LEFT VENTRICULAR DYSFUNCTION IN CRITICALLY ILL PATIENTS

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ABSTRACT

Background: Cardiac dysfunction is common in Intensive Care Unit (ICU) patients and can contribute to multiorgan failure and death. Despite this, few studies have been performed on pathogenies, prevalence, diagnosis and impact on mortality in unselected ICU patients.

Aim: The thesis aimed to assess the prevalence, significance, and etiologies behind systolic and diastolic LV dysfunction in critically ill patients, as well as explore the use of cardiac biomarkers.

Methods: Paper I was a prospective observational trial focusing on cardiac left ventricular (LV) systolic dysfunction in ICU patients. Patients underwent transthoracic echocardiography (TTE) within 24 hours of admission. A secondary analysis of the first cohort was performed in Paper II. Patients with normal systolic function and no cardiac disease were classified according to the European Association of Cardiovascular Imaging (EACVI) guidelines for diastolic dysfunction. In Paper III, a retrospective analysis focusing on cardiac biomarkers was performed using data from Paper I. Paper IV was a register study in which coronary angiography and cardiac magnetic resonance (CMR) results were systematically explored in ICU patients with Regional Wall Motion Abnormalities (RWMA).

Results: The prevalence of systolic dysfunction, defined as ejection fraction (EF)<50% or RWMA, was 25 % in unselected ICU patients. Half of the patients had systolic dysfunction unrelated to primary cardiac disease. No mortality increase was seen at 30 days (primary outcome), but the 90-day mortality was increased. (Paper I)

In total, 218 patients were included in Paper II. Of these, 21(10%) had diastolic dysfunction, and in 35(17%) diastolic function was indeterminate. A risk-adjusted model showed increased 90-day mortality in these patient groups. (Paper II)

NT-proBNP and hsTNT were associated with cardiac dysfunction but were not sensitive enough to use for screening of cardiac dysfunction in unselected ICU patients. However, biomarkers were linked to increased mortality even after adjustments for cardiac dysfunction, disease severity, age, and independently associated factors. (Paper III)

In the retrospective register study, 257 patients with RWMA were identified, and 53 of these had non-obstructed coronary arteries. The majority of patients with non-obstructed coronary arteries had reversible LV dysfunction. CMR showed Takotsubo or myocardial stunning as the most common reason for the RWMA in these patients. (Paper IV)

Conclusions: Systolic and diastolic dysfunction is common and associated with increased mortality in ICU patients. Biomarkers are useful as risk markers but are not advisable for screening for cardiac dysfunction. A substantial part of ICU-associated cardiac dysfunction is not caused by coronary artery disease; those patients often have reversible cardiac dysfunction.

Keywords: Left ventricular dysfunction; Left ventricular diastolic dysfunction; hsTNT; NT-proBNP; Coronary angiography; Regional wall motion abnormalities; Takotsubo syndrome; Septic cardiomyopathy; MINOCA; Cardiac disease; Intensive care unit; Echocardiography

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SAMMANFATTNING PÅ SVENSKA

Hjärtsvikt är vanligt hos intensivvårdspatienter. Det kan vara hjärtsvikten som gör att patienten behöver intensivvård exempelvis efter en större hjärtinfarkt, men patienter som är svårt sjuka kan också utveckla hjärtsvikt sekundärt till sin grundsjukdom. Denna avhandling är inriktad på vänsterkammarfunktionen i hjärtat hos intensivvårdspatienter. Hjärtsvikt delas in i systolisk svikt, en typ av pumpsvikt där hjärtat inte orkar tömma sig ordentligt på blod och diastolisk svikt, en typ av svikt där hjärtat inte fylls ordentligt med blod innan nästa slag. Vid vissa tillstånd förekommer också regionala väggrörlighetsstörningar, som innebär att en del av hjärtat rör sig sämre. Dessa tillstånd ökar risken för död hos hjärtpatienter, men det är inte helt klarlagt om detta även gäller patienter inom intensivvården. Diagnosen hjärtsvikt ställs vanligen med hjälp av ultraljud av hjärtat, så kallad ekokardiografi. Det är viktigt att skilja på hjärtsvikt orsakad av kranskärlssjukdom så kallad ischemisk kardiomyopati och hjärtsvikt som inte är orsakad av detta, icke-ischemisk kardiomyopati. För att skilja på dessa kan man bland annat undersöka patienten med kranskärlsröntgen.

Syftet med avhandlingen var att utvärdera förekomsten och effekten av systolisk och diastolisk hjärtsvikt hos intensivvårdspatienter. Samt att undersöka orsaken till dessa tillstånd och analysera användningen av hjärtspecifika blodprover inom intensivvården.

I delarbete I genomfördes ekokardiografi systematisk på alla intensivvårdspatienter på våra avdelningar. Denna studie visade att systolisk hjärtsvikt förekommer hos upp till 25 % av patienterna. Ungefär hälften av patienterna bedömdes ha icke-ischemisk hjärtsvikt. Patienter med systolisk hjärtsvikt avled i större utsträckning än patienter utan hjärtsvikt.

För delarbete II användes data från studie I. Hos patienter utan systolisk hjärtsvikt, uppskattades förekomsten av diastolisk hjärtsvikt enligt riktlinjer från europeiska kardiologföreningen. Ungefär 1 av 10 patienter hade diastolisk hjärtsvikt, vilket var associerat med en ökad risk att avlida.

I delarbete III undersöktes nivåerna av hjärtspecifika blodprover (hsTNT och NT-proBNP) hos intensivvårdspatienter. Nivåerna av blodproverna korrelerade väl med förekomst av hjärtdysfunktion, trots detta var de inte specifika nog för att kunna utesluta hjärtsvikt. Förhöjda nivåer av blodproverna var också förknippat med en ökad risk för död.

Delarbete IV var en registerstudie på patienter med regionala väggrörlighetsstörningar som genomgått kranskärlsröntgen i samband med intensivvård. Kranskärlsröntgen visade att 20 % av dessa patienter hade icke-ischemisk orsak till sina väggrörlighetsstörningar. Hos dessa var hjärtsvikten oftast reversibel och magnetkameraundersökningar visade att Takotsubo kardiomyopati var vanligt förekommande.

Sammanfattningsvis visar avhandlingen att systolisk och diastolisk hjärtsvikt är vanligt hos intensivvårdspatienter och associerat med ökad risk att avlida. Hjärtspecifika blodprover är användbara som riskmarkörer, men inte för att utesluta hjärtsvikt. En stor del av hjärtsvikten är inte orsakad av kranskärlssjukdom och dessa patienter har ofta reversibel hjärtsvikt

LIST OF PAPERS

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

I. **Regional left ventricular systolic dysfunction associated with critical illness: incidence and effect on outcome**
Cavefors O, Holmqvist J, Bech-Hanssen O, Einarsson F, Norberg E, Lundin S, Omerovic E, Ricksten SE, Redfors B, Oras J
ESC Heart Failure 2021; 8: 5415-5423

II. **Isolated diastolic dysfunction is associated with increased mortality in critically ill patients**
Cavefors O, Ljung Faxén U, Bech-Hanssen O, Lundin S, Ricksten SE, Redfors B, Oras J
J Crit Care. 2023 Aug;76:154290.

III. **Cardiac biomarkers for screening of cardiac dysfunction in critically ill patients**
Cavefors O, Einarsson F, Holmqvist J, Bech-Hanssen O, Ricksten SE, Redfors B, Oras J
Manuscript

IV. **RWMAs in critically ill patients with non-obstructed coronary arteries**
Rosen-Wetterholm E, Cavefors O, Redfors B, Ricksten SE, Omerovic E, Polte CL, Oras J
Acta Anaesthesiol Scand. 2023 Jul;67(6):746-754.

CONTENT

ABBREVIATIONS

ACE inhibitors	Angiotensin Converting Enzyme inhibitors
ACS	Acute Coronary Syndromes
AHA	American Heart Association
ANP	Atrial Natriuretic Peptide
ARDS	Acute Respiratory Distress Syndrome
AUC	Area Under the Curve
CAD	Coronary Artery Disease
cGMP	cyclic Guanosine Monophosphate
CI	Cardiac Index
CIC	Critical Illness Cardiomyopathy
CMR	Cardiac Magnetic Resonance imaging
CO	Cardiac Output
CO2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disorder
CRP	C-Reactive Protein
CW	Continuous Wave
Cx	Left Circumflex Artery
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
EF	Ejection Fraction

ESC	European Society of Cardiology
FRAC	Fractional Area Change
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICU	Intensive Care Unit
LA	Left Atrium
LAD	Left Anterior Descending
LAVI	Left Atrial Volume Index
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MAPSE	Mitral Annular Plane Systolic Excursion
MI	Myocardial Infarction
MINOCA	Myocardial Infarction Non-Obstructive Coronary Arteries
NA	Noradrenaline
NO	Nitric Oxide
NPV	Negative Predictive Value
NSTEMI	nonST Elevation Myocardial Infarction
NT-proBNP	N-Terminal pro Brain Natriuretic Peptide

OCT	Optical Coherence Tomography
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
PRICES	Preferred Reporting Items for Critical Care Echocardiography Studies
PW	Pulsed Wave
RCA	Right Coronary Artery
ROC	Receiver Operating Characteristic
RV	Right Ventricle
RWMA	Regional Wall Motion Abnormalities
SAPS 3	Simplified Acute Physiologic Score III
SERCA	Sarcoplasmic/Endoplasmic Reticulum C Adenosine Triphosphatase Pump
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
STEMI	ST Elevation Myocardial Infarction
TNT	Troponin T
TR Vmax	Tricuspid Regurgitation Maximum Velocity
TTE	Transthoracic Echocardiography
VA ECMO	Veno-Arterial Extra Corporeal Membrane Oxygenation
VF	Ventricular Fibrillation

VT	Ventricular Tachycardia
VTI	Velocity Time Integral

1 INTRODUCTION

Cardiac dysfunction associated with critical illness can manifest in several ways and for many reasons[1,2]. Cardiovascular disease is a common cause of Intensive Care Unit(ICU) admission in Sweden, associated with a mortality of up to 35 %[3]. Despite this, the prevalence and impact on mortality of cardiac dysfunction in general ICU patients are not widely studied.

1.1 HEMODYNAMIC SYSTEM

The goals of the hemodynamic system are transporting oxygen and energy to mitochondria and transporting carbon dioxide (CO2) and waste products to the lungs, kidneys, and liver. Transport is dependent on the circulation of red blood cells through the body[4]. The heart has a central role as a pump, and heart failure can result in low cardiac output(CO) with impaired tissue perfusion leading to mitochondrial dysfunction and tissue damage[5].

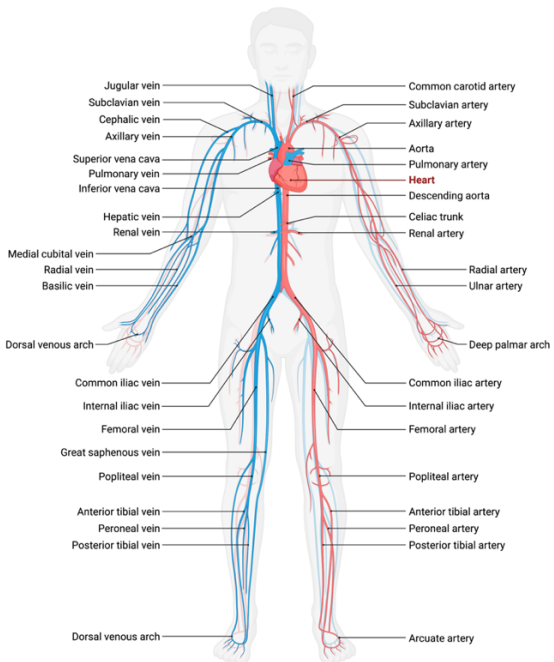

Figure 1. Anatomy of the cardiovascular system Created with biorender.com.

The heart consists of four chambers (Fig 2). Blood is pumped from the vena cava through the right heart into the pulmonary circulation and from the left heart into the systemic circulation. Venous blood enters the right atrium from the inferior and superior vena cava. Then it flows, both passively and as a result of atrial contraction, into the right ventricle (RV) through the tricuspid valve. When the RV contracts, the blood flows through the pulmonary valve into the pulmonary arteries. It then passes through the pulmonary vasculature, where the blood releases CO2 and becomes oxygenated. The blood then exits the pulmonary circulation through four pulmonary veins into the left atrium(LA), where it flows through the mitral valve into the left ventricle(LV) and from there on through the aortic valve into the systemic circulation[5]. The hemodynamic system is divided into; pulmonary circulation, consisting of the right atrium, RV, and pulmonary vessels, and systemic circulation, which consists of the LA, LV, and the blood vessels of the rest of the body. The pressures in the systems are different, with the systemic circulation having pressures around 120/80 mmHg and the pulmonary circulation having pressures around 25/8 mmHg[6]. To cope with the higher pressures of the systemic circulation, the left heart needs more contractile force and is, therefore, significantly thicker.

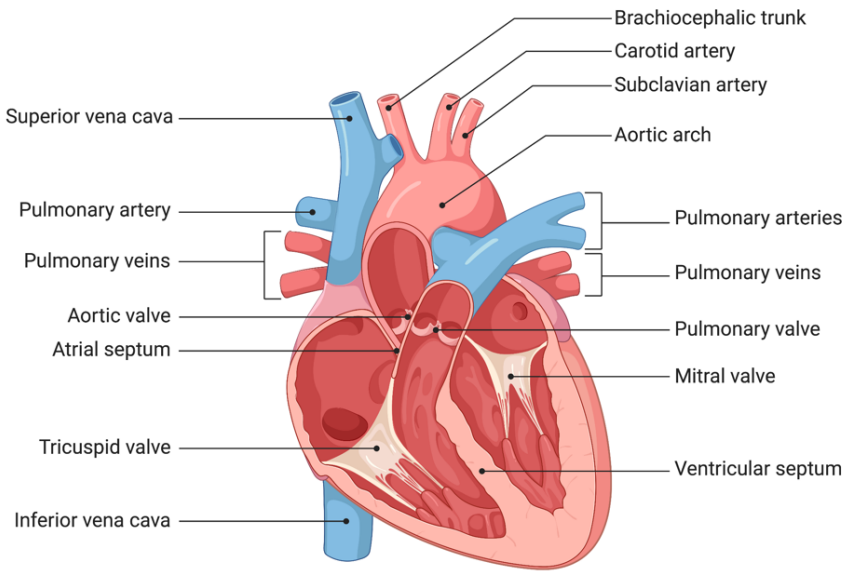

Figure 2. Cardiac anatomy. Created with biorender.com

1.1.1 LEFT VENTRICULAR FUNCTION

Functionally the heart has two distinct phases; systole, when the heart contracts, and diastole when the heart relaxes.

LV systolic function

Systole is subdivided into the isovolumetric contraction phase and the ejection phase. The heart contracts during the isovolumetric contraction phase, but the aortic and pulmonic valves stay closed. When the pressure in the LV exceeds the pressure of the systemic circulation (the diastolic blood pressure), the aortic valve is opened, and blood is expelled into the circulation. The contraction depends on the interaction between actin and myosin and is regulated by the troponin complex[7].
The systolic function of the LV consists of three types of motion[8].

1. The heart twists around its axis, similar to a towel being squeezed.
2. The atrioventricular plane (AV) has a significant longitudinal motion, moving blood through the heart as a pump. This action is described in echocardiography as Mitral Annular Plane Systolic Excursion(MAPSE)[9].
3. Radial contraction, in which the heart wall thickens.

Radial contraction is most often used in the assessment of regional systolic function. Areas with reduced thickening (<30%) are described as hypokinetic If there is no thickening, the area is described as akinetic, and if there is stretching or thinning, the area is described as dyskinetic[10]. When the LV is assessed by echocardiography, it is by convention split into 17 different segments, all in which function is described[10]. Specific coronary arteries supply the myocardium in these segments, but anatomic and functional variants are common[10]. The Left Anterior Descending (LAD) supplies most of the anterior and septal wall, while the left circumflex artery (CX) supplies the anterolateral parts, and the right coronary artery (RCA) supplies the posterior and inferior parts, including the SA node. Blockage of these arteries usually leads to regional wall motion abnormalities(RWMA) in the area supplied by the blocked vessel, most often caused by coronary artery disease (CAD)[11].

Traditionally, the focus in general cardiology and intensive care has been on LV systolic dysfunction. LV Systolic dysfunction can be global, often assessed with ejection fraction (EF) or localized to different areas of the LV represented by RWMA. It can also be a combination of both global dysfunction and a more pronounced regional dysfunction[11]. EF is defined as the amount of blood ejected during systole from the LV expressed as a percentage: (Left Ventricle End Diastolic Volume – Left Ventricle End Systolic Volume) / Left Ventricle

End Diastolic Volume x 100). The most used definitions in systolic heart failure are heart failure with reduced ejection fraction (HFrEF), defined as EF <40 %, and heart failure with mildly reduced ejection fraction (HFmrEF), which is defined as EF from 40-49%[12]. Interest in strain analysis using speckle tracking for assessing LV systolic function has increased in recent years[13]. Strain analysis has, however, not been included in routine clinical use outside of the evaluation of chemotherapy-associated cardiotoxicity, hypertrophic cardiomyopathy, and cardiac sarcoidosis[14].

LV diastolic dysfunction

Diastolic cardiac function is the passive and active relaxation of LV after systole, which leads to the heart's filling. The pressure in the LV depends on blood volume and the distensibility(compliance) of the ventricle. The first diastolic phase is the isovolumetric relaxation phase, in which the myocytes relax, but the valves remain closed. Relaxation during this period is active and depends on multiple processes[15]. The process starts when phospholamban becomes phosphorylated, causing calcium ions to be resequestered through the sarcoplasmic/endoplasmic reticulum C adenosine triphosphatase pump (SERCA) which relaxes the myosin-actin bindings[16-18]. The relaxation is augmented by elastic recoil from elements of the LV, e.g., collagen, that have been compressed during systole[19]. When the pressure in the LV falls below the LA pressure, the mitral valve opens, and blood flows into the LV because of the pressure difference, described as the rapid filling phase. In transthoracic echocardiography (TTE), the filling can be visualized by using Pulsed Wave (PW) doppler in the mitral inflow illustrated by an E-wave (Fig 3).

At the start of the rapid filling phase, the LV is highly compliant and easily distensible with relaxed cardiomyocytes, leading to minimal resistance of LV filling at a normal volume. When the heart fills, the AV plane displaces downward. The speed of this movement can be visualized with TTE, represented by the e' wave using tissue doppler imaging (TDI). Finally, the LA contracts contributing to 20-25 % of the filling of the LV in healthy individuals, although this can rise to 40 % in older individuals[20]. The filling of the LV from the atrial contraction can be visualized with PW doppler, shown as an A wave, and the corresponding AV plane motion speed can be seen on TDI, represented by an a' (Fig 3). The pressures needed to fill the LV are normally low, often <12mmHg. In diastolic dysfunction, structural and functional causes lead to loss of diastolic distensibility and relaxation properties in the LV. Consequently, the filling can only be maintained through increased LA pressure, pushing blood into the LV. In diastole, the pulmonary veins, the LA, and the LV form a common system continuing to the pulmonary capillary bed.

Therefore, increasing LV diastolic pressures lead to higher pressures in the pulmonary vasculature and eventually to pulmonary congestion and oedema[21,22]. When patients are symptomatic from their diastolic dysfunction, the diagnosis of heart failure with preserved ejection fraction (HFpEF) can be established[23,24]. In some patients, a specific reason behind diastolic dysfunction can be identified, such as infiltrative, restrictive, or inflammatory disease or genetic cardiomyopathies[25,26]. However, in most patients, no single reason can be established, and conditions associated with ageing contribute to diastolic dysfunction. These conditions include interstitial fibrosis, myocyte hypertrophy, inflammation, oxidative stress, impaired microcirculation, and energetic abnormalities[25-28]. Today, the prevalence of HFpEF is estimated to be 1-4% in the general population but is highly correlated with increasing age[29,30]. HFpEF is diagnosed using symptoms in conjunction with echocardiographic criteria and biomarkers[23]. However, these diagnostic criteria are hard to fulfil in ICU patients, and most ICU studies have, therefore, solely focused on assessing diastolic dysfunction parameters.

Frequently used markers for diastolic dysfunction in ICU studies are e' and E/e', although older studies often used E/A assessments. (Fig 3) The maximum tissue velocity of the AV plane during passive filling of the LV, e', can be used as a measurement of the relaxational properties of the LV. However, this value is strongly influenced by age[31]. It can be correlated to the filling of the LV using the PW-derived measurement of early filling illustrated by the E wave, resulting in a quota E/e', this parameter is less sensitive to ageing and correlate to invasively acquired capillary wedge pressures[32]. The relation between the passive and active filling(atrial contraction) of the LV (E and A wave) can also be used for diastolic assessment in patients with previous heart disease[31]. In addition, measurements of LA volume are used as enlargement is strongly associated with diastolic dysfunction[33] . Increased filling pressures of the LV lead to higher LA pressures and, as a result, higher pulmonary vascular resistance, which can be estimated using maximum tricuspid regurgitation velocity (TR Vmax). Hence, TR Vmax is also related to diastolic dysfunction and increased filling pressures in the absence of pulmonary disease[21,34]. Studies on diastolic dysfunction in critically ill patients have increased during the last decade, but similar to studies on systolic function, most research has been done in septic patients [35,36].

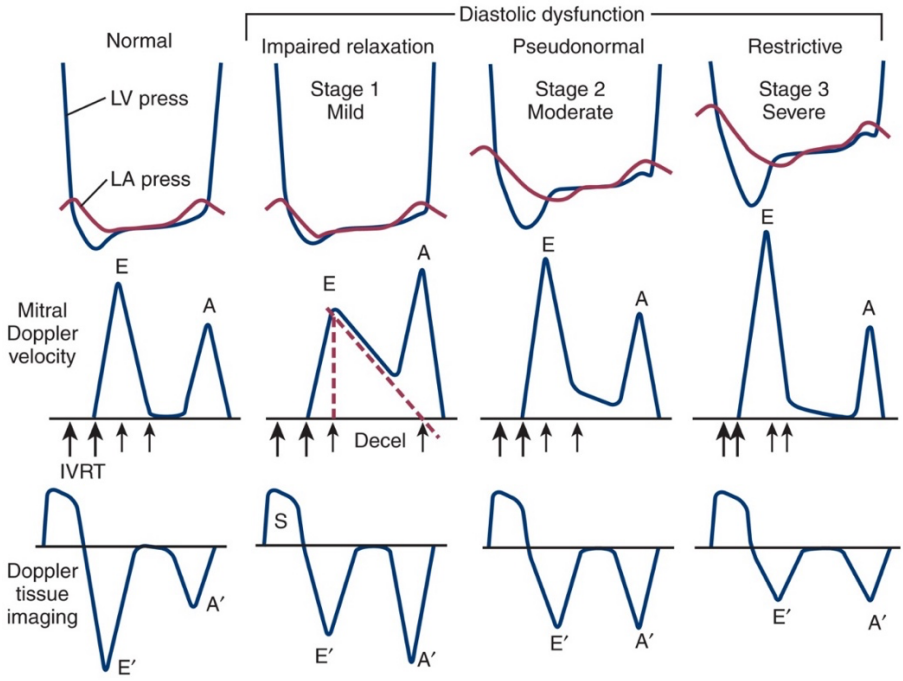

Figure 3. Transmitral Doppler LV inflow velocity. E: peak early diastolic flow velocity; A: peak late diastolic flow velocity caused by atrial contraction; E Decel: E wave diastolic deceleration time; E′, AV-plane velocity during early filling; A′, AV-plane velocity during filling produced by atrial contraction. Diastolic filling patterns: (1) normal pattern of relaxation and filling *(column 1 far left),* (2) impaired relaxation or type I mild diastolic dysfunction, (3) pseudonormal relaxation or type II moderate diastolic dysfunction, and (4) restrictive filling pattern or type III severe diastolic dysfunction. *Reproduced with permission from Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and heart failure with a preserved ejection fraction: part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105:1387–1393. Copyright © 2002 Lippincott Williams & Wilkins*

1.2 PREVALENCE AND IMPACT OF CARDIAC DYSFUNCTION IN GENERAL ICU

The pathophysiology, presentation, and clinical features in the different diagnoses seen in ICU-associated cardiac dysfunction overlap. In addition, critically ill patients often suffer from several medical conditions simultaneously, such as subarachnoid haemorrhage leading to Takotsubo, a cardiac arrest patient who develops sepsis, or a septic covid patient that develops myocarditis. Hence, in the individual ICU patient, the reason behind cardiac dysfunction might be challenging to distinguish. Despite this perspective, only a few studies have evaluated LV dysfunction associated with critical illness in unselected ICU populations but instead focused on specific groups such as sepsis or post-cardiac arrest patients.

Systolic LV dysfunction

The few available studies in a general ICU population, excluding cardiac patients, suggest a prevalence of systolic LV dysfunction between 7% and 19%[37-39]. Bossne et al. published a study of cardiac abnormalities in 467 patients in a medical ICU without primary cardiac patients. The study reported a prevalence of RWMA of 11,6 % and a prevalence of global systolic LV dysfunction, defined as EF <35%, of 8,6%. No associations to mortality were estabilished[38]. A more recent study with a similar design was performed in a general ICU in Portugal by Marcelino et al. in 2009. In total, 704 patients were prospectively included and examined with echocardiography. Multiple echocardiographic abnormalities were reported, such as LV dilatation and valvular disease. The study did not report on RWMA and defined global systolic dysfunction as fractional shortening (FS) < 28 %[40]. The prevalence of global systolic dysfunction was 18,8 %, and no associations to mortality were identified [37]. A larger single-centre prospective observational study focused on evaluating systolic LV function; the study was performed for three years, from 1998 to 2001. The authors included 574 non-septic and non-ischemic patients without suspicion of cardiac disease. Of these patients, 41(7%) had myocardial dysfunction with low LVEF and RWMA; interestingly, wall motion abnormalities were only observed in apical and basal segments. All patients who underwent follow-up echocardiograms had normalization of their cardiac function. Coronary angiography was performed in seven patients without significant coronary artery stenosis. No mortality analysis was done[39].

Diastolic LV dysfunction

A few papers have focused on assessing diastolic function in general ICU patients. Sturgess et al. prospectively classified 32 consecutive patients according to the 2009 diastolic guidelines by the European Association of Cardiovascular Imaging (EACVI)[41]. A third of the patients had diastolic LV dysfunction, but no outcome data was reported[42]. The same author published a retrospective study assessing diastolic function using TDI in 92 patients. Evidence of increased filling pressures, defined as E/e'>15, was seen in 15 % of patients. However, there was no association with mortality[43]. Another single-centre prospective study included 58 patients. Of these, 46% had diastolic dysfunction, according to the authors' definition, and hospital mortality in this group was increased[44]. A smaller single-centre study assessing cardiac biomarkers demonstrated lower E/e' ratios in survivors but did not report prevalence[45]. Combined with studies performed exclusively in septic patients, a metanalysis could not establish a mortality association with diastolic dysfunction in critically ill patients. Outside intensive care settings, the EACVI and American Society of Echocardiography (ASE) recommends several echocardiographic parameters to diagnose diastolic dysfunction and increased filling pressures in their guideline from 2016[34]. Only two studies have used the 2016 guidelines in an ICU setting[46,47]. Earlier diastolic guidelines from 2009 were compared to the 2016 guidelines, and a simpler definition was proposed by the authors in a study by Lanspa et al. [47]. The study retrospectively included 398 patients with sepsis or septic shock. Using the 2009 definition, 7% of patients were classified as diastolic dysfunction, and 66% were uncategorizable. The guidelines from 2016 classified 21% with abnormal diastolic function and 29% had indeterminate function. The simpler definition classified 51% of patients as having diastolic dysfunction. No mortality associations were found using any diastolic classification. Another study compared the 2009 guidelines with those from 2016 on ICU-days one and three in a prospective observational study, including 62 patients with severe sepsis or septic shock[46]. According to the 2016 guidelines, 60 % of patients had diastolic dysfunction, and 23 % had an indeterminate function. In patients with normal systolic LV function, 45 % were classified as diastolic dysfunction and another 25% with indeterminate diastolic function. The 2009 guidelines classified fewer patients as having diastolic dysfunction. No mortality or outcome analyses were performed.

In summary, significant knowledge gaps exist regarding the prevalence and associations to mortality of LV systolic and diastolic dysfunction in general ICU patients.

1.3 ICU-ASSOCIATED CARDIAC DYSFUNCTION

The prevalence and impact of specific diagnoses of LV dysfunction in intensive care patients are covered in the following segments.

1.3.1 SEPTIC CARDIOMYOPATHY

Cardiac involvement in severe sepsis and septic shock is well known, and most ICU literature regarding LV systolic and diastolic dysfunction focuses on these patients. Despite numerous original articles and reviews focused on cardiac dysfunction in sepsis, no universal definition of septic cardiomyopathy exists, and different studies have used different inclusion criteria[48-50]. Most agree that systolic dysfunction should be included in the classification, often defined as LVEF <50%. Newer studies have also included systolic dysfunction defined using myocardial strain[51-53]. In septic models of pigs and dogs, lower strain values have been shown to represent early septic cardiomyopathy, and in the ICU, more patients get diagnosed with septic cardiomyopathy using strain analysis compared to diagnosing with LVEF[54-56]. Nonetheless, the prognostic information is unclear, and strain has not been adopted into clinical standards[57,58]. Including diastolic dysfunction in septic cardiomyopathy broadens the definition, and diastolic dysfunction has been shown to correlate better with mortality than LVEF in patients with septic shock[36]. RV dysfunction is likely prevalent in septic patients, and biventricular involvement might constitute a worse prognosis than isolated LV dysfunction [59,60]. The lack of a standardized definition and possible overlap with other diagnoses, such as myocarditis and Takotsubo syndrome, make prevalence estimations hard. The prevalence of septic cardiomyopathy is estimated to be between 14-60 %, in septic patients, depending on definition and patient cohort[61-63]. The underlying pathogenies in septic cardiomyopathy are not established and might be multifactorial[64].

Pathogenesis

The proposed pathophysiological process causing septic cardiomyopathy can be classified into the following categories:

Inflammation

Several pathways in which inflammation can contribute to septic cardiomyopathy have been suggested. These include a direct effect of cytokines on cardiac myocytes, effects mediated by inducible NO synthase and oxidative stress[49,65,66].

Adrenergic hyperactivity

Sepsis-associated adrenergic hyperactivity might lead to Beta-adrenergic downregulation in the myocardium through a molecular switch in which the Beta - 2 receptor activates an inhibitory Gi pathway instead of the normal stimulating Gs pathway, resulting in cardiac dysfunction[67-69]. Similar pathophysiology has been described in the Takotsubo syndrome[67].

Mitochondrial dysfunction

Mitochondrial dysfunction has been proposed to underlie septic cardiomyopathy because of the lack of significant cell death and the reversibility of cardiac function in survivors with septic cardiomyopathy. This is supported by evidence of adequate tissue oxygen levels in cardiac circulation. Several mechanisms for mitochondrial dysfunction have been proposed[70,71].

Global ischemia

Global ischemia has been proposed as a mechanism for septic cardiomyopathy. However, a study reporting normal oxygenation in sinus coronarius and studies showing normal glucose levels in septic animal models have put this into question[70,72]. Myocardial hibernation has also been suggested, supported by changes in glucose metabolism and uptake despite preserved oxygenation and perfusion in animal models[73].

Microcirculatory dysfunction

Sepsis is associated with microcirculatory changes in other organs resulting in dysfunction, and a similar process could cause myocardial dysfunction[48].

Iatrogenic/stress-induced

High levels of vasopressor or inotropes could lead to histological alterations such as contraction band necrosis and contribute to septic cardiomyopathy, similar to Takotsubo syndrome[74-76].

Calcium responsiveness
Affected contractile performance has been suggested to be mediated through inflammatory reduced calcium responsivness[77].

Treatment
No causal treatment for septic cardiomyopathy is recommended[78]. Hemodynamic support might be necessary, but no clear evidence exists for the timing of initiating inotropic support, and no hemodynamic targets other than mean arterial pressure (MAP) >65mmHg have been established[78,79]. Supranormal cardiac output (CO) levels have been shown not to confer any mortality benefit and have even been linked to increased mortality[80,81]. No randomized studies of treatment with inotropes versus placebo for septic cardiomyopathy exist; nonetheless, most guidelines recommend using inotropes when signs of hypoperfusion persist despite adequate volume resuscitation and vasopressor [1]. Surviving sepsis guidelines recommend using dobutamine + noradrenaline (NA) or adrenalin based on a meta-analysis[78,82]. A French prospective randomized trial showed similar results for epinephrine vs norepinephrine + dobutamine in septic shock patients[83]. Early studies showed relatively promising effects of levosimendan in septic patients[84,85]. However, when levosimendan was studied in a larger cohort of septic patients requiring vasopressor, it did not affect mortality and was associated with an increased number of adverse events[86]. Interestingly a subgroup analysis of 52 patients with low cardiac index (CI) (<2.44 L/m2/min) had the same outcome as the other patients in the study[86]. A meta-analysis comparing levosimendan and dobutamine for the treatment of septic patients showed increased CI and LV stroke work index as well as a significant decrease of blood lactate in patients treated with levosimendan. Despite this, no difference in mortality or LVEF was found[87].

In treatment failure, veno-arterial extracorporeal membrane oxygenation (VA ECMO) for treating sepsis-induced cardiogenic shock is increasing [88,89]. Using short-acting B-blockade such as esmolol or landiolol might be beneficial for survival in septic patients with persistent tachycardia after initial resuscitation, as shown in a meta-analysis[90]. However, no studies have been performed on patients with septic cardiomyopathy.

1.3.2 TAKOTSUBO

Takotsubo syndrome is a relatively newly recognized disease, with the first cases being noticed in Japan during the 80s and a case series of five patients published by Sato et al. in 1990[91]. In cardiology, Takotsubo is overrepresented in middle-aged women, often associated with an identifiable physiological stressor[92]. It is estimated that 1-3 % of all patients presenting with ST-elevation on ECG, have Takotsubo[93,94]. The diagnosis and naming of Takotsubo have been under debate during the last decades, and different diagnostic criteria have been developed. The International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) criteria are currently recommended, although other criteria have been suggested and used by different authorithies[95-102]. Most patients present with reversible regional dysfunction not limited to myocardium supplied by specific coronary arteries[68,103]. Takotsubo is mainly described to present with four different patterns of RWMA[104]. (1) The apical type is the most prevalent in general cardiology patients, representing up to 80% of patients. The RWMA results in a characteristic appearance of the LV on ventricular angiograms resembling a Japanese fishing trap called Takotsubo, hence giving the diagnosis its name. (2) The second most common form is midventricular Takotsubo, representing about 15 % of patients. In midventricular Takotsubo, the mid segments of the LV are affected, but the function is preserved in apical and basal segments. (3) The third most prevalent form is the basal type, in which the basal segments of the LV are affected but with preserved function in the middle and apical segments. (4) Finally, the focal type, with only regional parts of the LV affected results in less pronounced circulatory effects. The focal type has been described as uncommon, representing <1 % of cases, but might be more prevalent in critically ill patients[104]. RV involvement is present in up to 35 % of cases and could constitute a worse diagnosis[92,105]. Takotsubo can also be classified into primary and secondary form[98,106]. In the primary form, accounting for up 80% of cases, patients seek medical care for cardiovascular reasons, and the trigger for Takotsubo is most often phycological stress[104,106]. The secondary form is the dominant form of Takotsubo seen in critically ill patients. In these patients, clear physical triggers, such as subarachnoid haemorrhage, pheochromocytoma, trauma, surgery, or exogenous use of catecholamines, are almost always identifiable[106-110]. A few studies in ICU patients indicate a prevalence of Takotsubo ranging from 3.5 to 28%[111-113]. Risk factors are female sex and admission for sepsis[114]. Patients present with more arrhythmias and a higher need for vasoconstrictors, compared to ICU patients without Takotsubo[112,113]. General cardiac patients with Takotsubo have an increased risk of death similar to myocardial infarction (MI), but in ICU patients most studies have not shown increased mortality risk[92,112,113].

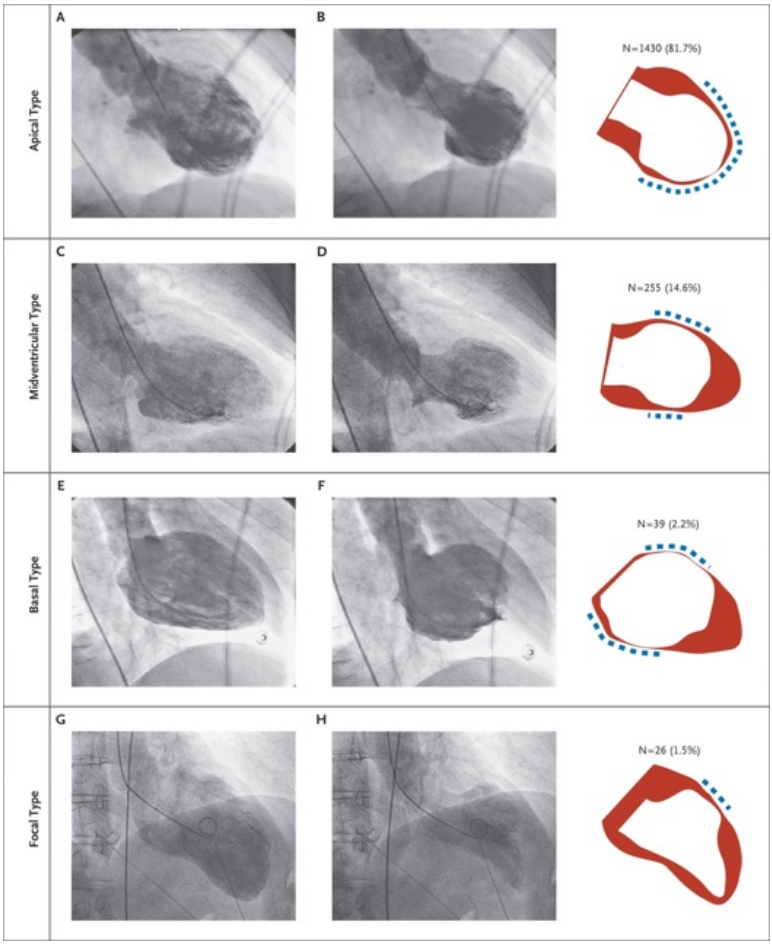

Figure 4. Cardiac ventriculography in patients with different types of Takotsubo. Reproduced with permission from Templin et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. New England Journal of Medicine 2015; 373: 929-38, Copyright Massachusetts Medical Society.[115]

Pathogenesis

Early hypotheses suggested that coronary artery thrombus with spontaneous dissolution or coronary artery spasm could cause Takotsubo syndromes[116,117]. However, none of these theories could explain why affected areas were not supplied by a single coronary artery[118,119]. Today the major hypothesis involves excessive stimulation of the myocardium by noradrenaline and adrenaline, released from the adrenal medulla and symptomatic nerve ends[68,103,120]. Support for this theory comes from studies on heart rate variability showing depressed parasympathetic activity and sympathomimetic predominance, as well as evidence of increased catecholamine levels in the coronary sinus,

possibly caused by locally increased catecholamine production[121,122]. Physiological or pharmacological triggers are often present, leading to high levels of catecholamines. In addition, animal studies have shown exogenous catecholamines to induce Takotsubo in animals[76,92]. Despite the evidence of high levels of catecholamines and adrenergic hyperactivity, the pathophysiology involved in explaining the resulting myocardial stunning is still under debate. Several theories exist:

Epicardial vessel spasms
Studies report a high prevalence of spasm-induced diseases in Takotsubo patients as well as reports of hyperreactivity in in the brachial artery, and there is also evidence of acetylcholine-induced vasospasm in early in the disease in some patients [123-125]. Epicardial vessel spasms could contribute to Takotsubo in a subset of patients, but not all patients have evidence of hyperreactive blood vessels.

Microcirculatory dysfunction
The effects of catecholamines on cardiovascular circulation are primarily in the microvasculature where alfa-1 and endothelin receptors are abundant[126]. The theory of microcirculatory dysfunction is supported by evidence of decreased coronary blood flow and signs of decreased perfusion in angiography[127-129]. In addition, a biomarker study showed different expressions of biomarkers in Takotsubo patients compared to patients with MI, and endomyocardial biopsies have shown apoptosis of microvascular endothelial cells in Takotsubo patients[130,131]. The use of adenosine, a potent vasodilator of cardiac microvasculature, in patients with acute Takotsubo has temporarily improved cardiac function, giving further support to this theory[132]. However, one study showed normal perfusion in a rat model of Takotsubo, challenging the theory of microcirculatory dysfunction[133]

Direct effects on cardiomyocytes
Catecholamines can impact the viability of myocytes, causing apoptosis by calcium overload through cyclic adenosine monophosphate. The resulting contraction band necrosis has been described in Takotsubo patients by Wittstein et al.[76,134]. Furthermore, studies have shown contractile dysfunction due to decreased calcium affinity, caused by increased dephosphorylation of phospholamban and increased sarcolipin, resulting in the downregulation of SERCA2a[135]. In addition, the ryanoid receptor has been implicated in acute cell death, and lipotoxicity caused by catecholamines has been seen in an animal model[136,137].

Effects though beta-receptors
The highest density of beta-adrenergic receptors in the mammalian heart is in the apex, possibly to compensate for less autonomic nerve innervation in this area[138,139]. The distribution increases susceptibility to catecholamines in the apex, which could lead to paradoxical negative inotropic effects described as "molecular switch". The beta-2 receptor switches from activating the inotropic Gs pathway to the negatively inotropic Gi pathway, possibly to protect the myocardium from overstimulation[140-142]. The Gi pathway is associated with nitric oxide (NO) synthase and contributes to decreased inotropy and inflammation. One study showed increased effects of NO signalling in Takotsubo patients, while a post-mortem analysis did show signs of NO-dependent inflammation[143,144]. However, this explanatory model cannot explain non-apical RWMA distribution. A study in rats has also questioned the importance of b-receptors in the development of Takotsubo[145]

Other theories
CMR has shown inflammation and downregulation of energy levels in Takotsubo patients [146,147].

Diagnosis
The diagnosis of Takotsubo is based on typical RWMA distribution and exclusion of CAD[148]. CAD can be present in other areas but should not be the cause of the wall motion abnormalities[95]. In case of fever, elevated inflammatory markers or pericardial effusion, CMR is recommended to rule out infectious myocarditis[148]. A scoring system has been proposed to better help with diagnosis[149]. Electrocardiogram (ECG) most often shows ST-elevations, T-wave inversion or ST segment depressions[92]. Several criteria systems have been developed to try and differentiate between ST segment elevations caused by acute coronary syndromes (ACS) and Takotsubo. However, coronary angiography is still mandatory to exclude CAD and set a correct diagnosis[150,151]. Almost all cases present with elevations of troponins, indicating damage to the myocardium, although the peak levels are less pronounced than in ACS[92]. NT-proBNP values are usually increased and typically reach peak concentrations within 24-48 hours; the levels seem to correlate with affected myocardium in CMR images[152,153]. Other, more specific, markers have been evaluated, including soluble lectin-like oxidized LDL receptor-1, circulating microRNAs and interleukins, but none are in clinical use[154-156]. CMR criteria for diagnosing Takotsubo are; classical RWMA distribution, oedema, and absence of late gadolinium enhancement (LGE)[105].

Treatment

No causal treatment exists for Takotsubo, and therapy is aimed at complications. In severe heart failure, inotropy could be used. Mechanical support with VA ECMO, Impella® and intraaortic balloon pump has been used[157-159]. In patients who develop LV outflow obstruction, it might be reasonable to try beta-blockers if no major contraindications are present[160]. Animal experiments also support using beta blockers to reverse myocardial depression, although no beneficial long-term effects have been seen in humans[161,162] . Angiotensin Converting Enzyme inhibitors (ACE inhibitors) have been associated with lower recurrences in a meta-analysis of observational data but are not universally recommended, and many contraindications to their use exist in critical care patients[160].

1.3.3 MYOCARDIAL INFARCTION IN ICU

MI is common in ICU patients, with studies indicating a mortality of up to 20%[163-165]. It can be the primary reason for ICU admission or develop during intensive care. The diagnosis of MI, according to the fourth universal definition of MI, requires clinical evidence of acute myocardial ischaemia and troponin levels above the 99th percentile upper reference limit, in addition to >1 of the following criteria[166]:

- Symptoms consistent with myocardial ischaemia, e.g., chest pain
- New ischaemic changes on ECG
- Findings of pathological Q waves on ECG
- New RWMA or loss of viable myocardium on imaging in patterns consistent with ischaemia

Five types of MI are defined. However, in ICU patients, two types of MI are most often seen; Type 1, with findings of a significant coronary occlusion on angiography or autopsy, and Type 2, with evidence of supply-demand mismatch unrelated to coronary thrombus such as anaemia in the bleeding patient or tachyarrhythmias causing cellular hypoxia in a patient with stable CAD. Type 2 MI generally carry a worse prognosis in relation to their underlying pathology [167-169]. MI has to be differentiated from increased troponins from other causes of cardiac injury, such as myocarditis and acute heart failure[170]. The diagnosis of MI is challenging in intensive care patients. Most patients are either sedated or not cognitively intact enough to recognize symptoms such as chest pain and dyspnoea, troponins are often elevated because of non-ischaemic reasons, and all RWMA might not be diagnosed even if patients with haemodynamic instability are screened[171,172]. In addition, Yousang et al. showed that many patients with ECG changes and troponin increase did not have angiographic evidence of significant CAD[173]. The

challenging diagnosis of MI in the ICU might be a reason for its recognition as a preventable cause of ICU mortality[174].

Treatment

Treatment options for MI in ICU patients are similar to those presenting with MI in a general population[166]. However, many of these treatments are not suitable for ICU patients. Patients might not be hemodynamically stable enough for beta-blockade or nitroglycerin, and a risk-benefit analysis must be done before subjecting patients to invasive procedures like coronary angiography with associated antiplatelet therapy[175]. There are no specific guidelines for managing ICU-related MI, except for cardiogenic shock patients, where management is recommended to follow general guidelines for acute heart failure. The mainstay of cardiogenic shock treatment is with inotropes, vasopressors, diuretics and if necessary mechanical circulatory support. Cardiogenic shock guidelines recommend using NA as the first-line vasopressor in case of severe hypotension, possibly combing this with inotropes, as studies have shown NA to be superior to other vasopressors[1,176]. No specific inotrope is recommended, but guidelines suggest that levosimendan or type-3-phosphodiesterase inhibitors might be superior to dobutamine in patients treated with beta-blockers[177,178].

1.3.4 MYOCARDITIS

In Sweden, the incidence seems to be rising, with around 900 cases per year and one-year mortality of almost 10%[179]. Patients often present with a prodromal phase consisting of fever and a flu-like illness in the weeks leading up to the disease. However, the classic presentation of severe acute myocarditis consists of fatigue, dyspnea, chest pain, palpitations, syncope and cardiogenic shock, or may result in sudden cardiac death[180,181]. Patients with severe disease such as LVEF <50%, sustained ventricular tachycardias or hemodynamic instability have a worse prognosis, with a risk of heart transplant or death within five years of almost 15 %[182]. Several biomarkers have been evaluated for diagnosing myocarditis, including; NT-proBNP, Troponin, T, C-reactive protein and soluble IL-1 receptor-like 1, but none are specific enough to diagnose myocarditis[183]. CMR is the non-invasive golden standard for the diagnosis of myocarditis. The Lake Louise Criteria are recommended, and LGE can help with the risk stratification of patients[184,185]. The golden standard for diagnosis is an endomyocardial biopsy from RV and LV combined with immunohistochemistry for inflammatory characterization and polymerase chain reaction for analyzing viruses[186].

Pathogenesis

Myocarditis is an inflammatory disease of the myocardium most often triggered by viruses, although it can be triggered by other infectious agents, systemic disease, drugs and toxic substances as well[187-190]. The most implicated viruses are adenoviruses, enteroviruses, parvovirus B19, cytomegalovirus, Epstein-Barr virus, human herpes virus 6, influenza viruses, hepatitis C and possibly coronaviruses[191-196]. The mechanism behind myocarditis seems to result from a triggering event with direct myocyte injury in conjunction with the patient's immune system[197,198]. Different mechanisms, including specific receptors such as the coxsackievirus-adenovirus receptor and specific proteinases, can cause direct myocyte damage[199,200]. The myocyte damage triggers the initial host immune response by the innate immune system where macrophages, natural killer cells, toll-like receptors 3 and 4, as well as interferon-α and -β have been shown to have a central role[201,202]. The activity of the innate immune system is followed by the activation of the adaptive immune system by specific T-lymphocytes. Although the initial activation of the immune system leads to decreasing viral load and damage, a continuing and unrestrained response, for example sustained production of interleukin-1 or tumor necrosis-α, leads to worsening myocarditis and might contribute to the development of dilated cardiomyopathy[203,204]. The exact mechanism causing myocardial dysfunction is complex, might be multifactorial and differ between triggers.

Treatment

If patients present with cardiogenic failure, treatment is recommended according to the usual guidelines for acute heart failure, including inotropes and mechanical circulatory suppoort[205,206]. Arrhythmias seem more prevalent than other acute cardiac conditions and are treated with usual antiarrhythmics and possibly implantable cardiac defibrillator[207,208]. In specific cases such as human immunodeficiency virus or hepatitis C associated myocarditis, anti-viral treatment is recommended[209,210]. Different immunomodulatory strategies might be tried for viral-negative myocarditis, including corticosteroids, azathioprine and intravenous immunoglobulins[211,212].

1.3.5 MYOCARDIAL INFARCTION NON-OBSTRUCTIVE CORONARY ARTERIES (MINOCA)

Some patients presenting with symptoms of MI have a non-significant obstruction of coronary arteries (most often classified as <50% lumen reduction). These patients are classified as MINOCA and are estimated to represent 5-9 % of all cases of MI[213-215]. Patients are younger and have less hyperlipidemia compared to CAD patients[214,216]. The prognosis depends on underlying diseases, but patients with increasing arteriosclerotic burden have a worse prognosis[217-219]. Different etiologies have been included in the definitions of MINOCA; some include conditions such as Takotsubo and myocarditits[220,221]. According to the revised concept by the AHA, the term MINOCA should only be used in patients with an ischemic aetiology to their clinical symptoms, encompassing patients with suspected MI based on biomarkers and clinical picture but no lesion >50% in a major epicardial vessel[222]. The following conditions should be excluded. 1) Other causes of troponin elevations, e.g., pulmonary embolism or sepsis. 2) Clinically missed obstructive coronary disease 3) Nonischemic mechanism. The diagnosis is categorical and requires investigations to find the underlying cause.

Diagnosis

Careful evaluation of angiographic findings and echocardiograms is recommended. Using intravascular ultrasound or optical coherence tomography (OCT) can also add to diagnostic certainty for specific diagnoses[223]. For patients with unknown aetiology, CMR can help identify other diseases such as Takotsubo and myocarditis[224].

Reasons behind MINOCA

Plaque Disruption

The term includes plaque erosion, plaque rupture and calcific nodules, which can trigger thrombus formation leading to distal embolization, coronary spasm and possibly transient thrombosis ending with spontaneous disruption[217,225]. Patients with plaque disruption have at least some degree of atherosclerosis[226].

Type 2 infarction

Type 2 infarction appears without significant coronary artery obstruction because of supply-demand mismatch[166]. Guidelines recommend that "the diagnosis of type 2 myocardial infarction in patients with MINOCA is set when a plausible cause exists (e.g., tachycardia, anaemia, hypotension) in the absence of clinical, angiographic, or invasive imaging modalities that would otherwise support a different diagnosis"[222].

Microvascular Dysfunction
The coronary microvasculature consists of small vessels but makes up a large part of the coronary resistance in patients with normal coronary arteries[227]. Dysfunction of the coronary microvasculature has been chiefly described instable angina, but some overlap with MINOCA, where micro-circulatory dysfunction could cause myocardial injury, could exist[228]. The delineation is hard as microvascular perfusion abnormalities also can be a consequence of MI[222].

Embolism or Thrombosis of the Coronaries
Coronary artery embolism with spontaneous dissolution seems to be an uncommon reason for MINOCA. A screening of 1776 MI patients showed a less than 3 % prevalence of coronary embolism, and most patients suffered from atrial fibrillation[229]. In MINOCA patients, several thrombophilia disorders have been implicated and might be present in up to 14 % of patients[214]. Several hypercoagulable states have also been implicated in contributing to spontaneous embolism[222].

Coronary Artery Dissection
Coronary artery dissection could cause constriction of the coronary artery and subsequent MI[230]. It appears more frequently in women and might contribute to up to 35 % of MI in women under 50 years of age[231]. Spontaneous coronary artery dissection might not be evident on initial angiographic examination, and OCT is recommended to increase diagnostic certinty[232].

Epicardial Coronary Vasospasm
Vasoconstriction of the coronary arteries results in vasospastic angina with dynamic ST elevations and clinical symptoms resulting from spasm[233]. It might also appear with significant CAD but is likely a common cause of MINOCA being implicated in up to 46 % of patients[234]. Diagnosis is mainly performed with acetylcholine provocation[235].

Treatment
Treatment for MINOCA patients depends on the underlying pathology. A more extensive Swedish register study in an unspecified MINOCA population reported beneficial effects of statins, ACE- inhibitors/Angiotensin Receptor Blockers and possible betablockade, but no beneficial effects of antithrombotic therapy[236].

1.3.6 POST-CARDIAC ARREST STUNNING

Post-cardiac arrest stunning is a part of post-cardiac arrest syndrome leading to decreased cardiac function following cardiac arrest. LV systolic dysfunction

is primarily described, but other studies have reported RV systolic dysfunction and LV diastolic dysfunction[237-240]. The cardiac dysfunction is described as reversible and most often with apical RWMA[239,241]. The reported prevalence after primary non-cardiac circulatory arrest ranges from 34 to 69%[239,242]. Shock and vasopressor need after cardiac arrest are associated with increased mortality, but no clear relation between heart failure or cardiac output and mortality has been established[239,243-248].

Pathophysiology

Several underlying pathophysiological processes have been implicated in the development of post-cardiac arrest stunning.

Ischemia-Reperfusion Injury

Reperfusion injury is one of the primary pathophysiological mechanisms proposed for multiorgan failure and cardiac dysfunction after cardiac arrest, and a similar process is described after cardiopulmonary bypass[249-251]. In myocytes, cellular ischemia causes failure of the Na/K ATPase pump leading to intracellular sodium overload, which is exaggerated by dysfunction of the Na/H exchanger because of intracellular acidosis. The increased intracellular sodium leads to oedema and activates the Na/Ca^{2+} exchanger, which in synergism with the failure of the Ca^{2+} ATPase, leads to calcium overload[252]. Calcium overload activates calcineurin and results in cellular apoptosis through mitochondrial permeability transition pores. In addition, it might affect the active relaxation of the heart muscle and lead to arrythmias[253]. When blood flow is restored, increased production of reactive oxygen species leads to further damage, which is further exaggerated by lactic acidosis[250,254].

Catecholamine toxicity

Cardiotoxicity mediated through catecholamines, seen in other syndromes such as Takotsubo, has also been implicated in post-cardiac arrest stunning[96,134,250]. Animal models have shown a correlation between adrenaline doses and post-resuscitation myocardial dysfunction, which can be treated with b-blockade. In addition, beta-receptor downregulation has been seen in cardiac arrest stunning in animals[255-257].

Inflammatory Dysfunction

The systemic effect of ischemia-reperfusion increases the production and release of inflammatory cytokines leading to Systemic Inflammatory Response Syndrome (SIRS)[258-260]. SIRS could lead to general vasoplegia, and various cytokines have direct cardio depressive effects, which could contribute to post-cardiac arrest stunning[49,66].

Treatment

No specific treatment exists for post-cardiac arrest stunning, but inotropy is recommended in case of heart failure and hypoperfusion. European Resuscitation Council recommends treatment with dobutamine as a first-line inotrope, based on two studies in swine[249,261,262].

1.4 BIOMARKERS

1.4.1 TROPONIN

Troponin is present in skeletal and cardiac myocytes and is a part of the contractile system. It facilitates and regulates the interplay between actin and myosin filaments. In the myocytes, cardiac troponin consists of three different subunits.
-Troponin T anchors the troponin complex to the actin filament
-Troponin C is the calcium-binding site
-Troponin I block the binding between myosin heads if insufficient calcium ions are present
Troponin C is also present in skeletal muscle; therefore, troponin T and I are used for diagnosing cardiac injury[263]. After MI, troponins rise within 4-10 hours and stay elevated for up to 10 days[264]. Troponins might rise from necrosis or apoptosis of cardiac cells but are not exclusively related to cell death[265]. Detection of troponins has been developed to help diagnose MI and has a clearly defined role in this scenario[166]. However, troponins might be elevated in other conditions often seen in ICU patients, such as kidney failure, sepsis, atrial fibrillation (AF), hypovolemia, myocarditis, heart failure, pulmonary embolism and myocarditis[266-269]. Nonetheless, in ICU patients rise of troponins has been associated with increased mortality, especially in patients with sepsis[270-272]. Together with NT-pro BNP, troponins have also proven useful in screening for Takotsubo in patients with subarachnoid haemorrhage but not in a more general population of critically ill patients[273]. Systematic screening using troponins has also been evaluated in identifying previously undiagnosed MI in critically ill patients[274].

1.4.2 NT-PROBNP

Brain-type natriuretic peptide (BNP), or B-type natriuretic peptide, was first isolated from the porcine brain in 1988, hence the name[275]. It was soon, however, established that it was mainly produced by cardiac cells. BNP is a natriuretic peptide similar to atrial natriuretic peptide (ANP) and C-type Natriuretic Peptide. It is primarily secreted as well as synthesized in the ventricular myocardium. In contrast to ANP, which is stored in granules and can be readily released into the circulation, most BNP increase is through de novo synthesis. The biological stimulus for increased BNP production and secretion mainly depends on myocardial wall stress. Both right and left ventricle myocardial wall stress seem to impact production, but other factors such as myocardial ischemia, effects of other neurohormones, tachycardia and corticosteroids play a role[276-280]. A pre-hormone of BNP (proBNP) is synthesized and released into the circulation, where proBNP is split into the C-

terminal fragment BNP consisting of 32 biologically active amino acids and the N-terminal fragment (NT-proBNP) composed of 76 amino acid which is biologically inactive[281,282]. The half-life of BNP is 20 minutes, resulting in detectable differences in status within 2 hours, while the half-life of NT-proBNP is approximately 120 min, reflecting changes in hemodynamics analyzable within about 12 hours[283,284]. In normal hearts, BNP and NT-proBNP levels reflect the other, but in patients with LV dysfunction, NT-proBNP levels are higher than BNP, making it a better marker for LV dysfunction[285]. The end effect of BNP in peripheral tissue is mediated through natriuretic peptide receptor type A, which increases intracellular cGMP production[286]. Increasing cGMP levels leads to vasodilatation, diuresis, a decrease in renin production and cardiac myocyte growth[280,287-290]. NT-proBNP is exclusively excreted by the kidneys, making renal failure an essential factor in assessing biomarker levels[291,292]. In cardiology, NT-proBNP has an established role as a screening tool for heart failure using a clearly defined cut-off[1]. However, multiple other parameters frequently observed in ICU patients, such as arrhythmias, ischemia, coronary endothelial dysfunction, liver failure, brain injury, sepsis and ARDS, influence NT-proBNP levels, potentially decreasing its use[293-295]. Despite this, BNP and NT-proBNP have been extensively studied in ICU patients, focusing on septic patients. They have been shown to correlate with myocardial function in septic patients, but not necessarily in more diverse patietens[296-299]. Studies have also used the marker in screening for diastolic dysfunction in ICU patients[44]. Levels of NT-proBNP are associated with mortality in many patient groups and seem to correlate with systolic LV and RV function, diastolic function, and volume status. However, no ICU studies have adjusted for cardiac function when using NT-proBNP for prognostication, and no current cut-off levels for NT-proBNP in intensive care patients have been established[300,301].

2 AIMS

The thesis was focused on LV function in a general population of critically ill patients. The aim was to evaluate the prevalence, impact on mortality and aetiology of systolic and diastolic LV dysfunction. In addition, the use of cardiac biomarkers and CMR was explored.

Specific goals:

1. Analyze the prevalence and effect on the mortality of LV *systolic* dysfunction in critically ill patients, focusing on non-ischemic LV dysfunction (Paper I)
2. Analyze the prevalence and effect on mortality of LV *diastolic* dysfunction in critically ill patients with normal systolic LV function (Paper II)
3. Analyze the use of cardiac biomarkers in critically ill patients, focusing on screening for cardiac dysfunction and risk stratification (Paper III)
4. Verify that patients with RWMA in the ICU can have non-obstructed coronary arteries and explore the use of CMR for pathophysiological classification in such patients (Paper IV)

3 PATIENTS AND METHODS

3.1 PATIENTS

3.1.1 PAPER I

The same study cohort was used for the first three papers. Patients admitted to the general or the neuro ICU of Sahlgrenska University Hospital were screened for inclusion. The neuro ICU admits patients with neurological and neurosurgical diseases, including stroke, hemorrhagic or traumatic brain injuries, and patients after major neurosurgery. The general ICU admits medical patients from all disciplines and surgical patients (vascular, upper abdominal surgery, trauma spinal surgery, and liver transplantations). Prospective inclusion was performed between the 28th of May 2018 and the 20th of January 2019 on 151 specific study days when resources were available. All eligible patients admitted to the ICUs during study days were consecutively included. The patient or the patient's next of kin (if the patient could not consent) was asked for permission. The study was registered in the international database ClinicalTrials.gov (reg no. NCT03787810). Inclusion criteria were: 1) Able to undergo TTE within 24 h of admission, 2) Age ≥18 years, 3) Failure of at least one organ system (Sequential Organ Failure Assessment (SOFA) >1)[302]. Based on a previous retrospective study, a power analysis estimated that 400 patients needed to be included to find a difference in mortality between patients with normal LV function and patients with LV dysfunction[303].

3.1.2 PAPER II

The same initial cohort was used for the second study, focusing on diastolic function in critically ill patients. Patients with reduced LVEF, RWMA or known cardiac disease were excluded. Inclusion criteria were: 1) LVEF > 50% 2) no history of cardiac disease, including cardiomyopathies, heart failure or CAD 3) absence of regional hypokinesia or significant valvular disease 4) no acute, ongoing cardiac disease, e.g. MI, 5) sinus rhythm at the time of inclusion and, 6) having two or more parameters, from the EACVI guidelines for assessment of diastolic function in patients with normal systolic LV function, measured[34].

3.1.3 PAPER III

The same initial cohort was used for the third study. Inclusion criteria were: 1) at least one cardiac biomarker (hsTNT and proBNP) analysed at the time of TTE 2) able to assess all types of cardiac dysfunction defined in the study.

3.1.4 PAPER IV

The hospital angiography register was merged with the local ICU register to identify patients who underwent angiography in connection with their ICU stay. Patients admitted from Jan 2012 to June 2019 were assessed for inclusion in the study. Inclusion criteria were; 1) underwent coronary angiography from 7 days before to 21 days after ICU admission, 2) TTE performed by the hospital echocardiography laboratory +/- 48 hours in relation to angiography, 3) presence of RWMA in at least two adjacent segments of the LV. Exclusion criteria were: 1) age below 18 years, 2) history of CAD, heart failure or cardiomyopathy.

3.2 CLINICAL DATA

3.2.1 PAPER I-III

On admission, the following parameters were recorded: sex, age, medical history, and severity of illness evaluated with Simplified Acute Physiologic Score III (SAPS 3) score and SOFA score as well as the reason(s) for admission according to SAPS 3[302,304]. In addition, verified or suspected sepsis, septic shock, MI and cardiac arrest were separately registered[78]. At the time of echocardiography, heart rate, blood pressure, dose of inotropic support and vasopressor, serum creatinine levels, lactate levels, PaO_2/FiO_2 and ventilator settings were documented. From the local ICU registry, time to death during the first 180 days following admission and 30-day mortality was acquired.

3.2.2 PAPER IV

Cause of admission according to SAPS 3 and total SAPS 3 score, respiratory data, hemodynamic data, as well as 30-and 90-day mortality was retrieved from the local ICU register. From the coronary angiography register, the following data was acquired: sex, age, body mass index, indication for angiography, results of angiography and angiographic interventions. The following data were obtained from the patient's medical records: the primary reason for ICU admission as stated by the admitting physician, medical history, NT-proBNP and troponin levels. Echocardiographic and CMR data were manually obtained from TTE and CMR reports.

3.3 ECHOCARDIOGRAPHIC EXAMINATION AND PROTOCOL

3.3.1 PAPER I

Included patients underwent a standard TTE, following international recommendations, within 24 hours of ICU admission[305,306].The following parameters were used: LVEF, presence and location of RWMA, velocity time integral (VTI) in the LV outflow tract, stroke volume, and cardiac output (CO). EF was estimated with Simpson Biplane and, if not feasible, by eyeballing. RWMA was assessed according to the standard 17-segment model[10]. LV dysfunction was classified as: LVEF <50% or RWMA. Patients were further classified as LV systolic dysfunction and cardiac disease (admitted with acute cardiac disease or a history of cardiac disease) and patients with LV systolic dysfunction and non-cardiac disease (no acute cardiac disease and no history of cardiac disease). A second expert in echocardiography reviewed a blinded number of normal examinations (n = 46) and all examinations with systolic LV pathology. Inter-agreement between the reviewers was 93% (kappa value 0.84). No examination interpreted as normal by the primary examiner was deemed to have pathology when reviewed.

3.3.2 PAPER II

The following parameters were used in Paper II: Lateral e'(e'_{lat}) and septal e' (e'_{sep}), tricuspid regurgitation maximum velocity (TR Vmax) and left atrial volume index (LAVI). Left atrial volume was calculated by the disc summation method, using apical 2 and 4 chamber views if possible and only the 4-chamber view if the 2-chamber view was missing[306]. LAVI was acquired by indexing left atrial volume to body surface area[306,307]. Maximal flow velocity was obtained during LV early (E-max) and late (A-max) diastolic filling, and the deceleration time of the E wave was assessed with PW Doppler at the mitral inflow. The following parameters were calculated: E/A ratio, $E/e_{average}$, or $E/(e'_{lat}$ or $e'_{sep})$ if only one parameter were available. A classification of the E/A ratio into normal, impaired, pseudo-normal, and restrictive patterns was performed[308]. A secondary review of the variables in Paper II was performed by an echocardiography expert in 22 randomly selected examinations, rendering a total of 108 diastolic measurements. Inter-agreement between reviewers was 93%, with a Kappa value of 0.83. The guidelines for the assessment of diastolic dysfunction by the EACVI were subsequently used to classify patients' diastolic function[34]. In patients with a normal systolic LV function, the following cut-off values are used; 1) $e'_{sep} < 7$ cm/s or $e'_{lat} < 10$ cm/s, 2) $E/e'_{average} > 14$ or $E/e'_{lat} > 13$, or $E/e'_{sep} > 15$, if only one is available, 3) TR Vmax > 2.8 m/s, and 4) LAVI > 34 ml/m^2. In the

EACVI guidelines, patients are classified as having diastolic dysfunction if > 50% of the assessed parameters are fulfilled. The function is indeterminate if 50% of the assessed parameters are fulfilled, and if < 50% of the criteria are fulfilled, the patient is deemed to have a normal diastolic function (Fig 5). The Preferred Reporting Items for Critical Care Echocardiography Studies (PRICES) consensus report suggests reporting deceleration time and E/A ratio as diastolic markers, in addition to the parameters used in the EACVI guidelines, and these markers were therefore reported[309].

A simplified definition of the diastolic function proposed by Lanspa et al. was used in a post hoc analysis[310]. Patients are classified using e'_{sep}. If < 8 patients are deemed to have diastolic dysfunction. Subclassification is based on E/e'; < 8 classifies patients as grade 1 diastolic dysfunction; 8-13 classifies patients as grade 2 diastolic dysfunction; and > 13 classifies patients as grade 3 diastolic dysfunction.

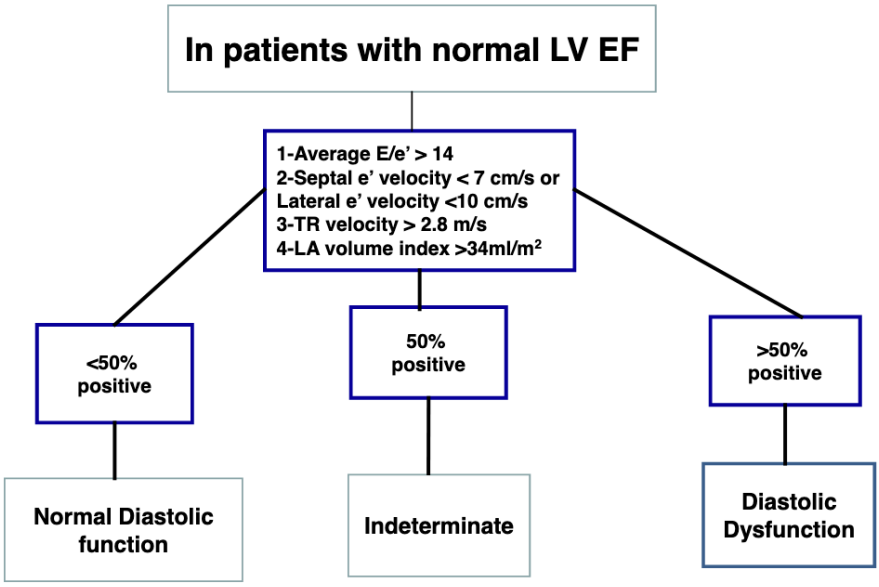

Figure 5 Assessment of diastolic function in patients with normal systolic function. TR-velocity = Maximum tricuspid regurgitation velocity, LA = Left atrium Reprinted from "Nagueh et al., Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Journal of the American Society of Echocardiography 2009; 22: 107-33[34]", with permission from Elsevier.

3.3.3 PAPER III

For Paper III, the following definitions were used for cardiac dysfunction:

Isolated LV systolic dysfunction: LVEF < 50% or RWMA in two or more adjacent segments with no *isolated RV systolic function* or *isolated LV diastolic dysfunction*.

Isolated LV diastolic dysfunction: Fulfilling criteria for diastolic dysfunction or indeterminate diastolic function according to the diastolic guidelines of the EACVI, and exhibiting no *isolated LV systolic dysfunction* or *isolated RV systolic dysfunction*[34].

Isolated RV systolic dysfunction: Fulfilling any of 1) tricuspid annular plane systolic excursion (TAPSE) < 17 mm; 2) RV tissue doppler derived tricuspid lateral annular systolic velocity wave (S') < 11 cm/s; or 3) fractional area change (FAC) < 35% with no *isolated LV systolic function* or *isolated LV diastolic dysfunction*.

Combined cardiac dysfunction: Fulfilling any criteria of *LV Systolic* or *LV diastolic dysfunction* and *Isolated RV systolic dysfunction*.

Any cardiac dysfunction: Fulfilling any criteria of cardiac dysfunction.

Normal cardiac function: Fulfilling no criteria of cardiac dysfunction.

3.4 BIOMARKERS, PAPER III

The laboratory of Clinical Chemistry at Sahlgrenska University Hospital Analyzes performed the analysis during the study period. Biomarkers were analyzed using immunoassay techniques; NT-proBNP was analyzed with the Elecsys assay (Roche) and hsTnT with the Roche high-sensitive troponin T assay.

3.5 ECHOCARDIOGRAPHIC CLASSIFICATION AND CMR, PAPER IV

Patients with RWMA in ≥2 segments were classified according to results of coronary angiography results into; 1) Patients with *RWMA and non-obstructed coronary arteries,* including patients with normal coronary arteries, mild coronary atheromatosis, or non-significant stenosis (< 50% of the lumen); and

2) Patients with *RWMA and obstructed coronary arteries*, including patients with significant coronary artery stenosis (> 50% of the lumen), thrombus, or emboli resulting in compromised coronary artery flow. A comprehensive analysis was done in the group with *RWMA and non-obstructed coronary arteries.* RWMA distribution was analyzed, and follow-up echocardiography was sought for and compared to echocardiography performed in conjugation with coronary angiography. CMR results were obtained, if available, and reviewed by a senior expert in CMR interpretation.

3.6 STATISTICS

Normally distributed variables were presented as the mean ± standard deviation and non-normally distributed variables as the median with interquartile range. ANOVA or T-test was used to compare means of normally distributed variables, and the Kruskal-Wallis or Mann-Whitney U test was used to compare distributions of non-normally distributed variables. (Paper I-IV). Fisher's Exact test was used for binary outcomes, and the Chi^2 test was used for comparing three or more outcomes between two groups (Paper I, III and IV). In Paper II, the Mantel Haenszel test, linear regression, and the Jonckheere-Terpstra test were used to analyze trends for binary, normally distributed, and non-normally distributed data, respectively, for the groups with normal, indeterminate, and diastolic dysfunction. Paper III used a quantile regression model of the median to analyze if renal failure or sepsis were associated with higher levels of hsTnT and NT-proBNP, independent of *any cardiac dysfunction*. Cut-off values for biomarkers in Paper III were analyzed using receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated. Youden's test was used to identify the highest relationship between sensitivity and specificity. Negative predictive value (NPV) and positive predictive value (PPV) were calculated.

All papers used logistic regression to calculate the risk of death at 30 or 90 days. Risk adjustments were performed by including these variables in the logistic regression model with the exposure variable to be tested. Kaplan Meier methodology with the log-rank test was used to compare incidences during 90 days from admission. Statistical analyses were performed with IBM SPSS version 24.0 (IBM, Armonk, New York).

3.7 ETHICAL PERMITS

3.7.1 PAPER I-III

The initial study was approved by the Regional Ethics Committee in Gothenburg, Sweden (registration number 036-18).

3.7.2 PAPER IV

Approval for the study was granted by the regional ethics committee of the University of Gothenburg (protocol number 994-14, Approval date Jan 18, 2015), which was further supplemented (protocol number 2021-06306-02). No consent was deemed necessary by the ethics committee because of the study's retrospective design.

4 RESULTS

4.1 PAPER I

In total, 479 patients were admitted to our ICU, fulfilling inclusion criteria during the study days. 51 of them were not included, 45 since they were not examined within 24 hours, and 6 did not want to participate. Of the 428 included patients, 17 were later excluded due to low-quality echo. Thus, 411 patients were used in the final analysis. Systolic LV dysfunction was seen in 24% of the total study cohort (n=100). According to definitions described in methods (page 29), 12% (n=48) patients were classified as having LV dysfunction due to a cardiac disease, and 12% (n=52) had LV dysfunction with non-cardiac disease.

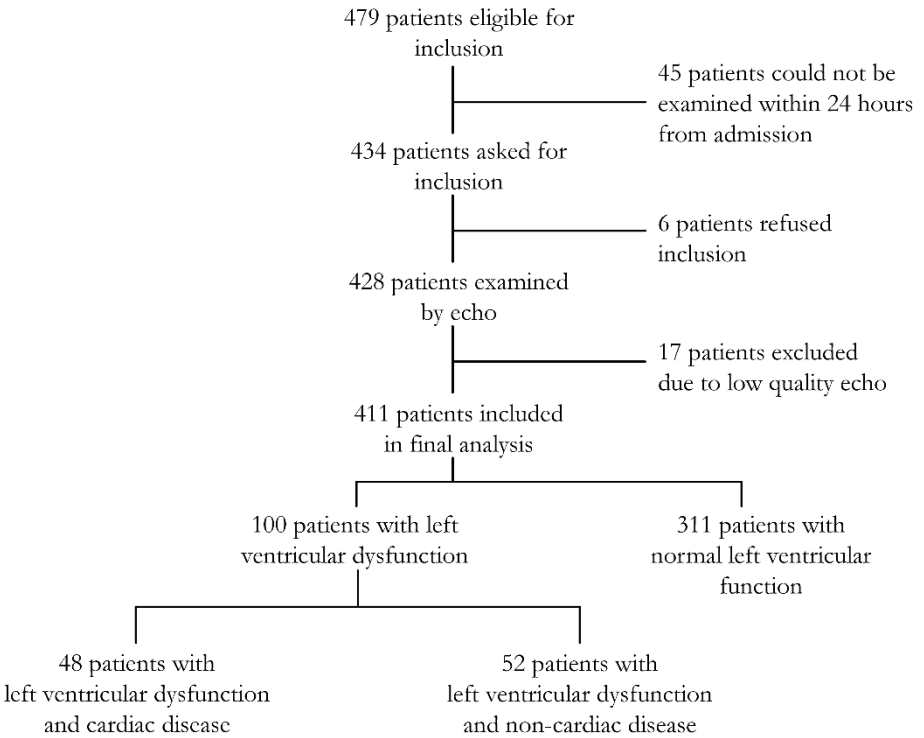

Figure 6. Patient inclusion Paper I Reproduced from "Cavefors et al. Regional left ventricular systolic dysfunction associated with critical illness: incidence and effect on outcome. ESC Heart Fail 2021; 8: 5415-23. [311]"with permission from John Wiley and Sons

Patients with systolic LV dysfunction had a higher degree of disease on admission, reflected by higher SOFA and SAPS 3 scores. Patients with LV dysfunction and non-cardiac disease were more commonly admitted due to sepsis, respiratory failure, or major bleeding. Patients with LV systolic dysfunction had lower LVEF, as well as lower VTI, indexed stroke volume and cardiac index (CI) (Table 1), than patients with normal systolic LV function. They also had a higher degree of hemodynamic compromise with higher noradrenaline doses and lower systolic blood pressures. Most patients had RWMA, +/- low EF, observed in 82 patients (82%). Apical and septal segments were most frequently affected in patients with systolic LV dysfunction and non-cardiac disease, while 12 patients presented with circumferential patterns of hypokinesia associated with classical Takotsubo syndrome.

In the group systolic LV dysfunction and non-cardiac disease, 13 of 52 patients underwent coronary angiography because of high suspicion of CAD. Two angiographies showed CAD (these patients were moved to the systolic LV dysfunction and cardiac disease group), while 11 angiographies were without significant coronary artery stenosis. Coronary angiography was not indicated in the remaining patients because of low clinical suspicion of CAD or dismal prognosis. A follow-up echocardiogram was available in 38 patients with LV dysfunction and non-cardiac diseases (six patients died shortly after admission, and eight were lost to follow-up due to early discharge). Recovery of cardiac function on follow-up echocardiogram was seen in 36 patients (95%).

Category	Variable	Normal left ventricular function (n = 312)	Left ventricular dysfunction		P-value
			Cardiac disease (n = 48)	Non-cardiac disease (n = 52)	
Echocardiographic data	LV end-diastolic diameter, cm	4.8 ± 0.5[b]	5.5 ± 1.0[a,c]	4.9 ± 0.7[b]	<0.001
	LV ejection fraction, %	60 ± 6[b,c]	39 ± 12[a,c]	46 ± 10[a,b]	<0.001
	Velocity time integral, cm^2	19 ± 9[b,c]	14 ± 7[a]	14 ± 6[a]	<0.001
	Stroke volume index, mL/m^2	44 ± 12[b,c]	31 ± 12[a]	32 ± 10[a]	<0.001
	Cardiac index, $L/min/m^2$	3.5 ± 1.2[b,c]	2.6 ± 1.0[a]	2.8 ± 0.8[a]	<0.001
	Patients with RWMA, n (%)	0 (0)[b,c]	40 (85)[a]	42 (81)[a]	<0.001
	Segments with hypokinesia, n	0 (0–0)[b,c]	6 (3–12)[a,c]	5 (2–7)[a,b]	<0.001
	Wall motion score index	1 (1–1)[b,c]	1.35 (1.18–1.94)[a,c]	1.29 (1.18–1.59)[a,b]	<0.001
Haemodynamic data	Mean arterial pressure, mmHg	79 ± 14[c]	77 ± 17	74 ± 12[a]	0.037
	Systolic blood pressure, mmHg	123 ± 24[b,c]	112 ± 28[a]	109 ± 20[a]	<0.001
	Diastolic blood pressure, mmHg	59 ± 12	61 ± 19	56 ± 10	0.243
	Heart rate, b.p.m.	83 ± 21[c]	88 ± 23	91 ± 22[a]	0.038
	Noradrenaline, µg/kg/min	0 (0–0.13)[b,c]	0.10 (0–0.24)[a]	0.15 (0.06–0.3)[a]	<0.001
	CVP, mmHg	7 (4–11)[c]	10 (9–15)	12 (9–16)[a]	<0.001
	S-Lactate, mmol/L	1.3 (1.0–1.9)[b,c]	1.9 (1.2–2.5)[a]	1.5 (1.2–2.9)[a]	0.001
Respiratory data	PaO_2/FiO_2 ratio	39 (29–51)	32 (26–46)	38 (23–48)	0.209
	Mechanical ventilation, n (%)	128 (59)	23 (51)	21 (60)	0.567

CVP, central venous pressure; LV, left ventricular; RWMA, regional wall motion abnormalities.
Segments of hypokinesia and wall motion score index (WMSI) were calculated for the patients with regional hypokinesia.
P-value was calculated for detection of significance between three groups with χ^2 test, ANOVA, or Kruskal–Wallis test, as appropriate.
[a] $P < 0.05$ vs. group 'normal'.
[b] $P < 0.05$ vs. group 'cardiac disease'.
[c] $P < 0.05$ vs. group 'non-cardiac disease'.

Table 1 Reproduced from "Cavefors et al. Regional left ventricular systolic dysfunction associated with critical illness: incidence and effect on outcome. ESC Heart Fail 2021; 8: 5415-23. [311]" with permission from John Wiley and Sons

The study's primary outcome was 30-day mortality. This was increased in patients with systolic LV dysfunction and non-cardiac disease (33%) vs patients with normal LV function (18%, P = 0.023). However, adjusting for age and SAPS 3 score resulted in non-significant results (P = 0.225). The secondary outcome of the study was 90-day mortality. This was significantly higher in patients with non-cardiac systolic LV dysfunction vs patients with normal systolic LV function (44% vs 22%, P = 0.002). A risk-adjustment analysis did not change this result [OR 2.40 (CI 1.18–4.88), P = 0.016]. We could not observe any statistical difference in 90-day mortality between patients with LV dysfunction and cardiac vs non-cardiac disease (P = 0.606). Furthermore, mortality was only increased in patients who presented with RWMA (P = 0.002), in contrast to patients presenting with global hypokinesia (P=0.302), as compared to patients with normal LV function. Further analysis could also link several hemodynamic parameters (low VTI, stroke volume, and CI) to an increased risk of death at 90 days. This was significant both in crude and risk-adjusted analyses. A combination of low CI and systolic LV dysfunction was associated with a pronounced mortality increase at 90 days (Fig 7).

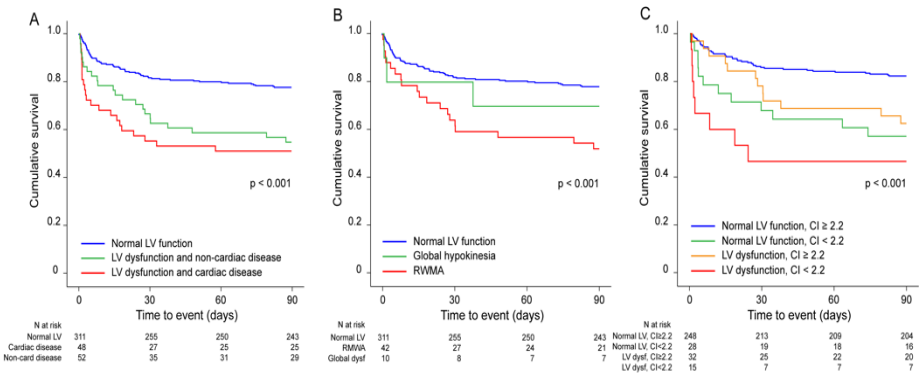

Figure 7. Reproduced from "Cavefors et al. Regional left ventricular systolic dysfunction associated with critical illness: incidence and effect on outcome. ESC Heart Fail 2021; 8: 5415-23. [311]" with permission from John Wiley and Sons

4.2 PAPER II

After the exclusion of patients with a chronic or acute cardiac disease(n=81), LV dysfunction or AF(n=62) and patients in which diastolic assessment was inadequate(n=50), 218 patients were included in paper II.
A varying amount of the four recommended diastolic parameters from the EACVI guideline could be evaluated in our patients. Four parameters were possible to evaluate in 145 (67%) patients, three variables in 45 (21%) patients, and two variables in 28 (13%) patients. In total, 162 (74%) patients were classified as having normal diastolic function according to the guidelines, and 21 (10%) fulfilled the criteria of diastolic dysfunction, while the diastolic function was indeterminant in 35 (16%) patients [34]. Patients with indeterminate or diastolic dysfunction had several different characteristics than those with normal diastolic function. They were of higher age, more commonly male and more often had previously diagnosed Chronic Obstructive Pulmonary Disorder (COPD), cerebrovascular disease, high blood pressure or peripheral artery disease. In addition, they had a higher burden of disease, exemplified by more elevated SAPS 3 scores. They also more commonly had a cardiovascular reason for admission. Moreover, the pO2/FiO2 ratio was lower; lactate levels were higher and suspected or verified sepsis was more prevalent in these groups. Regarding cardiac function, patients with indeterminate diastolic function or diastolic dysfunction had smaller LV end-diastolic diameters, and they had a correspondingly higher LVEF. Still, there were no differences in intraventricular septum thickness or cardiac output parameters. At 90 days, mortality was increased in patients who had indeterminate diastolic dysfunction ($P< 0.001$) or diastolic dysfunction ($P<0.001$) in comparison to patients who had normal LV diastolic function. A risk adjustment, incorporating patients' age and total SAPS 3 score, did not change the statistical significance. The analysis indicated increased risk of death in patients with indeterminate diastolic dysfunction (OR 4.3 [1.6–11.4], $p = 0.004$) and diastolic dysfunction (OR 5.1 [1.6–16.5], $p = 0.006$) compared to patients with normal diastolic function.

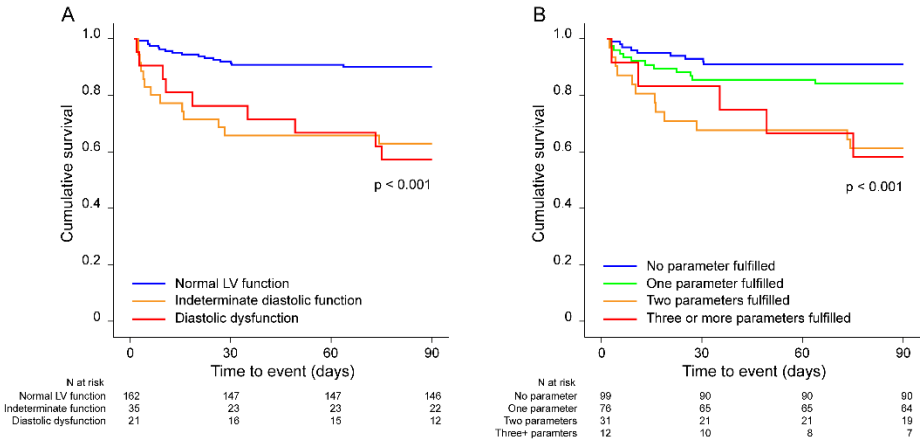

Figure 8. A) Mortality in patients with normal diastolic function vs indeterminate diastolic function or diastolic dysfunction. (B) Mortality in patients fulfilling no, one, two or three parameters of diastolic dysfunction. There were no significant differences in mortality between patients fulfilling no parameter or one parameter of diastolic dysfunction (P = 0.103). Mortality was significantly higher in patients fulfilling two parameters versus patients fulfilling one diastolic dysfunction parameter (P = 0.018). P-values presented in the figure are an overall comparison between groups. LV, left ventricle. Reproduced from "Isolated diastolic dysfunction is associated with increased mortality in critically ill patients Journal of Critical Care, Volume 76, 2023,154290" under Creative Commons CC-BY license.

4.3 PAPER III

In Paper III, we included 276 patients from the initial cohort of Paper I. We excluded 46 patients because of incomplete TTE and 89 because of missing biomarkers (Fig 9). Sensitivity analysis showed that included patients were a representative sample of the entire initial study population regarding SAPS 3, age and prevalence of *any cardiac dysfunction*. Most of the patients were non-surgical, male patients. The mean SAPS3 score was 59. Cardiac dysfunction was common, and most patients had a *combined dysfunction*, 100 patients (42%) presented with normal cardiac function.

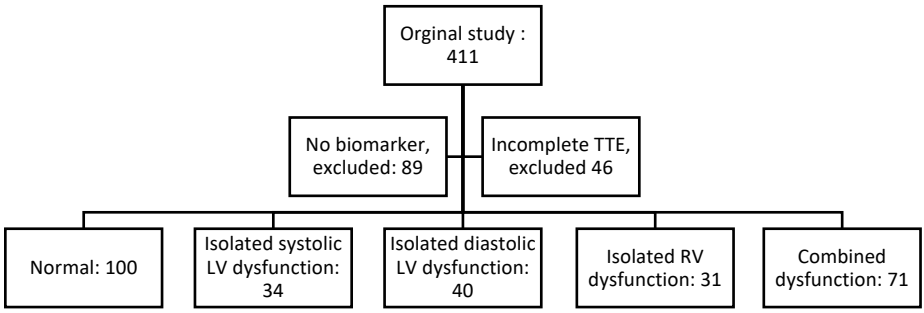

Figure 9. Patient inclusion in Paper III. TTE = Transthoracic Echocardiography, LV= Left Ventricular, RV = Right Ventricular

Biomarker levels were significantly higher in all groups of cardiac dysfunction, except in patients with *RV systolic dysfunction*, compared to patients with normal cardiac function. In the group with *isolated LV dysfunction,* the highest levels of hsTNT were observed, while patients with *combined LV and RV dysfunction* had the highest levels of NT-proBNP.

For *any cardiac dysfunction,* AUC in ROC curves were 0,788 for NT-proBNP and 0,757 for hsTNT. Youden's test identified optimal cut-off levels at 1145ng/L for NT-proBNP and 30,5 ng/L for hsTNT. The sensitivity, specificity, PPV and NPV analysis were done at the abovementioned levels, at 90 % sensitivity and 90% specificity. Using >90 % specificity for NT-proBNP and hsTNT rendered cut-off levels at 3265 and 80 ng/l, respectively. These levels resulted in a specificity of 39 %, leading to an NPV of 46 % and a PPV of 88% for both biomarkers. Using 90 % sensitivity gave a cut-off value of 247 ng/l for NT-proBNP and 14 ng/l for hsTNT. This cut-off value of NT-proBNP resulted in a specificity of 46 %, rendering a PPV of 72% and

an NPV of 72%. At the cut-off level of 14ng/l for hsTNT, the specificity was 48% resulting in a PPV of 75% and an NPV of 74%.

After adjustments for cardiac function, NT-proBNP levels were independently associated with renal failure and sepsis. Levels of hsTNT were independently associated with renal failure but not with sepsis.

Biomarker levels were associated with 90-day mortality in unadjusted data and in data adjusted for any cardiac pathology, SAPS 3 score and independently associated variables (sepsis and renal failure for NT-proBNP and renal failure for hsTNT)[304].

4.4 PAPER IV

After exclusions, as seen in Figure 10, 53 patients were classified as non-obstructed coronary arteries with RWMA based on the results from coronary angiography and were included in Paper IV. Another 204 patients were included and classified as RWMA with coronary artery obstruction based on coronary angiography results.

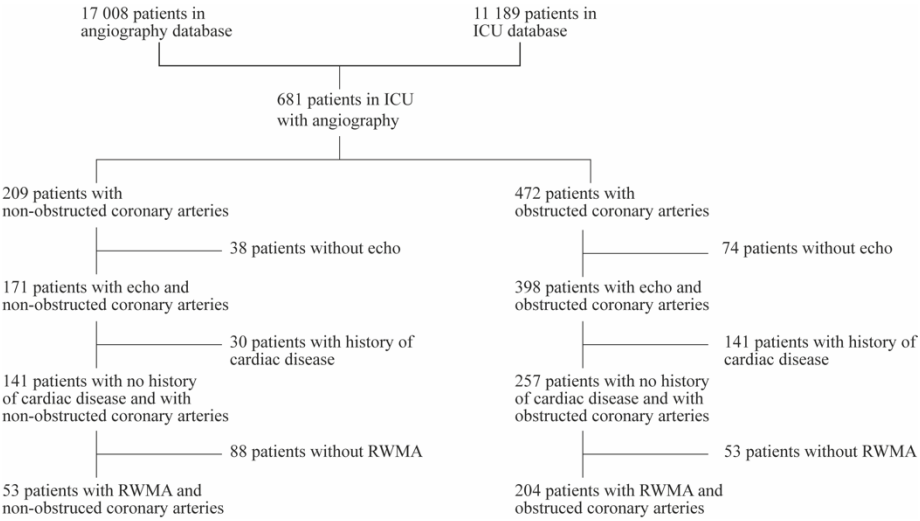

Figure 10. Patient inclusion in Paper IV. ICU, intensive care unit; RWMA, regional wall motion abnormalities. Reproduced from "Rosen-Wetterholm, E, Cavefors, O, Redfors, B, et al. RWMAs in critically ill patients with non-obstructed coronary arteries. Acta Anaesthesiol Scand. *2023; 1- 9." under Creative Commons CC-BY license.*[312]

Patients who were classified as non-obstructed coronary arteries were, compared to patients classified as obstructed coronary arteries, younger and more commonly female, and they also more often had a history of substance or alcohol abuse. In comparison, patients with coronary artery obstruction had a higher prevalence of smoking and more often suffered from renal disease, diabetes or hypertension.

Indications for coronary angiography differed between groups. The most common indication for angiography was ST-elevation in patients with obstructed coronary arteries. In contrast, patients with non-obstructed coronary arteries more often underwent coronary angiography to investigate heart failure or as a part of organ donation evaluation. Regarding echocardiographic features, there was no difference in LVEF or the number and location of affected segments when comparing the two groups.

Apical and septal RWMA were the most commonly affected segments both in patients with non-obstructed and obstructed coronary arteries (Fig 11).

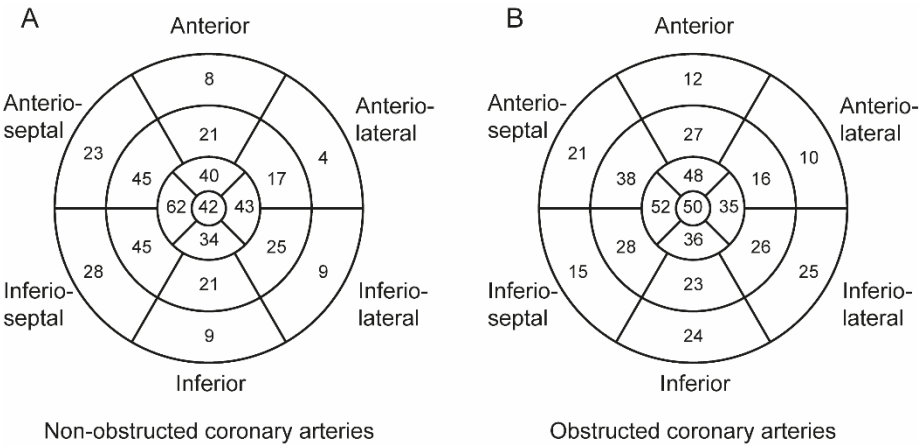

Figure 11. Percentage of patients having respective segment affected in (A) patients with non-obstructed coronary arteries and (B) obstructed coronary arteries. Reproduced from "Rosen-Wetterholm, E, Cavefors, O, Redfors, B, et al. RWMAs in critically ill patients with non-obstructed coronary arteries. Acta Anaesthesiol Scand*. 2023; 1- 9." under Creative Commons CC-BY license.*[312]

Findings on ECG were different between groups. ST-elevation was more often observed in patients with obstructed coronary arteries. However, more severe arrhythmias (i.e., AV block III or VT/VF), T-wave inversions, or a normal ECG was seen in patients with non-obstructed coronary arteries. Troponin levels were higher in patients with obstructed coronary arteries compared to patients with non-obstructed coronary arteries. In contrast, no significant differences were noted in levels of NT-proBNP. Mortality analysis carried out at day 90 could not detect any difference between patients with obstructed vs non-obstructed coronary arteries. Adjustments did not change this result.
Follow-up echocardiography could be retrieved in 72 % of patients with non-obstructed coronary arteries and RWMA. Analysis of these echocardiograms revealed that systolic LV function was normalized or near normalized in 78% of these patients. CMR was available in 14 of the patients with non-obstructed coronary arteries. The results of CMR indicated that 7 of 14 patients in this group suffered from Takotsubo or myocardial stunning. In patients without normalization of LV function, one patient was diagnosed with cardiomyopathy, one with non-acute myocarditis, one with cardiac amyloidosis and three with old, previously unknown, MI. No diagnosis was established in the remaining two patients (Table 3).

Patient	RWMA, main localization	n segment	Reversal of RWMA	LGE	Edema	Other	Preliminary diagnosis
1	Apical	5	Yes	None	N/A	–	TSS/stunning
2	Apical + midventricular	12	Yes	None	Yes	–	TSS/stunning
3	Septal	4	Yes	None	Yes	–	TSS/stunning
4	Apical	5	Yes	None	Yes	–	TSS/stunning
5	Lateral	2	Yes	None in affected segments	Yes	Intramural LGE in one segment outside RWMA	TSS/stunning, intramural LGE incidental finding
6	Apical	5	Yes	None in affected segments	N/A	Subendocardial LGE in one segment outside RWMA	TSS/stunning, ischemic scar incidental finding
7	Inferoseptal	4	Yes	None in affected segments	No	Subendocardial LGE in one segment outside RWMA	TSS/stunning, ischemic scar incidental finding
8	Septal	5	Yes, on follow-up echo	Transmural in one segment with RWMA	N/A	Prominent trabeculations and intertrabecular recesses	Minor MI + stunning. Non-compaction cardiomyopathy.
9	Lateral	5	No	Subendocardial in all segments with RWMA	No	Thin myocardium in affected segments	MI, old
10	Inferior	2	No	Subendocardial in all segments with RWMA	No	Thin myocardium in affected segments + calcified thrombus in coronary artery	MI, old
11	Inferobasal + midventricular	4	No	Subendocardial in all segments with RWMA	N/A	Thin myocardium in affected segments	MI, old
12	Septal + inferior	8	Yes	Intramural in three segments with RWMA	Yes	Scattered LGE	Myocarditis, acute
13	Apical + septal	9	No, but improvement	Intramural in two segments with RWMA	No	Scattered LGE	DCM
14	Septal	5	Yes, on follow-up echo	Intramural, in two segments with RWMA	No	–	Myocarditis, old

Table 2. Results of CMR. N/A, not possible to evaluate oedema with the MR protocol used. On follow-up echo refers to echocardiographic follow-up performed > 3 month after hospital admission. MI, myocardial infarction; RWMA, regional wall motion abnormalities; TSS, Takotsubo syndrome; LGE, late gadolinium enhancement; DCM, dilated cardiomyopathy; NCCM, non-compaction cardiomyopathy. Reproduced from "Rosen-Wetterholm, E, Cavefors, O, Redfors, B, et al. RWMAs in critically ill patients with non-obstructed coronary arteries. Acta Anaesthesiol Scand*. 2023; 1- 9." under Creative Commons CC-BY license.*[312]

5 DISCUSSION

5.1 ETHICAL CONSIDERATIONS

5.1.1 PAPER I-III

One ethical permit covered papers I-III and was approved by the Regional Ethics Committee in Gothenburg, Sweden (registration number 036-18). The ethical permit included TTE, blood samples and approval to perform coronary angiography after risk-benefit stratification. Patient consent was acquired from the patient or next of kin if the patient could not perceive information and make an informed consent.

The medical risks of interventions performed in studies I-III are few. As with all screening, there is a small risk that conditions that would not have impacted the patient's life were identified and treated, leading to complications related to treatment or increased anxiety. However, serious cardiac pathology could be identified and treated, leading to possible improvement in patient care. Another potential issue is the validity of informed consent in ICU patients. At the time of inclusion, most patients are treated for conditions that might lead to incapacitation in decision-making or even render the patient unconscious. It could be difficult for the researchers to know if the patient can fully understand the information. In addition, there is a risk that patients might feel pressured to consent to studies because of a perceived dependence on the researcher, who might know and work with the treating staff and clinician. To minimize these effects, the including clinician did not partake in direct clinical care, and study information was supplied in written and oral form. It was deemed that the benefits of the study outweighed the potential harm.

5.1.2 PAPER IV

Ethical approval for Paper IV was granted based on a previously acquired ethical permit from a study on stress-induced cardiomyopathy (protocol number 994-14, Approval date Jan 18, 2015), which was supplemented (protocol number 2021- 06306-). The initial ethical approval was for a chart review based on the local ICU register. The supplemental ethical approval included merging the hospital's angiographic register with the local ICU register to identify patients in the ICU who had undergone cardiac angiography and obtaining these results as well as CMR images. In addition, the timeframe for obtaining data was increased from 2014 to the end of 2021, and the principal investigator was changed. No consent was deemed necessary as it was a retrospective chart review. The ethical issues in this study are potential

privacy inclusions regarding confidential chart information. We deemed that the potential knowledge gained from the study compensated for the possible privacy intrusions.

5.2 METHODOLOGICAL PERSPECTIVES

5.2.1 PAPER I

Paper I was a large prospective observational study in unselected ICU patients. The strength of the study was its prospective inclusion and large sample size. In addition, the TTE images were assessed by a second blinded reviewer resulting in a high validity. The major limitation is the lack of coronary artery imaging to exclude CAD in patients with systolic LV dysfunction. However, performing a high-risk procedure in ICU patients was deemed unethical, except when the procedure's benefit outweighed the risk[175]. Another limitation is the single TTE examination in patients with normal systolic LV function. Most patients had probably developed LV dysfunction before ICU admission, as they were examined early. Consecutive examinations could have led to the detection of more patients with cardiac dysfunction and identified which patients subsequently develop cardiac dysfunction during ICU care[46]. Alternate systolic LV function assessment parameters, such as longitudinal strain analysis, MAPSE or LV S' on TDI, could have rendered different results[9,313]. Reporting these markers in critical care echocardiography studies is recommended today by the PRICES consensus document to enhance interpretation and relatability between studies[314]. However, this document was not published when the study was performed, and possible benefits of other markers of systolic LV function than EF and RWMA in ICU patients are yet to be defined[58,315].

The primary outcome of Paper I was 30-day mortality. The 30-day mortality was chosen as SAPS 3, used for outcome adjustments, is corrected for 30 days[304]. However, we could see a continued mortality difference even after 30 days and subsequently used 90-day mortality for the succeeding studies.

5.2.2 PAPER II

In this study, we analyzed diastolic LV function in selected patients from Paper I. Patients with known cardiac disease, LVEF <50% or RWMA, were excluded, as diastolic dysfunction always is present to some degree in these patientes[34,316]. In addition, patients with significant arrhythmias, e.g., AF, were excluded since arrhythmias can make fundamental diastolic markers inaccurate. We evaluated diastolic dysfunction using the accepted algorithm from EACVI[34]. The PRICES consensus report suggests reporting of E/A ratio

and deceleration time, in addition to the diastolic markers in the EACVI guidelines and these were therefore reported separately[34,309]. A posthoc analysis was performed using guidelines proposed by Lanspa et al. after a clear association was seen between doppler markers and mortality[310]. A few studies have compared EACVI guidelines from 2009 and 2016, as well as simplified definitions in septic patients[34,46,47,317], but no studies have excluded patients with established systolic dysfunction or prospectively enrolled patients. In this secondary analysis, E/e', TR-Vmax and e' were obtained in >90 % of patients, but LAVI was missing in 17 %. In total, all four recommended parameters were assessed in two-thirds of patients. Even though these numbers are similar to earlier studies evaluating using the EACVI guideline, a study focused on diastolic function could have had higher success in obtaining LAVI measurements[310,318]. Focusing on diastolic dysfunction would also have allowed a follow-up TTE to be performed in patients with diastolic function establishing possible reversibility and providing important information on aetiology.

5.2.3 PAPER III

Paper III was a secondary analysis of patients from Paper I, in which we evaluated the use of cardiac biomarkers for screening of cardiac dysfunction and prognostication in ICU patients. Echocardiographic data from Paper I was used, and clinically relevant cardiac dysfunction was defined. LV systolic dysfunction was defined as EF<50% with or without RWMA, as Paper I had shown increased mortality in this group. LV diastolic dysfunction was defined as an indeterminate diastolic function or diastolic dysfunction according to the EACVI guidelines as we in Paper II, similar to earlier studies, could show increased mortality in these groups[34,319,320]. Patients were classified as RV systolic dysfunction if any of the included three markers of RV function was abnormal, as these markers have been associated with increased mortality in previous studies[321,322].

Earlier studies have reported an association between sepsis and renal failure with increased cardiac biomarker levels. However, these studies have not adjusted for cardiac dysfunction associated with sepsis and renal failure, such as septic cardiomyopathy or cardiorenal syndrome[294,295,323]. In Paper III, we used a quantile regression model to examine if these associations were independent of cardiac function and independently associated conditions were used in our adjusted mortality analysis.

To establish if biomarkers were independently associated with mortality, we used a three step model adjusting for age, SAPS 3, independently associated

variables (renal failure for hsTNT, and sepsis and renal failure for NT-proBNP) and cardiac dysfunction.

5.2.4 PAPER IV

This paper was designed as a proof-of-concept study showing that RWMA can occur without coronary artery obstruction in critically ill patients. A significant selection bias is present in the selection of patients who underwent coronary angiography and CMR. It is exemplified by the fact that almost half of the patients were admitted because of cardiac arrest, usually representing 5-10% of ICU admission in Sweden[324]. Despite its drawbacks, the study's strength is the evaluation of coronary arteries in all included patients and the high prevalence of CMR in patients with non-obstructed coronary arteries and RWMA.

5.3 PREVALENCE OF LV DYSFUNCTION IN THE ICU

5.3.1 SYSTOLIC DYSFUNCTION

Despite its clinical significance, the incidence of systolic cardiac dysfunction in non-cardiac general ICU patients is not a widely studied subject. Three earlier studies report LV systolic dysfunction in 7-12 % of general non-cardiac ICU patients[37-39]. Other studies report on specific patient populations known to have an increased risk of cardiac dysfunction, such as septic patients or post-cardiac arrest patients, or evaluate particular diagnoses, for example, Takotsubo, in unselected ICU patients [61-63,111-113,239,242]. Our material identified LV systolic dysfunction in 24% of the patients. Half of these patients were regarded to have a primary cardiac cause for their dysfunction, as they were either admitted for cardiac dysfunction or had a history of cardiac disease, e.g., MI or heart failure. The remaining patients were classified as non-cardiac disease, representing approximately 13 % of the total ICU population. RWMA, with or without low EF, was seen in most patients. Despite several earlier studies reporting RWMA in non-cardiac patients, the rates were higher than we expected[325-327]. Typical forms of Takotsubo (midventricular and apical) were seen in about 3 % of the study population, which aligns with other ICU-oriented papers[112,113,303]. Our study indicates that systolic cardiac dysfunction is a common in non-cardiac ICU patients occurring in up to 15 % of the population and that most patients present with RWMA with or without low EF.

5.3.2 DIASTOLIC DYSFUNCTION

Diastolic function is, in general cardiology, assessed with echocardiography in conjunction with NT-proBNP and heart failure symptoms to identify patients suffering from HFpEF[23,24]. Several different echocardiographic parameters for diastolic assessment, with advantages and disadvantages, have been used. The current guidelines from EACVI and AHA recommended using the following parameters: lateral and septal e', E/A wave, E/e' quota, LAVI, TR Vmax and in some cases, assessment of pulmonary vein flow[34]. In intensive care, symptoms from heart failure, such as dyspnea, are often difficult to assess, and measurements of NT-proBNP have been shown in Paper III to be unreliable for identifying cardiac dysfunction. The focus is, therefore, solely on echocardiographic parameters to identify patients with diastolic dysfunction. Making clinically relevant assumptions regarding diastolic function is complicated by the lack of reference data for diastolic markers in severely ill patients with renal failure, ARDS and mechanical ventilation. Echocardiographic markers are also dependent on loading conditions and influenced by ageing[328-330]. The debate on how and which markers should be used is ongoing, exemplified by a letter to the editor regarding Paper II[331,332]. Nonetheless, research on diastolic dysfunction has received increased interest in intensive care settings over the last decade. The most commonly used markers in ICU studies are E/A quota and E/e'. Most studies have focused on special patient groups, predominantly sepsis, where diastolic dysfunction assed using E/e' has a solid association with mortality in contrast to EF[333]. Despite the frequent use of the most recent guidelines for diastolic dysfunction by the EACVI in cardiology, few studies have evaluated these in an intensive care settings. Studies in critically ill patients have estimated the prevalence of diastolic dysfunction between 20-92 % depending on cohort and definition, but no studies have excluded patients with systolic dysfunction[35]. Using the EACVI guidelines, we identified diastolic dysfunction in 10 % of the patients with otherwise normal cardiac function, while the function was indeterminate in another 15%. The mortality in patients with indeterminate function was similar to patients with diastolic dysfunction, possibly indicating that a large proportion of this group also suffered from diastolic dysfunction. The prevalence of diastolic dysfunction in critical patients is hard to estimate as the study populations and parameters are heterogeneous. Nonetheless, our study shows that diastolic dysfunction is common even in a selected group of patients with apparently normal systolic function, affecting mortality in up to 25 % of patients.

5.4 INFLUENCE OF LV DYSFUNCTION ON MORTALITY

5.4.1 SYSTOLIC DYSFUNCTION

Systolic LV dysfunction has been recognized in critically ill patients for decades; despite this, it is not clear if it is associated with increased mortality[334]. Metanalyses in sepsis have not shown low EF to be associated with increased mortality; some studies even indicate lower mortality in patients presenting with systolic LV dysfunction[36,334,335]. Similar results have been reported in other ICU-related cardiac diseases such as Takotsubo and post-cardiac arrest stunning[112,113,239,246-248]. Furthermore, two studies on a broader ICU population did not associate systolic LV dysfunction with mortality[37,38]. In Paper I, we could link systolic dysfunction, defined as EF<50% or RWMA, to 90-day mortality in patients with cardiac and non-cardiac disease. Mortality was even more pronounced if patients had low CO. Subgroup analysis of patients with non-cardiac LV dysfunction shows that patients with RWMA had increased mortality, but this was not seen for global dysfunction (EF <50% without RWMA).
In patients with primary cardiac dysfunction, increased mortality was expected, as seen in other studies on myocarditis and CAD[182,336]. However, the reasons for increased mortality are not as apparent in patients with non-cardiac LV dysfunction. Several reasons could contribute to death in patients with LV dysfunction and non-cardiac disease.

Acute heart failure

In some patients, low CO, caused by LV systolic dysfunction, could result in hemodynamic instability and inadequate tissue perfusion. In Paper I, a lower CO is seen in patients with LV dysfunction, demonstrated by lower CI and stroke volumes. Hemodynamic instability is reflected by the increased NA requirements in this group, and elevated lactate levels signify hypoperfusion. The risk associated with low CO is illustrated by 30-day mortality of over 50% in patients with systolic LV dysfunction and CI < 2.2 L/min/m^2. However, low CO cannot explain the increased mortality in all patients, as patients with CI> 2.2 L/min/m^2 or normal EF and RWMA also had increased mortality.

Chronic heart failure

A limitation in Paper I is the lack of TTE data from before hospital admission. Patients with systolic LV dysfunction could have had this before their admittance to the hospital and represent a patient cohort with more comorbidities and an increased risk of death. This is, nevertheless,

contradicted by the fact that most patients reversed their cardiac function on follow-up TTE.

Coronary artery disease
Undiscovered CAD could potentially contribute to increased mortality, and excessive adrenergic stimulation associated with ICU care could result in a sort of stress echocardiogram uncovering underlying stable localized coronary artery stenosis with resulting RWMA. However, all patients with systolic LV dysfunction were assessed by a cardiologist to exclude significant CAD. Moreover, in patients who underwent coronary angiography, selected because of high risk for CAD, only two of 13 had significant coronary stenosis. Furthermore, patients with follow-up TTE had a rapid recovery of cardiac function, usually within days, which is not seen with untreated MI[337]. In line with this, we could in Paper IV see that patients with significant coronary artery stenosis did not have reversibility of their LV function.

Risk marker
Another reason for the increased mortality in these patients could be that systolic LV dysfunction is a marker for more severe disease, representing cardiac involvement as a part of multi-organ dysfunction syndrome (MODS) and resulting in higher mortality from more advanced disease progression. We adjusted our data for age and SAPS 3 score. Some hemodynamic variables and circulatory diagnoses, such as cardiac arrest and septic shock, are included in SAPS 3, but heart failure is not included as a specific term. A higher SOFA score in patients with cardiac dysfunction supports this theory. Nonetheless, observational studies can only establish associations, and no clear cause-effect can be shown with this study type.

In contrast to most earlier studies, although most were performed specifically in sepsis, we found an association between LV systolic dysfunction and mortality in ICU patients without a primary cardiac reason for heart failure. This contrast was highlighted by a letter to the editor regarding Paper I[338].

There are two previous studies describing systolic LV function in general non-cardiac ICU patients. However, these were not focused on assessing systolic function but on assessing cardiac abnormalities by echocardiography. One study, by Bossne et al., with a similar size to Paper I, but only including medical patients, did not link EF <35 % or RWMA (not explicitly defined) to increased mortality[38]. The other study, by Marcelino et al., used Fractional Shortening < 28% to indicate systolic LV dysfunction in a study on echocardiographic abnormalities in 700 non-cardiac patients. No association

with mortality was established. It is possible that a focus on systolic function could have yielded different results or that the studies' patient populations explain the differences in mortality. Using FS as a surrogate marker for LV function might also have impacted the results.

In patients with septic cardiomyopathy, EF is not considered to be linked to mortality[36,335]. We could identify septic shock as a risk factor for LV systolic dysfunction, and around 30 % of the patients had suspected or verified sepsis. With over 400 included patients, our dataset is slightly smaller than the two larger metanalyses done in sepsis (570 and 762 patients) which both did not show a correlation between EF and mortality. Still, the metanalyses suffer from large heterogenicity and are mainly based on studies not focused on assessing LV function. In contrast to the metanalyses, the most extensive study in septic patients, reporting on 262 patients, showed isolated systolic dysfunction (defined as LVEF ≤ 50%) to be associated with increased mortality[339].

Furthermore, most studies do not systematically report RWMA, which was linked to mortality in our material. No mortality increase was seen in patients with low EF without RWMA, i.e., global LV dysfunction.

5.4.2 DIASTOLIC DYSFUNCTION

In Paper II, we analysed the impact of diastolic dysfunction on mortality in ICU patients. Patients were classified using current guidelines from AHA/EACVI in patients with normal systolic function and no known cardiac disease[34]. We could show that patients with diastolic dysfunction had an even more pronounced risk of death than patients suffering from LV systolic dysfunction, with a four-fold increased mortality risk. In patients with indeterminate diastolic dysfunction, the mortality was similar; the higher mortality in this group may result from diastolic dysfunction that we could not discern because of missing diastolic parameters. This is supported by the fact that a similar mortality increase was observed in patients with two or more pathological diastolic parameters. The increased mortality in patients with indeterminate function is also seen in other studies[319,320].

As seen in earlier studies, Paper II could also identify increased mortality in patients with low values of e' and high E/e'ratios[333]. However, caution must be taken when using single measurements of e', and to some extent, E/e', in evaluating diastolic function as values strongly correlate with ageing, which has not been considered in these studies[330]. Because of the strong correlation between Doppler-derived e' and E/e', a

posthoc analysis using simplified guidelines from Lanspa et al. was done[310]. Diastolic dysfunction grade 2 or 3 was associated with increased mortality.

A guideline approach identified more patients with potential or existing diastolic impairment in the ICU setting, and the association with adverse outcomes were more robust compared to single diastolic parameters.

As in systolic dysfunction, we cannot establish a causal link between increased mortality and diastolic dysfunction, and several reasons could contribute.

Acute heart failure
In contrast to patients with systolic LV dysfunction, there were no statistical differences in CO variables in patients with and without diastolic dysfunction. Nonetheless, diastolic dysfunction can result in pulmonary congestion caused by increased left-sided filling pressures, which possibly explains the lower PaO_2/FiO_2 ratio noted in patients with diastolic dysfunction. The lower PaO_2/FiO_2 ratio could lead to extubation failure and increased mortality[340-342]. Furthermore, higher lactate levels were recorded in patients with diastolic dysfunction, which might indicate impaired tissue perfusion despite similar CO.

Chronic heart failure
As in patients with systolic dysfunction, it is possible that patients already had diastolic dysfunction when they were admitted to the hospital. This could decrease patients' tolerance for critical illness and lead to increased mortality. Patients with diastolic dysfunction or indeterminate diastolic function shared similar attributes with HFpEF patients, such as female predominance, higher age, more hypertension and COPD, as well as smaller LVs and higher EF. The shared attributes point to diastolic dysfunction being present when patients were admitted[1]. The high prevalence of increased LAVI, a more chronic marker of diastolic dysfunction, also indicates that the diastolic dysfunction was present upon hospital admission [343]. We do not know if diastolic dysfunction was reversible, as patients with diastolic dysfunction did not undergo systematic follow-up echocardiography.

Risk marker
Diastolic dysfunction could also be a part of MODS, simply representing a risk marker for severe disease not identified by the used scoring system.

In patients with sepsis, multiple studies and a meta-analysis have established an association between mortality and diastolic dysfunction[36,333]. However, in general ICU patients, the association is not as strong. Mortality associated with

diastolic parameters has been seen in smaller studies. Two studies focusing on biomarkers, including 58 and 49 patients, respectively, showed associations between mortality and Doppler-derived diastolic markers[44,45]. In contrast, Sturgess et al. did a retrospective study with 92 patients, using E/e' as a diastolic marker, without a clear mortality association[43] . Garry et al. published a broader systematic review on diastolic dysfunction in ICU patients, although most included studies were in septic patients. The heterogenicity in diastolic markers was too large to allow a metanalysis, but 3 of 16 studies established an independent association between mortality and diastolic dysfunction[35]. Paper II is the most extensive study of diastolic function in general ICU patients performed to our knowledge, and no earlier study has shown an association with mortality in patients with isolated diastolic LV dysfunction. In addition, the 2016 guidelines have earlier only been evaluated in septic patients, were no association has been established with mortality[46,47].

5.5 AETIOLOGY OF CARDIAC DYSFUNCTION

The aetiology of critical illness-associated LV dysfunction is uncertain. Multiple aetiologies have been proposed for specific conditions such as septic cardiomyopathy, Takotsubo syndrome, MINOCA, and post-cardiac arrest stunning. The diagnostic criteria for these syndromes vary between experts, studies and organizations, making prevalence assumptions and pathophysiological research difficult.

The pathophysiological processes behind ICU-associated LV dysfunction also overlap in many aspects, and common pathophysiological processes and pathways are suggested for many conditions (Table 4).

	Takotsubo	Post-cardiac arrest stunning	Septic Cardiomyopathy	MINOCA
Inflammation	X[142,143,145,146]	X[258-260]	X[49,65,66]	
Adrenergic hyperactivity	X[139-141]	X[250,257]	X[69 67,68]	
Mitochondrial dysfunction			X[70,71]	
Global ischemia			X[73]	
Microcirculatory dysfunction	X[126-128,130]		X[48]	X[222]
Calcium responsiveness	X[133-135]		X[77]	
Epicardial vessel spasm	X[123,124]			X[233,234]

Table 3. Pathophysiological reasons for cardiac dysfunction.

Traditionally, most RWMA in ICU patients has been assigned to acute coronary syndromes [344-346]. However, several studies indicate that RWMA in critically ill patients can be caused by other conditions [39,111,325,347]. In Paper IV, we included patients with RWMA who underwent coronary angiography in conjunction with their ICU stay. In this population, a significant proportion of patients with RWMA had non-obstructed coronary arteries demonstrating that RWMA can be seen without significant CAD in critically ill patients. The actual proportion of patients without obstructed coronary arteries and RWMA

is probably higher as it was a highly selected population who underwent coronary angiography resulting in a pronounced selection bias. Results from Paper I further support that LV dysfunction without CAD is common in critically ill patients. In patients with presumed non-cardiac systolic dysfunction, RWMA was the most common presentation, and, as discussed earlier, the RWMA was most likely not caused by CAD. The aetiology of RWMA in patients without CAD is not established. A smaller proportion of patients in Paper I had typical apical or midventricular Takotsubo (3%), making this diagnosis likely in a subset of patients. It is also possible that some patients suffered from atypical Takotsubo with regional wall motion abnormalities, which has been shown to be more common in Takotsubo triggered by critical illness[104]. However, distinguishing between Takotsubo, postcardiac arrest stunning, MINOCA, and septic cardiomyopathy is difficult or impossible in ICU patients. The diagnostic criteria overlap, and patients often present with a combination of symptoms. It might be that these different diagnoses have the same pathophysiological background and that the diagnosis depends on the perception of the clinician or researcher. To establish a definitive diagnosis in these patients, angiography (CT or conventional) in combination with CMR would be beneficial. CMR has an established role in the workup for patients with unexplained regional hypokinesia[348,349]. The presence of oedema can distinguish old from acute injuries, and using LGE can differentiate an ischemic and a non-ischemic process [184,350]. In Paper IV, we systematically evaluated examinations with cardiac MRI in a smaller subset of patients. Most patients had CMR results indicating a diagnosis of Takotsubo or myocardial stunning. These results indicate that patients with reversible RWMA in ICU might suffer from Takotsubo syndrome, inflammatory disease or myocardial stunning.

Due to the heterogenicity of diagnostic criteria and the proposed similar pathophysiological process behind most ICU-associated cardiac dysfunction, it is cumbersome and often impossible to establish a cause for cardiac dysfunction in a specific patient. For these reasons, it could be clinically reasonable to consider encompassing various diagnoses under one more general term, such as Critical Illness Cardiomyopathy (CIC). This would enable more united management of these patients, including judicious fluid management and possibly inotropes[351,352]. As a definite diagnosis might be hard to establish, this type of patient group would also enable studies of management on a more clinically relevant material.

5.6 CARDIAC BIOMARKERS IN CRITICALLY ILL PATIENTS

5.6.1 SCREENING

In specific ICU populations, such as subarachnoid haemorrhage, biomarkers are helpful in screening for cardiac dysfunction[273,353]. A smaller study also indicated that a low BNP can be used to rule out significant cardiac dysfunction in ICU patients[354].

In Paper III, we demonstrate that ICU patients with cardiac dysfunction had significantly higher levels of biomarkers, establishing a clear association between biomarkers and cardiac dysfunction. In Paper IV, we could also show that levels of hsTNT are higher in patients with significant CAD compared to patients with non-significant coronary artery obstruction.

Despite the robust associations between biomarkers and cardiac dysfunction, hsTNT and NT-proBNP were only moderately helpful in screening for cardiac dysfunction. At ideal values, our analyses rendered an NPV of 58% and a PPV of 80-86 % for detecting any cardiac dysfunction. Using 90 % sensitivity, a clinically useful level for screening for cardiac dysfunctions, rendered low cut-offs; 14 ng/L for hsTNT and 247ng/L for NT-proBNP, resulting in specificities below 50%. Low specificity might be because of a high prevalence of confounding factors such as sepsis and renal failure in critically ill patients. The rendered cut-offs make biomarkers of limited use for screening for cardiac dysfunction in unselected ICU patients. Nonetheless, high levels of biomarkers indicate a need for a cardiac evaluation, and high levels of hsTNT should prompt an investigation of CAD.

5.6.2 RISK MARKERS

Earlier research has shown associations between increased levels of troponins and NT-proBNP with mortality in septic and general ICU patients[270-272,300]. However, no earlier studies have corrected the mortality association for cardiac dysfunction or other factors associated with increased biomarkers levels. It is, therefore, unclear if the biomarkers themselves are associated with increased mortality or if increased levels indicate a higher prevalence of other mortality-related factors, such as LV dysfunction or renal failure. In Paper III, we did a thorough correction using multiple steps to answer this question.

We showed a significant mortality increase in patients with increased levels of hsTNT and NT-proBNP after adjustment for illness severity, age, cardiac dysfunction, and factors associated with increased biomarkers levels (sepsis

and renal failure for NT-proBNP, and renal failure for hsTNT). This highlights the robustness of cardiac biomarkers as risk markers in ICU patients.

5.7 CLINICAL PERSPECTIVES

5.7.1 SCREENING FOR CARDIAC DYSFUNCTION

Our papers show that LV systolic and diastolic cardiac dysfunction is common in ICU patients and associated with an increased risk of death. Therefore, it would be reasonable to identify patients with LV dysfunction to be able to diagnose underlying cardiac disease and optimize treatment. Systematic echocardiography screening of all ICU patients is time- and resource-consuming. However, this could be reasonable as we, in Paper III, could see that approximately two-thirds of ICU patients have clinically relevant cardiac dysfunction. Even though screening all ICU patients with echocardiography could be beneficial and with few adverse effects, not all ICUs have the capability to implement this. Therefore, focusing on specific patient groups where systolic and diastolic dysfunction is more common might be needed. Increased levels of biomarkers are associated with significant cardiac dysfunction, and patients presenting with high levels of hsTNT or NT-proBNP should undergo echocardiography to identify underlying cardiac pathology. Furthermore, patients with hemodynamic instability, such as increased NA levels or lactate, also have a higher prevalence of LV dysfunction requiring assessment with echocardiography. Nonetheless, some patients will have significant cardiac dysfunction without increased cardiac biomarkers levels or hemodynamic compromise.

We advocate using a guideline-based approach when assessing diastolic function in critically ill patients. A multi-parameter approach seems to identify more patients with diastolic dysfunction and has a stronger association with mortality. Using the more feasible diagnostic criteria from Lanspa diagnosed more patients with diastolic dysfunction than the EACVI guidelines. However, only grade 2 or 3 was associated with increased mortality. The EACVI guidelines are less feasible but have the benefit of being more universally used with a similar association to mortality.

5.7.2 MANAGEMENT OF LV SYSTOLIC DYSFUNCTION

If systolic dysfunction is identified, further investigation should be performed. Patients with a high risk of CAD can be identified based on risk factors, presentation, symptoms, troponin levels, the pattern of RWMA and ECG changes[166]. In these patients, significant coronary stenosis should be excluded as these patients benefit from specific interventions, and a missed diagnosis of

MI might increase ICU mortality[174,355,356]. However, the benefit of coronary revascularization and associated anticoagulation must be weighed against the risks. An alternate diagnosis should be sought in patients with a low risk of CAD. If no early reversibility of cardiac function occurs, CMR is probably beneficial as this can establish several disorders and impact the management of patients[349,357].

Managing systolic dysfunction in critically ill patients is controversial, and establishing an etiological diagnosis might be challenging. Guidelines for managing septic cardiomyopathy, Takotsubo and post-cardiac arrest stunning recommend inotropy in cardiogenic shock with signs of hypoperfusion[1,249]. In Paper I, we could also show that low CI is related to high ICU mortality in patients with and without primary cardiac disease. However, there is no high-quality evidence supporting the use of inotropes in cardiology or ICU patients, and some studies indicate increased mortality from inotropic use[358,359]. More research is needed to determine in which situations patients might benefit from inotropic drugs and which therapy endpoints should be used. In the meantime, following current guidelines and using inotropes in selected patients where hypoperfusion persists despite fluid resuscitation and vasopressor seems reasonable.

In patients with non-ischemic RWMA and normal CO, no studies exist. A therapeutic approach that has gained interest in recent years is beta-blockade use in septic patients. Results from a few studies have shown potential benefits but are not ready for clinical use[360,361]. However, it would be interesting to study in patients with non-ischemic RWMA.

5.7.3 MANAGEMENT OF LV DIASTOLIC DYSFUNCTION

If patients have diastolic dysfunction, there is an associated mortality increase. The basis for this is, as discussed earlier, unclear and it is not known if patients develop diastolic dysfunction secondary to their ICU care or if most patients already have diastolic dysfunction when admitted to the ICU. Nonetheless, patients should undergo at least sub-acute investigations to exclude treatable conditions leading to diastolic dysfunction and asserted possible reversibility.

In general patients, treatment options for diastolic dysfunction are emerging. However, no treatment studies exist on critically ill patients, and management is based on careful supportive care[362-364]. In our view, patients presenting with diastolic dysfunction need a cautious evaluation of fluid status and management of preload.

6 CONCLUSIONS

The main findings of this thesis were:

Systolic dysfunction is common in an unselected cohort of critically ill patients and is associated with an increased risk of death. Most patients present with RWMA, and approximately half of the patients have non-ischemic LV dysfunction, which results in a similar mortality increase to patients with ischemic LV dysfunction.

Diastolic dysfunction is common in an unselected cohort of critically ill patients with normal systolic function and is associated with an increased risk of death. A multi-parameter approach appears superior to single diastolic dysfunction parameters and has stronger associations with mortality.

Cardiac biomarkers are associated with cardiac dysfunction in intensive care patients. They are independently associated with mortality and have a clear role in prognostication. However, sensitivity is too low to be useful in screening for cardiac dysfunction in critically ill patients.

In intensive care patients, a substantial part of LV regional hypokinesia is not caused by coronary artery obstruction. Reasons for RWMA in these patients are probably multifactorial. A common term of critical illness cardiomyopathy could be helpful to promote research in this patient population.

7 FUTURE PERSPECTIVES

The distinction between different types of ICU-associated cardiac dysfunction is not clear. Diagnostic criteria vary between studies and proposed pathophysiological basis overlap between different diagnoses. To enable increased collaboration, relatability and repeatability in critical illness-associated cardiac diseases, generally accepted criteria for ICU-associated cardiac dysfunction and how to distinguish between these would be beneficial. A consensus must be reached to study and treat these conditions properly.

The aetiology of cardiac dysfunction in critically ill patients without CAD, especially in patients with RWMA, is poorly understood. In Paper IV, we could see that CMR gave adequate information on aetiology in most patients, and a more extensive prospective study in which this could be performed systematically would be of benefit.

It is unknown if diastolic function improves when patients recover from critical illness. A study with repeated echocardiography over a longer time frame would be helpful to discern this.

Evidence on how to best manage cardiac dysfunction with hemodynamic instability in critically ill patients without CAD is scarce, and there is a need for further studies in this area. Initial research should focus on establishing hemodynamic targets and verifying whether treatment with inotropes is beneficial in critically ill patients with cardiac dysfunction. Based on Paper I, a good start could be to evaluate the use of inotropy in patients with systolic dysfunction and CI < 2.2 L/min/m^2, as these patients had a pronounced mortality increase.

In diastolic dysfunction, the use of established treatments for diastolic dysfunction in cardiology, such as glucose transporter 2 inhibitors and mineralocorticoid receptor antagonists, could be evaluated in critically ill patients[363,364].

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