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PROGNOSTIC FACTORS IN CARDIOGENIC SHOCK

FROM BENCH TO BEDSIDE - THE CARDSHOCK STUDY

Anu Kataja

ACADEMIC DISSERTATION

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ABSTRACT

Cardiogenic shock (CS) is a state of hypotension and systemic hypoperfusion caused by cardiac dysfunction. CS is the most severe form of acute heart failure and the leading cause of death among patients hospitalized for acute coronary syndrome (ACS), which is the most common etiology of CS. Prolonged hypotension activates neurohormonal compensatory mechanisms and triggers inflammatory responses. CS often leads to multi-organ failure and has a poor prognosis (short-term mortality > 40%). The most important treatment strategy in ACS-related CS is immediate revascularization, usually with percutaneous coronary intervention. CS patients are typically managed in intensive care units and require vasoactive medication, ventilatory support, and sometimes mechanical circulatory support. Patient selection for the most aggressive therapies with possible complications and limited availability requires risk assessment in the initial stage of CS, before organ failure has become irreversible.

The aim of this thesis was to evaluate easily available prognostic factors, including mental state evaluation and biomarkers of stress response and inflammation, in the early phase of CS. Data were from the CardShock study, a multinational, prospective, observational cohort of 219 CS patients with both ACS and non-ACS etiologies of CS. Patient recruitment was conducted between 2010 and 2012.

Study I investigated baseline blood glucose levels and their relation to clinical picture and prognosis in CS. Hyperglycemia is a common phenomenon among critically ill patients. However, it is unclear whether hyperglycemia is fully adaptive and physiological or harmful during acute illness. In this CS population, blood glucose levels were distributed rather equally between the groups of normoglycemia (4.0-7.9 mmol/L), and mild (8.0-11.9 mmol/L), moderate (12.0-15.9 mmol/L) and severe (> 16 mmol/L) hyperglycemia. Hypoglycemia (< 4.0 mmol/L) was rare. Severe hyperglycemia was associated with acidosis and hyperlactatemia, reflecting profound hypoperfusion. Mortality was highest (60%) among CS patients with severe hyperglycemia or hypoglycemia, whereas patients with normoglycemia had the best prognosis (26% mortality). Moreover, severe hyperglycemia was independently associated with increased mortality. The prognostic value of baseline blood glucose level was less pronounced in patients with known diabetes.

Study II evaluated the prevalence and prognostic significance of altered mental status (AMS) at the time of CS detection, and the associations of AMS to biochemistry and hemodynamic parameters. AMS is among the diagnostic criteria for CS as one of the clinical manifestations of end-organ hypoperfusion. Two-thirds of these CS patients presented with AMS at the time of shock detection as a sign of cerebral hypoperfusion. AMS was associated with lower systolic blood pressure and

lower left ventricular ejection fraction, acidosis, hyperlactatemia, and hyperglycemia. Of these, acidosis was independently associated with AMS. Moreover, AMS was associated with more than two-fold short-term mortality compared with normal mental status.

Study III examined the levels of growth differentiation factor 15 (GDF-15), a stress-responsive protein belonging to the transforming growth factor-β cytokine superfamily, in CS. The expression of GDF-15 is induced in many tissues and cell types in response to acute or chronic stressors. In this CS population, GDF-15 levels were very high already at the time of shock detection. High GDF-15 levels were associated with acidosis, hyperlactatemia, and biomarkers of cardiac, renal, and hepatic dysfunction. Moreover, high GDF-15 levels were independently associated with increased mortality. In addition, the kinetics of GDF-15 were different between survivors and non-survivors during the first days of shock. GDF-15 levels decreased among survivors as a positive response to treatment, whereas GDF-15 levels remained high or even increased among patients who subsequently died. For early risk stratification in CS, a $GDF\text{-}15_{12h}$ cut-off of 7000 ng/l was identified and found to provide incremental value to validated clinical risk scores.

Study IV analyzed the levels and kinetics of inflammatory markers in CS, including C-reactive protein (CRP), interleukin 6 (IL-6), and procalcitonin (PCT). Inflammatory response with subsequent vasodilation is thought to play an important role in the complex pathophysiology of CS. Inflammatory marker levels were considerably elevated during the first days of shock. PCT peaked at 24 hours, while CRP continued to rise until 48 to 72 hours. High PCT and IL-6 levels were closely associated with acidosis, hyperlactatemia, and clinical findings of systemic hypoperfusion. In addition, high levels of PCT and IL-6 were associated with poor prognosis. During the first days of CS, high inflammatory marker levels seemed to reflect shock severity rather than infectious complications.

In conclusion, patients in the early phase of CS present with various clinical and biochemical findings that reflect disturbed homeostasis, including hyperglycemia and AMS. In addition, high levels of GDF-15 and inflammatory markers are detected in CS, indicating organ dysfunction and profound circulatory failure. These should be regarded as warning signs of severe hypoperfusion and poor outcome and should be considered in early risk assessment.

TIIVISTELMÄ

Sydänperäinen shokki on äkillisen sydämen vajaatoiminnan vaikein muoto, jossa sydämen pumppaustoiminnan häiriö johtaa voimakkaaseen verenpaineen laskuun ja verenkierron vajaukseen. Sydänperäisen shokin yleisin syy on sepelvaltimotautikohtaukseen liittyvä sydänlihasvaurio, joka aiheuttaa noin 80% tapauksista. Verenpaineen lasku johtaa elimistössä neurohormonaalisten järjestelmien sekä tulehdusvasteen aktivoitumiseen ja usein monielinvaurioon. Sydänperäisen shokin ennuste on huono, sillä jopa puolet potilaista menehtyy sairaalahoidon aikana. Sydänperäinen shokki onkin yleisin kuolinsyy sepelvaltimotautikohtauksen vuoksi sairaalahoitoon joutuneilla potilailla. Tärkein hoitomuoto sepelvaltimotautikohtaukseen liittyvässä shokissa on välitön ahtautuneen sepelvaltimon avaaminen, useimmiten pallolaajennuksella. Potilaat vaativat tyypillisesti tehohoitoa, verenkiertoa tukevaa lääkitystä sekä hengityksen ja toisinaan myös verenkierron tukemista koneellisesti. Edellä mainitut hoitomuodot ovat raskaita, sisältävät huomattavia komplikaatioriskejä ja kuluttavat paljon terveydenhuollon voimavaroja. Näin ollen intensiivisimmät hoidot tulisi rajata potilaille, jotka niistä todennäköisimmin hyötyvät, ja hoito aloittaa välittömästi ennen pysyvien elinvaurioiden kehittymistä.

Tämän väitöskirjatyön tavoitteena oli tutkia sydänperäisen shokin alkuvaiheessa todettavia, helposti saatavilla olevia ennustetekijöitä kuten verikokeissa ja potilaan kliinisessä tutkimuksessa havaittavia poikkeavuuksia. Väitöskirjan aineisto on peräisin 219 potilaan CardShock-tutkimuksesta, joka on eurooppalainen etenevä, havainnoiva monikeskustutkimus. Potilasaineisto kerättiin vuosina 2010-2012.

Osatyössä I tutkittiin sydänperäiseen shokkiin sairastuneiden potilaiden alkuvaiheen verensokeritasoja ja niiden yhteyttä ennusteeseen. Koholla oleva verensokeritaso eli hyperglykemia on yleinen ilmiö vaikeasti sairailla potilailla. On kuitenkin epäselvää, onko verensokeritason nousu pääosin tarkoituksenmukainen ja fysiologinen ilmiö vai onko se itsessään haitallista äkillisen sairastumisen yhteydessä. Tässä potilasaineistossa verensokeritasot olivat jakautuneet suhteellisen tasaisesti normaalin verensokerin (4.0-7.9 mmol/L) sekä lievän (8.0-11.9 mmol/L), keskivaikean (12.0-15.9 mmol/L) ja vaikean (> 16 mmol/L) hyperglykemian välillä, kun taas matala verensokeri (< 4.0 mmol/L) oli harvinaista. Vaikea hyperglykemia oli yhteydessä veren matalaan pH-arvoon sekä kohonneeseen laktaattipitoisuuteen kuvastaen kudosten hapenpuutetta ja verenkierron vajausta. Kuolleisuus oli suurinta (60%) niillä potilailla, joiden tulovaiheen verensokeri oli joko hyvin korkea tai poikkeuksellisen matala. Vaikea hyperglykemia oli itsenäinen kuolleisuuden riskitekijä. Sen sijaan aiemmin todettu diabetes vähensi verensokerin ennustearvoa sydänperäisessä shokissa.

Osatyössä II tarkasteltiin sydänperäisen shokin alkuvaiheessa todetun poikkeavan tajunnantason merkitystä ja ennustevaikutusta. Kahdella kolmasosalla potilaista oli shokin toteamisvaiheessa poikkeava tajunnantaso oireena merkittävästä verenkierron vajauksesta. Poikkeava tajunnantaso oli yhteydessä matalaan verenpaineeseen, voimakkaasti alentuneeseen sydämen pumppaustoimintaan, veren matalaan pH-arvoon sekä kohonneisiin laktaatti- ja verensokeripitoisuuksiin. Näistä tekijöistä poikkeavaan tajunnantasoon oli itsenäisesti yhteydessä vain matala pH. Poikkeavaan tajunnantasoon liittyi yli kaksinkertainen kuolemanriski verrattuna niihin potilaisiin, joiden tajunnantaso säilyi normaalina shokista huolimatta.

Osatyössä III määritettiin GDF-15-nimisen proteiinin pitoisuuksia veressä sydänperäisen shokin ensipäivinä ja niiden yhteyttä ennusteeseen. GDF-15:n tarkat vaikutukset elimistössä ovat vielä osittain epäselviä, mutta sen eritys lisääntyy monissa kudoksissa vasteena äkillisiin ja pitkäaikaisiin sairauksiin. Tutkimus osoitti, että GDF-15-tasot ovat hyvin korkeita jo sydänperäisen shokin toteamishetkellä. Korkeaan GDF-15-pitoisuuteen liittyi veren matala pH-arvo, kohonnut laktaattiarvo sekä sydämen, munuaisten ja maksan toimintahäiriöitä kuvastavia muutoksia verikokeissa. Korkea GDF-15-pitoisuus oli yhteydessä lisääntyneeseen kuolleisuuteen, ja erityisen suuri kuolemanriski oli potilailla, joiden GDF-15-pitoisuus nousi hoidosta huolimatta. Sen sijaan GDF-15-tason lasku kuvasti suotuisaa vastetta hoitoon ja hyvää ennustetta.

Osatyössä IV tutkittiin tulehdusvastetta kuvastavien biomerkkiaineiden pitoisuuksia veressä sydänperäisen shokin alkuvaiheessa. Elimistön voimakkaan tulehdusreaktion ajatellaan olevan tärkeä tekijä sydänperäisen shokin kehittymisessä. Tutkimuksessa havaittiin, että tulehdusmerkkiaineet olivat selvästi koholla shokin ensipäivinä. Prokalsitoniini (PCT) saavutti huippuarvonsa 24 tunnin kohdalla, kun taas C-reaktiivinen proteiini (CRP) nousi 48-72 tuntiin asti. Korkeat PCT- ja interleukiini 6 (IL-6) -pitoisuudet liittyivät tiiviisti veren matalaan pH-arvoon ja kohonneeseen laktaattiarvoon sekä verenkierron vajausta kuvastaviin kliinisiin löydöksiin. Sen lisäksi korkeat PCT- ja IL-6-pitoisuudet ennustivat kuolleisuutta. Kokonaisuudessaan kohonneet tulehdusmerkkiaineet kuvastivat enemmänkin shokin vaikeusastetta kuin infektioita.

Yhteenvetona voidaan todeta, että sydänperäiseen shokkiin sairastuneilla potilailla on monia elimistön tasapainotilan vakavaa häiriintymistä kuvaavia löydöksiä, kuten muutoksia verensokeritasossa tai tajunnassa. Voimakkaasti koholla olevat GDF-15- sekä tulehdusmerkkiainepitoisuudet kuvastavat vaikeaa verenkierron vajausta ja suurta kuolemanriskiä. Näitä löydöksiä voidaan hyödyntää riskiarviossa jo sydänperäisen shokin alkuvaiheessa.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Kataja A, Tarvasmäki T, Lassus J, Cardoso J, Mebazaa A, Køber L, Sionis A, Spinar J, Carubelli V, Banaszewski M, Marino R, Parissis J, Nieminen MS, Harjola VP. The association of admission blood glucose level with the clinical picture and prognosis in cardiogenic shock - Results from the CardShock Study. Int J Cardiol 2017;226:48-52.

II. Kataja A, Tarvasmäki T, Lassus J, Køber L, Sionis A, Spinar J, Parissis J, Carubelli V, Cardoso J, Banaszewski M, Marino R, Nieminen MS, Mebazaa A, Harjola VP. Altered mental status predicts mortality in cardiogenic shock - results from the CardShock study. Eur Heart J Acute Cardiovasc Care 2018;**7**:38-44.

III. Hongisto M, Kataja A, Tarvasmäki T, Holopainen A, Javanainen T, Jurkko R, Jäntti T, Kimmoun A, Levy B, Mebazaa A, Pulkki K, Sionis A, Tolppanen H, Wollert KC, Harjola VP, Lassus J. Levels of Growth Differentiation Factor 15 and Early Mortality Risk Stratification in Cardiogenic Shock. J Card Fail 2019 25(11):894-901.

IV. Kataja A, Tarvasmäki T, Lassus J, Sionis A, Mebazaa A, Pulkki K, Banaszewski M, Carubelli V, Hongisto M, Jankowska E, Jurkko R, Jäntti T, Kasztura M, Parissis J, Sabell T, Silva-Cardoso J, Spinar J, Tolppanen H, Harjola VP. Kinetics of procalcitonin, C-reactive protein and interleukin-6 in cardiogenic shock - Insights from the CardShock study. Int J Cardiol 2021;322:191-196.

ABBREVIATIONS

ACS = acute coronary syndrome

AHF = acute heart failure

AKI = acute kidney injury

AMS = altered mental status

AUC = area under the curve

CABG = coronary artery bypass graft surgery

CI = confidence interval

CRP = C-reactive protein

CS = cardiogenic shock

CV = cardiovascular

DM = diabetes mellitus

eGFR = estimated glomerular filtration rate

GDF-15 = growth differentiation factor 15

HF = heart failure

hsTnT = high-sensitivity troponin T

IABP = intra-aortic balloon pump

ICU = intensive care unit

IL = interleukin

IQR = inter-quartile range

LVEF = left ventricular ejection fraction

MAP = mean arterial pressure

MCS = mechanical circulatory support

MI = myocardial infarction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio

PCI = percutaneous coronary intervention

PCT = procalcitonin

SD = standard deviation

SIRS = systemic inflammatory response syndrome

STEMI = ST-elevation myocardial infarction

1 INTRODUCTION

Cardiogenic shock (CS) is a state of hypotension and end-organ hypoperfusion caused by cardiac dysfunction (Chioncel et al. 2020, van Diepen et al. 2017, Zeymer et al. 2020). CS is a medical emergency and the most devastating form of acute heart failure (AHF). CS is the leading cause of death among patients hospitalized for acute coronary syndrome (ACS), which is the most common cause of CS (van Diepen et al. 2017, Harjola et al. 2015). Other etiologies of CS include acute decompensation of chronic heart failure, valvular dysfunction, and myocarditis, for instance. Severely depressed cardiac contractility, typically in the left ventricle, causes decreased cardiac output and hypotension, systemic hypoperfusion, and hypoxia (Buerke et al. 2011, van Diepen et al. 2017, Zeymer et al. 2020). Prolonged hypotension increases sympathetic tone, activates the hypothalamic-pituitary-adrenal axis and renin-angiotensin-aldosterone system, and triggers the inflammatory response. CS often leads to multi-organ failure and carries a poor prognosis, with short-term mortality > 40% (Chioncel et al. 2020, van Diepen et al. 2017).

The most important treatment strategy in ACS related CS is immediate revascularization, and surgery in the case of mechanical complications (Chioncel et al. 2020, van Diepen et al. 2017). Most CS patients are treated in intensive care units and require ventilatory support and vasoactive medication, and sometimes mechanical circulatory support. Despite the increased availability of revascularization therapies and advances in intensive care, the mortality rate of CS is still unacceptably high (Chioncel et al. 2020, van Diepen et al. 2017). Indeed, the complex pathophysiology of CS is only partially understood. It remains unclear why in cases of similar extent of myocardial damage some patients develop CS and others do not. The clinical picture of CS also varies substantially from mild hypotension to a profound, refractory shock state. Patients present with different hemodynamic profiles with varying levels of congestion and hypoperfusion (Chioncel et al. 2020, van Diepen et al. 2017). It is crucial to identify CS patients early and initiate treatment as soon as shock is detected before organ dysfunction becomes irreversible. Treatment of CS patients is expensive and requires extensive resources, both health care personnel and equipment with limited availability. Patient selection for advanced therapies with potentially detrimental side effects warrants objective risk stratification tools in the early course of CS.

Hyperglycemia is a common phenomenon among critically ill patients, both in diabetics and in patients with no history of diabetes (Deane et al. 2013, Marik et al. 2013, Mongkolpun et al. 2019, Plummer et al. 2014, Umpierrez et al. 2012). During acute illness, hyperglycemia partly reflects the activation of stress-response mechanisms, including the sympathoadrenal system and hypothalamic-pituitary-adrenal axis (Barth et al. 2007, Ichai et al. 2010, Marik et al. 2013 and 2014, Preiser et al.

2014). Elevated levels of catecholamines and cortisol promote gluconeogenesis, glycogenolysis, and insulin resistance, resulting in hyperglycemia. However, it is unclear to what extent stress hyperglycemia is adaptive and physiological, or if it is harmful. Similarly, there is a lack of consensus on the optimal glycemic control during acute illness (Ichai et al. 2010, Krinsley et al. 2019, Vanhorebeek et al. 2018). Hyperglycemia is associated with increased mortality in critically ill patients (Dungan et al 2009, Falciglia et al. 2009, Ichai et al. 2010, Jacobi et al. 2012). However, there are limited data on glucose levels and their prognostic significance in CS.

Altered mental status (AMS) is among the diagnostic criteria for CS as one of the clinical signs of end-organ hypoperfusion (van Diepen et al. 2017, Mebazaa et al. 2018). Moreover, mental state alterations are frequently encountered in critically ill patients (Bolton et al. 1993, Gofton et al. 2012). Patients may present with various symptoms deriving from the central nervous system, including somnolence, confusion, agitation, or actual delirium. These symptoms may reflect changes in cerebral blood flow and neurochemical transmission, neuroinflammation, endothelial dysfunction, and alterations in blood-brain-barrier permeability (Hughes et al. 2012, Williams 2013, Young 2013). Indeed, brain tissue is highly intolerant to ischemia, hypoxia, and hypercapnia. On the other hand, there are some special properties of brain tissue and cerebral blood flow, including the blood-brain barrier and cerebral autoregulation, that attempt to protect the brain from metabolic and hemodynamic changes. Mental state alterations have traditionally attracted limited attention in cardiology. Furthermore, the clinical and prognostic relevance of AMS in the setting of CS is unclear.

CS is characterized by systemic hypoperfusion and activation of neurohumoral and inflammatory responses. Biomarkers reflecting these cascades have attracted increasing interest, both in terms of illustrating the complex pathophysiology of CS and in risk stratification. Growth differentiation factor 15 (GDF-15) is a stress-responsive protein belonging to the transforming growth factor-β cytokine superfamily. GDF-15 is only weakly expressed under physiological circumstances, but the expression of GDF-15 is induced in many tissues and cell types in response to acute and chronic stressors (Wollert et al. 2012 and 2017). GDF-15 participates in processes that regulate inflammatory and apoptotic pathways. Elevated levels of GDF-15 have been described in many chronic diseases (such as several cancers and cardiovascular diseases), and GDF-15 is associated with increased mortality (Wollert et al. 2017). GDF-15 expression is also strongly upregulated in the presence of acute stressors such as hypoxia, tissue injury, inflammation, or oxidative stress. Especially high GDF-15 levels have been detected in septic patients (Mueller et al. 2015). Moderately elevated levels have been observed in ACS and AHF (Cotter et al. 2015, Kempf et al. 2007, Wollert et al. 2007), but data on GDF-15 among CS patients are scarce (Fuernau et al. 2014).

An extensive inflammatory response and subsequent vasodilation are thought to play an important role in the pathophysiology of CS and are associated with increased mortality (Parenica et al. 2017). Interleukin 6 (IL-6) is among the most important mediators in the inflammatory cascade and participates in a variety of biological processes, including regulation of the immune system, regenerative functions, and coagulation (Tanaka et al. 2006). IL-6 mediates inflammatory signals to the whole body and stimulates the production of most acute-phase proteins (including C-reactive protein [CRP]), in response to infection, tissue damage, or non-specific immune activation. CRP participates in inflammatory processes by activating the complement system, opsonizing pathogens, and participating in clearance of necrotic cells (Pepys et al. 2003). Compared to CRP, procalcitonin (PCT) is regarded as a more specific biomarker of systemic bacterial infection. However, in addition to bacterial endotoxins, the production of PCT is also stimulated in extra-thyroid tissues by interleukins in response to extensive tissue damage (Davies 2015, Maruna et al. 2000, Samsudin et al. 2017). Although the presence of an inflammatory response in CS is established, data on the actual levels and kinetics of PCT, CRP and IL-6 are lacking.

This thesis sought to assess the clinical and prognostic significance of baseline blood glucose level, AMS, and biomarkers, focusing on GDF-15 and inflammatory mediators, in CS patients from the prospective, observational, multinational CardShock study.

2 REVIEW OF LITERATURE

2.1 Cardiogenic shock

2.1.1 Definition

Cardiogenic shock (CS) is a state of hypotension, systemic hypoperfusion, and hypoxia caused by reduced cardiac output (Chioncel et al. 2020, van Diepen et al. 2017). CS is a medical emergency and the most severe form of acute heart failure (AHF). In most of the recent recommendations, the diagnosis of CS relies solely on the following clinical criteria: systolic blood pressure < 90 mmHg for 30 minutes in the absence of hypovolemia or need for vasopressor therapy to maintain systolic blood pressure > 90 mmHg and clinical and biochemical signs of end-organ hypoperfusion (AMS, oliguria, cold extremities, hyperlactatemia, or combinations thereof) (Chioncel et al. 2020, van Diepen et al. 2017, Mebazaa et al. 2018, Thiele et al. 2015 ja 2019). Some studies and expert recommendations have included signs of pulmonary congestion or objective hemodynamic measurements, such as reduced cardiac index (< 1.8 or < 2.2 l/min/m^2) or elevated pulmonary capillary wedge pressure (> 15 mmHg) for diagnosis (Mebazaa et al. 2018, Thiele et al. 2019, Zeymer et al. 2020). In the present CardShock study, the diagnosis of CS was set according to the afore-mentioned clinical criteria and without invasive hemodynamic measurements. This was also the case in two large, randomized trials on CS (IABP-SHOCK II and CULPRIT-SHOCK) (Thiele et al. 2013 and 2016).

2.1.2 Etiology and epidemiology

The most common cause of CS is acute coronary syndrome (ACS), which accounts for about 80% of CS cases. CS complicates approximately 5-10% of ST-elevation myocardial infarction (STEMI) cases and 2-3% of non-STEMI cases (Abbott et al. 2007, Babaev et al. 2005, De Luca et al. 2015, Reynolds et al. 2008, Zeymer et al. 2020). Of patients admitted to hospital due to AHF, approximately 2-3% present with CS (Chioncel et al. 2017). Most studies on CS focus solely on ACS-related CS, but a significant proportion of patients have other etiologies, including mechanical complications of acute myocardial infarction (MI) (ventricular septal or free wall rupture, acute severe mitral regurgitation caused by papillary muscle rupture), cardiac tamponade, arrhythmias, cardiomyopathies, acute myocarditis, high-risk pulmonary embolism, and decompensation of chronic congestive heart failure (HF) or chronic valvular heart disease (Chioncel et al. 2020, Thiele et al. 2015 ja 2019).

Among ACS patients, risk factors for CS include older age, comorbidities, STEMI, and anterior location of MI (Fang et al. 2006, De Luca et al. 2015, Redfors et al. 2015). The incidence of ACS-related CS has remained somewhat unchanged during the past decades; stable and both slightly decreasing and increasing trends have been reported (Goldberg et al. 2016, Lang et al. 2021, Lauridsen et al. 2020, De Luca et al. 2015, Redfors et al. 2015). Approximately 70 000-80 000 patients in Europe and 30 000-40 000 patients in the USA are hospitalized for CS each year, corresponding an incidence of approximately 10 per 100 000 person-years (Zeymer et al. 2020). A higher incidence of 30-50 per 100 000 person-years has also been reported (Lang et al. 2021).

2.1.3 Pathophysiology

Irrespective of the etiology, severe depression of myocardial contractility, especially in the left ventricle, usually triggers the shock. Systolic dysfunction results in reduced cardiac output, which in turn leads to hypotension, end-organ hypoperfusion, and hypoxia (Chioncel et al. 2020, van Diepen et al. 2017, Zeymer et al. 2020). Hypotension further lowers coronary artery perfusion pressure and worsens myocardial ischemia in ACS. In addition to low cardiac output, diastolic dysfunction results in further elevation in left ventricular end-diastolic and left atrial pressure, leading to pulmonary congestion, which aggravates hypoxia and ischemia (Buerke et al. 2011, Zeymer et al. 2020).

Neurohormonal compensatory mechanisms are activated in response to hypotension and systemic hypoperfusion. Sympathetic tone and hypothalamic-pituitary-adrenal axis activity increase, leading to increased release of adrenaline and noradrenaline from the adrenal medulla and cortisol from the adrenal cortex. Consequently, heart rate increases and myocardial contractility is temporarily enhanced, along with peripheral blood flow. However, these changes also increase myocardial and systemic oxygen demand and may have arrhythmogenic effects (van Diepen et al. 2017). Hypotension, hypoperfusion and sympathetic stimulus activate the renin-angiotensin-aldosterone system, leading to angiotensin II production, which is a potent vasoconstrictor of arterioles (Buerke et al. 2011, Zeymer et al. 2020). Additionally, angiotensin II causes aldosterone release from the adrenal cortex and vasopressin release from the pituitary gland, resulting in sodium and fluid retention. Angiotensin II also acts to enhance sympathetic adrenergic activity and causes adverse cardiac remodeling.

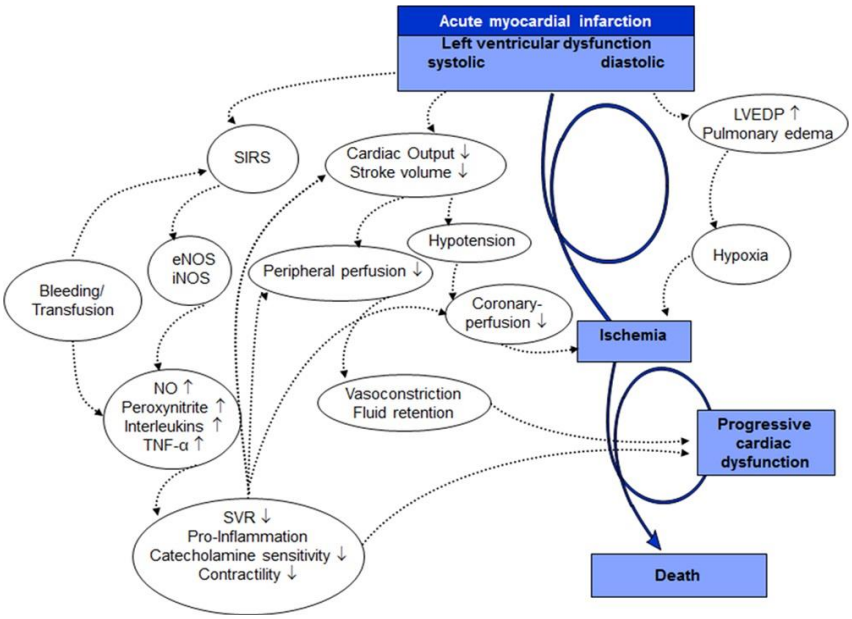

Figure 1. The pathophysiology of cardiogenic shock. Reproduced with permission from AHA Journals and Wolters Kluwer. SIRS = systemic inflammatory response, e/iNOS = endothelial/inducible nitric oxide synthase, NO = nitric oxide, TNF-α = tumor necrosis factor α, SVR = systemic vascular resistance, LVEDP = left ventricular end-diastolic pressure.

In addition to hemodynamic and neurohormonal changes, hypotension and hypoperfusion activate the systemic inflammatory response (Chioncel et al. 2020, van Diepen et al. 2017). It is also fortified by a large infarction site (Ong et a. 2018, Zeymer et al. 2020). Extensive inflammatory response is thought to play an important role in the pathophysiology of CS, and a significant proportion (18-54%) of CS patients present with signs of systemic inflammatory response syndrome (SIRS). A strong inflammatory response is also associated with increased mortality (Kohsaka et al. 2005, Parenica et al. 2017). Additionally, inflammatory mediators are thought to cause endothelial dysfunction and ventricular remodeling and also have myocardial depressant effects (Ong et al. 2018, Reynolds et al. 2008, Seropian et al 2015). Elevated plasma levels of multiple inflammatory mediators, such as interleukins and tumor necrosis factor, have been detected in CS (Andrie et al. 2012, Chioncel et al. 2020, Debrunner et al. 2008, Prondzinsky et al. 2012). Inflammatory cytokines induce nitric oxide synthase, resulting in excessive production of nitric oxide and subsequent vasodilation, which further

aggravates hypotension and hypoperfusion (Alexander et al. 2017, Hochman et al. 2003, Li et al. 2000). However, attempts to modify or restrict the inflammatory cascade and pathological vasodilation in CS patients have thus far not succeeded in mortality reduction. In the TRIUMPH trial, 398 patients with MI complicated by CS were randomized to receive either tilarginine, a nitric oxide synthase inhibitor, or placebo. Tilarginine had no effect on 30-day mortality in this CS population (Alexander et al. 2017). Finally, inflammatory response may further be fortified by endotoxemia that originates from intestinal hypoperfusion and venous congestion, leading to increased intestinal permeability and bacterial toxin translocation (Buerke et al. 2011, Chioncel et al. 2020, Ramirez et al. 2016, Zeymer et al. 2020).

The pathophysiology of CS is thus very complex; compensatory mechanisms, including neurohormonal activation and an inflammatory response that attempt to maintain homeostasis, form a vicious circle that leads to even more profound shock. Both pathologic vasoconstriction and vasodilation are involved in the process (Chioncel et al. 2020, van Diepen et al. 2017, den Uil et al. 2009). Partly reflecting multiple etiologies and the complex pathophysiology, the clinical presentations of CS constitute a broad spectrum of different hemodynamic phenotypes from pre-shock state to refractory CS. Patients may present with various levels of congestion and hypoperfusion, and with diverse systemic vascular resistance, central venous pressure, and pulmonary capillary wedge pressure (Chioncel et al. 2020, van Diepen et al. 2017). CS patients can be classified according to the clinical and hemodynamic presentation; although cardiac index is typically low (< 2.2 L/min/m^2), signs of peripheral hypoperfusion ('cold' vs. 'warm') and congestion ('wet' vs. 'dry') vary (van Diepen et al. 2017). It is also unclear why some patients with MI of the same size develop CS and some do not. Similarly, the reduction in left ventricular ejection fraction (LVEF) only partially correlates to the severity of shock and CS patients present with a broad range of LVEFs (Hochman et al. 2003, Reynolds et al. 2008). As a result of this cascade, prolonged hypotension and hypoperfusion often lead to multiple organ failure and death (Chioncel et al. 2020).

2.1.4 Prognosis and risk stratification

Despite the improved availability of early revascularization therapy and medical and supportive treatment options, CS has a poor prognosis with short-term mortality of 35-50% (Babaev et al. 2005, Chioncel et al. 2020, van Diepen et al. 2017, Fang et al. 2006, Goldberg et al. 2009 and 2016, Harjola et al. 2015). Factors associated with poor outcome include older age, previous MI or coronary artery bypass graft surgery (CABG), renal dysfunction, lower systolic blood pressure, lower LVEF,

hyperlactatemia, and clinical signs of end-organ hypoperfusion (Hochman et al. 2006, Sleeper et al. 2010, Thiele et al. 2013, Werdan et al. 2014). The mortality rate in CS is still unacceptably high and no significant reduction has been seen in the past 10 to 15 years (Chioncel et al. 2020, van Diepen et al. 2017, Zeymer et al. 2020). However, if a CS patient survives the acute phase, a relatively good long-term survival, approximating that of STEMI patients without CS, with rather good quality of life can be expected (Singh et al. 2007, Thiele et al. 2013, den Uil et al. 2009).

Early risk stratification has raised special interest in CS, as many of the most advanced treatment options, including immediate revascularization and ventilatory and mechanical circulatory support, are of limited availability and carry a high risk of complications. Objective risk assessment tools combining hemodynamic, biochemical, and clinical data have been incorporated to assist in patient selection and decision-making in intensive care. Based on the present study population, the CardShock risk score was generated to predict in-hospital mortality. The CardShock risk score consists of the following seven parameters available at the time of CS detection: age, AMS, previous MI or CABG, ACS etiology of CS, LVEF, blood lactate, and estimated glomerular filtration rate, yielding a maximum of nine points. Patients can be stratified into low (0-3 points), intermediate (4-5 points), and high (6-9 points) risk groups with observed mortalities of 9%, 36%, and 77%, respectively (Harjola et al. 2015).

2.1.5 Management of cardiogenic shock

The diagnosis of CS can be made by clinical evaluation and without invasive hemodynamic measurements. Etiology should be assessed immediately when CS is suspected. Electrocardiogram and echocardiography should be performed to detect ACS and to exclude or reveal valvular causes or mechanical complications of MI (Chioncel et al. 2020, van Diepen et al. 2017, Levy et al. 2015, Mebazaa et al. 2016, Ponikowski et al. 2016, Zeymer et al. 2020). Immediate angiography and revascularization in the case of acute MI are essential, whereas mechanical complications of MI require surgical correction.

Early revascularization has been the most important treatment strategy in ACS-related CS since the publication of results from the SHOCK Trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) in 1999 (Chioncel et al. 2020, van Diepen et al. 2017, Hochman et al. 1999). In the SHOCK Trial, 302 CS patients were randomly assigned to immediate revascularization or to initial medical stabilization. In the revascularization group, angioplasty accounted for 64% and CABG for 36% of revascularization attempts. Early revascularization resulted

in lower all-cause mortality at 6 months compared with initial medical stabilization (50% vs. 63%), although there was no statistically significant difference in 30-day mortality (Hochman et al. 1999). Survival benefit was also present at 1 and 6 years after CS (Hochman et al. 2001 and 2006).

Until recent years there has been a debate on whether a complete revascularization by immediate multivessel percutaneous coronary intervention (PCI) or revascularization of culprit coronary lesion only is more beneficial in ACS-related CS among patients with multivessel coronary artery disease. This question is essential, as most CS patients (>70%) present with multivessel disease, which is associated with higher mortality compared with single vessel coronary artery disease (Bertaina et al. 2018, Desch 2019, Thiele et al. 2019, Zeymer et al. 2017 and 2020). The multicenter, randomized CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock, n = 706) study showed a survival benefit in 30-day mortality in patients in the culprit-lesion-only group (with the option of staged revascularization of non-culprit lesions) compared with immediate multivessel PCI (mortality 43% vs. 52%, respectively) (Thiele et al. 2017). However, there was no statistically significant difference in 1-year mortality between the groups, although the risks for rehospitalization due to heart failure (5% vs 1%) and repeat revascularization (32% vs 9%) were slightly higher among patients with culprit-lesion-only PCI (Thiele et al. 2018). In ACS-related CS, current ESC (European Society of Cardiology) guidelines on myocardial revascularization recommend the culprit-lesion-only PCI strategy (Neumann et al. 2018). However, multivessel PCI may be considered in selected patients, for instance when identifying the culprit lesion is uncertain. A potentially increased risk of acute kidney injury (AKI) related to multivessel PCI must be considered when selecting the revascularization strategy (Bertaina et al. 2018). CABG should be considered in patients with multivessel coronary artery disease, depending on the coronary artery anatomy and when PCI seems unfeasible (Desch 2019, Neumann et al. 2018, Zeymer et al. 2020).

Hemodynamic instability is central to the pathophysiology of CS. Hypotension, systemic hypoperfusion, and relative hypovolemia call for cautious fluid therapy at the initial stage of CS to optimize the microcirculation and to ensure adequate cardiac preload (Chioncel et al. 2020). However, excess fluid resuscitation should be avoided to not exacerbate pulmonary, venous, and peripheral congestion.

In most CS cases, fluid therapy alone is insufficient to stabilize the patient, whereupon vasoactive medication is needed to achieve adequate perfusion. Vasopressors are drugs used to increase blood pressure during hypotension, and inotropes are used to improve myocardial contractility and to increase cardiac output. While vasoactive agents are usually needed to stabilize hemodynamics in CS, they also increase myocardial oxygen demand and may trigger arrhythmias (Chioncel et al. 2020).

Moreover, excessive vasoconstriction may impair microcirculation and aggravate tissue hypoperfusion (Werdan et al. 2014). Indeed, there is a lack of evidence-based data on the optimal vasoactive treatment strategy in CS. Noradrenaline, a potent vasoconstrictor, is often recommended as the first-line vasopressor to elevate blood pressure in CS, whereas dobutamine, a synthetic catecholamine acting mainly via $ß_1$ stimulation, is the first-line inotrope when needed. Other vasoactive agents used in the treatment of CS patients include the vasopressors dopamine and adrenaline and the inotropes levosimendan and milrinone. (Chioncel et al. 2020, van Diepen et al. 2017, Levy et al. 2015 and 2019, Mebazaa et al. 2016 and 2018, Ponikowski et al. 2016, Thiele et al. 2019, Werdan et al. 2014). However, use of adrenaline increases myocardial oxygen consumption and blood lactate level and is associated with increased risk of death (Levy et al. 2019, Tarvasmäki et al. 2016). Thus, adrenaline should be reserved for resuscitation use only. Moreover, to minimize complications and side effects, all vasoactive medication should be limited to the lowest dose and shortest duration possible (Chioncel et al. 2020, Levy et al. 2019, Mebazaa et al. 2018, Ponikowski et al. 2016, Thiele et al. 2019).

According to expert recommendations, a reasonable target mean arterial pressure (MAP) is approximately 65 (-70) mmHg for patients without previous hypertension, and possibly higher in patients with diagnosed hypertension (Chioncel et al. 2020, Levy et al. 2015, Thiele et al. 2015, Zeymer et al. 2020). It is essential to continuously assess the response to fluid therapy and vasoactive medication, as the primary objective of the treatment is to alleviate the tissue and end-organ hypoperfusion. In addition to clinical signs of hypoperfusion, including AMS, decreased urine output, and cool, clammy, and mottled skin, repeated arterial lactate and organ function marker (liver, kidney) measurements are needed to determine whether the treatment strategy is sufficiently effective (van Diepen et al. 2017, Levy et al. 2015).

If fluid resuscitation and vasoactive medication fail to stabilize hemodynamics, mechanical circulatory support (MCS) may be considered to alleviate systemic hypoperfusion and prevent multi-organ failure (Chioncel et al. 2020, Combes et al. 2020, Mebazaa et al. 2016). Until the last decade, intra-aortic balloon pump (IABP) was the most widely used MCS device. IABP improves coronary perfusion during diastole and lowers end-systolic pressure and thereby cardiac afterload. However, no survival benefit was found in patients treated with IABP in the large, randomized IABP-SHOCK II Trial (n = 600) and its routine use is no longer recommended (Neumann et al. 2018, Thiele et al. 2012, 2013 and 2018). IABP and other MCS devices, including left ventricular assist devices and extra-corporeal life support (veno-arterial extracorporeal membrane oxygenation, VA-ECMO), are recommended in refractory CS or as bridge therapies to recovery, surgical treatment, or cardiac

transplantation (Chioncel et al. 2020, van Diepen et al. 2017). In addition to the unproven benefit of MCS devices, these are costly therapies with high resource demands and carry a substantial risk of complications, such as thrombosis, bleeding, infections, limb ischemia, and hemolysis (Combes et al. 2020, Werdan et al. 2014). This highlights the importance of patient selection and optimal timing of MCS, both of which call for future randomized controlled trials (Combes et al. 2020, Mebazaa et al. 2016, Werdan et al. 2014).

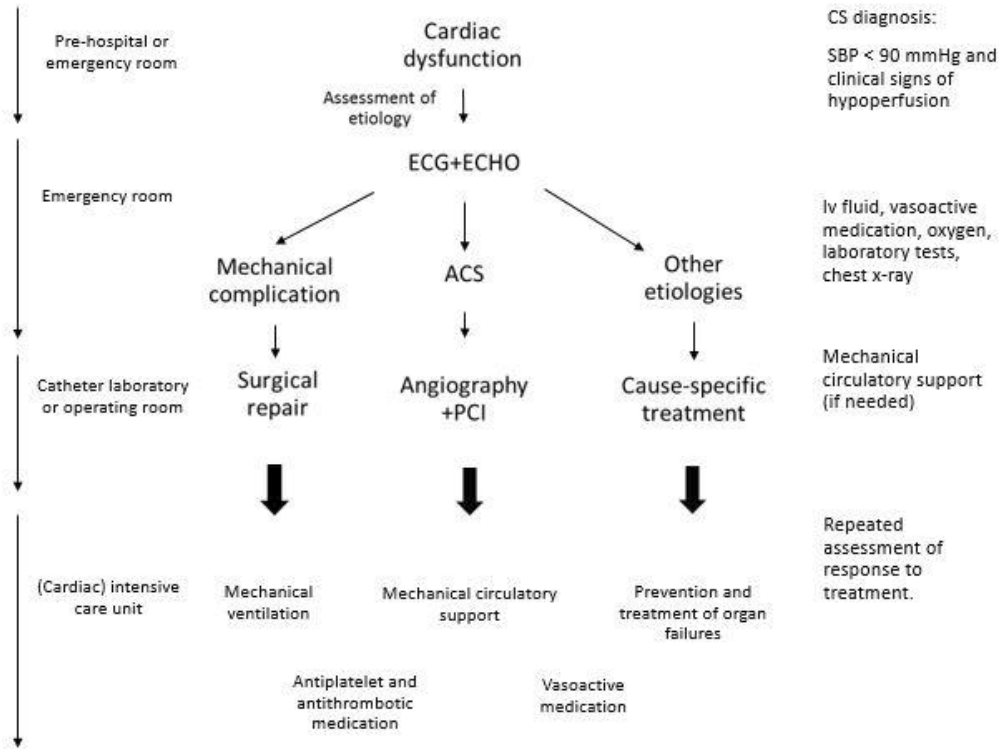

Figure 2. Diagnostics and management of cardiogenic shock. CS = cardiogenic shock, SBP = systolic blood pressure, ECG = electrocardiogram, ECHO = echocardiography, ACS = acute coronary syndrome, Iv = intravenous, PCI = percutaneous coronary intervention.

2.1.6 Organ dysfunction and complications

CS patients are typically treated in (cardiac) intensive care units (ICU), as most patients require vasoactive and ventilatory support, either invasively or non-invasively (Chioncel et al. 2020, van Diepen et al. 2017, Hongisto et al. 2017). Indwelling catheters and invasive ventilation render CS patients susceptible to infectious complications, such as ventilator-associated pneumonia and other nosocomial infections. Moreover, bacterial translocation from the intestinal tract is another possible origin of an infectious complication in CS (Brunkhorst et al. 1999, Cuinet et al. 2020). In a large, 1-day point prevalence study on approximately 14 000 unselected ICU patients, 51% were considered infected (Vincent et al. 2009). The reported prevalence of infections among CS patients varies substantially, possibly due to relatively small study populations and variable study settings. Moreover, it is difficult to differentiate bacterial infection from the inflammatory response in CS. In a study on 80 CS patients, Parenica et al reported that for up to 46% of the patients, the hospital stay was complicated by infection, most commonly of respiratory tract origin (Parenica et al. 2017). Conversely, no microbiologically confirmed infections were found in another study on 37 CS patients (Ramirez et al. 2016). A sub-study of the SHOCK Trial reported that 13% of the 302 CS patients were diagnosed with blood culture-positive infection; *Staphylococcus aureus* was the most commonly isolated pathogen (Kohsaka et al. 2007).

In addition to infections, another frequent complication among critically ill patients in general and in CS is AKI. Depending on the diagnostic criteria, the incidence of AKI among CS patients varies from 30% to over 50% and is associated with increased mortality (Chioncel et al. 2020, Lassus 2020, Marenzi et al. 2010, Tarvasmäki et al. 2018). Multiple factors reflecting hemodynamic derangements in CS predispose to AKI, including low arterial pressure, organ hypoperfusion, and venous congestion, and exposure to contrast agents during angiography and PCI (Chioncel et al. 2020). Additionally, neurohormonal activation and inflammatory response further aggravate renal dysfunction. Early correction of the potential hypovolemia and optimizing hemodynamics by ensuring adequate arterial pressure while simultaneously minimizing venous congestion are essential in preventing AKI (Lassus 2020). However, renal replacement therapy is sometimes necessary (in 10 to 15% of CS patients) (Lauridsen et al. 2015, Marenzi et al. 2010, Tarvasmäki et al. 2018). In addition to AKI, liver injury is a frequent complication in CS. Elevated liver enzymes are observed in approximately half of the patients, and both hypoperfusion and congestion presumably contribute to the liver injury (Chioncel et al. 2020, van Diepen et al. 2017, Jäntti et al. 2017, Lassus 2020). Moreover, an early increase in alanine aminotransferase levels is associated with organ hypoperfusion and increased mortality in CS (Jäntti et al. 2017).

2.2 BLOOD GLUCOSE LEVEL IN CARDIOGENIC SHOCK

2.2.1 Glucose metabolism

Glucose serves as a vital fuel for most human tissues. Constantly available circulating blood glucose is especially important to the central nervous system, which consumes a major part of glucose in basal metabolic state, mostly in an insulin-independent manner (Van Cromphaut et al. 2009, Sonneville et al. 2015). Glucose is cleaved from di- and polysaccharides by digestive enzymes found in the digestive tract after a carbohydrate-containing meal. As energy uptake from nutrition is periodic, extra energy is stored in the form of fat, protein, and, to a more limited extent, glycogen for future needs. Glycogen forms a minor portion of the body's total energy reserves, yet it is crucial for the continuous glucose supply to the central nervous system and for short intense muscle work. Muscle glycogen can be used only by muscles themselves, whereas liver glycogen can be made available for other tissues as well. This process (called glycogenolysis) releases glucose to the circulation when needed. Moreover, glucose can be synthesized in the liver through gluconeogenesis from lactate, pyruvate, carbon skeleton of nearly all amino acids, and from breakdown of lipids. Hence, the continuous availability of glucose is ensured by multiple mechanisms (Marik et al. 2013).

Under normal circumstances, blood glucose level is tightly controlled in healthy individuals mainly by insulin and glucagon (two hormones with antagonistic effects) secreted from pancreatic islets. However, this balance is affected by acute stressors and illnesses via sympathetic and parasympathetic nervous systems and hormones, including cortisol, growth hormone, and thyroid hormones (Angeli et al. 2015, Van Cromphaut et al. 2009). Insulin promotes glucose storage as glycogen in the liver and inhibits hepatic glycogenolysis and gluconeogenesis, thereby lowering basal circulating glucose concentration and limiting the post-prandial rise in blood glucose. In addition, insulin stimulates glucose transport into muscle and adipose cells and storage as muscle glycogen and triglycerides, respectively. In fat metabolism, insulin enhances storage and inhibits mobilization and oxidation of fatty acids, resulting in decreased levels of circulating free fatty acids and ketoacids. Moreover, insulin acts as an anabolic hormone by inhibiting proteolysis and promoting amino acid and protein storage. Glucagon, in turn, acts to maintain normoglycemia and prevent hypoglycemia. Virtually all the effects of glucagon are opposite to those of insulin, for instance the promotion of gluconeogenesis and glycogenolysis. Acute stressors, such as infections and tissue infarctions, promote increased glucagon secretion, resulting in hyperglycemia. Moreover, acute illness induces insulin resistance, characterized by reduced suppression of hepatic gluconeogenesis and reduced insulin-mediated glucose uptake by peripheral tissues due to changes in post-receptor insulin-signaling and down-regulation of insulin-dependent glucose transporters. However, non-insulin-

dependent glucose uptake is increased in the whole body (Van Cromphaut et al. 2009, Dungan et al 2009, Mongkolpun et al. 2019, Preiser et al. 2014).

Indeed, hyperglycemia is frequently (20-80% depending on the study population and threshold value) observed among critically ill patients, irrespective of previous history of diabetes mellitus (DM) (Deane et al. 2013, Marik et al. 2013, Mongkolpun et al. 2019, Plummer et al. 2014, Umpierrez et al. 2012). Hyperglycemia partly reflects the activation of stress-response mechanisms, including the sympathoadrenal system and hypothalamic-pituitary-adrenal axis, which are essential for survival. Acute hemorrhage, severe trauma, sepsis, and hypotension or shock of any cause induce the release of stress mediators, such as catecholamines and cortisol. In addition to the changes in cardiovascular system, activation of stress response modifies carbohydrate metabolism by promoting gluconeogenesis, glycogenolysis, and insulin resistance (Angeli et al. 2015, Barth et al. 2007, Dungan et al 2009, Ichai et al. 2010, Marik et al. 2013 and 2014, Mongkolpun et al. 2019, Preiser et al. 2014). Consequently, hyperglycemia emerges. However, to what extent stress hyperglycemia is physiological and adaptive remains unclear. Conflicting data on strict versus permissive glucose control have made it difficult to establish precise, evidence-based recommendations on the blood glucose target level during acute or critical illness (Ichai et al. 2010, Krinsley et al. 2019, Vanhorebeek et al. 2018). Severe (< 2.2 mmol/L) and even mild hypoglycemia (< 3.9 mmol/L) and repeated changes in blood glucose levels (large glycemic variability) should be avoided (Ichai et al. 2010, Jacobi et al. 2012, Mesotten et al. 2015, Umpierrez et al. 2012), but the upper limit of target level depends on the recommendation (8.0-10.0 mmol/L), the cause of hospitalization, treatment setting (ICU versus non-ICU), and the patient's previous glycemic balance (Jacobi et al. 2012, Mesotten et al. 2015, Umpierrez et al. 2012).

2.2.2 Blood glucose level in cardiogenic shock

Previous studies revealed an association between hyperglycemia and increased mortality in critical illness in general, in ACS, and in AHF (Angeli et al. 2015, Capes et al. 2000, Dungan et al 2009, Falciglia et al. 2009, Ichai et al. 2010, Jacobi et al. 2012, Lazzeri et al. 2015, Mebazaa et al. 2013, de Miguel-Yanes et al. 2015). In addition, stress hyperglycemia among ACS patients is also associated with increased risk of developing HF or CS (Capes et al. 2000). There are some studies on blood glucose levels in the CS setting. Vis et al investigated the admission glucose levels of 208 non-diabetic STEMI patients with CS treated with PCI. Admission blood glucose > 11.0 mmol/L was associated with high (60%) 1-year mortality, and the odds for mortality increased 16% for every 1

mmol/L increase in blood glucose level (Vis et al. 2007). Furthermore, in a study on the role of admission blood glucose level of 816 STEMI patients with CS, Yang et al found that higher blood glucose level was associated with increased 30-day mortality in non-diabetic patients, but not in diabetic patients (Yang et al. 2013). In a sub-study of the IABP-SHOCK II, the baseline blood glucose levels of 513 STEMI-related CS patients were analyzed and above-median glucose (> 11.5 mmol/L) was associated with increased mortality irrespective of previous diabetes history (Abdin et al. 2018). In addition, admission blood glucose > 10.6 mmol/L was integrated as a variable into to IABP-SHOCK II score in 30-day mortality prediction (Poss et al 2017). In a recent registry study on 1302 CS patients using the same blood glucose cut-off levels as in the present study (< 4.0 mmol/L, 4-8 mmol/L, 8-12 mmol/L, 12-16 mmol/L and > 16 mmol/L), Thoegersen et al reported a U-shape mortality curve both among diabetic and non-diabetic patients (Thoegersen et al. 2020). The patients with admission blood glucose level between 4 and 8 mmol/L had the best prognosis (30-day mortality of 33%), while mortality increased thereafter along with increasing glucose level. Hypoglycemic patients had the highest mortality (72%). Interestingly, no association between prognosis and blood glucose level was found at 24h after ICU admission. In a smaller study on 81 CS patients, Tada et al showed an association between higher blood glucose and mortality and a positive correlation between glucose and adrenaline levels (Tada et al. 2006). According to the study, a blood glucose level of 9.2 mmol/L had the highest combined sensitivity and specificity for predicting in-hospital mortality (AUC 0.75). Moreover, Valente et al showed that admission blood glucose > 11 mmol/L was associated with increased in-hospital mortality among 45 CS patients. However, no independent association between glucose and prognosis was found in multivariable analysis (Valente et al. 2007). Finally, Jaskiewicz et al reported the admission glucose level of 40 CS patients. The blood glucose level of CS patients was significantly higher than that of ACS patients without CS (15.4 mmol/L vs. 8.0 mmol/L, respectively), but no association between high blood glucose and mortality was found (Jaskiewicz et al. 2015).

2.3 ALTERED MENTAL STATUS IN CRITICAL ILLNESS

AMS is included in the diagnostic criteria for CS as a clinical sign of end-organ hypoperfusion (van Diepen et al. 2017, Mebazaa et al. 2018). Moreover, AMS is among the three variables (in addition to systolic blood pressure ≤ 100 mmHg and respiratory rate ≥ 22/min) in the quick Sequential Organ Failure Assessment score (qSOFA) in early sepsis diagnostics (Singer et al. 2016). Indeed, more than half of septic patients present with neurological symptoms (Bolton et al. 1993, Gofton et al. 2012, Sonneville et al. 2017, Young 2013). In addition, critical illness delirium is a well-known phenomenon in the ICU and is associated with increased mortality, prolonged hospitalization and, importantly, even chronic cognitive impairment (Girard et al. 2008, Jackson et al. 2015, Salluh et al. 2015, Slooter et al. 2020, Sonneville et al. 2017). In addition to delirium and AMS, the terms "acute encephalopathy" and "acute brain dysfunction" are used to describe alterations in patients' cognitive function, especially during critical illness (Slooter et al. 2020). Sepsis-associated encephalopathy is a well-established form of acute brain dysfunction, characterized by alterations in cerebral blood flow, endothelial dysfunction, blood-brain barrier permeability and neurochemical transmission, often with detectable lesions in magnetic resonance imaging and electroencephalogram abnormalities (Heming et al. 2017, Hughes et al. 2012, Polito et al. 2013, Tsuruta et al. 2016, Williams 2013, Young 2013). The same changes have been proposed as possible pathophysiological mechanisms in the development of critical illness delirium (Jackson et al. 2015, Williams 2013).

The prevalence of critical illness delirium varies from 20% to 80% depending on the screening method, diagnostic criteria used, and study population (Girard et al. 2008, Klein et al. 2014, Salluh et al. 2015, Thomason et al. 2005, Van Rompaey et al. 2009). Delirium may present as a decline from individual baseline cognition, and is characterized by fluctuating course, disorganized behavior, and disturbances in attention, consciousness, awareness, orientation, memory, and perception. However, particularly the hypoactive type of delirium with less pronounced mental state alterations may be underdiagnosed when structured delirium screening tests are used (Gusmao-Flores et al. 2012). Delirium is always the consequence of several factors, some of which are patient dependent and related to chronic diseases, while others are related to acute illness or environment. The latter factors are modifiable and deserve special attention in critical care (Van Rompaey et al. 2009). Reported risk factors for critical illness delirium include advanced age, comorbidities (especially dementia), alcohol consumption, infections, use of sedatives, physical restraints, use of multiple catheters and infusions, sleep deprivation, mechanical ventilation, severity of acute illness, polytrauma, and organ failure (Jackson et al. 2015, Thomason et al. 2005, Van Rompaey et al. 2009).

Hence, there are multiple factors related to both acute and chronic illnesses and treatment procedures and medications that threaten normal, physiologic cerebral activity. On the other hand, there are some very special properties in brain tissue and in cerebral blood flow that aim to protect the brain and make it less susceptible to metabolic and hemodynamic changes than in the rest of the body. The blood-brain barrier forms a unique, highly selective membrane between the blood and the central nervous system. Moreover, in contrast to almost every other organ, cerebral circulation is mainly controlled by the brain itself. Cerebral autoregulation ensures adequate blood flow and oxygen and energy supply to the brain tissue if mean arterial pressure remains between approximately 60 to 160 mmHg. At the same time, out of all body tissues, brain tissue is the least tolerant to ischemia, and cerebral blood flow is highly sensitive to concentrations of many circulating substances, including pCO_2 and pO_2. Intact autoregulation quickly adjusts the cerebral blood flow to meet local metabolic demands. However, prolonged severe hypotension interferes with cerebral autoregulation and may result in neuronal ischemia and injury (Klijn et al. 2010).

There are some studies on the prevalence and prognostic significance of mental state alterations among (non-surgical) acute cardiac patients, focusing mainly on actual delirium. Previous studies using the Confusion Assessment Method for the ICU (CAM-ICU) in diagnostics report a delirium prevalence of approximately 19% to 29% among patients treated in cardiac ICU (Lahariya et al. 2014, McPherson et al. 2013, Pauley et al. 2015). A study by Pauley et al on 590 patients admitted to cardiac ICU showed a CAM-ICU-positive delirium prevalence of 20% (Pauley et al. 2015). Patients with delirium tended to be older, more likely to have indwelling catheters, and to have been treated with renal replacement therapy or vasoactive medication compared with non-delirious patients. Importantly, those with a positive delirium screening test had a higher risk of developing CS. Delirium was also associated with longer ICU stay and higher in-hospital mortality (33% vs 5%). Lahariya et al analyzed a population of 309 patients admitted to cardiac ICU (Lahariya et al. 2014). The prevalence of delirium was 19%, and in addition to age, risk factors for delirium included higher total number of medications (especially opioids and benzodiazepines), presence of cognitive deficits, diabetes, congestive HF, atrial fibrillation, and CS. In addition, mortality was higher among delirious patients (27% vs 1%) as was length of ICU stay. McPherson et al investigated the prevalence and risk factors for delirium among 200 cardiac patients in medical-surgical cardiac ICU (McPherson et al. 2013). The prevalence of delirium was 29% among non-surgical cardiac patients and 24% in cardiac surgical patients. Importantly, the study showed that the hypoactive type of delirium was predominant (91%) among these patients. Risk factors for delirium included age, vascular disease (peripheral or cerebrovascular), benzodiazepine use, and the use of restraints or devices that precluded

mobilization. Iwata et al found that 27% of the 408 AHF patients admitted to ICU were diagnosed with delirium during the ICU stay. In-hospital mortality was significantly higher (14%) in these patients than in non-delirious patients (2%) (Iwata et al. 2020). A similar delirium prevalence (23%) was reported from a study of 611 AHF patients (Honda et al. 2016). In addition to increased mortality, delirium predicted further worsening of HF during hospitalization, while history of cerebrovascular disease, age, low serum albumin level, and high blood glucose level were independent determinants of delirium. In comparison, a delirium prevalence of 11% was observed in a study population of 624 acute MI patients (Jäckel et al. 2020). Many of the studies on delirium among acute cardiac patients focus on the elderly (> 65-75 years) (Noriega et al. 2015, Sato et al. 2017, Uthamalingam et al. 2011). In these studies, the prevalence of delirium was 17% to 21% and identified risk factors for delirium included age, dementia, cerebrovascular disease, catheters, immobilization, and restraints. Moreover, delirium was associated with higher mortality and increased risk for rehospitalization and functional decline at discharge and higher nursing home placement.

As is the case with critical illness delirium in general, the etiology of delirium in patients treated in cardiac ICU seems to be multifactorial. Some predisposing factors, such as high comorbidity and advanced age, are nonmodifiable, while others are related to the acute illness or treatments. These include pain, immobilization, procedures and catheters, environmental factors, infections, electrolyte disturbances, sleep deprivation, and medications (Ibrahim et al 2018, Jackson et al. 2015).

2.4 GROWTH DIFFERENTIATION FACTOR 15

Growth differentiation factor 15 (GDF-15) is a stress-responsive protein belonging to the transforming growth factor-β cytokine superfamily. Under physiological circumstances, GDF-15 is only weakly expressed in most tissues, reflected by low circulating levels of GDF-15. In contrast, placenta expresses and secretes high levels of GDF-15 during pregnancy (Wollert et al. 2012 and 2017). Moreover, the expression of GDF-15 is strongly induced during acute stressors (such as hypoxia, tissue injury, inflammation, oxidative stress) as well as in chronic diseases in many organs, including the kidney, liver, heart, and gastrointestinal tract. In addition to parenchymal cells, GDF-15 is expressed in adipocytes, endothelial cells, macrophages, and vascular smooth muscle cells (Anand et al. 2010, Wollert et al. 2012 and 2017). In most studies, 1200 ng/L is considered as the upper limit of normal. This is based on the rounded 90th percentile in a study on 429 apparently healthy elderly (median age 65 years, IQR 59-71) individuals (Kempf et al. 2007/I). The actual biological functions of GDF-15 are not fully understood and vary depending on the context and disease stage. GDF-15 participates in processes regulating inflammatory and apoptotic pathways in acute and chronic tissue injuries. Similarly, GDF-15 possesses both pro- and anti-inflammatory properties. The expression of GDF-15 is partly regulated by transcription factor p53, which has a fundamental role in regulating cell cycle, apoptosis, and genomic stability. The p53 pathway becomes activated in response to hypoxia, inflammation, oxidative stress, oncogene activation, and DNA damage (Wollert et al. 2012 and 2017).

Reflecting its multiple origins of secretion and its relationship with chronic inflammation, elevated levels of circulating GDF-15 are associated with not only increased risk of numerous chronic diseases (including several cancers and cardiovascular [CV] diseases), but also with increased risk of all-cause mortality (Wollert et al. 2017). Associations of GDF-15 with cardiac and vascular pathologies, such as left ventricular hypertrophy and dysfunction, coronary artery calcification, endothelial dysfunction, and arterial stiffness, have been observed. Mechanical stretch, ischemia, proinflammatory cytokines, and neurohormones (such as angiotensin II) induce expression of GDF-15 in cultured cardiomyocytes (Anand et al. 2010, Lind et al. 2009, Wollert et al. 2012 and 2017). Furthermore, elevated GDF-15 levels are associated with many risk factors for CV diseases, such as current smoking, diabetes, age, body mass index, and elevated levels of high-sensitivity C-reactive protein (CRP) and natriuretic peptides (Kempf et al. 2009, Wollert et al. 2012 and 2017). In optimally treated HF patients, GDF-15 levels correlate with hsTnT and NT-proBNP levels (Sharma et al. 2017). Moreover, elevated GDF-15 levels predict mortality in chronic HF (Anand et al. 2010, Kempf et al. 2007/II). GDF-15 also independently predicts CV mortality in patients with diagnosed coronary

artery disease, both in stable and unstable disease states (Anand et al. 2010, Kempf et al. 2009). GDF-15 may have protective, antiapoptotic, anti-inflammatory, and antihypertrophic properties when secreted from the myocardium in response to pressure-overload or ischemia (Wollert et al. 2012, Xu et al. 2006). In animal models, GDF-15 has shown anti-apoptotic and but also pro-hypertrophic effects on cardiomyocytes (Heger et al. 2010).

In addition to chronic diseases and inflammatory processes, the expression and secretion of GDF-15 is strongly upregulated during acute illnesses. For example, very high levels of GDF-15 (median > 16000 ng/L) have been detected in septic patients (Mueller et al. 2015). During the past two decades, GDF-15 has also raised special interest in acute CV processes. Elevated levels of GDF-15 have been described both in AHF and in ACS. High GDF-15 levels are associated with increased mortality among STEMI and non-STEMI patients. Moreover, higher GDF-15 levels correlate with higher risk of stroke, bleeding complications, recurrent MI, impaired microvascular perfusion, and reduced LVEF in ACS patients (Cotter et al. 2015, Hagstrom et al. 2016, Kempf et al. 2007/III, Wollert et al. 2007). The results from these studies are presented in more detail in Table 1. Indeed, GDF-15 expression is upregulated in cardiomyocytes during acute MI, possibly related to the ischemia and reperfusion injury (Kempf et al. 2006, Wollert et al. 2012). As mentioned, the actual biological functions of GDF-15 in an ischemic or failing heart remain unclear; it is unknown if GDF-15 has only potential protective or additional detrimental effects on myocardium and CV system in general (Eitel et al. 2011, Wollert et al. 2012).

However, in acute cardiac events and in chronic CV diseases, GDF-15 seems to be largely secreted from sources other than myocardium, reflecting systemic and extra-cardiac pathologies. Interestingly, in a study on 30 patients with end-stage non-ischemic dilated cardiomyopathy, the circulating GDF-15 levels were high (mean level circa 7000 ng/L), but cardiac mRNA and protein expression levels of GDF-15 were very low, suggesting peripheral sources of secretion. Moreover, high levels of circulating GDF-15 decreased to nearly normal values after implantation of a left ventricular assist device (Lok et al. 2012).

Table 1. Results from previous studies on GDF-15 levels among ACS and HF patients.

Study	Population	N	Result (GDF-15 level ng/L)
Wollert et al. 2007	Non-STEMI	2081	Median: 1450 ng/L, 1-year mortality: 1.5% (< 1200ng/L), 5% (1200-1800ng/L), 14% (> 1800ng/L)
Kempf et al. 2007	STEMI, treated with fibrinolytic therapy	741	Median: 1635 ng/L, 1-year mortality: 2% (< 1200ng/L), 5% (1200-1800ng/L), 14% (> 1800ng/L)
Anand et al. 2010 Val-HeFT	Chronic HF, symptomatic	1734	Median: 2040 ng/L at baseline. Follow-up 23 months: higher GDF-15 level was associated with higher mortality, renal dysfunction, older age, diabetes, and higher levels of CRP, hsTnT, and noradrenaline.
Eitel et al. 2011	STEMI, treated with PCI	238	Higher level of GDF-15 at baseline was inversely correlated with myocardial salvage in MRI. Increasing GDF-15 level after PCI was associated with larger infarct and reduced LVEF.
Cotter et al. 2015 RELAX-AHF	AHF	1161	Median: 4000 ng/L
Hagstrom et al. 2016 PLATO Trial	ACS	16876	Median: 1550 ng/L. Higher GDF-15 was associated with increased risk of CV and all-cause death, stroke, bleeding complications, and recurrent MI.

ACS = acute coronary syndrome, HF = heart failure, STEMI = ST-elevation myocardial infarction, CV = cardiovascular, MI = myocardial infarction, PCI = percutaneous coronary intervention, MRI = magnetic resonance imaging, LVEF = left ventricular ejection fraction, AHF = acute heart failure, CRP = C-reactive protein, hsTnT = high-sensitivity troponin T

Data on levels and prognostic significance of GDF-15 among CS patients are scarce. Besides the current research, to the author's knowledge there is only one study on GDF-15 levels in CS. In a sub-study of the IABP-SHOCK II Trial, baseline GDF-15 levels of 190 CS patients were analyzed (Fuernau et al. 2014). The median baseline GDF-15 level was 7662 ng/L and GDF-15 levels were significantly lower among 30-day survivors compared with non-survivors (6087 vs. 10926 ng/L). Similarly, patients with above-median baseline GDF-15 had higher mortality rates at 30 days than those in the below-median group. GDF-15 remained independently associated with increased mortality in multivariable regression analysis.

2.5 INFLAMMATORY MARKERS IN CARDIOGENIC SHOCK

2.5.1 Interleukin 6

Interleukin 6 (IL-6) is among the most important mediators in the inflammatory cascade and a major stimulator of most acute-phase proteins. IL-6 mediates a variety of biological functions, including regulation of regenerative processes, immune system, coagulation, and metabolism (Tanaka et al. 2006). IL-6 is produced by several cell types, most importantly monocytes and macrophages, but also by endothelial cells. In response to an infectious agent or tissue damage, IL-6 sends inflammatory signals to the whole body, leading to production of several acute-phase proteins such as CRP, hepcidin, fibrinogen, and serum amyloid A. The multiple IL-6-related functions play a critical role in a variety of pathological conditions, such as disseminated intravascular coagulopathy or increased vascular permeability, which are both important features of SIRS (Tanaka et al. 2006). In addition to the pro-inflammatory properties, IL-6 has anti-inflammatory effects, depending on its concentration and the concomitant presence of other cytokines. IL-6 level peaks early at 3 hours after exposure to bacterial toxins and returns to baseline after 8 hours, with a rather short half-life of about 100 minutes (Dandona et al. 1994, Gabay et al. 1999, Schett 2018, Schneider et al. 2007, Waage et al. 1989). In healthy adults, IL-6 level is low (< 3 ng/L) and often undetectable.

Studies in CS patients show considerable variability in IL-6 levels, possibly related to the relatively small study populations (n = 7-87) and different blood sampling time points (given the rapid kinetics of IL-6). The reported levels of IL-6 in previous studies on CS patients vary between approximately 30 and 2700 ng/L, being typically higher than in MI without shock but somewhat lower than in septic shock (Brunkhorst et al. 1999, Debrunner et al. 2008). High IL-6 levels are associated with increased risk of multiple organ failure and death in CS (Andrie et al. 2012, Geppert et al. 2002 and 2006, Jarai at al. 2009, Prondzinsky et al. 2012, Ramirez et al. 2016). The results from the largest studies on IL-6 levels among CS patients are shown in Table 2.

Table 2. Results from previous studies on IL-6 levels among CS patients.

Study	N	Result
Geppert et al. 2002	51	Baseline IL-6 was significantly higher among CS patients with MOF (median IL-6 > 200 ng/L) compared with CS without MOF (< 100 ng/L). Baseline IL-6 > 200 ng/L had an AUC of 0.97 in the prediction of MOF during ICU stay.
Jarai et al. 2009	58	High IL-6 at admission was independently associated with 30-day mortality in multivariable analysis including age, renal function, LVEF, and SOFA score. Proposed IL-6 cut-off value was 195 ng/L.
Andrie et al. 2012	87	IL-6 level at baseline: 31 ng/L (survivors) vs. 424 ng/L (non-survivors). IL-6 was the strongest predictor of 30-day mortality in multivariable analysis including age, renal function, blood lactate, dose of catecholamines, and cardiac power index.
Prondzinsky et al. 2012 IABP-SHOCK	40	Higher baseline IL-6 level among non-survivors (2710 ng/L) compared with survivors (373 ng/L). Decreasing IL-6 level in both groups during the first days of CS. No difference in IL-6 levels in patients treated with and without IABP.

IL-6 = interleukin 6, CS = cardiogenic shock, MOF = multiple organ failure, AUC = area under the curve, ICU = intensive care unit, LVEF = left ventricular ejection fraction, SOFA = sequential organ failure assessment, IABP = intra-aortic balloon pump

2.5.2 C-reactive protein

C-reactive protein (CRP) is an acute-phase protein that is secreted primarily from hepatocytes in response to infection, tissue damage, burns, malignancy, or non-specific immune activation (Pepys et al. 2003). CRP interacts with the C-polysaccharide of *Streptococcus pneumoniae* cell wall (Bray et al. 2016). Pro-inflammatory cytokines, particularly IL-6 and to a lesser degree tumor necrosis factor and IL-1, stimulate the production of CRP. CRP levels can increase up to 1000-fold in bacterial infections (normal level << 3 mg/L) (Pepys et al. 2003). While CRP serves as a marker of inflammation, infection, or tissue damage, CRP plays a role in the inflammatory process through the activation of complement and opsonization of pathogens. Moreover, CRP assists with clearance of apoptotic or necrotic cells by binding to their cell membranes (Bray et al. 2016). CRP level increases relatively slowly (6-12-24 hours) and has a half-life of 18 to 20 hours (Gabay et al. 1999, Pepys et al. 2003, Schneider et al. 2007, Sproston et al. 2018).

Tissue necrosis is a potent stimulus for many acute-phase proteins, including CRP. Consequently, myocyte necrosis during acute MI activates the cascade mentioned above and may result in elevated CRP levels that are to some extent proportional to myocardial injury (Pepys et al. 2003). However, as CS is a medical emergency affecting the entire body, myocardial damage presumably accounts for only a fraction of the CRP increase in CS. There are some rather small studies on CRP in CS settings that describe CRP levels between approximately 40 and 220 mg/L during the first days of shock. CRP levels detected in CS are typically higher than in ACS patients without shock. The prognostic value of CRP varies from study to study, as does the correlation with infections (Brunkhorst et al. 1999, Debrunner et al. 2008, Geppert et al. 2003, Lim et al. 2005, Parenica et al. 2017, Picariello et al. 2009, Ramirez et al. 2016, Shah et al. 2013). For instance, Ramirez et al reported no differences in peak CRP levels between survivors and non-survivors during the first 3 days of shock in a study on 37 CS patients (180 vs 223 mg/L, respectively) (Ramirez et al. 2016). Parenica et al described the trends of CRP levels among 80 CS patients in a study on infectious complications. No statistically significant difference was found in peak CRP values between patients with and without infection (166 vs 182 mg/L) (Parenica et al. 2017).

2.5.3 Procalcitonin

Procalcitonin (PCT), a peptide precursor of the hormone calcitonin, is produced by the parafollicular cells of the thyroid gland. PCT is cleaved into the active hormone intracellularly and calcitonin is then secreted from the thyroid gland into circulation. Therefore, under physiological circumstances, circulating PCT levels are below the limit of detection in healthy subjects. In the presence of systemic bacterial infection or sepsis, PCT production in extra-thyroid tissues rapidly increases in response to bacterial endotoxins (levels increase in 3-6 hours) (Maruna et al. 2000, Samsudin et al. 2017, Schuetz et al. 2011 and 2016). Moreover, PCT levels correlate with severity of infection and bacterial load. However, the actual site of non-thyroidal PCT production is still somewhat unclear, as is the biological function of the inflammation-related increase in circulating PCT levels. PCT is probably secreted by many parenchymal cells (especially hepatocytes) and the neuroendocrine cells of intestine and lungs, but also by granulocytes and other components of the immune system (Maruna et al. 2000, Picariello et al. 2009, Samsudin et al. 2017). There are no enzymes outside the thyroid gland that can cleave PCT into calcitonin. Consequently, PCT remains unchanged in the circulation with a half-life of 22 to 30 hours (Davies 2015, Maruna et al. 2000, Schneider et al. 2007). Several cut-off values for PCT to initiate, continue, or discontinue antibiotic treatment have been proposed, depending on the

disease in question and the study setting. In critically ill patients, the threshold value has commonly been 0.5 µg/L (Bouadma et al. 2010, de Jong et al. 2016, Samsudin et al. 2017, Schuetz et al. 2011 and 2016).

Although PCT is regarded as a relatively specific biomarker of systemic bacterial infection or sepsis, its non-thyroidal production and secretion are stimulated by inflammatory mediators, such as tumor necrosis factor and IL-6, which are present for instance in burns and extensive tissue damage (Davies 2015, Meisner 2014, Samsudin et al. 2017, Schneider et al. 2007, Schuetz et al. 2016). PCT levels up to > 100 µg/L can be observed in septic shock, while both normal (< 0.5 µg/L) and mildly elevated levels of PCT have been described in uncomplicated ACS (Buratti et al. 2001, Picariello et al. 2009, Vitkon-Barkay et al. 2018, de Werra et al. 1997). The studies on PCT in CS settings show considerable variability in PCT levels (means or medians 0.5-6.6 µg/L) (Andrie et al. 2012, Geppert et al. 2003, Parenica et al. 2017, Picariello et al. 2009, Ramirez et al. 2016, de Werra et al. 1997). In a study of 87 ACS-related CS patients, the median PCT level of survivors was significantly lower compared with non-survivors at 24 h (0.46 vs 2.42 µg/L) but not at baseline (Andrie et al. 2012). Parenica et al investigated infectious complications among 80 CS patients and found no difference in peak PCT value during the first days of shock between patients without and with infection (2.1 vs 1.4 µg/L), while PCT measured at 12 h showed prognostic significance in 90-day mortality prediction (AUC 0.76) irrespective of infection status (Parenica et al. 2017). In a study on 37 CS patients, survivors had significantly lower peak PCT (0.73 µg/L) compared with non-survivors (7.3 µg/L) during the first 3 days of hospitalization (Ramirez et al. 2016). Finally, in a study comparing CS patients (n = 40) with septic shock patients (n = 15), Geppert et al reported a median PCT of 0.8 µg/L among CS patients, which was significantly lower than that of septic patients (9.2 µg/L) (Geppert et al. 2003). In the same study, PCT levels > 2.0 µg/L were associated with multiple organ failure in the absence of infection.

In summary, while the presence of an inflammatory response is established in CS and is thought to play a key role in the pathophysiology, the data on inflammatory marker levels are based on rather small study populations. The reported levels of IL-6, CRP, and PCT and their association with prognosis and infections vary considerably. In many studies, only one measurement of each inflammatory biomarker is available and there is a lack of data on the kinetics of inflammatory marker levels during the first days of CS.

3 AIMS OF THIS STUDY

The aims of this study were to investigate the prognostic significance of clinically relevant factors, including blood glucose level, mental status, and biomarkers in cardiogenic shock and to assess their value in risk stratification. The specific aims were

1) To assess the association of baseline blood glucose level with clinical presentation and other biochemistry in CS, and to evaluate the prognostic significance of blood glucose level. (I)
2) To investigate the prevalence, clinical relevance, and prognostic significance of AMS in CS. (II)
3) To assess the levels and kinetics of GDF-15 in CS and to analyze the prognostic value of GDF-15 in risk stratification. (III)
4) To describe the kinetics of PCT, CRP, and IL-6 in CS and to assess their prognostic properties and relation to clinical presentation and biochemistry. (IV)

4 SUBJECTS AND METHODS

4.1 Study population

The present studies were based on The CardShock study (NCT01374867 at Clinicaltrials.gov), a prospective, observational multicenter study on CS. Patients (n = 219) were recruited in nine tertiary hospitals in eight countries across Europe (Czech Republic, Denmark, Finland, Greece, Italy, Poland, Portugal, and Spain) between October 2010 and December 2012. In addition to acute cardiac etiology of CS, the inclusion criteria were 1) systolic blood pressure < 90 mmHg for over 30 minutes despite adequate fluid challenge or continuous need for vasopressor therapy to maintain systolic blood pressure > 90 mmHg, and 2) clinical signs of hypoperfusion (AMS, cold extremities, oliguria < 0.5 ml/kg/h for the previous 6 hours, or blood lactate > 2 mmol/L). Both ACS and non-ACS (e.g. valvular causes, acute worsening of chronic HF) patients were included in the CardShock study. Patients with shock after cardiac or non-cardiac surgery were excluded from the study, as were patients with on-going hemodynamically significant cardiac arrhythmia. Patients had to be over 18 years of age and enrolled within 6 hours of the shock detection.

Patients were treated according to local clinical practice. Hemodynamic and clinical parameters were recorded, and blood was drawn for biochemical analyses at baseline (0h) and repeatedly at pre-specified time points (12 h, 24 h, 36 h, 48 h, 72 h, 96 h, and 120 h). Leukocytes, hemoglobin, arterial pH, blood lactate and blood glucose were analyzed locally. NT-proBNP, hsTnT, GDF-15 (assays from Roche Diagnostics, Basel, Switzerland), creatinine, and CRP (routine automated analyses) were analyzed centrally at ISLAB (Kuopio, Finland). PCT was analyzed by SphingoTec (Germany) and IL-6 was analyzed using R&D Systems (Minneapolis, MN, USA, analysis performed in Wroclaw University, Poland) from blood samples stored at -80°C. Estimated glomerular filtration rate (eGFR) was calculated from baseline creatinine values using the CKD-EPI equation (Levey et al. 2009).

Echocardiography was performed at baseline. Detailed data on demographics and medical history were collected. The primary outcome was 90-day all-cause mortality. Three patients were lost to follow-up. Vital status during the follow-up was determined through direct contact with the patient or next of kin, or through hospital and population registries. The CardShock study was conducted in accordance with the Declaration of Helsinki and approved by local ethics committees.

4.2 Statistical analyses

Categorical variables are presented as numbers (n) and percentages (%), continuous variables as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) for variables with a skewed distribution.

The medical history, clinical presentation, biochemical variables, and short-term (in-hospital, 90-day, or both) mortality were assessed and compared between groups defined in each sub-study. Between-group comparisons were performed with χ^2 test for categorical variables. When analyzing differences in continuous variables between two groups, Student's *t*-test was used for normally distributed variables and Mann-Whitney *U* test for variables with a skewed distribution. Multi-group comparisons for continuous variables were performed with analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate.

Correlations between two continuous variables were tested using Pearson's correlation (normally distributed variables) or Spearman's rank correlation (variables with a skewed distribution).

Univariate and multivariable logistic regression models were built to investigate the association of different variables with in-hospital or 90-day mortality. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Multivariable models were built separately for each sub-study. Area under the curve (AUC) of the receiver operating characteristics (ROC) curves were calculated to assess the ability of different variables to predict mortality.

Kaplan-Meier survival curves were used to illustrate differences in mortality between groups and statistical comparison was performed using the log-rank test. The endpoint of interest was 90-day mortality. A two-sided p-value < 0.05 was regarded as statistically significant. Statistical analyses were performed by SPSS 22.0-25.0 statistical software (IBM Corp., USA) except for the reclassification analyses in sub-study III, which were performed with R version 3.4.1 using PredictABEL package.

4.2.1 Study I

To analyze blood glucose levels in CS, we divided the study population into the following five categories according to blood glucose level at baseline: patients with hypoglycemia (glucose < 4.0 mmol/L), normoglycemia (4.0-7.9 mmol/L, reference group), and mild (8.0-11.9 mmol/L), moderate (12.0-15.9 mmol/L), or severe hyperglycemia (≥ 16.0 mmol/L). The range of normoglycemia was set according to a large, clinically oriented review on glucose management in critically ill patients,

supported by a commonly used approach in daily clinical practice (Mesotten et al. 2015). The same range of 3.9 mmol/L was used to categorize the hyperglycemic patients into three distinct, clinically relevant groups. In logistic regression analysis for mortality, the multivariable model included (in addition to blood glucose level, age, gender, and history of DM) baseline blood lactate and LVEF for their prognostic value in critical illness in general and particularly in CS, respectively (Khosravani et al. 2009, Sleeper et al. 2010). Normoglycemia was used as the reference glucose level.

4.2.2 Study II

The study population was dichotomized according to mental status at the time of enrollment. Mental status was assessed clinically by the study physician and categorized to be either altered or normal. Mental state evaluation was made by the last provided note in the medical record if the patient was sedated and intubated at the time of enrolment. AMS was defined as acute mental confusion, somnolence, agitation, or delirium. Medical history, patient characteristics, biochemistry, and prognosis were compared between patients with normal mental status and AMS.

Univariate- and multivariable regression analyses were performed to determine factors associated with AMS. Variables with p-value < 0.1 in univariate analysis were included in the multivariable model.

4.2.3 Study III

The study population was dichotomized according to the median baseline GDF-15 level (high and low GDF-15). Medical history, clinical characteristics, biochemical variables, and mortality were compared between these two groups. GDF-15 levels ≤ 1200 ng/L were considered normal (Kempf et al. 2007, Wollert et al. 2017). Differences in GDF-15 levels between survivors and non-survivors were analyzed using linear mixed modeling. GDF-15 values were log-transformed to normalize the distribution and the residuals. To assess the changes in GDF-15 levels over time and their relation to mortality, a delta variable (ΔGDF 0-48h) was created by calculating the greatest change in GDF-15 level during the first 48 hours between two samples ≥ 24 hours apart. The following three groups were generated according to ΔGDF: no change (≤ 30% decrease or increase), > 30% increase, or > 30% decrease in the GDF-15 level.

In Study III, a multivariable logistic regression model for 90-day mortality was adjusted with the variables in the CardShock risk score (age, ACS etiology, previous MI or CABG, and baseline eGFR,

blood lactate, LVEF, and AMS). To assess whether GDF-15 measured at different time points adds value in risk prediction compared with the CardShock risk score alone, AUCs of ROC curves were calculated and analyzed using the likelihood ratio test for nested models. Youden's index was used to define the optimal cut-off value of GDF-15 from the ROC curve. In addition, integrated discrimination index (IDI) was used to evaluate the potential enhancement in discrimination. Improvement in clinical risk stratification was assessed by calculating net reclassification improvement (NRI) using pre-specified categories of low (0-15%), intermediate (15-50%), and high (> 50%) mortality risk as previously defined for the CardShock risk score (Harjola et al. 2015).

4.2.4 Study IV

To analyze PCT levels and kinetics in CS, the study population was dichotomized to PCT < and ≥ 0.5 µg/L groups according to the maximum PCT level during the first 48 hours after shock detection (PCT_{max}). The cut-off level 0.5 µg/L is widely used as the upper limit of normal PCT to exclude systemic bacterial infection or sepsis and to discontinue antibiotic treatment in critically ill patients (Bouadma et al. 2010, de Jong et al. 2016, Picariello et al. 2009, Schneider et al. 2007, Schuetz et al. 2011). Medical history, clinical characteristics, biochemical variables, and 90-day mortality were compared between $PCT_{max} \geq 0.5$ µg/L (high PCT_{max}) and < 0.5 µg/L (low PCT_{max}) groups. IL-6 was measured at 12 hours from enrollment. For statistical analysis, the study population was divided into two groups by median IL-6 (high IL-6 and low IL-6). When analyzing CRP levels, the study population was dichotomized by the median peak CRP between baseline and 96 hours (high CRP_{max} and low CRP_{max}). Inflammatory marker levels were also compared between survivors and non-survivors.

Univariate and multivariable logistic regression models were built to evaluate the association of inflammatory marker levels with 90-day mortality. The model was adjusted with the variables in the CardShock risk score (age, ACS etiology, previous MI or CABG, AMS at enrollment and blood lactate, LVEF, and eGFR at baseline).

The study physician assessed clinically whether the patient had pneumonia or other infection at the time of enrollment. Moreover, infectious complications (catheter-related sepsis or ventilator-associated pneumonia) during the stay at intensive or coronary care unit (ICU/CCU) were recorded.

5 RESULTS

5.1 The CardShock study population

The study population and the main findings of The CardShock study have been described by Harjola, Lassus et al (Harjola et al. 2015). Patient characteristics are shown in Table 3. In brief, mean age was 67 years and 74% of patients were men. The most common co-morbidities were hypertension (60%), hyperlipidemia (46%), coronary artery disease (35%), diabetes (28%), chronic HF (16%), and atrial fibrillation (15%). Sixty-two patients (28%) had been resuscitated from cardiac arrest before study inclusion. Median time from shock detection to study inclusion was 105 minutes. Twenty-four percent of patients presented with shock already at hospital admission, 62% during the first 24 hours, and 14% ≥ 24 hours from admission.

Table 3. Patient characteristics, mortality, and medical history of the CardShock study population.

N	219	**Medical history, n (%)**	
Age, years (SD)	67 (12)	CAD	76 (35)
Women, n (%)	57 (26)	Previous MI	54 (25)
Etiology of CS, n (%)		Hypertension	132 (60)
ACS	177 (81)	Hyperlipidemia	100 (46)
STEMI	149 (68)	Chronic HF	36 (16)
Mechanical complication of MI	18 (8)	Diabetes	61 (28)
Worsening of chronic HF	23 (11)	Atrial fibrillation	32 (15)
Valvular causes	12 (5)	Asthma/COPD	25 (11)
Myocarditis	4 (2)	Renal insufficiency	25 (11)
Mortality, n (%)		Stroke/TIA	20 (9)
In-hospital mortality	80 (37)	Smoker	87 (40)
90-day mortality	89 (41)	History of PCI	32 (15)
Hospital length-of-stay, days	12 (7-25)	History of CABG	16 (7)

SD = standard deviation, ACS = acute coronary syndrome, STEMI = ST-elevation myocardial infarction, HF = heart failure, CAD = coronary artery disease, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease, TIA = transient ischemic attack, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery. Data are presented in numbers (n, %), means (SD), or medians (IQR).

ACS was the CS etiology in 81% of cases, of which 84% were STEMIs. Eighteen patients (8%) had a mechanical complication of acute MI. Non-ACS related causes of CS included acute worsening of chronic HF (11%), valvular causes (5%), and some cases of stress-induced cardiomyopathy and myocarditis.

Clinical presentation, hemodynamics, and biochemistry at baseline are shown in Table 4. Patients in the CardShock study population were hypotensive (mean arterial pressure 57±11 mmHg) and presented with low LVEFs (mean 33±14%) at baseline. LVEF was < 40% in 65% of the patients. Most of the patients had two or more clinical signs of systemic hypoperfusion (AMS, oliguria, cold extremities, or hyperlactatemia). More than half (56%) of the patients were treated with IABP during the ICU/CCU stay, and 13 patients (6%) with ventricular assist device or extra-corporeal life support (VA-ECMO). Coronary angiogram was performed in 94% of ACS patients; of these, 89% were treated with PCI. Nine patients (4%) underwent urgent CABG surgery. Twelve patients (5%) had valvular surgery. Most of the patients (63%) were invasively mechanically ventilated, and 30 patients (14%) received renal replacement therapy. Almost all patients (94%) were treated with vasopressors, inotropes, or both. Noradrenaline was the most common vasopressor (administered to 75% of patients), while 26% of patients received dopamine and 21% adrenaline. Of inotropic agents, dobutamine was administered to 49% and levosimendan to 24% of patients.

In-hospital and 90-day mortalities in the CardShock study population were 37% and 41%, respectively (Table 3). Over half of the deaths (48/89, 54%) occurred within the first 4 days of CS.

Table 4. Baseline hemodynamics, clinical characteristics, and biochemistry**.**

Hemodynamics		**Biochemistry**	
Systolic BP, mmHg	78 (14)	Blood hemoglobin (g/L)	128 (22)
Diastolic BP, mmHg	47 (10)	White blood cells, E9/L	14.5 (5.6)
MAP, mmHg	57 (11)	Blood lactate, mmol/L	2.8 (1.7-5.8)
Heart rate, bpm	90 (28)	Arterial pH	7.30 (0.13)
LVEF, %	33 (14)	Blood glucose, mmol/L	10.7 (7.8-15.9)
Sinus rhythm, n (%)	170 (78)	Sodium, mmol/L	137 (5)
Atrial fibrillation, n (%)	32 (15)	Potassium, mmol/L	4.2 (0.8)
Findings of hypoperfusion		Creatinine, µmol/L	106 (84-141)
Cold periphery, n (%)	207 (95)	eGFR, mL/min/1.73m^2	63 (29)
Altered mental status, n (%)	148 (68)	CRP, mg/L	15 (4-53)
Oliguria, n (%)	121 (56)	hsTnT, ng/L	2120 (387-5380)
Lactate > 2 mmol/L, n (%)	155 (72)	NT-proBNP, ng/L	2661 (580-9286)

BP = blood pressure, MAP = mean arterial pressure, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate, CRP = C-reactive protein, hs-TNT = high-sensitivity troponin T, NT-proBNP = N-terminal pro-B-type natriuretic peptide. Data are presented as numbers (%), means (SD), or medians (IQR).

5.2 STUDY I

5.2.1 Blood glucose levels in cardiogenic shock

Baseline blood glucose levels were recorded in 211 patients in the CardShock study. Blood glucose levels ranged from 2.0 mmol/L to 37.1 mmol/L, with a median of 10.7 mmol/L (IQR 7.8-15.9 mmol/L). Baseline glucose levels differed significantly between patients with previously diagnosed DM (14.5 mmol/L [11.5-20.6], n = 58) compared with patients without DM (9.2 mmol/L [7.5-13.5], n = 153) ($p < 0.001$). Fifty-five (26%) patients were normoglycemic (blood glucose 4.0-7.9 mmol/L) at time of enrollment, whereas 58 patients (27%) had mild (8.0-11.9 mml/L), 41 patients (19%) moderate (12.0-15.9 mmol/L), and 52 patients (25%) severe (≥ 16.0 mmol/L) hyperglycemia. Hypoglycemia (blood glucose < 4.0 mmol/L) was detected in 5 patients (2%) (Table 5). Although the groups did not differ in age or gender, patients with severe hyperglycemia had more ACS-related CS than other groups ($p = 0.03$). Patients with normoglycemia or mild hyperglycemia had less diagnosed hypertension, DM, or hyperlipidemia than in other groups (Table 5).

5.2.2 Association of blood glucose level with clinical presentation and biochemistry

There were no differences between groups in heart rate, systolic blood pressure, LVEF in baseline echocardiography, or presence of infection at time of enrollment. Severely hyperglycemic patients had higher blood leukocyte count and lactate level and lower arterial pH than patients with normoglycemia or mild to moderate hyperglycemia ($p < 0.001$). Although patients with hypoglycemia presented with the lowest arterial pH and highest levels of blood lactate, alanine aminotransferase, and NT-proBNP, the differences did not reach statistical significance (Table 6).

Table 5. Patient characteristics, medical history, and mortality stratified by baseline blood glucose level.

	All	Hypoglycemia	Normoglycemia	Mild hyperglycemia	Moderate hyperglycemia	Severe hyperglycemia	p-value
N (%)	211	5 (2)	55 (26)	58 (27)	41 (19)	52 (25)	
Female, n (%)	54 (26)	2 (40)	12 (22)	16 (28)	7 (17)	17 (33)	0.40
Age, years (SD)	67 (12)	65 (10)	65 (13)	67 (13)	68 (12)	67 (10)	0.82
BMI, kg/m^2	26.7 (4.0)	27.0 (3.1)	25.8 (4.5)*	25.9 (4.1)†	27.0 (3.6)	28.3 (3.2)*†	**0.01**
ACS etiology, n (%)	170 (81)	3 (60)	38 (69)	47 (81)	34 (83)	48 (92)	**0.03**
Medical history, n (%)							
Diabetes mellitus	58 (27)	1 (20)	4 (7)	11 (19)	15 (37)	27 (52)	**<0.001**
Hypertension	129 (61)	3 (60)	28 (51)	30 (52)	30 (73)	38 (73)	**0.04**
Hyperlipidemia	97 (46)	4 (80)	16 (29)	22 (38)	22 (54)	33 (63)	**0.002**
Coronary artery disease	72 (34)	3 (60)	16 (29)	16 (28)	13 (32)	24 (46)	0.15
Congestive heart failure	35 (17)	0 (0)	6 (11)	10 (17)	6 (15)	13 (25)	0.28
Previous MI	53 (25)	2 (40)	10 (18)	13 (22)	10 (24)	18 (35)	0.32
Mortality, n (%)							
In-hospital	77 (36)	3 (60)	12 (22)	19 (33)	14 (34)	29 (56)	**0.005**
90-day	85 (41)	3 (60)	14 (26)	22 (39)	15 (37)	31 (60)	**0.008**

BMI = body mass index, ACS = acute coronary syndrome, MI = myocardial infarction. Data are presented as numbers (%) and means (SD). p-values are for the differences between the groups (* and † indicate, between which two groups).

Table 6. Clinical presentation and biochemistry at baseline stratified by blood glucose level.

	All	Hypoglycemia	Normoglycemia	Mild hyperglycemia	Moderate hyperglycemia	Severe hyperglycemia	p-value
MAP; mmHg	57 (11)	54 (7)	58 (9)	59 (10)	55 (10)	54 (12)	0.07
LVEF; %	33 (14)	26 (9)	34 (15)	32 (14)	36 (14)	31 (13)	0.43
Infection, n (%)	30 (14)	0 (0)	9 (17)	8 (14)	8 (20)	5 (10)	0.56
Lactate >2 mmol/L, n (%)	150 (72)	4 (80)	30 (56)	39 (67)	31 (78)	46 (90)	**0.002**
AMS, n (%)	142 (68)	3 (60)	30 (55)	41 (73)	27 (68)	41 (79)	0.08
Oliguria, n (%)	115 (55)	3 (60)	23 (42)	35 (61)	21 (53)	33 (65)	0.14
Biochemistry							
Leukocytes; E9/L	14.4 (5.6)	13.8 (3.6)	11.9 (4.5)*	14.0 (5.5)†	14.5 (5.1)	17.3 (5.8)*†	**<0.001**
eGFR; ml/min/1.73m^2	63 (29)	59 (40)	63 (28)	69 (29)	66 (29)	56 (31)	0.30
ALT	62 (29-159)	466 (74-801)	64 (25-158)	47 (30-132)	59 (32-129)	89 (39-207)	0.41
Glucose; mmol/L	10.7 (7.8-15.8)	3.2 (2.7-3.5)	6.9 (6.2-7.6)	9.4 (8.7-10.6)	13.4 (12.7-14.5)	20.8 (18.8-25.2)	**<0.001**
Lactate; mmol/L	2.8 (1.7-5.6)	8.3 (2.7-14.0)	1.8 (1.2-3.2)*	2.6 (1.8-4.8)†	2.6 (2.1-4.6)‡	4.4 (3.3-8.4)*†‡	**<0.001**
Arterial pH	7.30 (0.13)	7.19 (0.22)	7.35 (0.12)*	7.30 (0.11)†	7.31 (0.11)‡	7.23 (0.14)*†‡	**<0.001**
NT-proBNP; ng/L	2501 (608-9015)	26300 (19129-33471)	3759 (550-9806)	2520 (647-8537)	2015 (563-8904)	2426 (601-7294)	0.33
hsTnT; ng/L	2120 (389-5417)	1052 (278-1828)	1717 (132-4925)	1485 (243-6462)	2616 (570-5244)	2629 (975-7842)	0.40
CRP; mg/L	15 (4-49)	61 (39-84)	22 (5-83)	9 (4-40)	18 (5-75)	12 (4-35)	0.24

MAP = mean arterial pressure, LVEF = left ventricular ejection fraction, AMS = altered mental status, eGFR = estimated glomerular filtration rate, ALT = alanine aminotransferase, NT-proBNP = N-terminal pro-B-type natriuretic peptide, hs-TNT = high-sensitivity troponin T, CRP = C-reactive protein. Data are presented as numbers (%), means (SD), and medians (IQR). p-values are for the differences between the groups (*, †, and ‡ indicate between which two groups).

5.2.3 Blood glucose level and prognosis in cardiogenic shock

There were statistically significant differences in prognosis between the groups. Patients with hypoglycemia or severe hyperglycemia had the highest 90-day mortality (60% for both groups), while normoglycemic patients had the most favorable outcome with 26% 90-day mortality ($p = 0.008$) (Table 5). Kaplan-Meier survival curves (log rank $p = 0.003$) are shown in Figure 3. Moreover, survivors had significantly lower blood glucose compared with non-survivors (medians 10.0 mmol/L vs. 12.7 mmol/L, $p < 0.01$). In univariate logistic regression analysis, higher baseline glucose level was associated with increased mortality (OR 1.06 per 1 mmol/L increase, 95% CI 1.02-1.11, $p = 0.005$). However, when patients with and without prior DM were analyzed separately, higher blood glucose level was associated with poor prognosis in patients without DM (OR 1.10, 95% CI 1.03-1.16, $p = 0.005$) but not in patients with diagnosed DM (OR 1.02, 95% CI 0.95-1.09, $p = 0.6$). Similarly, among patients with no diagnosed DM, survivors had significantly lower baseline blood glucose compared with non-survivors. However, no difference in glucose levels was found between survivors and non-survivors among diabetic patients. As a categorical variable (normoglycemia as reference), severe hyperglycemia was predictive of higher in-hospital mortality (OR 4.5, 95% CI 1.9-10.5, $p < 0.001$), whereas mild and moderate hyperglycemia showed no significant association with mortality. After adjusting for age, gender, baseline blood lactate, LVEF, and history of DM, severe hyperglycemia remained independently associated with increased mortality (OR 3.7, 95% CI 1.19-11.7, $p = 0.02$).

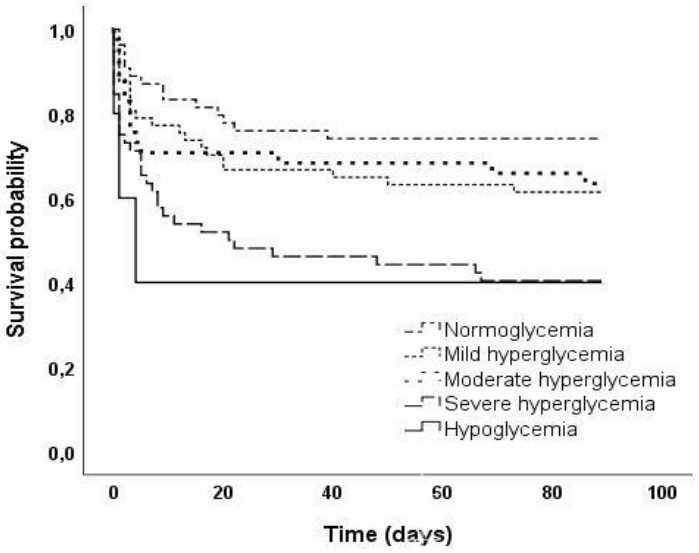

Figure 3. Kaplan-Meier survival curves stratified by baseline blood glucose level.

5.3 STUDY II

5.3.1 The prevalence and prognostic significance of altered mental status in cardiogenic shock

In the CardShock study, mental status was recorded as a clinical sign of hypoperfusion, which was part of the inclusion criteria at the time of enrollment. Four patients had missing values; the final study cohort for Study II consisted of 215 CS patients. Sixty-eight (32%) patients had normal mental status, whereas AMS was detected in 147 (68%) patients. Patients with AMS were older and more likely to have an ACS etiology of CS compared with patients with normal mental status (Table 7). No differences were found between the groups in medical history, gender, or alcohol abuse. Patients with AMS tended to have longer hospital length of stay.

AMS at enrollment was associated with poor prognosis; in-hospital mortality was 46% and 90-day mortality 51% compared with 18% and 22% for patients with normal mental status, respectively ($p < 0.001$ for both between-group comparisons, Table 7). In addition, AMS was an independent predictor of in-hospital mortality in CS (OR 3.0, 95% CI 1.1-8.1, $p = 0.03$) and was incorporated as a variable in the CardShock risk score for mortality prediction (Harjola et al. 2015).

5.3.2 Association of altered mental status with clinical presentation and biochemistry

The prevalence of other clinical signs of systemic hypoperfusion, including cold periphery and oliguria, did not differ between patients with altered and normal mental status (Table 7). In contrast, AMS was associated with acidosis and lower baseline systolic blood pressure and lower LVEF compared with patients with normal mental status. Similarly, hyperlactatemia and hyperglycemia were more evident among patients with AMS. No differences were observed between the groups in biomarkers of inflammation, myocyte injury, or cardiac and renal dysfunction.

Age, ACS etiology, acidosis, and higher levels of blood lactate and blood glucose were associated with AMS in univariate regression analysis. In addition to these variables, baseline LVEF, systolic blood pressure, gender, and resuscitation before study enrollment were included in the multivariable model. After multivariable adjustment, lower arterial pH was the only factor independently associated with AMS (OR 1.6 per 0.1 decrease in arterial pH, 95% CI 1.08-2.2, $p = 0.02$).

Table 7. Clinical picture, mortality, and biochemistry stratified by mental status at baseline.

	All	Altered mental status	Normal mental status	p-value
N (%)	215	147 (68)	68 (32)	
Age, years (SD)	67 (12)	68 (11)	64 (13)	**0.04**
ACS etiology, n (%)	175 (81)	125 (85)	50 (74)	**0.04**
Resuscitation, n (%)	61 (28)	49 (33)	12 (18)	**0.02**
Intubation, n (%)	133 (63)	109 (75)	24 (37)	**< 0.001**
Opiate medication (24h), n (%)	149 (71)	104 (72)	45 (67)	0.4
Receiving sedatives (24h), n (%)	132 (62)	109 (76)	23 (34)	**< 0.001**
Hospital LOS, days	13 (7-24)	15 (8-27)	11 (5-20)	**0.01**
Mortality, n (%)				
In-hospital	79 (37)	67 (46)	12 (18)	**< 0.001**
90-day	88 (41)	73 (51)	15 (22)	**< 0.001**
Hemodynamics				
Systolic BP; mmHg	78 (13)	76 (12)	80 (16)	**0.03**
LVEF; %	33 (14)	32 (14)	36 (14)	**0.05**
Lactate > 2 mmol/L, n (%)	152 (72)	112 (77)	40 (60)	**0.01**
Cold periphery, n (%)	203 (95)	142 (97)	61 (91)	0.09
Oliguria, n (%)	119 (56)	85 (59)	34 (50)	0.2
Biochemistry				
Blood leukocytes; E9/L	14.6 (5.7)	14.7 (6.0)	14.2 (4.8)	0.6
eGFR; ml/min/1.73m^2	62 (29)	61 (30)	66 (28)	0.3
Glucose; mmol/L	10.7 (7.8-16.0)	11.4 (8.2-17.6)	9.0 (7.3-13.4)	**0.01**
Lactate; mmol/L	2.8 (1.7-5.8)	3.4 (2.1-6.6)	2.3 (1.5-3.4)	**< 0.001**
Arterial pH	7.29 (0.13)	7.27 (0.14)	7.35 (0.09)	**< 0.001**
NT-proBNP; ng/L	2661 (608-9286)	2475 (590-8904)	3824 (626-9715)	0.7
hsTnT; ng/L	2260 (398-5380)	2580 (441-5784)	1717 (143-4180)	0.15

ACS = acute coronary syndrome, LOS = length-of-stay, BP = blood pressure, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal pro-B-type natriuretic peptide, hs-TNT= high-sensitivity troponin T. Data are presented as numbers (%), means (SD), and medians (IQR).

5.4 STUDY III

5.4.1 GDF-15 levels in cardiogenic shock

Baseline GDF-15 samples were available from 177 patients in the CardShock study. Baseline GDF-15 values ranged from 1123 ng/L to 115 660 ng/L. In the entire study population, the median GDF-15 was highest at baseline (9647 ng/L; IQR 4500-19 270) and then started to decrease. However, the kinetics of GDF-15 among survivors and non-survivors was different; GDF-15 levels decreased significantly during the first 24 hours among survivors (6640 ng/L at baseline vs. 4499 ng/L at 24 hours, $p < 0.001$), whereas the GDF-15 levels remained high or tended to increase (12 847 ng/L at baseline vs. 19 742 ng/L at 24 hours, $p = 0.14$) in non-survivors (Figures 4a and 4b). Moreover, non-survivors had significantly higher GDF-15 levels at all time points compared with survivors ($p < 0.001$). The evolution of GDF-15 over time between the groups was significantly different ($p < 0.001$ for time-group interaction).

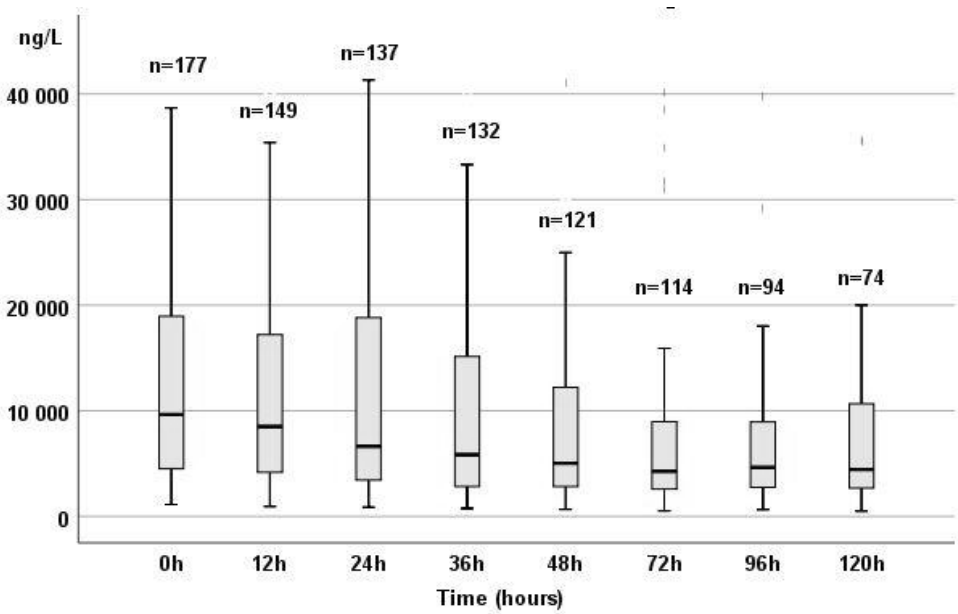

Figure 4a. GDF-15 levels in the entire study population.

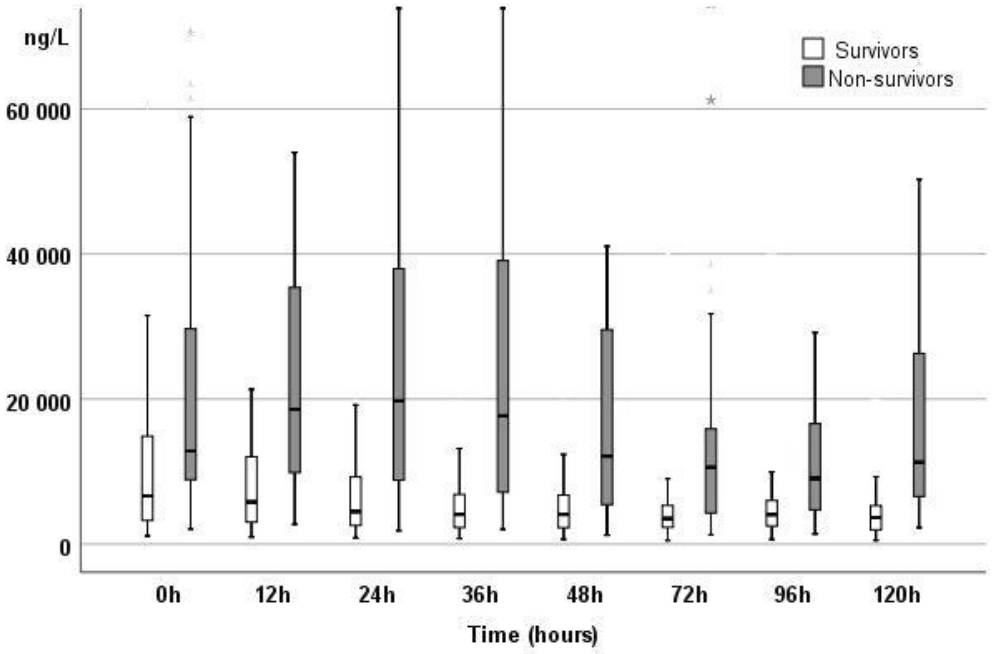

Figure 4b. GDF-15 levels among survivors (white) and non-survivors (grey).

5.4.2 Association of GDF-15 with patient characteristics, clinical presentation, and biochemistry

Baseline GDF-15 above median (high GDF-15) was associated with previously diagnosed diabetes and coronary artery disease. However, no differences were found in etiology of CS, age, or gender between groups. Similarly, the groups did not differ in baseline hemodynamic parameters or LVEF. High GDF-15 was associated with poorer renal function, higher levels of blood lactate, NT-proBNP, alanine aminotransferase, and CRP, and lower arterial pH at baseline (Table 8). The strongest correlations of GDF-15 in Spearman's correlation analyses were found with baseline lactate ($\rho = 0.47$, $p < 0.001$) and NT-proBNP ($\rho = 0.38$, $p < 0.001$). GDF-15 correlated negatively with baseline eGFR ($\rho = -0.45$, $p < 0.001$). No significant correlation was observed between GDF-15 and hsTnT at any time point.

Table 8. Clinical presentation, biochemistry, and mortality stratified by baseline GDF-15.

	All (n=177)	GDF-15 ≤ median (n=89)	GDF-15 > median (n=88)	p-value
Age, years (SD)	66 (12)	65 (12)	67 (13)	0.4
Female, n (%)	45 (25)	20 (23)	25 (28)	0.4
ACS etiology, n (%)	142 (80)	71 (80)	71 (81)	0.9
MAP; mmHg	57 (11)	57 (10)	57 (12)	0.8
LVEF; %	33 (14)	35 (14)	31 (14)	0.10
Altered mental status, n (%)	116 (66)	57 (64)	59 (67)	0.7
Oliguria, n (%)	93 (53)	38 (43)	55 (63)	**0.015**
Biochemistry				
Leukocytes; E9/L	14.0 (5.5)	13.5 (4.9)	14.6 (5.9)	0.20
CRP; mg/L	15 (4-53)	7 (4-40)	26 (5-75)	0.01
eGFR; ml/min/1.73 m^2	63 (29)	73 (28)	53 (27)	**< 0.001**
ALT; U/L	45 (20-93)	29 (17-52)	82 (33-152)	**< 0.001**
Arterial pH	7.30 (7.21-7.40)	7.35 (7.26-7.40)	7.30 (7.20-7.38)	**0.004**
Lactate; mmol/L	2.7 (1.7-5.8)	2.1 (1.3-3.7)	3.7 (2.3-6.7)	**< 0.001**
hsTnT; ng/L	2190 (393-5399)	1581 (347-4083)	2629 (441-8716)	0.06
NT-proBNP; ng/L	2581 (575-9323)	1360 (373-6627)	5029 (1581-12 300)	**< 0.001**
Mortality, n (%)				
In-hospital	66 (37)	22 (25)	44 (50)	**0.001**
90-day	73 (41)	24 (28)	49 (56)	**< 0.001**

MAP = mean arterial pressure, LVEF = left ventricular ejection fraction, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, ALT = alanine aminotransferase, hsTnT = high-sensitivity troponin T, NT-proBNP = N-terminal pro-B-type natriuretic peptide. Data are presented as numbers (%), means (SD), and medians (IQR).

5.4.3 GDF-15, prognosis, and risk stratification in cardiogenic shock

Patients with high GDF-15 had a significantly higher 90-day mortality (56% vs. 28%, $p < 0.001$) compared with those with low GDF-15 (Table 8). In multivariable logistic regression analyses after adjusting with the CardShock risk score variables, GDF-15 remained independently associated with increased mortality at all measured time points between baseline and 48 hours. The AUC of GDF-15 for 90-day mortality prediction at baseline was 0.70 (95% CI 0.62-0.77, $p < 0.001$) and 0.81 (95% CI 0.74-0.88, $p < 0.001$) at 12 h.

Based on the AUC values at different time points and emphasizing early risk stratification, GDF-15 measured at 12h (GDF-15_{12h}) was selected for further analyses. The cut-off of 7000 ng/L derived from the ROC curve was used as a binary variable in discrimination and reclassification analyses. Adding GDF-15_{12h} > 7000 ng/L to the prediction model based on the CardShock risk score improved discrimination (AUC 0.85 vs. AUC 0.83; $\chi^2 = 10.6$, p = 0.001 for comparison of nested models, IDI 0.053, 95% CI 0.012-0.094; p = 0.01) and risk classification to low, intermediate, and high mortality risk groups (NRI 0.18, 95% CI 0.06-0.30; p = 0.003), especially among survivors.

When analyzing changes in GDF-15 levels during the first 48 hours, an adequate number of samples was available from 146 CS patients. An increase of > 30% in GDF-15 level was observed in 43 (30%) patients, a decrease of > 30% in 83 (57%), and GDF-15 levels remained stable in 20 (14%) patients. Increasing GDF-15 level was associated with higher mortality compared with decreasing or stable GDF-15 levels in univariate logistic regression analysis, but not after adjustment for CardShock risk score variables.

5.5 STUDY IV

5.5.1 Levels of procalcitonin, C-reactive protein, and interleukin 6 in cardiogenic shock

For Study IV, PCT and CRP levels were analyzed in patients (n = 183), who had at least one PCT sample available between baseline and 48 hours. PCT_{max} ranged from 0.05 µg/L to 71.3 µg/L, with a median of 0.71 µg/L (IQR 0.24-3.4). Seventy-three (40%) patients had PCT_{max} level < 0.5 µg/L (low PCT_{max}), whereas 110 (60%) patients had at least one PCT value ≥ 0.5 µg/L (high PCT_{max}). Although patients with high PCT_{max} more often had hypertension or coronary artery disease, no differences between the groups were found in other patient characteristics or etiology of CS.

Median baseline CRP was 15 mg/L (4-53), while median peak $CRP_{max\ 0\text{-}96h}$ was 137 mg/L (59-247). IL-6 levels measured at 12 hours (n = 148) ranged from 2 to 859 ng/L (median 143 ng/L [74-346]). Median PCT value peaked at 24 hours, whereas CRP continued to rise until 48 to 72 hours (Figures 5a and 5b).

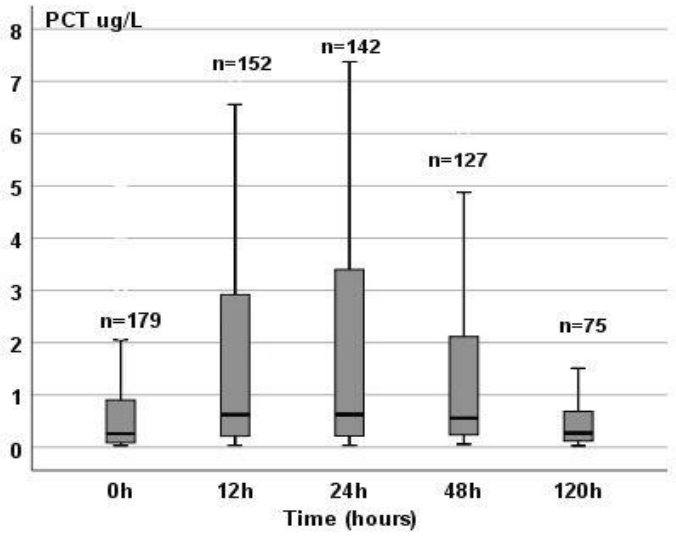

Figure 5a. PCT levels in the entire study population.

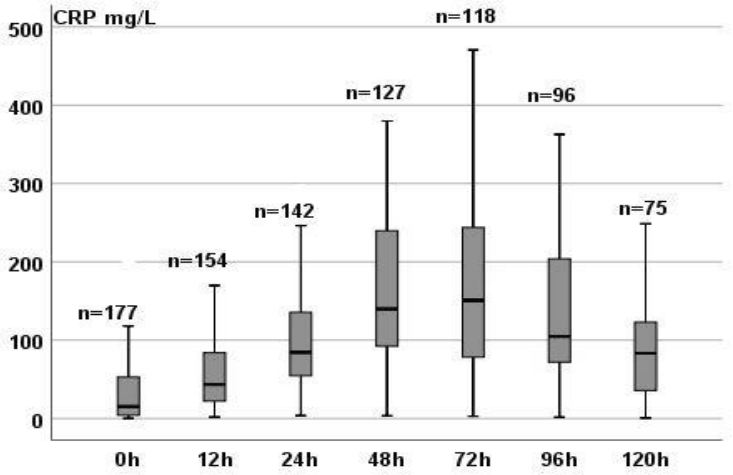

Figure 5b. CRP levels in the entire study population.

5.5.2 Association of inflammatory markers with clinical presentation and biochemistry

The prevalence of clinical signs of hypoperfusion, including AMS, oliguria, and hyperlactatemia, was significantly higher in patients with high PCT_{max} than in those in the low PCT_{max} group. Similar results were observed among patients with high IL-6 compared with low IL-6 (Table 9). Both high PCT_{max} and high IL-6 were associated with lower baseline arterial pH and LVEF and higher levels of blood lactate and GDF-15. In addition, high PCT_{max} was associated with higher baseline CRP, NT-proBNP, and higher blood leukocyte count. High IL-6 was associated with hyperglycemia and higher hsTnT. No differences were found in clinical presentation or biochemistry between the groups of high and low CRP_{max} except for prevalence of hyperlactatemia and higher hsTnT among patients with high CRP_{max}.

Rather strong associations in Spearman's correlation analysis were observed between PCT and GDF-15 (ρ = 0.56-0.68, $p < 0.001$ for all time points) and baseline PCT and initial ($\leq$ 12 h) CRP values (ρ = 0.55-0.58 $p < 0.001$). The correlation of PCT with NT-proBNP was moderate at baseline (ρ = 0.52, $p<0.001$) but weaker at later time points. Moreover, PCT correlated negatively with eGFR (ρ = -0.40 to -0.46, $p < 0.001$ between 12 h and 48 h). The strongest correlations of IL-6 were detected with $CRP_{24h-48h}$ (ρ = 0.53-0.60, $p < 0.001$), $GDF\text{-}15_{12h-48h}$ (ρ = 0.44-0.57, $p < 0.001$), and $PCT_{12h-48h}$ (ρ = 0.45-0.48, $p < 0.01$). None of the inflammatory markers correlated significantly with hsTnT. Baseline blood lactate correlated with $PCT_{12h-120h}$ (ρ = 0.47-0.55, $p < 0.001$) and mildly with IL-6 (ρ = 0.38, $p < 0.001$) but not with CRP.

Table 9. Clinical presentation, biochemistry, and mortality stratified by PCT and IL-6 levels.

	All	PCT_{max} < 0.5 µg/L	PCT_{max} ≥ 0.5 µg/L	p-value	IL-6 ≤ median	IL-6 > median	p-value
N (%)	183	73 (40)	110 (60)		74	74	
Age, years (SD)	66 (12)	67 (13)	66 (12)	0.6	65 (12)	68 (12)	0.1
ACS etiology, n (%)	144 (79)	61 (84)	83 (75)	0.2	56 (76)	61 (82)	0.3
Systolic BP; mmHg	77 (14)	75 (12)	79 (15)	0.1	79 (15)	77 (12)	0.4
LVEF; %	33 (14)	37 (15)	30 (12)	**0.001**	37 (14)	30 (12)	**<0.01**
AMS, n (%)	120 (66)	39 (54)	81 (74)	**<0.01**	38 (52)	58 (79)	**<0.001**
Oliguria, n (%)	98 (54)	32 (44)	66 (61)	**0.03**	30 (41)	49 (67)	**<0.01**
Hyperlactatemia, n (%)	128 (71)	38 (53)	90 (83)	**<0.001**	40 (55)	59 (81)	**0.001**
Infection, n (%)	26 (14)	7 (10)	19 (17)	0.1	12 (16)	11 (15)	0.8
Biochemistry							
Leukocytes; E9/L	14.1 (5.4)	12.6 (4.0)	15.1 (6.0)	**0.001**	13.4 (4.8)	13.9 (5.7)	0.6
eGFR; ml/min/1.73m^2	63 (29)	73 (30)	56 (27)	**<0.001**	69 (27)	60 (30)	0.05
CRP; mg/L	15 (4-53)	6 (3-37)	22 (6-78)	**0.001**	8 (4-40)	19 (4-67)	0.2
Glucose; mmol/L	10.7 (7.7-15.9)	9.7 (7.6-13.4)	12.2 (7.9-18.8)	0.06	8.8 (7.3-13.9)	11.0 (8.5-17.7)	**0.03**
Arterial pH	7.30 (0.13)	7.33 (0.13)	7.28 (0.13)	**0.02**	7.36 (0.10)	7.27 (0.14)	**<0.001**
Lactate; mmol/L	2.7 (1.7-5.8)	2.2 (1.3-3.1)	3.4 (2.2-6.5)	**<0.001**	2.3 (1.3-3.4)	3.4 (2.1-6.8)	**<0.001**
hsTnT; ng/L	2120 (387-5380)	1444 (356-4179)	2580 (398-6811)	0.1	1600 (339-4050)	2693 (691-9125)	**0.04**
NT-proBNP; ng/L	2661 (580-9286)	1404 (335-6701)	4697 (1126-10 938)	**<0.01**	2236 (354-7422)	3300 (819-9816)	0.1
PCT; µg/L	0.26 (0.09-0.92)	0.10 (0.07-0.16)	0.66 (0.26-1.62)	**<0.001**	0.18 (0.07-0.53)	0.46 (0.11-1.37)	**<0.01**
GDF-15; ng/L	9647 (4500-19 270)	6316 (2782-12 303)	12899 (6172-29 559)	**<0.001**	6456 (2855-14 074)	11646 (5330-20 678)	**<0.01**
IL-6 (at 12h); ng/L	143 (74-346)	93 (47-154)	222 (84-429)	**<0.001**			
CRP_{max}; mg/L	137 (59-247)	96 (31-180)	176 (103-293)	**<0.001**	121 (46-198)	195 (114-295)	**<0.001**
PCT_{max}; µg/L	0.71 (0.24-3.42)	0.16 (0.10-0.30)	2.12 (0.90-6.59)	**<0.001**	0.46 (0.16-1.09)	2.14 (0.59-6.59)	**<0.001**
90-day mortality, n (%)	76 (42)	22 (30)	54 (50)	**<0.01**	16 (22)	42 (57)	**<0.001**

BP = blood pressure, LVEF = left ventricular ejection fraction, AMS = altered mental status, eGFR = estimated glomerular filtration rate, CRP = C-reactive protein, hsTnT = high-sensitivity troponin T, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PCT = procalcitonin, GDF-15 = growth-differentiation factor 15, IL-6 = interleukin 6.

5.5.3 Inflammatory markers and prognosis in cardiogenic shock

High PCT_{max} was associated with increased 90-day mortality compared with low PCT_{max} (50% vs. 30%, p = 0.008) (Table 9). Similarly, high IL-6 was associated with poor prognosis (57% vs. 22% among low IL-6, p < 0.001). There was no difference in mortality between high and low CRP_{max}. Non-survivors had higher PCT levels from 12 hours onwards and higher CRP levels from 24 hours onwards compared with survivors (Figures 6a and 6b, p < 0.001 for all pairwise comparisons). In addition, IL-6 was higher among non-survivors (270 ng/L [126-464] vs. 107 ng/L [55-224] in survivors, p < 0.001).

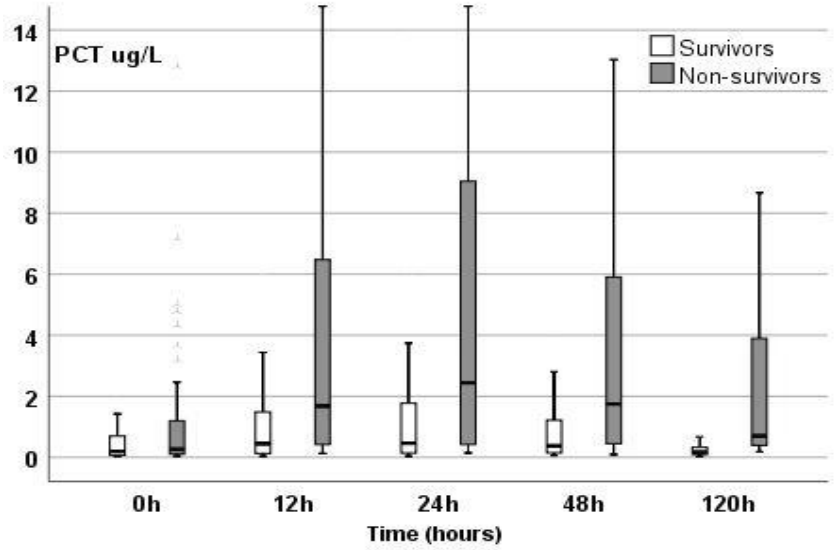

Figure 6a. PCT levels among survivors (white) and non-survivors (grey).

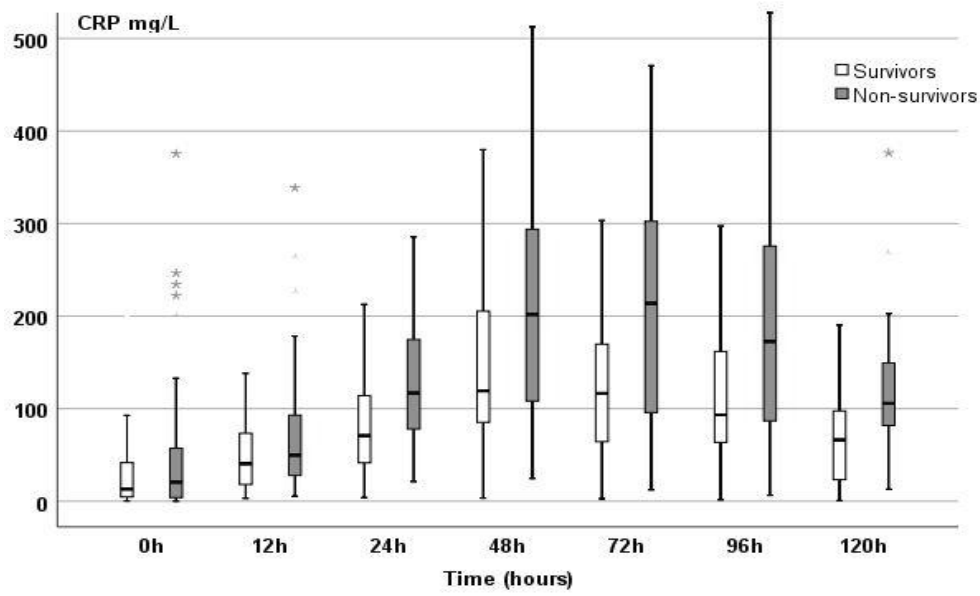

Figure 6b. CRP levels among survivors (white) and non-survivors (grey).

High PCT_{max} was associated with increased mortality both as a continuous and categorical variable in univariate logistic regression analysis but did not independently associate with increased mortality in multivariable analysis. High IL-6 was associated with increased mortality both in univariate and in multivariable models, whereas CRP_{max} showed no prognostic significance. Kaplan-Meier survival curves of the inflammatory markers for 90-day mortality are shown in Figure 7.

5.5.4 Inflammatory markers and infections in cardiogenic shock

At the time of enrollment, 16 patients (9%) were diagnosed with pneumonia and 13 patients (7%) with other infection. None of the inflammatory marker levels differed significantly during the first days of CS between patients with and without infections at baseline. Fourteen patients (8%) were diagnosed with catheter-related sepsis and 21 patients (12%) with ventilator-associated pneumonia during the ICU/CCU stay. There was no association between infectious complications and 90-day mortality. Patients with ventilator-associated pneumonia had higher PCT_{max} than those without (3.4 µg/L [0.67-6.6] vs. 0.63 µg/L [0.17-2.6], $p < 0.01$) and higher CRP levels from 36 hours onwards. In contrast, no correlation was found in the inflammatory marker levels between patients with and without catheter-related sepsis.

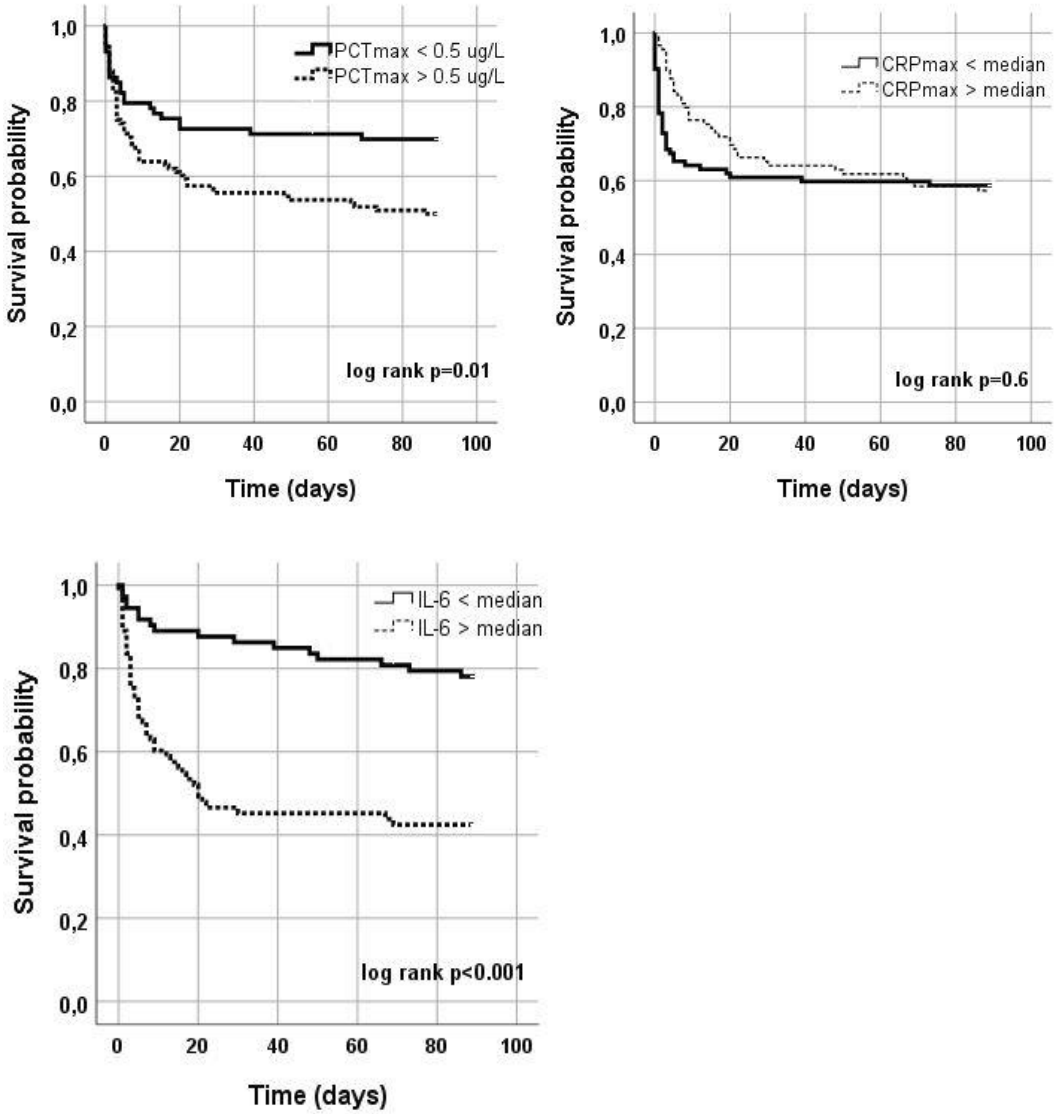

Figure 7. Kaplan-Meier survival curves stratified by PCT_{max}, CRP_{max}, and median IL-6.

6 DISCUSSION

6.1 The CardShock study

The prospective, multinational CardShock study offered a unique insight into the contemporary clinical picture of CS patients with both ACS and non-ACS etiologies. The detailed data on hemodynamics, biochemistry, and management of CS patients provided invaluable information to both researchers and clinicians who treat CS patients. Among the most important features of this study population, in addition to its size, is the short time frame in the enrollment process. As CS is a medical emergency with a sudden start and high mortality during the first days of shock, the decisions on different treatment strategies must be made promptly, specifically before irreversible organ injuries have occurred. This emphasizes the importance of early risk stratification, which this thesis is focused on. Moreover, there is an urgent need for objective risk-assessment tools in patient selection for the most advanced therapies, including mechanical circulatory support, as such therapies carry a high risk of complications and are of limited availability. This thesis provides new information on easily available clinical and biochemical parameters that may be used in daily clinical practice in risk assessment when treating CS patients. Moreover, the thesis examines the pathological mechanisms related to the disturbed homeostasis and inflammatory cascades in CS.

6.2 Blood glucose level in cardiogenic shock (I)

6.2.1 Association of blood glucose level with clinical presentation and biochemistry

Baseline blood glucose levels were distributed rather evenly between the groups of normoglycemia and mild, moderate, and severe hyperglycemia in this CS population. Patients with severe hyperglycemia were most likely to have previously diagnosed DM, while normoglycemic patients had the lowest prevalence of DM. Critical illness and its neurohormonal changes accentuate the peripheral insulin resistance and excessive hepatic glucose production related to DM (Cornell 2015, Preiser et al. 2014). In contrast, hypoglycemia was rare among CS patients. Indeed, hypoglycemia can be regarded as a pathological reaction during critical illness and is associated with increased mortality (Deane et al. 2013, Ichai et al. 2010, Krinsley et al. 2007 and 2011, Marik et al. 2013). In Study I, hypoglycemic patients presented with low LVEF, acidosis, and high levels of NT-proBNP and blood lactate, reflecting severe cardiac failure and systemic hypoperfusion. Moreover, elevated alanine aminotransferase levels suggest hepatic congestion and hepatocyte injury, which may partially explain the low glucose levels and hyperlactatemia through disturbed gluconeogenesis and

glycogenolysis, and lactate clearance, respectively (Barth et al. 2007, De Jonghe et al. 1999, Laribi et al. 2014, Nikolaou et al. 2013, Preiser et al. 2014).

In addition to hypoglycemic patients, acidosis and hyperlactatemia were particularly evident among CS patients with severe hyperglycemia. Low cardiac output and hypotension cause insufficient tissue perfusion and oxygen supply, resulting in anaerobic metabolism, hyperlactatemia, and acidosis. Indeed, there is a strong connection between blood lactate and glucose, as lactate can be converted to glucose in the liver through gluconeogenesis (Kubiak et al. 2018, Mongkolpun et al. 2019). To some extent, increased lactate production may thus explain hyperglycemia during critical illness and the levels should be interpreted together rather than separately (Kaukonen et al. 2014). Furthermore, hypotension and hypoperfusion activate stress response mechanisms including the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which lead to increased release of catecholamines and cortisol into circulation. Collectively, this stimulates hepatic glycogenolysis and gluconeogenesis, inhibits insulin-dependent glucose uptake by muscles, and consequently elevates blood glucose level (Marik et al. 2013, Mongkolpun et al. 2019, Preiser et al. 2014). Moreover, both endogenous and exogenous catecholamines promote glycogenolysis and glycolysis in muscles, further elevating blood lactate level (Barth et al. 2007, Garcia-Alvarez et al. 2014, Kubiak et al. 2018). Excluding patients with severe hepatic failure, lactate clearance may remain normal or even increase during critical illness (Revelly et al. 2005). Thus, in addition to being a marker of hypoperfusion and stress response, hyperglycemia and hyperlactatemia reflect increased glucose turnover and a hypermetabolic condition (Fuernau et al. 2019, Kubiak et al. 2018, Van Cromphaut et al. 2009).

6.2.2 Blood glucose level and prognosis in cardiogenic shock

Study I revealed that baseline blood glucose level has prognostic significance in CS. Mortality was highest among patients with severe hyperglycemia or hypoglycemia, while normoglycemic patients had a more favorable prognosis. A similar J-shape association curve of blood glucose concentrations and mortality was observed among critically ill patients in general (Boonen et al. 2014, Mesotten et al. 2015, Preiser et al. 2014, Umpierrez et al. 2012). In Study I, patients with normoglycemia presented with relatively mild abnormalities in blood lactate and arterial pH, suggesting that homeostasis was generally well maintained despite hypotension and shock. In contrast, severe hyperglycemia was independently associated with increased mortality in multivariable analysis. Besides being an indicator of CS severity, extremely high blood glucose levels may thus be harmful as such, possibly through negative effects on serum osmolality and fluid balance (Liamis et al. 2014, Marik et al. 2013). Moreover, extreme hyperglycemia induces cellular toxicity in mainly insulin-

independent cells, such as neurons, hepatocytes, renal tubular cells, and immune cells (Boonen et al. 2014). Insulin resistance eventually promotes lipolysis, resulting in increased levels of circulating free fatty acids. This lipotoxic effect further aggravates insulin resistance and inflammatory state, and damages ischemic myocardium (Dungan et al 2009). In the context of ACS-related CS, hyperglycemia may also have adverse effects on platelet reactivity and endothelial dysfunction, thereby worsening the prothrombotic state (Angeli et al. 2015). In addition, hyperglycemia has been shown to associate with microvascular obstruction and no-reflow phenomenon after PCI among patients with STEMI (Iwakura et al. 2003, Ota et al. 2015). Thus, extremely high blood glucose levels have multiple effects that might play a role in the vicious circle of CS. However, due to the observational nature of this study, the causality between high blood glucose level and poor prognosis remains unproven.

When patients with and without prior DM were analyzed separately, blood glucose levels of non-survivors were significantly higher compared with survivors among patients without DM but not among patients with previously diagnosed DM. This suggests that the predictive value of baseline blood glucose in CS is modified by diabetic status. Among patients with DM, multiple factors affect blood glucose level during acute illness, including type of DM medication (or absence thereof), individual glycemic balance, nutrition, and, naturally, insulin resistance and hepatic overproduction of glucose (type 2 DM) (Capes et al. 2000, Dungan et al 2009). Thus, it seems that severe hyperglycemia among non-diabetics indicates a more profoundly disturbed homeostasis than that in diabetics. Similar observations have been made about the role of previously diagnosed DM on the prognostic significance of blood glucose levels (Deane et al. 2013, Dungan et al 2009, Egi et al. 2008, Falciglia et al. 2009, Lazzeri et al. 2015). As the central nervous system is highly dependent on continuous blood glucose supply, it can be stated that avoiding hypoglycemia at the expense of hyperglycemia is physiological to some extent during acute critical illness (Sonneville et al. 2015). Similarly, some authors have proposed that instead of the absolute level of hyperglycemia, it is the relative level and patient's previous glycemic balance that should be considered during acute illness (Krinsley et al. 2013 and 2019, Marik et al. 2014, Mongkolpun et al. 2019, Plummer et al. 2014, Roberts et al. 2015).

In conclusion, very high or low blood glucose levels in CS indicate seriously disturbed homeostasis and profound systemic hypoperfusion. Moreover, baseline blood glucose level has prognostic significance in CS, as the mortality is highest among patients with severe hyperglycemia or hypoglycemia. Blood glucose is an inexpensive and systemically measured point-of-care test in critical care and possesses broad utility in risk stratification among CS patients.

6.3 Altered mental status in cardiogenic shock (II)

6.3.1 Altered mental status and clinical picture in cardiogenic shock

Most patients in this CS population presented with AMS at the time of enrollment. The prevalence of AMS was equal to that observed in the IABP-SHOCK II Trial (Thiele et al. 2013) and, interestingly, was also equal to that among septic patients (Chung et al. 2020, Gofton et al. 2012). Study II showed that CS patients with AMS were older and more likely to have an ACS etiology of CS compared with patients with normal mental status. Age is a risk factor for acute brain dysfunction and delirium in critical illness (Huai et al. 2014, Hughes et al. 2012, Zaal et al. 2015). Furthermore, the correlation between AMS and ACS may be related to the sudden onset of myocardial infarction and the consequent hemodynamic derangement and drop in blood pressure. This is in contrast to worsening of chronic HF, with more gradual hemodynamic changes and possible adaptation. Indeed, AMS was associated with low systolic blood pressure and LVEF. As previously mentioned, cerebral blood flow and autoregulation are impaired by continued hypotension, which may even result in neuronal injury and induce ischemia or hyperemia of the brain tissue (Bhate et al. 2015, Schramm et al. 2012). Moreover, patients with AMS had higher blood lactate levels and lower arterial pH than patients with normal status. These both indicate systemic hypoperfusion and inadequate oxygen supply. AMS was also associated with higher blood glucose level, which may reflect more profound hypoperfusion and increased release of stress mediators, as discussed above. Importantly, this study revealed a strong and independent association between low arterial pH and AMS in CS. Acidosis is indeed harmful to cerebral tissue as it disrupts the balance between excitatory and inhibitory neuronal activity and may cause neuronal injury and cell death (Huang et al. 2015, Liu et al. 2016, Nedergaard et al. 1991, Wang et al. 2011). Specifically, acidosis interferes with inhibitory cortical neurons, resulting in hyper-excitability of cerebral excitatory neurons, which may manifest as deterioration of cognitive behaviors (Huang et al. 2015, Liu et al. 2016). Hence, AMS seems to reflect several hemodynamic and biochemical derangements in CS, of which acidosis might directly affect cerebral function, especially in the light of the aforementioned imbalance in neuronal activity.

6.3.2 Altered mental status in risk stratification in cardiogenic shock

Study II revealed that clinically assessed alteration in mental state has prognostic significance in CS. Mortality among patients with AMS was more than two-fold compared with patients with normal mental status. Previous studies have shown an association of critical illness delirium and increased mortality both in general and in cardiac ICUs (Girard et al. 2008, Lahariya et al. 2014, Pauley et al.

2015, Salluh et al. 2015). However, the present study illustrated that mental state evaluation as part of routine clinical assessment without any structured screening tool is useful in risk stratification already at the time of CS detection. Even mild manifestations of mental state alterations are relevant in CS and indicate acidosis, hypoperfusion, and poor prognosis. Interestingly, a similar finding was observed in a study on septic patients, where only mild changes in mental state at ICU admission were independently associated with high mortality (Sonneville et al. 2017). What emphasizes the importance of mental state assessment in CS is that other clinical signs of hypoperfusion have some limitations in clinical practice; oliguria requires several hours of follow-up to detect and virtually all patients had cold periphery at the time of enrolment. Consequently, these both perform sub-optimally in early risk assessment in CS. Moreover, assessing mental status repeatedly offers important information on systemic perfusion, and change over time should be considered either a positive response to treatment or a warning sign of progressive hypoperfusion. In contrast, actual delirium is a more constant state and takes longer to resolve. Finally, the clinical importance of detected AMS was emphasized as it was incorporated in the CardShock risk score as a variable (Harjola et al. 2015).

Clinical assessment of mental status should thus be performed for every cardiac patient admitted to the emergency department. As brain tissue is highly sensitive to metabolic changes and cerebral circulation is strictly controlled locally by autoregulation, any alteration in mental status should be regarded as a significant warning sign of disrupted homeostasis and systemic hypoperfusion. In CS, AMS is particularly associated with acidosis and high mortality, and calls for immediate action to improve organ perfusion.

6.4 Growth differentiation factor 15 in cardiogenic shock (III)

6.4.1 GDF-15 levels and association with clinical presentation and organ dysfunction

GDF-15 levels in this CS population were very high at baseline; essentially all patients presented with GDF-15 levels above the upper limit of normal (1200 ng/L). Moreover, the median GDF-15 level in Study III was two- to five-fold higher than that previously reported among AHF or STEMI patients without CS (Cotter et al. 2015, Kempf et al. 2007). It appears that expression of GDF-15 increases very rapidly in response to CS.

However, the actual site of GDF-15 secretion in CS is somewhat unclear. Under physiological circumstances, GDF-15 is only weakly expressed. However, its expression is strongly upregulated in most tissues in response to tissue injury, hypoxia/ischemia, or inflammation (Anand et al. 2010,

Wollert et al. 2017). In Study III, GDF-15 was associated with biochemical markers of cardiac, hepatic, and renal dysfunction and hyperlactatemia and acidosis, which indicate systemic hypoperfusion. Interestingly, we found no correlation between GDF-15 and extent of myocardial injury as assessed by hsTnT levels. Previous studies have shown that GDF-15 expression is upregulated in cardiomyocytes in response to pressure overload and during acute MI through ischemia and reperfusion injury (Kempf et al. 2006, Xu et al. 2006). However, as previously discussed, GDF-15 is by no means cardiac-specific. Reflecting other sources of secretion, among patients with advanced non-ischemic dilated cardiomyopathy, GDF-15 expression from cardiomyocytes was very low despite high levels of circulating GDF-15 (Lok et al. 2012). Especially in the context of CS with systemic hypoperfusion affecting virtually every organ, the extra-cardiac sources of GDF-15 secretion seem probable and may be more important than myocardial secretion of GDF-15. The results of Study III support this hypothesis since the association of GDF-15 with markers of systemic hypoperfusion and multi-organ injury was stronger than that with myocyte necrosis. Hence, although the actual biological functions of GDF-15 need further research to be elucidated, it seems to reflect extensively organ failures and systemic hypoperfusion in CS.

6.4.2 GDF-15 and prognosis in cardiogenic shock

GDF-15 levels differed significantly between survivors and non-survivors already at the time of CS detection. Furthermore, there was a marked difference in the kinetics of GDF-15 between these two groups. Among survivors, GDF-15 levels decreased during the first 24 hours, whereas GDF-15 levels of non-survivors remained high or even increased. Hence, decreasing GDF-15 level may be a marker of resolution of hypoperfusion and shock, while increasing GDF-15 level suggests poor outcome. Furthermore, Study III revealed that GDF-15 with a cut-off of 7000 ng/L offers a tool in risk assessment and mortality prediction during the first days of shock. Early risk stratification is of great clinical importance in CS, as treatment usually occurs in ICU (of limited availability and considerable expense) and requires a broad range of advanced therapies including revascularization, invasive ventilation, and occasionally mechanical circulatory support. Patient selection for the most aggressive therapies should be made early enough before organ injuries have become irreversible, whereas futile invasive therapies should not be initiated. Clinicians need objective risk assessment tools in the difficult decision of selecting patients for or excluding them from certain treatment options. Accordingly, GDF-15 seems to provide additional value in risk stratification during the first days of CS.

In conclusion, GDF-15 levels are very high early in CS and reflect end-organ dysfunction and hypoperfusion. Moreover, high GDF-15 levels are associated with increased mortality, and the kinetics of GDF-15 differs significantly between survivors and non-survivors in the early course of CS, making GDF-15 a new, useful biomarker in risk stratification.

6.5 Inflammatory markers in cardiogenic shock (IV)

6.5.1 Levels of procalcitonin, C-reactive protein, and interleukin 6 in cardiogenic shock

The levels of PCT, CRP, and IL-6 were markedly elevated in this CS population during the first days of shock. The levels presented here were higher than described in AHF or STEMI without CS, yet lower than in sepsis or septic shock (Clec'h et al. 2004, Demissei et al. 2016, Picariello et al. 2009 and 2011). IL-6 is among the most important inflammatory mediators in human body with a diversity of functions both in physiological and in pathological processes, including regulation of immune system and regenerative functions, for instance. Clearly elevated IL-6 levels measured at 12 hours from the study enrollment confirm the presence of intense inflammatory response in CS. IL-6 then stimulates the production of PCT and CRP, among other acute-phase proteins. CRP is known to be a very non-specific indicator of inflammatory cascade activation. In addition to infections, elevated CRP levels can be seen in malignancies, burns, traumas, tissue damages of any cause, and in many autoimmune diseases (Pepys et al. 2003). PCT, in contrast, is considered a relatively specific biomarker of bacterial infection (Muller et al. 2000, Samsudin et al. 2017). In Study IV, the majority of CS patients had PCT level higher than 0.5 µg/L, the threshold value commonly used to exclude systemic bacterial infection. Only a small proportion of patients had any infection at baseline, and no correlation was found between infections and inflammatory markers. Thus, it is plausible that the strong inflammatory response accounts for the upregulation of the nonthyroidal secretion of PCT in CS. However, the fact that up to 40% of these CS patients had maximum PCT level below 0.5 µg/L may be of great value in diagnosing infections, especially if PCT level starts to increase after the typical time of peaking described in Study IV.

6.5.2 Inflammatory markers and prognosis in cardiogenic shock

PCT reached peak level already at 24 hours both among survivors and among patients who later died. However, the PCT levels of non-survivors were significantly higher compared with survivors from 12 hours onwards. In contrast, CRP levels continued to rise until 48 to 72 hours, reflecting the slower kinetics of this protein. A statistically significant difference in CRP levels of survivors and non-survivors was detected from 24 hours onwards. Moreover, IL-6 levels measured at 12 hours were more than two-fold greater among non-survivors compared with survivors. There was thus a clear connection between higher inflammatory marker levels and increased mortality in CS. High PCT_{max} ($\geq$ 0.5 μg/L) and IL-6 above median were associated with relative risks of 1.7 and 2.6 of 90-day mortality compared with low PCT_{max} (< 0.5 μg/L) and IL-6 below median, respectively. In contrast, CRP_{max} did not show prognostic significance. However, it is essential to consider the kinetics of all these biomarkers when analyzing their prognostic properties. As with CRP, the typical time of peaking between 48 and 72 hours is relatively late, especially considering a critical illness with a sudden onset. In CS, a substantial number of the deaths occur during the first days of shock, before many biomarkers reach their peak values. Possibly related to this, neither PCT nor CRP possessed independent value in mortality prediction. In contrast, higher IL-6 was independently associated with increased 90-day mortality after adjustment for the CardShock risk score variables. A similar association between IL-6 and mortality was observed in another study on CS patients (Andrie et al. 2012). IL-6 serves as a major component of the inflammatory response system with a rapid rise in circulating levels in the presence of an acute stressor. The strong inflammatory response partly reflects the severity of shock but also plays a role in the development of CS through for instance nitric oxide overproduction and pathological vasodilation, which further aggravates the hypotension (Hochman et al. 2003, Li et al.2000). The results from Study IV support this theory that the exaggerated inflammatory response is detrimental as such.

6.5.3 Association of inflammatory markers with clinical picture, biochemistry, and infections

Indeed, high IL-6 levels showed especially strong associations with clinical and biochemical signs of systemic hypoperfusion, including acidosis and hyperlactatemia. In addition, we found an association between high IL-6 levels and end-organ injury, as reflected by biomarkers indicating cardiac and renal dysfunction. High PCT_{max} showed similar associations. Study IV thus suggests a close connection between hypoperfusion and inflammatory response. Moreover, both IL-6 and PCT correlated significantly with GDF-15, which is also a marker of systemic hypoperfusion and end-

organ dysfunction in CS (Study III). Hence, there might be some similarities in the mechanisms that lead to increased gene expression and secretion of GDF-15 and non-thyroidal PCT, although the main origins and the biological functions of these biomarkers in the presence of systemic hypoperfusion and inflammation are still unclear. Of note, none of these inflammatory markers had significant associations with hsTnT in correlation analysis. The extent of myocyte necrosis may not thereby play a key role in the development of the intensity of inflammatory response. This emphasizes the complex pathophysiology of CS; CS patients present with a large range of LVEFs, reflecting varying sizes of myocardial insult (Hochman et al. 2003, Reynolds et al. 2008). However, intense inflammatory response with circulating inflammatory mediators may have myocardial depressant actions, further impairing systolic function (Reynolds et al. 2008).

We found no significant correlations between inflammatory markers and clinically detected infections at baseline. Overall, the prevalence of infections at the time of enrollment was relatively low. As ACS accounts for the etiology of CS in most cases, the onset of shock is sudden and infectious complications typically emerge later during the ICU/CCU stay. For instance, Parenica et al reported the median time between the hospital admission and the onset of infection to be 48 h among 80 CS patients (Parenica et al. 2017). In this light, it is also understandable that no correlation between infections and poor prognosis was found in our study; similar results have also been reported previously (Parenica et al. 2017). In other words, many CS patients die before the typical onset of infectious complications. Moreover, the challenge of differentiating between bacterial infection and non-infectious systemic inflammatory response is frequently encountered by clinicians who treat critically ill patients. It seems that in CS, the strong inflammatory response and the concomitant rise in inflammatory biomarker levels may easily conceal the infection-related changes. Similarly, in previous studies, high PCT levels among CS patients were associated with multiple organ failure rather than infections (Geppert et al. 2003). However, as CS patients are typically treated in ICU with mechanical ventilation and several indwelling catheters, nosocomial infections are a major risk and call for early diagnostics and antimicrobial treatment. In addition, bacterial translocation from the intestinal tract creates another source of infectious complications (Brunkhorst et al. 1999, Cuinet et al. 2020). Recognizing the typical kinetics of PCT and CRP presented here may assist in the difficult task of differentiating between inflammatory response and an infectious complication in CS.

Our results thus highlight the presence of a strong inflammatory response in CS and the close connection of inflammation with profound systemic hypoperfusion and organ dysfunction. It is

crucial to minimize the extent and duration of hypotension and hypoperfusion, as they may trigger a disproportionate inflammatory response with uncontrolled cascade of circulatory effects, further aggravating the hypoperfusion.

6.6 Limitations

Some limitations of the studies included in this thesis must be acknowledged. In Study I, no data on previous glycemic balance and DM medication or the possible use of insulin treatment in the early phase of CS were available. However, as blood glucose level was measured at the time of shock detection, it is likely that only few, if any, patients had been treated with insulin during the hospital stay by the time of blood sampling. Moreover, among patients with diagnosed DM, multiple factors affect the blood glucose level during acute illness, only one of which is previous DM medication. In Study II, an important limitation was that no structured screening methods, such as CAM-ICU, were used in mental state evaluation. However, the main purpose of this study was to investigate the significance of a clinically performed, quick mental state assessment emphasizing the real-life setting. In Study III, the main limitation was the lack of external validation in another CS population when proposing the cut off level in risk prediction. Nevertheless, this was to our knowledge the first study to analyze temporal trends of GDF-15 in CS using serial sampling, and thus offered new insight into the relevance of this biomarker. In Study IV, a minor limitation was the lack of systematically collected samples in infection diagnostics. The responsible physician assessed clinically whether the patient had an infection at the time of enrollment. However, as the onset of CS is usually sudden, only few patients are likely to have an infectious complication at the detection of shock, which was the finding also in this study. Moreover, diagnosing infections in the presence of a strong inflammatory response is very challenging, as is differentiating bacterial pneumonia from pulmonary congestion in chest x-ray.

6.7 Clinical implications and future directions

The CardShock study is one of the largest contemporary studies on CS, offering unique and detailed data on the clinical picture, biochemistry, and management of CS patients in European tertiary hospitals.

The results presented in this thesis have several clinical implications. Firstly, as a routinely used test, blood glucose measurement at baseline may help identify CS patients with the most disturbed homeostasis and highest mortality risk already at the time of shock detection (I). However, due to the observational nature of the present study, the causality between low or extremely high blood glucose level and poor prognosis remains unclear. Randomized interventional trials are warranted to determine whether targeting normoglycemia would benefit CS patients.

Secondly, mental state evaluation should be performed on every CS patient at the time of shock detection. As cerebral tissue is highly protected against metabolic and hemodynamic derangements, any alteration in mental state should be regarded as a warning sign of severe hypoperfusion and acidosis (II). Moreover, as acidosis is known to harm cerebral tissue, future studies analyzing neuronal biomarkers may reveal a potential association between clinically detected AMS and neuronal injury.

Thirdly, the biomarker studies (III, IV) of this thesis provide novel information on the levels of GDF-15 and inflammatory markers during the first days of CS. The significance of GDF-15 has raised special interest extensively in the research fields of acute and chronic cardiovascular diseases and oncology in recent years. However, the actual biological functions of GDF-15 remain unclear. Consequently, the potential of GDF-15 as a treatment target requires further investigation. In CS, GDF-15 seems to be especially useful in early risk stratification due to its rapid secretion in response to shock and its different kinetics among survivors and non-survivors during the first days of CS. The study on inflammatory markers highlights the presence of strong inflammatory response in CS and the association of hypoperfusion and inflammation. Recognizing the typical kinetics of inflammatory marker levels in CS helps not only in risk stratification, but perhaps also in the frequent challenge encountered by clinicians treating CS patients, namely differentiating between inflammatory response and infectious complications. Even more importantly, the study revealed the close connection between hypoperfusion and inflammation. However, analyzing the causal relationship between these two is extremely difficult, as they are part of the same vicious circle in the complex pathophysiology of CS. As long as there are no treatments that target the actual inflammatory

cascades, every effort should be made to minimize the duration and extent of hypotension and hypoperfusion to restrict the inflammatory response.

Indeed, the pathophysiological mechanisms behind CS should be further elucidated to get a better understanding of why some of the patients with similar extent of myocardial injury develop CS and some do not. Despite improvements in the techniques and availability of immediate revascularization, the mortality rates of CS remain high. Hence, the major challenge in the future is to find ways to restrict the vicious circle of hypoperfusion and inflammation in CS. Moreover, CS patients are a heterogenous group, both in terms of demographics and clinical picture. There is a need to improve patient profiling and thereby allocate the most aggressive therapies to the patients that would derive the greatest benefit, and to avoid futile treatments. Objective early risk stratification by using validated risk scores that combine hemodynamic data to novel biomarkers and CS phenotypes, may eventually lead to more personalized medicine and, hopefully, a better prognosis.

7 CONCLUSIONS

This thesis investigated easily available and clinically relevant factors, including biochemistry and clinical status, at the early phase of CS, and assessed their prognostic significance. As a routinely measured and inexpensive test, blood glucose may help identify high-risk patients with particularly disturbed homeostasis very early in CS. (I) Both severe hyperglycemia and hypoglycemia indicate profound hypoperfusion and an increased risk of death. In addition, an extremely high blood glucose level may be harmful as such. Based on the observations in Study II, mental state evaluation deserves special attention in CS patients admitted to the emergency department. Any alteration in mental status should be regarded as a warning sign of significant acidosis and systemic hypoperfusion. AMS at the time of CS detection is associated with poor prognosis and calls for immediate interventions to improve organ perfusion.

The biomarker studies in this thesis evaluated the levels and temporal trends of GDF-15 and inflammatory markers in CS. GDF-15 offers a new tool in risk stratification during the first days of shock, as high GDF-15 levels are associated with organ dysfunction and increased mortality. (III) The kinetics are diverse between survivors and non-survivors. An early decrease in GDF-15 levels suggests resolution of CS, whereas increasing GDF-15 level during the first days of CS is associated with poor prognosis. For early risk stratification in CS, a GDF-15_{12h} cut-off of 7000 ng/l was identified and found to provide incremental value to validated clinical risk scores. Our study on inflammatory markers highlights the presence of a strong inflammatory response in CS. (IV) PCT levels peak at 24 hours, while CRP continues to increase until 48 to 72 hours. There is a strong connection between clinical and biochemical findings of systemic hypoperfusion and high levels of PCT and IL-6 in CS. Moreover, high levels of PCT and IL-6 are associated with increased mortality. Finally, high levels of inflammatory markers appear to be associated with shock severity rather than infection during the first days of CS.

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