:444-7.
30. Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. Intensive Care Med 2011;37:60-7.
31. Bourgoin A, Leone M, Delmas A, Garnier F, Albanese J, Martin C. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. Crit Care Med 2005;33:780-6.
32. Thooft A, Favory R, Salgado DR, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. Crit Care 2011;15:R222.
33. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007;369:306-18.
34. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. Lancet Neurol 2011;10:349-56.
35. Banki N, Kopelnik A, Tung P, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. J Neurosurg 2006;105:15-20.
36. Krishnamoorthy V, Mackensen GB, Gibbons EF, Vavilala MS. Cardiac Dysfunction After Neurologic Injury: What Do We Know and Where Are We Going? Chest 2016;149:1325-31.
37. Burch GE, Meyers R, Abildskov JA. A new electrocardiographic pattern observed in cerebrovascular accidents. Circulation 1954;9:719-23.
38. Tung P, Kopelnik A, Banki N, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke 2004;35:548-51.
39. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. J Am Coll Cardiol 1994;24:636-40.
40. Mayer SA, LiMandri G, Sherman D, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 1995;83:889-96.
41. Provencio JJ. Subarachnoid hemorrhage: a model for heart-brain interactions. Cleve Clin J Med 2007;74 Suppl 1:S86-90.
42. Baguley IJ. The excitatory:inhibitory ratio model (EIR model): An integrative explanation of acute autonomic overactivity syndromes. Med Hypotheses 2008;70:26-35.
43. Mann DL, Kent RL, Parsons B, Cooper Gt. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992;85:790-804.
44. Mallov S. Effect of cardiotoxic concentrations of catecholamines on Na+-Ca2+ exchange in cardiac sarcolemmal vesicles. Exp Mol Pathol 1984;40:206-13.
45. Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke 2002;33:1671-6.
46. Daaka Y, Luttrell LM, Lefkowitz RJ. Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A. Nature 1997;390:88-91.

47. Dujardin KS, McCully RB, Wijdicks EF, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. J Heart Lung Transplant 2001;20:350-7.
48. Temes RE, Tessitore E, Schmidt JM, et al. Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrhage. Neurocrit Care 2010;13:359-65.
49. Naidech AM, Kreiter KT, Janjua N, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. Circulation 2005;112:2851-6.
50. Parekh N, Venkatesh B, Cross D, et al. Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. J Am Coll Cardiol 2000;36:1328-35.
51. Bulsara KR, McGirt MJ, Liao L, et al. Use of the peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:524-8.
52. Pinnamaneni S, Aronow WS, Frishman WH. Neurocardiac Injury After Cerebral and Subarachnoid Hemorrhages. Cardiol Rev 2017;25:89-95.
53. Badano L, Stoian J, Cervesato E, et al. Reproducibility of wall motion score and its correlation with left ventricular ejection fraction in patients with acute myocardial infarction. Am J Cardiol 1996;78:855-8.
54. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1-11.
55. D'Hooge J, Heimdal A, Jamal F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr 2000;1:154-70.
56. Amundsen BH, Helle-Valle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-93.
57. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 2011;12:167-205.
58. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513-21.
59. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol 2002;282:H1041-6.
60. Morimont P, Lambermont B, Ghuysen A, et al. Effective arterial elastance as an index of pulmonary vascular load. Am J Physiol Heart Circ Physiol 2008;294:H2736-42.

61. Lang RM, Badano LP, Mor-Avi V, et al. 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.
62. Oras J, Grivans C, Dalla K, et al. High-Sensitive Troponin T and N-Terminal Pro B-Type Natriuretic Peptide for Early Detection of Stress-Induced Cardiomyopathy in Patients with Subarachnoid Hemorrhage. Neurocrit Care 2015;23:233-42.
63. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
64. Ryan T, Burwash I, Lu J, et al. The agreement between ventricular volumes and ejection fraction by transesophageal echocardiography or a combined radionuclear and thermodilution technique in patients after coronary artery surgery. J Cardiothorac Vasc Anesth 1996;10:323-8.
65. Cheung AT, Savino JS, Weiss SJ, Aukburg SJ, Berlin JA. Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology 1994;81:376-87.
66. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 2005;111:3411-9.
67. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-21.
68. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525-33.
69. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005;112:3738-44.
70. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65-75.
71. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77-84.
72. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28:1171-81, e2.
73. Fernandez-Teran MA, Hurle JM. Myocardial fiber architecture of the human heart ventricles. Anat Rec 1982;204:137-47.
74. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673-80.

75. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J 2016;37:1642-50.
76. Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. J Am Soc Echocardiogr 2009;22:776-92; quiz 861-2.
77. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107:526-31.
78. Samad BA, Alam M, Jensen-Urstad K. Prognostic impact of right ventricular involvement as assessed by tricuspid annular motion in patients with acute myocardial infarction. Am J Cardiol 2002;90:778-81.
79. Innelli P, Esposito R, Olibet M, Nistri S, Galderisi M. The impact of ageing on right ventricular longitudinal function in healthy subjects: a pulsed tissue Doppler study. Eur J Echocardiogr 2009;10:491-8.
80. Giusca S, Dambrauskaite V, Scheurwegs C, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96:281-8.
81. Maffessanti F, Gripari P, Tamborini G, et al. Evaluation of right ventricular systolic function after mitral valve repair: a two-dimensional Doppler, speckle-tracking, and three-dimensional echocardiographic study. J Am Soc Echocardiogr 2012;25:701-8.
82. Pirat B, McCulloch ML, Zoghbi WA. Evaluation of global and regional right ventricular systolic function in patients with pulmonary hypertension using a novel speckle tracking method. Am J Cardiol 2006;98:699-704.
83. Matias C, Isla LP, Vasconcelos M, et al. Speckle-tracking-derived strain and strain-rate analysis: a technique for the evaluation of early alterations in right ventricle systolic function in patients with systemic sclerosis and normal pulmonary artery pressure. J Cardiovasc Med (Hagerstown) 2009;10:129-34.
84. Vitarelli A, Conde Y, Cimino E, et al. Assessment of right ventricular function by strain rate imaging in chronic obstructive pulmonary disease. Eur Respir J 2006;27:268-75.
85. 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;13:259-64.
86. McLean AS, Huang SJ, Hyams S, et al. Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. Crit Care Med 2007;35:1019-26.
87. Pulido JN, Afessa B, Masaki M, et al. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo Clin Proc 2012;87:620-8.
88. Orde SR, Pulido JN, Masaki M, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. Crit Care 2014;18:R149.
89. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.

90. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 2004;30:1834-7.
91. Luecke T, Roth H, Herrmann P, et al. Assessment of cardiac preload and left ventricular function under increasing levels of positive end-expiratory pressure. Intensive Care Med 2004;30:119-26.
92. Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. Intensive Care Med 2015;41:1529-37.
93. Cheatham ML, Nelson LD, Chang MC, Safcsak K. Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. Crit Care Med 1998;26:1801-6.
94. Albanese J, Leone M, Delmas A, Martin C. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Crit Care Med 2005;33:1897-902.
95. Altiere RJ, Douglas JS, Gillis CN. Pharmacological analysis of norepinephrine responses in rabbit pulmonary blood vessels. J Pharmacol Exp Ther 1983;224:579-89.
96. Boo YC, Jo H. Flow-dependent regulation of endothelial nitric oxide synthase: role of protein kinases. Am J Physiol Cell Physiol 2003;285:C499-508.
97. Davies PF. Flow-mediated endothelial mechanotransduction. Physiol Rev 1995;75:519-60.
98. Coetzee AR, Fourie PR, Badenhorst E. The load independence of the end-systolic pressure-length relationship of the heart. S Afr Med J 1989;76:191-4.
99. Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg 1989;69:35-40.
100. De Hert SG, Vermeyen KM, Adriaensen HF. Influence of thiopental, etomidate, and propofol on regional myocardial function in the normal and acute ischemic heart segment in dogs. Anesth Analg 1990;70:600-7.
101. Zhou W, Fontenot HJ, Liu S, Kennedy RH. Modulation of cardiac calcium channels by propofol. Anesthesiology 1997;86:670-5.
102. Martin C, Perrin G, Saux P, Papazian L, Albanese J, Gouin F. Right ventricular end-systolic pressure-volume relation during propofol infusion. Acta Anaesthesiol Scand 1994;38:223-8.
103. Mulier JP, Wouters PF, Van Aken H, Vermaut G, Vandermeersch E. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. Anesth Analg 1991;72:28-35.
104. Berger D, Takala J. Determinants of systemic venous return and the impact of positive pressure ventilation. Ann Transl Med 2018;6:350.
105. Brienza N, Dambrosio M, Cinnella G, Conte M, Puntillo N, Bruno F. [Effects of PEEP on intrathoracic and extrathoracic blood volumes evaluated with the COLD system in patients with acute respiratory failure. Preliminary study]. Minerva Anestesiol 1996;62:235-42.
106. Koolen JJ, Visser CA, Wever E, van Wezel H, Meyne NG, Dunning AJ. Transesophageal two-dimensional echocardiographic evaluation of biventricular