Comorbidity in heart failure

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Comorbidity in Heart Failure

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Introduction

Vincent M. van Deursen

Heart failure is a clinical syndrome characterized by the heart's inability to meet the body's circulatory demands. Typical symptoms include dyspnea, fatigue, edema and exercise intolerance, accompanied by objective signs of cardiac dysfunction.[1] The population prevalence of chronic heart failure in The Netherlands was 1% in 2003, and 20-30% in people over the age of 70, and continues to rise. Contributing factors include an ageing population, improved treatment for chronic heart failure and acute myocardial infarction, resulting in better survival. Heart failure has been described as a burgeoning epidemic, with Engelfriet et al. predicting a 50% rise in incidence by 2025 in The Netherlands.[2]

Heart failure may be caused by any condition affecting cardiac function. Persistent pressure or volume overload, myocardial disease or loss of heart muscle. The primary cause remains ischemic heart disease. Other common aetiologies include valvular disease, hypertension, myocarditis and cardiomyopathies.

Heart failure is the leading cause of death in the Western world, with a 60% mortality rate within five years of diagnosis.[3] Official statistics frequently underestimate heart failure mortality rates, as cause of death is coded by underlying disease (i.e. coronary artery disease). Despite the development of new therapies, both short-term and long-term mortality remains high.[4,5] It would appear the 'benefit ceiling' for available therapies has almost been reached. Therapies not primarily focused on heart failure may reduce morbidity and mortality.[6,7]

In summary, heart failure is generally recognized as a major and escalating health care problem in industrialized countries. The number of patients with heart failure is set to rise in years to come for several reasons. First, the proportion of elderly patients, which have the highest incidence of risk factors such as coronary artery disease and hypertension, is increasing rapidly. Second, therapeutic developments have improved survival in heart disease patients, shifting the burden towards chronic illness.[3]

Comorbidity in heart failure

In recent decades, growing evidence has accumulated about other diseases and dysfunction of other organs in patients with heart failure. These 'comorbidities' frequently accompany heart failure and result in worse quality of life and clinical outcome.

The term comorbidity has multiple meanings; first, to indicate a medical condition existing simultaneously with but independently of another condition in a patient; and second, to indicate a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient.[8]

Prevalence

Numerous studies have found comorbidities are highly prevalent in patients with heart failure, but almost all focus on a single comorbidity – anemia (prevalence of 37%),[6]

cerebral dysfunction (30-60%),[9] renal dysfunction (up to 55%),[10] liver dysfunction (30-60%)[11] and sleep apnea (60%).[12]
However, to the best of our knowledge, only two studies have focused on multiple comorbidities in patients with heart failure. Examining twenty non-cardiac comorbidities, the first found that 96% of all heart failure patients older than 65 years were found to have at least one comorbidity, and 40% had 5 or more comorbidities.[13] The other study focused on an even older population, namely geriatric patients.[14]

Pathophysiology

The pathophysiologic processes underlying the interaction between heart failure and comorbid conditions are complex and remain largely unresolved. High prevalence of comorbidities in patients with heart failure suggests a common risk factor or a causal relationship. Although a common risk factor causing multiple different comorbidities is possible, it is reasonable to believe that heart failure itself might be a cause of multiple other comorbidities.[15] This is supported by the finding that the prevalence of comorbidities is associated with the severity of heart failure, measured using the New York Heart Association (NYHA) functional classification.[16]

Several mechanisms in heart failure may contribute to the dysfunction of other organs. First, hemodynamic derangements - the hallmark of the heart failure syndrome – may cause dysfunction in other organs.[17-21] Second, heart failure causes neurohormonal changes which can lead to other organ dysfunction. Heart failure can alter neurohormonal status by affecting balance – for instance hormonal, neural, structural, and local balance.[19] Third, the drugs used to treat heart failure may affect comorbidities (e.g. beta-blockers affect COPD; ACE inhibitors impact kidney function and anemia).

Hemodynamic changes are of special interest. As cardiac output, blood is preferentially redistributed to certain organs at the expense of others.[19] In mild heart failure, the heart's output is still normal at rest, but the output increase normally seen during exercise is blunted, leading to a smaller increase in skeletal muscle blood flow. In patients with severe heart failure, cardiac output is already reduced at rest. The heart and brain receive normal blood flow at the expense of skeletal muscles and kidneys. As a percentage of output, cerebral and coronary blood flow even increase.[17,18]

Pathophysiologic mechanisms are complex and may differ for individual comorbidities. Therefore, comorbidities must be studied separately to identify pathophysiologic associations.

Of all the comorbidities examined, only two are directly related to an organ - Renal dysfunction and liver dysfunction. Other comorbidities, such as sleep apnea and cognitive dysfunction, do not have clear substrates that can be studied easily. Renal dysfunction and liver dysfunction are relatively easy to assess and can be studied on a continuous scale, rather than dichotomized into dysfunctional or not.

Prognosis

Heart failure is the leading cause of death in the Western world and has a 5-year mortality of 60%.[3] The presence of comorbidities further impairs survival.[6,7,22] Most of the research on comorbidities in heart failure was related to a single organ or comorbidity. However, when multiple comorbidities are taken into consideration, a strong association is observed between non-cardiac comorbidities and adverse clinical outcomes. Hospitalization rates increase in the presence of comorbidities. In fact, patients with five or more comorbidities account for 81% of all hospital days experienced by all heart failure patients.

We are also interested in factors that account for worse prognosis. Although it is difficult to study factors that explain the association between comorbidities and prognosis, we will focus primarily on hemodynamic factors such as central venous pressure and cardiac output.[13]

Aims

In summary, the prevalence, pathophysiology and prognostic implications of (multiple) comorbidities in patients with heart failure remain unresolved. Therefore the main aims of the present thesis are:

1. To assess the prevalence of individual and multiple comorbidities in patients with heart failure;
2. To study whether the prevalence of comorbidities is higher in patients with heart failure than in age-matched controls;
3. To study pathophysiologic mechanisms connecting heart failure and individual comorbidities, as well as determinants of multiple comorbidities;
4. To establish the prognostic influence of individual and multiple comorbidities.

In chapter 1, we examine multiple comorbidities in a broad spectrum of European patients with chronic heart failure. We focus on the prevalence, determinants, regional variation and prognostic implications of multiple comorbidities. In chapters 2-6, we study renal and liver dysfunction separately in patients with chronic and acute decompensated heart failure.

In chapter 2, we study whether hemodynamic factors could play a pathophysiological role in renal dysfunction. We evaluate the association between invasively measured hemodynamic parameters, renal dysfunction and prognosis. Chapter 3 focuses on tubular renal function in patients with chronic heart failure. We try to determine whether tubular renal function is a better renal parameter for assessing renal function compared to two frequently used biomarkers of chronic kidney disease. In contrast with chapters

2 and 3, chapter 4 studies renal function in patients with acute decompensated heart failure. We examine the pathophysiologic associations and prognostic implications of (change in) creatinine in hospitalized patients.

Chapter 5 studies whether hemodynamic factors are of pathophysiological importance in liver dysfunction. In addition, associations between abnormal liver function tests and prognosis are assessed. In chapter 6 we investigate liver function tests in patients admitted with acute decompensated heart failure. We examine the prognostic value of (change in) impaired liver function.

Chapter 7 reviews the prevalence of the most studied organ-related comorbidities in heart failure, i.e. renal dysfunction, liver dysfunction, cerebral and cognitive dysfunction, anaemia, chronic obstructive pulmonary disease, diabetes mellitus, depression, stroke and sleep apnea. We also provide potential explanations for the observed associations between comorbidities and heart failure, as well as examining their prognostic implications.

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Chapter 1

Comorbidities in heart failure

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Comorbidities in patients with heart failure
An analysis of the European Heart Failure pilot survey

Abstract

Aims

Co-morbidities frequently accompany heart failure (HF), contributing to morbidity, impairment of quality of life and increased mortality. We assessed the prevalence, determinants, regional variation and prognostic implications of co-morbidities in patients with chronic HF in Europe.

Methods

3226 European outpatients with chronic HF were included in this analysis of the ESC Heart Failure pilot survey. The following co-morbidities were considered: diabetes, hyper- and hypothyroidism, stroke, COPD, sleep apnoea, chronic kidney disease (CKD) and anaemia. Prognostic implications of co-morbidities where evaluated using population attributable risks (PAR), and patients were divided into geographic regions. Clinical endpoints were all-cause mortality and HF hospitalization.

Results

The majority of patients (74%) had a least one co-morbidity, the most prevalent being CKD (41%), anaemia (29%) and diabetes (29%). Co-morbidities were independently associated with higher age ($p<0.001$), higher NYHA functional class ($p<0.001$), ischemic aetiology of HF ($p<0.001$), higher heart rate ($p=0.011$), history of hypertension ($p<0.001$) and atrial fibrillation ($p<0.001$). Only diabetes, CKD and anaemia were independently associated with a higher risk of mortality and/or HF hospitalization. There were marked regional differences in prevalence and prognostic implications of co-morbidities. Prognostic implications of co-morbidities (PAR) were: CKD=41%, anaemia=37%, diabetes=14%, COPD=10% and <10% for all other co-morbidities.

Conclusion

In this pilot survey, co-morbidities are prevalent in patients with chronic HF and are related to the severity of heart failure. The presence of diabetes, CKD and anaemia was independently related to increased mortality and HF hospitalization, with the highest population attributable risk for CKD and anaemia

Introduction

Heart failure is characterized by high morbidity and mortality and a poor quality of life.[1] There is growing awareness that co-morbidities frequently accompany heart failure and lead to greater morbidity, a further decrease in quality of life and increased mortality.[2-6] The prevalence of comorbidities is higher in patients with more severe signs of heart failure. This suggests either common etiological factors - such as age and cardiovascular risk factors - or a causal relationship with heart failure. However, determinants of multiple co-morbidities remain unknown.

While numerous studies focus on a single co-morbidity, only few studies have examined multiple non-cardiac co-morbidities in patients with heart failure.[5,7,8] In a cross-sectional study of 122,630 elderly (>65 years) patients with heart failure, the prevalence of co-morbidities was 96%.[5] It was calculated that patients with more than 5 co-morbidities are responsible for 81% of all hospital days experienced by all heart failure patients. However, regional differences have not been studied and determinants of multiple co-morbidities remain unknown.

The present study examines multiple co-morbidities in a broad spectrum of patients with chronic heart failure. We focus on the prevalence, determinants, regional variation and prognostic implications of co-morbidities in a broad spectrum of patients with chronic heart failure in Europe.

Methods

The HF Pilot of the EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC) was a prospective, multicentre, observational survey.[9] The aim was to include a broad spectrum of patients with heart failure from outpatient clinics and those admitted to a hospital. Outpatients were diagnosed with chronic heart failure according to the clinical judgment of a cardiologist. Admitted patients had pre-existing heart failure or new-onset heart failure requiring intravenous therapy. A total of 5,118 patients were included, 1,892 (37%) in-hospital patients with acute HF and 3,226 (63%) outpatients with chronic HF, recruited from 136 cardiology centres in 12 European countries. These countries were selected on the basis of previous performances in the Euro Heart Surveys and geographical distribution. The National Cardiology Societies of each country agreed to participate in the program and were asked to select hospitals of different levels of complexity. The aim was to involve a broad spectrum of cardiology units. The number of participating centers for each country was decided according to the number of inhabitants. We used all 3,226 outpatients to obtain a representative chronic heart failure population for analysis.

Regions

Four geographical regions were defined as follows: Western European countries (Austria [N=86], France [N=37], Germany [N=138], and The Netherlands [N=76]), Eastern European countries (Romania [N=120] and Poland [N=243]), Southern European countries (Greece [N=115], Italy [N=1387] and Spain [N=532]), and Northern European countries (Denmark [N=174], Norway [N=126], and Sweden [N=201]).

Co-morbidities

Co-morbidities were determined based on the case record form as assessed by the treating physician. We used all non-cardiac co-morbidities that were assessed in this survey. Co-morbidities consisted of diabetes (N=3223), thyroid dysfunction (N=3171), stroke (N=3206), chronic obstructive pulmonary disease (COPD, N=3202), sleep apnoea (either in medical history or self-reported, N=3197), chronic kidney disease (CKD, defined as estimated GFR (eGFR)<60 mL/min/1.73 m^2, as well as eGFR on a continuous scale, N=2547), and anaemia (using the World Health Organisation definitions of haemoglobin <13 g/L (8.1 mmol/L) in men and <12 g/L (7.5 mmol/L) in women, as well as haemoglobin on a continuous scale, N=2522). The number of co-morbidities per patient was also assessed. No additional diagnostic tests were performed to determine the presence of specific co-morbidities.

End-points

To study the prognostic association with co-morbidities, all-cause mortality and heart failure hospitalization were assessed, with a median follow-up of 364 (335-367) days.

Statistical analyses

Data are presented as mean ± standard deviation for continuous variables, and as frequencies and percentages for categorical variables. Categorical variables were compared using chi-square tests. Continuous variables were compared using Student's T-test.

Cox proportional hazards models were used to estimate hazard ratios for all-cause mortality and heart failure hospitalizations. In multivariate multivariable analyses, the following variables with significant univariable associations with outcome at $P \leq 0.10$ were included in the model: age, sex, aetiology, hypertension, atrial fibrillation, congestion, body surface area, systolic blood pressure and heart rate.

Population attributable risks (PAR) were computed as confirmatory analyses using the package epiR. The estimated attributable fraction in the population was reported with 95% confidence intervals. The attributable fraction is the proportion of deaths in the population that is attributable to the co-morbidity, as previously used by Yusuf et al.[10]

A P-value of < 0.05 was considered statistically significant. All tests were two-sided. The statistical analyses were performed at the ANMCO Research Center, Florence, Italy, on behalf of the European Society of Cardiology, with R (version 2.14.0).

Table 1. Baseline characteristics, according to patients with 0 or 1 comorbidity and patients with more than 1 comorbidity.

	All patients N=3226	<= 1 comorbidiy N=1417	> 1 comorbidity N=1167	P value
Age (years)	66±14	63±14	71±11	<0.001
Male gender (%)	2268 (70)	1029 (73)	797 (68)	0.02
Body Mass Index (kg/m2)	28±5	28±5	28±5	0.12
NYHA class				<0.001
I (%)	511 (16)	299 (21)	103 (9)	
II (%)	1797 (56)	828 (59)	600 (52)	
III (%)	854 (26)	277 (20)	431 (37)	
IV (%)	56 (2)	11 (1)	28 (2)	
SBP (mmHg)	125±20	125±20	125±21	0.62
Heart rate (b.p.m.)	72±14	72±15	72±13	0.17
Congestion				
Only elevated JVP	242 (8)	90 (6)	105 (9)	0.01
Only edema	592 (19)	237 (17)	276 (24)	<0.001
Ischaemic aetiology (%)	1305 (41)	499 (35)	556 (48)	<0.001
ICD/CRT(-D) (%)	745 (23)	110 (8)	122 (10)	0.02
Hypertension (%)	1875 (58)	733 (52)	787 (68)	<0.001
History of AF (%)	1289 (40)	486 (34)	586 (50)	<0.001
Medication use				
ACE-i/ARBs	2833 (89)	1280 (91)	992 (86)	<0.001
Beta-blockers	2774 (87)	140 (88)	962 (83)	<0.001
Diuretics	2649 (83)	1088 (77)	1041 (90)	<0.001
Aldosterone blockers	1396 (44)	595 (42)	527 (46)	0.10
Comorbidities				
Chronic kidney dysf.	1035 (41)	211 (15)	780 (73)	<0.001
eGFR	68±26	79±23	54±22	<0.001
Anemia	727 (29)	124 (9)	589 (55)	<0.001
Hemoglobin	13.4±1.9	14.1±1.5	12.6±1.9	<0.001
Diabetes	934 (29)	165 (12)	697 (54)	<0.001
COPD	484 (15)	75 (5)	363 (31)	<0.001
Stroke	337 (11)	52 (4)	244 (21)	<0.001
Sleep apnea	128 (4)	19 (1)	104 (9)	<0.001
Hypothyroidism	272 (9)	37 (3)	199 (18)	<0.001
Hyperthyroidism	101 (3)	21 (2)	68 (6)	<0.001

JVP=jugular venous pressure; SBP=systolic blood pressure; AF=atrial fibrillation; ICD=implantable cardioverter; CRT(-D)=cardiac resynchronization therapy(-defibrillator); ACE-i=angiotensin-converting enzyme-inhibitor; ARBs=angiotension II receptor blockers, COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate.

Results

Mean age of the 3,226 included patients was 66±14 years and 70% were men. Most patients were in NYHA-class II or III (56% and 26%) and 41% had an ischemic cause of heart failure. Table 1 shows other baseline characteristics of the study cohort.

Prevalence of co-morbidities

Of all patients, 74% had at least one co-morbidity. CKD (41%), anaemia (29%) and diabetes (29%) were the co-morbidities with the highest prevalence (Table 1). COPD (15%) and stroke (11%) were also common. Sleep apnoea had a prevalence of 4%. Hypothyroidism (9%) was more prevalent than hyperthyroidism (3%). Of all patients, only 26% (N=610) had no co-morbidity, 30% had 1 co-morbidity, 23% had 2 co-morbidities and 43% had 2 or more co-morbidities.

Characteristics of patients with multiple co-morbidities

Patients with co-morbidities were older (P<0.001) and had a higher NYHA class (P<0.001). When multiple co-morbidities were present, patients were more likely to have heart failure due to ischemic aetiology (P<0.001) with hypertension (P<0.001) and

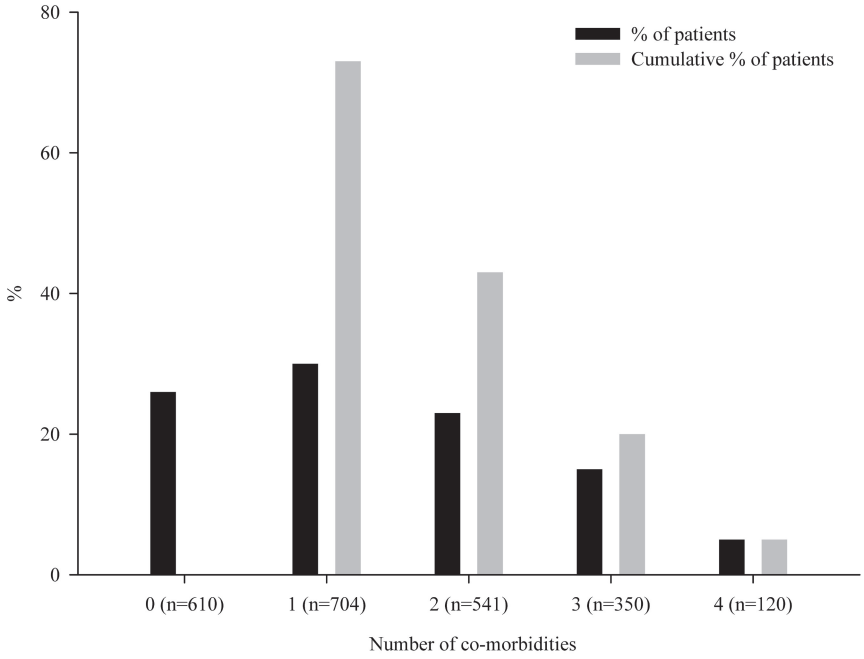

Figure 1. The prevalence of multiple comorbidities. Blue bars are the percentages of the number of comorbidities. The red bars are the cumulative percentages.

Table 2. Univariate and multivariate associations between comorbidities and all-cause mortality.

		Univariate		Multivariate	
	N deaths (%)	HR (95% CI)	P value	HR (95 % CI)	P-value
Chronic kidney dysf.	130 (5%)	2.77 (2.08-3.69)	<0.0001	1.50 (1.06-2.11)	0.0212
Anemia	107 (4%)	3.12 (2.36-4.12)	<0.0001	1.69 (1.22-2.35)	0.0017
Diabetes	90 (3%)	1.57 (1.21-2.04)	<0.0001	1.74 (1.28-2.37)	0.0004
COPD	52 (2%)	1.76 (1.29-2.40)	<0.0001	1.37 (0.96-1.94)	0.0819
Stroke	32 (1%)	1.35 (0.93-1.97)	0.1109	1.20 (0.79-1.82)	0.3873
Sleep apnea	8 (0%)	0.85 (0.42-1.72)	0.6509	1.00 (0.48-2.06)	0.9894
Hypothyroidism	27 (1%)	1.47 (0.98-2.19)	0.0617	1.31 (0.83-2.07)	0.2412
Hyperthyroidism	10 (0%)	1.41 (0.75-2.65)	0.2915	1.16 (0.58-2.30)	0.6720

Multivariate hazard ratio's (HR) are corrected for age, gender, etiology, hypertension, atrial fibrillation, congestion, body surface area, systolic blood pressure and heart rate per comorbidity.

atrial fibrillation (P<0.001). Although more frequently treated with diuretics (P<0.001), patients with multiple co-morbidities received less ACE-inhibitor, angiotensin receptor blocker and beta-blocker therapy (all P<0.001).

Of all patients without co-morbidities, 15% had clinical signs of congestion (elevated jugular venous pressure (JVP) >6 cm or peripheral edema); of all patients with 1, 2, 3 or ≥4 co-morbidities, respectively 24%, 27%, 33% and 36% had clinical signs of either elevated JVP or peripheral edema (P<0.001).

Co-morbidities and prognosis

Of all co-morbidities, diabetes, COPD, CKD and anaemia were significantly associated with all-cause mortality (Table 2). In multivariable analyses, after adjustment for other confounders, CKD (HR 1.50 [95% CI: 1.06-2.11], P=0.0212), anaemia (HR 1.69 [1.22-2.35], P=0.0017) and diabetes (HR 1.74 [1.28-2.37], P=0.0004) remained significantly related with all-cause mortality. COPD (HR 1.37 (0.96-1.94), P=0.0819) was borderline significant.

CKD (HR 1.59 [1.23-2.06], P=0.001), anaemia (HR 1.44 [1.13-1.84], P=0.0034) and diabetes (HR 1.31 [1.04-1.65], P=0.0239) were also independently associated with heart failure hospitalizations, as was hypothyroidism (HR 1.46 [1.06-2.01], P=0.0221) (Table 3).

Confirming these findings, the prognostic implication for the whole population was highest for CKD, with a population attributable risk (PAR) of 41% (95% CI: 29-51%). In other words, 41% (29-51%) of all-cause mortality in the population is attributable to the co-morbidity CKD. Anaemia had the second highest PAR of 37% (27-46), followed by diabetes (14% [5-23]) and COPD (10% [3-16]). All other co-morbidities had a mean PAR below 5%. In terms of mortality, 18 patients without co-morbidities (1%), 171 patients

with at least one co-morbidity (7%), including 27 patients (1%) with more than three co-morbidities, died. Figure 2 shows that patients with 1-3 co-morbidities have a higher mortality rate (HR 3.24 [1.99-5.30], P<0.001) and higher rates of heart failure hospitalizations (HR 1.95 [1.44-2.64], P<0.001) than patients without co-morbidities. Patients with >3 co-morbidities had an even higher mortality rate (HR 9.33 [5.14-16.96], P<0.001) and were re-hospitalized more frequently (HR 4.74 [3.10-7.23], P<0.001) than patients without co-morbidities.

Geographical regions

In figure 1 the prevalence of co-morbidities is divided into European regions. Eastern European patients (n = 363) had less CKD (28% vs. 39%, 43% and 42%) compared to Northern (n = 501), Southern (n = 2025) and Western (n = 337) European regions respectively. The prevalence of anaemia was much lower in Eastern European patients (17% vs. 29%, 32% and 24%). Northern European patients had a much lower prevalence of diabetes (16% vs. 32%, 33% and 29%) compared to Southern, Western and Eastern European regions, respectively. Geographical differences were minimal for hyperthyroidism, stroke and COPD. Hypothyroidism was twice as common in Southern and Western Eu-

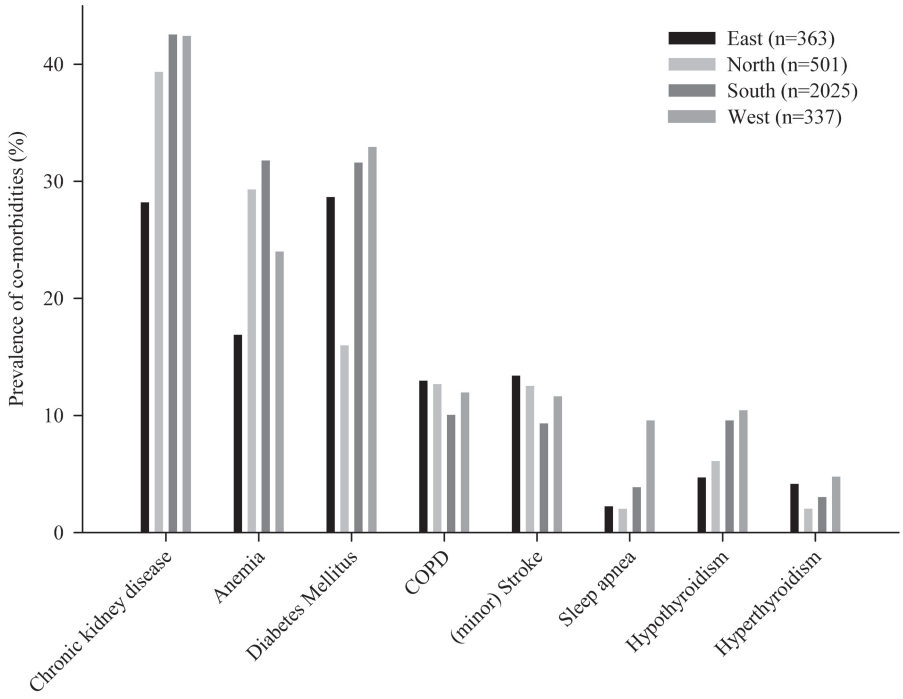

Figure 2. The prevalence of multiple comorbidities per geographical regions in Europe (East, North, South and West).

Table 3. Univariate and multivariate associations between comorbidities and heart failure hospitalization.

	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Chronic kidney dysf.	2.16 (1.75-2.66)	<0.0001	1.59 (1.23-2.06)	0.0005
Anemia	2.12 (1.72-2.61)	<0.0001	1.44 (1.13-1.84)	0.0034
Diabetes	1.47 (1.21-1.79)	<0.0001	1.31 (1.04-1.65)	0.0239
COPD	1.45 (1.14-1.84)	0.0026	1.09 (0.82-1.44)	0.5745
Stroke	1.17 (0.88-1.57)	0.2844	1.09 (0.79-1.52)	0.5839
Sleep apnea	1.22 (0.78-1.91)	0.3742	0.94 (0.56-1.58)	0.8156
Hypothyroidism	1.66 (1.25-2.21)	<0.0001	1.46 (1.06-2.01)	0.0221
Hyperthyroidism	1.20 (0.73-1.97)	0.4753	1.07 (0.64-1.81)	0.7877

Same abbreviations and multivariate models as Table 3.

ropean countries (both 10% vs. 5% and 6%). Sleep apnoea was diagnosed more often in Western European countries (10% vs. 2%, 2% and 4%).

Overall, patients from the Northern European countries had fewer co-morbidities (72%) than Western European countries (77%), followed by Eastern (78%) and Southern European countries (80%).

Discussion

This study examines multiple co-morbidities in a broad spectrum of patients in chronic heart failure. In this pilot survey, we found that the majority of patients had a least one co-morbidity, and the number of co-morbidities increased with the severity of heart failure. Diabetes, CKD and anaemia had the highest prevalence and were independently associated with both mortality and HF hospitalization.

Prevalence of co-morbidities

CKD, anaemia and diabetes were the most common co-morbidities in our chronic heart failure patients, along with COPD and stroke. These findings are consistent with other reports.[11-14]

In the absence of active screening, we found a much lower prevalence for sleep apnoea in our population, in stark contrast with the prevalence of up to 60% reported in recent literature.[15-22] This discrepancy underscores the need for better screening for co-morbidities, particularly in cases where symptoms overlap with those of heart failure. The same holds true for COPD, where prevalence is reported up to 50%.[23,24] In another study, only 43% of patients with evidence of COPD during spirometry self-reported having COPD.[25]

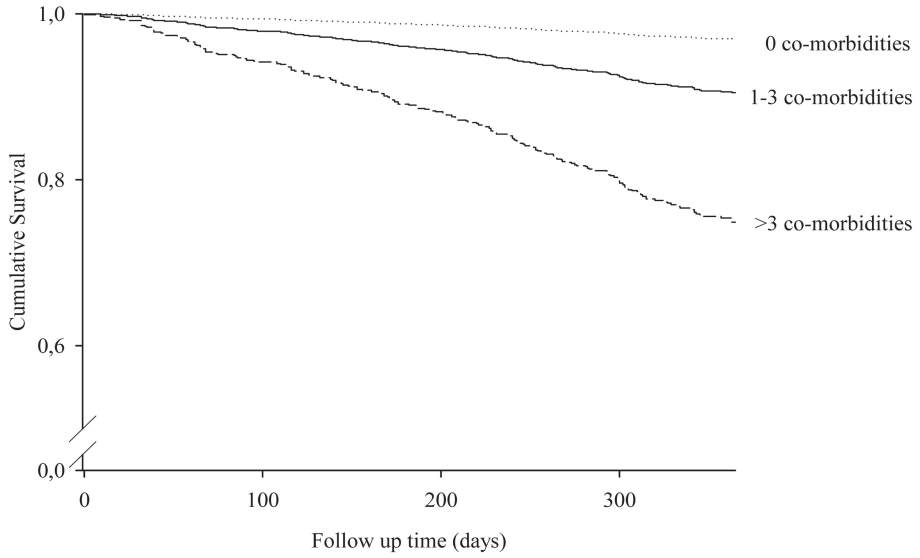

Figure 3a. Mortality among groups of multiple comorbidities. Groups are defined as 0 comorbidities, 1-3 co-morbidities and >3 comorbidities.

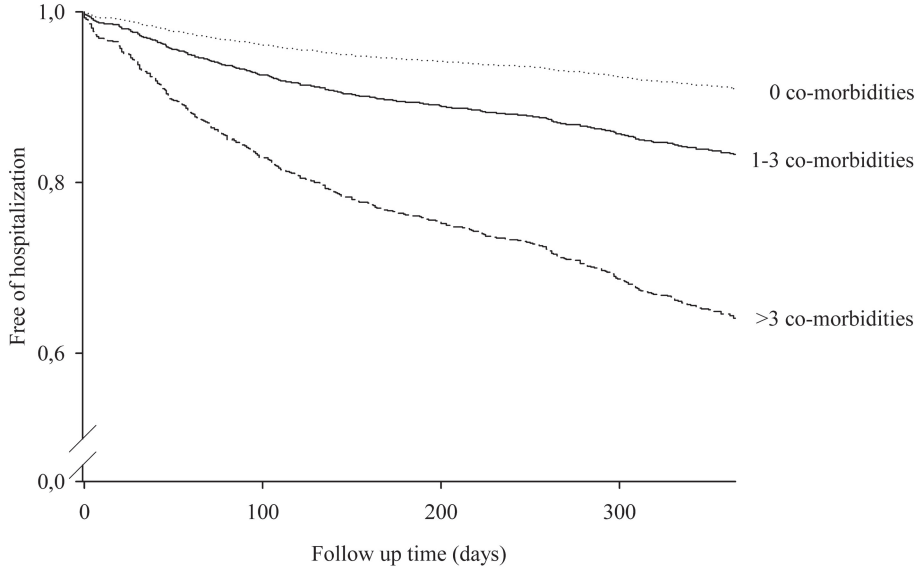

Figure 3b. HF-hospitalization among groups of multiple comorbidities for. Groups are defined by 0 comorbidities, 1-3 comorbidities and >3 comorbidities.

We found that hypothyroidism had a higher prevalence compared to hyperthyroidism. This could be due to the effect of amiodarone therapy on thyroid dysfunction. In patients with persistent atrial fibrillation, hypothyroidism has been reported to have a prevalence of 31% in those treated with amiodarone compared to 7% in the control group.[26]

We found a high prevalence of co-morbidities in patients with chronic heart failure - Nearly half had two or more co-morbidities. In a cross-sectional study of 122,630 patients with heart failure, the prevalence of co-morbidities was even higher.[5] This difference is likely due to the greater number of co-morbidities assessed in the cross-sectional study.

Determinants of co-morbidities

Literature shows a high prevalence of co-morbidities in patients with heart failure. Although co-morbidities might cause heart failure, it is reasonable to believe that heart failure itself might be a cause of multiple other co-morbidities.[6] This is supported by the finding that the prevalence of co-morbidities is associated with the severity of heart failure, measured with the New York Heart Association (NYHA) functional classification.[27] Next to neurohormonal changes and the negative effect of heart failure medication, hemodynamic factors could play a pathophysiological role as well.[13,28-31]

We found that patients with co-morbidities were older and had more advanced heart failure, reflected by a higher NYHA class and a higher prevalence of hypertension and atrial fibrillation, although a causal relationship cannot be established based on the data. Patients with heart failure of ischemic aetiology had more co-morbidities, and patients with more co-morbidities had more clinical signs of congestion (elevated JVP or peripheral edema). This is consistent with our previous findings that congestion plays a pathophysiological role in renal and liver dysfunction.[13,31] Organs in heart failure may also be affected by impaired hemodynamics, reflected by elevated venous pressure, among other factors.[6]

Importantly, we found that patients with co-morbidities were less likely to be receiving evidence-based therapies, such as ACE-inhibitors, angiotensin receptor blockers and beta-blockers. In accordance, previous studies have shown thatsicker patients are more likely to have side effects or contraindications.[32-34]

Population attributable risk

The term attributable risk is the difference in the rate of a condition (for instance mortality) between an exposed population and an unexposed population (presence or absence of a co-morbidity). Attributable risk was first described in 1953 and has been used since.[10,35] Interestingly, attributable risks combine incidence with effect. For our analyses, population attributable risk can be described as the reduction in mortality that would be observed if the population was entirely unexposed to a certain co-morbidity, compared with the mortality pattern in patients without that co-morbidity.

When co-morbidities were considered separately, we found that CKD and anaemia had the highest PAR. All-cause mortality could also be attributed to diabetes and stroke, while other co-morbidities lacked a significant PAR. The high PARs for CKD and anaemia are driven by the combination of high prevalence and a strong association with mortality.

Prognosis and co-morbidities

Previous studies have shown a strong association between co-morbidities and adverse clinical outcomes.[3,4,11] It has been calculated that patients with five or more co-morbidities are responsible for 81% of all hospital days experienced by all heart failure patients.[5] Our findings confirm that patients with increasing numbers of co-morbidities have an increasing risk of both mortality and heart failure hospitalization.

Accordingly, we found that CKD, anaemia and diabetes remained significantly and independently related to all-cause mortality and heart failure hospitalizations. This is in accordance with other studies reporting on CKD and anaemia separately. This supports a causal relationship between heart failure and co-morbidities, linking them to disease severity.

Diabetes was also associated with a poorer prognosis in heart failure. In acute heart failure, diabetic patients had worse outcome compared to non-diabetics.[36] The relationship with prognosis is less clear in patients with chronic heart failure.[37-39]

Regarding sleep apnoea, we did not find an association with outcome in the present study, although other studies show that sleep apnoea is associated with increased mortality.[40,41] We believe that this difference can be explained by underreporting due to a lack of screening, as explained previously. Other studies show that, after adjustment for confounders, sleep apnoea doubles the mortality risk in patients with heart failure.[40,41]

Geographical regions

Patients from the Northern European countries were less likely to have co-morbidities, followed by Western, Eastern and Southern European countries, in ascending order. This was largely driven by diabetes, which had a low prevalence in Northern European countries compared to the other regions. However, patients from Eastern European countries were less likely to have CKD and anaemia. Hypothyroidism was slightly more commonly diagnosed in Southern and Western Europe, while sleep apnoea was more commonly diagnosed in Western Europe.

In addition to prevalence, there were also marked regional differences in the prognostic implications of co-morbidities. In Eastern and Northern European patients, all-cause mortality was less attributable to diabetes, COPD and CKD, compared to patients from Southern and Western European patients. In Southern and Northern European countries, mortality was less attributable to stroke.

Limitations

As is the case for all surveys, the voluntary participation and recruitment of patients imposes limitations that must be acknowledged. First, as mentioned in the main article, this pilot study tried to balance the methodological need for consecutive enrolment with the practical feasibility by reducing the workload for centres with limited recruitment to 1 day per week for 8 months. Second, the study population may not represent the general heart failure population. Participating centres were selected proportionally to the size of the population of the participating countries, accounting for the different technological levels of the cardiology centres invited to participate. Another important limitation is that the diagnosis of heart failure was made by the treating physician, and both diagnosis and events were not adjudicated.

There are many potential explanations for the regional differences observed. These include a lack of screening for co-morbidities in various regions of Europe, or imperfect representativeness of the regional populations. Hospital care practices also differ between countries and centres. However, the observed differences may also be 'real' and thus related to the heterogeneous European epidemiology, with regional variation in prevalence, cardiovascular risk factors and cardiovascular event rates.[42]

Conclusion

This is the first study to examine multiple co-morbidities in a broad spectrum of patients with chronic heart failure. This pilot survey showed that the majority of patients had a least one co-morbidity, with CKD, anaemia and diabetes being most prevalent, and that the number of co-morbidities increased with the severity of heart failure. Diabetes, CKD and anaemia were independently associated with both mortality and HF hospitalization. However, there were marked differences in prevalence and prognostic implications of co-morbidities across various European regions.

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Chapter 2

Renal Function and Hemodynamics

Kevin Damman, Vincent M. van Deursen, Gerjan Navis, Adriaan A. Voors, Dirk J. van Veldhuisen and Hans L. Hillege

Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease

Abstract

Objectives

We sought to investigate the relationship between increased central venous pressure (CVP), renal function, and mortality in a broad spectrum of cardiovascular patients.

Background

The pathophysiology of impaired renal function in cardiovascular disease is multifactorial. The relative importance of increased CVP has not been addressed previously.

Methods

A total of 2,557 patients who underwent right heart catheterization in the University Medical Center Groningen, the Netherlands, between January 1, 1989, and December 31, 2006, were identified, and their data were extracted from electronic databases. Estimated glomerular filtration rate (eGFR) was assessed with the simplified modification of diet in renal disease formula.

Results

Mean age was 59 ± 15 years, and 57% were men. Mean eGFR was 65 ± 24 ml/min/1.73 m^2, with a cardiac index of 2.9 ± 0.8 l/min/m^2 and CVP of 5.9 ± 4.3 mm Hg. We found that CVP was associated with cardiac index ($r = -0.259$, $p < 0.0001$) and eGFR ($r = -0.147$, $p < 0.0001$). Also, cardiac index was associated with eGFR ($r = 0.123$, $p < 0.0001$). In multivariate analysis CVP remained associated with eGFR ($r < -0.108$, $p < 0.0001$). In a median follow-up time of 10.7 years, 741 (29%) patients died. We found that CVP was an independent predictor of reduced survival (hazard ratio: 1.03 per mm Hg increase, 95% confidence interval: 1.01 to 1.05, $p = 0.0032$).

Conclusions

Increased CVP is associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease.

Introduction

Renal dysfunction is a strong and independent predictor of prognosis in the general population but also in patients with diabetes, hypertension, coronary artery disease, and heart failure.[1-7] The pathophysiology is multifactorial and associated with decreased renal perfusion, atherosclerosis and inflammation, endothelial dysfunction, and neurohormonal activation.[8-10] We recently showed that in patients with cardiac dysfunction secondary to pulmonary hypertension, not only was renal perfusion strongly associated with renal function impairment but also with venous congestion.[11] However, it is unclear whether this observation is limited to those patients with reduced cardiac function and pulmonary hypertension or whether it also may be present in patients with a mixture of cardiovascular diseases with varying etiologies and treatments. In addition, there are only limited data on the relationship between venous congestion, as estimated by central venous pressure (CVP) and the impact on prognosis, even in patients with and without heart failure. The studies that have been conducted are either small or include only non-invasive assessment of increased venous congestion, such as jugular venous pressure.[12-15] In the present study, we therefore aimed to investigate the relationship between CVP, renal function, and mortality in patients with a mixture of cardiovascular diseases with varying etiologies and treatments.

Methods

Case identification

Using the patient registration system of the University Medical Center Groningen, the Netherlands, all patients that underwent right heart catheterization between January 1, 1989, and December 31, 2006, were identified.

Data extraction

Retrospective chart review was performed to analyze characteristics of all patients that were identified during the electronic search. For each patient, date of birth, sex, race, and weight and height were collected. Comorbid conditions, including hypertension, coronary artery disease, cardiac valve disease, congenital heart disease, history of stroke, hypercholesterolemia, and diabetes, in addition to medical treatment at the time of catheterization also were extracted for each patient. Furthermore, the reason for performing right heart catheterization was identified. The study was approved by the institutional review board of the University Medical Center Groningen.

Heart catheterization

Hemodynamic variables obtained during catheterization included systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), cardiac output (thermodilution, l/

min), and right atrial pressure as indicator of CVP (CVP, mm Hg). Cardiac index (l/min/m^2) was determined as cardiac output divided by the body surface area, which was calculated as: 0.007184 · weight $^{0.425}$ · length $^{0.725}$. Measurements obtained from cardiac catheterization were obtained from the patient during a resting state.

Renal function measurement

Serum creatinine at the day of catheterization was extracted. For the patients who did not have laboratory measurements on the day of catheterization, measurements obtained within 3 days before catheterization were taken as the baseline value. Of patients included in the study, 2,282 (89%) had at least 1 serial creatinine measurement within 3 days of catheterization. Renal function was estimated as glomerular filtration rate (GFR) by using the simplified modification of diet in renal disease equation (estimated glomerular filtration rate [eGFR] [ml/min/1.73 m^2] · 186.3 · [serum creatinine] $^{-1.154}$ · age $^{-0.203}$ · [0.742 if female]).[16] Estimated GFR values >200 ml/min/1.73 m^2 were set equal to 200 ml/min/1.73 m^2, according to Coresh et al.[17]

Mortality data

Survival status was determined using the electronic patient registration database of the University Medical Center Groningen. Follow-up started directly after right heart catheterization. The primary end point consisted of death from any cause.

Statistical analysis

Data are given as mean ± standard deviation when normally distributed, as median and interquartile range when skewed distributed, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated by means of 1-way analysis of variance, the Kruskal-Wallis test, and chi-square or Fisher exact tests, when appropriate. Two-sided p values were used, taking $p < 0.05$ to be statistically significant. CVP was divided into tertiles to assess relationships between baseline characteristics and CVP. A fractional polynomial parameterization of exposure was used to explore nonlinearity between different predictors and renal function. In this technique, each exposure value is expressed as a polynomial of degree >1 (e.g., quadratic, cubic, and so on), yielding an estimated model with multiple predictors (i.e., separate predictors for the linear, quadratic, terms, respectively). We used a Cox proportional hazards survival model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). At first, in multivariate analysis, CVP was fitted into a stepwise multivariate Cox regression analysis on a continuous scale. In secondary analysis, CVP was fitted into the model and, in multiple steps, the model was adjusted for other variables and parameters. The internal validity of the regression model was assessed by the bootstrap resampling technique.[18] For each of 100 bootstrap samples, the model was refitted and tested on the original sample to obtain

Table 1. Primary Indication for Heart Catheterization.

	Percentage of Patients
Aortic valve disorders	29
Aortic valve stenosis	23
Aortic valve insufficiency	6
Mitral valve disorders	15
Mitral valve insufficiency	14
Mitral valve stenosis	1
Pulmonary valve disorders	1
Pulmonary valve insufficiency	0.8
Pulmonary valve stenosis	0.2
Heart failure	16
Coronary artery disease	13
Pre transplantation (non-cardiac)	11
Rhythm disorders	5
Pulmonary hypertension	3
Congenital heart disease	2
Post heart transplantation	2
Other	6

a bias-corrected estimate of predictive accuracy. Statistical analyses were performed using SPSS version 12.0 (Chicago, Illinois) and STATA version 9.0 (College Station, Texas).

Results

Baseline characteristics

A total of 3,757 right heart catheterizations were conducted between 1989 and 2006. Of these, 2,557 (68%) were first or only right heart catheterization of unique patients and formed the study population. Main reasons for right heart catheterization are shown in Table 1. Aortic and mitral valve disorders accounted for 44% of indications, whereas in 16%, acute or chronic heart failure was the predominant reason. Mean age was 59 ± 15 years, and 57% were men (Table 2). In the total study population, both mean cardiac index (2.9 ± 0.8 l/min/m^2) and mean CVP (5.9 ± 4.3 mm Hg) were within the normal range. The distribution of CVP among the study population is shown in Figure 1. Mean eGFR was moderately impaired: 65 ± 24 ml/min/1.73 m^2.

The distribution of different factors over tertiles of CVP is shown in Table 2. Most of the characteristics were equally distributed across tertiles of CVP, except for the highest tertile (CVP >6 mm Hg). Both cardiac output and cardiac index were significantly lower

Table 2. Baseline Characteristics According to Tertiles of CVP.

	Total	Tertile 1 (0 to 3 mm Hg)	Tertile 2 (4 to 6 mm Hg)	Tertile 3 (>6 mm Hg)	p Value for Trend
n	2,557	911	855	791	
Age (yrs)	59 ± 15	60 ± 15	59 ±15	58 ± 15	0.0032
Sex (% male)	57	59	58	54	NS
SBP (mm Hg)	133 ± 29	133 ± 28	134 ± 27	129 ± 31	0.0100
DBP (mm Hg)	68 ±13	66 ± 16	68 ± 12	69 ± 13	0.0010
Cardiac output (l/min)	5.5 ± 1.6	5.7 ± 1.6	5.5 ± 1.5	5.0 ± 1.5	< 0.0001
Cardiac index (l/min/m^2)	2.9 ± 0.8	3.1 ± 0.7	3.0 ± 0.7	2.7 ± 0.8	< 0.0001
CVP (mm Hg)	5.9 ± 4.3	2 ± 1	5 ± 1	11 ± 4	< 0.0001
eGFR (ml/min/1.73 m^2)	65 ± 24	65 ± 23	67 ± 24	62 ± 24	0.0001
Medical history (%)					
Heart failure	16	15	15	19	NS
Coronary artery disease	24	24	25	24	NS
Congenital heart disease	5	5	5	7	0.0189
Valve disease	51	50	55	49	NS
Hypercholesterolemia	6	7	5	6	NS
Diabetes mellitus	9	8	8	10	NS
Hypertension	20	21	20	18	NS
Stroke	5	4	5	6	NS
Medication					
Diuretics	42	37	38	53	0.0001
Beta-blocker	28	25	29	31	0.0388
ACEi or ARB	38	36	32	45	0.0001
Aldosteron antagonist	9	5	6	15	0.0001

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; CO = cardiac output; CVP = central venous pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NS = not significant; SBP = systolic blood pressure.

in the highest tertile compared with lower tertiles ($p < 0.0001$), corresponding to $r = -0.259$ ($p < 0.0001$) for the association between CVP and cardiac index. Furthermore, patients in the highest tertile were treated more frequently with angiotensin-converting enzyme inhibitor/angiotensin-II receptor blockers, beta-blockers, diuretics, and aldosterone antagonists. Prevalence of heart failure showed a trend toward increasing with higher tertiles of CVP ($p = 0.0781$), whereas congenital heart disease was also more prevalent in the highest tertile. Finally, eGFR was significantly lower in the highest tertile of CVP, compared with both lower tertiles ($p < 0.001$).

Curvilinear fitting and the relationship between CVP and eGFR.

Figure 1 shows the curvilinear relationship between CVP and eGFR in the total study population as obtained by fractional polynomial modeling. Estimated GFR showed a small increase when CVP increased from 1 to 6 mm Hg. However, in CVP values >6 mm Hg, a steep decrease is observed with increasing CVP values. This finding resulted in a partial correlation of $r = 0.064$, $p = 0.0218$ in patients with CVP >6 mm Hg, and $r = -0.212$, $p < 0.0001$ in patients with CVP >6 mm Hg (adjusted for age, sex, and cardiac in-

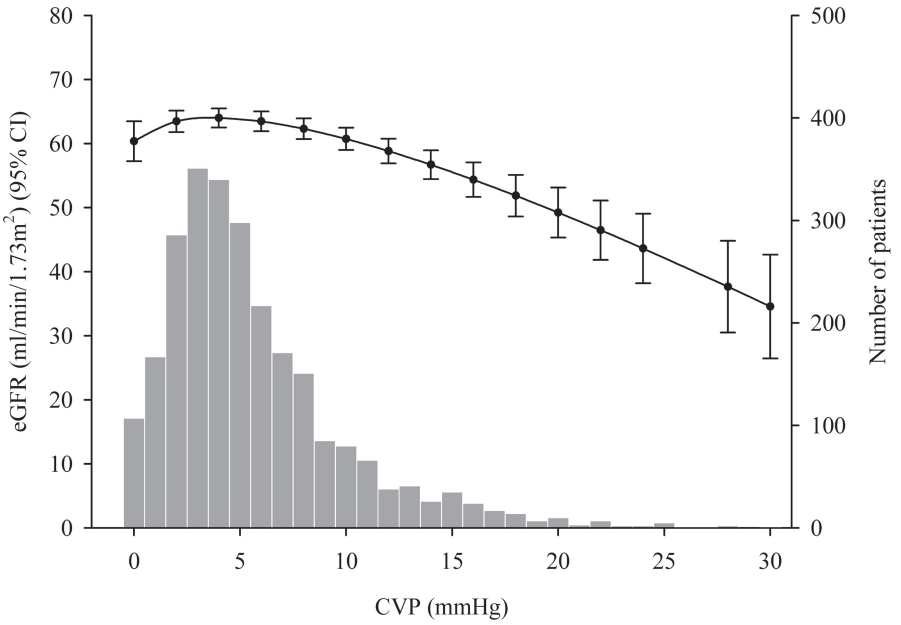

Figure 1. Distribution of CVP and Curvilinear Relationship Between CVP and eGFR in the Study Population. Adjusted for age, sex, and cardiac index. The curvilinear model had the following individual polynomial components for the relationship between CVP and eGFR: First order: $Y = -25.8 \cdot (CVP + 1) / 10$ (Wald 28.2, $P < 0.0001$) and second order: $Y = 35.7 \cdot ((CVP + 1) / 10)^{0.5}$ (Wald 17.4, $p < 0.0001$). CVP = central venous pressure; eGFR = estimated glomerular filtration rate.

dex). On a continuous scale, CVP was also significantly associated with eGFR ($r = -0.110$, $p < 0.0001$) after transformation.

Besides CVP, age ($r = -0.438$, $p < 0.0001$), sex ($r = 0.137$, $p < 0.0001$), and cardiac index ($r = 0.249$, $p < 0.0001$) were associated with eGFR. In addition, lower eGFR values also were found to be related with the use of any type of cardiovascular medication and a history of diabetes and hypertension. There was a significant interac- tion between CVP and cardiac index on the relationship with eGFR. The observed biphasic relationship between CVP and eGFR was most pronounced in patients with relatively normal cardiac index (Figure 2).

In multivariate analysis, CVP remained associated with eGFR ($r = -0.108$, $p < 0.0001$, adjusted for covariates), which was confirmed by bootstrap analysis (Online Table 1). After adjustment for the year of catheterization, the association between CVP and eGFR was numerically unchanged: $r = -0.105$, $p < 0.0001$. Excluding patients with a history of heart transplantation, who were likely to receive renal function compromising immunotherapy, CVP remained associated with eGFR ($r = -0.108$, $p < 0.0001$) in multivariate analysis. Including only patients without heart failure, similar associations were present ($r = -0.080$, $p = 0.0034$). Excluding both heart transplant recipients and heart failure pa-

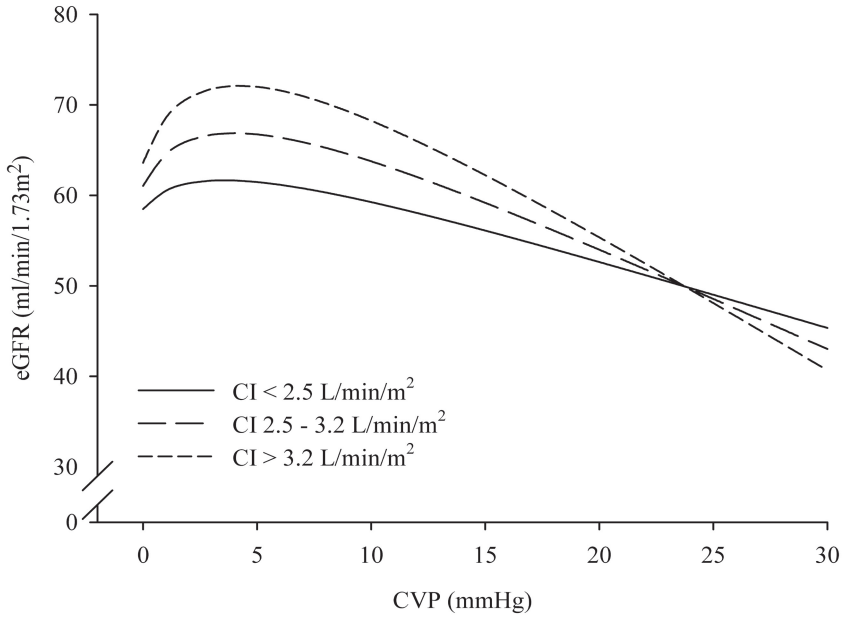

Figure 2. Curvilinear Relationship Between CVP and eGFR According to Different Cardiac Index Values. P = 0.0217 for interaction between cardiac index and CVP on the relationship with eGFR. Solid line = cardiac index < 2.5 l/min/m^2; dashed line = cardiac index 2.5 to 3.2 l/min/m^2; dotted line = cardiac index > 3.2 l/min/m^2. CVP = central venous pressure; eGFR = estimated glomerular filtration rate.

tients, the association between CVP and eGFR remained (r = -0.079, p = 0.0042).

CVP and mortality

Mortality data were available in all patients, whereas time of death was available in 2,424 (95%) of patients. Median follow-up among survivors was 10.7 years and, during follow-up, 741 (29%) of the patients died. Crude mortality ranged from 24% in the lowest tertile to 29% and 35% in the 2 highest tertiles of CVP (p < 0.0001 for trend). On a continuous scale, greater CVP levels were associated with impaired survival (HR: 1.05 per mm Hg increase, 95% CI: 1.04 to 1.07, p < 0.0001). Kaplan-Meier survival curves for tertiles of CVP are shown in Figure 3, showing that patients with the greatest CVP in particular were at risk for increased mortality (HR for CVP >6 mm Hg vs. ≤6 mm Hg: 1.49, 95% CI: 1.26 to 1.76, p < 0.0001). Baseline eGFR (HR: 1.09 per 10 ml/min/1.73 m^2 decrease, 95% CI: 1.05 to 1.13, p < 0.0001) and cardiac index (HR: 0.74 per l/min/m^2 increase, 95% CI: 0.66 to 0.84, p < 0.0001) also were strong predictors of mortality. Other factors associated with reduced survival are shown in Table 3. In stepwise multivariate Cox regression analysis, CVP remained significantly associated with reduced survival (HR: 1.03 per mm Hg increase, 95% CI: 1.01 to 1.05, p = 0.0032) (Table 3). Finally, we fitted a second

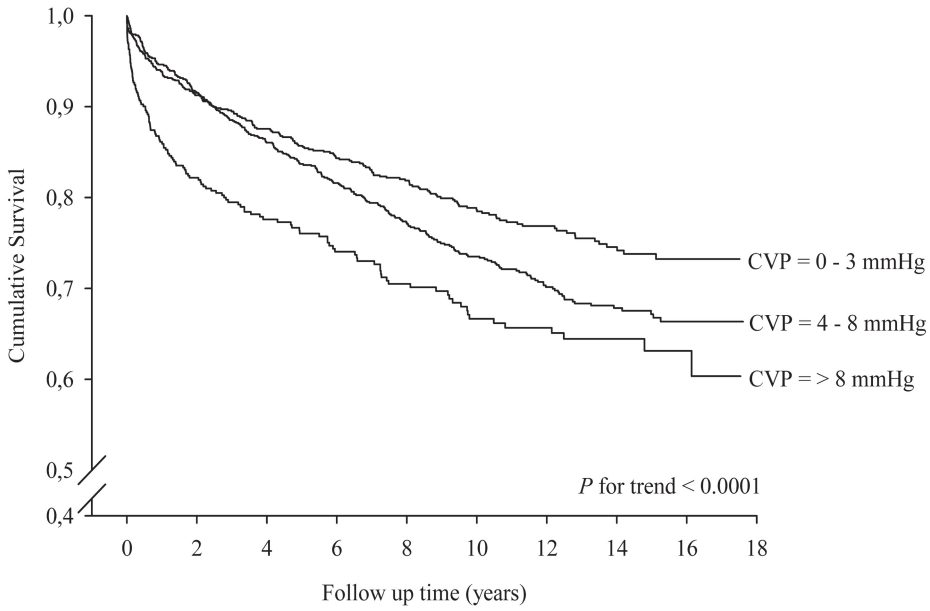

Figure 3. Kaplan-Meier Analysis of Event-Free Survival According to Tertiles of CVP. HR: 1.22 (95% CI: 1.00 to 1.49), p = 0.0466 for CVP 4 to 6 mm Hg; HR: 1.65 (95% CI: 1.35 to 2.01), p < 0.0001 for CVP >6 mm Hg, both compared with CVP 0 to 3. CI = confidence interval; HR = hazard ratio; CVP = central venous pressure; eGFR = estimated glomerular filtration rate.

Table 3. Multivariate Stepwise Cox Regression Model.

	Univariate		Multivariate		
Variables	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**Wald statistic**	**P-value**
Age (per 10 year increase)	1.05 (1.00-1.10)	0.0880	1.21 (1.12-1.31)	25.4	< 0.0001
Gender	1.03 (0.88-1.20)	0.713			
Cardiac index (per l/min/m^2 increase)	0.74 (0.66-0.84)	< 0.0001	0.81 (0.71-0.93)	9.1	0.0026
CVP (per mmHg increase)	1.05 (1.04-1.07)	< 0.0001	1.03 (1.01-1.05)	8.7	0.0032
eGFR (per 10 ml/min/1.73 m^2 decrease)	1.09 (1.05-1.13)	< 0.0001			
Medication					
Diuretic use	1.43 (1.22-1.67)	< 0.0001			
ACEi or ARB use	1.29 (1.10-1.52)	0.0017			
Aldosterone Antagonist use	1.92 (1.50-2.45)	< 0.0001	1.50 (1.10-2.02)	6.9	0.0087
Medical History (%)					
Coronary artery disease	1.26 (1.05-1.50)	0.0112			
Diabetes mellitus	1.83 (1.44-2.31)	< 0.0001	1.76 (1.34-2.31)	16.6	< 0.0001
Indication for catheterization					
Aorta insufficiency	0.63 (0.43-0.93)	0.0203			
Congenital heart disease	0.36 (0.17-0.77)	0.0078			
Pre transplantation (non-cardiac)	1.50 (1.21-1.85)	< 0.0001	2.54 (1.90-3.40)	39.2	< 0.0001
Heart failure	1.48 (1.21-1.85)	0.0001	1.71 (1.34-2.20)	18.1	< 0.0001
Rhythm disorders	0.49 (0.29-0.82)	0.0062			

ACEi= angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; CVP = central venous pressure; eGFR= estimated glomerular filtration rate.

model, adjusting CVP for other covariates (Online Table 2). CVP remained an independent predictor of impaired survival (HR: 1.03 per mm Hg increase, 95% CI: 1.01 to 1.05, p = 0.0144). To account for the effects of changing therapy during the study inclusion time, we adjusted for the year of catheterization. This secondary analysis yielded similar results (HR: 1.03 per mm Hg increase, 95% CI: 1.00 to 1.05, p = 0.0207). Excluding patients with known heart failure and heart transplant recipients, CVP was still associated with mortality (HR: 1.03 per 5 mm Hg increase, 95% CI: 1.00 to 1.06, p = 0.0369).

Discussion

The present study shows that increased CVP is associated with impaired renal function in a broad spectrum of cardiovascular patients who underwent right heart catheterization. In addition, the slope between CVP and impaired eGFR was steeper with relatively preserved cardiac function. Finally, an increased CVP was a strong and independent determinant of all-cause mortality, which was especially observed in patients with a CVP >6 mm Hg.

There are only limited data on the relationship between increased CVP and renal impairment. Studies in animals have shown that increasing renal venous pressure leads to a reduction in glomerular filtration, which was probably mediated by a decreased renal perfusion.[19] Renal vein constriction led to a decrease in GFR in rats,[20] whereas renal function decreased when renal vein pressure was increased in dogs, but only when cardiac output was reduced.[21] We recently showed that in patients with reduced cardiac function, secondary to pulmonary hypertension, increased CVP was strongly associated with renal impairment, especially when renal perfusion was already impaired.[11] Early studies on increased renal vein pressure in heart failure patients and animals showed a marked reduction in renal blood flow as well as water and salt excretion,[22,23] but the effect on GFR was not uniform. One small report showed a strong relationship between CVP and renal blood flow in advanced heart failure.[24]

Drazner et al.[13] reported that in patients with increased jugular venous pressure on examination, serum creatinine was significantly greater. In patients who underwent elective cardiac surgery, pre-operative presence of high CVP was a strong predictor of the occurrence of acute renal injury, independent of the presence of low CO.[25]

However, especially in patients with preserved cardiac function, data regarding the relationship between CVP and renal function are scarce. Diastolic dysfunction, a disease characterized by increased filling pressures, often coexists with renal failure and vice versa.[26-28] Interestingly, a recent study showed that renal dysfunction is even more important in defining mortality risk in patients with preserved cardiac function compared with those with systolic dysfunction.[29-30] Our present study confirmed that increased CVP is an important risk factor for decreased renal function in patients with preserved and decreased cardiac function.

Curvilinear effect of CVP with eGFR

We observed a biphasic relationship between eGFR and increasing CVP. In the physiologic ranges of CVP, up to 6 mm Hg, eGFR increases gradually. This subtle increase in eGFR may be a reflection of increased cardiac filling to preserve cardiac function by Frank-Starling mechanism (pre-load), and subsequent renal perfusion.[31] This gradual increase in eGFR was observed across the full spectrum of low to high cardiac index. We observed a decrease in eGFR when CVP increases above 6 mm Hg. In these patients, the equilibrium among venous return, CO, and CVP may have shifted toward a plateau phase or optimum, where CO is not further increased in response to greater CVP.[32] Greater CVP levels will then decrease renal perfusion pressure, which will further impair eGFR. However, if greater CVP levels preserve CO, and despite this mechanism, eGFR decreases with greater CVP, this action suggests that increased CVP also may exert an effect on GFR in this group of patients, independent of renal perfusion.

Importantly, the relationship between CVP and GFR is bound to be bidirectional. Not only may CVP influence GFR, but even mildly impaired renal function may initiate salt and water retention, resulting in increased cardiac filling pressures.[33] Because of the cross-sectional nature of our analysis, we were unable to investigate the cause-effect associations, and our present analysis must be regarded as hypothesis generating.

CVP and eGFR in patients with and without cardiac dysfunction

Of particular interest is the interaction between cardiac index and CVP on eGFR. Patients who have a combination of reduced perfusion (cardiac index) and increased venous congestion (CVP) suffer from fluid overload and decreased organ perfusion, leading, among other things, to renal dysfunction. We showed that patients with high CVP levels often also have decreased cardiac index and reduced eGFR. Remarkably, CVP and cardiac index showed an interaction on the relationship with eGFR, with an even more pronounced relationship in patients with relatively normal cardiac index. This further strengthens the observation of a relationship between CVP and eGFR, which is not exclusively due to reduced cardiac systolic function. It also challenges the intuitive notion that fluid overload, although deleterious from a cardiovascular perspective, will invariably be beneficial from the point of view of preservation of renal function. Because our analysis does not allow to dissect cause and effect relationships, however, it might also well be that the relatively normal cardiac index is maintained at the expense of the increased CVP. In that case, apparently, such a renal hemodynamic profile does not translate into better renal function. Our present findings seem inconsistent with our earlier findings, showing that patients with reduced renal perfusion in particular are prone to a detrimental effect of CVP on GFR.[11] However, we did not measure renal hemodynamics or renal function by clearance techniques in the present study, and the population was also different. Furthermore, our previous study consisted of patients with much lower cardiac indexes, all of which makes a comparison difficult. Nevertheless, this inconsistency needs to be further addressed in future studies.

New therapeutic agents in the treatment of acute heart failure that are specifically targeted at improvement of cardiac function and reducing venous congestion recently have shown promising results regarding renal function. A substudy of the SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) study, in which levosimendan was compared with dobutamine, showed that improvement of renal function was more pronounced in the group receiving levosimendan, despite the obvious positive inotropic effect of dobutamine.[34] The specific venodilatory effect observed with levosimendan, with subsequent reduced CVP, may be the pathophysiologic mechanism, supporting a direct pathophysio- logic link between CVP and renal impairment.[35]

CVP and mortality

Increased CVP and jugular venous pressure predispose to the development of heart failure in patients with cardiac dysfunction and have been associated with reduced survival in patients with heart failure.[12,13,36] Small studies have shown that invasive assessment of CVP is a predictor of cardiovascular outcome in patients with advanced heart failure.[14,15] In other selected patient populations, such as patients who underwent Fontan surgery or lung transplantation, greater CVPs were strong predictors of outcome.[37,38] The prognostic importance of increased CVP in patients with normal cardiac function has not been reported previously. We show that in a selected patient population, increased CVP remained a determinant of all-cause mortality, independent of cardiac function. This association with mortality was most prominent in patients with severely increased CVP, even after adjustment for other baseline characteristics. This finding was additive to the observation that greater CVP levels predispose to lower eGFR, which may influence survival by different mechanisms.

Clinical implications

Increased CVP frequently is observed in patients with and without reduced cardiac function, comprising almost 20% of patients in the present patient population. Recognition of these patients is essential because not only is renal dysfunction much more frequently observed, but the risk of mortality also increases with increasing CVP levels. Treatment to selectively lower CVP may be favorable to reduce symptoms and signs of congestion, improve GFR, and improve prognosis.

Study limitations

The present study comprises a selected patient population that had a specific indication for right heart catheterization. Patients undergoing right heart catheterization are prone to have greater right-sided filling pressures, and the present observations may therefore not represent the general cardiovascular population. However, this is a large cohort study, with invasive cardiac function and CVP measurements across the full range. Second, this

is a retrospective analysis, and no invasive data are available on renal blood flow and true GFR in these patients. Furthermore, it should be addressed that our study population had very different catheterization indications, medical history, and medication regime, all of which could have influenced our results. In our study, the presence of heart failure was a clinical diagnosis, rather than related to reduced cardiac index on catheterization. Therefore, the prevalence of heart failure in our study is most likely underestimated. The relationship between increased CVP and renal perfusion has been observed in heart failure. However our present study is the first to show an independent effect of CVP on renal function. Finally, the retrospective nature of this study and the cross-sectional design limited our ability to investigate the cause-effect relationship between renal impairment and increased CVP, which may actually mutually influence each other.

Conclusion

Increased CVP is associated with impaired renal function and is independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease.

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Chapter 3

Renal tubular damage

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Prognostic Value of Plasma NGAL for Mortality in Heart Failure Patients

Abstract

Background

In patients with heart failure (HF), renal dysfunction is associated with a poor outcome. We aimed to assess the prognostic value of plasma Neutrophil Gelatinase Associated Lipocalin (NGAL), a novel marker of renal tubular damage, in HF patients with or without renal dysfunction, and compare it with two frequently used biomarkers of chronic kidney disease.

Methods

Plasma NGAL, estimated GFR (eGFR) and cystatin C were assessed in 562 heart failure patients. Chronic kidney disease was defined as eGFR<60 mL/min/1.73 m^2. Outcome was all-cause mortality at 36 months.

Results

Mean age was 71±11, 61% were men and 97% were in New York Heart Association functional class II/III. Mean baseline eGFR was 54±20 mL/min/1.73 m^2, mean cystatin C was 11.2 (7.7-16.2) mg/L and median plasma NGAL was 85 (60-123) ng/mL. Higher plasma NGAL levels were independently associated with an increased risk of all cause mortality, in patients with and without chronic kidney disease (HR (per SD increase in log NGAL)=1.45 [1.22-1.72], P<0.001 & HR=1.51 [1.06-2.16], P=0.023 respectively). Similarly, both in patients with high and low cystatin C (median cut-off), higher plasma NGAL levels were independently associated with an increased risk of all cause mortality. Moreover, when NGAL was entered in the multivariable risk prediction model, eGFR (P=0.616) and cystatin C (P=0.937) were no longer associated with mortality.

Conclusions

Plasma NGAL predicts mortality in heart failure patients, both in patients with and without chronic kidney disease, and is a stronger predictor for mortality than the established renal function indices eGFR and cystatin C.

Introduction

Moderate to severe chronic kidney disease (CKD), mainly expressed by estimated glomerular filtration rate (GFR) <60 ml/minute/1.73 m^2, is strongly associated with increased mortality among patients with heart failure whereas these findings are far less established in the presence of mild impaired renal function.[1,2]

Interestingly, serum creatinine is relatively insensitive to changes in the GFR and kidney disease is not only reflected by GFR. In patients with intrinsic kidney failure, tubulointerstitial damage is an established marker for renal disease as well.[3] In different etiologies of kidney failure, tubulointerstitial hypoxia seems to be an early marker for the development of kidney failure.[4-13] Several studies showed that tubular markers are increased before an increase of creatinine is observed.[14-17]

We recently demonstrated that urinary markers of tubular damage, such as N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1) and Neutrophil Gelatinase Associated Lipocalin (NGAL), were elevated in patients with heart failure.[3,18] In addition, the tubular markers urinary NAG and KIM-1 were related to a poor prognosis, independent of eGFR.[19] Also, in a much larger sub study of the GISSI-HF trial, urinary NGAL levels were independently associated with cardiovascular outcome.[19] Few studies in heart failure patients have indicated that higher plasma markers of tubular damage are also related to an increased risk of mortality.[20-24]

However, the prognostic value of plasma tubular damage in patients with normal or mildly impaired renal function has been less well described.[23] The aims of this study were firstly to assess the role and performance of the tubular marker plasma NGAL as a prognostic marker of mortality in heart failure patients with both normal and impaired renal function. Secondly, we aimed to compare the prognostic value of plasma NGAL with two frequently used biomarkers of CKD.

Methods

Patient population

This is a retrospective analysis of the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH), a multicenter, randomized, open trial, designed to compare usual care, basic support and intensive support in patients with heart failure, conducted between 2002 and 2007 in The Netherlands.[25,26] Patients were included just before discharge of their hospitalization for acute decompensated heart failure. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the locally appointed ethics committees. All patients provided written informed consent for the main study. Of all 1023 patients from the COACH, 562 patients had baseline plasma available for this analysis. Demographic and clinical data were collected from chart review.

Renal function

We calculated estimated GFR (eGFR, mL/min/1.73 m^2) using the simplified Modification of Diet in Renal Disease formula (186.3 x (serum creatinine (mg/dL))$^{-1.154}$ x age$^{-0.203}$ x (0.742 if female))[27] at discharge and after 6 months. Cystatin C was measured using a Luminex assay by Alere San Diego (R&D). Plasma NGAL was measured using a simultaneous enzyme-linked immunosorbent assay (ELISA). The primary antibody was biotinylated and bound to a neutravidin plate. The secondary antibody was labeled with fluorescein, which serves as a hapten for an anti-fluoroscein antibody labeled with alkaline phosphatase (AP). All other liquid handling steps were performed with a Beckman Biomek FX.

Other biomarkers

To account for the possible inflammatory association of NGAL, C-reactive protein was measured using a bead-based immunoassay performed in microtiter plates. The primary antibody was conjugated to modified paramagnetic Luminex beads obtained from Radix Biosolutions; purified C-reactive protein was biotinylated.

B-type natriuretic peptide (BNP) was measured using a bead-based immunoassay performed in microtiter plates. The primary antibody was conjugated to modified paramagnetic Luminex beads obtained from Radix Biosolutions; the secondary antibody was biotinylated. Fluorescent signals were generated using Streptavidin-R-Phycoerythrin (SA-RPE: Prozyme PJ31S).

Outcome

The extended outcome of the COACH trial consisted of mortality assessed at 36 months, for which additional ethical committee approval was obtained.

Statistical analyses

Patients were divided into two groups according to the value of eGFR: the CKD group (eGFR < 60 ml/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) equation) and the non-CKD group (eGFR ≥ 60 ml/min/1.73 m^2). Because previous research suggests a difference in risk curves for CKD and non-CKD heart failure patients the analyses were conducted separately by the presence of CKD.[2] Data are presented as mean ± standard deviation when normally distributed, as median and interquartile range when non-normally distributed and as frequencies and percentages for categorical variables. Differences between baseline variables were evaluated by Student's t test, Kruskal-Wallis test, Mann-Whitney U or chi-square tests where appropriate. For the Kaplan-Meier curves, CKD classification and medians of plasma NGAL and cystatin C were used as cut-off points.

Table 1. Baseline characteristics of patients according to CKD and non-CKD.

	All patients n = 562	CKD n = 347	Non-CKD n = 205	P-value
Age (years)	71 ± 11	74 ± 10	66 ± 11	< 0.001
Gender (% female)	39	42	33	0.005
LVEF (%)	32 ± 14	33 ± 14	32 ± 15	0.493
NYHA (%)				< 0.001
2	47	39	59	
3	50	57	39	
4	3	4	2	
Systolic BP (mmHg)	118 ± 21	119 ± 22	116 ± 20	0.067
Diastolic BP (mmHg)	69 ± 12	68 ± 12	70 ± 12	0.122
Heart rate (bpm)	74 ± 13	74 ± 13	75 ± 13	0.43
Medical history (%)				
Hypertension	42	49	31	< 0.001
Peripheral arterial disease	16	18	12	0.009
Myocardial infartion	41	45	34	0.044
Atrial fibrillation	45	49	40	0.014
Stroke	15	18	11	0.061
COPD	28	31	24	0.084
Laboratory				
Cystatin C (mg/l)	11.2 (7.7-16.2)	12.6 (8.7-19.2)	8.8 (7-12.6)	< 0.001
NGAL (ng/ml)	85 (60-123)	104 (72-151)	65 (51-85)	< 0.001
Creatinine (µmol/l)*	115 (91-145)	138 (117-167)	87 (77-101)	< 0.001
Hemoglobin (g/dl)	13 ± 2	12.8 ± 1.9	13.7 ± 2	< 0.001
BNP (pg/ml)	454 (202-904)	480 (214-997)	416 (185-785)	0.078
CRP (mg/l)	2.3 (0.9-5.1)	2.3 (1-5.5)	2.3 (0.8-4.9)	0.093
Medication use (%)				
ACE inhibitor	72	68	79	< 0.001
Angiotensin receptor blocker	11	12	10	0.699
Beta blocker	67	64	71	0.207
Diuretic	95	96	95	0.238
Statin	39	39	38	0.576
Calcium antagonist	14	13	15	0.645

* for mg/dL divide by 88.4. Abbreviations: ACE: Angiotensin Converting Enzyme; BNP: Brain-type Natriuretic Peptide; Bpm: beats per minute; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; NGAL: Neutrophil Gelatinase Associated Lipocalin; NYHA: New York Heart Association functional class.

Cox proportional hazard analysis was used to assess whether plasma NGAL is a predictor of prognosis. NGAL showed a log-linear functional shape with the response variable and was transformed to a log scale. In consecutive models, plasma NGAL was adjusted for age and gender, eGFR and finally for the final model, consisting of diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, BNP and treatment (fully adjusted model).[28] For confirmatory analysis, BNP was replaced with NT-proBNP. Interactions between plasma NGAL and both eGFR and cystatin C were tested. To evaluate predictive utility of plasma NGAL, eGFR and cystatin C, areas under the curve (AUCs) of receiver operating characteristics (ROC) curves were calculated. Furthermore, we calculated the incremental value of plasma NGAL by means of the integrated discrimination index (IDI) and net reclassification index (NRI) for the model of all significant variables, versus this model plus plasma NGAL. Cut-off values of mortality were arbitrarily set at 10% and 30%.

A P value <0.05 was considered statistically significant. Statistical analyses were performed using R Statistics (version 2.13.2) and STATA (version 10, College Station, Texas).

Results

A total of 562 patients were available for this analysis. These patients did not significantly differ from the 461 excluded patients that originally participated in COACH (supplementary table). Mean age was 71±11, 61% were men, 97% were in New York Heart Association functional class II or III and 53% had been previously hospitalized due to

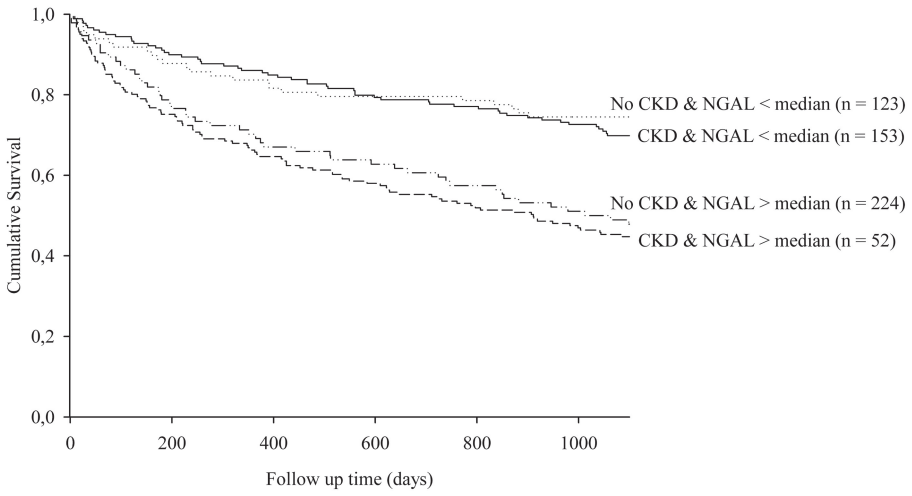

Figure 1. Three years mortality (CKD and non-CKD vs low/high NGAL) - Kaplan-Meier curves showing the association between all cause mortality and low/high eGFR (cut-off point 60 ml/min/1.73m^2) and low/high NGAL (cut-off point 84.62 ng/ml).

Table 2. Risk models of the predictive value of plasma NGAL, eGFR and cystatine-C in heart failure patients with and without CKD.

	All patients		CKD		Non-CKD	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
eGFR alone (per SD increase)	1.50 (1.30-1.72)	<0.001	1.54 (1.19-1.98)	<0.001	1.02 (0.66-1.56)	0.938
eGFR, age-sex-adj.	1.41 (1.21-1.64)	<0.001	1.51 (1.17-1.96)	0.002	0.93 (0.60-1.43)	0.726
eGFR, fully adjusted	1.28 (1.10-1.49)	0.001	1.26 (0.94-1.67)	0.121	1.04 (0.62-1.77)	0.858
eGFR, fully adjusted with NGAL	1.04 (0.88-1.24)	0.616	0.87 (0.63-1.21)	0.413	1.00 (0.60-1.67)	0.993
Cyst C alone (per SD increase)	1.15 (1.02-1.30)	0.020	1.04 (0.90-1.19)	0.623	1.24 (0.96-1.62)	0.100
Cyst C, age-sex-adj.	1.11 (0.98-1.26)	0.093	1.04 (0.90-1.20)	0.573	1.18 (0.91-1.55)	0.217
Cyst C, fully adjusted	1.09 (0.96-1.23)	0.208	1.07 (0.92-1.24)	0.406	1.08 (0.82-1.44)	0.572
Cyst C, fully adjusted with NGAL	0.99 (0.87-1.14)	0.937	0.98 (0.84-1.15)	0.836	1.03 (0.77-1.38)	0.844
NGAL alone (per SD increase)	1.61 (1.42-1.83)	<0.001	1.48 (1.27-1.72)	<0.001	1.62 (1.17-2.23)	0.003
NGAL, age-sex-adj.	1.51 (1.32-1.72)	<0.001	1.44 (1.23-1.68)	<0.001	1.44 (1.03-2.00)	0.033
NGAL, fully adjusted	1.47 (1.27-1.69)	<0.001	1.45 (1.22-1.72)	<0.001	1.51 (1.06-2.16)	0.023
NGAL, fully adjusted with eGFR	1.44 (1.22-1.69)	<0.001	1.51 (1.24-1.85)	<0.001	1.51 (1.06-2.16)	0.024
NGAL, fully adjusted with cyst C	1.47 (1.27-1.70)	<0.001	1.45 (1.22-1.74)	<0.001	1.50 (1.04-2.16)	0.026

* (per 5ml/min/m^2 decrease). Abbreviations: CI: Confidence Interval, cyst C: cystatin C; HR: Hazard Ratio, NGAL: Neutrophil Gelatinase Associated Lipocalin. Fully adjusted model: adjusted for age, sex, diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, BNP and treatment allocation.

heart failure. Mean baseline eGFR was 54±20 mL/min/1.73m^2, mean cystatin C was 11.2 (7.7–16.2) mg/l and median plasma NGAL was 85 (60-123) ng/ml.

Table 1 shows the baseline characteristics of the patients according to CKD and non-CKD. CKD patients were older, were in a higher NYHA class, were less likely to receive an ACE inhibitor, had higher levels of cystatin C and NGAL, lower levels of hemoglobin (all P < 0.001) and had more co-morbidities.

Plasma NGAL, eGFR and prognosis

After a follow up of 3 years, 232 (41%) patients died. The mortality in patients with CKD was 49% (N = 57/205) after three year versus 28% (170/347) in the non-CKD-group (HR 0.48 [0.36-0.65], P < 0.001).

Figure 1 shows the Kaplan Meier curves for the occurrence of all-cause mortality. Curves are shown for 4 groups (CKD and non-CKD, and high and low NGAL). Within the groups of NGAL, there was no difference in mortality between the two CKD groups.

Overall, higher plasma NGAL levels were independently associated with increased mortality. In all consecutive models (plasma NGAL adjusted for age and gender, adjusted for eGFR and finally for the fully adjusted model with BNP), higher plasma NGAL levels were independently associated with an increased risk of all cause mortality (HR: 1.44 per

SD increase in log NGAL, 95% CI 1.22-1.69, P < 0.001) (Table 2). The prognostic values (area under the curve [AUC]) of plasma NGAL and eGFR are shown in table 3. IDI improved significantly adding NGAL to the fully adjusted model (0.029, P < 0.001) whereas NRI almost reached the level of statistical significant (0.062, P = 0.054). When BNP was replaced with NT-proBNP, results remained consistent.

Divided in CKD and non-CKD, plasma NGAL levels remained significantly associated in the consecutive models with three years mortality, in CKD patients and in non-CKD patients whereas eGFR was only univariate associated with mortality in CKD patients. Furthermore, eGFR was no longer significantly associated with mortality in CKD patients when plasma NGAL was introduced in the crude, age and sex adjusted and fully adjusted model (Table 2).

Plasma NGAL, cystatin C and prognosis

In accordance with eGFR, we divided cystatin C into two groups. Figure 2 shows the Kaplan Meier curves for the occurrence of all-cause mortality (high and low cystatin C, and high and low NGAL). Within the groups of NGAL, there was no difference in mortality between the two cystatin C groups.

Again, higher plasma NGAL levels were independently associated with increased mortality, in all consecutive models (adjusted for age, gender and cystatin C, and finally for the fully adjusted model with cystatin C) (Table 2). The prognostic value of plasma NGAL including cystatin C (measured by AUC) for the total group was higher than the AUC of cystatin C without NGAL (table 3). IDI improved significantly adding NGAL to the fully adjusted model (0.027, P < 0.001) whereas NRI did not show improvement in discrimi-

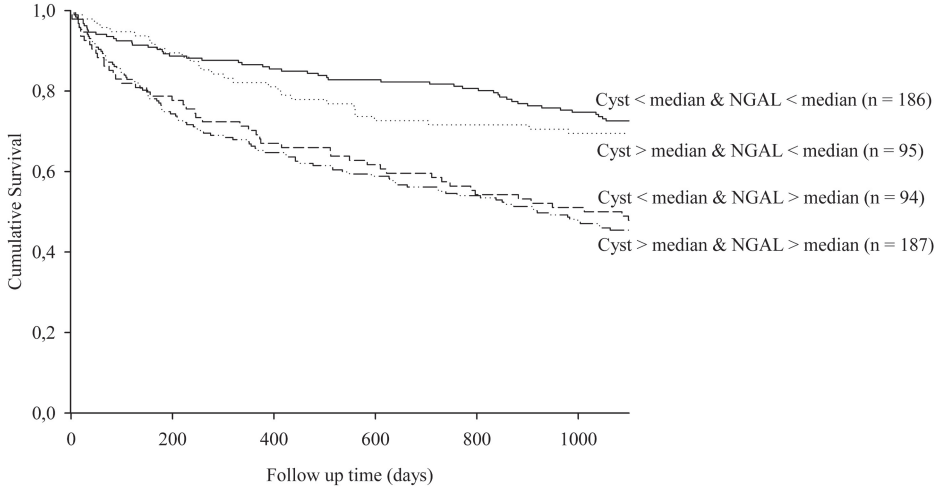

Figure 2. Three years mortality (low/high cystatin C vs low/high NGAL) - Kaplan-Meier curves showing the association between all cause mortality and low/high cystatin C (cut-off point 11.2 mg/l) and low/high NGAL (cut-off point 84.62 ng/ml).

Table 3. AUC of models comparing the prognostic value of eGFR and NGAL in heart failure patients with and without CKD.

	All patients	CKD	Non-CKD
eGFR	0.643 (0.596-0.689)	0.596 (0.537-0.654)	0.487 (0.389-0.585)
eGFR, fully adjusted	0.791 (0.753-0.829)	0.786 (0.748-0.824)	0.756 (0.715-0.796)
Cyst C	0.565 (0.517-0.613)	0.515 (0.452-0.573)	0.586 (0.498-0.673)
Cyst C, fully adjusted	0.786 (0.748-0.824)	0.781 (0.743-0.820)	0.758 (0.718-0.798)
NGAL	0.672 (0.627-0.717)	0.636 (0.579-0.693)	0.634 (0.549-0.720)
NGAL, fully adjusted	0.798 (0.761-0.835)	0.794 (0.756-0.831)	0.773 (0.734-0.812)
	P=0.287 vs eGFR Fam	P=0.131 vs eGFR Fam	P=0.074 vs eGFR Fam
	P=0.099 vs Cystatin C Fam	P=0.021 vs Cystatin C Fam	P=0.109 vs Cystatin C Fam
NGAL, fully adj.+eGFR	0.798 (0.761-0.835)	0.794 (0.756-0.831)	0.772 (0.734-0.812)
	P=0.877 vs NGAL Fam	P=0.593 vs NGAL Fam	P=0.275 vs NGAL Fam
NGAL, fully adj.+cyst C	0.799 (0.761-0.836)	0.794 (0.756-0.832)	0.773 (0.734-0.812)
	P=0.315 vs NGAL Fam	P=0.892 vs NGAL Fam	P=0.925 vs NGAL Fam

Abbreviations: NGAL: Neutrophil Gelatinase Associated Lipocalin. Fam: Fully adjusted model: adjusted for age, sex, eGFR, diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, BNP and treatment allocation.

nation (-0.025, P = 0.409). When BNP was replaced with NT-proBNP, results remained consistent. The discrepancy in significance could be explained because IDI can be seen as the continuous version if NRI with probability differences used instead of categories.

Divided into high and low cystatin C groups, plasma NGAL levels remained significantly associated in the consecutive models with three years mortality, whereas cystatin C was not significantly associated with mortality in both groups. Furthermore, cystatin C was no longer significantly associated with mortality in CKD patients when plasma NGAL was introduced in the crude, age and sex adjusted and fully adjusted model (Table 2).

Discussion

This study shows that plasma NGAL predicts mortality in heart failure patients, both in patients with and without chronic kidney disease. Moreover, plasma NGAL is a stronger predictor for mortality than the frequently used biomarkers of impaired renal function eGFR and cystatin C.

Plasma NGAL and prognosis

NGAL is a 25 kDa lipocalin-superfamily glycoprotein that is considered to play a role in acute kidney injury in a diverse range of settings.[16,29] In normal circumstances, only small amounts can be found in plasma and urine. However, during and after acute kidney injury, NGAL levels rise quickly and massively.[30]

In the present study we found that plasma NGAL is independently associated with mortality. This confirms our recent study in which we found that tubular damage in heart failure was prevalent in chronic heart failure and related to impaired survival, independent of GFR and albuminuria.[18] In this small study, we were unable to establish the prognostic value of urinary NGAL in chronic heart failure. However, in a much larger sub study of the GISSI-HF trial, urinary NGAL levels were independently associated with outcome.[19]

Bolignano and colleagues found prognostic significance of plasma NGAL levels in 46 patients with chronic heart failure.[20] In three confirmative smaller studies, serum NGAL, measured at admission for acute heart failure, predicted death only when NGAL was dichotomized by an optimally taken cut off point.[21,22]

In the CORONA study, with 1415 patients with chronic heart failure of ischemic etiology, plasma NGAL was an univariate predictor of all-cause mortality, cardiovascular death and hospitalization. However, plasma NGAL was no longer a significant predictor when adjusted for GFR and NT-proBNP.[23] In contrast, Alvelos and colleagues showed that plasma NGAL was an independent predictor of increased risk of short term death and/or readmission in patients with acute heart failure.[22] In the recent GALLANT trail, in which plasma NGAL was measured in 186 patients with acute heart failure at discharge, plasma NGAL was an even better prognostic indicator compared to BNP.[24]

Plasma NGAL in non-CKD patients

This study shows that plasma NGAL predicts mortality in heart failure patients, even in non-CKD patients. Taking into consideration that creatinine is a marker of kidney function and NGAL is a marker of kidney injury, there are several arguments why tubular damage in heart failure patients is associated with prognosis whereas glomerular function in the mild impaired renal function ranges is not.

First, in heart failure patients, decreased perfusion may be a key deleterious factor for the kidneys. Because the tubulus is more vulnerable to hypoxic damage,[4-12] it is possible that small declines in renal function result in tubular damage where the renal cortex stays intact, maintaining GFR.[4,31] Therefore, tubular damage might better reflect a decreased perfusion than eGFR.[30]

Second, in the acute setting, tubular markers are increased while creatinine is still normal.[14-17] A possible mechanism is that decreased renal perfusion in heart failure leads to compensatory glomerular hyperfiltration.[32] In fact, renal blood flow can decrease by 30-40% without apparently affecting functional GFR.[31] Notably, tubular markers reflect renal injury, instead of renal function. Tubular markers, such as plasma NGAL, are therefore likely to be more sensitive than creatinine.

Third, creatinine levels are dependent of muscle metabolism, weight, age and sex. Although formulas partly overcome this limitation, creatinine is still actively secreted by the proximal tubule, especially when GFR is low, making creatinine less useful in extremes of true GFR.

Plasma NGAL compared with eGFR and cystatin C

We show that plasma NGAL is a more powerful predictor of mortality than eGFR. The results of the incremental value of plasma NGAL over eGFR are almost similar when compared with the results of a more sensitive glomerular marker cystatin C.[33,34] While eGFR is regularly used in daily practice, cystatin C can be seen as a more accurate reflection of glomerular function. In acute settings, creatinine is known to be a slower marker.[33,34] Creatinin based formulas are less accurate in extremes of true eGFR[27] and this is one of the factors why cystatin C is superior to creatinine.[35-38] Moreover, cystatin C is less dependent on body mass, decreased muscle mass and cachexia, which are present in patients with chronic heart failure.[39-42]

Nevertheless, even when related to and adjusted for cystatin C, plasma NGAL remained to have a better prognostic value. This might indicate that in heart failure patients, tubular damage might better reflect an impaired hemodynamic status as compared with glomerular function.

Limitations

Recognizing the importance of renal biomarkers in heart failure for improving risk stratification, there are several concerns in analyzing different biomarkers. It would be best to approach the accuracy of risk prediction with a multi-marker approach.

Primary renal disease was not excluded at baseline in this study. Therefore, the observed relationships could have been affected by underlying renal disease, where associations between tubular damage, glomerular function and outcome can be different. Larger studies are required to confirm our results, preferably with a specific intervention to investigate effects rather than associations. Also, we do not have information on cause of death.

Kidney disease may not only be identified by low GFR or tubular damage. Unfortunately we do not have sufficient data on albuminuria in the COACH-cohort.[43,44]

We assessed plasma NGAL, rather than urinary NGAL, which may be more affected by specific confounders such as bacterial infection, presence of cancer or COPD and inflammation,30 although C-reactive protein was not correlated with plasma NGAL in the present study. Plasma levels of NGAL still increase markedly (up to 16-fold) in the setting of renal tubular injury. Plasma NGAL also has the advantage of easy collection, because plasma is already collected in the clinical setting.[45]

Conclusions

The present study shows the incremental prognostic value of plasma NGAL in heart failure patients with and without renal dysfunction. Moreover, plasma NGAL is a stronger predictor for mortality than frequently used biomarkers of chronic kidney disease.

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Chapter 4

Renal function in acute heart failure

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Effects of Nesiritide on Renal Function During Hospitalization for Acute Decompensated Heart Failure Results from ASCEND-HF

Abstract

Background

Contradictory results have been reported on the effects of nesiritide on renal function in patients with acute decompensated heart failure (ADHF). We studied effects of nesiritide on renal function during hospitalization for ADHF.

Methods

A total of 7141 patients were randomized to receive either nesiritide or placebo. Baseline and discharge creatinine and blood urea nitrogen (BUN) measurements were available in 4708 patients. Worsening renal function was defined as an increase of serum creatinine >0.3 mg/dL and >25% at any time during hospitalization.

Results

Median (25th–75th percentile) baseline creatinine was 1.2 (1.0–1.6) mg/dL and median baseline BUN was 25 (18–38) mmol/L. Changes in both serum creatinine and BUN were similar in nesiritide-treated (p=0.20) and placebo-treated (p=0.41) patients. In a multivariate model, independent predictors of an increase in serum creatinine were a lower baseline BUN, higher systolic blood pressure, prior weight gain, and lower baseline potassium (all p<0.0001). The frequency of worsening renal function during hospitalization was similar in the nesiritide and placebo group (14.1% and 12.8%, respectively; odds ratio with nesiritide 1.12 [0.95–1.32], p=0.19) and was not associated with death or rehospitalization at 30 days. However, both baseline and discharge creatinine were associated with death or rehospitalization (both p<0.0001).

Conclusions

Nesiritide did not affect renal function in patients with ADHF. Both baseline and discharge renal function, but not worsening renal function, were associated 30 day mortality or rehopitalization.

Introduction

Nesiritide is recombinant B-type natriuretic peptide (BNP)[1-4] approved for use in patients with acute heart failure, due to its ability to reduce pulmonary-capillary wedge pressure and improve dyspnea.[3,5] Yet after approval, it was suggested that nesiritide might cause renal toxicity and increase mortality. Specifically, in a meta-analysis of five randomized studies with 1269 acute heart failure patients compared with placebo, intravenous nesiritide increased the rate of worsening renal function by 50%, although confidence intervals around this estimate were wide.[7,8] These concerns led to a marked decrease in the use of this nesiritide.[6]

The Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) was conducted to re-evaluate the efficacy and safety of nesiritide, compared with placebo added to standard-of-care in 7144 acute decompensated heart failure patients. Overall, compared with placebo, nesiritide did not improve (or worsen) clinical outcomes and nesiritide did not increase the risk of worsening renal function (pre-defined as more than a 25% decrease in estimated glomerular filtration rate [eGFR]).[9]

The present analysis was a retrospective analysis of ASCEND-HF, in which we examined the detailed effects of nesiritide on renal function, clinical predictors on changes in creatinine and blood urea nitrogen (BUN) during hospitalization, and the relationship between changes in renal function and outcomes.

Methods

ASCEND-HF was a randomized, double blind, placebo-controlled trial of nesiritide in addition to standard of care.[10] The trial was conducted from May 2007 through August 2010 at 398 international centers. Patients were included if they were hospitalized for heart failure occurring within 24 hours before they received their first intravenous treatment for heart failure, or if they had received a diagnosis of acute decompensated heart failure (ADHF) less than 48 hours after hospitalization for another cause, and underwent randomization within 24 hours after intravenous treatment. Patients were excluded if they had a high-risk of hypotension (systolic pressure <100 mm Hg or 110 mm Hg with the use of intravenous nitroglycerin), other contraindications for vasodilators, persistent uncontrolled hypertension, normal levels of BNP or N-terminal (NT-) pro-BNP, chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis), or clinically significant anaemia.[10] Eligible patients were randomly assigned in a 1:1 ratio to receive nesiritide or placebo, in addition to standard therapy. After a recommended (but optional) intravenous bolus of nesiritide, at a dose of 2 μg per kilogram, nesiritide was administered as a continuous infusion of 0.010 μg per kilogram per minute for 24 hours or more for up to 7 days.

The ASCEND-HF study was approved by each participating center's ethics committee or institutional review board, and all participants were provided written informed consent (ClinicalTrials.gov number, NCT00475852).

Patients for Analyses

A total of 7141 patients underwent randomization; of these, 7007 (98%) received the study drug and were included in the modified intention-to-treat analysis. The study groups were well-balanced and similar to the intention-to-treat group.[9] Our retrospective analysis of ASCEND-HF focuses on the 4708 patients who had a baseline and at least one follow-up creatinine measurement available for review.

Worsening Renal Function

Worsening renal function was defined as an increase of serum creatinine >0.3 g/dL (26.5 μmol/L) in combination with >25% increase in creatinine during hospitalization. Creatinine was measured at baseline, after 24 hours, at the end of treatment and at discharge. By measuring worsening renal function by relative and absolute rates we accounted for the exponential relationship between serum creatinine and eGFR.[11,12]

Endpoints

The primary endpoint of interest in this study is the composite of rehospitalization for heart failure and death from any cause within 30 days post-event. Other endpoints of interest include the separate outcomes of rehospitalization for heart failure or death from any cause within 30 days, and death from any cause within 180 days. The following criteria were required for hospitalization events to be classified as due to heart failure: typical clinical manifestations of worsening heart failure and the addition of (or increase in) treatment specifically for worsening heart failure with an intravenous pharmacologic agent, or mechanical or surgical intervention or ultrafiltration, hemofiltration, or dialysis specifically for management of persistent or worsening heart failure.

Statistical Analyses

Change in creatinine was defined as the change from baseline to discharge; in Table 1, the change is displayed in quintiles. Presenting factors, baseline medications, and medical history information is reported as counts and frequencies for discrete factors and either the mean with standard deviation or 50th, 25th, and 75th percentiles. A Wilcoxon rank-sum test was performed for continuous factors and a chi-square test was performed for binary measurements.

Regression modeling was generated to assess the pre-specified baseline factors on change in creatinine. In order to verify that modeling assumptions were met, plots were

generated to view the residuals of each independent predictor and outcome. The BUN, BNP, and NT-proBNP were all modeled using a log transformation. A proc univariate test for normality was also generated to ensure modeling assumptions were met. The stepwise procedure was selected using a p-value of 0.05 for entry and to stay in the model. Interaction between treatment and baseline factors were reviewed. An additional outcome of interest is mortality or heart failure re-hospitalization by 30 days and mortality within 180 days of randomization. SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Results

The clinical characteristics of 4708 patients who were included in the present study did not significantly differ from the 2433 patients who were excluded, due to missing creatinine serial data (data not shown). Table 1 shows the baseline characteristics of the included population. In short, median age was 65 ± 14 year, and 34% were female. Nesiritide treatment was given to 50% of the included patients. A history of hypertension was present in 72% of patients and 35% had a history of myocardial infarction. Median weight was 78 (64–95) kg with a median change in weight of -2.3 (-5.0 – -0.6) kg during hospitalization. Loop diuretics were administered in 82% of all patients within the first 24 hours.

Change in Renal Function

Median creatinine concentration increased from 1.2 (1.0–1.6) mg/dL at baseline to a maximum of 1.4 (1.1–1.9) mg/dL, during hospitalization. Median BUN concentration increased from 25 (18–38) mmol/L at baseline to a maximum of 33 (23–50) mmol/L, during hospitalization. The change in both serum creatinine and BUN was similar in nesiritide- and placebo-treated patients (p=0.20 and p=0.41, respectively) as shown in Figure 1 and supported by the cumulative distribution curves shown in figure 2.

In Table 1, patients were grouped by quintiles of serum creatinine change between baseline and discharge. Patients with the greatest increase in creatinine were older, more often female, more often had diabetes, had higher left ventricular ejection fraction (LVEF), higher NT-proBNP levels (although the highest values were seen in the first quintile), a higher baseline systolic blood pressure, and more cardiovascular comorbidities including diabetes. Patients in the highest quintile more often received loop diuretics within the first 24 hours, had a higher weight at baseline, and more decrease in weight during hospitalization.

Worsening renal function at any time from randomization through discharge occurred in 13.4% of the patients and the frequency was similar in the nesiritide and placebo groups (14.1% and 12.8%, respectively; odds ratio with nesiritide 1.12; 95% confidence

Table 1. Clinical Characteristics According to Quintiles of Change in Serum Creatinine between Baseline and Discharge.

		Change in Creatinine (Discharge Level–Baseline Level) (g/dL)					
	Total	**<-0.15**	**-0.15–0.001**	**0.001–0.101**	**0.101–0.239**	**>0.239**	**p-value**
Number of patients	4708	941	947	915	964	941	
Nesiritide	2355 (50.0)	466 (49.5)*	461 (48.7)*	466 (50.9)*	478 (49.6)*	484 (51.4)*	0.754
Placebo	2353 (50.0)	475 (50.5)*	486 (51.3)*	449 (49.1)*	486 (50.4)*	457 (48.6)*	-
Age, years (SD)	65.4 (14.2)	65.8 (14.3)	64.2 (14.5)	63.6 (14.2)	65.0 (14.4)	68.1 (13.3)	< 0.001
Female sex	34.1%	27.4%	35.4%	34.8%	34.2%	38.9%	< 0.001
Median weight (kg)	77.5 (64.0–94.7)	75.0 (62.2–92.0)	77.0 (63.0– 2.9)	77.0 (63.0–93.0)	79.0 (64.0–96.6)	79.5 (67.2–97.7)	< 0.001
Median SBP	123 (110–140)	120 (110–134)	120 (110–137)	122 (110–137)	125 (110–140)	130 (114–145)	< 0.001
Median DBP	74.0 (66.0–84.0)	73.0 (65.0–82.0)	74.0 (68.0–83.0)	75.0 (68.0–84.0)	75.0 (66.0–85.0)	75.0 (65.0–85.0)	0.283
Median heart rate	82.0 (72.0–94.0)	82.0 (72.0–94.0)	83.0 (72.0–95.0)	83.0 (72.0–96.0)	82.0 (72.0–95.0)	80.0 (70.0–90.0)	0.001
Race	4707						< 0.001
White	2503 (53.2%)	492 (52.3%)	502 (53.0%)	459 (50.2%)	495 (51.3%)	555 (59.0%)	
Black	805 (17.1%)	142 (15.1%)	136 (14.4%)	168 (18.4%)	200 (20.7%)	159 (16.9%)	
Asian	1198 (25.5%)	269 (28.6%)	271 (28.6%)	254 (27.8%)	237 (24.6%)	167 (17.7%)	
Other	201 (4.3%)	38 (4.0%)	38 (4.0%)	33 (3.6%)	32 (3.3%)	60 (6.4%)	
Medical history							
HF-PEF	15.5%	13.7%	13.5%	12.7%	16.8%	20.6%	< 0.001
Myocardial infarction	34.7%	33.0%	36.2%	32.2%	33.4%	38.7%	0.018
Atrial fibrillation	36.4%	38.7%	36.0%	34.8%	33.7%	38.8%	0.073
Hypertension	72.2%	68.8%	67.3%	69.8%	73.3%	81.6%	< 0.001
Diabetes mellitus	42.0%	39.5%	41.3%	37.5%	42.6%	48.8%	< 0.001
Medication use							
ACE-inh/ARB	62%	60%	62%	61%	63%	62%	0.782

	Change in Creatinine (Discharge Level–Baseline Level) (g/dL)						
	Total	**<-0.15**	**-0.15–0.001**	**0.001–0.101**	**0.101–0.239**	**>0.239**	**p-value**
Aldosteron antagonist	27%	28%	28%	28%	25%	24%	0.057
Beta blockers	59%	57%	58%	57%	59%	62%	0.264
Loop diuretics	90%	90%	90%	90%	90%	90%	0.939
Oral/topical nitrates	23%	23%	23%	22%	21%	27%	0.073
Digoxin	27%	29%	28%	30%	25%	23%	0.003
Hydrazaline	7%	7%	6%	6%	6%	11%	< 0.001
Anticoagulant	24%	25%	22%	25%	24%	25%	0.427
Inotropes	4%	5%	4%	4%	4%	2%	0.014
Vasodilators	14%	13%	16%	13%	11%	16%	0.002
Loop diuretic in first 24h	3845 (81.7%)	752 (79.9%)	740 (78.1%)	739 (80.8%)	801 (83.1%)	813 (86.4%)	< 0.001
Baseline laboratory							
eGFR (mL/min/m^2)	62 ± 25	48 ± 18	65 ± 23	70 ± 23	66 ± 25	60 ± 27	< 0.001
Creatinine (mg/dL)	1.2 (1.0–1.6)	1.5 (1.3–1.9)	1.2 (1.0–1.4)	(0.9–1.3)	(1.0–1.4)	(1.0–1.6)	< 0.001
BUN (mmol/L)	25 (18–38)	33 (23–50)	24 (18–36)	22 (16–32)	23 (17–33)	26 (18–38)	< 0.001
Hemoglobin (g/dL)†	12.7 (11.3–14.0)	12.8 (11.5–14.0)	12.7 (11.4–14.1)	12.7 (11.3–14.0)	12.7 (11.3–13.9)	12.4 (11.0–13.8)	< 0.001
BNP (pg/ml)	967 (521–1776)	1135 (587–2326)	1006 (482–1802)	889 (490–1540)	944 (528–1770)	913 (524–1594)	0.001
NT-proBNP (pg/dL)	4269 (2000–9065)	5750 (2318–12000)	3865 (1935–7868)	3712 (1735–7358)	4010 (1906–8404)	4790 (2127–10000)	< 0.001
Sodium	139 (136–141)	138 (135–141)	139 (136–141)	139 (136–141)	139 (136–141)	139 (136–-141)	< 0.001
Potassium	4.1 (3.7–4.4)	4.2 (3.8–4.6)	4.1 (3.7–4.4)	4.0 (3.7–4.3)	4.0 (3.7–4.4)	4.1 (3.7–4.4)	< 0.001
Median LVEF	30.0 (20.0–36.0)	25.0 (20.0–35.0)	28.0 (20.0–35.0)	28.0 (20.0–35.0)	30.0 (20.0–37.0)	30.0 (24.0–40.0)	< 0.001
Median change in SBP	-8 (-20, 3)	-4 (-16, 8)	-7 (-18, 4)	-8 (-20, 4)	-10 (-21, 1)	-10 (-27, 1)	< 0.001
Median change in weight	-2.3 (-5.0, -0.6)	-2.3 (-5.0, -0.5)	-2.0 (-4.5, -0.4)	-2.2 (-4.8, -0.5)	-2.1 (-4.6, -0.7)	-2.7 (-5.2, -1.0)	0.006

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; CO = cardiac output; CVP = central venous pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NS = not significant; SBP = systolic blood pressure.

Table 2. Characteristics Independently Related to Changes in Creatinine.

	Parameter Estimate	Standard Error	t-value	Pr >|t|	P-value
Intercept	0.32977	0.05367	6.14	<0.0001	0.0212
Planned treatment	0.00127	0.00939	0.14	0.8921	0.0017
Log BUN	-0.09123	0.00874	-10.44	<0.0001	0.0004
Baseline SBP (mmHg)	0.00230	0.00028	8.15	<0.0001	0.0819
Baseline DBP (mmHg)	-0.00183	0.00041	-4.49	<0.0001	0.3873
Potassium (mmol/L)	-0.04013	0.00818	-4.90	<0.0001	0.9894
Prior weight gain	0.03898	0.00992	3.93	<0.0001	0.2412

All abbreviations can be found in Table 1.

interval, 0.95–1.32, p=0.19), regardless of the degree of baseline renal insufficiency (OR 1.01 [0.79-1.28, p=0.955 in patients with baseline eGFR <60 ml/min/1.73m^2, and OR 1.24 [0.98-1.57], p=0.076 in patients with baseline eGFR ≥60 ml/min/1.73m^2).

Using a multivariable stepwise model, we defined characteristics that were related to changes in creatinine (Table 2). In summary, a lower baseline BUN (log β -0.091, p<0.0001), a higher systolic blood pressure (β 0.002 in standard deviation [SD], p<0.0001), a lower diastolic blood pressure (β -0.002, p<0.0001), a lower baseline potassium (β -0.040, p<0.0001), and prior weight gain (β 0.039, p<0.0001), were all significantly related to an increase in serum creatinine. Treatment with nesiritide did not have a significant relation to a change in creatinine (β 0.001, p=0.89).

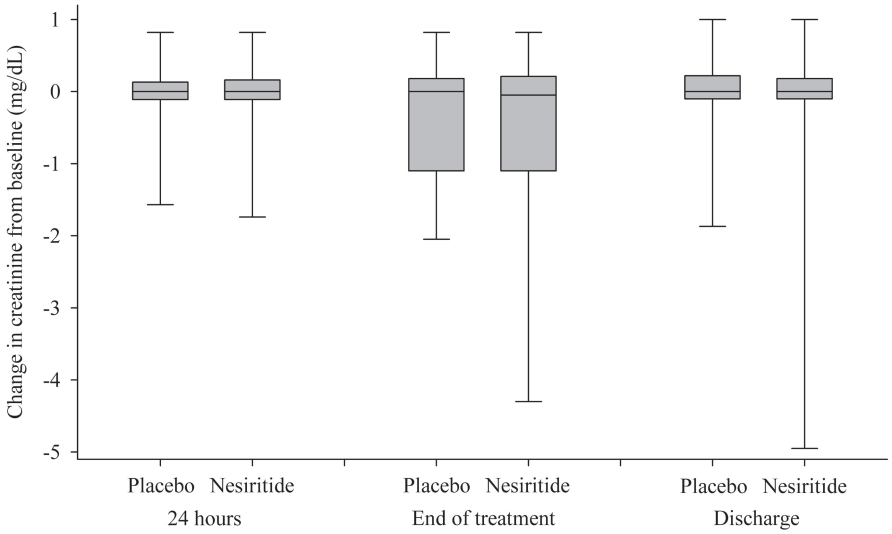

Figure 1a. Patients Randomized to Either Nesiritide or Placebo. This figure displays the changes in (a) serial creatinine levels.

Table 3. The Prognostic Value of Serum Creatinine at Different Time Points for 30-day Mortality.

Measure of Creatinine	Univariate Hazard Ratio	Chi-square	p-value
Baseline creatinine (per 1.5 fold increase)	1.487	61.31	<0.001
Discharge creatinine (per 1.5 fold increase)	1.533	40.88	<0.001
Change in creatinine (per 0.3 increase)	1.090	1.60	0.206

Table 4. The Prognostic Value of Serum Creatinine at Different Time Points for 30-day Death or Re-hospitalization.

Measure of Creatinine	Univariate Hazard Ratio	Chi-square	p-value
Baseline creatinine (per 1.5 fold increase)	1.357	117.95	<0.001
Discharge creatinine (per 1.5 fold increase)	1.417	108.13	<0.001
Change in creatinine (per 0.3 increase)	1.001	0.02	0.902

Predictive Value of Creatinine in relation to Clinical Outcomes

The prognostic value of serum creatinine and change in serum creatinine at different time points is shown in Tables 3 and 4. Table 3 shows that creatinine at baseline (Chi-square 61.3, p<0.0001) and at discharge (Chi-square 40.9, p<0.0001) both had a strong association with 30-day mortality. Creatinine at baseline and at discharge also had a strong association with the combined endpoint of 30-day mortality or re-hospitalization

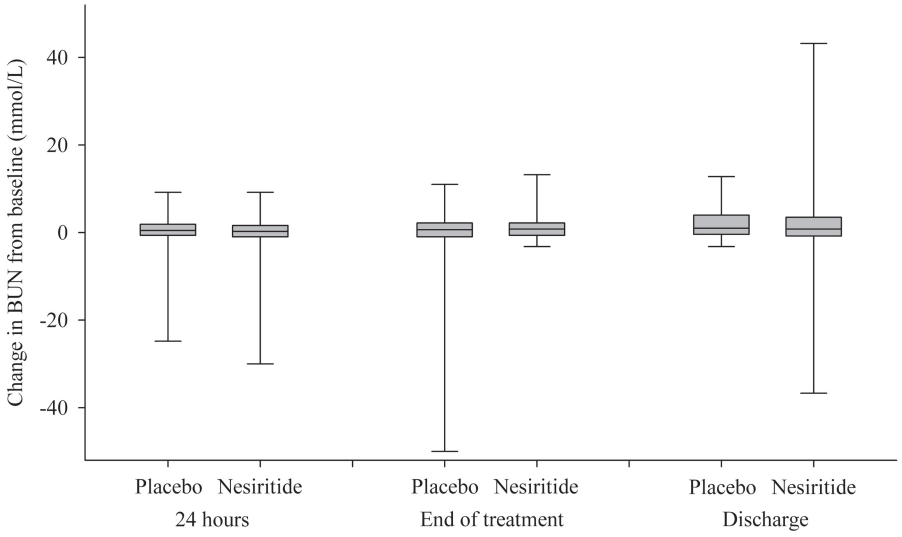

Figure 1b. Patients Randomized to Either Nesiritide or Placebo. This figure displays the changes in (b) BUN levels in patients randomized to either nesiritide or placebo. BUN indicates blood urea nitrogen.

(Chi-square 118.0 and 108.1, both p<0.0001). Conversely, increase in creatinine between baseline and discharge had no association with either 30-day mortality (Chi-square 1.6, p=0.21) or the combined endpoint (Chi-square 0.02, p=0.90).

Overall, worsening renal function was not associated with the combined endpoint of mortality and heart failure hospitalization within 30 days (hazard ratio [HR] 1.12 [0.81–1.50], p=0.52), nor with the separate endpoint of death within 30 days (HR 0.96 [0.51–1.82], p=0.90), nor with heart failure hospitalization within 30 days (HR 1.16 [0.83–1.62], p=0.40).

Discussion

In the present renal retrospective analysis of the ASCEND-HF trial, we found that nesiritide did not have any effect on changes in creatinine or BUN during hospitalization in patients with ADHF. Baseline and discharge renal function, but not worsening renal function, were associated with 30 day death and death or re-hospitalization.

Worsening Renal Function

Renal dysfunction is prevalent in patients with both chronic and acute heart failure, and may influence patients' treatments and outcomes.[13] It is known that 20-40% of patients with acute heart failure have an increase in creatinine, which is generally defined as

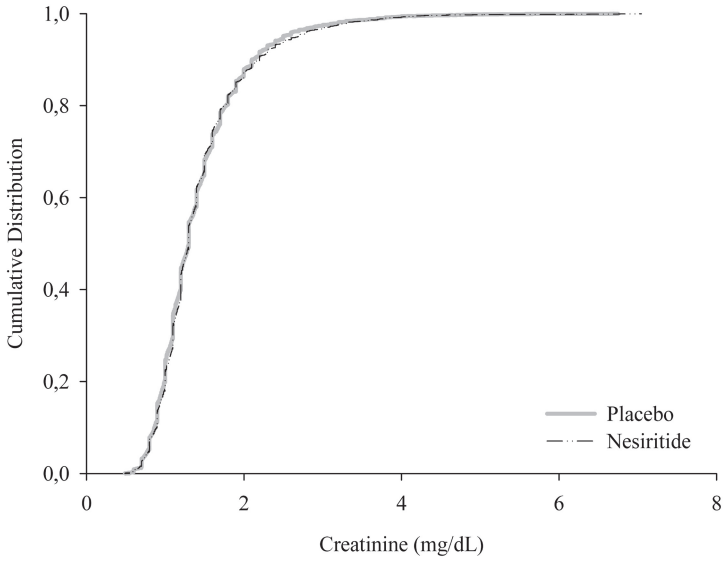

Figure 2a. Cumulative Distribution Curve. This figure displays the cumulative distribution curves of both nesiritide and placebo on (a) creatinine at end of treatment.

worsening renal function.[13] We also found that the prevalence of diabetes was higher in patients with more worsening renal function, confirming previous studies.[27,28]

In our study, we found that baseline renal function was mildly impaired and decreased further during hospitalization. Predictors of a decline in renal function (measured using creatinine on a continuous scale) included higher systolic and lower diastolic blood pressure, lower potassium levels, more prior weight gain, and lower BUN levels; thereby confirming previous studies.[12,14-16]

Nesiritide

In a meta-analysis of five randomized studies that included 1269 ADHF patients, the frequency of worsening renal function was found to be 50% more prevalent in the nesiritide group.[7] Therefore, the neutral effects of nesiritide on renal function in the present study is markedly different from the meta-analysis. There are several potential explanations for this difference. First, it should be noted that from 3 studies, data cannot be obtained, since they have not been published.[30] In the remaining 2 studies, nesiritide was not compared with placebo, as in ASCEND-HF, but with either dobutamine[29] or nitroglycerin,[3] and we cannot exclude the possibility that these agents may have had a positive effect on renal function. Second, ASCEND-HF excluded patients with high risk of hypotension (systolic pressure <100 mm Hg or 110 mm Hg with the use of intravenous nitroglycerin), while the VMAC and Precedent had less strict exclusion criteria for hypotension (90 mm Hg and

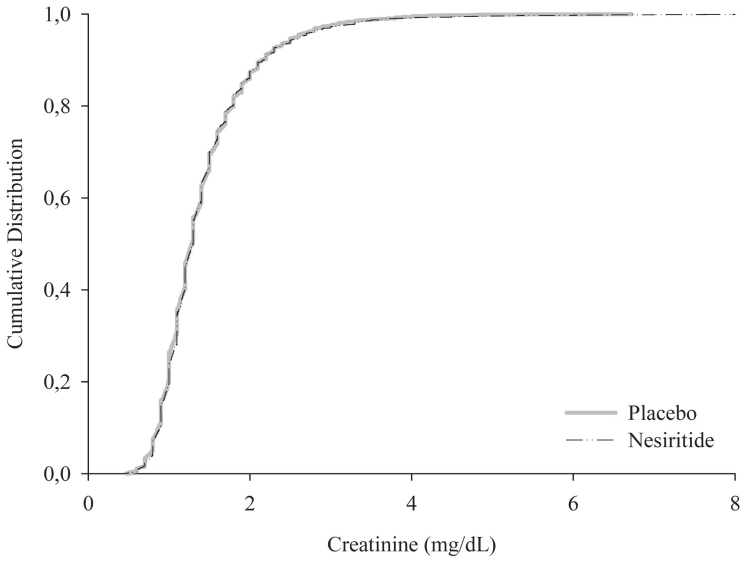

Figure 2b. Cumulative Distribution Curve. This figure displays the cumulative distribution curves of both nesiritide and placebo on (b) discharge/day 10.

85 mm Hg respectively). Third, in the meta-analysis, the confidence intervals around the estimate were wide, suggesting that larger studies were needed. Also, after publication of the meta-analysis data from another study suggested that nesiritide might even improve renal function.[17] With 7141 patients, ASCEND-HF had definitive power to demonstrate a meaningful difference in renal function between placebo and nesiritide and no difference was found.[9]

The present retrospective analysis of ASCEND-HF presents a more detailed report on the associations between nesiritide and other clinical predictors on changes in creatinine and blood urea nitrogen (BUN) during hospitalization, as well as the drug's association with clinical outcomes. We demonstrated that there was not a significant relationship between nesiritide and change in renal function (measured by creatinine or BUN) when corrected for clinical characteristics and other laboratory measurements.

Since hypotension is related to worsening renal function in acute decompensated heart failure,18 there was some concern that patients with hypotension had a higher rate of renal impairment compared to those without hypotension. We found this concern to be true in the overall group, as well as within each treatment group. Importantly, the overall relative risk of increased serum creatinine was the same within both treatment groups. So despite there being some correlation between hypotension and renal dysfunction, there was no evidence of a stronger correlation when using nesiritide.

Outcomes

We assessed the association between baseline and discharge creatinine and short-term outcomes, as well as the change in creatinine between baseline and discharge both as a continuous measure and as a categorical one (looking at "worsening renal function"). Both serum creatinine at baseline and serum creatinine at discharge had a strong association with both 30-day mortality and with the combined endpoint of 30-day mortality or re-hospitalization. Both continuous change and worsening renal function were not associated with short-term outcomes.

In contrast to other studies, we did not find worsening renal function to be associated with worse short-term outcomes in patients with ADHF.[11,12,19-24] There are several potential explanations for this disparity. First, there could be a measurement bias. Most studies do not measure creatinine routinely, so in those that did, there was probably a reason, which perhaps means that these patients were more likely to have worsening of symptoms, non-response to diuretics, related to clinical outcomes. The theory of measurement bias is supported by a recent study comprised of 599 patients who had their serum creatinine levels routinely measured.[25] The authors of this study concluded that worsening renal function is not an independent predictor of outcomes in patients with ADHF. Interestingly, they found that worsening renal function was prognostic in patients with persistent signs of congestion, suggesting a differential effect of worsening renal function.

According with our findings, the prospective randomized DOSE-trial found that patients that were given high dose of diuretics had greater diuresis and more favorable outcomes, although transient worsening of renal function occurred.[26] This might suggests that an increase in creatinine caused by a good diuretic response might be related to a better outcome.

Limitations

The present study has several limitations. First, our study has limitations due to the retrospective nature of this analysis. Second, our study has a possible selection bias inherent in clinical trial populations. For instance, our study population largely consists of North American patients, possibly limiting the generalizability of our findings.

Third, 2433 patients did not have serial creatinine values, which could have potentially biased the finding that worsening renal function did not predict patient outcomes. For example, patients who lacked serial creatinine values could have developed worsening renal function in-hospital and died before their serial creatinine was measured. Nevertheless, due to the design of ASCEND-HF, this study is more likely to have missing data because of less specific reasons, whereas other studies are more likely to have missing values because patients had no clinical suspicion to have worsening renal function or worse clinical outcomes.

Conclusions

In the present renal retrospective analysis of ASCEND-HF, examining 4708 patients who were hospitalized with ADHF, nesiritide did not affect renal function. In addition, both baseline and discharge renal dysfunction was associated with a higher 30 day mortality and re-hospitalization, while the change in renal function and/or worsening renal function was not.

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Chapter 5

Liver Function and Hemodynamics

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Andre P. van Beek, Dirk J. van Veldhuisen and Adriaan A. Voors

Abnormal liver function in relation to hemodynamic profile in heart failure patients

Abstract

Background

We studied the relation between liver function abnormalities and hemodynamic profile in patients with heart failure (HF).

Methods

In 323 HF patients, liver function was determined by aspartate and alanine aminotransferase (AST, ALT), alkaline phosphatase, g-glutamyl transpeptidase (GGT), lactate dehydrogenase, and direct and total bilirubin (Bili dir, Bili tot). Central venous pressure (CVP) and cardiac index (CI) were determined invasively. Follow-up consisted of time to all-cause mortality.

Results

Mean age was 53 ± 15 years, and 60% were male. In multivariable analysis, all liver function tests related to CVP, but higher CVP was predominantly related to GGT ($r = 0.336$, $P < 0.001$) and Bili dir ($r = 0.370$, $P < 0.001$). Only elevated AST ($r = -0.177$, $P < 0.01$), ALT ($r = -0.130$, $P < 0.05$), and Bili tot ($r = -0.158$, $P < 0.01$) were associated with both low CI and elevated CVP. The prognostic value of abnormal liver function tests was related to their interaction with CI and CVP.

Conclusions

Elevated liver function tests mainly indicate higher CVP, whereas only the presence of elevated AST, ALT, or Bili dir may indicate a low CI. The absence of prognostic information in the presence of invasive hemodynamic measurements suggests that abnormal liver function tests in HF reflect a poor hemodynamic status.

Introduction

Despite initiation of new therapies, both the short- and long-term mortality rate of patients with heart failure is still high.[1,2] This may be at least partly attributable to frequently present comorbidities.[3-5]

Heart failure itself is characterized by impaired organ perfusion resulting from both forward failure and increased central venous pressure (backward failure). We recently showed that both forward and backward failure are the most important determinants of renal dysfunction in heart failure.[6,7] Liver function abnormalities are frequently found in patients with heart failure and are related to a poor outcome.[8-15] Individual small reports have highlighted the importance of either high central venous pressure or reduced hepatic perfusion.[12,16-18] However, the relative contribution of reduced perfusion (forward failure) or venous congestion (backward failure) in causing alterations in specific markers of liver function has not been established.

We studied the relation between liver function abnormalities and forward and backward failure in patients with heart failure.

Methods

Retrospective chart review was done to analyze characteristics of all patients that underwent right heart catheterization between January 1, 1989, and December 31, 2006, at the University Medical Center Groningen, The Netherlands. For each patient, date of birth, gender, weight, and height were collected. Comorbid conditions, medical history, laboratory values including serum creatinine and hemoglobin levels, and use of medication were also collected. Left ventricular ejection fraction (LVEF) measured within a 6-month interval before or after catheterization was recorded. For the present analysis, all patients with a diagnosis of clinical heart failure at the time of right heart catheterization were included.

Heart catheterization

Hemodynamic variables obtained during catheterization included systolic blood pressure (SBP, mm Hg), diastolic blood pressure (DBP, mm Hg), cardiac output (thermodilution, l/min), and right atrial pressure as indicator of central venous pressure (CVP, mm Hg). Cardiac index (l/min/m^2) was determined as cardiac output divided by the body surface area. Body surface area was calculated as $0.007184 \cdot \text{weight}^{0.425} \cdot \text{length}^{0.725}$. Body mass index was calculated as weight/length^2. Measurements obtained from cardiac catheterization were obtained from the patient during a resting state.

Liver function testing

Laboratory measurements were extracted from samples drawn within 3 days before catheterization. Liver function tests that were extracted included aspartate aminotransferase (AST, upper limit of normal [ULN] 40 U/l), alanine aminotransferase (ALT, ULN 30 U/l), alkaline phosphatase (ALP, ULN 120 U/l), g-glutamyl transpeptidase (GGT, ULN 65 U/l), lactate dehydrogenase (LDH, ULN 235 U/l), direct bilirubin (Bili dir, ULN 5 mmol/l), and total bilirubin (Bili tot, ULN 26 mmol/l). Abnormal liver function tests were defined as values above the upper limit of normal. To account for confounding by drug-induced liver injury, we investigated medication use of all patients that showed either a hepatocellular profile (ALT > 3 · ULN), a cholestatic profile (ALP > 2 · ULN, ALT/ALP < 2) or a mixed profile (ALP and ALT > ULN) of liver injury, according to Chang et al.[19] In addition, we also screened patients with liver function tests values higher than 5 times ULN. After exclusion of subjects on possible hepatotoxic medication, a history of hepatitis or substance abuse, and missing laboratory samples within 3 days before right heart catheterization, 323 heart failure patients were available for the present analysis.

Mortality data

Survival status was determined using the electronic patient registration database of the University Medical Center Groningen. Follow up started directly after right heart catheterization. The end point of interest was death from any cause.

Statistical analysis

Data are given as mean 6 standard deviation when normally distributed, as median and interquartile range when skewed distributed, and as frequencies and percentages for categorical variables. Differences between baseline variables were evaluated by means Student t-test, the Kruskal-Wallis test, and Chi-square≤ or Fisher exact tests, when appropriate. CI and CVP were ranked to arbitrary high versus low values (CI ≤ / > 2.5 l/min/m^2 and CVP ≤ / > 8 mm Hg), corresponding to the lower limit of normal values of CI and higher upper limit of normal values of CVP, corresponding to hemodynamic profiles in heart failure.[20] Accordingly, we stratified patients to 4 different hemodynamic profiles.

1. Patients with a normal / high cardiac index (> 2.5 l/min/m^2) and normal / low CVP (≤ 8 mm Hg)
2. Patients with a normal / high cardiac index (> 2.5 l/min/m^2) and a high CVP (> 8 mm Hg)
3. Patients with a low cardiac index (≤ 2.5 l/min/m^2) and a normal / low CVP (≤ 8 mm Hg)
4. Patients with a low cardiac index (≤ 2.5 l/min/m^2) and a high CVP (> 8 mm Hg)

Table 1. Baseline characteristic according to different hemodynamic profiles.

	Total	High CI Low CVP	Low CI Low CVP	High CI High CVP	Low CI High CVP
n (%)	323	171 (53)	71 (22)	29 (9)	52 (16)
Age (y)	53 ± 15	53 ± 15	54 ± 15	56 ± 11	50 ± 16
Gender (% male)	60	59	61	48	68
Systolic BP (mm Hg)	121 ± 28	124 ± 25	114 ± 29 *	118 ± 27	105 ± 21 †,¥
Diastolic BP (mm Hg)	67 ± 12	68 ± 12	65 ± 10	65 ± 11	71 ± 12 ‡
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	27 ± 4 ‡	25 ± 4
CVP (mm Hg)	6 ± 6	4 ± 2	4 ± 2	12 ± 3	15 ± 6
Cardiac index (l/min/m^2)	2.7 ± 0.8	3.2 ± 0.6	2.1 ± 0.3	3.2 ± 0.6	1.9 ± 0.4
Cardiac output (l/min)	5.2 ± 1.6	6.2 ± 1.4	3.9 ± 0.7	6.3 ± 1.5	3.6 ± 0.9
LVEF (%)	28 ± 13	31 ± 13	26 ± 12 *	32 ± 13	22 ± 13 †,¥,¶
Hemoglobin (g/dl)	13.5 ± 1.9	13.6 ± 2.0	14.1 ± 1.5	12.1 ± 2.6 †,§	13.7 ± 1.9 ¥
Creatinine (mg/dl)	1.18 (1.00-1.41)	1.08 (0.94-1.29)	1.16 (1.01-1.35)	1.30 (0.99-1.71) *	1.32 (1.13-1.55) †,‡
eGFR (ml/min/1.73 m^2)	63 ± 21	68 ± 21	63 ± 18	54 ± 21 †,‡	59 ± 20 *
Liver function tests					
GGT (U/l)	48 (26-100)	30 (20-56)	46 (30-87) †	82 (42-245) †,‡	102 (54-147) †,§
ALP (U/l)	87 (66-106)	79 (62-94)	88 (70-112) †	95 (74-133) *	96 (77-117) †
Bili Tot (mmol/l)	16 (10-26)	13 (8-16)	20 (13-26) †	19 (14-27) †	30 (18-46) †,¥,§
Bili Dir (mmol/l)	6 (4-12)	5 (3-8)	7 (4-11) *	9 (7-14) †,‡	16 (7-25) †,§
AST (U/l)	28 (23-38)	25 (22-33)	31 (23-42) †	29 (22-39)	36 (26-56) †,¥
ALT (U/l)	29 (19-43)	24 (17-39)	30 (21-44) *	24 (16-33)	29 (21-78) †,¥
LDH (U/l)	256 (220-321)	238 (207-287)	278 (234-343) †	317 (257-429) †	284 (239-362) †
Medication (%)					
Diuretics	61	47	67 †	72 *	86 †,‡
Beta-blocker	33	27	36	36	47 *
ACEi or ARB	58	51	57	64	63
Aldosterone-antagonist	19	12	30 †	40 †	26 *

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CI = cardiac index; CVP = central venous pressure; eGFR = estimated glomerular filtration rate; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = g-glutamyl transpeptidase; LDH = lactate dehydrogenase; Bili = bilirubin; dir = direct; tot = total; LVEF = left ventricular ejection fraction. *P < 0.05 vs. high CI, low CVP; † P < 0.01 vs. high CI, low CVP; ‡ P < 0.05 vs. low CI, low CVP; ¥ P < 0.01 vs. low CI, low CVP; § P < 0.05 vs. high CI, high CVP; ¶ P < 0.01 vs. High CI, High CVP.

Initial linear regression analyses for liver function parameters were performed using partial correlation coefficients, adjusted for age and gender. Afterwards, multivariable regression analysis included CI, CVP, age, and gender into the model. Interactions between CI and CVP were modeled and a P value < 0.1 was deemed as a significant interaction. To account for possible confounding by body mass index, a history of diabetes, SBP, and DBP, these factors were introduced as covariates in a secondary multivariable model. We used a Cox proportional hazards model to estimate hazard ratios for all-cause mortality with 95% CI. Multivariable models were constructed in the following way: liver function tests with noninvasive variable, liver function test with invasive measurements (CVP and CI), and a stepwise multivariable model. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, Chicago, version 12.0, and STATA, College Station, TX, version 9.0.

Results

Baseline characteristics of the patient population are shown in Table 1. Age was 53 ± 15 years, and 60% were male. Direct bilirubin (62%) and LDH (65%) were often abnormal in this heart failure patient cohort, whereas AST (18%) or ALT (43%) abnormalities were

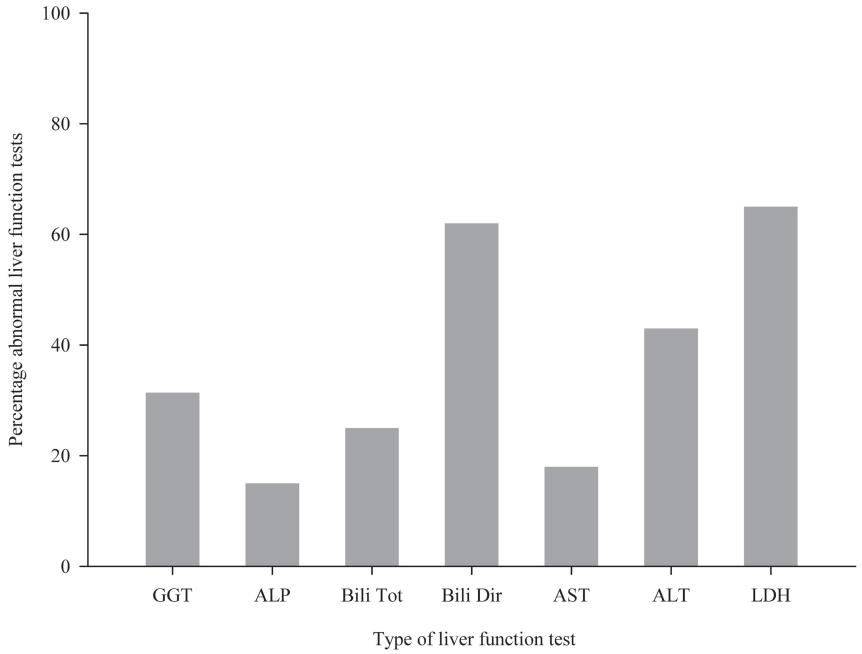

Figure 1. Percentages of abnormal liver function tests in patients with heart failure. ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = g-glutamyl transpeptidase; LDH = lactate dehydrogenase; bili dir = direct bilirubin; bili tot = total bilirubin.

much less common (Figure 1). When stratified for different hemodynamic profiles, there were marked differences in these 4 groups with respect to liver function tests. In general, patients with lower CI tended to have significantly higher values of liver function parameters, whereas a similar, but less pronounced pattern was observed in patients with higher CVP, but relatively normal CI levels. In patients with both high CVP and low CI, the highest values of most liver function parameters were observed.

Liver function tests and hemodynamic parameters

Table 2 summarizes linear regression analysis, adjusted for age and gender and for all liver function tests, highlighting the association with CVP and CI. All liver function tests showed a significant relationship with CVP and an inverse relationship with CI. Comparing CVP and CI, the relationship with CVP was stronger for all liver function tests compared with CI. We found significant interactions between CVP and CI on the relationship with total bilirubin, AST, and ALT, but with not direct bilirubin, LDH, ALP, or GGT

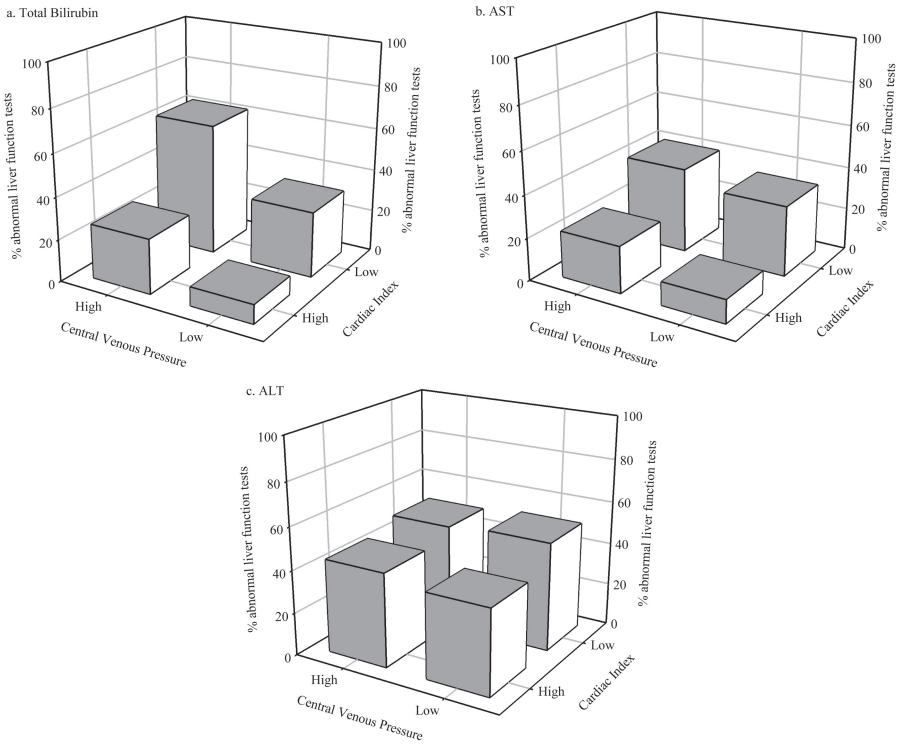

Figure 2. Prevalence of abnormal liver function tests in subgroups of CI and CVP: interaction between CI and CVP. (A) Total bilirubin, (B) AST, (C) ALT. CI = cardiac index; CVP = central venous pressure; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2. Univariate regression analysis for different liver function tests in 323 heart failure patients.

	GGT§	ALP§	Bili tot§	Bili dir§	AST§	ALT§	LDH§
CI	-0.229†	-0.154*	-0.295‡	-0.190*	-0.310‡	-0.236‡	-0.108
CVP	0.367‡	0.193†	0.423‡	0.424‡	0.319‡	0.257‡	0.223‡

Table 3. Multivariable regression analysis for different liver function tests in 323 heart failure patients.

	GGT§	ALP§	Bili tot§	Bili dir§	AST§	ALT§	LDH§
CI	-0.094	-0.084	-0.158†	-0.040	-0.177†	-0.130*	-0.026
CVP	0.318‡	0.161†	0.357‡	0.350‡	0.156†	0.120*	0.199†
P for interaction	NS	NS	0.017	NS	0.011	0.010	NS
Adjusted r^2	0.184	0.064	0.198	0.145	0.153	0.162	0.044

Table 4. Cox proportional hazard analysis for different parameters of liver function in 323 heart failure patients.

	Univariate		Multivariate (1)		Multivariate (2)	
	Hazard Ratio	P value	Hazard Ratio	P value	Hazard Ratio	P value
GGT §	1.81 (1.07-3.08)	0.028	1.05 (0.40-2.77)	NS	1.37 (0.69-2.72)	NS
ALP §	4.12 (1.33-12.8)	0.014	1.39 (0.14-14.2)	NS	2.68 (0.72-10.1)	NS
Bili tot §	1.44 (0.68-3.04)	NS	3.07 (0.59-15.9)	NS	0.73 (0.29-1.84)	NS
Bili dir §	1.77 (0.99-3.16)	NS	2.04 (0.59-7.05)	NS	1.25 (0.62-2.57)	NS
AST §	1.77 (1.05-2.97)	0.033	3.44 (1.22-9.75)	0.020	1.16 (0.60-2.21)	NS
ALT §	1.09 (0.63-1.89)	NS	2.32 (0.93-5.79)	0.070	0.85 (0.48-1.50)	NS
LDH §	2.26 (1.07-4.76)	0.033	5.80 (1.30-26.0)	0.022	1.47 (0.62-3.49)	NS

CI = cardiac index; CVP = central venous pressure; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = g-glutamyl transpeptidase; LDH = lactate dehydrogenase; Bili dir = direct bilirubin; Bili tot = total bilirubin. Partial correlation coefficients are shown adjusted for age and gender. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$; § Log-transformed. (1)Adjusted for age; gender; eGFR; left ventricular ejection fraction; hemoglobin; history of diabetes mellitus, coronary heart disease, and hypertension; systolic blood pressure; diastolic blood pressure; medication use. (2)Adjusted for CI and CVP.

Table 5. Different hemodynamic profiles and expected abnormal levels of liver function tests.

	Low CVP	High CVP
High CI	GGT =	GGT ↑ ↑
	ALP =	ALP ↑
	Bili tot =	Bili tot ↑
	Bili dir =	Bili dir ↑
	AST =	AST ↑
	ALT =	ALT ↑
	LDH =	LDH ↑
Low CI	GGT =	GGT ↑ ↑
	ALP =	ALP ↑
	Bili tot ↑	Bili tot ↑ ↑
	Bili dir =	Bili dir ↑ ↑
	AST ↑ ↑	AST ↑ ↑
	ALT ↑	ALT ↑ ↑
	LDH =	LDH ↑

CI = cardiac index; CVP = central venous pressure; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = g-glutamyl transpeptidase; LDH = lactate dehydrogenase; Bili dir = direct bilirubin; Bili tot = total bilirubin.

(Table 3). Figure 2 shows the percentages of abnormal liver function tests when both CVP and CI were ranked to high versus low, visualizing the significant interaction between CVP and CI on these liver function tests. Most liver function tests showed an increase in percentages of abnormal values with decreasing CI and increasing CVP. AST and ALT were particularly increased when CI was low, and GGT was particularly increased when CVP was high. Bilirubin tests were increased both with elevated CVP and low CI. In multivariable analysis, CVP remained significantly associated with all liver function tests (Table 3). In contrast, CI remained only significantly associated with AST, ALT, and total bilirubin. In a second multivariable analysis, which included body mass index, SBP, DBP, and a history of diabetes as covariates, the associations between CI, CVP, and liver function tests were unaffected (coefficients not shown).

Liver function tests and prognosis

During a median follow-up time of 7.9 (4.1-11.8) years, a total of 122 (36%) patients died. Table 4 summarizes the relationship between the individual liver function tests and prognosis. In univariate analysis, GGT, ALP, AST, and LDH levels were significant predictors of all-cause mortality. In addition, both CVP (HR 1.03 per mm Hg [1.00-1.06], $P < 0.05$) and CI (HR 0.61 per l/min/m^2 [0.45-0.83], $P = .0016$) significantly determined

prognosis. After adjustment for noninvasive covariates, AST and LDH remained significantly associated with impaired survival, whereas ALT showed a trend with survival (P = 0.070). However, after adjustment for hemodynamic factors (CI and CVP), none of the liver function tests remained associated with impaired survival, which was attributable to inclusion of both parameters (CI and CVP) into the model.

Discussion

In the present study, we show that liver function abnormalities are frequently observed in patients with heart failure-in particular, high levels of direct bilirubin, LDH, and GGT. Most parameters of liver function were predominantly related to CVP, whereas only AST, ALT, and total bilirubin were also related to a reduced CI. CVP and CI showed a significant interaction on the association with liver function parameters, indicating a mutually mediating role of both parameters on the relationship of each individual parameter with liver function. Finally, levels of GGT, ALP, and especially AST and LDH were predictors of all-cause mortality, but not independent of CI and CVP.

Prevalence and Pathophysiology of Liver Function Abnormalities in Heart Failure

The presence of liver function abnormalities in heart failure has long been recognized.[11,14] In our analysis, the prevalence of liver function abnormalities ranged from as little as 15% to as much as 65%, depending on definition and type of liver function abnormality. We observed similar per- centages of abnormal levels GGT, bilirubin levels, and a higher percentage of abnormal levels of ALT and AST compared with a study by Lau et al.[18] In comparison with a recent substudy of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials we found similar percentages of abnormal levels of ALP, but much higher percentages of abnormal levels of other liver function tests.[8]

The pathophysiology of liver failure in heart failure patients has been attributed to either venous congestion leading to hepatic congestion or reduced cardiac output leading to hepatic hypoxic injury.[12,14,18] Liver failure in heart failure includes necrosis in the central zone of hepatic lobules resulting from direct compression and congestion.[13] Interestingly, low perfusion seems to be less important because oxygen consumption can easily be increased when hepatic blood flow is decreased,[12] because 70% of the blood supply of the liver is dependent of the portal system, whereas only 30% is delivered by the hepatic artery.[21] A nonhemodynamic factor that may be related to liver failure is poor nutrition state of heart failure patients, leading to fatty liver and fibrosis.[22]

The present study offers more insight in the association of a combination of congestion and reduced perfusion with the presence of liver function abnormalities. Historically, increased levels of AST and ALT in heart failure have been attributed to hepatocellu-

lar damage from decreased perfusion, whereas especially increased bilirubin levels, high ALP levels, and low ALT/ALP ratio in heart failure have been associated with cholestatic liver injury from an increased CVP. Kubo et al have shown that with increasingly severe heart failure, the occurrence of liver function abnormalities increases.[17] This seemed to be parallel to an increase in CVP and decrease in cardiac output, although no interaction or multivariable analysis was performed. Our present univariate analyses are consistent with their findings, resulting in moderate relationships between CVP and liver function tests, and even weaker relationships with CI. Interestingly however, to the best of our knowledge, no other data are available in heart failure patients to support this generally accepted concept. We found significant interactions between CVP and CI on the relationship with liver function tests. Essentially, all levels of liver function parameters increased with decreasing CI and increasing CVP, except for ALT and AST. Both ALT and AST only showed elevations when CI was reduced. Because these abnormalities often coexist, this finding seems to be a reflection of the pathophysiology of liver function abnormalities in heart failure being a combination of congestion and reduced cardiac output. A similar analysis for total bilirubin levels was carried out by Shinagawa et al in 183 acute heart failure patients.[15] Their analysis showed that especially the combination of congestion and reduced perfusion led to elevated total bilirubin levels, consistent with our present findings. Unfortunately, no data on other parameters of liver dysfunction were shown. Lau et al showed that, especially, GGT and bilirubin levels were increased in patients with elevated CVP.[18] Together with our findings, this suggest that elevations in GGT, ALP, LDH, and bilirubin levels are dependent of both reduced perfusion and congestion, whereas AST and ALT levels are mainly determined by reduced hepatic perfusion. This suggests that low hepatic perfusion in heart failure mainly predisposes to hepatocellular liver injury (high AST and ALT), whereas cholestatic liver injury is primarily observed when CVP is particularly high (high bilirubins, GGT, ALP). Additionally, our findings may help to identify patients in different hemodynamic profiles, according to abnormal values, or combination of abnormal values of different liver function test (Table 5).

Prognosis

Several reports have addressed the prognostic importance of liver function abnormalities in the setting of heart failure. Batin et al showed that individual abnormal liver function tests were related to increased mortality, including bilirubin and AST.[9] Shinagawa also emphasized the importance of elevated total bilirubin levels, whereas direct bilirubin, ALP, and GGT were also related to cardiac events.[15] In a recent report, Allen et al reported independent prognostic information of bilirubin in the CHARM study population, but in our present study, we were unable to find a relationship between bilirubin levels and mortality.[8] We did, however, find that GGT, ALP, LDH, and AST were significantly related to mortality in univariate analysis. Even after correction for easily obtainable, noninvasive covariates, AST and LDH remained significant predictors of prognosis. Interestingly,

after adjustment for hemodynamic derangement (CVP and CI), none of these liver function tests remained associated with reduced survival.

This observation seems to indicate that the severity of liver function abnormalities is related to the type of liver function test and the relative contributions of CVP and CI. The prognostic importance of these abnormalities seems to be more a reflection of the poor hemodynamic status of these patients, instead of underlying secondary hepatic injury.

Limitations

This is a retrospective analysis of a selected patient population, which includes patients who were identified in the early 1990s. Considering the improvement in medical therapy in patients with heart failure in recent years, our heart failure population may have a higher prevalence of liver function abnormalities compared with the general heart failure population now. We carried out multiple comparisons in a limited set of patients, which increases the change of finding significant relationships. Our results should therefore be confirmed in other studies. Furthermore, changes in liver function abnormalities were not assessed and we cannot assess whether the observed abnormalities are transient or permanent. We did not evaluate neurohormonal activation, echocardiographic assessment of tricuspid regurgitation, or measured hepatic blood flow, all of which could potentially influenced the results. In our analysis, we have tried to exclude patients who were on hepatotoxic medication, but we cannot account for over-the-counter products with possible harmful effects on liver function, such as acetaminophen. Finally, we could not assess other reasons for liver test abnormalities in heart failures, such as hemochromatosis, because ferritin measurements were not routinely performed, and were therefore not available for this analysis.

Conclusion

Liver function abnormalities are frequently observed in patients with heart failure. Elevated CVP showed the stron- gest relationship with liver function abnormalities. Despite interactions between CI and CVP, only AST, ALT, and total bilirubin were related to both CVP and CI, whereas both GGT and direct bilirubin were the most prominent parameters related to CVP, in the absence of reduced CI. Finally, the prognostic information of liver function abnormalities in heart failure was blunted by elevated CVP and low CI, suggesting that liver function abnormalities are a reflection of poor hemodynamic status in these patients.

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Chapter 6

Liver function in acute heart failure

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Liver function, in-hospital and post-discharge clinical outcome in patients with acute heart failure
Results from Pre-RELAX-AHF

Abstract

Background

Elevated plasma concentrations of liver function tests are prevalent in patients with chronic heart failure (HF). Little is known about liver function in patients with acute HF. We aimed to assess the prevalence and prognostic value of serial measurements of liver function tests in patients admitted with acute decompensated HF.

Methods

We investigated liver function tests from all 234 patients from the Pre-RELAX-AHF study at baseline and during hospitalization. The endpoints were worsening HF through day 5, 60 day mortality or rehospitalization and 180 day mortality.

Results

Mean age was 70±10 years, 56% were male and most patients were in NYHA III/IV (73%). Abnormal liver function tests were frequently found for ALT (12%), AST (21%), alkaline phosphatase (12%) and total bilirubin (19%), while serum albumin (0%) and total protein (1%) were not elevated. In-hospital changes were very small. On a continuous scale, baseline ALT and AST were associated with 180 day mortality (HR (per doubling)=1.52, P=0.030 and HR (per doubling)=1.97, P=0.013) and worsening HF through day 5 (HR (per doubling)=1.72, P=0.005 and HR (per doubling)=1.95, P=0.008). Albumin was associated with 180 day mortality (HR=0.86, P=0.001) but not with worsening HF (HR=0.95, P=0.248). Total protein was only associated with worsening HF (HR=0.91, P=0.004).

Conclusions

Abnormal liver function tests are often present in patients with acute HF and are associated with an increased risk for mortality, rehospitalization and in-hospital worsening HF.

Introduction

Abnormal liver function tests are frequently found in patients with heart failure.[1] In chronic heart failure, the prevalence of abnormal liver function tests is 30-60%, depending on which liver function is measured.[2,3]

Liver function tests are expected to be impaired due to hemodynamic changes.[2] Impaired cardiac output mainly relates to aspartateaminotransferase (AST), alanineaminotransferase (ALT) and bilirubin, while increased central venous pressure is related to all liver function tests, especially gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALKP) and bilirubin.[2,4,5] Pathophysiologic mechanisms other than hemodynamic mechanisms, remain largely unknown.

Liver function is less well studied in patients with acute heart failure.[6-8] These patients are most likely to have impaired hemodynamics, making this group vulnerable to impaired liver function. Here, we study the prognostic value of (changes in) impaired liver function tests in patients with acute heart failure.

Methods

The Pre-RELAX-AHF (Relaxin for the treatment of patients with acute heart failure) was a multicentre, randomized, placebo-controlled, parallel-group, dose-finding phase IIb study, in which 234 patients with acute heart failure were recruited from 54 sites in 8 countries and enrolled within 16 hours of presentation.[9] Inclusion criteria were dyspnoea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), mild or moderate renal insufficiency and systolic blood pressure greater than 125 mmHg. Patients were randomly assigned to standard care plus 48-hour intravenous infusion of placebo or relaxin in different doses. The study was approved by the relevant ethics board at every participating site, and all patients provided written informed consent.

Liver function tests

Liver function tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKP), total bilirubin (Bili tot), albumin and total protein. Abnormal liver function tests were defined as values above the upper limit of normal. All of these liver function tests were measured at baseline, during hospitalization (day 1 to discharge/day 7) and day 14.

Endpoints

The endpoints of interest for this analysis were the composite endpoint of death and rehospitalization for heart failure within 60 days and death within 180 days. In-hospital

Table 1. Baseline characteristics.

	All patients (N=234)
Age (years)	70.2 (10.5)
Male Sex	131 (56.0%)
Weight (kg)	81.2 (17.3)
Heart Rate (beats/min)	83.0 (15.9)
SBP (mmHg)	147.5 (19.9)
Ejection Fraction (%)	38.5 (14.3)
Ejection Fraction (<40%)	87 (60.4%)
NYHA class	
I	4 (1.9%)
II	51 (24.8%)
III	92 (44.7%)
IV	59 (28.6%)
Medical history	
Hospitalized for HF (Past Year)	79 (34.2%)
Ischaemic Heart Disease	162 (70.4%)
Hypertension	198 (85.7%)
Diabetes	100 (43.9%)
Mitral Regurgitation	67 (29.0%)
Atrial Fibrillation/Flutter	109 (47.4%)
Laboratory values	
Troponin (≥0.1 and <3x ULN)	38 (17.0%)
eGFR (MDRD formula)	53.6 (16.9)
Creatinine (umol/L)	115.0 (41.7)
BUN (mmol/L)	9.7 (4.1)
Sodium (mmol/L)	140.4 (3.9)
Hemoglobin (g/dL)	13.0 (1.8)
Elevated (NT-pro-)BNP	140 (59.8%)
Treatment at baseline (%)	
ACE Inhibitors	141 (62.1%)
ARB	12 (5.3%)
Beta blocker	131 (57.7%)
Aldosterone inhibitor	75 (33.0%)
Nitrates	50 (22.0%)
Calcium-channel blocker	33 (14.5%)
Digoxin	48 (21.2%)
Liver function tests	
ALT (U/L)	21 (15-36)
Above ULN	24 (12%)
AST (U/L)	26 (20-34)
Above ULN	45 (21%)
Alkaline phosphatase (U/L)	84 (68-107)
Above ULN	27 (12%)
Bilirubin (U/L)	10 (7-17)
Above ULN	40 (19%)
Albumin (g/L)	40 (37-43)
Above ULN	1 (0%)
Total Protein (g/L)	69 (64-72)
Above ULN	3 (1%)

[+] P-values computed for comparison of baseline congestion classification with two sided t-test for continuous variables and Chi-square test for categorical variables unless otherwise stated. * Wilcoxon Rank Sum Values are presented as mean ± standard deviation, n (%) or median (25th-75th percentile). Elevated (NT-pro-)BNP is defined as NT-pro-BNP >= 3000 or BNP >= 250. Abbreviations: kg: kilogram; Adm.: administration; NYHA: New York Heart Association; AHF: Acute heart failure; ULN: upper limit of normal; eGFR: estimated Glomerular filtration rate; SBP: systolic blood pressure; BUN: blood urea nitrogen; NT-proBNP: N-terminal pro-BNP; BNP: brain-type natriuretic peptide; ACE: angiotension converting enzyme; ARB: angiotensin receptor blocker; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

worsening heart failure was defined by a physician-assessment through day 5 on the basis of worsening signs or symptoms of heart failure together with the need for addition or initiation of intravenous medications or mechanical support to treat acute heart failure.

Statistical analyses

Data are presented as mean ± standard deviation when normally distributed, as median and interquartile range when non-normally distributed, and as frequencies and percentages for categorical variables. Differences between groups were evaluated by Student's t test, Wilcoxon rank sum, or Chi-square tests, when appropriate. Linear regression analyses were used to identify associations with liver function tests.

Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for a 1-unit change for baseline predictors of all-cause mortality and the combined endpoint of all-cause mortality or HF rehospitalization. Restricted cubic splines were used to examine the linearity assumption of the predictors with outcome and appropriate transformations were applied to predictors that were nonlinear. For non-linear predictors a log2 transformation was used and the associated HR can be interpreted as the hazard associated with a doubling of the value. Univariable summaries, adjusted for baseline value, were also provided to examine the association between improvement at day 5 and at any time to day 5 in liver function tests with outcome. Kaplan-Meier curves and a log-rank test were performed to assess the effect of baseline liver function tests by quartile on outcome.

A P value < 0.05 was considered statistically significant. Data were verified and analyzed using commercially available software (SAS, version 9.2; SAS Institute, Inc).

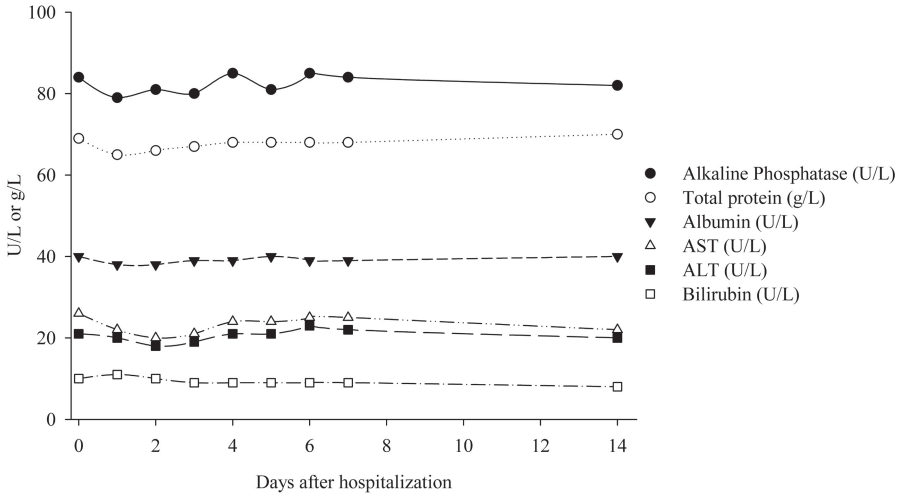

Figure 1. Change of liver function tests during hospitalization.

Table 2. Association between liver function tests and death (through day 180), death or rehospitalization (through day 60) and worsening heart failure (through day 5).

	Mortality		Mortality or HF-hospitalization		Worsening heart failure	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
ALT (U/L)*	1.52 (1.04-2.21)	0.0304	1.45 (1.01-2.07)	0.0433	1.72 (1.18-2.49)	0.0047
AST (U/L)*	1.97 (1.15-3.37)	0.0133	1.89 (1.14-3.13)	0.0133	1.95 (1.19-3.20)	0.0081
Alkaline phosphatase (U/L)	1.01 (0.99-1.02)	0.1453	1.01 (1.00-1.02)	0.0263	1.00 (0.99-1.01)	0.9623
Bilirubin (umol/L)	0.97 (0.91-1.04)	0.4063	0.99 (0.95-1.05)	0.8939	0.98 (0.94-1.03)	0.5174
Albumin (g/L)	0.86 (0.78-0.94)	0.0011	0.86 (0.79-0.93)	0.0002	0.95 (0.88-1.03)	0.2482
Total Protein (g/L)	0.97 (0.90-1.05)	0.5026	0.94 (0.88-1.00)	0.0681	0.91 (0.85-0.97)	0.0037

* Hazard ratios for ALT: alanine aminotransferase and AST: aspartate aminotransferase are reported per doubling (log2 transformed values). The log transformation was used due to the non-linear relationship of the parameters with outcome.

Table 3. Association between prognosis and improvement of liver function through day 5 (on a continuous scale, and adjusted for baseline value).

	Mortality		Mortality or HF-hospitalization		Worsening heart failure	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
ALT (U/L)*	0.73 (0.36-1.46)	0.3729	0.77 (0.41-1.43)	0.4039	1.28 (0.53-3.07)	0.5849
AST (U/L)*	1.08 (0.53-2.17)	0.8386	1.09 (0.58-2.06)	0.7940	1.13 (0.49-2.58)	0.7737
Alkaline phosphatase (U/L)	0.55 (0.06-5.45)	0.6066	1.08 (0.19-6.11)	0.9344	2.17 (0.46-10.2)	0.3250
Bilirubin (umol/L)	0.99 (0.96-1.01)	0.2905	1.00 (0.98-1.02)	0.9642	1.00 (0.99-1.02)	0.8226
Albumin (g/L)	0.09 (0.02-0.45)	0.0036	0.28 (0.07-1.08)	0.0638	0.48 (0.14-1.63)	0.2382
Total Protein (g/L)	0.57 (0.22-1.44)	0.2332	0.50 (0.23-1.10)	0.0845	0.65 (0.17-0.69)	0.2680

* Hazard ratios for ALT: alanine aminotransferase and AST: aspartate aminotransferase are reported per doubling (log2 transformed values). The log transformation was used due to the non-linear relationship of the parameters with outcome.

Results

Baseline characteristics are presented in table 1. Mean age was 70 ± 10 years and 56% were male. Systolic blood pressure at baseline was 148 ± 20 mmHg, and most were most patients were in NYHA III (45%) and IV (29%). Seventy percent had a history of ischemic heart disease.

Prevalence of liver function tests

Liver function tests were abnormal for ALT (12%, median 21 U/L, [25th percentile 15 U/L - 75th percentile 36 U/L], AST (21% median 26 U/L [20 U/L - 34 U/L]), ALKP (12%, median 84 U/L [68 U/L - 107 U/L]) and total bilirubin (19% median 10 umol/L [7 umol/L - 17 umol/L]), while albumin (0%, median 40 g/L [37 g/L - 43 g/L]) and total protein (1%, median 69 g/L [64 g/L - 72 g/L]) were mostly normal. Figure 1 shows that there were no substantial changes in liver function tests during hospitalization up to day 14.

Prognosis

On a continuous scale, higher ALT (HR 1.52 (1.04-2.21) per doubling, P = 0.030), higher AST (1.97 (1.15-3.37) per doubling, P = 0.013) and lower albumin (HR 0.86 (0.78-0.94), P = 0.001) were associated with 180 day mortality. For the combined endpoint of mortality or rehospitalization through day 60, higher ALT (HR 1.45 (1.01-2.07) per doubling, P = 0.043), higher AST (HR 1.89 (1.14-3.13) per doubling, P = 0.013), lower albumin (HR 0.86 (0.79-0.93), P < 0.001) and higher ALKP (HR 1.01 (1.00-1.02), P = 0.026) had a significant association, while lower total protein showed a trend (HR 0.94 (0.88-1.00), P = 0.068).

Worsening heart failure was associated with higher baseline value of ALT (HR 1.72 (1.18-2.49) per doubling, P = 0.005), higher AST (HR 1.95 (1.19-3.20) per doubling, P = 0.008), and lower total protein (HR 0.91 (0.85-0.97), P = 0.004).

These results are confirmed when liver function tests are divided into quartiles. In figure 2, higher quartiles of ALT (P = 0.005) and AST (P = 0.036) and lower quartiles of albumin (P = 0.046) are related with higher rates of mortality through day 180. For the combined endpoint of mortality or rehospitalization through day 60, higher quartiles of ALT (P = 0.019) and ALKP (P = 0.030), and lower quartiles of albumin (P = 0.015) and total protein (P = 0.026) are associated with worse prognosis (Figure 3).

Only change in albumin was significantly associated with all-cause mortality (HR 0.09 per unit increase (0.02-0.45), P = 0.004). No other significant changes between change in liver function test and prognosis could be found, but it should be noted that 95% confidence intervals were wide (Table 3).

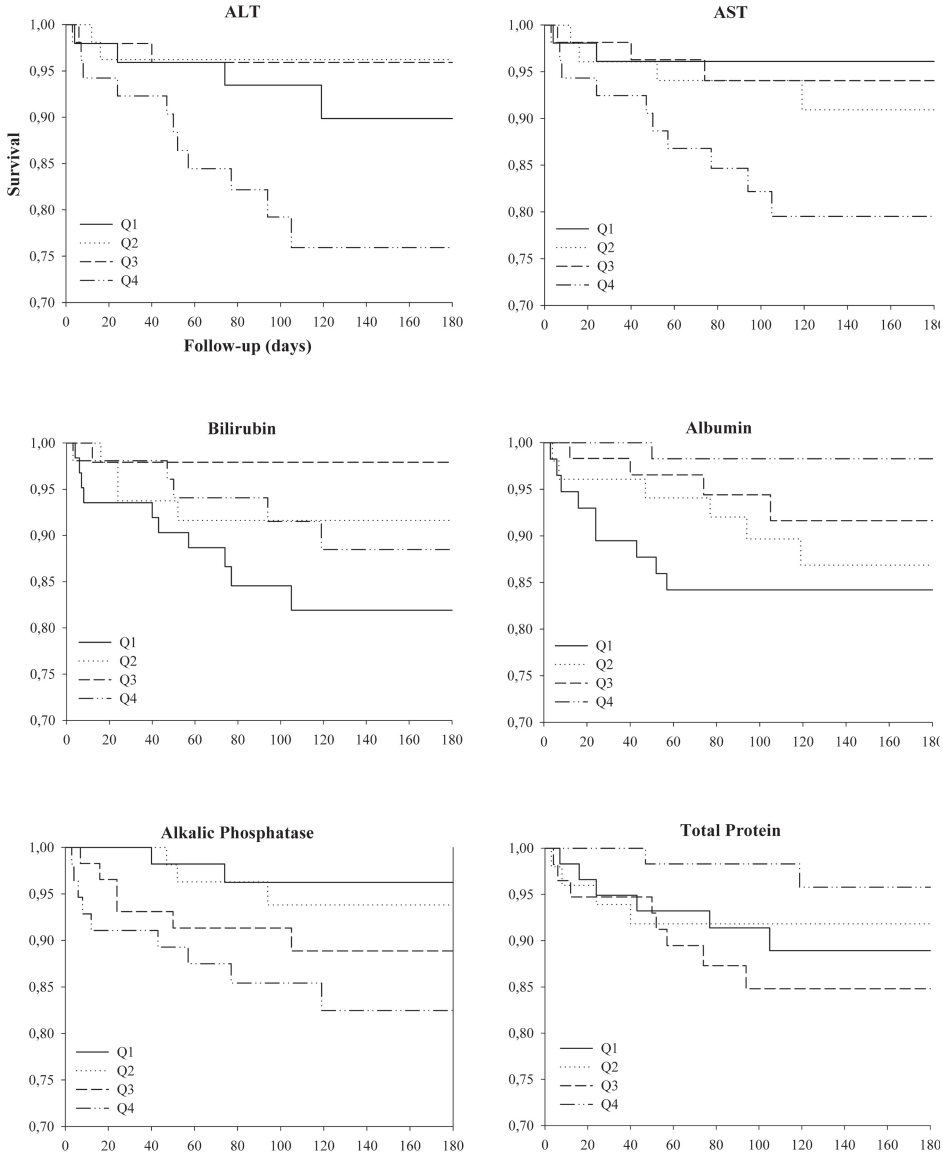

Figure 2. Mortality per quartiles of each liver function test (through day 180).

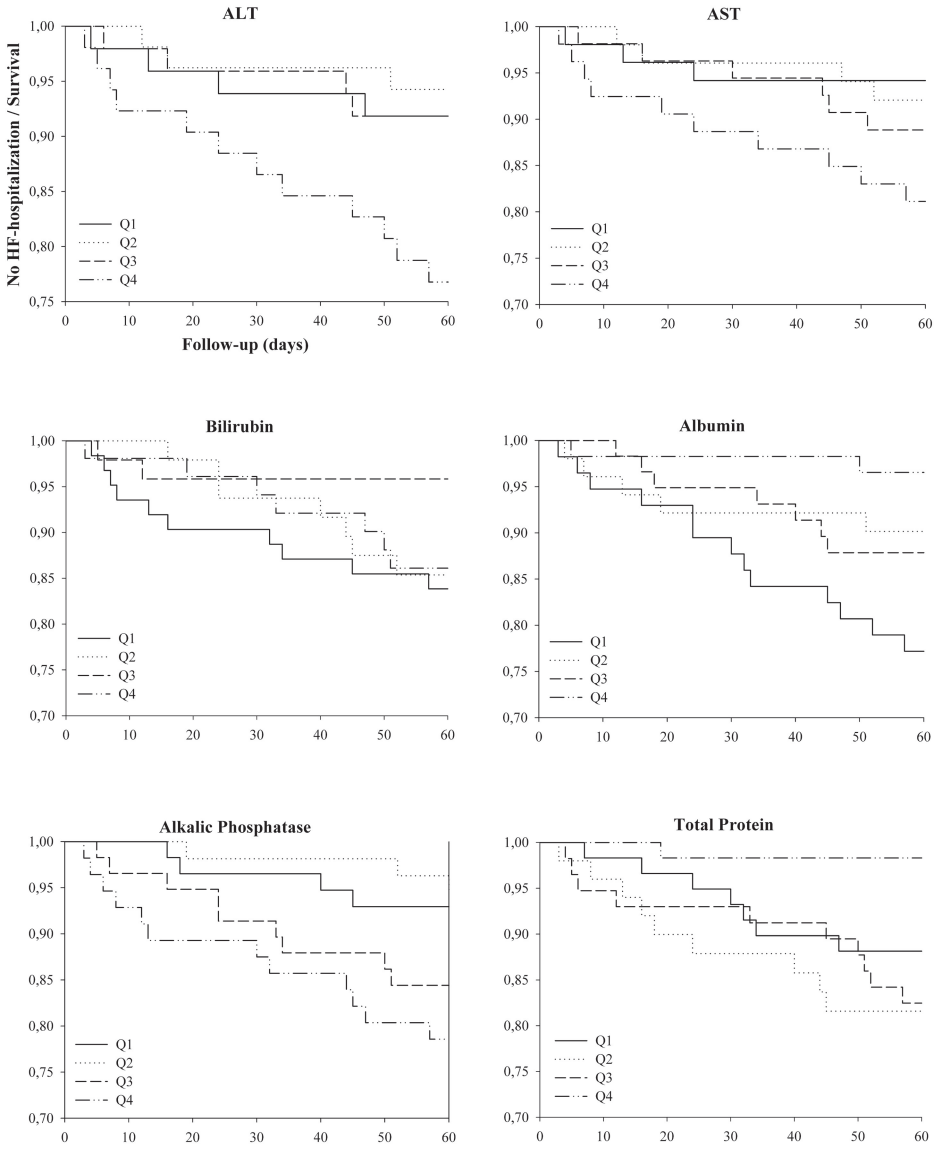

Figure 3. Death or HF-hospitalization per quartiles of each liver function test (through day 60).

Discussion

Abnormal liver function tests were often present in patients with acute heart failure with ALT, AST and albumin being associated with an increased mortality, rehospitalization risk and in-hospital worsening heart failure. We did not find an association between changes in liver function tests and prognosis.

Prevalence

Abnormal liver function tests are frequently found in patients with chronic heart failure with a prevalence between 30-60%, depending on which liver function test is measured.[1-3,10,11] However, liver function is less well studied in patients with acute heart failure.[6-8]

We found that abnormal liver function tests are prevalent in patients with acute heart failure as well. We found that 20% of patients with acute heart failure had abnormal AST and total bilirubin, 10% had abnormal ALT and ALKP but almost no patients had abnormal levels of albumin and total protein. These results are similar with previous reports, with the exception of albumin which had a prevalence of 17-44% in other studies.[6,7] We also found that liver function tests changed minimally during hospitalization, which was similar to a previously published report.[6]

Pathophysiology

Abnormal liver function tests show a relationship with elevated central venous pressure and reduced hepatic perfusion.[2,4,5,8,12] The pathophysiology of liver failure in heart failure patients consists of hepatic hypoxic injury, due to reduced cardiac output, and necrosis in the central zone of hepatic lobules originating from direct compression and congestion.[11] In other words, low hepatic perfusion in heart failure mainly predisposes to hepatocellular liver injury (high AST and ALT), whereas cholestatic liver injury (high bilirubins, GGT, ALKP) is primarily observed when congestion is present.[2]

In a previous study in patients with chronic heart failure, we found that none of the liver function tests remained associated with mortality after adjustment for hemodynamic factors (congestion and cardiac output).[2] This suggests that the abnormal liver function tests are a reflection of the poor hemodynamic status, instead of secondary hepatic injury. Nevertheless, liver function tests could be useful as an easy prognostic assessment in the acute setting.

Interestingly, when cardiac function is restored by a left ventricular assist device, AST, ALT and total bilirubin return to normal within 1 or 2 months, further suggesting that impaired haemodynamics in patients with heart failure are the cause of abnormal liver function tests.[13] Non-hemodynamic factors, such as poor nutrition, can lead to fatty liver and fibrosis, and are therefore associated with decreased liver function in heart failure patients.[14] Vice versa, decreased liver function can lead to worsening heart failure due to hypoalbuminemia and low-osmolalic state, causing fluid overload and oedema.[5]

Prognosis

In chronic heart failure, some reports show that especially bilirubin is associated with mortality, while other individual reports show, mostly univariate, an inconsistent prognostic value of AST, ALKP and gamma-glutamyl transpeptidase (GGT).[3,15,16]

In three different studies in patients with acute heart failure, AST, ALT and ALKP were associated with 180 day mortality in 1134 patients;[8] AST, ALT and albumin were associated with 180 day mortality in 189 patients;[7] and albumin and bilirubin were associated with 180 day mortality in 2061 patients.[6] Two other studies showed prognostic value of total bilirubin levels.[3,16] In the present study we found that especially AST and ALT were associated with worse prognosis. Furthermore, decreased albumin was associated with mortality and decreased total protein was associated with in-hospital worsening heart failure.

Combining these results, we observed that mainly hepatocellular damage (AST and ALT) is related to mortality in patients with acute heart failure. Nevertheless, other studies have also reported that cholestatic profiles (bilirubin and ALKP) of liver function abnormalities can be related with prognosis.[3,15,16]

Except for a change in albumin, we did not find other statistically significant associations between changes in liver function overtime and clinical outcome, in contrast to other studies.[6,18] This might be related to the small sample size of our study. While the present study may yield meaningful results with respect of the prognostic significance of baseline values of the liver exams, it may be too small to allow an assessment of the prognostic value of changes in these exams, where interindividual variability is likely larger. In a much larger study, changes in liver exams during hospitalization were clearly related with mortality.[18]

Limitations

Although most liver function tests were available for the analysis, we did not have values for gamma-glutamyltransferase (GGT). We did not have information about neurohormonal activation, echocardiographic assessment of tricuspid regurgitation, hepatic blood flow, or hepatotoxic medication which could influence the results.

An important limitation of this study is its limited sample size, and therefore its limited statistical power, as indicated before.

Conclusion

We found that abnormal liver function tests are often present in patients with acute heart failure and are associated with increased mortality, rehospitalization and in-hospital worsening heart failure.

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Chapter 7

Comorbidities in heart failure - review

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Comorbidities in heart failure

Abstract

Heart failure is a clinical syndrome characterized by poor quality of life and high morbidity and mortality. Comorbidities frequently accompany heart failure and further decrease in both quality of life and clinical outcome. We describe that the prevalence of comorbidities in patients with heart failure is much higher compared to age-matched controls. We will specifically address the most studied organ-related comorbidities, that is, renal dysfunction, cerebral dysfunction, anaemia, liver dysfunction, chronic obstructive pulmonary disease, diabetes mellitus and sleep apnoea. The pathophysiologic processes underlying the interaction between heart failure and comorbid conditions are complex and remain largely unresolved. Although common risk factors are likely to contribute, it is reasonable to believe that factors associated with heart failure might cause other comorbid conditions. Inflammation, neurohumoral pathway activation and hemodynamic changes are potential factors. We try to provide explanations for the observed association between comorbidities and heart failure, as well as its impact on survival.

Introduction

Heart failure is a clinical syndrome characterized by poor quality of life and high morbidity and mortality. Moreover, patients with heart failure often suffer from multiple comorbidities that further impair quality of life and prognosis.[1] Braunstein et al. found that 40 % of patients with heart failure had 5 or more non-cardiac comorbidities.[2]

Heart failure itself carries a poor prognosis, with a 5-year survival rate of only 50 % despite optimal therapy.[1] The presence of comorbidities impairs survival further still (Table 1). There is a strong association between non-cardiac comorbidities and adverse clinical outcomes. Hospitalization rates increase when comorbidities are present. Patients with multiple comorbidities account for 81 % of all hospital days experienced by all heart failure patients.[2]

The pathophysiologic processes underlying the interaction between heart failure and comorbid conditions are complex and remain largely unresolved. Inflammation, neurohumoral pathway activation and shared risk factors each have an effect, as do hemodynamics. Heart failure causes hypoxia and insufficient perfusion of organs.[3,4] Other reports also show that organ dysfunction can be caused by increased venous pressure.[5,6]

In this review, we describe comorbidities that have been documented in patients with heart failure (Table 1) and subsequently specifically address the most studied organ-related comorbidities, that is, renal dysfunction, cerebral dysfunction, anaemia, liver dysfunction, chronic obstructive pulmonary disease (COPD), diabetes mellitus and sleep apnoea. We try to provide explanations for the observed association between the comorbidities and heart failure, as well as their impact on survival.

Prevalence of comorbidities in heart failure compared with age-matched controls

Prevalence of comorbidities is high in patients with heart failure.[2] This can partly be explained by the higher age of patients with heart failure, as elderly patients are more likely to have comorbid conditions. However, there is evidence to suggest comorbidities in patients with heart failure are more prevalent than in age-matched controls. In order to assess the prevalence of comorbidities in patients with heart failure compared to age-matched controls, we used data from Dutch institutions, including reports and National Public Health Compass data from the Institute for Public Health and the Environment (RIVM) and GP registries.

These data indicate that renal dysfunction (35 vs. 5 %), sleep apnoea (60 vs. 1 %), anaemia (50 vs. 15 %), diabetes mellitus (20 vs. 13 %), liver dysfunction (40 vs. 10 %) and chronic obstructive pulmonary disease (40 vs. 30 %) are present much more frequently in patients with heart failure (Figure 1). On a critical note, definitions for the presence of comorbidities may vary, and reported prevalence figures for comorbidities in patients with

heart failure may be overestimated due to selection bias. Nevertheless, comorbidities in patients with heart failure seem to be higher compared to healthy patients of similar age.

Specific comorbidities related with heart failure

Anaemia

Prevalence

About 37 % of heart failure patients have anaemia, but prevalence varies widely due to different definitions and disease severity.[7] The World Health Organisation criteria are most commonly used, defining anaemia as haemoglobin <12 g/dL (7.5 mmol/L) in women haemoglobin <13 g/dL (8.1 mmol/L) in men.

Pathophysiology

Renal failure is an important factor in the complex relationship between anaemia and heart failure (e.g. intrinsic renal disease, renal artery stenosis). Other factors include lower levels of erythropoietin, raised central venous pressure and low arterial pressure.[4,8] Because renal dysfunction is related to both anaemia and heart failure, a vicious circle may be present, named the cardiorenal anaemia syndrome.[9]

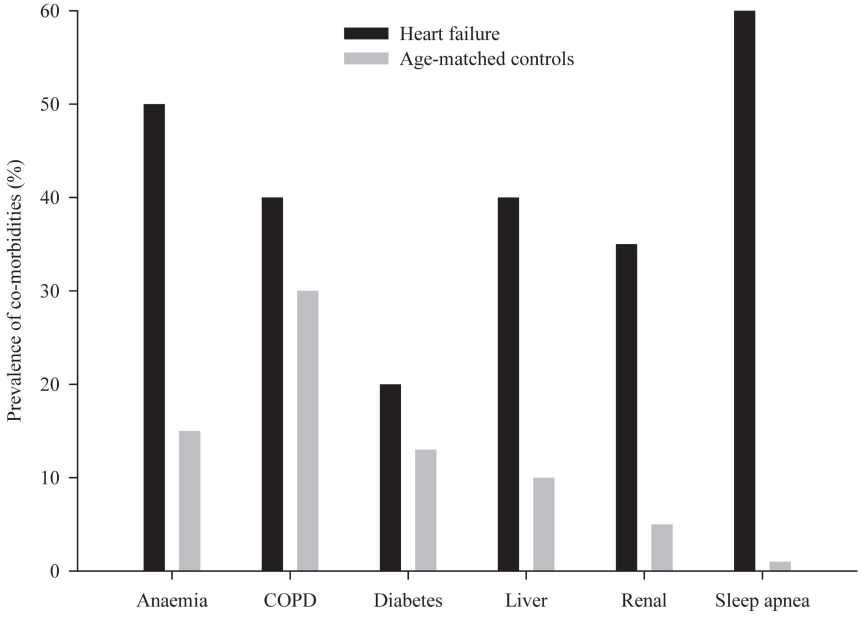

Figure 1. Prevalence of comorbidities in heart failure: Prevalence of comorbidities in patients with heart failure (dark) compared to age-matched controls.

Table 1. All comorbidities in heart failure: Summary of all comorbidities in heart failure, including prevalence, hazard ratio for mortality and number of articles by MeSH-search.

	Prevalence (%)	Related with mortality	MeSH-search (N articles)
Anaemia	37	Yes	1.010
Cerebral dysfunction	28-58	Yes	407
Cognitive dysfunction	50-60	Yes	116
COPD	10-50	Yes	449
Depression	22	Yes	577
Diabetes	6-44	Yes	2.100
Erectile dysfunction	85	-	36
Gout/hyperuricemia	-	Yes	34
Hypertension	60-70	Yes	4.734
Iron deficiency	50-60	Yes	168
Kidney dysfunction	Up to 55	Yes	1.610
Liver dysfunction	30-60	Yes	521
Sleep apnoea	60	Yes	641
Stroke	5	Yes	720

There are several pathways via which heart failure can cause anaemia. Firstly, neurohormonal activation (renin–angiotensin–aldosterone system (RAAS) and vasopressin is accompanied by salt and fluid retention, leading to increased extracellular volume and lower haemoglobin levels ('pseudoanaemia').[10] Although this so-called pseudoanaemia is related to fluid retention, it is not accompanied by signs and symptoms.[10]

Secondly, heart failure is accompanied by haematinic deficiencies. The mechanism is probably related to poor intake, blood loss due to aspirin or warfarin, malabsorption and cardiac cachexia.[11] Of patients with anaemia and heart failure, half are iron deficient and less than one-third are B12- or folate deficient.[12,13]

Thirdly, heart failure is associated with a low-systemic state of inflammation.[5] Chronic inflammation leads to anaemia due to erythropoietin (EPO) resistance as well as reduced bone marrow proliferation.[14]

Fourthly, patients without anaemia also showed deficient bone marrow function.[15] Intrinsic pathways for these effects are seen in vitro, suggesting general dysfunction of haematopoietic cells is present in patients with heart failure even without serum effects.

Finally, the use of heart failure medication (i.e. ACE inhibitors and beta-blockers) might also be associated with the prevalence of anaemia. Intervention in RAAS activation leads to lower haematopoietic activity.[16] In the SOLVD trial, the risk of anaemia increased by more than 50 % in patients randomized to enalapril.[17] This may be explained by N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), as levels of this erythropoiesis-inhibiting factor

increased due to ACE inhibitors, resulting in decreased haematopoiesis and anaemia.[16] Use of beta-blockers has also been related to a higher occurrence of anaemia.[18]

Impact on survival

Anaemia is associated with increased mortality and morbidity in patients with heart failure. In a meta-analysis of 150,000 patients with chronic heart failure, 47 % of anaemic patients died with a minimal follow-up of 6 months compared with 30 % in the non-anaemic group.[7] In a registry of more than 1 million patients, anaemia had an additive prognostic effect to heart failure and renal failure; annual mortality was 4 % in patients without heart failure, renal failure and anaemia and rose to 23 % in patients with the combination of all three.[19] Interestingly, patients with pseudoanaemia had a worse prognosis than those with true anaemia.[20]

In short, about one-third of patients with heart failure have anaemia, depending on the definition used and disease severity. The underlying pathophysiology is complex and multifactorial and leads to higher mortality rates. The prognosis is worse for age-matched controls.

Cerebral dysfunction

Prevalence

Cognitive impairment has a prevalence of 28–58 % in patients with heart failure.[21–23] In a systematic review, the risk for the presence of cognitive impairment increased by more than 60 % in patients with heart failure compared to control subjects.[21] However, inconsistent definitions of cognitive impairment are used as cognition is a complex system with several domains.[24,25] Therefore, multiple different assessments are advised.

Pathophysiology

The aetiology of cognitive impairment in patients with heart failure is largely unclear, as only a limited number of heart failure studies have systematically assessed the cognitive function. Nevertheless, it is thought that loss of cerebral function in patients with heart failure is partly due to a higher rate of cerebral infarcts and cerebral atrophy and may be explained by atherosclerosis as a common risk factor. However, cerebral hypoperfusion is another possible cause for cerebral abnormalities, and significant regional blood flow abnormalities were found in patients with heart failure.[26] However, it should be noted that the brain is relatively protected by strongly developed autoregulatory mechanisms. Hypothetically, with further deterioration in cerebral blood flow, autoregulation will eventually fail in patients with severe heart failure, resulting in the development of cerebral dysfunction.

Impact on survival

Little is known about mortality rates relating to cerebral dysfunction. In a small number of studies, both cognitive impairment and dementia were associated with increased mortality.[27,28] Speculatively, cognitive impairment may contribute to hospitalization and worsening heart failure because it leads to the inability to manage complex medical regimes and failure to recognize worsening clinical status.[29]

In brief, cognitive impairment in heart failure is higher than in controls, with a prevalence of up to 58 %. Although vascular disease could be a common pathway, the brain is potentially another organ influenced by hemodynamic profiles.

Chronic obstructive pulmonary disease

Prevalence

Chronic obstructive pulmonary disease and heart failure often occur in the same patient. The diagnosis of either is difficult, as both diseases result in symptoms of restrictive and obstructive pulmonary abnormalities in combination with muscular changes.[30] The prevalence of chronic obstructive pulmonary disease in patients with heart failure ranges from 10 to 50 %, where recent studies tend to report higher percentages.[31] Compared with general population, the prevalence of chronic obstructive pulmonary disease in patients with heart failure was seven times higher in a large Scottish database.[32]

Notably, prevalence was often based on self-reporting, whereas spirometry would be preferable. In fact, only 43 % of patients with evidence of COPD during spirometry self-reported the presence of COPD, highlighting the need for better screening for this comorbidity.[33]

Pathophysiology

The common prevalence may be caused by common risk factors. Smoking is an obvious common risk factor. Other possible mechanisms include inflammation, hypoxia, oxidative stress and sympathetic nervous system malfunction.[34] For instance, low-grade inflammation is observed in heart failure and plays a role in the atherosclerotic process, and there is abundant evidence of systemic inflammation in patients with COPD.[35] Other suggested mechanisms include development of interstitial fibrosis, reduced lung volume due to cardiomegaly and interstitial and alveolar fluid, and weakness of the respiratory muscles.[36]

COPD may also cause heart failure by increasing pulmonary blood pressure. A small study showed that patients with COPD display both left and right ventricular dysfunction.[37] This may partly explain the high cardiovascular mortality among patients with COPD.

Impact on survival

COPD limits survival substantially. Survival is strongly correlated with pulmonary function as well as self-reported COPD.[33]

In summary, the prevalence of COPD in heart failure ranges up to 50 %. This is seven times higher than in age- matched controls. While the pathophysiologic link is unclear, smoking and inflammation as common risk factors may be part of the explanation.

Diabetes

Prevalence

Prevalence of both diabetes and heart failure is increasing dramatically worldwide.[38] The prevalence of diabetes is 4–7 % in the normal population and ranges from 12 to 44 % in patients with heart failure, depending on the severity of heart failure and whether a decreased left ventricular ejection fraction is present.

Pathophysiology

The incidence of diabetes in heart failure is higher than in patients without heart failure (odds ratio 1.6) with an absolute incidence of diabetes in patients with heart failure of 28 % over 3 years.[39] In diabetic patients, heart failure is twice as common in men and five times as common in women, compared with age-matched controls.[40]

Heart failure is associated with impaired glucose metabolism and poor glycaemic control. In addition, the severity and progression of heart failure is associated with increased insulin resistance.[41] The risk of development of heart failure is also increased in patients with diabetes and impaired glucose tolerance.[42]

Diabetes is believed to cause metabolic derangement in the heart in addition to contractile dysfunction and loss of normal microvasculature.[43] This results in a higher rate of myocardial infarction in diabetic patients and affects left ventricular ejection fraction.[44] These underlying mechanisms are encompassed by the controversial entity 'diabetic cardiomyopathy'.[43] Changes in the diabetic heart include intramyocardial microangiopathy, the accumulation of collagen and other glycation end-products and increased turnover of free fatty acids.[44]

Another explanation is that mutual entities may predispose to both diabetes and heart failure. The Framingham and SOLVD studies found that diabetic patients were more obese, had impaired lipid and glucose profiles and had more hypertension.[45,46] Patients with diabetes are also more at risk for developing coronary artery disease, predisposing them to the development of heart failure.

Impact on survival

Cardiovascular morbidity and mortality is increased in patients with diabetes.[47] Accord-

ingly, patients hospitalized with heart failure and diabetes have worse outcome than patients with only heart failure.[48]

In short, heart failure and diabetes frequently coexist. Pathophysiologic mechanisms remain unclear although common pathways may exist. Prognosis is worse when diabetes mellitus is present in patients with heart failure.

Kidney dysfunction

Prevalence

Chronic kidney disease is usually defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2. Chronic kidney disease is probably the best known comorbidity in patients with heart failure, with a prevalence ranging up to 55 %.[4,49]

Pathophysiology

The common coexistence of cardiac and renal failure could be explained by a major common risk factor for both heart failure and renal disease, such as (coronary) arterial disease, hypertension or diabetes. On the other hand, there seems to be a reciprocal relationship, in which cardiac failure can cause renal failure and vice versa. For example, congestion in heart failure has been shown to be a predictor of renal function, while patients with end-stage renal disease often develop cardiac dysfunction.[4,50] The pathophysiology of concomitant renal dysfunction in heart failure is strongly related to both decreased cardiac output and increased central venous pressure.[51,52] Increased central venous pressure can compromise renal perfusion as well. Furthermore, several neurohormonal pathways (e.g. RAAS) and heart failure therapies have a negative impact on renal function and vasoactive agents and can thereby modulate the relationship between haemodynamics and renal function.[53]

Chronic kidney dysfunction (CRS type 4) is known to be associated with worse cardiovascular outcome.[54] Next to shared risk factors like smoking, obesity, hypertension and dyslipidaemia, other pathological factors may be involved. Observations from specific biomarker studies suggest a pathophysiologic mechanism involving chronic inflammation, subclinical infections and accelerated atherosclerosis, which predisposes to the development of heart failure.

Impact on survival

Renal function is a well-known predictor of morbidity and mortality in patients with heart failure.[55] In a registry of more than 1 million patients, the risk of mortality increased in patients who had both heart failure and renal dysfunction, compared to patients with heart failure or renal dysfunction alone.[19] Deterioration of renal function over time is also a potent predictor of mortality and hospitalization, resulting in a 60 % increase in relative

risk compared to patients with stable renal function.[56]

In summary, chronic kidney disease is a well-known comorbidity in patients with heart failure with a prevalence ranging up to 55 % and is related to poor prognosis. Among other factors, such as hypoperfusion, medication, neurohormonal and inflammatory activation, decreased cardiac output and increased central venous pressure might explain its common prevalence and subsequent poor prognosis.[51,57]

Liver dysfunction

Prevalence

The presence of liver enzyme abnormalities in heart failure has long been recognized.[58] We and others have shown that abnormal liver enzymes are frequently found in patients with heart failure, with a prevalence of 30–60 %, depending on which liver enzyme is measured.[6,59]

Pathophysiology

Interestingly, most abnormal liver enzymes show a relationship with increased venous congestion, while only some seem to be related to reduced cardiac output. Decreased cardiac output mainly relates to aspartateaminotransferase (AST), alanineaminotransferase (ALT) and bilirubin, where increased central venous pressure is related to all liver enzyme tests, especially gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP) and bilirubin.[6,60]

When heart function is restored by a left ventricular assist device, liver enzyme levels, specifically AST, ALT and total bilirubin, return to normal within 1 or 2 months, providing further evidence that impaired haemodynamics in patients with heart failure are the cause of abnormal liver enzyme levels.[61] This is in agreement with individual small reports that highlight the importance of either high central venous pressure or reduced hepatic perfusion.[60,62] One reason why low perfusion could be less important for liver function may be the fact that oxygen consumption can easily be increased even if hepatic blood flow is decreased. The liver is dependent on the blood supply delivered by the hepatic artery, but this accounts for only 30 % of the blood received. The remaining 70 % comes from the portal system.[63] In contrast, the liver is directly connected to the central venous system, which could explain its sensitivity to raised central venous pressure. Vice versa, liver dysfunction can lead to increased fluid overload due to hypoalbuminemia and low-osmolality state, potentially leading to worsening of heart failure.

Impact on survival

With regard to prognosis, several reports have addressed the prognostic importance of liver enzyme abnormalities in the setting of heart failure.[59,64] However, it is possible

that the relation between abnormal liver enzymes and impaired prognosis is due to the relationship between liver enzymes and congestion. We found that levels of GGT, ALP, AST and LDH were predictors of all-cause mortality. Even after adjustment for easily obtainable non-invasive covariates, AST and LDH remained significant predictors of prognosis, but not independently of CVP and cardiac index.[6] This suggests that liver enzyme abnormalities are a reflection of poor hemodynamic status in these patients, rather than an underlying secondary hepatic injury that leads to worse prognosis.

In summary, abnormal liver enzymes have prevalence up to 60 %, which is higher than in age-matched controls. Elevated liver enzymes seem to be related to a combination of congestion and reduced cardiac output. Low hepatic perfusion in heart failure mainly predisposes to hepatocellular liver injury (high AST, ALT and bilirubins), whereas cholestatic liver injury (high bilirubins, GGT and ALP) is primarily observed when congestion is present. Bilirubin levels are dependent of both reduced perfusion and congestion. Although individual abnormal liver enzyme levels are related to higher mortality, this merely seems to reflect poor hemodynamic status.

Sleep apnoea

Prevalence

The sleep apnoea syndrome is characterized by complaints of daytime sleepiness and repetitive breathing cessation during sleep. This syndrome can be divided into two main subcategories: obstructive sleep apnoea syndrome (OSAS) and central sleep apnoea syndrome (CSAS). Sleep apnoea syndrome (SAS) is a condition often unrecognized in heart failure patients, as excessive sleepiness has a symptomatic overlap with heart failure. Both OSAS and CSAS can be present in heart failure, with CSAS being far more common.[65] The prevalence of SAS in heart failure is about 60 %, while it affects 2–4 % of the middle-aged working population.[66]

Pathophysiology

CSAS with a crescendo and decrescendo flow pattern (so-called Cheyne Stokes) may be considered a consequence of heart failure and is largely driven by changes in pCO_2. Patients with chronic heart failure have high filling pressures which can lead to pulmonary oedema, especially at night. As a consequence, pulmonary J receptors are stretched, leading to hyperventilation. $PaCO_2$ subsequently drops under the so-called apnoea threshold and the patient stops breathing.[67] The apnoea and/or hypopnea that arises causes an imbalance in the myocardial oxygen delivery/consumption ratio, as well as activation of sympathetic and other neurohumoral systems and increasing right and left ventricular afterload.[68] In turn, the filling pressure will increase, feeding into a vicious circle.

OSAS is caused by a combination of abnormalities in pharyngeal anatomy, pharyngeal

function and ventilatory control during sleep. OSAS is a risk factor for cardiovascular diseases and hypertension and can lead to heart failure.[69]

Impact on survival

Both OSAS and CSAS are associated with increased mortality.[70,71] After adjustment for confounders, patients with both heart failure and SAS have a mortality rate twice that of patients with heart failure alone.

In brief, sleep apnoea is more prevalent in heart failure than age-matched controls, often goes unrecognized and is related with mortality. Central sleep apnoea is the most common variant in patient with heart failure, with hemodynamic factors playing a pathophysiologic role.

Other comorbidities

Previously discussed comorbidities are the most studied organ-related comorbidities. Many other comorbidities are prevalent in patients with heart failure (Table 1). These comorbidities will become an increasingly common problem as patients with heart failure are getting older.

Heart failure is accompanied by a two- to threefold increased risk of stroke compared to controls. There is an annual stroke rate of 1.3–3.5 %, but up to 16 % in patients with concomitant atrial fibrillation.[72] The prevalence of stroke is about 5 % in patients with heart failure. Because of newer high-resolution magnetic resonance imaging techniques, the prevalence of silent strokes is found to be between 20 and 40 %.[73,74] There are several mechanisms associated with increased stroke risk in patients with heart failure.[73] The most recognized reason for stroke in heart failure patients is cardioembolic stroke due to atrial fibrillation and/or left ventricular hypokinesia.[75,76] Secondly, there is a hypercoagulable state due to the activation of the sympathetic nervous system, activation of the renin–angiotensin–aldosterone system and presence of endothelial dysfunction.[77,78] Stroke in heart failure patients is associated with a poorer outcome and higher mortality.[79]

Patients with heart failure often have cognitive impairment, with a prevalence of up to 50–60 %.[21,80] The underlying pathophysiological mechanisms are difficult to identify and are still unclear, but cerebral hypoperfusion and multiple cardiogenic emboli provide possible explanations.[21] Also, cognitive dysfunction may coincide with heart failure. Evidence suggests that low cardiac output is independently associated with impairment of multiple cognitive domains.[81] In fact, multiple studies reported significant improvement in cognitive function in patients who had received transplants.[82,83] Cognitive dysfunction is associated with a poor prognosis, but it remains unclear whether this is a direct effect of heart failure per se[21], or whether it reflects general cardiovascular risk markers that are associated with cognitive dysfunction.[84]

Erectile dysfunction has a prevalence of 85 % in patients with heart failure with an average age of 60 years.[85] The pathophysiology can be divided into intrinsic and extrinsic factors. Intrinsic factors include decreased cardiac output, decreased exercise capacity and neurohormonal and vascular changes, including atherosclerosis. Extrinsic factors are psychological factors and side effects from medications.[86]

Pathophysiologic explanations for high prevalence of comorbidities in heart failure

In the previous section, the prevalence of comorbidities was shown to be much higher in heart failure patients compared to an age-matched population. Higher prevalence figures suggest a common risk factor or a causal relationship.

A common risk factor as a common cause may be challenged, as it is unlikely that one factor can cause all comorbidities including heart failure. Moreover, because all comorbidities have heart failure as a common denominator, it is likely that heart failure may cause or worsen predisposed comorbidities. Therefore, a causal relationship, where heart failure and other comorbidities may aggravate each other, seems to be more likely. Several mechanisms in heart failure may contribute to failure of other organs. Firstly, heart failure causes neurohormonal changes that cause other organs to dysfunction. Heart failure can change neurohormonal status by affecting these balances—for instance, hormonal (angiotensin and vasopressin), neural (parasympathetic and sympathetic nerves), structural (hypertrophy and remodelling) and local factors (pH, ions and adenosine).[87]

Secondly, the drugs used to treat heart failure may affect comorbidities (e.g. beta-blockers and COPD; ACE inhibitors and kidney dysfunction and anaemia).

Thirdly, hemodynamic changes might cause other organs to fail as well. Hemodynamic derangements are the hallmark of the heart failure syndrome, and because the heart provides perfusion for the entire body, a deterioration of cardiac output affects all organs. Interestingly, blood is redistributed to certain organs at the expense of others.[87] In mild heart failure, resting cardiac output is still normal, but during exercise, the increase in cardiac output is suppressed, leading to a smaller increase in skeletal muscle blood flow. In patients with severe heart failure, however, resting cardiac output is already reduced. The heart and brain receive normal blood flow at the expense of skeletal muscle and renal blood flow. As a percentage of cardiac output, cerebral and coronary blood flows are even increased.[3] Patients with heart failure can be divided into four hemodynamic profiles, based on whether or not forward failure (low perfusion) and backward failure (congestion) are present.[88] Further research is needed to establish which patients with heart failure are susceptible to developing comorbidities. Although associations have been found between heart failure and various diseases and organ dysfunctions, evidence for a causal relation is largely lacking. Ultimate proof should come from intervention studies aimed at improving the function of one selected organ and that study the effects on the other

organ(s). So far, proposed pathophysiologic explanations are largely speculative, and further research should be focussed on elucidating common pathophysiology and potential treatment targets.

Conclusion

The prevalence of comorbidities in heart failure patients is much higher compared to non-heart failure patients of similar age. Although common risk factors are likely to contribute, it is reasonable to assume that heart failure itself may be the cause of comorbidities. Chronic underperfusion of organs as well as increased venous pressure secondary to heart failure could explain why comorbidities are frequently present in patients with heart failure.

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Summary and future perspectives

Vincent M. van Deursen

Heart failure is a clinical syndrome characterized by the heart's inability to meet the body's circulatory demands. It can cause a number of symptoms, including dyspnea, edema and exercise intolerance.[1] Patients with heart failure have a poor quality of life and high morbidity and mortality.[2] In recent decades, growing evidence has accumulated about other diseases and dysfunction of other organs in patients with heart failure. These 'comorbidities' frequently accompany heart failure and result in worse quality of life and clinical outcome.

Aims

This thesis aimed to assess:

1. The prevalence of individual and multiple comorbidities in patients with heart failure;
2. Whether the prevalence of comorbidities is higher in patients with heart failure than in age-matched controls
3. The pathophysiologic mechanisms connecting heart failure and individual comorbidities as well as determinants of multiple comorbidities
4. The prognostic influence of individual and multiple comorbidities.

Comorbidities

While numerous studies focus on a single comorbidity, only few previous studies focused on multiple non-cardiac comorbidities in patients with heart failure.[3,4] However, regional differences have not been studied and determinants of multiple co-morbidities remain unknown.

Chapter 1 examines multiple comorbidities in a broad spectrum of European patients with chronic heart failure. A total of 3226 outpatients with chronic heart failure were included in this analysis. We focused on the prevalence, determinants, regional variation and prognostic implications of comorbidities.

We conclude that the majority of patients had a least one comorbidity, and the number of comorbidities increased with the severity of heart failure. The presence of diabetes, chronic kidney disease and anemia were independently associated with increased risks of mortality and heart failure hospitalizations, with the highest population attributable risks for chronic kidney disease and anemia. Interestingly, there were marked differences in prevalence and prognostic implications of comorbidities in various regions across Europe.

The pathophysiologic mechanisms connecting heart failure and comorbidities remain largely unknown. These mechanisms are complex and may be different for individual comorbidities. Therefore, comorbidities must be studied separately to find pathophysiologic associations.

Of all the comorbidities, only two are directly related to an organ – renal and liver dysfunction. Anemia, for example, is studied in blood and related to bone marrow dysfunction and renal dysfunction. Other comorbidities, such as sleep apnea and cognitive dysfunction, do not have clear substrates that could be easily studied.

Renal dysfunction and liver dysfunction are relatively easy to study and can be evaluated on a continuous functional scale rather than dichotomized into dysfunctional or not.

Renal dysfunction

One of the most important comorbidities in heart failure is renal dysfunction. Renal dysfunction is a strong, independent predictor of prognosis in the general population and in patients with heart failure.[5,6] Heart failure and renal dysfunction share risk factors - hypertension, diabetes, and underlying atherosclerotic disease. Moreover, heart failure can cause renal dysfunction and vice-versa. The complex reciprocal interaction is called the cardiorenal syndrome.[7] Cardiorenal syndrome is classified into 5 subtypes, according to the underlying pathophysiologic mechanisms. We are interested in cardio-renal syndrome types 1 (acute) and 2 (chronic) - acute/chronic abnormalities in cardiac function that result in acute/chronic kidney disease.

In chapters 2-4 we assess the prevalence of renal dysfunction in patients with chronic and acute decompensated heart failure and the impact on prognosis. We also try to identify pathophysiological mechanisms, including which renal parameters best assess renal function in heart failure.

The pathophysiology of renal dysfunction in patients with heart failure is multifactorial and associated with decreased perfusion, atherosclerosis, inflammation, endothelial dysfunction, and neurohormonal activation.[8-10] Previous small studies in animals and humans suggested that central venous pressure might be associated with renal function.[11-14]

In addition to cardiac output, central venous pressure is an important hemodynamic factor in patients with heart failure. While decreased cardiac output occurs when the heart fails to pump enough blood to the organs, central venous pressure rises if the heart fails to handle the blood returning from the organs. This 'backward failure' leads to congestion in systemic capillaries, leading to excess fluid accumulation in the body (edema). It is unclear whether central venous pressure may be related to renal function in a broad spectrum of patients cardiovascular disease.

In chapter 2, we assessed associations between renal dysfunction and hemodynamics in 2,557 patients who underwent right heart catheterization in the University Medical Center Groningen, the Netherlands, between 1989 and 2006.

We found that the two most important predictors of renal dysfunction are decreased cardiac output and increased central venous pressure. Central venous pressure was also a strong and independent determinant of all-cause mortality.

To better understand the pathophysiological mechanisms connecting renal dysfunction and heart failure, it is important to determine which renal parameters best assess renal function in patients with heart failure.

Renal function is usually measured by using serum creatinine to estimate glomerular filtration rate. Although estimated glomerular filtration rate is strongly associated with increased mortality in patients with heart failure, these findings are far less well-established in the presence of mild renal impairment.[6,15] Creatinine has limitations, such as relative insensitivity to small changes in actual glomerular filtration rate and dependency on muscle metabolism, weight, age and sex.

In addition to glomerular function, renal function also encompasses tubular function. In patients with intrinsic kidney failure, tubulointerstitial damage is an established marker for renal disease.[16] Several studies showed that tubular markers are elevated before a risk in creatinine is observed.[17-20] However, the prognostic value of plasma tubular damage markers in patients with normal or mildly impaired renal function is less well described.[21]

One of the tubular markers that can be measured in plasma is Neutrophil Gelatinase Associated Lipocalin (NGAL).

Chapter 3 assesses the role and performance of the tubular marker plasma NGAL as a prognostic marker for mortality in heart failure patients with both normal and impaired renal function. Secondy, the prognostic value of plasma NGAL is compared with creatinine and cystatin C, two frequently used biomarkers of chronic kidney disease.

In 562 patients with heart failure, NGAL predicted mortality, in patients with both preserved and impaired renal function. Moreover, plasma NGAL was a stronger predictor for mortality across the full range of renal function than the frequently used biomarkers such as creatinine. This may indicate that in heart failure patients, tubular damage may better reflect an impaired hemodynamic status than glomerular function.

As mentioned earlier, the complex reciprocal interaction between the heart and the kidneys is classified into 5 subtypes of the cardiorenal syndrome.[7] In chapters 2 and 3, we have studied the prevalence, pathophysiologic mechanisms and prognostic implications of type 2 cardiorenal syndrome (chronic). In chapter 4, we focus on type 1 cardiorenal syndrome (acute) - acute abnormalities in cardiac function that result in acute kidney disease.

In acute heart failure, 20-40% of patients experience a rise in creatinine, which can be categorized into worsening renal function.[13] Despite a high prevalence, many pathophysiologic mechanisms remain unresolved. Previous studies showed worsening renal function may influence outcomes, although results are not consistent.[15,22-24]

In a retrospective analysis of a prospective randomized trial with a total of 7141 patients, we aimed to investigate the effects of nesiritide on renal function during hospitalization for acute decompensated heart failure. Of greater interest for this thesis, we also exam-

ined the pathophysiologic associations and prognostic implications of (change in) creatinine. Baseline and discharge creatinine values were available in 4708 patients, allowing changes in renal function to be studied.

In this study, baseline renal function was mildly impaired and decreased further during hospitalization. Predictors of decline in renal function included higher systolic and lower diastolic blood pressure, lower potassium levels, more prior weight gain, and lower blood urea nitrogen levels, consistent with previous research.[25,26]

We conclude nesiritide did not affect renal function in patients with acute decompensated heart failure, despite concerns raised by previous, smaller studies. Interestingly, we found both baseline and discharge renal function, but not worsening renal function or change in creatinine, were associated with 30-day mortality or re-hospitalization.

There are several potential explanations for why change in creatinine was not associated with worse short-term outcome, in contrast to findings in other studies.[15,22,23] For example, most studies do not measure creatinine routinely, so in those that did, there was probably a reason. The reason could be worsening symptoms, non-response to diuretics, and an expectation of worse clinical outcomes.[24] Supporting this hypothesis, a recent study in which serum creatinine levels were measured routinely, worsening renal function was not independently related to prognosis.[24] Interestingly, that study found that worsening renal function was prognostic in patients with persistent signs of congestion, suggesting a differential effect of worsening renal function. Additionally, the prospective, randomized DOSE-trial found that patients that were given high doses of diuretics had greater diuresis and more favorable outcomes, despite exhibiting more frequent transient worsening renal function.[27] This suggests an increase in creatinine reflects decongestion due to response to diuretic therapy rather than true worsening of renal function in some patients.

Liver dysfunction

Liver function abnormalities, like renal dysfunction, are common in patients with heart failure. Although the presence of liver enzyme abnormalities in heart failure has long been recognized,[28] the pathophysiologic mechanisms and the prognostic value of abnormal liver function tests remain largely unknown. In chapters 2-4, we observed renal dysfunction was associated with both reduced cardiac output and increased central venous pressure. Individual small reports have highlighted the importance of high central venous pressure and reduced hepatic perfusion.[29-31]

In chapters 5 and 6, we assess prevalence of liver dysfunction in patients with chronic and acute decompensated heart failure and the impact on prognosis. We also try to elucidate pathophysiological mechanisms, focusing on hemodynamic factors such as cardiac output and central venous pressure.

A few studies have highlighted the importance of either high central venous pressure or reduced hepatic dysfunction.[29-31] However, the independent contribution of reduced cardiac output or increased central venous pressure in causing abnormalities in specific liver function tests has not been studied.

In chapter 5, we studied liver function in 323 patients with heart failure by determining aspartate and alanine aminotransferase (AST, ALT), alkaline phosphatase (ALKP), g-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH) and direct and total bilirubin. Central venous pressure and cardiac output were determined invasively.

We show that abnormal liver enzymes are frequently found in patients with heart failure, with a prevalence of 30–60%, depending on the liver enzyme measured. Most abnormal liver enzymes show a relationship with increased venous congestion, while only some seem to be related to reduced cardiac output. Decreased cardiac output mainly correlates with AST, ALT and bilirubin, while increased central venous pressure is associated with all liver enzyme tests, particularly GGT, ALKP and bilirubin.

One reason low perfusion may be less important for liver function is the fact that oxygen consumption can easily be increased even if hepatic blood flow is decreased, because only 30% of the liver's blood supply is dependent on the hepatic artery.[32] The remaining 70% is provided by the portal system.

In terms of prognosis, we found that levels of GGT, ALKP, AST and LDH were predictors of all-cause mortality. Importantly, all liver function tests were non-significantly associated with all-cause mortality after correction for central venous pressure and cardiac output. Therefore, it is likely that the relationship between abnormal liver function tests and prognosis is merely a reflection of poor hemodynamic status.

Less is known about liver function in patients with acute decompensated heart failure[33-35] while these patients are most likely to have impaired hemodynamics, making them vulnerable to impaired liver function. Previous reports have shown that the prevalence of abnormal liver function tests in acute decompensated heart failure is similar to chronic heart failure. In this hospitalized population, the interesting question is whether liver function test results change in response to therapy during re-hospitalization.

The prognostic value of impaired liver function tests in patients with acute heart failure is also less well established compared to chronic heart failure. Only one study assessed the in-hospital changes in liver function tests, and found albumin and bilirubin were associated with 180-day mortality in 2061 patients admitted with acute heart failure.[33]

In chapter 6, we investigated liver function tests at baseline and during hospitalization in 234 patients with acute decompensated heart failure. We examined the prognostic value of (change in) impaired liver function by assessing relationships with in-hospital worsening heart failure through day 5, 60-day mortality or re-hospitalization and 180-day mortality.

We found that abnormal liver function tests are prevalent in patients with acute decompensated heart failure - 20% of patients had abnormal AST and bilirubin, 10% had abnormal ALT and ALKP but almost no patients had abnormal levels of albumin and total protein. Liver function tests changed minimally during hospitalization, consistent with previously published data.[33]

As is also observed in chronic heart failure, abnormal liver function tests are common in acute heart failure patients and associated with an increased risk of mortality, re-hospitalization and in-hospital worsening heart failure. However, changes in liver function tests were very small and not associated with prognosis.

Comorbidities

In chapter 7, we describe the prevalence of the most studied organ-related comorbidities in heart failure, i.e. renal dysfunction, cerebral and cognitive dysfunction, anaemia, liver dysfunction, chronic obstructive pulmonary disease, diabetes mellitus, depression, stroke and sleep apnea. We also provided potential explanations for the observed association between comorbidities and heart failure, as well as effects on survival.

For the first time, we show the prevalence of comorbidities to be much higher in heart failure patients compared to an age-matched population. Although the pathophysiologic mechanisms are complex, remain largely unresolved and differ per comorbidity, we state multiple pathophysiologic factors are involved, including shared risk factors, inflammation, neurohumoral pathway activation and hemodynamic factors. The interactions between these factors make understanding the pathophysiology even more complex.

Future perspective

This thesis has provided an overview of the prevalence, pathophysiology and prognosis of comorbidities in patients with heart failure. We have shown that comorbidities are frequently observed in patients with acute and chronic heart failure, and that prevalence is higher compared to age-matched controls. Patients with more severe heart failure – higher NYHA class - had more comorbidities, confirming the hypothesis that heart failure causes comorbidities. We have shown that hemodynamic factors are an important pathophysiologic link and that prognosis is worse when (multiple) comorbidities are present.

However, many questions remain unanswered. For one, we must try to determine which heart failure patients develop which comorbidities. The complexity of the underlying network of pathophysiological mechanisms, with the potential for multiple interactions, complicates matters considerably. As a first step, comorbidities should be studied individually, testing one hypothesis at a time. Given the marked regional differences, smaller, national studies may be preferable. However, it is likely certain factors have a role in not one, but multiple comorbidities.

In addition to studying individual comorbidities one hypothesis at a time, it is therefore essential that we collect as much data as we can. Developments in information technology have helped advance knowledge by leaps and bounds – although the medical field has yet to fully grasp and deploy the potential benefits offered. Other industries have demonstrated the major benefits of gathering large quantities of data. Such datasets require a different analytical approach to that commonly seen in the medical sciences – students t-test will need to make way for support vector machines and neural network computing.

Data storage efficiency should increase, as the information we currently 'harvest' is encoded in medical correspondence and images that are almost impossible to analyze. Rather than writing down or dictating a blood pressure measurement, time of measurement, systolic and diastolic blood pressure measurements should be entered as unique entities, and allow the computer to generate the requisite sentence. This will free doctors to concentrate their attention on more important matters.

We should not limit data capture to variables seen by doctors, such as medical history, physical examination, medical conclusions, and so forth. Nurses collect data all day long as well, data crucial to better understanding the patient's in-hospital journey. Machines also handle data which are not stored in analyzable entities; automatic storage of MRI, CT, echocardiographic and catheter instrument data in a single database could provide invaluable insights. In fact, implantable cardiac devices already store data for the manufacturers, data that could be helpful in the healthcare industry as well. Genetic material should also be included to allow genetic and epigenetic effects to be evaluated.

And one can only dream of what we could do if we could store and analyze all data that is generated by the patients themselves. Should we alert heart failure patients when they have twittered too many times that they have eaten 'salted herring'? At the very least, we should look into variables that might explain which patients develop comorbidities and which patients do not. Because the answer to this complex pathophysiological web of riddles will not be found inside the hospital walls alone.

In conclusion, comorbidities frequently accompany heart failure and worsen morbidity and mortality. Although heart failure has a potential causal relation, the complex pathophysiological mechanisms remain unresolved.

Comorbidities could be studied separately, but it is likely certain factors have a role in not one, but in multiple comorbidities. Therefore, comorbidities must be studied simultaneously as well. In 1894, William Osler stated that in order "to know fully many of the most important diseases a man must be familiar with their manifestations in many organs" (William Osler, The army Surgeon, Medical News, Philidelphia, 1894).

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Dutch summary

Vincent M. van Deursen

Hartfalen is een klinisch syndroom waarbij het hart niet in staat is om het lichaam van zijn behoefte te voorzien. Het gaat gepaard met het vasthouden van vocht, kortademigheid en verminderde inspanningstolerantie.[1] Patiënten met hartfalen hebben een slechte kwaliteit van leven en een verhoogde kans op ziekenhuisopname en sterfte.[2] Er komt steeds meer bewijs dat patiënten met hartfalen andere ziekten hebben. Deze 'comorbiditeiten' komen vaak voor bij hartfalen en verslechteren de kwaliteit van leven en verhogen de sterftekans.

Doelen

Dit proefschrift heeft als doel om te achterhalen:

1. wat de prevalentie is van individuele en gezamenlijke comorbiditeiten bij hartfalen;
2. of de prevalentie van comorbiditeiten hoger is bij hartfalen dan bij leeftijdsgenoten;
3. wat de mechanismen zijn tussen hartfalen en verschillende comorbiditeiten, evenals de factoren die geassocieerd zijn met meerdere comorbiditeiten;
4. wat de prognostische betekenis is van individuele en meerdere comorbiditeiten.

Comorbiditeiten

Hoewel talrijke studies zich op een afzonderlijke comorbiditeit hebben gericht, zijn er weinig studies die zich richten op meerdere niet-cardiale comorbiditeiten bij patiënten met hartfalen.[3,4] Tot nu toe is onbekend welke factoren zorgen voor meerdere comorbiditeiten bij patiënten met hartfalen.

Hoofdstuk 1 onderzocht meerdere comorbiditeiten in 3226 Europese patiënten met chronisch hartfalen. We hebben ons gericht op de prevalentie, determinanten, regionale variatie en prognostische implicaties van comorbiditeiten.

We concludeerden dat de meerderheid van de patiënten ten minste één comorbiditeit had en dat het aantal comorbiditeiten toenam met de ernst van hartfalen. De comorbiditeiten diabetes, chronische nierziekte en anemie waren onafhankelijk geassocieerd met een verhoogd risico op ziekenhuisopname en sterfte. Interessant om te vermelden is dat er duidelijke verschillen waren in verschillende regio's van Europa.

In de volgende hoofdstukken hebben we gekeken naar de comorbiditeiten die direct gerelateerd zijn aan een orgaan - nierfunctiestoornissen en leverfunctiestoornissen. Hierdoor zijn ze relatief eenvoudig te bestuderen op een continue schaal. Dit maakt het makkelijker om te kijken naar de nog onbekende complexe mechanismen tussen hartfalen en comorbiditeiten.

Nierfunctiestoornissen

Een van de belangrijkste comorbiditeiten bij hartfalen is nierinsufficiëntie.[5-7] We weten dat hartfalen nierfunctiestoornissen kan veroorzaken, en andersom kunnen nierfunctiestoornissen ook hartfalen veroorzaken. Beide worden veroorzaakt door gemeenschappelijke risicofactoren zoals een hoge bloeddruk, diabetes en onderliggend atherosclerose.

In de hoofdstukken 2-4 onderzochten we zowel de prevalentie van nierfunctiestoornissen bij patiënten met chronisch en acuut hartfalen als de invloed op de prognose. We probeerden ook om enkele mechanismen te identificeren.

De mechanismen tussen nierfunctiestoornissen en hartfalen zijn veelzijdig en complex. Verminderde perfusie, atherosclerose, inflammatie, endotheel disfunctie en neurohormonale activatie zijn enkele factoren die meespelen.[8-10] Ook zou een verhoogde centraal veneuze druk een rol kunnen spelen.[11-14]

De centraal veneuze druk is naast het hartminuutvolume een belangrijke hemodynamische factor bij patiënten met hartfalen. Het hartminuutvolume is bij deze patiënten verminderd omdat het hart niet in staat is om voldoende bloed rond te pompen naar de organen. De centraal veneuze druk stijgt wanneer het hart niet in staat is om het bloed vanuit de organen weg te pompen. Dit leidt uiteindelijk tot ophoping van overtollig vocht in het lichaam (oedeem).

In hoofdstuk 2 bevestigden we de associaties tussen nierfunctiestoornissen en hemodynamiek bij 2557 patiënten met hartfalen. We vonden dat een verminderde hartminuutvolume en een verhoogde centrale veneuze druk de twee belangrijkste voorspellers waren van nierfunctiestoornissen. Een verhoogde centraal veneuze druk was daarnaast een onafhankelijke voorspeller voor overlijden.

Om een beter inzicht te krijgen in de mechanismen tussen hartfalen en nierfunctiestoornissen hebben we gekeken naar verschillende markers voor de nierfunctie. Hoewel de glomerulaire marker kreatinine meestal wordt gebruikt, heeft kreatinine ook een aantal tekortkomingen.[6,15] Zo wordt kreatinine beïnvloed door factoren als leeftijd, geslacht, spiermetabolisme en gewicht en is kreatinine relatief ongevoelig voor kleine wijzigingen in de nierfunctie.

In hoofdstuk 3 hebben we onder andere gekeken naar NGAL (Neutrofiel Gelatinase Geassocieerd Lipocaline). Dit is een schademarker van het tubulaire deel van de nier en is verhoogd bij patiënten met hartfalen.[16-21] In 562 patiënten met hartfalen zagen we dat NGAL een sterkere voorspeller is voor sterfte dan kreatinine. We zagen zelfs dat NGAL was verhoogd bij normale waarden van kreatinine. Dit kan erop wijzen dat tubulaire nierschade de verslechterde hemodynamische status beter weerspiegelt dan de glomerulaire functie bij patiënten met hartfalen.

Naast chronisch hartfalen hebben we ook gekeken naar acuut hartfalen. Van de patiënten die worden opgenomen met acuut hartfalen weten we dat de nierfunctie in 20-40% nog verder achteruit gaat.[13] Het is echter nog onduidelijk welke mechanisme meespelen. Ook weten we niet zeker of een verslechtering van de nierfunctie zorgt voor een hogere sterfte.[15,22-24]

In hoofdstuk 4 hebben we in 7141 patiënten met acuut hartfalen gekeken naar de effecten van het medicijn nesiritide op de nierfunctie. Voor dit proefschrift is het van belang dat we ook keken naar de verandering van de nierfunctie, gemeten met kreatinine.

Voorspellers van een verslechtering van de nierfunctie waren een hogere systolische bloeddruk, een lagere diastolische bloeddruk, gewichtstoename vóór opname, een lager kalium en een lager ureum.[25,26]

We concludeerden dat een slechte nierfunctie geassocieerd is met een hogere sterfte, maar dat verdere verslechtering van de nierfunctie niet geassocieerd is met ziekenhuisopnames of sterfte binnen dertig dagen.

Een mogelijke verklaring is dat een toename van kreatinine in sommige patiënten niet betekent dat de nierfunctie is afgenomen, maar dat de medicijnen voor hartfalen goed werken.[27] Deze patiëntengroep krijgt namelijk vaak een diureticum dat bij een positief effect het kreatinine kan verhogen.

Leverfunctiestoornissen

Leverfunctiestoornissen komen vaak voor bij patiënten met hartfalen. Hoewel dit al langer bekend is, blijven de mechanismen en de prognostische waarde van afwijkende leverfuncties grotendeels een raadsel.[28]

Net als bij nierfunctiestoornissen laten kleine studies het mogelijke belang zien van een hoge centraal veneuze druk en verminderde leverperfusie.[29-31] Echter, de onafhankelijke bijdrage van een verminderd hartminuutvolume en verhoogde centraal veneuze druk op de leverfunctie is niet onderzocht.

In de hoofdstukken 5 en 6 onderzochten we de prevalentie van leverfunctiestoornissen bij patiënten met chronisch én acuut hartfalen alsmede de invloed op prognose. We keken ook naar mogelijke mechanismen, met name de hemodynamische factoren zoals hartminuutvolume en centrale veneuze druk.

In hoofdstuk 5 onderzochten we de leverfunctie bij 323 patiënten met chronisch hartfalen door het bepalen van verschillende leverfunctietesten. We zagen dat 30-60% van de patiënten een afwijkende leverfunctie had, afhankelijk van welke leverfunctietest werd gemeten.

De meeste abnormale leverfunctietesten waren geassocieerd met een verhoogde centraal veneuze druk, terwijl slechts enkele geassocieerd waren met een verminderd hart-

minuutvolume. Een mogelijke verklaring waarom een lage perfusie minder belangrijk is voor de leverfunctie, is dat de lever in gezonde toestand meer bloed krijgt dan nodig is. In meer detail, slechts 30% van bloedtoevoer van de lever is afhankelijk van de leverslagader, terwijl de resterende 70% vanuit het portaal systeem komt.[32]

Verder vonden we dat een aantal leverfunctietesten geassocieerd waren met een verhoogde sterftekans. Belangrijker is dat deze relatie verdween als we corrigeerden voor het hartminuutvolume en de centraal veneuze druk. Waarschijnlijk is de relatie tussen afwijkende leverfunctietesten en verhoogde sterftekans enkel een afspiegeling van de hemodynamische toestand van de patiënt.

Naast chronisch hartfalen hebben we de leverfunctie ook bekeken bij patiënten met acuut hartfalen. Over de leverfunctie in patiënten die opgenomen worden met acuut hartfalen is minder bekend.[33-35] Deze patiëntengroep is interessant omdat de hemodynamiek bij deze patiënten verstoord is waardoor de leverfunctie mogelijk kwetsbaar is. We hebben ook gekeken naar de verandering van de leverfunctie tijdens de opname en of dit invloed had op de sterfte.

In hoofdstuk 6 hebben we 234 patiënten onderzocht die werden opgenomen met acuut hartfalen. Zowel bij binnenkomst als tijdens de ziekenhuisopname waren de leverfunctietesten gemeten. We hebben naar meerdere eindpunten gekeken, waaronder verergering van hartfalen tijdens de ziekenhuisopname, sterfte of heropname binnen 60 dagen, en naar sterfte binnen 180 dagen.

We zagen dat de meeste leverfunctietesten afwijkend waren met een prevalentie van 10-20%. De leverfunctietesten veranderden echter minimaal tijdens de ziekenhuisopname, wat consistent is met een eerder gepubliceerd onderzoek.[33] Net als bij chronisch hartfalen zagen we dat de meeste leverfunctietesten geassocieerd waren met verhoogde sterfte en heropname. Echter, verandering van de leverfunctietesten tijdens opname waren klein en niet geassocieerd met sterfte en heropname.

Comorbiditeit

In hoofdstuk 7 beschreven we de prevalentie van de meest bestudeerde orgaan-gerelateerde comorbiditeiten in hartfalen - nierinsufficiëntie, cerebrale en cognitieve dysfunctie, anemie, lever disfunctie, chronische obstructieve longziekte, diabetes mellitus, depressie, beroerte en slaapapneu. Tevens beschreven we mogelijke verklaringen voor de waargenomen associatie tussen deze comorbiditeiten en hartfalen, evenals de nadelige effecten op de overleving.

Voor de eerste keer lieten we zien dat de prevalentie van comorbiditeiten in patiënten met hartfalen hoger is in vergelijking met leeftijdsgenoten. We zagen dat meerdere mechanismen hierbij betrokken waren - gedeelde risicofactoren, ontsteking, neurohormonale

activatie en ook hemodynamische factoren. Echter, de mechanismen verschillen per comorbiditeit en zijn nog grotendeels onopgelost.

Toekomstperspectief

Dit proefschrift geeft een overzicht van de prevalentie, mechanismen en prognose van comorbiditeiten bij patiënten met hartfalen. We hebben aangetoond dat comorbiditeiten vaak voorkomen bij patiënten met acuut en chronisch hartfalen, en dat de prevalentie hoger is in vergelijking met leeftijdsgenoten. De observatie dat patiënten met ernstiger hartfalen vaker comorbiditeiten hebben is in lijn met de hypothese dat comorbiditeiten veroorzaakt kunnen worden door hartfalen, waarbij hemodynamische factoren een rol lijken te spelen. Tevens hebben we aangetoond dat de prognose slechter is wanneer een patiënt meerdere comorbiditeiten heeft.

Er blijven echter veel vragen onbeantwoord. Zo moeten we er onder andere proberen achter te komen welke patiënten met hartfalen comorbiditeiten ontwikkelen. Hiervoor zullen we elke comorbiditeit individueel moeten bestuderen, waarbij we elke hypothese één voor één bij langs gaan.

Het is echter waarschijnlijk dat sommige factoren een rol spelen in meerdere comorbiditeiten tegelijk met meerdere interacties onderling. Naast het bestuderen van individuele comorbiditeiten is een tweede aanpak daarom essentieel; zoveel mogelijk gegevens verzamelen. Hiervoor moeten we gebruik maken van de informatietechnologie, die zich de afgelopen jaren sterk heeft ontwikkeld. Andere sectoren hebben reeds aangetoond dat er grote voordelen zitten aan het verzamelen van grote hoeveelheden data. Helaas is de medische sector achtergebleven met het benutten van deze voordelen.

Dergelijke grote datasets vereisen ook een andere analytische aanpak dan de medische sector tot nu toe gewend is – de simpele t-test zal plaats moeten maken voor support vector machines en neural network computing.

Ook de manier waarop data wordt opgeslagen zal moeten veranderen. De informatie die we op dit moment 'oogsten' is gecodeerd in brieven en beelden die bijna onmogelijk te analyseren zijn. Daarom moet we data niet dicteren in brieven maar per variabele opslaan – bij een bloeddrukmeting moet bijvoorbeeld automatisch de tijd van de meting, de systolische bloeddruk en diastolische bloeddruk worden opgeslagen. Nadat deze unieke entiteiten zijn ingevoerd, kan de computer automatisch de vereiste zin in een brief genereren. Een extra voordeel is dat artsen hierdoor tijd besparen die ze kunnen gebruiken om zich op belangrijkere zaken te concentreren.

We moeten ons overigens niet beperken tot de gegevens die artsen genereren, zoals

medische anamnese, lichamelijk onderzoek, medische conclusies, enzovoort. Verpleegkundigen verzamelen namelijk ook gegevens. Deze data is cruciaal voor een beter begrip van de reis die de patiënt in het ziekenhuis aflegt. Ook machines verwerken gegevens die nu niet worden opgeslagen in analyseerbare entiteiten. We zouden moeten overgaan op automatische opslag van data afkomstig van MRI, CT, echocardiografie en zelfs katheter-instrumenten. Ook genetisch materiaal kunnen we aan zo'n dataset toevoegen. Deze grote datastromen bevatten waardevolle informatie die wij in de medische wetenschap nog niet benutten. Informatie die implanteerbare cardiale apparaten genereren wordt nu alleen opgeslagen door de fabrikanten.

Men kan alleen maar dromen over wat we zouden kunnen doen met de data die wordt gegenereerd door de patiënt zelf. Denk bijvoorbeeld aan twitter. Als we deze data kunnen opslaan en analyseren komen we er mogelijk achter waarom sommige patiënten wel worden opgenomen en anderen niet. Sturen we patiënten met hartfalen in de toekomst een sms als ze te vaak 'zoute haring' twitteren? Dit is nu nog moeilijk voor te stellen, maar we weten al wel dat er talloze vragen in de gezondheidszorg zijn waarvan we het antwoord niet binnen de muren van het ziekenhuis gaan vinden. Zo ook de vraag waarom sommige patiënten comorbiditeiten ontwikkelen en anderen patiënten niet.

Concluderend, comorbiditeiten komen vaak voor bij patiënten met hartfalen en verhogen de ziektelast en de sterftekans. Hoewel hartfalen mogelijk een rol speelt bij het ontstaan van comorbiditeiten blijven de complexe mechanismen onopgelost. We moeten comorbiditeiten en mogelijke mechanismen zowel afzonderlijk onderzoeken als ook tegelijkertijd. In 1894 werd al gezegd dat een man een ziekte pas compleet begrijpt wanneer hij weet welke gevolgen deze ziekte heeft in andere organen (William Osler, The army Surgeon, Medical News, Philidelphia, 1894).

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Appendix I

Bibliography

Vincent M. van Deursen

Verkorte biografie

Vincent Michiel van Deursen is in 1986 geboren in Leeuwarden waarna hij via Tytsjerk naar Groningen is verhuisd. Hij heeft zijn VWO diploma voor zowel natuur&techniek als natuur&gezondheid behaald aan de Christelijke Scholengemeenschap Comenius. Na een jaar Internationaal Hotel Management op de Christelijke Hogeschool Nederland te hebben gedaan, is hij geneeskunde gaan studeren.

In vijf en een half jaar heeft hij de studie geneeskunde als eerste van zijn lichting afgerond. Tijdens zijn studie is hij met een beurs van de Junior Scientific Masterclass begonnen met zijn promotieonderzoek bij zijn promotores prof. dr. A.A. Voors en prof. dr. D.J. van Veldhuisen. Hij heeft twee prospectieve studies opgezet: BRAIN-HF onderzoekt de breinfunctie en -perfusie bij patiënten met hartfalen ten opzichte van gezonde controles; en SNURC onderzoekt slaapapneu bij patiënten met hartfalen en dan met name de prevalentie en karakteristieken alsook de validatie van een simpel screening-apparaat.

Naast zijn geneeskundestudie is hij twee jaar voorzitter geweest van de Groningen Talent Group - een multidisciplinair exclusief netwerk waarvan elk jaar ongeveer veertig mensen onder de dertig jaar worden geselecteerd uit de vijftigduizend jongeren in Groningen. Vanwege het ondernemende karakter van deze groep is hij betrokken geweest bij het hogere management van het Universitair Medisch Centrum Groningen (UMCG), de Rijksuniversiteit Groningen, de Hanze University Groningen en de gemeente Groningen Ook is hij bestuurslid geworden van de Assistenten Vereniging van het UMCG.

Tijdens zijn studie is hij mede-oprichter en CEO geworden van de Atlas-holding. Atlas Medical B.V. ontwikkelt en produceert hardware en software op maat. Dit met als doel het ondersteunen van medisch wetenschappelijk onderzoek en de medische praktijk.

Op zesentwintig jarige leeftijd heeft Vincent dit proefschrift ‘Comorbidity in heart failure’ verdedigd waarna hij direct zal beginnen met de opleiding tot cardioloog.

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Appendix II

Statements

Vincent M. van Deursen

1. De verstoorde hemodynamiek bij hartfalen zorgt voor het ontstaan van comorbiditeiten. (dit proefschrift)

2. Leverfunctiestoornissen bij hartfalen zijn een reflectie van de ernst van het hartfalen. (dit proefschrift)

3. Kreatinine is een overschatte marker voor het bepalen van de nierfunctie bij hartfalen. (dit proefschrift)

4. Verslechtering van de nierfunctie bij hartfalen kan een gunstig teken zijn. (dit proefschrift)

5. In de praktijk worden comorbiditeiten bij hartfalen vaak gemist; Dit is vooral het geval bij slaapapneu. (dit proefschrift)

6. De manier van het doen van onderzoek moet in de toekomst veranderen door meer gebruik te maken van de huidige informatietechnologieën en Kernel-rekenmethoden. (dit proefschrift)

7. A is A.

8. Tegenstellingen bestaan niet.

9. Elke stelling is waar of niet waar. Er is geen tussenweg.

10. Mensen die zeggen dat je niet alles zwart-wit moet zien snappen niet dat grijze gebieden veroorzaakt worden door een slechte differentiatie.

11. Als iedereen aan zichzelf denkt wordt niemand vergeten.

12. Een plan hebben is goed maar een planning maken is slecht. Dit komt omdat de tweede stap afhankelijk is van de uitkomst van de eerste.

13. Iedereen weet dat 2,5 plus 3,5 gelijk is aan 6. Dus als je 3,5 afrondt naar 4, moet je 2,5 afronden naar 2.

14. Wanneer een groep (of persoon) fouten stigmatiseert, verdrijven ze creativiteit en daarmee innovatie.