Visualizing congestion with ultrasound – diagnostic and therapeutic implications
*Focused cardiothoracic ultrasound protocol of the heart and lungs (CaTUS)*

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**Academic dissertation**
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Kuopio, March 2018
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**Abbreviations**

ACE = angiotensin converting enzyme  
ADH = anti-diuretic hormone  
Afib = Atrial fibrillation  
AHF = Acute Heart Failure  
ARDS = acute respiratory distress syndrome  
ARNI = Angiontensin Receptor Neprilysin Inhibitor  
AT2 = angiotensin receptor two  
CPE = cardiogenic pulmonary edema  
CVP = Central venous pressure  
Echo = echocardiography  
ECG = electrocardiogram  
ED = emergency department  
EVLW = extravasated lung water  
HF = Heart Failure  
HFmrEF = Heart failure with mid-range ejection fraction  
HFpEF = Heart failure with preserved ejection fraction  
HFrEF = Heart failure with reduced ejection fraction  
ICU = intensive care unit  
LSFP = left-sided filling pressures  
LUS = lung ultrasound  
LVEF = Left ventricular ejection fraction  
MRA = mineralocorticoid receptor antagonist  
PAC = pulmonary artery catheter  
RAAS = Renin angiotensin aldosterone system
1. Bibliography, List of original publications

This thesis is based on the following publications:


Abstract

Background

The syndrome of Acute Heart Failure (AHF) is a very common cause for hospitalization, and carries a poor prognosis both in hospital and after discharge. The syndrome is caused by a various disease of the cardiovascular system and the heart. Congestion due to elevated cardiac filling pressures is the key physiological feature in AHF. There is to date very little evidence-based therapy existing for AHF and hospitalizations are lengthy and expensive.

The aim of this thesis is to investigate a cardiothoracic rapid ultrasound protocol (CaTUS) in allowing an individual approach to be taken considering diagnosis, treatment monitoring and treatment guidance in AHF.

Methods

We enrolled 4 partly overlapping populations for this thesis. In our first study, we enrolled a total of 100 dyspneic ED patients in whom we tested CaTUS for diagnosing AHF, with the protocol done immediately upon arrival in the ED. Except for diagnosing AHF, CaTUS was also tested for diagnosing other conditions causing dyspnea in this study. In our second study on early monitoring of AHF, we enrolled 60 hospitalized AHF patients who had CaTUS done 3 times during the first 24 hours, thereafter 24 hours later and finally once more prior to discharge. In our third study evaluating the prognostic impact of CaTUS among other congestion parameters, we enrolled a sample of 100 hospitalized AHF patients, to whom CaTUS was done at baseline, at 24 and 48 hours and finally at the day of discharge. In our fourth study, we enrolled a small 20-patient AHF population, who had their treatment guided by the CaTUS protocol. The treatment results in this population were compared with treatment results in the previously enrolled 100-patient population enrolled before, who had received conventional in-hospital treatment for AHF.
Results

The CaTUS protocol performed very well for diagnosing AHF, as well as for differential diagnostics in dyspneic patients. Sensitivity was 100 % and specificity 95.8 % for diagnosing AHF as compared to a golden standard consisting of a brain natriuretic peptide-value of > 400 ng/l or > 100 ng/l in combination on chest x-ray as evaluated by an independent radiologist on the radiology ward.

During early treatment, CaTUS was able to identify early treatment responders and distinguish them from non-responders, which seemed to be relevant since early responders often expressed a favorable treatment response throughout hospitalization and a significantly better post-discharge prognosis.

For determining post-discharge prognosis, inferior vena cava index at discharge seemed to be the most relevant congestion parameter, indicating whether an AHF patient is sufficiently decongested.

Finally, CaTUS-guided decongestive therapy seemed safe, was associated with greater decongestion by all parameters, and seems to have been associated with fewer re-hospitalizations due to AHF.

Conclusion

CaTUS seems useful for diagnosing, monitoring and guiding decongestive therapy in AHF.

Tiivistelmä

Tutkimme kohdennetun rintakehän alueen ultraäänitutkimuksen käyttöä akuutin sydämen vajaatoiminnan diagnosoinmiseen, hoidon seuraamiseen sekä hoidon ohjaamiseen. Pienissä aineistoissamme protokollan tarkkuus akuutin sydämen vajaatoiminnan diagnosoinmiseen oli
Suomenkielinen abstrakti

Tausta


Metodit

Kokosimme neljä eri osittain päällekkäästä väestöryhmää tähän projektiin. Ensimmäisessä tutkimuksessamme keräsimme 100 hengenahdistus-potilasta ensiavusta, joilla testasimme ultraääni-protokollan käytettävyyttä oireyhtymän diagnoosimisessa. Toisessa tutkimuksessamme tutkimme protokollan käytettävyyttä alkuvaheen hoidon seurannassa, ja suoritimme protokollan-mukaisen tutkimuksen tulovaiheen lisäksi 12, 24 sekä 48 tunnin kohdalla, sekä vielä kerran kotiutumista edeltävästi. Kolmannessa tutkimuksessamme, tutkimme ultraääni-protokollan käytettävyyttä kotiutumisen-jälkeisen ennusteen
määrittämisessä sadalla akuutista sydämen vajaatoiminnasta kärsivällä potilaalla.
Neljännessä tutkimuksessamme, testasimme ultraääni-protokollan avulla toteutettua hoitoa pienellä 20 potilaan aineistolla, ja vertasimme hoitotuloksia tavanomaisesti hoidettujen potilaiden tuloksiin

**Tulokset**

Ultraääni-protokolla toimi hyvin akuutin sydämen vajaatoiminnan diagnoosomisessa herkkyyden oltua 100 % ja spesifisyyden 95.8 % verrattuna kultaiseen standardiin.

Alku vaiheen hoidon aikana protokolla onnistui löytämään varhain hoitoon vastaavat potilaat, ja näiden aikaisin hoitoon vastanneiden potilaiden hoitovaste säilyi usein suotuisana läpi sairaalajakson.

Kolmannessa tutkimuksessamme, alaonttolaskimosta laskettu kongestio-indexi oli ennusteellisesti merkittävin kongestio-parametri ennustaa kotiotumisen jälkeistä kuolleisuutta ja riskiä joutua uudelleen sairaalahoitoon.

Viimeisimmässä tutkimuksessamme, ultraääni-ohjattu hoito oli turvallista ja johti parempiin hoitotuloksiin verrattuna tavanomaisesti hoidettuihin potilaihin, ja näytti siltä että protokolla-hoidetuilla potilailla oli pienempi riski joutua lähiaikoina uudelleen sairaalahoitoon.

**Konkluusio**

Kehittämämme rintakehän ultraääni-protokolla vaikutti olevan hyödyllinen akuutin sydämen vajaatoiminnan diagnoosomiseen, hoidon seurantaan sekä hoidon ohjaukseen.
1. Introduction

Acute Heart Failure (AHF) is one of the leading causes for hospitalization in western countries and is caused mainly by elevated intra-vascular filling pressures due to disease of the heart, kidneys and cardiovascular system. Elevated intra-vascular filling pressures cause congestion, which remains the primary determinant of symptoms, prognosis as well as the primary treatment target in AHF. Despite several evidence-based therapies existing for chronic heart failure (HF) with reduced ejection fraction, AHF still remains a poorly studied syndrome with little, if any, evidence-based therapies existing to date and carries a very poor prognosis. Even the exact definition and optimal treatment targets within this syndrome remain are unclear to some degree. Nevertheless, it is somewhat agreed that congestion, and especially prognostically ominous pulmonary congestion, should be targeted with decongestive treatment in AHF. Since elevated vascular filling pressures, rather than low cardiac output, is the main pathophysiological feature causing symptoms in AHF, treatments reducing filling pressures, i.e. diuretics, vasodilators and sometimes vasoactive medications constitute the mainstay of medical treatment in AHF.

Medical AHF therapy today mainly consists of older medications, and there are not many promising new treatment options in terms of medications or devices expected to arrive in the near future. Nevertheless, one way to improve therapy in AHF with the medications already existing could be improved diagnostics and monitoring of the patients, which also constitute the topics that this thesis will focus on. Ultrasound constitutes an intriguing imaging modality optimal for focused assessment of the greater blood vessels, heart and lungs, the very key organs affected in AHF via congestion.

Ultrasound can be used to rapidly monitor congestion in AHF all the way from swift diagnosis in the emergency department, during in-hospital treatment and prior to discharge. Whether this could improve diagnostics, treatment and prognosis of AHF patients remains to be seen.

2. Review of the literature

2.1 Definition and pathophysiology of Heart failure
Heart failure (HF) is a syndrome rather than a disease, and is caused by a varying combination of disease of the heart, cardiovascular system and kidneys. Traditionally, the physiologic basis of this syndrome has been considered as structural heart disease causing reduced cardiac output, which in turn activates the neuro-hormonal and renal compensation mechanisms, resulting in increased sodium and fluid retention, increased vascular resistance and sympathetic activation of the nervous system, which all, in turn, result in elevated intravascular filling pressures. As per definition, HF cannot exist without structural heart disease. Nevertheless, diagnosing HF is not easy, especially in the elderly who often present with a heavy burden of co-existing cardiovascular disease including renal failure, and especially false positive diagnosis is considered as a common problem in dyspeptic elderly patients.

Structural heart disease is defined in the guidelines as impaired systolic and/or diastolic function of the heart. Systolic dysfunction is defined as a depressed left-ventricular ejection fraction (LVEF). Based on the LVEF, a patient suffering from HF is further classified in the newest guidelines as having either Heart Failure with a reduced ejection fraction (HFrEF, LVEF <40 %), heart failure with mid-range ejection fraction (HFmrEF, LVEF 40-49 %) or heart failure with preserved ejection fraction (HFpEF, LVEF => 50 %). In case of mid-range or preserved LVEF, further evidence of structural heart disease, such as significant valvular disease or diastolic dysfunction, is required for diagnosing HF. As the guidelines also acknowledge, diagnosing HFmrEF and especially HFpEF is cumbersome due to the lack of a validated golden standard for diagnosis, while diagnosis in case of HFrEF or significant valvular diseases is more straight-forward. Diagnosing HFmrEF or HFpEF caused by diastolic dysfunction is mainly done using echocardiography. No single echocardiographic marker alone is, however, significantly accurate for diagnosing diastolic dysfunction alone, and furthermore, echocardiographic markers of diastolic dysfunction are less well established in patients with chronic atrial fibrillation (Afib), which is a common rhythm in HF patients.

The terminology regarding definition of diastolic function can at times be somewhat confusing. According to the latest guidelines, echocardiographic evaluation of whether diastolic dysfunction is present should include filling pressure – dependent parameters, such as E/e’ and left atrial size, as well as parameters considered rather filling pressure-independent, such as tissue Doppler velocities. Evaluation of cardiac filling pressures should also always be included in evaluation of diastolic dysfunction with echocardiography.
regardless of LVEF\textsuperscript{8}, and grading of diastolic dysfunction (grade 1-4) also is bounded with evaluation of filling pressures. Grade 1 diastolic dysfunction, however, indicating impaired relaxation without elevated filling pressures, is considered a normal finding in the elderly, despite the nomenclature including the word “dysfunction”. Thus, a patient with grade 1 diastolic dysfunction might actually not have structural heart disease at all, but a normal heart slightly stiffened by aging \textsuperscript{1,8}.

Diagnostic controversies are most prevalent in patients with multiple cardiovascular comorbidities, and especially in the presence of severe renal failure \textsuperscript{9}. Renal failure and vasoconstriction can cause diastolic dysfunction and increased cardiac filling pressures also in young patients with a structurally normal heart, as can be the case in severe pre-eclampsia in pregnant women \textsuperscript{10,11}. In patients with renal failure, renal disease also causes sodium and fluid retention leading to hypertension and impaired relaxation of the heart, all of which in turn can cause elevation of intra-vascular and intra-cardiac filling pressures, which constitute the pathognomonic features of HF \textsuperscript{9,12}. Whether such patients with mild heart disease, renal failure, but signs and symptoms of elevated filling pressures are actually suffering mainly from HF or renal failure can be up for debate \textsuperscript{12}. Nevertheless, adequate, guideline-based decongestive and prognosis-improving treatment is similar regardless of the nomenclature used for describing the syndrome.

\section*{2.2 History of HF}

As our understanding of the syndrome of HF has grown during the past decades, the proposed definitions of this syndrome have also evolved, as can be seen in the following definitions presented by renowned authors in a review into the history of HF \textsuperscript{13};

\begin{table}[h]
\centering
\begin{tabular}{|p{\textwidth}|}
\hline
-“The very essence of cardiovascular practice is the early detection of heart failure” (Sir Thomas Lewis, 1933) \\
-“A condition in which the heart fails to discharge its contents adequately” (Thomas Lewis, 1933) \\
- “A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure” (Paul Wood, 1950) \\
- “A pathophysiological state in which an abnormality of cardiac function is responsible for \\
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<tr>
<th>Description</th>
<th>Reference</th>
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<td>the failure of the heart to pump blood at a rate commensurate with the requirements of the</td>
<td>(E Braunwald, 1980)</td>
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<tr>
<td>metabolising tissues”</td>
<td></td>
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<tr>
<td>&quot;Heart failure is the state of any heart disease in which, despite adequate ventricular filling,</td>
<td>&quot;Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart’s output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits” (H Denolin, H Kuhn, H P Krayenbuehl, F Loogen, A Reale, 1983)</td>
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<tr>
<td>the heart’s output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits” (H Denolin, H Kuhn, H P Krayenbuehl, F Loogen, A Reale, 1983)</td>
<td></td>
</tr>
<tr>
<td>&quot;A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses” (Philip Poole-Wilson, 1985)</td>
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<tr>
<td>&quot;[A] syndrome ... which arises when the heart is chronically unable to maintain an appropriate blood pressure without support” (Peter Harris, 1987)</td>
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<tr>
<td>&quot;A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy&quot; (Jay Cohn, 1988)</td>
<td></td>
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<tr>
<td>“Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure” (Task Force of the European Society of Cardiology, 1995).</td>
<td></td>
</tr>
<tr>
<td>Heart failure is a chronic, progressive condition in which the heart muscle is unable to pump enough blood through to meet the body's needs for blood and oxygen (AHA 2018).</td>
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Although descriptions of HF-like symptoms and disease are known to have existed already in ancient societies, it wasn’t until the 16th hundreds when the composition of the circulation was discovered, allowing deeper understanding of the cardiovascular system by human kind. In the very beginning, venipuncture and other rather primitive therapies were used in attempts to relieve congestion. Digitalis, a medication extracted from a wild plant named “Digitalis purpurea”, was one of the first medications used for treating HF, and was described by William Withering as beneficial for treatment of HF already in the late 17-hundreds. In the 19-hundreds, diuretics were introduced, and in 1958, the first safe diuretics without major side effects (Thiazides) arrived. The first diuretics introduced prior to thiazides contained toxic compounds causing unbearable side effects. As reduced cardiac output is considered the major trigger in the syndrome of HF, pharmacologic therapies presenting positive inotropic actions were firstly under focus when investigating potentially beneficial
therapies\textsuperscript{13,14}, a concept still existing in modern textbooks of physiology. It wasn’t until later that the quite opposite idea of down-regulating the tonus of the heart and cardiovascular system using neuro-hormonal blockade arose as a treatment option for HF.

The randomized controlled landmark study CONSENSUS firstly described the benefit of Enalapril, an angiotensin converting enzyme (ACE) inhibitor in 1987\textsuperscript{15}, and around that time, sporadic descriptions of the prognostically beneficial effect of beta blockers in HF were also described\textsuperscript{16}. Nevertheless, it was not until the mid-90’s that the large randomized controlled trials on the three major beta blockers studied in HF, i.e. metoprolol, bisoprolol and carvedilol, came out\textsuperscript{17,18,19}. Patients in these trials were already on angiotensin converting enzyme inhibitors and diuretics and some also on digitalis, the only inotrop drug still used for treating outpatients with chronic HF due to its possible prognosis-improving capability\textsuperscript{20,21}. The subsequent meta-analysis on the effects of beta blockers in HF, published in 2001 and including these 3 major trials\textsuperscript{22}, elegantly summarizes the evidence we have on beta blockers in HF today. Due to the fact that the medications mentioned above where studied before beta blockers, we do not know the isolated prognostic effect of beta blockers in HF very well, but we do know that they improve prognosis when added to the previously studied medications, i.e. mainly ACE-inhibitors. Nowadays, neuro-hormonal blockade using beta blockers, ACE-inhibitors (or angiotensin receptor two (AT2)-inhibitors) and mineralocorticoid receptor antagonists (MRA) constitutes the cornerstone of prognosis-improving treatment in HFrEF\textsuperscript{12}. One controversy regarding beta blockers exists, however, and that is their lack of prognostic benefit in HFrEF patients with atrial fibrillation\textsuperscript{23}, the reason for which is not fully understood to date.

Lately, more focus has been put on the exploring different phenotypes of HF and AHF. From a hemodynamic point of view, we know today that most signs and symptoms of HF and AHF are caused by elevated intravascular and intracardiac filling pressures rather than reduced cardiac output, although reduced cardiac forward flow often is considered the true origin of the syndrome\textsuperscript{24}. This is especially true in HFpEF, in which hypertension, and a “vascular component” are predominant features, and cardiac output at rest often is normal or close to normal\textsuperscript{25,26}. In HF with reduced ejection fraction, in turn, fluid overload, systemic venous congestion and reduced cardiac output are often more pronounced hemodynamic features, whereas arterial blood pressures often are within the normal range, or only slightly elevated.
As the HF syndrome worsens and enters the phase of advanced HF, symptoms of low cardiac output, including the prognostically ominous decline in systemic arterial blood pressure, start to get increasingly prevalent within the clinical picture while symptoms of elevated intra-vascular filling pressures worsen simultaneously \(^1,^2,^27\). At this stage, the prognosis of HF patients is already severely compromised, in fact worse than with most malignancies \(^25,^27\).

In the last decades, the mechanisms by which these different hemodynamic features are affecting optimal treatment have become better understood. As it was previously thought that inotropes and diuretics would tackle the main pathophysiological issues of fluid overload and decreased cardiac output associated with HFrEF, they were thought to constitute the optimal treatment targets in HFrEF. However, vasodilators and drugs with negative inotropic effect have instead proven revolutionary for improving prognosis in HFrEF patients \(^1,^2\). Moreover, some subsets of HFrEF patients also have device therapies available as prognosis-improving treatment, such as Cardiac Resynchronization therapy pacemakers (CRT-P) and defibrillating pacemakers (ICD-P) \(^1,^2\), as can be recognized in the therapeutic algorithm for treatment of HFrEF from the 2016 ESC guideline below.
For HF patients with preserved or mid-range LVEF, in turn, there is still today a lack of evidence-based prognosis-improving treatment. The virtually only positive data on treatment for HFmrEF and HFpEF come from subgroup analyses of both the CHAMPION- and the TOPCAT-trial, were adjusted or add-on diuretic therapy seemed to benefit HF patients with a preserved or close to preserved LVEF.\textsuperscript{28,29} Putting all this data together, it perhaps seems like medications with a diuretic mechanism of action might be beneficial for HF patients with a preserved LVEF. Therefore, results from trials of glucosuric diabetes drugs and the new Sacubitril-Valsartan drug (ARNI) on patients with preserved LVEF are highly awaited, since both groups of medications are known to have a profound diuretic effect\textsuperscript{30,31}. To summarize, it is now clear that neurohormonal blockade, along with many available device therapies, benefit patients with HFrEF, whereas diuretic therapies might be beneficial for patients with HFmrEF and HFpEF, but this remains to be further investigated in future studies.

2.3 Definition of Heart Failure and Acute Heart Failure
According to the literature, AHF is a syndrome in which symptoms of HF worsen acutely, resulting in signs and symptoms of acutely elevated intravascular filling pressures and/or decreased cardiac output. AHF may occur as the first manifestation of HF without a history of previous HF, i.e. as “de novo” AHF, or as worsening of previously chronic HF. The syndrome of AHF also has been named in many other ways than AHF in the literature, e.g. as “acutely decompensated heart failure” but in this publication, the abbreviation AHF will be used throughout the text for clarity. Around one third of all AHF episodes are triggered by an acute coronary syndrome (ACS), and perhaps expectedly, the prevalence of ACS is significantly larger in de novo AHF than in acute worsening of previously known chronic HF, as is the proportion of other acute triggers such as arrhythmias. The prevalence of both ACS and atrial fibrillation (Afib) in de novo AHF is approximately 40 % as compared to approximately 25 % in decompensated chronic HF.

AHF patients may present with a large variety of clinical phenotypes, ranging from frank cardiogenic shock to acute right ventricular failure with low cardiac output and absence of pulmonary congestion. In the literature, several different and partly overlapping classifications of AHF have been proposed, but in clinical practice, assessment of congestion and hemodynamic profiling is of high clinical relevance, as is highlighted in the recent ESC 2016 HF guideline. Most commonly, AHF patients are suffering from a varying degree of pulmonary congestion resulting in extra-vasated lung water (EVLW) due to elevated filling pressures in the pulmonary vasculature without apparent signs of severely reduced forward blood flow. Simultaneously, a varying degree of systemic venous congestion is mostly present. However, AHF due to only systemic venous congestion secondary to elevated right-sided filling pressures without signs and symptoms of pulmonary congestion is rare, since liver enlargement, subcutaneous edema, weight gain, elevation of central venous pressure and splanchnic venous distension are commonly better tolerated than pulmonary congestion. Hence, dyspnea is often the leading symptom causing Emergency department (ED) visits and hospitalizations in AHF and pulmonary decongestion the primary treatment target to be aimed for with decongestive treatment. In summary, AHF is mostly a condition associated with signs and symptoms secondary to congestion and elevated intra-vascular filling pressures rather than with low cardiac output, and dyspnea due to pulmonary congestion caused by elevated left-sided intra-cardiac filling pressures is often the major symptom bringing the patient to the ED.
Some criticism regarding the absence of a validated, exact definition of AHF has arisen in recent times. In the large multinational AHF database registries, diagnostic ICD 10-codes, and diagnostic criteria used for defining AHF have been somewhat varying, and diagnostic criteria in the registries have especially been quite different from inclusion criteria used in recent large drug studies on AHF. Thus, it seems like the population described in real-world registries is a different patient population as compared to the population that took part in the drug studies. Moreover, the definition of pulmonary congestion, a very fundamental and prognostically important finding in AHF, has been defined very variably in larger trials, as is emphasized in the recent publication by Platz et al. According to the guideline-based definition for AHF, a patient suffering from chronic or newly onset HF who seeks immediate medical attention due to feeling subjectively worse, may be classified as having AHF. Thus, the definition of AHF is partly based on subjective sensations of the patient, as another similar patient with some degree of congestion might be treated as an outpatient or would not seek medical attention at all due to larger tolerance of symptoms. Thus, AHF patients may enter the ED with an ambulance in very severe state of illness, they might walk in with symptoms similar to a common cold or, alternatively, they might not come at all, but perhaps take a few extra tablets of diuretics back home. This lack of a clear-cut, exact definition of the syndrome has been proposed to interfere slightly with studying the syndrome of AHF.

Another important issue is the association between comorbidities and AHF, and whether possible acute comorbidities co-existing with AHF are considered as triggers of, or secondary to AHF. As an example, pulmonary obstruction often accompanies pulmonary congestion, but the evidence regarding optimal treatment of pulmonary obstruction in the setting of pulmonary congestion, and even distinction between the cardiac and the pulmonary component is such a scenario, is uncertain to date. The same is true for the treatment and diagnosis of pneumonia in combination with pulmonary congestion. It is also often up for debate whether an exacerbation of pulmonary obstruction in association with pulmonary congestion is a trigger or a consequence of increased pulmonary extravasated lung water (EVLW). In real life clinical practice, it is also not too uncommon to even see patients presenting with the combination of pulmonary infection, pulmonary obstruction and pulmonary congestion, especially in a patient with a history of both chronic pulmonary disease and HF. In such a case, it might be hard to tell which of these commonly coexisting
acute comorbidities should be considered the primary diagnosis, and whether which
diagnosis is a trigger or a consequence of AHF. Nevertheless, assessing for signs of pulmonary
congestion should preferably be done in all dyspneic patients entering the ED, and in case
congestion is identified, the patient should primarily be classified as having AHF \(^1,2\). What we
further do know is that intra-vascular filling pressures and cumulative fluid load should be
kept as low as possible in acute respiratory failure-patients, regardless of the principal
etiology, highlighting the rationale that treating or preventing pulmonary congestion seems to
allow for better pulmonary recovery also in diseases not considered to fulfill criteria for AHF
\(^40\). This makes sense, since EVLW, i.e. excess fluid inside the lung parenchyma, makes the
lungs more vulnerable to other pulmonary insults and hinder recovery of these diseases as
well. On the other hand, although EVLW might be caused by my primary pulmonary disease per se (non-cardiac pulmonary edema), diagnosis of pulmonary parenchymal disease should
optimally always include estimation of intravascular filling pressures as a very common
trigger for EVLW, as is highlighted in the acute respiratory distress syndrome (ARDS) and
pulmonary disease guidelines \(^40,41\). This is relevant since pulmonary parenchymal disease also
makes it difficult to assess the magnitude of pulmonary congestion on regular pulmonary
imaging such as chest x-ray, CT or LUS, if intra-cardiac hemodynamics with e.g. Echo or
pulmonary artery catheterization (PAC) are not assessed separately \(^40\). In other words,
cardiogenic pulmonary edema cannot be ruled out solely based on pulmonary imaging
without assessing filling pressures separately \(^40\). Thus, identifying and treating congestion
does still play an essential role in the setting of acute respiratory failure, despite gaps in
knowledge regarding optimal combinational treatment for coexisting acute pulmonary
comorbidities and pulmonary congestion. Moreover, despite the lack of evidence,
simultaneous treatment of the commonly existing infection, pulmonary obstruction and
congestion in patients with respiratory distress syndromes probably is quite common in real
life \(^37,38,42\) as they commonly coexist \(^43\), and since respiratory failure is a life-threatening
disease.

Nevertheless, despite some variation in the common criteria used for defining AHF in
combination with possible acute comorbidities accompanying it, the syndrome of AHF mainly
features with signs and symptoms secondary to elevated intravascular and intra-cardiac
filling pressures. Signs and symptoms secondary to low cardiac output with or without the
combination of elevated filling pressures is a more uncommon clinical scenario \(^1,2\). In the
latter case, when severely depressed cardiac output is causing signs and symptoms despite elevated intra-cardiac filling pressures, the patient in question is per definition in a state of advanced heart failure or franc cardiogenic shock, i.e. the most severe form of AHF, resulting in very high short-term mortality 44.

2.4. Development and prevention of AHF

It is of interest what kind of changes in hemodynamics and patient status is preceding acute “decompensation” of de novo or previously existing HF, i.e. the syndrome of AHF. As mentioned briefly above, de novo AHF, as per definition, means that the syndrome is occurring for the first time, and a clear trigger, such as an acute coronary syndrome or arrhythmia, more often coexists than in worsening of a chronic HF syndrome 12,32. The other scenario in the case of de novo AHF, in case of no acute trigger is present, is that a chronic underlying HF syndrome has remained undiagnosed until it acutely worsens, resulting in AHF. Hence, since de novo AHF means that no previous heart disease has been diagnosed, it is obviously very hard to prevent except from treating cardiovascular diseases and risk factors as well as possible.

Most cases of AHF are, however due to acute decompensation of chronic HF, in which case the situation is quite different since one of the main goals with treating chronic HF should be prevention of hospitalizations due to AHF 1. AHF is always a non-desirable event in HF patients, associated with worse prognosis, a vulnerable post-discharge period, increased morbidity and excess costs for both society and the patients 27,32. Previously it was thought that asymptomatic elevation of intra-vascular filling pressures might not be detrimental as long as the patient can tolerate them. Unique, delicate hemodynamic data from the CHAMPION trial, however, taught us that even an asymptomatic filling pressure elevation disposes a clear risk factor for acute decompensation of chronic HF 45. This elevation of cardiac filling pressures is in fact also often asymptomatic until very close to the possibly awaiting acute decompensation resulting in AHF. Moreover, the CHAMPION study showed us that by tackling these filling pressures with medical treatment before they cause AHF mainly by intensifying diuretics, it is possible to avoid decompensation. 46 Furthermore, pulmonary artery pressure-guided decongestive treatment was even more effective for preventing hospitalizations in patients with a close-to-normal or normal LVEF than for patients with
HFrEF \(^{28}\), which is intriguing, since this patient group is lacking other prognosis-improving evidence-based medical treatment to date.

In HFrEF it is evident that, apart from adequate diuretic therapies, appropriate prognosis-improving therapies, i.e. mainly medical neuro-hormonal blockade, revascularization and device therapies, also prevent hospitalizations effectively \(^{1,2,15,22}\). In the CHAMPION trial, objective monitoring for hypovolemia using the pulmonary artery pressure-monitoring device also resulted in a higher adherence to neuro-hormonal blockade medical therapy, which might otherwise often be too easily stopped in fear of hypovolemia-related adverse events, and this phenomenon of greater adherence to prognosis-improving drug therapies probably further contributed to the positive results in that study \(^{46}\).

Despite the lack of prognosis-improving evidence-based medical treatment in HFP EF and HFmrEF, is lacking, it should be kept in mind that treating hypertension improves prognosis also in this patient group \(^{47}\). Naturally, arrhythmias and other comorbidities should also be treated according to usual standards in these patients \(^{1,2}\). Moreover, spironolactone is probably beneficial in those HFP EF and HFmrEF patients with an elevated natriuretic peptide value, suggesting a true HF diagnosis \(^{48}\), since this subgroup gained benefit from spironolactone in the TOPCAT trial. There was also a trend towards benefit of high-dose treatment with 100mg of Spironolactone daily during 4 days in the ATHENA-HF trial \(^{49}\), especially in patients with and LVEF > 45 \%, without any signs of adverse events. Randomized controlled data on diuretics is scarce, but a Cochrane review from 2012 on patients with chronic HF, gathering all randomized controlled trials on the subject, found that use of diuretics as compared to placebo was associated with lower mortality (odds ratio 0.24) and lower rate of hospitalization for AHF (odds ratio 0.07) \(^{50}\). Moreover, diuretics compared to other active medications, such as ACE-inhibitors or digoxin, were associated with increased exercise capacity in this review. This review is of clinical relevance despite the rather small studies included since non-randomized data on the prognostic impact of medications associated with severe disease, e.g. diuretics, is always controversial due to the difficulty of performing adequate propensity score matching, as is explained in more detail later.

In the future, trials regarding medical therapy with Angiotensin Receptor Neprilysin Inhibitor (ARNI) \(^{51}\) and Sodium-glucose co-transporter 2 (SGLT2) inhibitors \(^{52}\) for patients with a preserved or mid-range LVEF are eagerly awaited. The same is true regarding ablation
therapy for Afib, which has already proven effective for improving prognosis in HFrEF patients with a left atrium of up to 6 cm on echocardiography. Putting it all together, physicians should make every attempt to provide our HF patients with the optimal prognosis-improving therapies available, since AHF episodes are expensive for society and detrimental for the patients.

2.5. Diuretics in HF and AHF

Signs and symptoms of congestion are a fundamental part of the clinical picture seen in the syndromes of HF and AHF and diuretics are in turn considered the primary treatment of choice for treating congestion. Moreover, when the patient is congestive, renin and aldosterone levels are low, and therefore blockade of the renin angiotensin aldosterone system (RAAS) with ACE or AT2 inhibitors is considered less useful until the state of acute congestion has been treated and relieved. On the contrary, add-on diuretic treatment with MRAs seems to present beneficial diuretic (and blood pressure-lowering) effects in patients with resistant hypertension, and this effect was especially strong in patients with low renin levels due to sodium- and fluid overload. Although diuretics have been used in HF for a long time, their role in treating HF and AHF is still controversial, and they therefore deserve a separate mentioning in this thesis. In patients without persistent diuretic resistance, diuretics allow almost limit-less lowering of blood pressure and filling pressures, as long as sufficient cardiac output can be maintained. The most used diuretics, i.e. loop diuretics, thiazide-like diuretics and potassium sparing diuretics, all work by increasing urine output of the kidneys mainly via natriuresis, i.e. increased urine excretion of both sodium and water. In addition, loop diuretics have also been shown to increase aquareisis, i.e. excretion of water without sodium, to some degree via inhibiting the effects of anti-diuretic hormone (ADH) especially in states of over-secretion of this hormone, often seen in congestive HF patients. For increasing aquareisis, vasoperessin antagonists such as Tolvaptan, an oral, non-peptide, selective vasopressin V2-receptor antagonist, have also been studied for treating congestion. The V2-receptor antagonists are potent, aquaretic diuretics which have proven effective for short-term relief of congestion, but due to the lack of long-term effect on congestion their use has remained rather modest. They are, however, recommended in the newest ESC HF guidelines as potential treatment for volume overload in association with persistent hyponatraemia.
The major concern regarding diuretics have been associated with their adverse effect of activating the RAAS and increasing sympathetic tone via neuro-hormonal actions associated with the autonomous nervous system \(^{60}\). As mentioned previously in brief, there are also reports on the association of diuretic therapy with worse outcomes in HF \(^{61}\), but these types retrospective analyses are always prone to be severely biased despite vigorous propensity score matching since sicker HF patients will need larger amounts of diuretics. Thus, retrospective, non-randomized database studies are very poorly suited for evaluating safety of treatment tackling features associated with poor prognosis in a certain disease \(^{62,63}\). Hence, larger medical peer reviewed journals are also increasingly critical towards conclusions based on non-randomized registry data \(^{64}\).

Unfortunately, large randomized controlled trials on the prognostic effect on diuretics as compared to placebo in congestive HF patients will probably never take place due to ethical reasons and lack of financial interest \(^{64}\). Nevertheless, high-dose diuretic regimens in AHF, such as those used in the DOSE-AHF and CARESS-HF trials have proven to provide relief of congestion without any signs of harm regarding renal function or other important markers of adverse events and worse prognosis \(^{65}\). The only randomized controlled trial on the subject, i.e. DOSE-AHF, was underpowered for assessment of prognosis, although high-dose treatment in that trial was associated with slightly improved dyspnea relief and a delayed enhancement of renal function after a transient decline \(^{66}\). Thus, there is to date no reason not to treat congestion adequately with decongestive treatment, as is also suggested in the guidelines \(^{1,2}\). Findings based on registry data also remind us that AHF patients discharged with residual congestion experience a worse post-discharge prognosis, as is discussed more in detail further in this thesis, but due to the same chance of bias associated with diuretic treatment and prognosis, this does not automatically mean that treating congestion more vigorously in a randomized trial would improve prognosis.

2.6 Diagnosing AHF

2.6.1. Diagnostic work-up
Diagnosing AHF in the ED has proven to be difficult, and accuracy of clinical examination alone has been studied to be poor \(^{67,68}\). In a patient with suspected AHF, diagnostic workup should be started already in the pre-hospital setting and continued in the ED \(^1\). The primary goal should be to establish the diagnosis in a timely manner in order to initiate therapy as fast as possible, and often therapy and further investigations are undertaken simultaneously \(^{1,2}\). Diagnostics should include swift differential diagnostics regarding other life-threatening conditions that might exist in parallel, or be the primary cause for the patient’s symptoms in case AHF is not. Diagnosing AHF, however, still remains a challenging task in the ED, even after vigorous clinical workup including NPs, and as misdiagnosis seems to be associated with worse prognosis \(^69\), the importance of prompt, accurate and rapid diagnostics in the ED can probably not be stressed enough, as is especially emphasized in the recent guidelines. Apart from clinical examination, other tests that often should be undertaken include electrocardiogram (ECG), chest x-ray, vital parameters and laboratory parameters. ECG should be taken in all AHF patients and is often abnormal in AHF \(^70\). Chest x-ray is often undertaken although its accuracy is not optimal, and especially low positive predictive values have been reported \(^71\), and LUS seems to be more accurate for evaluating the presence of pulmonary congestion \(^72\), as is discussed more in detail below.

Of various laboratory parameters, natriuretic peptides are the most accurate laboratory test in diagnosis of AHF. Natriuretic peptides have improved the diagnostic accuracy of AHF considerably especially due to their excellent negative predictive values \(^{67,73}\) and using natriuretic peptides for diagnosing AHF has thus received the only I A class AHF-related recommendation in the HF guidelines \(^{1,2}\). Elevated natriuretic peptides as a pathophysiologic hallmark of myocardial stretch and congestion in AHF are now also considered part of the definition of AHF and therefore included in the inclusion criteria of many big pharmaceutical studies \(^{33,34}\). Natriuretic peptides are also part of the diagnostic criteria for HF with a LVEF > 40 % \(^1\) might determine whether such patients respond to pharmacological therapy \(^48\). The downside regarding natriuretic peptides is their weak positive predictive values in an acute care setting, especially in case of renal failure \(^67\). Nevertheless, they have provided a big improvement regarding recognition, diagnosis and prognostic stratification in HF and AHF \(^{67,68,69,74}\).

### 2.6.2. Evaluating pulmonary congestion
Since recognition of AHF or cardiac pulmonary edema (CPE) is most commonly done in the emergency department (ED) or within intensive care, cardiothoracic ultrasound protocols combining LUS and echocardiography (Echo) for evaluating AHF or CPE have also been studied mainly in ED- and intensive care unit (ICU) -settings. Despite some promising results, ultrasound protocols used in these studies so far have been associated with somewhat problematic methodological issues, especially regarding certain subgroups such as patients in atrial fibrillation, as can be seen in here below.

Table 1. Previous studies combining echocardiography and lung ultrasound within a single protocol for diagnosing acute heart failure or cardiogenic pulmonary edema

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>Protocol duration</th>
<th>Methodology for estimating LAP in Afib</th>
<th>LAP evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajimoto et al.</td>
<td>94.3</td>
<td>91.9 %</td>
<td>&lt; 1min</td>
<td>Unclear</td>
<td>12 (±4) min</td>
<td>-</td>
</tr>
<tr>
<td>Silva et al.</td>
<td>0.93</td>
<td>12 (±2) min</td>
<td>+</td>
<td></td>
<td>9 (±2) min</td>
<td>+</td>
</tr>
<tr>
<td>Bataille et al.</td>
<td>100 %</td>
<td>91 %</td>
<td>+</td>
<td></td>
<td>9 (±2) min</td>
<td>+</td>
</tr>
<tr>
<td>Sekiguch et al.</td>
<td>*</td>
<td>&lt;10 min</td>
<td>+</td>
<td></td>
<td>Afib patients excluded</td>
<td></td>
</tr>
<tr>
<td>Gallard et al.</td>
<td>83 %</td>
<td>83 %</td>
<td>Not reported</td>
<td>Afib patients excluded</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Russel et al.</td>
<td>93 %</td>
<td>86 %</td>
<td>+</td>
<td></td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; LAP, echocardiographically estimated left atrial filling pressure; Afib, atrial fibrillation; min, minutes. * Cut-off analysis using R-package found E/e; ejection fraction, inferior vena cava index and left-sided pleural effusion significant for differentiating cardiogenic pulmonary edema and acute respiratory distress syndrome (ARDS); **, exact references in text.

On the other hand, LUS alone also seems to provide excellent accuracy for diagnosing CPE in the ED, where acute pulmonary disease of different kind probably remains less of a differential diagnostic issue than in the ICU. As Echo also is thought to be rather difficult to learn and time-consuming, the enthusiasm for implementing Echo-associated protocols into ED practice has not been overwhelmingly big to this day. At the time being, immediate echocardiography in AHF is indicated by the guidelines only in the setting of hemodynamic instability. However, as ultrasound devices and ED physicians educated in ultrasound become more common, ultrasound is likely to become more common at the bedside prior to initiation of treatment. Thus, it might be that future ED physicians will first put the probe on the patient’s chest for a rapid exam of the lungs, pleurae and heart in their dyspneic patients,
while simultaneously taking a more precise anamnesis, instead of primarily taking out their stethoscope and listen in silence.\textsuperscript{84,85}

### 2.7. Ultrasound of the heart and lungs in AHF

Lung ultrasound has become a new increasingly used tool for diagnosing various pulmonary and cardiovascular disease states.\textsuperscript{86,87,88} Lung parenchyma was originally deemed as an impossible area to investigate by ultrasound due to the high content of air entrapped in the parenchyma\textsuperscript{89}. In the 1980s, sporadic reports about artifacts seen on ultrasound in patients with various pulmonary parenchymal conditions were reported without really knowing what they represented\textsuperscript{90,91}. It was not until the 1990s that the true value of lung parenchymal ultrasound was started to be seen\textsuperscript{92}, mainly via the pioneer in this field, a French Intensivist named David Lichtenstein\textsuperscript{88} who published numerous reports on the use of LUS in various clinical scenarios. While originally studied mainly for diagnosing a broad spectrum of pulmonary diseases\textsuperscript{87}, the main field of use with LUS today has become diagnosing EVLW as a sign of pulmonary congestion in left-sided AHF\textsuperscript{88}. The genesis of B-lines is not fully understood to date, but is mainly associated with deflection of the ultrasound beams at the point where air and water constitute an interface. Thus, B-lines on LUS are artefacts arising only when water as a sign of EVLW is present around the air-filled alveolar spaces in the lungs. Moreover, the amount of these B-lines has been shown to linearly correlate with the water content inside the lungs, ranging from slight extra-vasation to frank pulmonary edema\textsuperscript{88}. It is noteworthy, though, that B-lines can arise also in case of interstitial pulmonary disease, e.g. fibrosis or pneumonia, but can sometimes be differentiated by slight differences in the pleural texture by experienced sonographers, even without cardiac imaging\textsuperscript{87}. Persistent B-lines despite adequate decongestive treatment or in the absence of signs of elevated left-sided filling pressures may naturally also raise suspicion towards interstitial pulmonary disease.

LUS is highly sensitive and specific for detecting EVLW, for which it has outperformed the accuracy of traditional chest x-ray when compared with computed tomography and thermodilution methods as golden standard methods for detecting EVLW in various trials\textsuperscript{93,94}. LUS has also performed excellent in diagnosing cardiogenic pulmonary edema (CPE) as a sign of left-sided AHF without the aid of echocardiography, reaching a sensitivity and specificity of \textgreater 90 \% in a large meta-analysis on ED patients, using a cardiologist-panel review
as a reference diagnosis \(^{72}\). LUS can also be applied for diagnosing a variety of other pulmonary conditions other than AHF and CPE such as pneumothorax and pneumonia among dyspneic ED patients. Differential diagnostics in patients with suspected AHF is a very important issue in the ED, as well as on the wards \(^{1,2}\) and hence, this capability is considered a big advantage with LUS, with its differential diagnostic capacity naturally enhanced further when combined with echo \(^{81,95}\).

A typical ultrasound machinery in the ED might have several probes including e.g. from a high-frequency linear probe, a lower frequency curvilinear probe and an even lower frequency cardiac probe. While the higher frequency probes are used mainly for imagining blood vessels and for procedures, LUS can be done both using the curvilinear probe and cardiac probe, with the exception for assessing pneumothorax, for which the cardiac probe is normally not used due to its lower resolution at more superficial structures \(^{87}\). So, to conclude, for imaging EVLW, either a cardiac or a curvilinear probe is normally used depending on user preference. When combining lung and cardiac ultrasound, as is the case in our studies included in this thesis, using the cardiac probe for both naturally makes imaging faster.

EVLW due to AHF-related congestion normally encompasses both lungs to a large extent, and hence, focal B-lines as a sign of EVLW or a consolidation unilaterally should raise a suspicion towards an infective or solid process within the pulmonary parenchyma, which in most cases is pneumonia \(^{87}\). Besides being an important differential diagnostic disease to take into account when suspecting AHF, pulmonary infection is also common in combination with wet, congested lungs in AHF \(^{4}\). In a large meta-analysis constituting over 1000 patients, LUS performed very well in diagnosing pneumonia, yielding a sensitivity and a specificity of 94 % for both, which is considered considerably better than with chest x-ray, which only detects approximately 2/3 of pneumonias as compared with CT \(^{96}\). Moreover, LUS has a practically 100 % sensitivity and specificity for diagnosing pleural fluid, and is also very accurate for diagnosing pneumothorax, outperforming chest x-ray in both of these conditions as well \(^{97}\). Reports on LUS for diagnosing other pulmonary diseases, such as sarcoidosis, ARDS and pulmonary malignancies has also been reported \(^{87}\). Since the mid-nineties, numerous studies on LUS for diagnosing pulmonary congestion or AHF have been published, as well as two studies assessing the prognostic impact of residual
pulmonary congestion on LUS at discharge after hospitalization for AHF. These studies have used a variety of scanning protocols, ranging from 2-28 scanned lung zones and a variety of devices, including hand-held devices. The major studies on this subject are summarized in Table below.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nr of zones</th>
<th>Probe</th>
<th>Criteria for pos exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coiro, 2005 (^98)</td>
<td>8/28</td>
<td>Cardiac</td>
<td>1 pos zone bilateral/&gt;30BL</td>
</tr>
<tr>
<td>Gargani, 2015 (^99)</td>
<td>28</td>
<td>Cardiac</td>
<td>&gt; 15 BL</td>
</tr>
<tr>
<td>Cibinel, 2012 (^97)</td>
<td>6</td>
<td>3.5 Mhz Convex</td>
<td>2 pos zones bilater.</td>
</tr>
<tr>
<td>Pivetta, 2015 (^100)</td>
<td>6</td>
<td>Curvilinear 5-3 Hz</td>
<td>2 pos zones bilater.</td>
</tr>
<tr>
<td>Volpicelli, 2006 (^101)</td>
<td>8</td>
<td>Convex 3.5 Mhz</td>
<td>2 pos zone bilater</td>
</tr>
<tr>
<td>Lichtenstein, 1997 (^102)</td>
<td>4</td>
<td>3/3.5 Mhz Cardiac</td>
<td>quantitative</td>
</tr>
<tr>
<td>Gargani, 2008 (^103)</td>
<td>28</td>
<td>Cardiac 2,5-3.5 Mhz</td>
<td>&gt;5 BL</td>
</tr>
<tr>
<td>Lichtenstein, 2008 (^104)</td>
<td>2/4/6</td>
<td>5 mhz Microconvex</td>
<td>1 pos zone bilater</td>
</tr>
<tr>
<td>Liteplo, 2009 (^105)</td>
<td>2/8</td>
<td>2-5 Mhz curvilinear</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Jambrik, 2004 (^103)</td>
<td>2/28</td>
<td>2,5-3,5 mhz Cardiac</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Volpicellei, 2008 (^106)</td>
<td>11</td>
<td>3,5 Mhz Convex</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Platz, 2015 (^107)</td>
<td>4/8</td>
<td>Cardiac</td>
<td></td>
</tr>
</tbody>
</table>

While results in these studies have been good in general, some criticism has been raised about the variety of techniques and methodology used, as everything starting from positioning of the patient, loop length recorded, probe and machinery as well as number of scanning zones can vary the results of the study to some degree, which should probably be taken into account when analyzing the results of a LUS exam \(^107\). The studies in the table above also differ in whether they assess B-lines as a sign of congestion in a qualitative manner, i.e. based on a cutoff for a significant amount of B-lines, or in a quantitative manner, i.e. based on the counted number of B-lines as a continuous number. It is further noteworthy that the optimal technique to be used probably also depends on the clinical setting and severity of patient symptoms, e.g. outpatient setting vs. ED, since more severe congestion can be visualized reliably using less scanning zones. Thus, a faster scanning protocol consisting of fewer scanning zones is has been sufficiently accurate in severely ill patients \(^87\). Nevertheless, while all the methodologic issues regarding scanning techniques mentioned above need to be acknowledged, LUS can already be acknowledged as a well-established and accurate modality for diagnosing pulmonary congestion and AHF. Moreover, as the use of hand-held devices, generally lacking the Doppler features for estimating left-sided cardiac filling pressures, is likely to expand in the future \(^84\), B-lines make up the un-ability of hand-held devices to left-
sided filling pressures by allowing identification of EVLW as an in-direct sign and mere consequence of elevated left-sided cardiac filling pressures and their effect on the lung parenchyma.

Echocardiography (Echo) with modern machinery, in turn, can be used for a thorough evaluation of underlying cardiac disease, hemodynamics and flow, including intra-cardiac filling pressures, and is therefore considered highly useful in the diagnosis of AHF. In an emergency setting, Echo can further be helpful for facilitating rapid diagnosis of other cardiothoracic emergencies, including pulmonary embolism, cardiac tamponade and valvular catastrophes. Furthermore, the extent of a single Echo exam can be varied depending on the clinical scenario at hand, meaning that different faster or more thorough protocols can be used depending on the time available as well as on the expertise level of the sonographer. The question of when and how often Echo should be done in HF and during a hospitalization for AHF is a controversial one. In HF, the guidelines clearly state that Echo is should be done as part of the initial evaluation and diagnostic workup. Moreover, Echo provides important prognostic information, and insights into the hemodynamic state of a chronic HF patient. Therefore, Echo is probably also useful for monitoring outpatient HF patients during titration of therapy, although this remains to be better studied. Current guidelines are a little less mandatory about the role of Echo in AHF, and the most recent 2016 ESC guideline states that immediate Echo upon presentation is only mandatory in case of hemodynamic instability, while it is otherwise recommended within 48 hours after presentation.

LUS and Echo can be easily combined in a sequential manner using the same probe, making combination of the two techniques in a sequential manner feasible. These two techniques theoretically complement each other; as Echo only is capable of providing an estimation of left-sided cardiac filling pressures (LSFP) and patients are known to tolerate very variable levels of LSFP without ending up hospitalized, LUS can provide direct evidence of prognostically ominous pulmonary congestion as a consequence of elevated LSFP, indicating that the individual pulmonary threshold for tolerable LSFPs has been exceeded. On the other hand, Echo as an adjunct to LUS should help determine whether bilateral EVLW is cardiac in origin, i.e. due to elevated LSFP, or due to a rarer etiology such as infection or acute respiratory distress syndrome (ARDS), in which signs of pulmonary hypertension in
combination with low LSFP should be seen on Echo, a pattern also often to be seen with pulmonary embolism\textsuperscript{113,114}. In case of borderline findings on LUS, Echo might also help in evaluating whether the patient is in danger of developing pulmonary congestion due to readily increased filling pressures\textsuperscript{112}. This was the rationale for developing our Cardiothoracic Ultrasound Protocol (CaTUS), studied by us in this thesis for diagnosing AHF, as well as for monitoring and guiding decongestive treatment in AHF.

\section*{2.8. Treatment in AHF}

\subsection*{2.8.1. General considerations}

The journey of an AHF patient often starts in the ED, where swift diagnosis and treatment initiation is considered of utmost importance in this cardiovascular emergency\textsuperscript{1,2,5}. Rapid treatment initiation has also been suggested to be associated with better prognosis, although this association is hard to investigate in an evidence-based manner\textsuperscript{69,115}. The primary aim with rapid treatment initiation in AHF is to achieve a rapid decrease in intra-vascular filling pressures, which might in turn result in rapid relief of symptoms and congestion\textsuperscript{111}. This chain of favorable events can optimally be seen already within hours among treatment-responsive patients\textsuperscript{116,117}. Thus, it seems possible to get patients on a favorable treatment trajectory already during the first hours of treatment.

After the initial treatment phase is initiated, decongestive treatment is normally continued on hospital wards, i.e. either regular wards or under closer surveillance e.g. in a coronary care unit (CCU), while symptoms, congestion parameters, renal function and hemodynamics are being monitored\textsuperscript{1,2}. The ultimate goal during the entire hospitalization is naturally to get patients adequately decongestive and ready for discharge while minimizing adverse events\textsuperscript{1-3}. The optimal time point at which it is safe to discharge AHF patients, however, is still ill defined, and length of hospitalization varies greatly between regions and hospitals depending on, among other things, health insurance policies and cultural issues\textsuperscript{118\textsuperscript{-119}}. There are, however, still many unsolved, important issues remaining to be tackled within in-hospital AHF treatment. For the AHF syndrome per se, there is a lack of evidence-based therapy with an impact on prognosis, and hence, most guideline-determine therapies are still relying on
class C-evidence \(^1\text{-}^2,^5\), while hospitalizations remain to be lengthy and expensive \(^119\). How to optimally monitor AHF patients is also unclear. A substantial proportion of AHF patients are today discharged despite signs and symptoms of residual congestion, and this patient group unfortunately has been shown to present with a poor post-discharge prognosis, including high mortality and re-hospitalization rates \(^98,^99,^120\).

The reason why so many patients are discharged insufficiently decongested is not clear, but might have to do with factors such as inappropriate amounts of fluid and sodium given intravenously in combination with insufficient use of diuretics, resulting in failure to achieve a negative sodium and fluid balance during hospitalization \(^121\). While we do not have randomized controlled trials from adequately sized trials yet to tell us whether more complete decongestion could result in a more favorable post-discharge prognosis, registry data, despite its flaws, strongly suggests so \(^64\). Moreover, as more aggressive decongestion with high-dose diuretics has NOT been associated with excess adverse events, as was proven in the only larger randomized trial on the subject \(^110,^122\) and greater decongestion, on the other hand, has been associated with a greater relieve of symptoms in this syndrome with high morbidity \(^111,^122\) there is to date no evidence supporting withdrawal of more aggressive decongestive treatment in AHF.

### 2.8.2. Monitoring and guiding AHF treatment

As was mentioned before, decongestion is considered the main goal with in-hospital AHF treatment \(^1\text{-}^3,^5,^123\). As achieving adequate decongestion has proven to be difficult and residual congestion at discharge is associated with poor outcomes, the question how to optimally monitor decongestive AHF treatment, especially during beginning of hospitalization, is considered an important issue within AHF, which would need to be better studied. As clinical examination seems too inaccurate for detecting congestion \(^67,^68\) other methods of monitoring decongestion have been studied. The recent randomized PRIMA 2 – trial on natriuretic peptide – guided AHF treatment was negative \(^124\), as was the former ESCAPE – trial on pulmonary artery catheter (PAC) – guided AHF treatment \(^125\), leaving ultrasound of the lungs and heart as largely un-explored options for monitoring AHF treatment \(^5,^6\). In the PRIMA 2 – trial, treatment of AHF targeting a > 30 % reduction in NT-proBNP value during hospitalization in patients with a baseline NT-proBNP value of > 1700 ng/L did not reduce the

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dual endpoint of 180-day all-cause mortality or re-hospitalization for AHF and days alive out of the hospital during 180 days as compared to conventional treatment. In the ESCAPE – trial, in turn, decongestive treatment aiming at reducing invasively measured filling pressures in combination with clinical assessment did not improve 6-month post-discharge prognosis in terms of mortality or re-hospitalization for AHF as compared to treatment guided by clinical assessment alone.

Echo-derived cardiac filling pressure-estimation and pulmonary congestion on LUS have both been shown to predict post-discharge prognosis after hospitalization for AHF, indicating that these parameters might have potential for monitoring decongestive treatment. Thus, these modalities might also provide sensible treatment targets, although specific thresholds to aim for with decongestive treatment remain to be determined. Little is also known about the chronologic interplay and evolvement of these parameters during in-hospital decongestive treatment, i.e. how fast and in which order improvement can be seen in patients who respond to treatment. What we do know from studies on vaso-active drugs is that left-sided cardiac filling pressures seem to have the potential to decrease very rapidly, foreseeing resolution of pulmonary congestion and a decline in right-sided filling pressures as a result of initial decongestive treatment. Moreover, resolution of pulmonary congestion has been shown to be further facilitated by non-invasive ventilation. As response to treatment often varies greatly between patients, the possibility to detect treatment-responsive and non-responsive patients early is also a compelling one, since identifying non-responders could allow for early intensification of treatment.

As monitoring is of little clinical utility if it is not translatable into beneficial treatment decisions, monitoring techniques should optimally also be able to guide therapy, i.e. result in clinically meaningful interventions. In other words, we would need to know how to interpret the information that we are receiving while monitoring our patients during decongestive treatment, in order to carry out effective decongestive therapy while avoiding possible adverse events and excess costs associated with over-aggressive treatment or prolonged hospitalizations. To date, there is very little evidence regarding guidance of HF or AHF treatment. Since signs and symptoms of AHF are mainly caused by elevated intra-vascular filling pressures and decreasing filling pressures is considered the main goal with decongestive therapies, optimal monitoring techniques should optimally be able to assess the
volume status and hemodynamic status of our patients as relevant treatment targets.\textsuperscript{123} Apart from available and studied techniques for monitoring volemic status and hemodynamics during decongestive treatment, such as natriuretic peptides, ultrasound of the heart and/or lungs and invasive monitoring, other more pragmatic techniques, such as blood pressure-guided decongestive therapies, are yet to be tested in future trials.

Decongestive treatment in AHF has previously been carried out under constant fear of causing kidney injury and/or hypovolemia. It was long thought that hypovolemia and low cardiac output are the major risk factors regarding kidney injury in AHF, but in recent years, elegant, novel trials have given us new intriguing knowledge on this topic. Regarding the association of intravascular filling pressures, perfusion pressure and renal function, it actually seems like the biggest risk for worsening renal function during hospitalization consists of excess renal venous congestion instead of low cardiac output, as was demonstrated by the elegant 2009 landmark study by Mullens et al in an ICU setting.\textsuperscript{128} In this study, increased central venous pressures were significantly and clearly associated with worsening renal function, whereas left-sided filling pressures, cardiac index and mean systemic arterial blood pressure were not. Naturally, the study by Mullens et al. might not have distinguished between cause and consequence, since patients who developed kidney injury had worse renal function at baseline, and might thus have had a renal tendency to pick up fluid load, increasing central venous pressure levels. On the other hand, arterial hypotension might also trigger renal failure in septic patients, indicating that preserving adequate arterial blood pressure probably is of importance in low-output HF and cardiogenic shock.\textsuperscript{129} Hence, a decongestion strategy where decongestive treatment is continued until arterial blood pressure normalizes or drops below normal might be worth testing, since decreasing venous congestion until blood pressures decline into the normal range might be a point where renal perfusion pressures are close to optimal on both sides of the kidney. Systolic blood pressure on admission, indicating adequate cardiac output, has also proven to have strong prognostic significance in AHF,\textsuperscript{118,130} which might further be a sign emphasizing the importance of blood pressure as a simple and objective monitoring tool also during AHF treatment. On the other hand, some degree of hypovolemia and perhaps kidney injury might arise following aggressive diuretic treatment already before arterial hypotension can be seen,\textsuperscript{131} and some hypertensive AHF patients might not be fluid overloaded at all. Thus, it is probably safer to use other measures of
volemia, such as IVC Echo, instead of clinical parameters only, but again, such different strategies regarding decongestion-targets would need to be better tested in future trials.

As the negative PRIMA II and ESCAPE trial-results might firstly come off as surprising and disappointing, the authors of both trials have suggested that them to be a result of the high-quality guidelines-based treatment that both groups received in the trials. Thus, proper guidelines-based therapy might be the most relevant therapy when treating AHF. This idea is supported by the positive results on preventing AHF in the CHAMPION trial, using old-fashioned, conventional medication, i.e. mainly diuretics whenever a patient was presenting a rise in filling pressures, indicating a risk of developing AHF \(^{45,46}\).

Ultrasound-guided decongestive therapy, in turn, is still lacking a proper sized randomized controlled trial on its efficacy, so we do not yet know whether this would be the right way to go. However, as compared to invasive monitoring, as was investigated in the ESCAPE trial, ultrasound poses the benefit of being non-invasive, thus reducing the possible negative impact of PAC-guided treatment on results due to adverse events caused by the device itself.

The CHAMPION trial was indeed the only positive trial on hemodynamically guided decongestive therapy to date, although it was performed in an out-patient setting, i.e. in chronic HF patients rather than in AHF patients. However, as the primary endpoint was preventing hospitalization for worsening chronic HF, i.e. AHF, in patients showing increasing filling pressures which constitute the main treatment target and pathophysiological feature in AHF as well, the trial deserves some specific discussion. As mentioned briefly above, the CHAMPION trial compared PAC-guided therapy with conventional therapy. Pulmonary artery pressures were measured invasively with the CardioMEMS device, and readings of increased pulmonary artery pressures lead to intensification of decongestive therapy mainly by intensifying diuretic therapy \(^{42}\), but other medications, i.e. mainly vasodilators, were also used for treatment intensification. Importantly, the absence of low pulmonary artery pressures interpreted as lack of hypovolemia, also advocated intensification of neuro-hormonal guidelines-based medical treatment and hence, patients in the device group received more medical neuro-hormonal blockade, probably enhancing treatment results especially in HFrEF patients \(^{42}\). This study also differed very much from the ESCAPE trial, where monitoring opportunities in an ICU setting were excellent also in the control group (including CVP
reading, echo etc.), probably also partly mitigating the possible benefits of PAC-guided therapy. In an outpatient setting, in turn, the congestive state is mostly evaluated by means of clinical examination, in the absence of more accurate techniques.

3. Aims of this study

This study was planned in order to assess the utility of combined cardiac- and pulmonary ultrasound in dyspnea and AHF, in the ED, during early treatment and prior to discharge for diagnosing AHF, monitoring decongestive treatment and finally also to guide treatment. More thoroughly, the aims were as follows:

1) To assess the sensitivity and specificity of both echocardiography and LUS for diagnosing AHF as well as for diagnosing other conditions mimicking AHF and causing dyspnea in the ED. The aim was also to assess whether combining Echo and LUS would provide improved accuracy over either one of the modalities alone.

2) To assess the utility of the combined cardiothoracic ultrasound protocol (CaTUS) for monitoring treatment-responsiveness in AHF patients during the early hours of in-hospital AHF treatment.

3) To assess whether CaTUS can be used to determine whether prognostically meaningful treatment targets have been met with decongestive treatment before discharging the patient.

4) To assess whether CaTUS could be feasible for guiding decongestive treatment in AHF

4. Subjects and Methods

4.1. Study population and data collection

This was a retrospective observational study based on a convenience sample of patients enrolled in a tertiary care hospital ED. The sample size was a pre-defined convenience sample based on available resources without power analyses. As we wanted to assess the use of our ultrasound protocol for both diagnosis in dyspneic, undifferentiated ED patients, and for follow up and treatment guidance of AHF patients, the enrollment process was three-phasic
the first population sample was planned to enroll approximately 100 dyspneic patients without a set diagnosis in the ED, as it was expected that approximately half of these patients would have the syndrome of AHF. Thereafter, we continued to enroll patients diagnosed with AHF until we would have a population of 100 hospitalized AHF patients who were followed up with the CaTUS protocol on a daily basis. For the final phase of the study testing the use of CaTUS for guiding decongestive therapy, we further enrolled a small pilot population of 20 patients using the same inclusion criteria, who had their decongestive treatment then guided with the CaTUS protocol.

The CaTUS protocol studied in this thesis was a combination LUS with echocardiographic evaluation of bilateral cardiac filling pressures for diagnosis, treatment monitoring and treatment guidance in AHF. This CaTUS protocol differentiated from previous similar cardiothoracic ultrasound protocols mentioned earlier in many ways. CaTUS is composed of a straight-forward Echo- and LUS-protocol, and this combination lasted less than 3 minutes on average. It is based on a 6-zone LUS scanning protocol, of which 4 zones evaluate B-lines, and two basal zones evaluate pleural fluid, combined with echocardiographic evaluation of left-sided (E/e’) as well as right-sided (Inferior vena cava index (IVC)) cardiac filling pressures. Importantly, E/e’ as a measure of left-sided pressures, is feasible also in atrial fibrillation, a condition present in up to 30-40 % of AHF patients, making it feasible as such for most AHF patients.

4.2 Diagnosing AHF

In our first study named “Rapid cardiothoracic ultrasound protocol (CaTUS) for diagnosis of acute heart failure in the emergency department”, published in the European Journal of Emergency, we compared the CaTUS protocol, i.e. a combination of B-lines, pleural fluid, medial E/e’ and the IVC index for diagnosing AHF. We then further compared these parameters alone and in different combinations, in order to find out which combination of parameters could be most useful for diagnosing AHF in an ED setting. Inclusion criteria consisted of adult patients with dyspnea at rest, while exclusion criteria consisted of pulmonary fibrosis, confusion or mechanical ventilation, mitral stenosis and chronic dialysis. As reference diagnosis for AHF, structural heart disease as a substrate for HF and either 1) an elevated BNP (>100 ng/l) combined with pulmonary congestion on x-ray, or 2) a clearly
elevated BNP (>400 ng/l), providing a higher positive predictive value, were used. Structural heart disease was determined as 1) an EF <40 %, 2) significant valve disease or 3) Diastolic dysfunction according to Nagueh et al's recent statement paper ⁰.

4.3 Assessment of early treatment response

In our second article named “Assessment of early treatment response by rapid cardiothoracic ultrasound in acute heart failure: cardiac filling pressures, pulmonary congestion and mortality” on 60 patients hospitalized for AHF, we investigated the sequential changes in bilateral intra-cardiac filling pressures on Echo, pulmonary congestion on LUS, symptoms and natriuretic peptides during beginning of treatment. These variables were assessed at baseline, at 12 (+/-3) hours, at 24 (+/-3) hours, at 48 (+/-3) hours and finally at discharge, with a special interest on which parameters might show the first signs of treatment-responsiveness. Inclusion and exclusion criteria were identical to those mentioned in the first article.

4.4. Assessment of post-discharge prognosis

In our third article named “Focused Cardiothoracic Ultrasound (CaTUS) for monitoring decongestion in Acute Heart Failure”, we compared the prognostic significance of numerous different congestion markers either as changes during the time of hospitalization or as absolute values on the day of discharge. The aim was to explore which of these congestion parameters would represent the strongest predictors of 6-month post-discharge prognosis, including both all-cause mortality, as well as the combined endpoint of all-cause mortality or re-hospitalization for AHF, in order to find out which congestion parameters would manifest themselves as the optimal treatment targets to aim for with decongestive treatment. The study population in this article consisted of 101 patients hospitalized for AHF, with the identical inclusion and exclusion criteria as described in the previous two articles.

4.5. Guiding treatment

In our fourth article called “Focused echocardiography and lung ultrasound protocol for guiding treatment in Acute Heart Failure “, we tested the use of the CaTUS protocol for guiding decongestive treatment in a small subgroup of 20 patients, and the results were compared with an earlier enrolled control group of 100 patients treated according to normal hospital
standards. Inclusion and exclusion criteria were again identical as described above in this study. For establishing the treatment protocol to be used in this study, we utilized the information gathered from the second and third articles which showed that while E/e’ seemed to represent the fastest-reacting objective congestion parameter during the first 24 hours of treatment, preceding pulmonary decongestion on LUS, IVCi on the day of discharge seemed like the prognostically most relevant treatment target to be aimed for during hospitalization. Thus, we aimed used a treatment protocol which was designed to intensify decongestive treatment until a non-plethoric, reactive IVC could be seen on Echo. In case of signs of hypoperfusion, decongestive treatment was halted after achieving either a dry LUS without pulmonary congestion, or an E/e’ (medial) <15.

4.6. The CaTUS protocol

The CaTUS protocol included LUS, medial E/e’ and IVCi on focused echo, and is illustrated in Figure 1. CaTUS was considered positive for AHF if presenting with both an E/e’ >15 and a congestive LUS as defined below. Both Echo and LUS were done with the Philips CX 50 – machinery, using the cardiac probe (5-1Mhz) for examining both the heart and the lungs. A figure illustrating the different anatomical signs for obtaining the images within the CaTUS protocol is presented here below:
All CaTUS measurements were done with the patient in a supine position, with the upper body slightly elevated for maximum patient comfort. Slight leftward rotation of the patient was allowed only if necessary for sufficient visualization, in order to avoid postural alteration of cardiac filling pressures. LUS included bilateral examination of two pulmonary fields per side, the apical and mammillar region in a mid-clavicular line, for evaluating B-lines. Additionally, the lower basal regions in an axillary line bilaterally were evaluated for pleural effusion (Figure 1). B-lines were positive for one region if presenting ≥3 B-lines within one intercostal space⁸⁷, and a positive region for B-lines bilaterally was considered as a positive examination for pulmonary congestion. Pleural fluid was defined as >5 mm of dependent fluid seen in the inter-pleural space. LUS was considered congestive within the CaTUS protocol if presenting either bilateral B-line positive regions or bilateral pleural fluid. Decongestion on LUS was defined as resolution of both bilateral B-lines and pleural fluid, and in the second study, patients discharge without pulmonary congestion were named LUS-responders.

The E-wave was recorded using pulse wave doppler (PW) at the tips of the opened mitral valve. If the patient was in sinus rhythm, or any other regular rhythm, three consecutive cycles at end expiration were recorded, and the average of these three E-waves was registered. If the patient was presenting with an irregular rhythm, such as atrial fibrillation or extra-systolia, five consecutive cycles and the average of these five E-waves was registered. Sweep speed was adjusted to fit a proper number of cardiac cycles into one picture frame. The e’-wave was measured using tissue pulse wave doppler (TDI PW) with the sample volume placed at the medial mitral annulus. The medial E/e’ was chosen over an average/lateral value due to fear of excess dyssynchony causing lateral enhancement of the lateral e’-wave in patients with decreased LVEF and wide QRS. The E/e’ was obtained in the four-chamber window using minimal angulation. Gain settings were optimized to obtain a crisp, clear signal without signal aberration. The IVC index was graded based on maximum diameter, using a cutoff of 21mm and respiratory variation using a cutoff of 50 %¹¹⁴. IVC measurements were performed 1 to 2 cm caudally of the first hepatic vein ¹¹⁴. In the first study on diagnosing AHF and the second study on early treatment monitoring, the IVC index was graded from 1-3. Grade 1 indicated a maximum diameter of < 21 mm and a respiratory variation of > 50 % (non-plethoric), Grade 3 a diameter of >21 mm and respiratory variation of < 50 % (plethoric) and Grade 2 either a diameter > 21 mm or a respiratory variation of < 50 %. In the third study assessing prognosis and the last study on ultrasound-guided treatment,
the IVC index was graded 1-5, with grade 1 meaning a completely constricting (empty) IVC, grade 5 dilated IVC and hepatic veins without any detectable respiratory variation, and grades 2-4, in turn, corresponding to grades 1-3 as described in the first 2 studies.

All CaTUS examinations were done by a single sonographer, with over five years of experience in both LUS and Echo in daily practice. Since this was a single center, single operator study, LUS-classification, as well as echocardiographic filling pressure measurements (E/e’ and IVC grading) were validated on a separate subset of 20 patients with experienced blinded validators (one validator for LUS and another for filling pressures), being reported in the results section. Regarding congestion on LUS, the validation resulted in an inter-observer agreement of 100% and thus a Kappa coefficient of 1.0. Regarding E/e’ (as a continuous variable), the mean inter-observer coefficient of variation was 9.99%.

4.7. Statistical analysis

SPSS version 23 was used for statistical analysis. Continuous variables were presented as mean values including standard deviation (SD) or median values including interquartile range (IQR) as was appropriate. Categorical variables were presented as counts and percentages. Differences between two groups were determined by unpaired t-test or Mann-Whitney U test for continuous variables and Pearson chi-square for grouping variables. Differences in survival between groups were analyzed with the log-rank test, and graphically displayed with Kaplan-Meier survival curve. Univariate analysis and multivariable analyses by Cox proportional hazards model were performed to assess the association between variables and prognostic outcomes.

5. Results

The results of all the four articles, including the first article on diagnosis, the second article on early treatment monitoring, the third article on pre-discharge assessment and the fourth article on treatment guidance using CaTUS, will be presented in this Results section.

5.1. Diagnosing AHF and other conditions among dyspneic patients in the ED
The first study on diagnosing AHF aimed included a convenience sample of 100 dyspneic patients which was achieved after screening 105 patients, of which 5 were excluded and 100 patients meeting the inclusion criteria were included. Of the included 100 patients, 52 had AHF and 48 another cause for dyspnea according to the golden standard reference method of a clearly elevated BNP (>400ng/l) or an elevated BNP (100 - 399 ng/l) if accompanied by pulmonary congestion on chest x-ray in patients with structural heart disease on Echo.

According to baseline characteristics, the golden standard diagnostic method divided the study population into two clearly different types of populations based on whether they were deemed as having AHF or some other reason for dyspnea. The AHF population had an almost 8-fold median BNP level and an over 2-fold mean E/e´ value as compared to the non-AHF population. Furthermore, a bilateral, significant B-line profile was present in >96 % and pleural fluid in >69 % of the AHF population indicating severe pulmonary congestion in this group.

The main results regarding diagnostic accuracy of LUS, Echo and the CaTUS protocol as a whole can be seen in the table below.

**Table 2. Diagnostic accuracy of CaTUS, LUS and E/e´ alone, as well as CaTUS in combination with the IVC index**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaTUS</td>
<td>100 % (CI 91.4-100 %)</td>
<td>95.8 % (CI 84.6-99.3 %)</td>
<td>0.979</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BL-profile on LUS alone</td>
<td>96.2 % (CI 86.8-99.5%)</td>
<td>81.3 % (CI 67.4-91.1 %)</td>
<td>0.887</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e´ &gt; 15 alone</td>
<td>100 % (CI 91.4-100 %)</td>
<td>84.9 % (CI 71.9-92.8 %)</td>
<td>0.925</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CaTUS + (IVC ≥ gr.2)</td>
<td>86.5 % (CI 73.6-94.0 %)</td>
<td>97.1 % (CI 88.8-99.5 %)</td>
<td>0.918</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CaTUS + (IVC ≥ gr.3)</td>
<td>40.4 % (CI 27.3-54.9 %)</td>
<td>100 % (CI 93.3-100 %)</td>
<td>0.702</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CaTUS, Cardiothoracic Ultrasound Protocol; BL-profile, bilateral B-lines in at least one scanning zone bilaterallyLUS, lung ultrasound; E/e´, medial ratio of early diastolic E-wave to e´-wave; IVC, inferior vena cava

Regarding LUS alone, B-lines performed well in our study already without Echo, providing a
sensitivity of 96.2 %, a specificity of 81.3 % and an area under the curve (AUC) of 0.887 for diagnosing AHF. We also evaluated the diagnostic performance of bilateral pleural fluid alone, which provided a sensitivity of 69.8 % and a specificity of 93.4 % for diagnosing AHF.

When describing the performance of focused Echo alone, medial E/e’ performed even slightly better than B-lines on LUS, yielding a sensitivity of 100 %, specificity of 84.9 % and an AUC of 0.925 for diagnosing AHF. In our population, a medial e’ of <8, indicating impaired relaxation regardless of LVEF, further presented a sensitivity of 96.4 % and a specificity of 100 % for identifying patients with structural heart disease on conventional Echo. E/e’ and LUS also correlated very well, with E/e’ as a continuous value presenting an AUC of 0.95 for identifying B-lines on LUS, and the optimal cutoff value for E/e’ using ROC analysis with Youden’s index was 14.8, being very close to the guidelines-based cutoff of 15 as a marker of elevated left-sided filling pressures which was used in this study as well.

The E/e’-cutoff of 15 used in this study as a qualitative cutoff, provided a Kappa coefficient of 0.796 for diagnosing B-lines on LUS. Thus, in conclusion, B-lines and E/e’ were strongly correlated with each other and also performed well alone for diagnosing AHF. Despite the excellent diagnostic values of Echo and LUS alone, CaTUS without the IVC index, combining medial E/e’ and either BL-lines or pleural fluid on LUS presented the best diagnostic accuracy for diagnosing AHF, yielding a sensitivity of 100 %, a specificity of 95.8 % and an AUC of 0.979.

CaTUS also proved useful for diagnosing other cardiac and pulmonary conditions than AHF as an evident cause for dyspnea. Of the most common causes for dyspnea other than AHF, LUS identified focal B-lines in 80 % of the patients eventually diagnosed with pneumonia, while LUS was normal in all patients with either bronchitis or hyperventilation/dyspnea of unknown origin. All patients with dyspnea of unknown origin, in turn, were discharged home from the ED without hospitalization in this study. Furthermore, the focused Echo exam within the CaTUS protocol identified visual signs of right ventricular pressure load in 80 % of the patients who were diagnosed with pulmonary embolism. CaTUS also revealed a few cardiothoracic emergencies, including type-A aortic dissection, mitral chordae rupture and pericardial tamponade, and these conditions naturally required immediate surgical attention.
Perhaps surprisingly, the IVC index did not add any additional accuracy for diagnosing AHF in addition to the dual combination of LUS and Echo. 8 out of 54 patients with AHF presented with a normal (grade 1) IVC, and all of these patients were hypertensive (systolic blood pressure >160 mmHg). Adding the IVC index using either the liberal (grade 2-3) - criteria, or the tighter (grade 3) - criteria actually worsened the total accuracy of the CaTUS protocol, with the exact numbers of diagnostic accuracy of these combinations presented in Table 2 above. When using the liberal IVC criteria (maximum diameter >21 mm or respiratory variation < 50 %), specificity was slightly improved but at a clear cost of sensitivity, and overall accuracy was worse as compared to the dual combination of E/e´ and LUS by themselves. The tighter IVC criteria (both a maximum diameter of >21 mm and respiratory variation < 50 %), in turn, resulted in a significantly worse sensitivity despite enhanced specificity and an even worse overall accuracy as compared again to the dual combination of E/e´ and LUS (Table 2). Thus, the area under the curve for diagnostic accuracy regarding AHF was optimal with the dual combination of LUS + E/e´, while it was worsened by adding the IVC index.

When testing different combination of LUS and IVCi without the E/e´, the combination of an IVCi grade 3, i.e. of >21 mm and < 50 % respiratory variation, *+* a positive LUS yielded a specificity of 93.7 % for diagnosing AHF, as compared to a specificity of 81.3 % for B-lines alone, but at the cost of sensitivity, resulting in an even worse total diagnostic accuracy compared to the other combinations.

In conclusion, the dual combination of E/e´ and B-lines only, *without* the IVC, was the most accurate diagnostic combination for diagnosing AHF in this study.

5.2. Monitoring early hours of decongestive treatment in AHF

In the second article of this thesis, we investigated early treatment monitoring in AHF. Since we wanted to investigate the sequential inter-play of improvement in various congestion parameters among treatment-responsive patients, we classified our population into LUS-responders and LUS-non-responders depending on whether they would get rid of their pulmonary congestion on LUS during their hospitalization course. Of note, all patients had
pulmonary congestion on LUS upon presentation, since it was an inclusion criteria at baseline. Patients then experiencing resolution of pulmonary congestion on LUS were named responders in this article, and represented 53 % of the entire population. Thus, the remaining 47 % of the patients were discharged with residual congestion on LUS.

We found that LUS-responders experienced a rapid decrease in left-sided cardiac filling pressures (E/e’) which resulted in simultaneous rapid symptom relief, and foresaw resolution of pulmonary congestion, while natriuretic peptides and IVC index declined later, as can be seen in the figure below.

**Figure 1 a-d. Decline in cardiac filling pressures, i.e. E/e’, Inferior Vena Cava Index (IVCi), Symptomatic Visual Analogue Scale (VAS) score (1-10) and Brain Natriuretic Peptides (BNP) during early course of hospitalization.**
21 patients in the whole study population experienced an early E/e’-decline of > 3U during the first 12 hours, and 18/21 (86 %) of these patients were to become responders, meaning that an early decline in E/e’ seemed to predict LUS-responsiveness with a high positive predictive value.

When further analyzing the behavior of E/e’ among responders, an interesting phenomenon was seen, differing a bit from the traditional understanding of cardiac filling pressures and echocardiography; the decrease in E/e’ was a combination of a simultaneous decrease in the E-waves and a simultaneous increase in the tissue Doppler e’-waves, indicating a simultaneous improvement in both filling pressures (E-wave) and cardiac relaxation (e’-wave). Thus, the improvement in their E/e’-ratios was a sum of a simultaneous decrease in E-waves and a decrease in TDI-e’-waves.

Regarding the effect of different congestion parameters on post-discharge prognosis, absence of pulmonary congestion on LUS (LUS-response) on the day of discharge was the only congestion parameter independently predicting both 6-month post-discharge all-cause mortality, as well as the composite endpoint of 6-month all-cause mortality or re-hospitalization for AHF on multivariable analysis in this 60-patient population. However, this type of analysis will be redone in our third article using a larger 100 patient population, probably more suitable for multivariate analysis, as is discussed below. The initial BNP value also remained significant in the model, whereas the decline in- or the discharge BNP value did not.

When analyzing baseline characteristics in responders as compared to non-responders, little difference was seen, but a trend towards less de-novo HF and less chronic pulmonary disease and more pleural fluid was seen among non-responders. BNP was higher and eGFR lower among non-responders, indicating more severe cardio-renal disease burden.

When comparing treatment-related parameters in responders as compared to non-responders, responders had a significantly larger improvement in nearly all treatment response-related parameters, i.e. E/e’, IVCi, BNP, symptoms and cumulative fluid loss.
When analyzing the other congestion parameters and their kinetics during early treatment, symptoms declined rapidly alongside E/e’ in among responders, as can be seen in the Figure above. Symptoms, in turn, declined linearly also among non-responders, who in turn experienced very little at all decline in filling pressures during the entire hospitalization. Of the other congestion parameters, IVC index declined clearly slower, while BNP seemed rather useless for monitoring treatment, hovering vaguely in both groups as can be seen in the figure as well.

5.3. Analyzing the effect of different congestion parameters on post-discharge prognosis in the whole 100 patient population

In our third article investigating pre-discharge assessment of patients, we looked into which congestion parameters would seem to be prognostically most significant prior to discharge. In this study, we divided the population in this study into survivors and non-survivors based on whether they were alive or diseased after the 6-month follow-up time, and the baseline characteristics of the entire population, as well as when comparing the two groups, can be seen in the table here below:

Table 3. Baseline characteristics in the whole population, as well as in survivors compared to non-survivors

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n=101)</th>
<th>6-month survivors (n=74)</th>
<th>6-month Non-survivors (n=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.2±10.8</td>
<td>74.7±11.4</td>
<td>80.2±7.5</td>
<td>0.022</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 (50 %)</td>
<td>36 (49 %)</td>
<td>15 (56 %)</td>
<td>0.654</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45 (45 %)</td>
<td>33 (45 %)</td>
<td>12 (44 %)</td>
<td>0.989</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (82 %)</td>
<td>60 (81 %)</td>
<td>23 (85 %)</td>
<td>0.633</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>49 (49 %)</td>
<td>34 (46 %)</td>
<td>15 (56 %)</td>
<td>0.392</td>
</tr>
<tr>
<td>Previous HF</td>
<td>63 (62 %)</td>
<td>41 (55 %)</td>
<td>22 (81 %)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145±32.5</td>
<td>148±32.7</td>
<td>136±32.0</td>
<td>0.106</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>84.1±21.9</td>
<td>86.8±22.3</td>
<td>77.0±21.6</td>
<td>0.046</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>40 (40 %)</td>
<td>29 (39 %)</td>
<td>11 (41 %)</td>
<td>0.888</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>40 (40 %)</td>
<td>30 (41 %)</td>
<td>10 (37 %)</td>
<td>0.713</td>
</tr>
<tr>
<td>VAS score (0-10)</td>
<td>6.2±2.6</td>
<td>6.1±2.7</td>
<td>6.4±2.5</td>
<td>0.034</td>
</tr>
<tr>
<td>Rales on auscultation</td>
<td>30 (30 %)</td>
<td>24 (32 %)</td>
<td>6 (22 %)</td>
<td>0.320</td>
</tr>
</tbody>
</table>
Obstruction on auscultation 18 (18 %) 13 (18 %) 5 (19 %) 0.912
Respiratory rate (/min) 23.0±5.9) 23.1±5.8) 22.9±6.1 0.870

Echo parameters
Ejection fraction (%) 42.3±16.5) 42.0±17.0) 43.2±16.0 0.761
E/e’ 20.6±4.2) 20.8±3.7 20.3±4.7 0.595
e’ 5.69±1.58) 5.78±1.52) 5.43±1.66 0.328
Significant valve disease 58 (57 %) 43 (58 %) 15 (56 %) 0.818
Estimated PaPs (mmHg) 67.4±18.9) 64.9±18.3) 73.3±19.5 0.125
IVC index (1-5) 3.19±0.63) 3.14±0.63) 3.33±0.62 0.161
RV dysfunction 28 (28 %) 20 (27 %) 8 (30 %) 0.796

Laboratory
Median BNP (ng/l) 715 (365-1676) 679 (346-1200) 1342 (568-2365) 0.015
Mean eGFR (ml/min/1.73m²) 56.3±25.5 60.8±25.1) 44.0±25.8 0.003
Mean hemoglobin (g/l) 120.0±20.7) 121.1±22.7) 117.6±17.7 0.469

Values are expressed as mean +/- standard deviation (SD) except for BNP expressed as median (25th-75th interquartile percentile). Categorical variables are expressed as percentage of cases. HF, heart failure; BP, blood pressure; VAS, visual analog scale; EF, ejection fraction; RV, right ventricle; PaPs, systolic pulmonary artery pressure; IVC, inferior vena cava; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate;

Comparing the baseline characteristics of these two groups, non-survivors had significantly less de-novo HF and were significantly older than survivors. Non-survivors also seemed to present with more symptoms and a slower heart rate on presentation and had a higher BNP and a lower eGFR on presentation.

During treatment course, survivors presented with a larger decline in symptoms, systolic blood pressure and BNP, and also presented a trend towards a larger decline in bilateral cardiac filling pressures and a trend towards a larger decrease in eGFR. On the day of discharge, almost all congestion parameters except E/e’ were significantly more improved among survivors, despite a shorter length of hospitalization among survivors. Interestingly, despite showing a seemingly larger worsening of eGFR during treatment, the discharge eGFR was still better among survivors, due to the better value on admission. Of note, part of the larger decline in systolic arterial blood pressure during treatment among survivors, was also due to the non-significantly higher systolic blood pressure upon presentation. Thus, AHF
patients presenting with higher systolic arterial blood pressure on admission and getting it lowered during hospitalization did better in terms of post-discharge prognosis in this study.

Regarding the primary focus in this study, i.e. post-discharge prognosis, eGFR on presentation, cumulative fluid loss, IVCi on discharge and symptomatic status on discharge were the only independently significant predictors of post-discharge 6-month mortality on multivariate analysis, whereas age, eGFR on presentation, and IVCi on discharge were the only independently significant predictors of the combined endpoint of 6-month all-cause mortality or AHF-related re-hospitalization. Thus, comparing a wide spectrum of congestion parameters, including E/e’, IVCi, BNP, symptoms, cumulative fluid loss and decline in renal function, IVC index on the day of discharge (although not as change during hospitalization course) was the only treatment-related congestion parameter predicting both endpoints independently on multivariable analysis as can be seen in the Table here below:

Table 3 a-b. Cox regression analysis of effects of baseline and treatment related parameters on prognosis. Parameters are analyzed as absolute changes during hospitalization course as well as discharge values

<table>
<thead>
<tr>
<th>Six-month all-cause mortality</th>
<th>Univariate analysis</th>
<th>Multi-variable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.02-1.10</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.19</td>
<td>0.56-2.53</td>
</tr>
<tr>
<td>Left ventricular EF (%)</td>
<td>0.99</td>
<td>0.97-1.02</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>1.10</td>
<td>0.52-2.35</td>
</tr>
<tr>
<td>Significant valve disease</td>
<td>0.82</td>
<td>0.41-1.66</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.05</td>
<td>0.00-5.71</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.06</td>
<td>0.49-2.32</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>0.98</td>
<td>0.96-0.99</td>
</tr>
<tr>
<td>Initial SBP (mmHg)</td>
<td>0.99</td>
<td>0.97-1.00</td>
</tr>
<tr>
<td>Initial BNP/100 (ng/l)</td>
<td>1.05</td>
<td>1.03-1.07</td>
</tr>
<tr>
<td>Initial eGFR (ml/min)</td>
<td>0.98</td>
<td>0.96-0.99</td>
</tr>
<tr>
<td>Initial E/e’</td>
<td>0.98</td>
<td>0.90-1.07</td>
</tr>
<tr>
<td>Initial IVC index</td>
<td>1.54</td>
<td>0.82-2.86</td>
</tr>
</tbody>
</table>
Changes during treatment

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multi-variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in eGFR (ml/min)</td>
<td>0.98 0.95-1.01 0.134</td>
<td></td>
</tr>
<tr>
<td>Decline in BNP/100 (ng/l)</td>
<td>1.05 0.99-1.11 0.123</td>
<td></td>
</tr>
<tr>
<td>Decline in E/e`</td>
<td>0.96 0.90-1.04 0.333</td>
<td></td>
</tr>
<tr>
<td>Decline in IVC index</td>
<td>0.95 0.88-1.02 0.136</td>
<td></td>
</tr>
<tr>
<td>Resolution of congestion (LUS)</td>
<td>0.36 0.16-0.70 <strong>0.013</strong></td>
<td></td>
</tr>
<tr>
<td>Cumulative fluid loss (liters)</td>
<td>0.75 0.65-0.88 &lt;0.001 0.83 0.71-0.95 <strong>0.008</strong></td>
<td></td>
</tr>
</tbody>
</table>

On discharge

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multi-variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final E/e`</td>
<td>1.01 0.95-1.08 0.667</td>
<td></td>
</tr>
<tr>
<td>Final IVC index</td>
<td>1.77 1.10-2.87 <strong>0.020</strong> 1.74 1.01-3.00 <strong>0.046</strong></td>
<td></td>
</tr>
<tr>
<td>E/e`&lt;15</td>
<td>0.93 0.55-1.92 0.843</td>
<td></td>
</tr>
<tr>
<td>Final BNP/100 (ng/l)</td>
<td>1.05 1.03-1.07 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.25 0.12-0.54 &lt;0.001 0.249 0.11-0.55 <strong>0.001</strong></td>
<td></td>
</tr>
</tbody>
</table>

Six-month combined all-cause mortality or re-hospitalization for AHF

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Multi-variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 1.01-1.07 <strong>0.023</strong></td>
<td>1.03 1.00-1.06 <strong>0.04</strong></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.08 0.62-1.87 0.778</td>
<td></td>
</tr>
<tr>
<td>Left ventricular EF (%)</td>
<td>0.99 0.98-1.01 0.818</td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>1.00 0.57-1.78 0.990</td>
<td></td>
</tr>
<tr>
<td>Significant valve disease</td>
<td>1.51 0.85-2.66 0.157</td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.58 0.08-4.21 0.591</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.28 0.73-2.22 0.389</td>
<td></td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>0.98 0.97-1.00 <strong>0.018</strong></td>
<td></td>
</tr>
<tr>
<td>Initial SBP (mmHg)</td>
<td>0.99 0.98-1.00 <strong>0.042</strong></td>
<td></td>
</tr>
<tr>
<td>Initial BNP/100 (ng/l)</td>
<td>1.03 1.00-1.05 <strong>0.012</strong></td>
<td></td>
</tr>
<tr>
<td>Initial eGFR (ml/min)</td>
<td>0.98 0.97-0.99 <strong>0.001</strong> 0.98 0.97-0.99 <strong>0.03</strong></td>
<td></td>
</tr>
<tr>
<td>Initial E/e`</td>
<td>0.98 0.92-1.04 0.510</td>
<td></td>
</tr>
<tr>
<td>Initial IVC index</td>
<td>1.14 0.73-1.79 0.571</td>
<td></td>
</tr>
</tbody>
</table>

Changes during treatment

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multi-variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in eGFR (ml/min)</td>
<td>0.98 0.96-1.00 <strong>0.031</strong></td>
<td></td>
</tr>
<tr>
<td>Decline in BNP/100 (ng/l)</td>
<td>1.02 0.97-1.04 0.288</td>
<td></td>
</tr>
<tr>
<td>Decline in E/e`</td>
<td>0.95 0.91-1.02 0.151</td>
<td></td>
</tr>
<tr>
<td>Decline in IVC index</td>
<td>0.71 0.52-0.98 <strong>0.036</strong></td>
<td></td>
</tr>
<tr>
<td>Resolution of congestion (LUS)</td>
<td>0.60 0.35-1.04 <strong>0.070</strong></td>
<td></td>
</tr>
<tr>
<td>Cumulative fluid loss (liters)</td>
<td>0.91 0.81-1.02 0.107</td>
<td></td>
</tr>
</tbody>
</table>

On discharge

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multi-variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final E/e`</td>
<td>1.02 0.98-1.07 0.507</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All</th>
<th>Treatment-arm</th>
<th>Standard care arm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.0 (SD 10.6)</td>
<td>75.3 (SD 9.65)</td>
<td>76.2 (SD 10.8)</td>
<td>0.736</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td>Male gender</td>
<td>50.0 %</td>
<td>50.0 %</td>
<td>50.0 %</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.0 %</td>
<td>50.0 %</td>
<td>44.0 %</td>
<td>0.622</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85.8 %</td>
<td>85.0 %</td>
<td>90.0 %</td>
<td>0.434</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>45.8 %</td>
<td>35.0 %</td>
<td>48.0 %</td>
<td>0.287</td>
</tr>
<tr>
<td>Previous HF</td>
<td>60.8 %</td>
<td>55.0 %</td>
<td>62.0 %</td>
<td>0.558</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2.5 %</td>
<td>5.0 %</td>
<td>2.0 %</td>
<td>0.433</td>
</tr>
</tbody>
</table>

**Clinical parameters**

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Male gender</th>
<th>50.0 %</th>
<th>50.0 %</th>
<th>50.0 %</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145 (SD 30.7)</td>
<td>144 (SD 18.6)</td>
<td>145 (SD 32.5)</td>
<td>0.892</td>
<td></td>
</tr>
<tr>
<td>Pulse rate (/min)</td>
<td>84.5 (SD 22.6)</td>
<td>86.2 (SD 26.8)</td>
<td>84.1 (SD 21.9)</td>
<td>0.723</td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>47.5 %</td>
<td>35.0 %</td>
<td>50.0 %</td>
<td>0.220</td>
<td></td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>38.3 %</td>
<td>30.0 %</td>
<td>40.0 %</td>
<td>0.383</td>
<td></td>
</tr>
<tr>
<td>Dyspnea VAS score (0-10)</td>
<td>6.15 (SD 2.53)</td>
<td>5.89 (SD 2.02)</td>
<td>6.20 (SD 2.62)</td>
<td>0.633</td>
<td></td>
</tr>
<tr>
<td>Rales on auscultation</td>
<td>30.0 %</td>
<td>30.0 %</td>
<td>30.0 %</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Obstruction on auscultation</td>
<td>20.0 %</td>
<td>10.0 %</td>
<td>18.0 %</td>
<td>0.381</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>22.6 (SD 5.67)</td>
<td>20.7 (SD 3.61)</td>
<td>23.0 (SD 5.93)</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Respiratory support</td>
<td>39.2 %</td>
<td>35.0 %</td>
<td>40.0 %</td>
<td>0.796</td>
<td></td>
</tr>
</tbody>
</table>

**Echo parameters**

<table>
<thead>
<tr>
<th>Echo parameter</th>
<th>Male gender</th>
<th>42.34</th>
<th>42.6 (SD 14.2)</th>
<th>42.3 (SD 16.5)</th>
<th>0.945</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular EF (%)</td>
<td>42.64</td>
<td>42.8 (SD 14.2)</td>
<td>42.6 (SD 16.5)</td>
<td>0.945</td>
<td></td>
</tr>
<tr>
<td>E/e`</td>
<td>20.67</td>
<td>20.8 (SD 4.05)</td>
<td>20.6 (SD 4.21)</td>
<td>0.859</td>
<td></td>
</tr>
<tr>
<td>e`</td>
<td>5.79</td>
<td>6.29 (SD 1.25)</td>
<td>5.69 (SD 1.58)</td>
<td>0.113</td>
<td></td>
</tr>
<tr>
<td>Significant valve disease</td>
<td>56.7 %</td>
<td>55.0 %</td>
<td>57.0 %</td>
<td>0.869</td>
<td></td>
</tr>
<tr>
<td>Estimated SPaP (mmHg)</td>
<td>66.7 (SD 18.7)</td>
<td>64.1 (SD 17.9)</td>
<td>67.4 (SD 18.9)</td>
<td>0.558</td>
<td></td>
</tr>
<tr>
<td>IVCi</td>
<td>3.28 (SD 0.65)</td>
<td>3.74 (SD 0.57)</td>
<td>3.20 (SD 0.63)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>30.0 %</td>
<td>45.0 %</td>
<td>27.0 %</td>
<td>0.109</td>
<td></td>
</tr>
</tbody>
</table>

**Laboratory**

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Male gender</th>
<th>696 (342-1497)</th>
<th>543(296-900)</th>
<th>715 (365-1676)</th>
<th>0.072</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (ng/l)</td>
<td>57.2 (SD 25.3)</td>
<td>61.7 (SD 24.2)</td>
<td>56.3 (SD 25.5)</td>
<td>0.391</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>120 (SD 20.7)</td>
<td>119 (SD 20.1)</td>
<td>120 (SD 20.9)</td>
<td>0.822</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean +/- standard deviation (SD) except for BNP expressed as median (25th-75th interquartile percentile). Categorical variables are expressed as number of cases (%). HF, heart failure; BP, blood pressure; VAS, visual analog scale; EF, ejection fraction; E/e`, medial E to e` ratio; RV, right ventricle; eSpaP, estimated systolic pulmonary artery pressure; IVCi, inferior vena cava index (scale 1-5); BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate;

When looking at the decline in all congestion parameters, including bilateral filling pressures, BNP, symptoms, pulmonary congestion on LUS and cumulative fluid loss, as well as these parameters on discharge, a uniform improvement in these parameters, as well as better values on the day of discharge was seen regarding all these parameters, as is presented in the table here below:
Table 5. Treatment related parameters in the treatment arm compared to the standard care arm

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm n=20</th>
<th>Standard care arm N=100</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in E/e'</td>
<td>6.48 (SD 2.92)</td>
<td>2.62 (SD 4.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Decrease in IVCi (1-5)</td>
<td>1.79 (SD 1.02)</td>
<td>0.39 (SD 0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% decrease in BNP (ng/l)</td>
<td>35.9 (SD 26.3)</td>
<td>16.6 (SD 61.1)</td>
<td>0.029</td>
</tr>
<tr>
<td>LOH (days)</td>
<td>3.74 (SD 2.02)</td>
<td>6.85 (SD 4.22)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cumulative fluid loss (ml)</td>
<td>5447 (SD 5364)</td>
<td>3072 (SD 3059)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease in eGFR (ml/min/1.73m²)</td>
<td>3.47 (SD 8.64)</td>
<td>4.41 (SD 13.8)</td>
<td>0.778</td>
</tr>
<tr>
<td><strong>On the day of discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final E/e'</td>
<td>14.4 (SD 3.14)</td>
<td>18.0 (SD 5.63)</td>
<td>0.007</td>
</tr>
<tr>
<td>Final IVCi (1-5)</td>
<td>1.21 (SD 0.91)</td>
<td>1.82 (SD 0.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>Final BNP (ng/l)</td>
<td>249 (172-408)</td>
<td>426 (242-1015)</td>
<td>0.011</td>
</tr>
<tr>
<td>Pulmonary decongested on LUS</td>
<td>80 %</td>
<td>53 %</td>
<td>0.039</td>
</tr>
<tr>
<td>E/e' &lt;15</td>
<td>63 %</td>
<td>35 %</td>
<td>0.020</td>
</tr>
<tr>
<td>Pulmonary decongestion or E/e' &lt;15</td>
<td>95 %</td>
<td>63 %</td>
<td>0.007</td>
</tr>
<tr>
<td>Asympotmatic at discharge</td>
<td>95 %</td>
<td>72 %</td>
<td>0.036</td>
</tr>
<tr>
<td>Final eGFR (ml/min/1.73m²)</td>
<td>58.3 (SD 24.2)</td>
<td>51.9 (SD 23.8)</td>
<td>0.287</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>15.8 %</td>
<td>20.8 %</td>
<td>0.617</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>0 %</td>
<td>4.0 %</td>
<td>0.378</td>
</tr>
</tbody>
</table>

Values are expressed as mean +/- standard deviation (SD) except for BNP expressed as median (25th-75th interquartile percentile). Categorical variables are expressed as number of cases (%). E/e’, medial E to e’ ratio; IVCi, inferior vena cava index (scale 1-5); BNP, brain natriuretic peptide; LOH, length of hospitalization; eGFR, estimated glomerular filtration rate; LUS, lung ultrasound

Thus, in this study, patients in the treatment arm experienced greater decongestion as defined by all objective congestion parameters, and also presented a trend towards less adverse events and a smaller decrease in eGFR, despite a significantly, almost 50 % shorter mean length of hospitalization. The treatment group also did not experience any adverse events related with hypoperfusion, and CaTUS-guided treatment thus seemed safe. The treatment group also experienced a significantly lower event rate regarding the combined endpoint of 6-
month all-cause mortality or re-hospitalization for AHF, with this endpoint mainly driven by fewer re-hospitalizations.

6. Discussion

This compilation of four studies on the use of cardiothoracic focused ultrasound in AHF concludes that the CaTUS protocol seems useful for diagnosing AHF, monitoring AHF treatment and potentially also for guiding treatment. Regarding diagnosis, focused Echo and LUS both provided excellent diagnostic accuracy already by themselves, but combining them still slightly enhanced diagnostic accuracy. Regarding monitoring, it seems like Echo-derived left-sided cardiac filling pressures may be able to distinguish non-responders from treatment-responders already during the first 12 hours of treatment, while decongestion on LUS was seen slightly slower. Right-sided echo-indices, in turn, were clearly slower markers of treatment response, but seemed to be prognostically relevant prior to discharge, as IVC index on the day of discharge was the only treatment-related congestion parameter predicting 6-month survival regarding both all-cause mortality as well as the composite endpoint including all-cause mortality and AHF-related re-hospitalization. CaTUS also seems feasible and safe for guiding treatment, and the results from our small, unevenly distributed pilot study - population indicate that ultrasound-guided AHF treatment might be associated with greater decongestion resulting in reduced re-hospitalization rates.

6.1. Diagnosis and use of cardiac and lung ultrasound in dyspnea and AHF

In our first study on AHF diagnosis, the CaTUS protocol provided a high diagnostic accuracy for diagnosing AHF, which was higher than in most of the other studies on somewhat similar protocols 78,79,80,81,82,83. This was, however, to our best knowledge the first study so far to include a uniform measure of left-sided cardiac filling pressures, i.e. the E/e⁻ ratio, also measured and feasible in patients with atrial fibrillation, which was almost as common as sinus rhythm in our population. As the methodology for estimating left-sided filling pressures, especially in patients with atrial fibrillation, was unclear in most of the previous studies on the subject, this might have influenced results in those studies.
As LUS already provided an > 90 % sensitivity and specificity for diagnosing AHF in the meta-analysis 72, combining LUS with E/e’ could be expected to result in even better accuracy for diagnosing AHF, which also was the case in our study. As 8 out of 54 patients with AHF presented with a normal (grade 1) IVC, probably representing more “vascular” phenotype of AHF, i.e. a phenotype with more vasoconstriction and less fluid load, this weakened the sensitivity of the IVC as part of the diagnostic protocol. Hence, our study implies that although a plethoric IVC supports the diagnosis of AHF with reasonable specificity, the sensitivity of a narrow IVC is not sufficient to exclude AHF, at least not in hypertensive patients.

Since the study protocol was written, new guidelines have come out on evaluating left-sided cardiac filling pressures with Echo by Nagueh et al 8. In the new guideline, the most significant refinement is the recommendation to start with the E/A-ratio instead of the E/e’-ratio also in patients with preserved EF. Naturally, the E/A-ratio can only be calculated in patients with sinus rhythm. In patients with atrial fibrillation, however, the new guideline is slightly more un-determined, recommending a mixture of indices, including the septal E/e’ which we used as well, for evaluating left-sided filling pressures on Echo. Although the new guideline does provide improved and clarified methodology regarding patients in sinus rhythm as compared to the older guidelines, they do not define the optimal order or number of parameters to be used in combination for evaluating filling pressures in atrial fibrillation. We wanted a simple protocol using only one parameter, and taking into account all the evidence and guidelines existing on evaluating filling pressures both in patients with or without sinus rhythm, regardless of LVEF, we came to the conclusion that E/e’ seemed like the most reasonable single parameter. Therefore, evaluation of left-sided filling pressures on Echo was based solely on E/e’ in our study in all patients, regardless of their rhythm at presentation.

An interesting fact regarding studies on E/e’ has been the heterogeneity of results, of which some are very promising 133, 134, and other, such as the recent EURO-FILLING-study, rather disappointing 135, 136. Within the heterogeneity of these studies, however, there seems to be a trend for E/e’ to work better in patients with preserved LVEF, with less dyssynchrony in terms of bundle branch block and pacing, as well as in patients without significant mitral valve disease. Regarding the mitral valve, mitral stenosis and significant calcification naturally
make E/e’ useless as soon as the mitral valve starts to develop a gradient or the annular motion is restricted.

Due to the varying results in studies on the E/e’- ratio, we also retrospectively reviewed all 30 patients with a medial E/e’ >15 and in sinus rhythm, and re-evaluated whether these patients would have elevated left-sided filling pressures according to the newer guidelines. Of these 30 patients, 29 had elevated left-sided filling pressures on Echo according to this recent guideline by Nagueh et al., whereas one patient had intermediate left-sided filling pressures. Hence, medial E/e’ in our population correlated well with filling pressures evaluated according to the recent guidelines in patients with sinus rhythm. Furthermore, 29 out of these 30 patients also had structural heart disease as is determined in the guidelines on conventional echo, meaning that an E/e’ > 15 seems like a specific finding for structural heart disease regardless of EF, as is also implied for patients with a preserved EF in the guideline by Nagueh et al. In our population, the one patient with an E/e’ >15 without structural heart disease was suffering from pre-eclampsia with massive fluid load, anuria, renal failure and hypertensive crisis, thus seemingly resulting in purely “vascular” elevated cardiac filling pressures, probably explaining the elevated E/e’. E/e’ is, however, theoretically an imperfect marker of myocardial disease per se, since the E-wave as a nominator in the equation, mainly is a measure of left-sided cardiac filling pressures, whereas the tissue doppler e’-wave, in contrast, is considered a relatively filling pressure-independent marker of relaxation, which can be considered more a measure of true diastolic function per definition. Moreover, e’ as a marker of impaired relaxation also seemed like an accurate tool for screening structural heart disease as defined in our study, again regardless of EF.

The rather varying evidence in studies on E/e’ has led to the diastolic function - guidelines going in a more comprehensive, multi-parametric direction, which has resulted in improved accuracy. Nevertheless, LSFP is still considered a very essential and fundamental parameter in HF and AHF patients. As invasive LSFP-evaluation using pulmonary artery catheters is diminishing and the use of Echo increasing, echocardiographic evaluation of diastolic function and filling pressures is becoming ever more important. In our study, E/e’ indeed seemed to work well for evaluating left-sided filling pressures, while E/e’, and especially e’ also seemed to work well for identifying and screening structural heart disease.
For estimating right-sided filling pressures, echocardiographic evaluation of the IVC (IVC index = IVCi) has gained a firm position in the guidelines although its correlation with central venous pressures has been modest. The IVC has also been shown to react dynamically to fluid resuscitation and to predict intravascular, as well as overall volume status. Central venous pressure (CVP), in turn, is considered a rather poor predictor of fluid status and volume-responsiveness and might thus have been a suboptimal golden standard for evaluating IVC index. It might also be that the IVC index actually is an even better measure of intravascular fluid status than a static CVP measurement, which often is helpful at both ends of the spectrum regarding severe hypo- or hypervolemia, but is not that accurate in the middle, i.e. when close to normovolemia. The CVP as a surrogate for right atrial pressure, is physiologically considered as a variable describing distribution of blood between the venous and the arterial capacitor spaces within the systemic blood circulation rather than a “backwards force” limiting venous return and is strongly affected by cardiac output per se as well. The venous recoil force, driving venous blood into the right atrium, is in turn dependent also on the capacitor space of the circulation. Under normal conditions, this capacitor space is rather spacious and flaccid, and hence, most of the blood volume is lying dependent within the circulation without causing pressure towards the right atrium. Thus, as CVP per definition is a pressure-measurement, it is clear that besides intravascular volume, its value depends also on the capacitance of the capacitor space, i.e. the cardiovascular chambers and vessels. The IVC index, in turn, readily takes into account central venous vessel volume as diameter reflects volume with an exponential correlation. As the effect of increased blood volume on CVP is dependent on vascular capacitance and venous recoil, while IVCi readily estimates volume of the central venous vessels, the IVC index probably therefore is a better measure of fluid status than CVP, which is considered to reflect blood volume better at the extreme ends of volemic status, where vascular capacitance also reaches its extremes (severe hypo- or hyper-volemia). Moreover, vasoconstriction might further alter vascular capacitance, also amplifying the discrepancy between IVCi and CVP. This could theoretically also result in a narrow IVC on Echo in AHF, despite elevated CVP and some degree of fluid overload, a phenomenon sometimes described in the presence of “vascular” AHF, and also seen in our first study on diagnosing AHF where cardiothoracic ultrasound performed better without the IVC.
Nevertheless, for diagnosing AHF, IVC index as assessed by a hand-held device has also worked well also alone \(^{79}\), and the IVC index in combination with B-lines on LUS also presented a good PPV in our first study included in this thesis. Hence, since IVC index and LUS are both rapid to perform, this dual combination might be useful, when positive for the ED clinician, even without simultaneous evaluation of left-sided filling pressures.

Although the main focus often is on B-lines when diagnosing AHF with LUS, pleural fluid is also often seen in AHF and should not be overlooked. When pleural fluid is present, especially bilaterally, it strongly supports the diagnosis of AHF, and often is a sign of more advanced or long-standing pulmonary congestion \(^ {88}\). In our study, bilateral B-lines showed a very good sensitivity for diagnosing AHF, but were present also in 18.8 \% of non-AHF patients, thus reducing their specificity slightly in this study, a finding that seems logical due to the fact that B-lines might express also non-cardiac EVLW. However, in the meta-analysis on B-lines for diagnosing AHF, this type of reduction in specificity was not seen \(^ {72}\). As expected, the opposite was true regarding bilateral pleural fluid, which presented a high specificity for diagnosing AHF alone in our study, a finding also reported previously \(^ {97}\). Thus, the rationale for including pleural fluid within the CaTUS protocol as a criterion for pulmonary congestion seemed sensible, and this also resulted in a high sensitivity of the protocol, despite including the dual, conditional combination LUS and Echo, of which both were required for the protocol to be positive for AHF. The specificity of E/e’ or LUS in combination, in turn, was expectedly better than either one alone, since the protocol required both LUS and E/e’ to be serially positive in order for the whole protocol to be positive. Bilateral B-lines alone on LUS in case of normal filling pressures is considered a slightly unspecific sign for AHF, as it might be due to pulmonary disease alone \(^ {40}\), whereas elevated filling pressures without pulmonary congestion, in turn, is a common scenario in outpatients with more advanced baseline cardiac disease and HF \(^ {149}\). As addition of the IVC into the protocol led to a decreased accuracy and sensitivity due to a small hypertensive AHF-subgroup within our population presenting with a narrow IVC, E/e’ in combination with LUS, including B-lines and pleural fluid, seemed like the optimal diagnostic combination regarding diagnosis of AHF.

Regarding differential diagnostics, CaTUS provided diagnostic clues in terms of isolated B-lines and visual right ventricular load in a substantial proportion of pulmonary embolisms and pneumonias, and also revealed a few cardiothoracic emergencies requiring immediate
treatment. Furthermore, all patients with dyspnea of unknown origin and a normal CaTUS protocol were discharged home from the ED without hospitalization, suggesting that a protocol like CaTUS might help to decide which patients can be discharged straight home from the ED without requiring hospitalization.

Finally, it is noteworthy that ultrasound, including Echo, is a tool that is clearly enhancing diagnostics in the ED, probably improving patient prognosis and streamlining ED function as well. Echo has gained a strong ground for diagnosing AHF, as well as for yielding with differential diagnostics, and further helps to phenotype the patients. Echo is also a very constitutional part of diagnosing the syndrome of HF, and in identifying the underlying cardiac disease as a more precise diagnosis causing the syndrome. Thus, in the presence of equipment and knowledge, performing Echo rather sooner than later is likely to benefit both patients and treating physicians. Taking into account the excellent performance of LUS alone in diagnosing AHF, it is likely that our protocol, combining echocardiographic signs of elevated filling pressures with LUS refined with evaluation for pleural fluid in severely dyspneic patients with structural heart disease, might be close to the definition of AHF per se. Considering the absence of validated golden standard diagnostic criteria for AHF and the constitutional position of ultrasound for diagnosing the syndrome, it is clear that defining the optimal diagnostic golden standard in a setting like ours is somewhat cumbersome, since board reviews as well as other golden standard methods might theoretically be “worse” than the method studied. Nevertheless, in our study, the methods seemed to agree very well, and cardiothoracic ultrasound seemed beneficial for diagnosing AHF as well as many other causes for dyspnea in the ED.

6.2. Monitoring decongestive treatment

The reasons behind the difficulty of achieving adequate decongestion in AHF are poorly understood, but could be related to unfavorable sodium- and fluid balance during hospitalizations, i.e. too little use of diuretics in relation to the total sodium and water load during hospitalizations, perhaps due to fear of renal failure and hypo-perfusion due to over-diuresing patients. For decongestive treatment, diuretics are considered the most relevant group of drugs, as most patients are considered to be fluid and sodium overloaded. Since diuretics work by excreting sodium and fluid via the kidneys, and AHF
patients very often present with co-existing renal failure, this makes the issue of decongestion perhaps even more a renal, than a cardiac issue, which, in the presence of both renal and cardiac failure, is often named the cardio-renal syndrome\textsuperscript{155}. Thus, it is not surprising that major prognostic factors among AHF patients include renal function and diuretic responsiveness\textsuperscript{153,156,157}. Hyponatremia as a marker of increased water gain, which is more difficult to excrete with diuretics, is also a marker of poor prognosis\textsuperscript{158,159}.

The relation between renal function and diuretic responsiveness, i.e. the ability to diurese, however, is not that simple. Although baseline renal function is a clear prognostic marker in AHF patients, renal function also tends to change during decongestive treatment\textsuperscript{160}. The interaction of diuresis and renal function has been poorly understood until lately, and diuretics have even been considered renal-toxic. However, landmark studies by Mullens et al.\textsuperscript{128} and Valente and Testani et al.\textsuperscript{153,156}, have shown fluid overload itself to be detrimental to kidney function, and that a decline in eGFR might not matter too much at all in case of adequate decongestion, a situation consequently named \textquotedblleft pseudo-acute kidney injury\textquotedblright\textsuperscript{155,161}. The worst outcomes in turn have been seen in the case of persistent congestion in combination with simultaneously declining renal function and poor diuretic response, a very classic form of the cardio-renal syndrome, probably mainly associated with systemic venous congestion and high CVP\textsuperscript{161}. Putting all this together, our primary goal should probably be to decongest our patients while accepting some degree of decline in renal function, in order to improve our patient outcomes. This seemed to be the case also in our study, where a decline in eGFR did not associate with poorer outcomes, but rather with adequate decongestion. Considering the way diuretics work, doses of loop diuretics should probably be increased aggressively enough, due to the steep dose-response curve, and in case of diuretic resistance, combination with thiazides and/or mineralocorticoid receptor antagonists should be attempted, without forgetting the option of ultrafiltration in case of non-responsiveness\textsuperscript{1,2}.

6.3. Early treatment monitoring

According to guidelines and common clinical practice, the treatment of AHF is often divided into 1) acute first-line treatment during the first hours/day, mainly involving vasodilators and diuretics and 2) continuous decongestive treatment preparing the patient for discharge,
mainly involving diuretics and 3) initiation/optimization of prognosis-enhancing anti-adrenergic treatment (ACE-inhibitors, B-blockers, devices etc.) \textsuperscript{1,2}.

Although hospitalizations for AHF mostly last several days\textsuperscript{4}, increasing amount of attention has lately been drawn towards rapid initiation of treatment during the first hours, since this is thought to be associated with improved prognosis \textsuperscript{1,5}. Costly and lengthy hospitalizations are also of economic concern \textsuperscript{14}. First-line treatment has been shown to provide a rapid decrease in cardiac filling pressures and symptoms \textsuperscript{162,163}. This hemodynamic effect seems to be faster with vasodilators than that achieved with diuretics \textsuperscript{162,164}. Hence, vasodilators are considered the perhaps most important drug group for very early initiation of decongestive treatment, although they have not been shown to improve prognosis \textsuperscript{165}.

In the vast majority presenting with adequate perfusion (“wet and warm”) \textsuperscript{1}, decongestive treatment during the first hours of hospitalization mostly consists of vasodilators and diuretics \textsuperscript{166}. Prompt, early furosemide for AHF in turn has been associated with improved prognosis in a registry-based study \textsuperscript{115}, although randomized trials on the subject are lacking. Hence, administering loop diuretics alongside vasodilators in the early phase of treatment is recommended in the guidelines \textsuperscript{1,2} Aggressive dosing of loop diuretics has moreover been proven to enhance diuresis and relieve symptoms more efficiently as compared to a more conservative strategy, as was proven in the only randomized controlled landmark study on the subject \textsuperscript{66}, although differences remained small in this study.

In our second study, we investigated the CaTUS protocol for monitoring early treatment - response in terms of cardiac filling pressures and pulmonary congestion with a special emphasis on the first 12 hours of treatment. The aim was to evaluate which signs of congestion improve first among treatment-responsive patients after initiation of AHF treatment. We further hypothesized that identifying non-responders early might be important since it could allow intensification of decongestive treatment early on. We further hypothesized that an early treatment response could be associated with a favorable treatment course.
In this study, early improvement in cardiac filling pressures could be seen already during the first 12 hours (Figure 1), which is line with previous studies\textsuperscript{162,163}. More precisely, left-sided cardiac filling pressures (E/e’) declined substantially already during the first 12 hours of treatment in treatment-responders, followed closely by resolution of pulmonary congestion, while right-sided filling pressures in terms of the IVC index reacted slower. These patients were also very likely to continue on a favorable treatment course, resulting in substantial decrease in cardiac filling pressures, resolution of pulmonary congestion and excellent post-discharge prognosis.

Among non-responders, who per definition remained pulmonary congested until discharge, there was little improvement at all in cardiac filling pressures during the entire hospitalization, including the first 12 hours of treatment. These patients were discharged with pulmonary congestion and displayed a very poor post-discharge prognosis. Symptoms, in turn, declined substantially in both groups, and hence seem unreliable for determining treatment-responsiveness objectively, since this finding suggests that patients might become asymptomatic despite prognostically ominous pulmonary congestion.

When looking closer into the initial decline in E/e’ during the first 12 hours in our study, this decline interestingly seemed to be a result of both a decreasing E-wave and an increasing e’-wave. As e’ is considered a rather load-independent marker of relaxation, as was discussed above, it seemed like initial therapy also improved diastolic relaxation of the heart besides lowering left-sided filling pressures. Thus, in our study, E/e’ seemed to be a better marker than E/A-ratio or E-wave alone for estimating treatment-responsiveness early on. Since this was the first study on serial Echo-derived measurements of left-sided filling pressures during AHF therapy to our best knowledge, we cannot compare our findings with previous studies.

Finally, when comparing the effect of different congestion parameters on post-discharge prognosis, resolution of pulmonary congestion seemed to be the most relevant congestion parameter on multivariable analysis, although our 60-patient population in this study might have been a little small for performing multivariable analysis, and the third study is better suited for evaluating this topic.
6.4. Getting ready for discharge

After AHF patients have gone through initial stabilization and treatment initiation, the focus turns towards achieving adequate decongestion for the patient to be discharged. As most patients are fluid over-loaded, this is mainly strived for using diuretic therapy. Nevertheless, multiple studies have proven this to be difficult, as a substantial proportion of patients today are discharged with residual congestion evaluated by either clinical examination or pulmonary imaging, and these patients display a poor post-discharge prognosis with high mortality and re-admission rates. This was the case in our population as well, where patients discharged with residual pulmonary congestion displayed an over 50% rate of 6-month death or re-hospitalization for AHF.

How to optimally assess pre-discharge congestion is not clearly defined to date. In two landmark studies by Gargani et al. and Coiro et al., congestion on LUS prior to discharge was a strong predictor of post-discharge prognosis, clearly outperforming clinical examination. As IVC index and left-sided filling pressures on Echo also have predicted post-discharge prognosis, LUS and Echo seem helpful for evaluating whether patients are adequately decongested prior to discharge. As Echo-derived filling pressure - measurements also reflect filling pressures in real time, they would logically seem suitable also for monitoring decongestive treatment on a day-to-day basis.

In our third study, we used a larger sample of 100 patients and investigated which congestion parameters as markers of treatment success would have the largest impact on prognosis. This was also, to our best knowledge, only the second study to date combining two congestion parameters that have previously been shown to affect post-discharge prognosis, i.e. IVC index and pulmonary congestion on LUS, and the first study to include a more precise scaled measure of fluid status and right-sided cardiac filling pressures in terms of the 5-scale IVC index, used in this study. This was in contrast to our second study, which used only a 3-classed IVC index. Indeed, the 5-classed IVC index used in the third study measured on the day of discharge turned out to be the most relevant congestion parameter regarding both post-discharge end points, i.e. 6-month mortality rates or the combined end point of 6-month mortality or re-hospitalization for AHF on multivariate analysis. The 5-classed IVC index on
the day of discharge in this third study outperformed all other measured congestion parameters, including fluid balance, symptoms and even pulmonary congestion on LUS for predicting both post-discharge mortality and re-hospitalization for AHF. Thus, achieving a non-plethoric IVC, reflecting euvoelema, seemed like the prognostically most significant marker of adequate decongestion prior to discharge. This effect then also outperformed the prognostic value of LUS-derived pulmonary congestion on multivariable analysis, perhaps indicating a reactive IVC to represent a later stop on the way towards thorough decongestion. While the IVC index has been shown to have prognostic value at the end of a AHF hospitalization \(^{167}\), the only study, to our best knowledge, to compare LUS and IVC in the same analysis as predictors of post-discharge prognosis was the study in 2005 by Coiro et al \(^{98}\). In this study, IVC was simply studied based on a diameter-cutoff without classification based on respiratory variation also, and B-lines on LUS outperformed the IVC in this study, although the IVC also was significant regarding post-discharge prognosis on univariate analysis. Interestingly, symptom status at discharge was also a strong, independent predictor of post-discharge mortality, but not for the combined event including re-hospitalization. Why symptom status at discharge predicted all-cause mortality rather than re-hospitalization should probably be evaluated in further studies, but might have to do with possible other co-morbidities than AHF, causing dyspnea and negatively affecting mortality.

Another important notification in this study was that congestion parameters at discharge in general seemed more prognostically significant than relative changes during hospitalization. This seems to indicate that the day of discharge perhaps is an especially important time point for assessing whether the patient is ready to be discharged safely, and this evaluation should be done with ultrasound rather than by clinical examination alone.

We also sought to evaluate other prognostic measures during AHF treatment, and in line with previous studies on the subject \(^{156,157}\), a declining eGFR was associated with better prognosis on univariate analysis, and thus might represent more of a treatment effect following normalization of intra-vascular fluid status due to adequate decongestion rather than a feared adverse event. This effect also was eliminated on multivariable analysis, and responders presented a greater decline in eGFR in our second study, thus supporting the idea that a decline in eGFR mostly reflects adequate decongestion.
Regarding kinetics among congestion parameters, results were in line with the smaller second study with 60 patients; E/e‘ was the fastest reacting congestion parameter during the first 24 hours of treatment, followed thereafter by resolution of pulmonary congestion, whereas IVC index displayed a less steep and rather linear response curve. Natriuretic peptides, in turn, seemed less rather useless, as their kinetics did not follow the day-to-day kinetics of the other congestion parameters.

6.5. Guiding treatment

Finally, our fourth study tested CaTUS-guided therapy in a small pilot population of 20 patients, and compared the results with treatment results of those seen in the 100-patient follow-up population studied in the third study of our thesis.

AHF treatment today is mainly guided by clinical judgment supported by laboratory results. Due to the rather unsatisfactory treatment results in AHF, hemodynamic guidance of decongestive treatment has also raised some interest in the past. The ESCAPE trial in year 2005 studied whether additional treatment targets in terms of close-to-normal intra-cardiac filling pressures would add efficacy to standard in-hospital treatment in sick enough AHF patients to receive a pulmonary artery catheter (PAC). The study was negative, but as it was performed in an intensive care setting, many patients probably had CVP measurements, Echos and vigorous clinical monitoring performed, probably explaining the good treatment results seen also in the control group. The CHAMPION trial, in turn, was a positive randomized trial on treatment guidance in chronic HF to avoid hospitalization for AHF, using an implantable device for measuring pulmonary artery pressure as a surrogate for increased cardiac filling pressures and fluid overload. In this trial, prompt intensification of decongestive therapy, which consisted mainly of diuretics in this study, helped to reduce hospitalizations as a pre-specified endpoint in the intervention group.

In our fourth study, CaTUS-guided treatment resulted in significantly greater decongestion as measured by all congestion parameters, despite shorter hospitalizations and non-significantly less adverse events, without any significant differences in between the two groups in baseline parameters. Furthermore, the treatment arm displayed a significantly better 6-month post-discharge prognosis, mainly driven by lesser hospitalizations. This study of ours was to our
best knowledge the first study to date on serial ultrasound-guided decongestive therapy in AHF patients. The groups in this study, however, were in-balanced, and patients were enrolled in a sequential, non-randomized fashion. Nevertheless, this study was designed mainly to assess feasibility and safety of ultrasound-guided decongestive therapy.

The possible benefit of ultrasound-guided AHF therapy in comparison with conventional treatment would need to be tested in a properly sized and designed RCT. Possible benefits over PAC-guided therapy, as took place in the ESCAPE trial, includes absence of adverse events and feasibility outside the ICU. When compared to natriuretic peptide-guided therapy, which was tested in the recent, negative PRIMA II – trial 124, ultrasound poses the benefit of true real-time evaluation of congestion and filling pressures. Although the CHAMPION trial was an outpatient trial, it seemed to prove the concept that intensifying decongestive treatment in patients with elevated filling pressures might help to stop these patients from sliding into AHF. Thus, this concept, using medications already existing, might be beneficial also in AHF patients inside the hospital, and ultrasound might be an interesting modality capable of evaluating filling pressures and guiding treatment in a similar manner like the CARDIOMEMS device in the CHAMPION trial.

7. Summary and conclusion

An AHF patient typically starts his journey by getting hospitalized via an ED 1.2.7, were diagnosis of this syndrome is set and treatment initiated. Thereafter, treatment is further fine-tuned during hospitalization, before it is time to get the patient prepared for discharge. Focused cardiothoracic ultrasound of the heart and lungs seems useful at each step along this journey. Furthermore, ultrasound might also be useful for guiding decongestive treatment, although this issue will require further adequately sized randomized controlled trials.

In a patient presenting with dyspnea in the ED, focused ultrasound of the heart and lungs seemed helpful for diagnosing AHF. Moreover, although the prevalence of AHF among dyspneic patients in our ED was approximately 50 %, this type of an ultrasound protocol also seemed helpful for diagnosing various other serious conditions and diseases, causing dyspnea in the other half of dyspneic ED patients, having some other reason for dyspnea than AHF, such as pulmonary infection, pulmonary embolism or some kind of cardiothoracic emergency.
During the first hours of treatment in those diagnosed with AHF, ultrasound seemed helpful for monitoring whether patients were responding to filling pressure-lowering therapy. Since patients who did not display an early reduction in filling pressures had a much lower probability of getting decongested and a worse prognosis, identifying these non-responders early might be important by providing an early time window for identifying treatment. On the other hand, the high treatment success during hospitalization among early responders might indicate that aggressive early treatment might be important for getting patients on a favorable treatment response-trajectory, possibly carrying them towards decongestion towards the end of hospitalization.

Prior to discharge, measuring the diameter and flaccidity of the inferior vena cava with ultrasound strongly and independently predicted post-discharge prognosis in terms of both re-hospitalization and all-cause mortality. Thus, this rapidly and feasibly measurable ultrasound parameter probably represents a measure of thorough systemic decongestion. As AHF patients are vulnerable regarding adverse events shortly after discharge from the hospital, discharging them with residual congestion probably results in higher post-discharge event rates 120.

Finally, as ultrasound seemed beneficial for diagnosing and monitoring congestion, the question naturally arose whether it could be used for guiding therapy. Our small pilot study eventually showed that focused cardiothoracic ultrasound of the heart and lungs indeed seems feasible for guiding medical therapy, as no concerns regarding practical issues or safety arose in this study. Moreover, patients treated via ultrasound-guidance had very short duration of hospitalization while still experienced a much higher rate of complete decongestion and significantly lower post-discharge re-hospitalization rates than conventionally treated AHF patients. These results, however, need to be interpret with great caution, since this was a non-randomized, non-blinded single center study, with greatly imbalanced group sizes. Hence, the future is open for large randomized controlled trials on ultrasound-guided medical AHF therapy, as every attempt should be undertaken to discover prognostically beneficial evidence based therapy for treating congestion in hospitalized patients.
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