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Heart failure in patients with chronic obstructive pulmonary disease  
with special reference to primary care



# Heart failure in patients with chronic obstructive pulmonary disease with special reference to primary care

Elżbieta Kaszuba



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DOCTORAL DISSERTATION

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<b>Title and subtitle:</b> Heart failure in patients with chronic obstructive pulmonary disease with special reference to primary care.		
<b>Abstract</b>		
<p><b>Background:</b> Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are two major conditions, which are common in the Swedish population and which to a large extent are managed in Swedish primary care. When both conditions coexist, similarities in symptoms and signs cause diagnostic difficulties. Unrecognized HF in patients with COPD has serious clinical implications. Despite the fact that coexistence of COPD and HF is common; the conditions have mostly been studied separately. <b>Aim:</b> To describe diagnostic and epidemiological aspects of COPD, coexisting HF, other comorbidities and to evaluate thoracic impedance cardiography (ICG) as a method in the assessment of heart function in patients with heart failure.</p> <p><b>Methods : Study design:</b> All four papers were descriptive and non-interventional. Papers III and IV were register-based. <b>Study populations:</b> Paper I: Patients aged <math>\geq 65</math> years with a registered diagnosis of COPD (n=172) in two primary care (PC) centres in Blekinge. Paper II: Patients with a registered diagnosis of HF in the outpatient HF unit in Karlshamn. Paper III: The adult population in Östergötland. Paper IV: Patients aged <math>\geq 35</math> years with COPD diagnosis in Blekinge. <b>Main outcome measures:</b> Paper I: Percentage of patients with elevated NT-proBNP, percentage of patients with abnormal left ventricular function assessed by echocardiography, and association between elevated NT-proBNP and symptoms, signs, and electrocardiography. Paper II: Association between hemodynamic parameters measured by ICG and the value of ejection fraction (EF) by echocardiography. Paper III: Prevalence of HF in patients with COPD, percentage of patients treated in PC, secondary care or both, distribution of levels of other comorbidities measured by resource utilization band (RUB) using ACG Case-Mix System. Paper IV: Odds ratios of mortality- univariate analysis and with adjustment for age, sex and other comorbidities.</p> <p><b>Results: Paper I:</b> Using NT-proBNP <math>\geq 1200</math> pg/mL HF was detected and confirmed in 5.6% of patients with COPD. An elevated level of NT-proBNP was only associated with nocturia and abnormal electrocardiography. <b>Paper II:</b> A significant association between three of four ICG parameters describing systolic function of left ventricular function (pre-ejection period, left ventricular ejection time and systolic time ratio) and EF measured by echocardiography was found. The fourth parameter (ejection time ratio) was not associated with EF. No association between ICG parameters describing cardiac work and EF by echocardiography was found. <b>Paper III:</b> The prevalence of HF in patients with COPD was 18.8%, while it was 1.6% in patients without COPD. Age-standardized prevalence was 9.9% and 1.5%, respectively. Standardized relative risk for the diagnosis of HF in patients with COPD was 6.6. Comorbidity levels were significantly higher in patients with COPD and coexisting HF compared to patients with either COPD or HF alone. PC was the only care provider for 20.7% of patients with COPD and coexisting HF and participated furthermore in shared care of 21.7% of those patients. <b>Paper IV:</b> Estimated mortality in patients with COPD and coexisting HF was 7 times higher than in patients with COPD alone - odds ratio 7.1 (95% CI 3.9-12.8). Adjusting for age and male sex resulted in odds ratio 3.8 (95% CI 2.0-7.2). Further adjusting for other comorbidities resulted in odds ratio 3.3 (95% CI 1.7-6.3). The mortality was strongly associated with the highest comorbidity level – RUB 5 where the odds ratio was 5.2 (95% CI 2.6-10.4).</p> <p><b>Conclusions:</b> Using NT-proBNP as an initial step for the diagnosis of HF in patients with COPD, considerably fewer cases of HF were than would be expected from the results of previous studies. The results from paper II do not support the application of ICG in order to determine left ventricular function and increase the accuracy of the diagnosis of HF. HF in patients with COPD is common in the Swedish population. Patients with coexisting COPD and HF have higher levels of other comorbidities than patients with COPD or HF alone. This group of multimorbid patients is, to a great extent, managed within Swedish PC. Coexisting HF considerably increases the odds of mortality in patients with COPD. Other comorbidities are the strongest predictor of mortality in patients with COPD and coexisting HF, which is why it is important to recognize and adequately treat other comorbidities early in those patients in order to improve survival.</p>		
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# Heart failure in patients with chronic obstructive pulmonary disease with special reference to primary care

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*Any knowledge that doesn't lead to new questions quickly dies out:  
it fails to maintain the temperature for sustaining life.*

Wisława Szymborska



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# Abstract

## Background

Chronic obstructive pulmonary disease (COPD) and heart failure are two major conditions, which are common in the Swedish population and which to a large extent are managed in Swedish primary care. When both conditions coexist, similarities in symptoms and signs cause diagnostic difficulties. Unrecognized heart failure in patients with COPD has serious clinical implications. Despite the fact that coexistence of COPD and heart failure is common; the conditions have mostly been studied separately.

## Aim

The aim of this thesis was to describe diagnostic and epidemiological aspects of COPD, coexisting heart failure, other comorbidities and to evaluate thoracic impedance cardiography (ICG) as a method in the assessment of heart function in patients with heart failure.

The specific aims for each paper were the following:

Paper I: To study the efficacy of diagnosing of heart failure in patients with COPD in primary care. Paper II: To evaluate ICG as a method in the assessment of left ventricular function in patients with heart failure. Paper III: To study the prevalence of heart failure in patients with COPD in the Swedish population. To describe where patients with COPD and coexisting heart failure are treated and to study other comorbidities in patients with COPD and coexisting heart failure. Paper IV: To study the importance of heart failure and other comorbidities for mortality in patients with COPD.

## Methods

**Study design:** Papers I-III: Descriptive, non-interventional, cross-sectional design. Paper IV: Descriptive, non-interventional, prospective design. Papers III and IV were register-based.

**Study populations:** Paper I: Patients aged  $\geq 65$  years with a registered diagnosis of COPD (n=172) in two different primary care centres in Blekinge County. Paper II: Patients with a registered diagnosis of chronic heart failure (n= 36) in the outpatient heart failure unit at Blekinge County Hospital in Karlshamn. Paper III: The adult population ( $\geq 19$  years) in Östergötland County (n=313 977). Paper IV: Patients aged  $\geq 35$  years with the diagnosis of COPD in Blekinge County (n=1011).

**Main outcome measures:** Paper I: Percentage of patients with elevated NT-proBNP, percentage of patients with abnormal left ventricular function assessed by

echocardiography, and association between elevated NT-proBNP and symptoms, signs, and electrocardiography. Paper II: Association between hemodynamic parameters measured by ICG and the value of ejection fraction as a determinant of left ventricular systolic function in echocardiography. Paper III: Prevalence of heart failure in patients with COPD, percentage of patients treated in primary-, secondary care or both, distribution of levels of other comorbidities measured by resource utilization band (RUB) using Adjusted Clinical Groups Case-Mix System. Paper IV: Odds ratios of mortality- univariate analysis and with adjustment for age, sex and other comorbidities.

## Results

**Paper I:** Using NT-proBNP threshold  $\geq 1200$  pg/mL heart failure was detected and confirmed in 5.6% of patients with COPD. An elevated level of NT-proBNP was only associated with nocturia and abnormal electrocardiography.

**Paper II:** A significant association between three of four ICG parameters describing systolic function of left ventricular function (pre-ejection period, left ventricular ejection time and systolic time ratio) and ejection fraction measured by echocardiography was found. The fourth parameter (ejection time ratio) was not associated with ejection fraction. No association between ICG parameters describing cardiac work and ejection fraction by echocardiography was found.

**Paper III:** The prevalence of heart failure in patients with COPD was 18.8%, while it was 1.6% in patients without COPD. Age-standardized prevalence was 9.9% and 1.5%, respectively. Standardized relative risk for the diagnosis of heart failure in patients with COPD was 6.6. Comorbidity levels were significantly higher in patients with COPD and coexisting heart failure compared to patients with either COPD or heart failure alone. Primary care was the only care provider for 20.7% of patients with COPD and coexisting heart failure and participated furthermore in shared care of 21.7% of those patients.

**Paper IV:** Estimated mortality in patients with COPD and coexisting heart failure was seven times higher than in patients with COPD alone - odds ratio 7.1 (95% CI 3.9-12.8). Adjusting for age and male sex resulted in odds ratio 3.8 (95% CI 2.0-7.2). Further adjusting for other comorbidities resulted in odds ratio 3.3 (95% CI 1.7-6.3). The mortality was strongly associated with the highest comorbidity level – RUB 5 where the odds ratio was 5.2 (95% CI 2.6-10.4).

## Conclusions

Using NT-proBNP as an initial step for the diagnosis of heart failure in patients with COPD in primary care, considerably fewer cases of heart failure were found than would be expected from the results of previous studies. The diagnostic tools, which are available for the general practitioner, are not sufficient and do not allow for an accurate diagnosis of heart failure in patients with COPD.

When using ICG in assessment of left ventricular function in patients with chronic heart failure we found that only three of four ICG parameters, which describe systolic function of the left ventricle, were significantly associated with ejection fraction measured by echocardiography. We could not confirm previously suggested associations between ICG parameters and ejection fraction measured by echocardiography. The results from the present study do not support the application of ICG in order to determine left ventricular function and increase the accuracy of the diagnosis of heart failure.

Heart failure in patients with COPD is common in the Swedish population. Patients with coexisting COPD and heart failure have higher levels of other comorbidities than patients with COPD or heart failure alone. This group of multimorbid patients is, to a great extent, managed within Swedish primary care. Coexisting heart failure considerably increases the odds of mortality in patients with COPD. Other comorbidities are the strongest predictor of mortality in patients with COPD and coexisting heart failure, which is why it is important to recognize and adequately treat other comorbidities early in those patients in order to improve survival rates.

## Abbreviations

COPD	chronic obstructive pulmonary disease
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
LVEF	left ventricle ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFmrEF	heart failure with mild ranged ejection fraction
NYHA	the New York Heart Association
GOLD	the Global Initiative for Chronic Obstructive Lung Disease
BNP	B-type natriuretic peptide
NT-proBNP	N-terminal pro-BNP
ICG	thoracic impedance cardiography
ICD 10	International Classification of Diseases and Related Health Problems, 10th revision
ACG Case-Mix System	Adjusted Clinical Groups Case-Mix System
RUB	resource utilization band
SD	standard deviation
IQR	interquartile range
CI	Confidence Interval

## Original papers

*This thesis is based on the following papers:*

- I. Kaszuba E, Wagner B, Odeberg H, Halling A: Using NT-proBNP to detect chronic heart failure in elderly patients with chronic obstructive pulmonary disease. *ISRN Family Med.* 2013 Jun 9;2013:273864. doi: 10.5402/2013/273864. eCollection 2013.
- II. Kaszuba E, Scheel S, Odeberg H, Halling A: Comparing impedance cardiography and echocardiography in the assessment of reduced left ventricular systolic function. *BMC Res Notes.* 2013 Mar 26;6:114. doi: 10.1186/1756-0500-6-114
- III. Kaszuba E, Odeberg H, Råstam L, Halling A: Heart failure and levels of other comorbidities in patients with chronic obstructive pulmonary disease in a Swedish population: a register- based study. *BMC Res Notes.* 2016 Apr 12;9:215. doi: 10.1186/s13104-016-2008-4
- IV. Kaszuba E, Odeberg H, Råstam L, Halling A: Impact of heart failure and other comorbidities on mortality in patients with chronic obstructive pulmonary disease. Manuscript.

# Background

One of the most common causes of consultations in primary care is dyspnea [1]. Behind this symptom, the general practitioner can find a minor health problem or a serious one.

This thesis dealt with two serious disorders that can be present as dyspnea: chronic obstructive pulmonary disease (COPD) and heart failure. COPD and heart failure are chronic and severe conditions characterized by a progressive course. Both are common in the Swedish population [2, 3] and associated with prevalent occurrence of other comorbidities and high mortality [4, 5]. In Sweden, most patients with COPD and the majority of patients at risk of heart failure, e.g. with coronary heart disease, atrial fibrillation and hypertension, are treated in primary health care.

Heart failure might be overlooked in patients with COPD due to similarities in symptoms and signs. When diagnosing heart failure, evidence of cardiac dysfunction should be objectively verified using echocardiography [6]. Echocardiography, however, is not always easily available in Swedish primary care. Echocardiography is performed after referral and requires input from secondary care.

Taking those facts into consideration I wanted to study:

- I. How effective are recommended diagnostic procedures in primary care when diagnosing heart failure in patients with COPD.
- II. Whether a new method - thoracic impedance cardiography (ICG)- can be used in order to assess left ventricular function in patients with heart failure.
- III. How prevalent heart failure in patients with COPD is in the Swedish population and where patients with coexisting heart failure and COPD are treated: primary- or secondary care.
- IV. How important heart failure and other comorbidities are for mortality in patients with COPD.



# Definitions and terminology

## **Chronic obstructive pulmonary disease (COPD)**

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [7] COPD is defined as a common preventable and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. The diagnosis of COPD should be established by spirometry. The persistent airflow limitation is defined by a value of a quotient of two parameters measured by spirometry: forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). The quotient  $FEV1/FVC < 0.7$  after inhalation of bronchodilating medicine is a diagnostic criterion of COPD.

Classification of severity of COPD is based on airflow limitation measured by post-bronchodilator FEV1 expressed as percent of predicted value:

Stage I:  $FEV1 \geq 80\%$

Stage II: FEV1 50-79%

Stage III: FEV1 30-49%

Stage IV:  $FEV1 < 30\%$  or  $< 50\%$  with presence of chronic respiratory failure.

The use of combined assessment, which includes the degree of airflow limitation, symptoms assessment and risk of exacerbations, has recently been recommended by GOLD in order to guide management choices. Thus COPD is classified as:

A: Minor symptoms, airflow limitation stage I or II and non or 1 exacerbation not leading to hospitalization,

B: Major symptoms, airflow limitation stage I or II and non or 1 exacerbation not leading to hospitalization,

C: Minor symptoms, airflow limitation stage III or IV and  $\geq 2$  exacerbations or 1 exacerbation leading to hospitalization,

D: Major symptoms, airflow limitation stage III or IV and  $\geq 2$  exacerbations or 1 exacerbation leading to hospitalization.

The diagnostic criteria for COPD and classification according to GOLD are well established in Sweden. However, the modification regarding airflow limitation, with respect to age, was previously used when defining COPD. In patients 65 years and older, the quotient 0.65 was recommended instead of 0.7 [8].

This modification has been removed and the latest national recommendations are in agreement with GOLD [9, 10].

## Heart failure

The definition of heart failure has evolved and changed during the time and mirrored the increase of knowledge in the field.

At the end of the 1960s and in the 1970s heart failure was defined only from hemodynamic perspective as ‘a state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory venous filling pressure’[11]. In the 1980s abnormalities of left ventricular function and neurohormonal regulation were added [12] with the definition: ‘a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity’. In the year 2005 ‘objective evidence of cardiac dysfunction at rest’ was included in the definition of European Society of Cardiology [13] while the American College of Cardiology/American Heart Association definition remained more hemodynamically orientated ‘heart failure is a complex clinical syndrome that can result from any structural or functional disorder that impairs the ability of the ventricle to fill with or eject blood’ [14]. The newest guidelines, from 2016, for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology [6] define heart failure as ‘a clinical syndrome characterized by typical symptoms, e.g. breathlessness, ankle swelling and fatigue that may be accompanied by signs, e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress’. The guidelines underline that this definition is restricted to patients with symptoms and does not comprise asymptomatic cardiac abnormalities.

When taking a time aspect into consideration about heart failure we use the following terms: acute, subacute, chronic heart failure [6]. However, there are no fixed timeframes defined for when to use these terms.

In older studies, the term of congestive heart failure was frequently used. Congestion refers to evidence of retention of sodium and water. If congestion predominates in systemic venous circulation we refer to right-sided heart failure and if congestion predominates in pulmonary venous circulation we refer to left-sided heart failure. Those conditions, however, generally do not occur separately.

The classification based on left ventricle function is commonly used in clinical practice and trials. Left ventricular function is measured by echocardiography, which is the “gold standard” and described by left ventricle ejection fraction (LVEF) [15].

Heart failure was previously classified into two types [16]:

1. Heart failure with normal LVEF ( $\geq 50\%$ ) or diastolic heart failure
2. Heart failure with reduced LVEF ( $<50\%$ )

The newest proposal of the European Society of Cardiology [6] is to classify heart failure into three types:

1. Heart failure with preserved LVEF  $\geq 50\%$  (HFpEF)
2. Heart failure with mild-range LVEF 40-49% (HFmrEF)
3. Heart failure with reduced LVEF  $< 40\%$  (HFrEF)

The New York Heart Association's (NYHA) classification is related to the severity of symptoms and widely used both in clinical practice and in trials [17].

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.

Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.

Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV: Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

The American College of Cardiology and American Heart Association proposed classification into five stages [14, 18]:

Stage A: Patients at high risk of developing heart failure due to conditions strongly associated with the development of heart failure without signs or symptoms and without structural or functional abnormalities of the heart.

Stage B: Patients with structural heart disease that is strongly associated with the development of heart failure, but without symptoms and signs of heart failure.

Stage C: Patients with current or prior symptoms of heart failure associated with underlying structural heart disease.

Stage D: Patients with advanced structural heart disease and refractory symptoms of heart failure requiring specialized interventions.

This classification underlines the fact that heart failure is a continuum, which starts with risk factors and proceeds through asymptomatic changes in the heart, clinical manifestation to disability and death.

# Epidemiology of COPD and heart failure in Sweden

Between 4.4 and 7.7% of the Swedish population is estimated to have COPD [2]. The prevalence increases with age. In the year 2003, 5% of smokers had COPD at the age of 45 years while 50% of smokers had COPD at the age of 75 years [19]. In the year 2009, the general prevalence of COPD was 6.3%, despite the decreasing prevalence of smoking in Sweden [20].

The prevalence of heart failure in the general population in Sweden is between 2 and 3% and rises with age to approximately 10-20% at 70-80 years of age [3][21, 22]. The incidence has increased mainly due to an increasing proportion of elderly people in Sweden.

Both COPD and heart failure patients use a large part of resources in Swedish health care and place a heavy economic burden due to high prevalence and the chronic and progressive course of both conditions [3, 23-25].

## Diagnosing of COPD and heart failure in Swedish primary care.

### **Chronic obstructive pulmonary disease**

COPD in Sweden is usually diagnosed in primary care without involvement of secondary care. Spirometry is required in order to make a valid diagnosis of COPD according to the GOLD criteria [26] and is recommended with the highest priority by Swedish National Guidelines for asthma and COPD when COPD is suspected [9]. Spirometry is widely available in Swedish primary care. In the year 2000, a spirometer was available in 77% of primary care centers in central Sweden [27]. In the year 2009, spirometry was accessible in 99% of primary care centers participating in the study in different parts of Sweden [28]. Spirometry is usually performed in a primary care center by a specially trained asthma/COPD nurse. After a spirometry examination, the diagnosis of COPD is usually made by a general practitioner. In exceptional cases, it might happen that spirometry is performed at the lung disease unit in secondary care.

### **Heart failure**

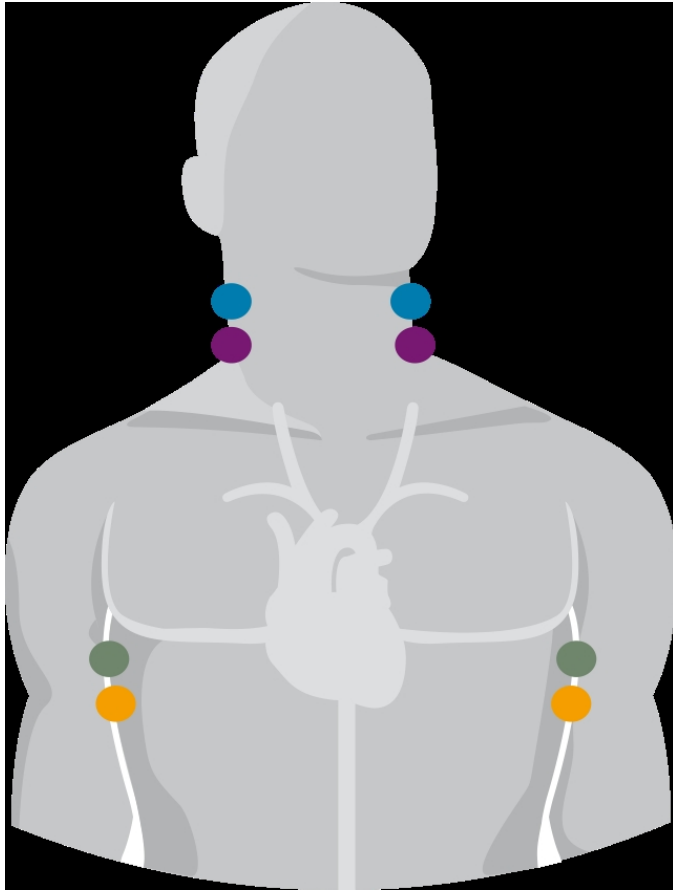
An accurate heart failure diagnosis requires evidence of an impaired heart function, which can be shown by echocardiography. Echocardiography in Sweden is performed within secondary care after referral from a general practitioner and is not easily available in many parts of the country. It is performed only in about 30% of patients with suspected heart failure in Swedish primary care [29, 30].

The diagnosis of heart failure is usually made clinically. Assessment of probability of heart failure in the same patient cases differs considerably between different general practitioners [31].

Testing of natriuretic peptides is a recommended tool which might be used by a general practitioner in order to improve the correctness of heart failure diagnosis [32]. In 1988, B-type natriuretic peptide (BNP) was isolated from porcine brain tissue [33] and described in 1995 as ‘emergency cardiac hormone against ventricular overload’ with the following effects: improvement of myocardial relaxation, decreasing of vasoconstriction, sodium retention and antidiuretic effects caused by the activated rennin-angiotensin-aldosterone system [34]. BNP is synthesized in the ventricular myocardium under the circumstances of volume expansion or pressure overload as pre-proBNP. This inactive form is cleft first to pro-BNP and thereafter to biologically active BNP and aminoterminal (N-terminal) fragment NT-proBNP. The role of natriuretic peptides as a biomarker for heart failure has developed and both BNP and NT-proBNP were suggested as useful tools in diagnosing heart failure [35, 36] and included in guidelines for heart failure in Europe and America [13, 37, 38]. The fact that many factors affect the levels of natriuretic peptides should be taken into consideration when interpreting the results. Age, female sex, arrhythmia including atrial fibrillation, renal insufficiency are associated with increased levels, while obesity, common antihypertensive medications are associated with lower levels of natriuretic peptides [39]. According to the latest European Society Guidelines for heart failure 2016 [6], natriuretic peptides are recommended as an initial investigation in patients presenting with symptoms that suggest heart failure. Patients with normal levels of natriuretic peptides are unlikely to have heart failure and do not require echocardiography.

## Thoracic impedance cardiography

Thoracic impedance cardiography (ICG) is a non-invasive investigation method. Impedance is a measure of resistance against alternating current. How to use ICG in clinical practice is simple, similar to electrocardiography, and an examination can be performed by the general practitioner. Two pairs of dual electrodes are placed on the patient’s neck and chest as shown in Figure 1.



**Figure 1.** Electrode placement for impedance cardiography measurement (after permission of Medizinische Messtechnik GmbH Ilmenau, Germany).

The inner sensors apply a non-perceptible current, the outer sensors measure the impedance. The impedance changes during every heartbeat due to changes in blood volume and blood flow velocity in the aorta. Changes in impedance are used to calculate different hemodynamic parameters. Each parameter has defined reference values in a healthy person. ICG parameters are presented in Table 1.

**Table 1.**

The list of ICG parameters.

ICG parameter		unit
Heart rate	HR	l/min
Heart period	HPD	ms
Stroke volume	SV	ml
Stroke index	SI	ml/min
Cardiac output	CO	l/min
Cardiac index	CI	l/min/m <sup>2</sup>
Left cardiac work	LCW	kg·m
Left cardiac work index	LCWI	kg·m/m <sup>2</sup>
Velocity index	VI	1/1000/s
Acceleration index	ACI	1/100/s <sup>2</sup>
Heather index	HI	Ohm/s <sup>2</sup>
Thoracic fluid content	TFC	1/kOhm
Pre-ejection period	PEP	ms
Left ventricular ejection time	LVET	ms
Systolic time ratio	STR	
Ejection time ratio	ETR	%
Systolic vascular resistance	SVR	ml/min
Systolic vascular resistance index	SVRI	ml/min/m <sup>2</sup>

A meta-analysis of the validity of cardiac output measurement by ICG found a moderately good correlation between cardiac output measured by ICG and other techniques, such as thermodilution, dye dilution, Fick technique and radionuclide angiography [40].

ICG was considered to be reproducible in ambulatory patients with heart failure [41] and was suggested as a useful tool in management of patients with heart failure in order to detect worsening of left ventricular function [42], predict decompensation in patients with stable heart failure [43, 44], follow-up patients with heart failure and choose an optimal treatment [45, 46]. Those facts made me take an interest in using ICG as a possible tool in assessment of ventricular function in general practice.

## Coexistence of COPD and heart failure

The link between COPD and atherosclerosis as a basic factor underlying cardiovascular diseases, which leads to heart failure, can be explained by traditional risk factors, e.g. smoking, low socioeconomic status and sedentary lifestyle and a number of novel risk factors. The novel risk factors comprise systemic inflammation, vascular dysfunction as a consequence of oxidative and physiologic stress, accelerated aging mechanisms in patients with COPD and upregulation of proteases [47]. All those factors affect endothelium, vascular smooth muscles and extracellular matrix and lead to atherosclerosis.

Occurrence of cardiovascular diseases in patients with COPD is well-known in clinical practice and well-described in several studies [48-50]. Heart failure should not be considered an isolated diagnosis but rather a consequence of cardiovascular diseases.

Patients with COPD present a risk of developing heart failure 4.5 times higher than age-matched controls [51].

The prevalence of heart failure in patients with COPD older than 65 years of age in primary care was found to be approximately 20% [52, 53]. There were no prior Swedish data about prevalence of heart failure in patients with COPD.

Despite improved treatments for COPD and heart failure, both conditions are still characterized by a high mortality rate. COPD is predicted to be the third most common cause of death and disability worldwide by 2030 [4]. The 5-year survival in patients with heart failure was 53% compared with 93% in aged and sex matched general population [5]. The prevalence and burden of heart failure and COPD correlate with the aging of the population. The proportion of elderly in Sweden is the highest in the world with 17.4% of the population aged  $\geq 65$  years and that figure is expected to increase until the year 2020 [54]. This implies that management of COPD and heart failure will be a challenge in future primary care in Sweden. The risk of overlooking or misdiagnosing heart failure in patients with COPD is high due to similarities in symptoms and signs and lack of immediate access to echocardiography as an objective tool in assessment of left ventricular function.



## Comorbidities in patients with COPD and heart failure

As mentioned above the prevalence of COPD and heart failure increases with age.

Age is the most important factor, which influences multimorbidity defined as occurrence of two or more long-term chronic conditions in an individual [55]. Multimorbidity was widely reported in previous studies separately for patients with COPD [48, 50, 56-58] and heart failure [59-64]. This thesis dealt with patients with COPD and coexisting heart failure. When describing other conditions in those patients the term ‘other comorbidities’ was used throughout the thesis.

# Aims of the thesis

The general aim of this thesis was to describe diagnostic and epidemiological aspects of coexisting heart failure and COPD in the Swedish population and to evaluate impedance cardiography in assessment of left ventricular function in patients with heart failure.

The specific aims for each paper were the following:

**Paper I:** To study how effective recommended procedures in primary care are when diagnosing heart failure in patients with COPD.

**Paper II:** To study the association between ICG parameters and ejection fraction measured with echocardiography.

**Paper III:** To study the prevalence of heart failure in patients with COPD in a Swedish population, describe where patients with coexisting heart failure and COPD are treated: primary- or secondary care and describe other comorbidities in this group of patients.

**Paper IV:** To describe importance of heart failure and other comorbidities for mortality in patients with COPD.



# Methods

**Study design:** All the studies were descriptive and non-interventional. A cross-sectional design was used in papers I-III and a prospective design in paper IV.

## **Data collection and study populations**

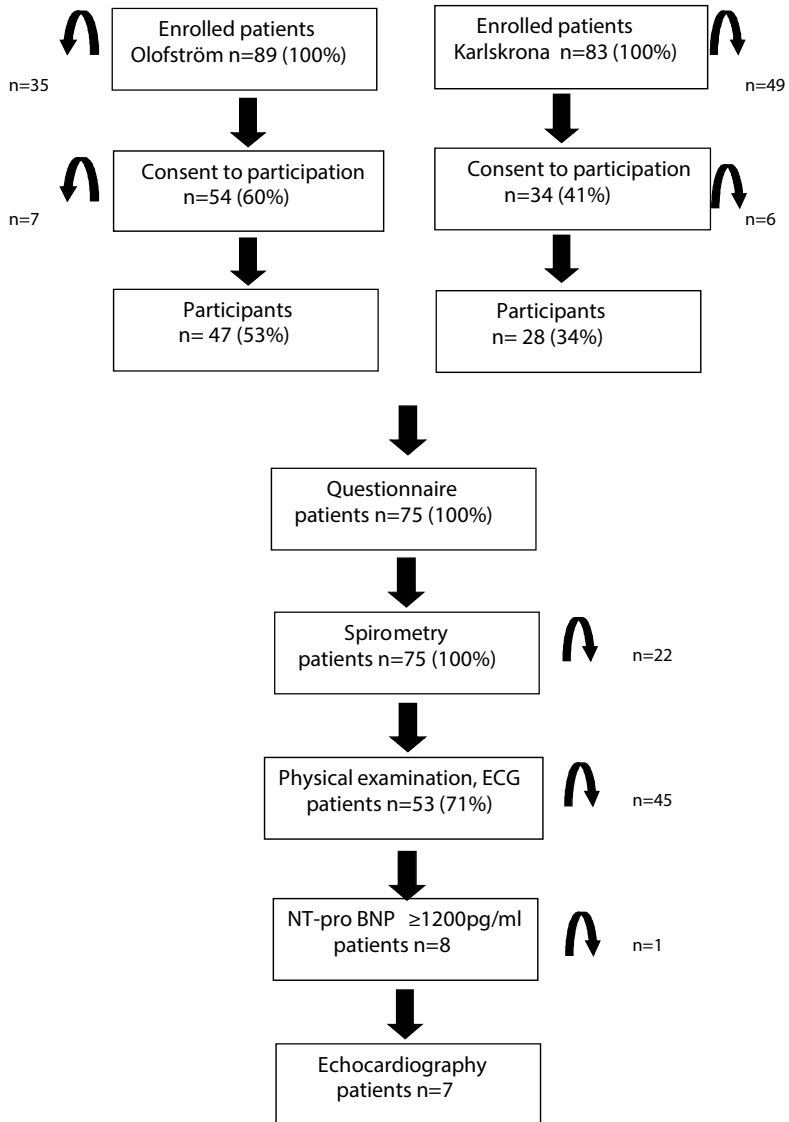
Papers I and II were based on original material collected for the purpose of the studies. Papers III and IV were register-based.

### **Paper I**

The study was conducted in two different primary care centers during the period 16 April 2008 - 13 June 2008 in Blekinge County. This county has approximately 150 000 inhabitants and is located in south-eastern Sweden. The first primary care center was located in Olofström, the second one in Karlskrona. During the study period, Olofström municipality had 13 198 inhabitants, with 22.7% aged 65 years and older and Karlskrona municipality had 62 338 inhabitants with 19% aged 65 years and older [65].

The study included patients aged 65 years and older with the following diagnosis codes according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD 10): J44 (COPD) and J41, J42 (chronic bronchitis) registered during the period 1 January 2008 - 16 April 2008 according to the electronic patient record.

Data on the patient flow during the study are shown in Figure 2.



**Figure 2.**  
Flowchart of the method in paper I.

At the time of the study, 9265 patients were registered at the primary care center in Olofström; a total of 1905 (20.6%) patients were aged 65 years and older. At the primary care center Tullgården in Karlskrona a total of 9002 patients were registered; 1508 (16.8%) were aged 65 and older.

Exclusion criteria comprised impaired cognitive function and/or anticipated difficulties in carrying out spirometry due to immobility, psychiatric disorders or terminal illness.

Informed consent was obtained from each participant.

## **Paper II**

The data were collected in the outpatient heart failure unit at the Blekinge County Hospital in Karlshamn in Sweden during the period 6 February 2009 – 6 March 2009. There were 63 patients registered at the heart failure unit. All registered patients were invited to participate by letter sent by a cardiologist. No reminder was sent. Exclusion criteria comprised significant aortic valve insufficiency and severe aortic stenosis, both of which influence ICG measurement. Informed consent was obtained from each participant.

## **Paper III**

The data were obtained from the Care Data Warehouse register in Östergötland County in Sweden [66]. The register collects data concerning consultation and diagnosis transferred every month from all public- and private care units in both primary- and secondary care. Diagnoses are recorded according to ICD 10. We used data from the year 2006. The study population included people older than 19 years.

## **Paper IV**

The data were obtained from the Blekinge County council health care register. The register collected data concerning diagnosis at each consultation in all public- and private care units in both primary- and secondary care. Diagnoses were recorded according to ICD 10. The study population comprised people aged  $\geq 35$  years. The data from 1 January to 31 December 2007 were analyzed. The whole population of the county could be studied because of the centralized listing system in place in the primary care center in Blekinge County at that time. Date of death was collected from 1 January 2008 to 31 August 2015 and obtained from the Blekinge County council. Individuals who left Blekinge County during observation time were excluded from the study.

# Study procedures

## **Paper I**

As a first step, we wanted to confirm the diagnosis of COPD found in medical records and classify the degree of severity of COPD according to the GOLD criteria [26]. For this purpose, all participants were examined with spirometry (Spirare 3, Diagnostica, Norway), if spirometry had not already been carried out during the past year.

Patients with a confirmed diagnosis of COPD were examined regarding chronic heart failure.

They were asked in an interview about the following symptoms: breathlessness, orthopnoea, night cough, nocturia, walking distance. Physical examination included: weight and height, heart and lung auscultation, blood pressure measurement after five minutes' rest in the sitting position and the presence of peripheral edema. Positive findings from heart and lung auscultation were determined as rales and the third heart sound.

All patients were examined by electrocardiography and tested with natriuretic peptide.

The natriuretic peptide was determined as NT-proBNP (Immolute 2500, Siemens Healthcare Diagnostics AB Sweden). Patients with NT-proBNP level of  $\geq 1200$  pg/ml were referred for echocardiography to assess left ventricular (LV) function using the following echocardiographic criteria:

EF  $\geq 55\%$ : Normal systolic LV function

EF 40-54%: Mildly impaired systolic LV function

EF 30-39%: Moderately impaired LV function

EF  $<30\%$ : Severely impaired LV function

Abnormal LV relaxation and/or distensibility during normal EF were described as diastolic dysfunction.

## **Paper II**

The patients were examined by means of echocardiography and ICG during one consultation. Both echocardiography and ICG were performed once on each patient. Echocardiography was performed by an experienced cardiologist using Vivid 7, GE equipment. EF was calculated according to modified Simpson's formula. The following echocardiographic criteria were used to describe left ventricle systolic function: EF  $\geq 50\%$  normal systolic function, EF 40-49 % mildly impaired systolic function, EF 30-39% moderately impaired systolic function, EF

<30% severely impaired systolic function. ICG was performed by the author using Niccom<sup>TM</sup> monitor (Medis. Medizinische Messtechnik GmbH, Germany) [67].

ICG measurement was obtained after 10 minutes' resting, in the supine position, with the head elevated between 30-45 degrees to provide better comfort for the patient.

None of the ICG parameters can be directly compared with EF due to differences in both methods of examinations. ICG parameters were divided into the following groups:

1. Expression for cardiac work: cardiac output, stroke volume, left cardiac work.
2. Contractility: velocity index, acceleration index, Heather index.
3. Fluid status: thoracic fluid content.
4. Expression for systolic function: pre-ejection period, left ventricular ejection time, systolic time ratio and ejection time ratio.
5. Expression for the vascular resistance the heart works against: systolic vascular resistance.

### **Papers III and IV**

Similar procedures were used when handling the register data in papers III and IV.

An individual was identified as having COPD or heart failure if the ICD 10 diagnosis code J44 or I50 was recorded on at least one consultation in primary or secondary care including hospitalization. The code J44 comprised the following: J44 chronic obstructive lung disease, J44.0 chronic obstructive lung disease with acute infection in lower airways, J44.1 chronic obstructive lung disease with acute exacerbation, unspecified, J44.8 other specified chronic obstructive lung disease including chronic bronchitis with emphysema. The register did not allow to follow the distribution of severity of COPD. The code I50 comprised: I50.0 chronic heart failure including congestive heart failure, right heart failure secondary to left heart failure, I50.1 left ventricular failure with or without lung edema and cardiac asthma, I50.9 heart failure, unspecified.

In order to describe comorbidity the diagnosis-based Adjusted Clinical Groups (ACG) Case-Mix System 7.1 was used. Each individual was assigned one of six comorbidity levels called resource utilization bands (RUB) graded from 0 to 5 where 5 means very high morbidity and need of care. When identifying the place where patients received care in paper III we used information where the diagnosis of heart failure and COPD was made: primary-, secondary care or both.





# Statistical analyses

Data were analyzed in STATA version 10 (Stata Corporation, Texas, USA).

Distribution of categorical variables was presented as numbers. Distribution of continuous variables in paper I was presented as the mean and standard deviation (SD) except NT-proBNP value, which was presented as the mean and interquartile range (IQR) due to a skewed distribution. Distribution of continuous variables in other papers was presented as the mean and 95% Confidence Interval (CI).

Comparisons in groups were made in papers I and II. Mann-Whitney test was chosen for comparison of mean values in paper I due to small groups and skewed distribution. In paper II, Kruskal-Wallis test was used to compare variables in more than two groups and show differences between the groups.

Differences in proportions in the groups in all papers were tested with the chi-square test.

A p-value of  $< 0.05$  was considered significant.

Univariate logistic regression was used in paper IV to show the effect of heart failure, age, sex and comorbidity on mortality in patients with COPD. Multiple logistic regression was then performed in order to adjust the estimated odds ratio to age, sex and other comorbidities.



# Ethical consideration

All the study protocols were approved by the Regional Ethics Review Board.

Studies I, II and IV were approved by the Regional Ethics Review Board in Lund. Case numbers were respectively 50/2008, 533/2008, 2015/169. Study III was approved by Regional Ethics Review Board in Linköping, case number 147/05 and 29/06. Study I was registered at ClinicalTrials.gov. Identifier NCT01801722.

Participation in the studies was voluntary. Written, informed consent was obtained from each participant in studies I and II. In the register studies III and IV the presumed consent was used. Information about the studies was published in local newspapers and patients had the possibility to contact the researcher and desist from participation. The included patients could withdraw from the studies at any time.

Time and effort was made to protect individual data. Only researchers and qualified personnel were involved in data collection. Thereafter all data were encrypted and presented at a group level. The risk of harm for study participants was considered to be low. No study procedure was considered to cause pain or have an adverse effect.



# Results

## Paper I

An initial 75 participants were enrolled in the study. The diagnosis of COPD could not be confirmed with spirometry in 22 of the 75 patients (29%) and those patients were excluded from further examination. Statistical analysis was made on the 53 participating patients with confirmed COPD.

The group was comprised of 25 women (47%) and 28 men (53%). The mean age was 75.4 years (SD 7.9), 76.3 (SD 7.6) for men and 74.4 (SD 8.2) for women.

Spirometry showed COPD in stage one in 10 patients (19%), stage two in 28 patients (54%), stage three in 11 patients (21%) and stage four in one patient (2%). The severity of COPD could not be classified in two patients (4%) as they were older than 90 years and no reference of FEV1 is available for this age group. A median of NT-proBNP was 228 pg/ml (IQR 89-561). An NT-proBNP level equal to or above 1200 pg/ml was found in eight out of 53 patients (15%).

These eight patients were significantly older than the other participants ( $p = 0.03$ ). There was no correlation between the NT-proBNP level and COPD stage ( $p = 0.9$ ).

Patients with an increased level of NT-proBNP ( $\geq 1200$  pg/ml) were classified as having suspected heart failure and referred for echocardiography. One patient died while awaiting examination. Only two out of seven patients (28%) with suspected heart failure had a reduced EF (20 and 35%). One out of seven patients (14%) had signs of diastolic dysfunction. We were only able to confirm the diagnosis of chronic heart failure in three out of 53 patients, which constitutes 5.6% of the study population. Nocturia was the only registered symptom found more commonly among patients with suspected heart failure, NT-proBNP  $\geq 1200$  pg/ml. We found a strong correlation between elevated NT-proBNP and abnormalities on electrocardiography ( $p = 0.007$ ).

## Paper II

The consent for participation was obtained from 37 out of 63 (59%) patients registered at the heart failure unit. Those 37 patients were enrolled in the study. ICG could not be performed in one patient due to distortions in the ICG signal and

that patient was excluded. The mean age of 36 patients was 68.3 years (CI 64.2-72.4).

The group was comprised of 28 men (78%) and eight women (22%). The mean age for men was 68.2 (95% CI 64.0 -72.4) and for women it was 68.5 (95% CI 54.7-82.3). None of the patients met the exclusion criteria. None of the patients reported any discomfort or adverse reaction associated with ICG measurement.

Normal left ventricular systolic function was presented in 13 out of 36 patients (36%), mildly impaired in nine patients (25%), moderately and severely impaired each in seven patients (19%), respectively.

A significant association between three of four ICG parameters describing left ventricular systolic function (pre-ejection period, left ventricular ejection time and systolic time ratio) and ejection fraction measured by echocardiography was found. The fourth parameter (ejection time ratio) was not associated with ejection fraction. No association between ICG parameters describing cardiac work and ejection fraction by echocardiography was found.

The results are presented in Table 2.

**Table 2.**

Distribution of ICG parameters (value and 95% CI) in groups with different ejection fraction (EF).

EF	≥50% (n=13)	40-49% (n=10)	30-39% (n=6)	<30% (n=7)	p-value
CI	2.808 (2.56-3.5)	3.14 (2.42-3.53)	2.6 (2.46-3.29)	2.7 (2.05-2.92)	0.1180
SI	42.15 (37.04-47.27)	35.95 (26.96-44.83)	36.86 (28.77-44.94)	38.83 (27.46-50.2)	0.2708
PEP	110.31 (94.38-126.23)	108.4 (95.71-121.1)	139.5 (110.23-168.77)	148 (125.2-170.79)	0.0069*
LVET	323.08 (285.77-360.38)	292.7 (271.06-314.34)	262 (222.78-301.22)	268.43 (212.7-324.15)	0.0462*
STR	0.35 (0.29-0.41)	0.38 (0.32- 0.43)	0.54 (0.41-0.66)	0.75 (0.4-0.77)	0.0031*
ETR	37.15 (34.65-39.66)	37.3 (32.02-42.58)	32.66 (30.04-35.29)	34.57 (32.51-36.63)	0.1934
VI	33.77 (29.28-38.26)	38.4 (29.9-46.9)	35.17 (20.42 -49.9)	40 (26.12-53.88)	0.61
ACI	51.84 (42.92-60.77)	64.6 (44.59-84.61)	66 (41.33-90.67)	68.14 (50.3-85.98)	0.26
HI	7.9 (5.81-9.98)	10.03 (6.44-13.61)	6.18 (2.98-9.39)	5.8 (2.59-9.0)	0.1006
LCWI	3.17 (2.7-3.63)	3.95 (2.96-4.93)	3.02 (2.5-3.52)	2.87 (2.38-3.35)	0.2624
SVRI	2452 (2099-2806)	2435 (1899-2971)	2662 (2179-3145)	2511 (1743-3279)	0.8549
TFC	35.12 (28.25-41.99)	33.89 (28.27-39.51)	39.63 (30.32-48.95)	43.99 (31.94-56.03)	0.1461

## Paper III

The study population consisted of 313977 individuals. The diagnosis of heart failure was registered in 1.8% and the diagnosis of COPD was registered in 1.2% of the study population. The mean age in patients with the diagnosis of heart failure was 78.4 years (CI 78.0-78.7). The mean age of patients with the diagnosis of COPD was 70.5 years (CI 70.2-70.9). The prevalence of both diagnoses increased with age (Table 3).

**Table 3.**

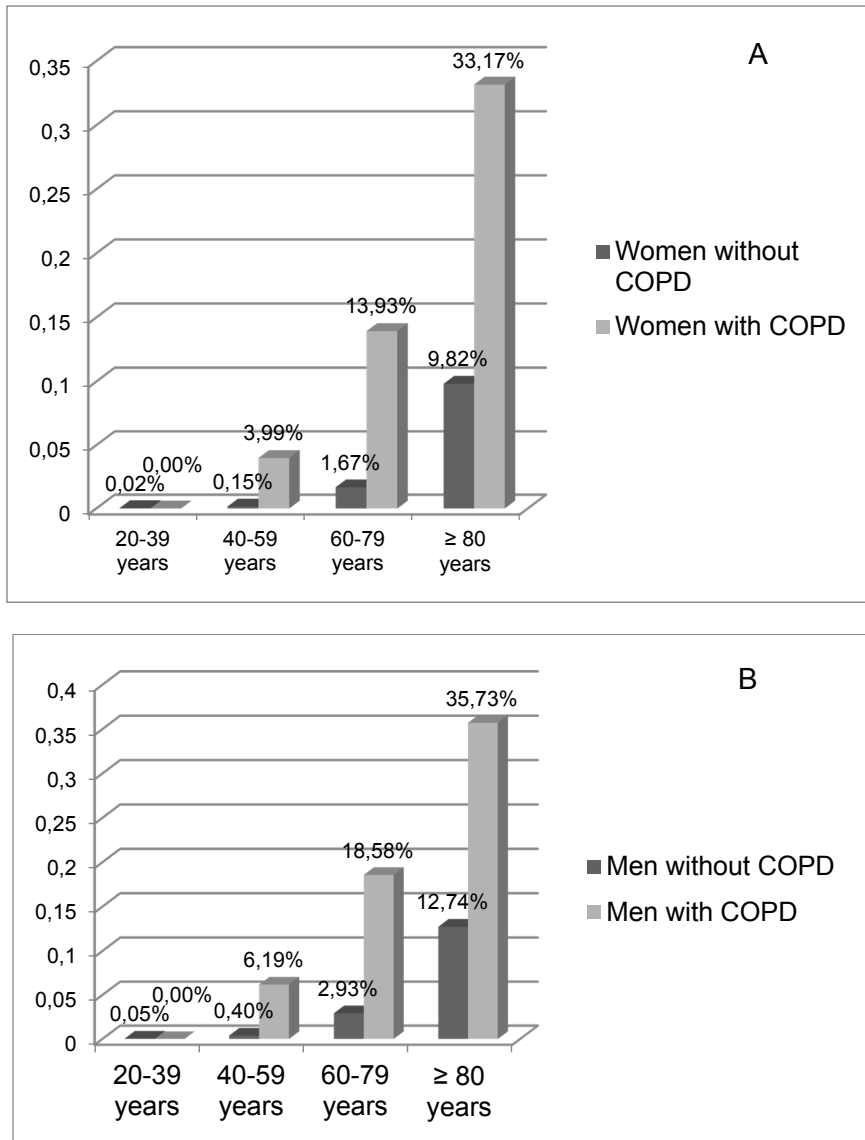
Prevalence of diagnoses COPD, heart failure and coexisting COPD and heart failure in the study population.

Variables	20-39 years	40-59 years	60-79 years	>80 years	Total
Women	47419	53539	41359	16386	158703
Men	52020	55164	3843	9647	155274
COPD in total population	31 (0.03%)	536 (0.4%)	2280 (2.8%)	889 (3.4%)	3736 (1.2%)
Heart failure in total population	34 (0.03%)	328 (0.3%)	2132 (2.6%)	3045 (11.6%)	5539 (1.8%)
Heart failure in patients without COPD	34 (0.03%)	302 (0.3%)	1765 (2.3%)	2738 (10.9%)	4839 (1.6%)
Heart failure in patients with COPD	0 (0%)	26 (4.6%)	367 (16.1%)	307 (34.5%)	700 (18.8%)

The prevalence of the diagnosis of heart failure in patients with the diagnosis of COPD was 18.8% and 1.6% in patients without COPD. After standardizing for age the prevalence was 9.9% and 1.5%, respectively. Standardized relative risk of the diagnosis of heart failure in patients with COPD was 6.6.

The prevalence of the diagnosis of heart failure increased with age in women and men in both groups and reached 35.7% in men with COPD $\geq$  80 years (Figure 3).





**Figure 3.** Prevalence of the diagnosis of heart failure in female (A) and male patients (B) with and without COPD in different age groups.

The prevalence of the diagnosis of heart failure was significantly higher in both women and men with COPD compared to women and men without COPD in all age groups apart from the age group 20-39 years.

The most common comorbid condition in patients with COPD alone and coexisting COPD and heart failure was essential (primary) hypertension coded with either I10 or I10.9 while in patients with heart failure alone the most comorbid condition was atrial fibrillation coded with I48 or I48.9. The comorbid diagnoses are summarized in Table 4.

**Table 4 .**  
Summary of the most common diagnostic codes.

<b>Patients with COPD n=3736</b>	<b>Code</b>	<b>Number (%)</b>	<b>Patients with heart failure n=4839</b>	<b>Code</b>	<b>Number (%)</b>	<b>Patients with COPD and heart failure n=700</b>	<b>Code</b>	<b>Number (%)</b>
Essential (primary) hypertension	I10, I10.9	1196 (32)	Atrial fibrillation and atrial flutter, unspecified	I48, I.48.9	2311 (47.8)	Essential (primary) hypertension	I10, I10.9	284 (40.6)
Observation for suspected disease or condition	Z03.9	628 (16.8)	Essential (primary) hypertension	I10, I10.9	2303 (47.6)	Observation for suspected disease or condition	Z03.9	251 (35.9)
Heart failure, unspecified	I50.9	526 (14.1)	Observation for suspected disease or condition	Z03.9	1472 (30.4)	Atrial fibrillation and atrial flutter, unspecified	I48.9	199 (28.4)
Unspecified acute lower respiratory infection	J22	383 (10.3)	Chronic ischemic heart disease, unspecified	I25.9	1427(29.5)	Old myocardial infarction	I25.2	166 (23.7)
Type 2 diabetes mellitus, without complications	E11.9	350 (9.4)	Type 2 diabetes mellitus, without complications	E11.9	958 (19.8)	Type 2 diabetes mellitus, without complications	E11.9	149 (21.3)
Atrial fibrillation and atrial flutter, unspecified	I48.9	312 (8.4)	Old myocardial infarction	I25.2	910 (18.8)	Chronic ischemic heart disease, unspecified	I25.9	136 (19.4)

The levels of other comorbidities were significantly higher in patients with coexisting heart failure and COPD compared to patients with heart failure or COPD alone (Table 5).

**Table 5.**  
Distribution of levels of other comorbidities measured by RUB (resource utilization band) in the study population.

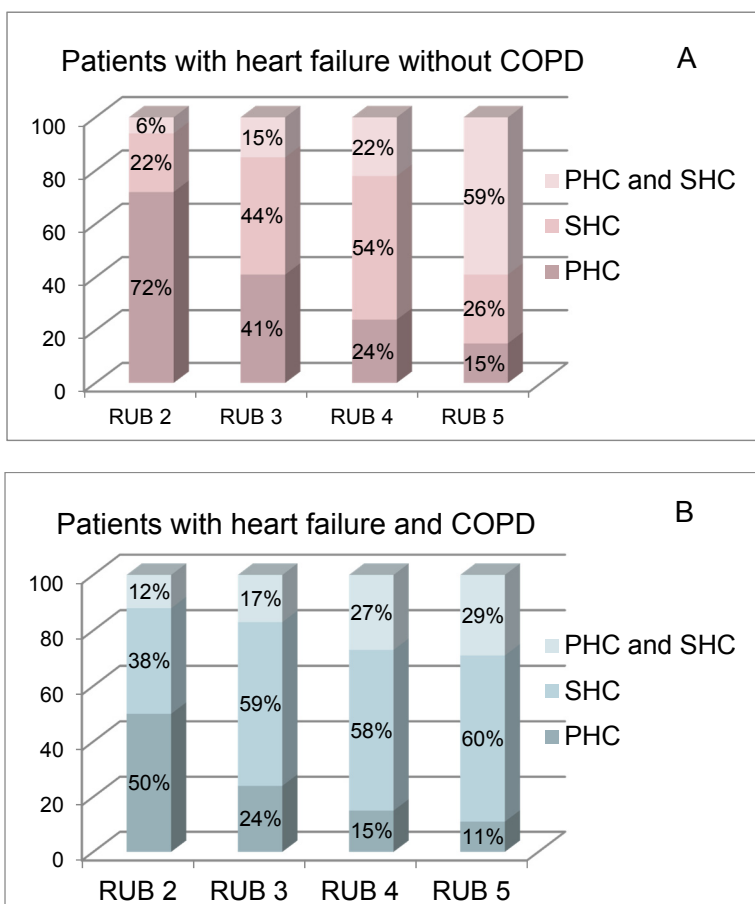
	<b>Total</b>	<b>Patients without COPD</b>		<b>Patients with COPD</b>		<b>p-value*</b>
		No heart failure	Heart failure	No heart failure	Heart failure	
RUB 0	102071 (32.51%)	101835 (33.34%)	81 (1.65%)	150 (4.49%)	5 (0.71%)	0.000
RUB 1	44126 (14.05%)	43855 (14.36%)	86 (1.78%)	181 (5.96%)	4 (0.57%)	0.001
RUB 2	65322 (20.8%)	64533 (21.13%)	282 (5.83%)	481 (15.84%)	26 (3.71%)	0.000
RUB 3	89042 (28.36%)	84602 (27.7%)	2514 (51.95%)	1603 (52.80%)	323 (46.14%)	0.000
RUB 4	10383 (3.31%)	8512 (2.79%)	1234 (25.50%)	434 (14.30%)	203 (29%)	0.000
RUB 5	3033 (0.97%)	2065 (0.68%)	642 (13.27%)	187 (6.16%)	139 (19.89%)	0.000
Total	313977 (100%)	305402 (100%)	4839 (100%)	3036 (100%)	700 (100%)	0.000

\*p-value describes differences between groups with and without COPD

The proportion of individuals with higher levels of other comorbidities (RUB 3-5) was 95% in the group with coexisting COPD and heart failure, while in the group with heart failure alone it was 90.7% and in the group with COPD alone it was 73.3%.

Primary care was the only care provider to 36.2% of patients with a diagnosis of heart failure and 20.7% of patients with coexisting COPD and heart failure. Furthermore, primary care participated in shared care of 21.5% of patients with the diagnosis of heart failure alone and 21.7% of patients with coexisting diagnoses of heart failure and COPD.

The share of care given by primary- and secondary care varied depending on levels of other comorbidities both in patients with heart failure without COPD and patients with coexisting COPD and heart failure (Figure 4).



**Figure 4.** Share of care in patients with heart failure without (A) and with (B) chronic obstructive pulmonary disease.

The higher the level of other comorbidities the larger was the participation of secondary care. Among patients with the highest level of other comorbidities (RUB 5) in the group with coexisting COPD and heart failure, 11% received care only in primary care, 29% received shared care and 60% received care only in secondary care.

## Paper IV

The study population consisted of 91 227 individuals aged  $\geq 35$  years of which 51.1% were female and 48.9% were male. The diagnosis of COPD was registered in 1011 individuals of which 27 (2.7 %) moved and were excluded from the study. The final analyses were made on data from 984 individuals of which 53% were female and 47% were male. The mean age in patients with the diagnosis of COPD was 71.1 (95% CI 70.4-71.8). The mean age for women was 69.4 (95% CI 68.5-70.4) and for men 72.9 (95% CI 72.0-73.8).

Comorbidity levels described by RUB were distributed as follows: RUB 3- 71.14 % (n=700), RUB 4 -21.65% (n=213), RUB 5 -7.22% (n=71).

We found a diagnosis of heart failure in 10.06% (n=99) of patients with the diagnosis of COPD.

Univariate analysis resulted in an odds ratio of 7-year mortality of 7.06 (95% CI 3.88-12.84) in patients with COPD and coexisting heart failure. The level of other comorbidities was the next most important variable which influenced mortality (Table 6).

**Table 6.**

Odds ratios of mortality in patients with COPD – univariate analyses of different variables used.

Univariate	OR (95%CI)
Heart failure	7.06 (3.88-12.84)
Age	1.13 (1.11-1.14)
Male sex	1.78 (1.38-2.30)
RUB 4	2.03 (1.48-2.78)
RUB 5	4.78 (2.61-8.74)

Adjusting for age resulted in odds ratio 3.76 (95% CI 1.98-7.16) and for age and male sex in odds ratio 3.75 (95% CI 1.79-3.26 (1.70-6.25)). Further adjusting for other comorbidities resulted in odds ratio 3.26 (95% CI 1.70-6.25). Adjusted odds ratios are presented in Table 7.

**Table 7.**

Odds Ratios (OR) of mortality in heart failure in patients with COPD adjusted for different variables used.

<b>Variables</b>	<b>OR (95%CI)</b>
Heart failure	7.06 (3.88-12.84)
Heart failure, age	3.76 (1.98-7.16)
Heart failure, age, male sex	3.75 (1.97-7.15)
Heart failure, age, male sex, other comorbidities	3.26 ( 1.70-6.25)

Multiple logistic regression showed that mortality was associated with age and male sex but the strongest risk factor for mortality was the highest comorbidity level – RUB 5 where the odds ratio was 5.19 (95% CI 2.59-10.38). Results are presented in Table 8.

**Table 8.**

Importance of different variables for mortality in patients with COPD. Odds ratios (OR) were adjusted for all other variables.

<b>Variables</b>	<b>Adjusted OR (95%CI)</b>
Heart failure	3.26 (1.70-6.25)
Age	1.12 (1.10-1.14)
Male sex	1.37 (1.02-1.85)
RUB 4	1.82 (1.26-2.65)
RUB 5	5.19 (2.59-10.38)

# Discussion

## Summary of the main results

We found heart failure in 5.6% of the study population using NT-proBNP as an initial step for the diagnosis of heart failure in patients with COPD in Swedish primary care. This was considerably less than expected based on the results of previous studies [53, 68].

When using ICG in assessment of left ventricular function in patients with stable heart failure, we found that only three of four ICG parameters, which describe systolic function of left ventricle, were significantly associated with EF measured by echocardiography. However, no association between ICG parameters describing cardiac work and ejection fraction by echocardiography was found.

The prevalence of heart failure in patients with COPD in the Swedish population found in paper III was 18.8%, whereas in patients without COPD it was 1.6%. After standardizing for age the prevalence was 9.9% and 1.5%, respectively. Standardized relative risk for the diagnosis of heart failure in patients with COPD was 6.6. The prevalence of the diagnosis of heart failure in patients with the diagnosis of COPD found in paper IV was 10.1%.

The levels of other comorbidities were significantly higher in patients with COPD and coexisting heart failure compared to patients with either COPD or heart failure alone. Swedish primary care participates to a great extent in the care of patients with COPD and coexisting heart failure. Mortality in patients with COPD and coexisting heart failure is, as expected, higher than in patients with COPD alone. Age, male sex and other comorbidities are risk factors for mortality in patients with COPD and coexisting heart failure of which other comorbidities have the most importance.



# Strengths and limitations

## Paper I

The most important limitation of this study was a high drop-out rate. When planning the study, a sample size analysis was made in order to estimate the precision of the study. If the prevalence in this study was 20.5% as previously reported [53] and 100 patients participated in the study, 95% CI would be 13-29%. If the prevalence in the study population were lower than 20.5%, 95% CI would be 5-18%. The precision in both cases was considered good enough. The inclusion and exclusion criteria were clearly defined in order to find an eligible study population. There were a number of reasons for the low participation, which were not anticipated. The study was conducted in two different primary care centers; one located in a smaller community (Olofström) and the other one in a larger town (Karlskrona). A total of 172 patients who met the inclusion criteria were found to be eligible to participate in the study: a diagnosis of COPD in medical records and an age of 65 years or more. None of the patients met the exclusion criteria. The participation rate was, however, low. The low participation rate could not be explained by age or sex. The participation rate differed between the two primary care centers. Only 41% of eligible patients in Karlskrona gave consent to participate compared to 60.7% in Olofström. The proximity to hospital and secondary care units in Karlskrona was considered a possible explanation and therefore the diagnosis registers were analyzed with respect to prevalence of COPD patients from the participating primary care centers; only 15 patients from the primary care center in Karlskrona and 11 from Olofström were found. This suggested that management in secondary care was not the reason for the low participation in Karlskrona.

Despite the fact that diagnosing of COPD using spirometry was well-established in Swedish primary care, it was surprising that the diagnosis of COPD could not be confirmed in 29% of participants, which was another reason for drop-out. The study procedure was anchored in clinical practice and present guidelines for the diagnosis of heart failure [69]. The tools available for the Swedish general practitioner when making the diagnosis of heart failure were used in a structured way; the same for each participant and under routine conditions. This should be considered as the strength of the study because it could show how those tools worked in real life in primary health care. The whole study was driven by the hypothesis that testing of NT-proBNP can be a tool for a general practitioner in order to find patients with suspected heart failure among patients with COPD eligible for further examination with echocardiography. Various alternatives regarding the choice of the cut-off point of NT- BNP for the purpose of the study were deliberated in the research group. The study population consisted of elderly

people whose levels of NT-proBNP are higher [70]. Even COPD alone could result in elevated levels of NT-pro BNP [71]. Studies from emergency settings suggested different cut-off points depending on age: in patients aged 50-75 years 900 ng/l and in patients  $\geq$  75 years 1800 ng/l [70]. Two threshold values of NT-proBNP were used in the guidelines for the diagnosis of chronic heart failure[69]. The diagnosis of chronic heart failure was considered unlikely below 400 pg/ml, likely above 2000 pg/ml and uncertain in between. The lower threshold did not seem to be appropriate with regard to age and presence of COPD and the mean of two thresholds – the value of 1200 pg/ml was chosen for the purpose of this study. Other comorbidities and medication, which can influence NT-proBNP values, were not analyzed because the study was considered to be too small for such analysis. The level of 125 pg/ml was suggested as ‘the optimal cut point’ in patients with COPD aged 65 years and older with regard to comorbidities and medication [72]. The same level was suggested in the study conducted in the general population in primary care aged 21-80 years [73]. That study was published after our study and suggested the level of 125 pg/ml in order to risk-stratify waiting lists for echocardiography after referral from primary care. That level, however, is considerably lower than recommended by ESC. Eventually, NT-proBNP value of 1200 pg/ml was arbitrarily chosen.

## **Paper II**

Similar to paper I, the limitation of this study was the small number of participants. Consent for participation was obtained from 37 out of 63 (58.7%) patients registered at a heart failure unit. The way to raise participation might have been to send a reminder, which was not done.

## **Paper III and IV**

These were register-based studies. The primary source of data in both studies were health care registers from routine care. The strength of those studies was that the data covered the whole population in the Östergötland County in paper III and in Blekinge County in paper IV.

The main limitations were completeness of the data and validity of the diagnoses. In both registers, all consultations were recorded in electronic charts and the diagnosis was required at each consultation. In both studies, the data were analyzed from both primary- and secondary care in order to increase completeness of the data.

Validity of the diagnoses is frequently called into question in register studies. Validating of the diagnoses demands time and effort and it is difficult to carry out with each use of register data for research purposes. We had access to coded data and validating of the diagnoses was not possible due to ethical reasons and legal

regulations. We had to rely on previous studies in which the diagnoses of COPD and heart failure in Swedish registers were considered to be acceptable for being used in epidemiological research [74, 75].

The Care Data Warehouse register in Östergötland was considered useful in estimating the prevalence of chronic diseases such as diabetes, hypertension, ischemic heart disease, asthma and COPD. The period of analysis corresponded to better capturing of cases [76]. The one-year period was analyzed to capture the diagnosis of COPD in both studies. That choice was anchored in Swedish clinical practice where patients with COPD are actively checked and summoned for a nurse-led follow-up at least once a year.

## Meaning of the results.

Paper I showed the difficulties in diagnosing of heart failure in patients with COPD in primary health care. The diagnostic tools, which are available for the general practitioner, are not sufficient and do not allow an accurate diagnosis of heart failure in patients with COPD. Heart failure might be underdiagnosed in patients with COPD.

The use of impedance cardiography in order to determine left ventricular function and increase the accuracy of the diagnosis of heart failure cannot be recommended due to ambiguity regarding interpretation of the results which was showed in paper II. Paper III showed that heart failure in patients with COPD is common in the Swedish population. Patients with COPD and coexisting heart failure have higher levels of other comorbidities than patients with COPD or heart failure alone. This group of multimorbid patients, with high need of care, is managed to a great extent by Swedish primary care. Paper IV showed that coexisting heart failure considerably increases the odds of mortality in patients with COPD. The mortality in patients with COPD and coexisting heart failure is strongly associated with age, male sex and other comorbidities but other comorbidities are the strongest predictor.

# Conclusion

This thesis contributes to the field of the research regarding COPD, heart failure and multimorbidity in primary care.

Paper I points to diagnostic difficulties and shows the need for better procedures when diagnosing heart failure in patients with COPD. ICG is a tempting method but its' use in order to increase the accuracy of heart failure diagnosis needs further experience and research. Epidemiological studies, which the thesis contains, deal with prevalence of heart failure and other comorbidities in patients with COPD. Heart failure is common in patients with COPD in the Swedish population. Patients with COPD and coexisting heart failure are characterized by higher levels of other comorbidities than patients with COPD or heart failure alone. Other comorbidities significantly influence survival in patients with COPD and coexisting heart failure. In Sweden, primary care participates to a great extent in the care of patients with COPD and coexisting heart failure. Early recognition and adequate treatment of these patients is important in order to improve survival rates.



# Future studies

The findings of the diagnostic and epidemiological parts of this thesis can give ideas when planning further studies. Diagnostic procedures in primary care should be revised with regards to multimorbidity. Guidelines concerning separate diseases are not easily applicable in multimorbid patients. ICG is still an interesting tool when diagnosing and monitoring heart failure. As a continuation of the epidemiological part, further work should be considered in order to find what kind of other comorbidities are of importance in patients with COPD and coexisting heart failure, what kind of patients in this group tend to have more other comorbidities and find factors of importance.

Primary care in future is going to face multimorbidity to a greater extent than secondary care. The majority of older patients, where multimorbidity is common, are treated in primary care; it will be a challenge to find ways to study multimorbidity. Swedish primary care has an excellent opportunity to conduct population based research due to access to large databases in the form of diagnosis based registers at an individual level. It would be preferable to use register based data directly in scientific research if the quality of data was validated, which is not often the case. It should be a common interest that data in registers would have a good validity and completeness. Cross referencing patients in registers regarding chronic diseases may generate hypotheses for futures studies concerning multimorbidity. Based on those hypotheses, we would be able to design prospective studies in order to learn more about multimorbidity and find factors which influence different outcomes in multimorbid patients.



# Svensk sammanfattning

Det finns flera anledningar att studera samtidig förekomst av kronisk obstruktiv lungsjukdom (KOL) och hjärtsvikt. Först och främst är det två kroniska sjukdomar som har hög prevalens i samhället. Risken att utveckla hjärtsvikt hos patienter med KOL är fyra och en halv gång högre än i åldersmatchade kontroller. Prevalensen av ej diagnosticerad hjärtsvikt hos patienter med KOL äldre än 65 år i primärvården är cirka 20%. Prevalensen av KOL hos patienter med hjärtsvikt ligger också runt 20%. Hjärtsvikt är associerat med dålig prognos och hög dödlighet. Femårs mortaliteten hos patienter med hjärtsvikt är sex gånger högre än i den generella populationen. KOL och hjärtsvikt har gemensamma, ospecifika symtom som gör att hjärtsvikt kan förbises hos patienter med KOL och vice versa. Prevalensen och sjukdomsördan av hjärtsvikt och KOL ökar med stigande ålder. Andelen äldre i Sverige är den högsta i världen med 17,4% av personer i åldern  $\geq 65$  år och förväntas öka fram till år 2020. Omhändertagande av patienter med samtidig hjärtsvikt och KOL kommer att bli en utmaning för den framtida sjukvården. Trots att hjärtsvikt och KOL ofta förekommer samtidigt och har allvarliga kliniska och ekonomiska konsekvenser, har sjukdomarna mestadels studerats separat, särskilt på populationsnivå.

Syftet med denna avhandling var att beskriva diagnostiska och epidemiologiska aspekter av KOL och samtidig förekomst av hjärtsvikt och att utvärdera impedanskardiografi som en metod som skulle kunna tillämpas för bedömning av hjärtfunktionen hos patienter med hjärtsvikt i primärvården på ett enkelt sätt.

Avhandlingen består av fyra delarbeten vars specifika syften var följande:

1. Att beskriva hur den rekommenderade utredningsgången för att diagnostisera hjärtsvikt hos patienter med KOL fungerar i primärvården. Den utredningsgång som är tillgänglig i primärvården består av anamnes, klinisk undersökning och provtagning av natriuretiska peptider, i vårt fall NT-proBNP. För att ställa en tillförlitlig hjärtsviktsdiagnos remitteras patienter för ekokardiografi som utförs inom sekundär vård.
2. Att finna vilka impedanskardiografiska parametrar som är associerade med ejektion fraktion mätt med ekokardiografi som är gold standard för bedömning av den systoliska vänsterkammarmfunktionen.
3. Att studera förekomsten av hjärtsvikt hos patienter med KOL i den svenska befolkningen, beskriva var patienter med KOL och samtidig



hjärtsvikt erhåller vård och beskriva annan komorbiditet hos patienter med KOL och samtidig hjärtsvikt.

4. Att beskriva betydelsen av annan komorbiditet och hjärtsvikt för dödlighet hos patienter med KOL.

Med användning av NT-proBNP som ett första steg för att diagnostisera hjärtsvikt hos patienter med KOL i primärvården hittades betydligt färre patienter med hjärtsvikt än förväntat från resultaten från tidigare studier. De diagnostiska verktyg som finns tillgängliga för allmänläkaren är inte tillräckliga och tillåter inte en säker diagnos av hjärtsvikt hos patienter med KOL.

Parallell undersökning med impedanskardiografi och ekokardiografi hos patienter med kronisk hjärtsvikt visade signifikant association mellan tre av fyra impedanskardiografiska parametrar som beskriver den systoliska vänsterkammerfunktionen och ejektions fraktion mätt med ekokardiografi. Tidigare rapporterade associationer mellan andra impedanskardiografiska parametrar som ansågs beskriva den systoliska vänsterkammerfunktionen kunde inte bekräftas. På grund av tvetydighet vad gäller tolkningen av resultaten kan tillämpning av impedanskardiografi för att bedöma vänsterkammerfunktionen inte rekommenderas enligt resultaten i avhandlingens delarbete 2.

Förekomsten av hjärtsvikt hos patienter med KOL i den svenska populationen var 18,8% medan hos patienter utan KOL var det 1,6%. Efter standardisering för ålder var prevalensen 9,9% respektive 1,5%. Standardiserad relativ risk för hjärtsvikt hos patienter med KOL var 6,6. Annan komorbiditet var signifikant högre hos patienter med KOL och samtidig hjärtsvikt jämfört med patienter med antingen enbart KOL eller hjärtsvikt. Den svenska primärvården deltar i stor utsträckning i vård av patienter med KOL och samtidig hjärtsvikt.

Dödlighet hos patienter med KOL och samtidig hjärtsvikt är 7 gånger högre än hos patienter med enbart KOL. Ålder, manlig kön och annan komorbiditet är riskfaktorer för dödlighet hos patienter med KOL och samtidig hjärtsvikt, varav annan komorbiditet har den största betydelsen. Därför antyder resultaten att det är viktigt att hjärtsvikt och annan komorbiditet hos patienter med KOL upptäcks så tidigt som möjligt och behandlas adekvat.

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Paper I





## Clinical Study

# Using NT-proBNP to Detect Chronic Heart Failure in Elderly Patients with Chronic Obstructive Pulmonary Disease

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**Objective.** To detect chronic heart failure in elderly patients with a registered diagnosis of chronic obstructive pulmonary disease (COPD) treated in Swedish primary health care using natriuretic peptide NT-proBNP. **Design.** A cross-sectional study. **Setting.** Two primary health care centres in southeastern Sweden each with about 9000 listed patients. **Subjects.** Patients aged 65 years and older with a registered diagnosis of COPD. **Main Outcome Measures.** Percentage of patients with elevated NT-proBNP, percentage of patients with abnormal left ventricular function assessed by echocardiography, and association between elevated NT-proBNP and symptoms, signs, and electrocardiography. **Results.** Using NT-proBNP threshold of 1200 pg/mL, we could detect and confirm chronic heart failure in 5.6% of the study population with concurrent COPD. An elevated level of NT-proBNP was only associated with nocturia and abnormal electrocardiography. **Conclusions.** We found considerably fewer cases of heart failure in patients with COPD than could be expected from the results of previous studies. Our study shows the need for developing improved strategies to enhance the validity of a suspected heart failure diagnosis in patients with COPD.

## 1. Introduction

When a general practitioner encounters an elderly patient with chronic obstructive pulmonary disease (COPD) presenting with shortness of breath, cough, and greater fatigue than usual, it is easy to suspect COPD exacerbation. However, these symptoms are unspecific and may also be consistent with a heart failure diagnosis.

Prevalence of chronic heart failure in elderly patients with COPD carried in a primary health care was found to be 20.5% [1]. A review of previous studies showed that prevalence of heart failure or left ventricular systolic dysfunction in patients with COPD varied between 10% and 46% [2]. The highest prevalence of chronic heart failure was reported among patients with symptomatic dyspnoea [3].

Most patients with COPD and/or chronic heart failure in Sweden are managed in primary health care. Assessment of probability of chronic heart failure by judgment of clinical symptoms in the same patients differs considerably among

general practitioners [4]. Similarities in signs and symptoms make it more difficult to diagnose chronic heart failure in patients with COPD. Access to echocardiography in primary health care in Sweden is limited; therefore, this essential diagnostic tool is not immediately available in routine care. Determination of natriuretic peptides constitutes an important component of the European Society of Cardiology (ESC) algorithm for the diagnosis of chronic heart failure [5].

Natriuretic peptides enhance validity of heart failure diagnosis in elderly patients with COPD [6]. The aim of the present study was to evaluate if the analysis of NT-proBNP might be used as an initial step for the diagnosis of chronic heart failure in patients with COPD in primary health care and to select patients for a further examination by echocardiography.

Furthermore, the patients with elevated NT-proBNP were compared with the other participating patients for different symptoms and electrocardiographic abnormalities.

## 2. Material and Methods

The study was conducted in two different primary health care centres during the period 16 April 2008–13 June 2008 in Blekinge county. Blekinge county with approximately 150 000 inhabitants is located in southeastern Sweden. Olofström municipality has 13 198 inhabitants, with 22.7% 65 years and older. Karlskrona municipality has 62 338 inhabitants with 19% 65 years and older [7].

The study included patients aged 65 years and older with the following diagnosis codes according to ICD 10: J44 (COPD), J41 and J42 (chronic bronchitis) registered during the period 1 January 2008–16 April 2008 according to the electronic patient record.

Data on the patient flow during the study are shown in Figure 1.

At the time of the study, 9265 patients were registered at the primary health centre in Olofström, 1905 (20.6%) aged 65 years and older. At the primary health centre Tullgården in Karlskrona, 9002 patients were registered and 1508 (16.8%) aged 65 and older.

Exclusion criteria comprised impaired cognitive function and/or anticipated difficulties in carrying out spirometry due to immobility, psychiatric disorders, or terminal illness.

Informed consent was obtained from each participant.

In order to confirm the diagnosis of COPD and classify the degree of severity of COPD according to the GOLD criteria [8], all participants were examined with dynamic spirometry (Spirare 3, Diagnostica, Norway), if spirometry had not already been carried out during the past year.

Patients with a confirmed diagnosis of COPD were examined regarding chronic heart failure.

In an interview, we asked the patients for the following symptoms: breathlessness, orthopnoea, night cough, nocturia, and walking distance. A threshold for walking distance of 100 meters was used [9]. Physical examination included weight and height, heart and lung auscultation, blood pressure measurement after 5 minutes' rest in the sitting position, and the presence of peripheral oedema. Positive findings from heart and lung auscultation were determined as rales and the third heart sound.

All patients were examined by electrocardiography.

Since the regional ethics committee questioned the need to perform chest X-rays in all participants because of the risk associated with radiation, a chest X-ray was performed only if clinical examination gave rise to suspicion of pulmonary congestion.

The natriuretic peptide was determined as NT-proBNP (Immulite 2500, Siemens Healthcare Diagnostics AB, Sweden). Patients with the NT-proBNP level of  $\geq 1200$  pg/mL were referred for echocardiography to assess left ventricular (LV) function using the following echocardiographic criteria:

- (i) EF  $\geq 55\%$  normal systolic LV function,
- (ii) EF 40–54% mildly impaired systolic LV function,
- (iii) EF 30–39% moderately impaired LV function,
- (iv) EF  $< 30\%$  severely impaired LV function.

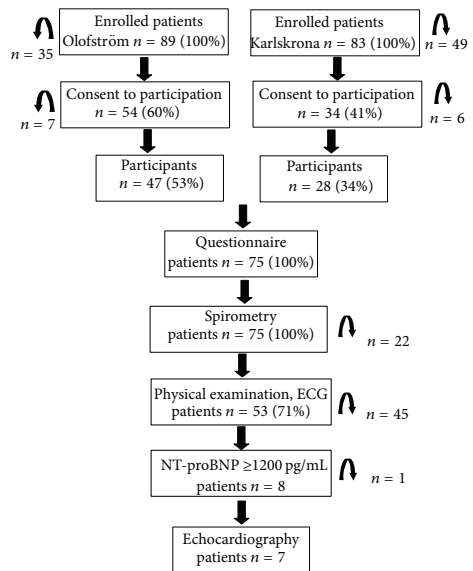


FIGURE 1

Abnormal LV relaxation and/or distensibility during normal EF were described as diastolic dysfunction.

The study was approved by the research ethics committee at Lund University.

The study was registered at ClinicalTrials.gov NCT01801722.

## 3. Statistics

Data were analysed in the STATA version 10 (Stata Corporation, Texas, USA). Distribution of categorical variables is presented as numbers. Distribution of continuous variables was presented as mean and standard deviations (SD) except NT-proBNP which was presented as the median and interquartile range (IQR). Mann-Whitney's test was used for comparison of mean values. Differences in proportions in the groups were tested with the chi square test. A *P* value of  $< 0.05$  was considered significant.

## 4. Results

The mean age of the 75 participating patients was 75.3 (SD 7.6), while the age of 108 patients who did not participate was 77.2 (SD 7.7). There was no significant difference in age ( $P = 0.09$ ) or gender ( $P = 0.16$ ) distribution between those groups.

Dynamic spirometry in the participating patients showed FEV1  $> 65\%$  in 22 of the 75 patients (29%). As the diagnosis of COPD could not be confirmed in these 22 patients, they were excluded from the study.

Statistical analysis was done on the 53 participating patients with confirmed COPD.

The group comprised 25 women (47%) and 28 men (53%). The mean age was 75.4 years (SD 7.9), 76.3 (SD 7.6) for men, and 74.4 (SD 8.2) for women.

Spirometry showed COPD in stage 1 in 10 patients (19%), stage 2 in 28 patients (54%), stage 3 in 11 patients (21%), and stage 4 in 1 patient (2%). The severity of COPD could not be classified in 2 patients (4%) as they were older than 90 years and no reference of FEV1 is available for this age group. A median of NT-proBNP was 228 pg/mL (IQR 89–561).

Distribution of NT-proBNP in relation to COPD stages is presented in Figure 2.

An NT-proBNP level equal to or above 1200 pg/mL was found in 8 out of 53 patients (15%).

These 8 patients were significantly older than the other participants ( $P = 0.03$ ). We did not find a correlation between the NT-proBNP level and COPD stage ( $P = 0.9$ ).

Patients with an increased level of NT-proBNP ( $\geq 1200$  pg/mL) were classified as having suspected chronic heart failure and referred for echocardiography. One person died while awaiting examination. Only 2 out of 7 patients (28%) with suspected chronic heart failure had a reduced EF (20 and 35%). One out of 7 patients (14%) had signs of diastolic dysfunction. We were only able to confirm the diagnosis of chronic heart failure in 3 out of 53 patients, which constitutes 5.6% of the study population.

Correlations between symptoms, clinical findings, and NT-proBNP are presented in Table 1. Nocturia was the only registered symptom found more commonly among patients with suspected heart failure, that is, with NT-proBNP  $\geq 1200$  pg/mL. We found a strong correlation between elevated NT-proBNP level and an abnormal electrocardiography ( $P = 0.007$ ).

The abnormalities found were the following: complete or incomplete left bundle branch block, pathological Q wave, ST-T changes, atrial fibrillation, and signs of left ventricular hypertrophy.

## 5. Discussion

The purpose of this study was to evaluate whether the determination of NT-proBNP can help a general practitioner to make a valid diagnosis of chronic heart failure in patients with COPD. Using the threshold of NT-proBNP of  $\geq 1200$  pg/mL, we found that 5.6% of the participating patients had chronic heart failure. We found considerably fewer cases of chronic heart failure than could be expected from the results of previous studies.

We chose elderly patients with COPD as a study population due to the previously reported higher prevalence of chronic heart failure in this group [10].

Data are also available showing that the risk of developing chronic heart failure in elderly patients with COPD is at least two times higher than in age-matched controls [11].

We do not believe that the low prevalence of chronic heart failure found in our study is due to a generally low prevalence of chronic heart failure in the Swedish population.

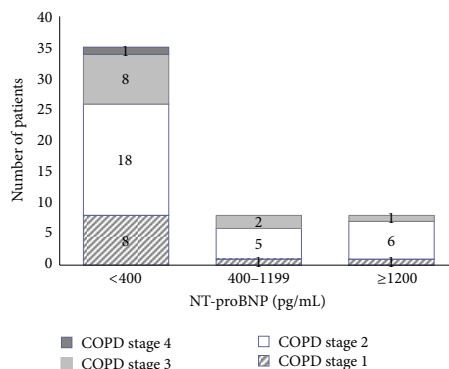


FIGURE 2: Distribution of NT-proBNP in relation to COPD stage.

Sweden has the highest proportion of elderly in the world and prevalence of chronic heart failure in Sweden is comparable with other countries [12].

The limitation of our study is a high drop-out rate. Firstly, the response ratio was low and the participation ratio differed considerably between participating primary health centres.

We hypothesized that this could depend on the specialist care at the Blekinge County Hospital. This statement particularly concerned primary health centre in Karlskrona due to the vicinity of the hospital. However, when we explored hospital diagnosis registers in 2008, we found only 15 patients from primary health centre in Karlskrona and 11 patients from primary health centre in Olofström with the diagnosis of COPD. Moreover, we only found 2 patients with a combined diagnosis of COPD and chronic heart failure, both from Karlskrona.

Secondly, definite COPD could not be diagnosed in 22 (29%) of participants. The number of patients with an unconfirmed COPD diagnosis was 37.8% in a primary health centre study in The Netherlands [3].

The main question in our study was if testing of NT-proBNP can help general practitioner select COPD patients for a confirmatory investigation of chronic heart failure using echocardiography. Symptoms and signs were of no help in the diagnosis of chronic heart failure, except probably for nocturia, which was more frequent in COPD patients with elevated NT-proBNP. There was a strong correlation between an abnormal ECG and an elevated NT-proBNP, which confirms the fact that a normal ECG makes diagnosis of chronic heart failure less likely [13].

An elevated level of natriuretic peptides is an important component of the ESC diagnostic algorithm. Two threshold values are used. The diagnosis of chronic heart failure is considered unlikely below 400 pg/mL, likely above 2000 pg/mL, and uncertain in between. The level of natriuretic peptides can be increased in patients with COPD [14]. Age is one of the main factors influencing the NT-proBNP level [15]. We chose an NT-proBNP level of 1200 pg/ml as a reasonable level



TABLE 1: Correlations between symptoms, clinical findings, and NT-proBNP.

	NT-proBNP	<1200 n = 45	≥1200 n = 8			P value
	Positive	Negative	Positive	Negative		
<b>Symptoms</b>						
Breathlessness	37 (82%)	8 (18%)	7 (87%)	1 (13%)		0.714
Night cough	8 (18%)	34 (76%)	0 (0%)	8 (100%)		0.178
Orthopnoea	3 (7%)	39 (86%)	1 (13%)	7 (87%)		0.609
Nocturia	31 (69%)	14 (31%)	8 (100%)	0 (0%)		0.066
Walking distance	13 (29%)	26 (58%)	1 (13%)	6 (85%)		0.313
<b>Clinical findings</b>						
Heart auscultation	3 (7%)	42 (93%)	1 (13%)	7 (87%)		0.565
Peripheral oedema	21 (47%)	24 (53%)	3 (37%)	5 (63%)		0.631
ECG abnormalities	22 (49%)	23 (51%)	8 (100%)	0 (0%)		0.007

at which to suspect chronic heart failure in elderly patients with COPD.

The value of 1200 pg/mL also constitutes the mean of the two threshold levels of the ESC algorithm. If the lower threshold level of 400 pg/mL had been used in our study, 17 out of 53 patients (32%) would have been eligible for echocardiography. Only 3 out of 7 (42%) patients with levels ≥1200 pg/mL had abnormal findings in echocardiography. Furthermore, their NT-proBNP levels were rather high: 1682 pg/mL, 1877 pg/mL, and 4413 pg/mL, indicating that the small number of patients found with abnormalities in echocardiography was not explained by a too high threshold of NT-proBNP.

The natriuretic peptides can be used in the general population as a tool to evaluate left ventricular systolic dysfunction [16] and to make a diagnosis of heart failure more accurate [17, 18]. A newer study from Denmark suggests that NT-proBNP can be used to risk stratify waiting lists for echocardiography in PHC [19]. There is a possibility that NT-proBNP used for screening patients eligible for echocardiography is not suitable when patients with suspected chronic heart failure also have COPD. Improving strategies to enhance validity of the chronic heart failure diagnosis in patients with COPD should be of interest for general practitioners. Our study is small and a more extended study is needed to settle this issue from the primary health care perspective.

## Conflict of Interests

All the authors declare that they do not have any conflict of interests. They do not have any financial relation with the commercial identities mentioned in the paper.

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Paper II





RESEARCH ARTICLE

Open Access

# Comparing impedance cardiography and echocardiography in the assessment of reduced left ventricular systolic function

Elzbieta Kaszuba<sup>1,2\*</sup>, Sergej Scheel<sup>1</sup>, Håkan Odeberg<sup>1,2</sup> and Anders Halling<sup>1,2,3</sup>

## Abstract

**Background:** An early and accurate diagnosis of chronic heart failure is a big challenge for a general practitioner. Assessment of left ventricular function is essential for the diagnosis of heart failure and the prognosis. A gold standard for identifying left ventricular function is echocardiography. Echocardiography requires input from specialized care and has a limited access in Swedish primary health care. Impedance cardiography (ICG) is a noninvasive and low-cost method of examination. The survey technique is simple and ICG measurement can be performed by a general practitioner. ICG has been suggested for assessment of left ventricular function in patients with heart failure. We aimed to study the association between hemodynamic parameters measured by ICG and the value of ejection fraction as a determinant of reduced left ventricular systolic function in echocardiography.

**Methods:** A non-interventional, observational study conducted in the outpatients heart failure unit. Thirty-six patients with the diagnosis of chronic heart failure were simultaneously examined by echocardiography and ICG. Distribution of categorical variables was presented as numbers. Distribution of continuous variables was presented as a mean and 95% Confidence Interval. Kruskal-Wallis test was used to compare variables and show differences between the groups. A p-value of <0.05 was considered significant.

**Results:** We found that three ICG parameters: pre-ejection fraction, left ventricular ejection time and systolic time ratio were significantly associated with ejection fraction measured by echocardiography.

**Conclusions:** The association which we found between EF and ICG parameters was not reported in previous studies. We found no association between EF and ICG parameters which were suggested previously as the determinants of reduced left ventricular systolic function.

The knowledge concerning explanation of hemodynamic parameters measured by ICG that is available nowadays is not sufficient to adopt the method in practice and use it to describe left ventricular systolic dysfunction.

**Keywords:** Heart failure, Reduced left ventricular systolic function, Impedance cardiography, Echocardiography

## Background

Chronic heart failure (HF) is a complex syndrome characterized by a long period of sub-clinical symptoms and progressive process associated with poor prognosis. The five-year mortality is six times higher than in general population [1]. The prevalence of chronic HF in general population in Sweden is between 2 and 3% and rises with age to approximately.

10-20% at 70–80 years of age [2,3]. The incidence has increased mainly due to an increasing proportion of the elderly in Sweden [4]. It entails one of the highest costs-of-illness with approximately 2% of the Swedish health care budget [2,5]. Similar data about prevalence, incidence and costs were reported in other European countries [6,7] and USA [8].

The majority of patients at risk of chronic HF, e.g. with coronary heart disease and hypertension, are treated in primary health care.

An early and accurate diagnosis of HF is a big challenge for a general practitioner. Assessment of left

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ventricular function is essential for the diagnosis of HF and the prognosis. The 5-year survival rate correlates with reduced left ventricular systolic function and decreases in patients with HF to 53% compared with 93% in age- and sex- matched general population [1]. A gold standard for identifying reduced left ventricular function is echocardiography [9]. The European Society of Cardiology considers echocardiography to be mandatory for the establishment of HF diagnosis and highly recommended if HF is suspected [6]. Echocardiography requires input from specialized care. Its accessibility is limited in Swedish primary health care and it is performed only in about 30% of patients with suspected HF [10,11]. Determination of ejection fraction (EF) by echocardiography is routinely used for description of left ventricular systolic function. Potential utility of impedance measurement for assessment of left ventricular function has been suggested since the 1990s [12] with clinical application in patients with HF [13,14]. Impedance cardiography (ICG) is a noninvasive and low-cost method of examination. The survey technique is simple and ICG measurement can be performed by a general practitioner. ICG is considered to be reproducible in ambulatory patients with stable heart failure [15] and has been suggested as a tool to be used by nurses to detect worsening of left ventricular systolic function in patients with heart failure [16].

We aimed to study the association between ICG parameters and the value of EF in echocardiography. If the association was found, ICG could be a method to evaluate reduced left ventricular function.

## Methods

This was a non-interventional, observational study. The study was conducted in the outpatients heart failure unit at the Blekinge County Hospital in Karlshamn in Sweden during the period 6 February 2009 – 6 March 2009. Informed consent was obtained from each participant. There were 63 patients with the diagnosis of chronic HF registered at the heart failure unit. All registered patients were offered participation by a letter send by a cardiologist. No reminder was send. Heart failure unit is the secondary care unit. Patients are referred there from primary care if difficulties with management of chronic HF occur. Diagnosis of chronic HF was established before referral. We thought that it was not necessary to question the diagnosis and we did not penetrate the way it was made.

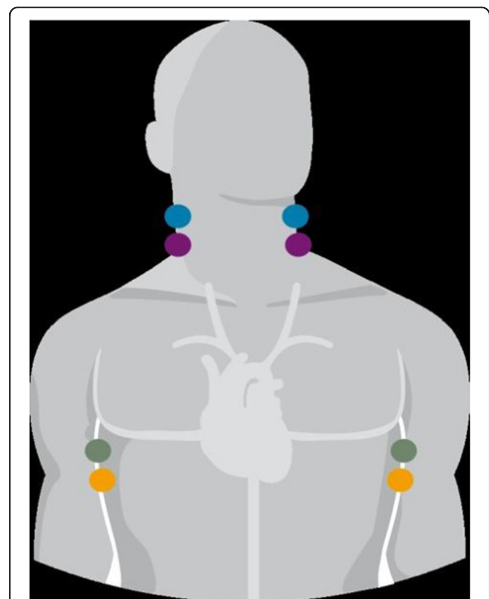
Exclusion criteria comprised significant aortic valve insufficiency and severe aortic stenosis, both of which influence ICG measurement.

The patients were examined by means of echocardiography and ICG during one consultation.

Both echocardiography and ICG were performed once in each patient. Echocardiography was performed by an experienced cardiologist using Vivid 7, GE equipment. EF was calculated according to modified Simpson's formula. The following echocardiographic criteria were used to describe left ventricle systolic function: EF  $\geq$  50% normal systolic function,

EF 40–49% mildly impaired systolic function, EF 30-39% moderately impaired systolic function, EF  $<$ 30% severely impaired systolic function. ICG was performed by a general practitioner with experience of survey technique using Niccomo™ monitor (Medis. Medizinische Messtechnik GmbH, Germany).

Two pairs of dual sensors were placed on the patient's neck and two on the sides of the chest (Figure 1). The skin was prepared in the way similar to the electrocardiography examination. The outer sensors apply a very low constant and alternating current, imperceptible to the patient. The inner sensors measure the baseline impedance of the thorax. Impedance changes with each heartbeat due to changes in the volume and velocity in the aorta. The changes in impedance are used to calculate stroke volume, cardiac output and other hemodynamic parameters. Table 1 contains the list of ICG parameters measured by Niccomo™.



**Figure 1** Electrode placement for impedance cardiography measurement.

**Table 1 The list of ICG parameters**

ICG parameter		Unit
Heart rate	HR	1/min
Heart period	HPD	ms
Stroke volume	SV	ml
Stroke index	SI	ml/min
Cardiac output	CO	l/min
Cardiac index	CI	l/min/m <sup>2</sup>
Left cardiac work	LCW	kg · m
Left cardiac work index	LCWI	kg · m/m <sup>2</sup>
Velocity index	VI	1/1000/s
Acceleration index	ACI	1/100/s <sup>2</sup>
Heather index	HI	Ohm/s <sup>2</sup>
Thoracic fluid containece	TFC	1/kOhm
Pre-ejection period	PEP	ms
Left ventricular ejection time	LVET	ms
Systolic time ratio	STR	
Ejection time ratio	ETR	%
Systolic vascular resistance	SVR	ml/min
Systolic vascular resistance index	SVRI	ml/min/m <sup>2</sup>

ICG measurement was obtained after 10 minutes resting, in the supine position with the head elevated between 30–45 degrees for better comfort of the patient. Data were transferred to an external disc and analysed thereafter regarding their adequacy.

None of ICG parameters can be directly compared with EF due to differences in both methods of examinations. ICG parameters were divided into the following groups:

1. Expression for cardiac work: cardiac output, stroke volume, left cardiac work.

2. Contractility: velocity index, acceleration index, Heather index.
3. Fluid status: thoracic fluid content.
4. Expression for systolic function: pre-ejection period, left ventricular ejection time, systolic time ratio and ejection time ratio.
5. Expression for the vascular resistance the heart works against: systolic vascular resistance.

We decided to analyse cardiac output, stroke volume, left cardiac work and systolic vascular resistance related to the body surface as cardiac index, stroke index, left cardiac work index and systolic vascular resistance index.

The study was approved by the research ethics committee at Lund University.

### Statistics

Data were analysed in the STATA version 10 (Stata Corporation, Texas, USA). Distribution of categorical variables was presented as numbers. Distribution of continuous variables was presented as a mean and 95% Confidence Interval. Kruskal-Wallis test was used to compare variables and show differences between the groups. A p-value of <0.05 was considered significant.

### Results

We obtained consent for participation from 37 patients out of 63 patients registered at heart failure unit. Those 37 patients were enrolled into the study. ICG could not be performed in one patient due to distortions in the ICG signal and this patient was excluded from further calculations. The mean age of 36 patients was 68.3 years (CI 64.2–72.4).

The group comprised 28 men (78%) and 8 women (22%). The mean age for men was 68.2 (95% CI 64.0–72.4) and for women 68.5 (95% CI 54.7–82.3). None of

**Table 2 Distribution of ICG parameters (value and 95% CI) in groups with different ejection fraction**

EF	≥50% (n = 13)	40-49% (n = 10)	30-39% (n = 6)	<30% (n = 7)	p-value
CI	2.808 (2.56–3.5)	3.14 (2.42–3.53)	2.6 (2.46–3.29)	2.7 (2.05–2.92)	0.1180
SI	42.15 (37.04–47.27)	35.95 (26.96–44.83)	36.86 (28.77–44.94)	38.83 (27.46–50.2)	0.2708
PEP	110.31 (94.38–126.23)	108.4 (95.71–121.1)	139.5 (110.23–168.77)	148 (125.2–170.79)	0.0069*
LVET	323.08 (285.77–360.38)	292.7 (271.06–314.34)	262 (222.78–301.22)	268.43 (212.7–324.15)	0.0462*
STR	0.35 (0.29–0.41)	0.38 (0.32–0.43)	0.54 (0.41–0.66)	0.75 (0.4–0.77)	0.0031*
ETR	37.15 (34.65–39.66)	37.3 (32.02–42.58)	32.66 (30.04–35.29)	34.57 (32.51–36.63)	0.1934
VI	33.77 (29.28–38.26)	38.4 (29.9–46.9)	35.17 (20.42–49.9)	40 (26.12–53.88)	0.61
ACI	51.84 (42.92–60.77)	64.6 (44.59–84.61)	66 (41.33–90.67)	68.14 (50.3–85.98)	0.26
HI	7.9 (5.81–9.98)	10.03 (6.44–13.61)	6.18 (2.98–9.39)	5.8 (2.59–9.0)	0.1006
LCWI	3.17 (2.7–3.63)	3.95 (2.96–4.93)	3.02 (2.5–3.52)	2.87 (2.38–3.35)	0.2624
SVRI	2452 (2099–2806)	2435 (1899–2971)	2662 (2179–3145)	2511 (1743–3279)	0.8549
TFC	35.12 (2.43–3.17)	33.89 (2.65–3.63)	39.63 (2.17–3.02)	43.99 (2.11–3.28)	0.1461

\* p value of <0.05.



the patients had significant aortic valve insufficiency or severe aortic stenosis. None of the patients reported any discomfort or adverse reaction associated with ICG measurement.

Normal left ventricular systolic function was presented in 13 out of 36 patients (36%), mildly impaired in 9 patients (25%), moderately and severely impaired each in 7 patients, respectively (19%). Three ICG parameters: pre-ejection fraction, left ventricular ejection time and systolic time ratio were associated with EF with significant p-value.

The results are presented in Table 2.

## Discussion

The purpose of this study was to find whether there is any association between EF measured by echocardiography and hemodynamic parameters measured by ICG.

We found associations between EF and three of four ICG parameters which describe systolic function of the left ventricle: pre-ejection period, left ventricular ejection time and systolic time ratio. We did not find any association between EF and the fourth parameter which describes systolic function - ejection time ratio, though it is directly proportional to left ventricular ejection time. We cannot explain this. The technique of ICG examination was correct. Only one examination had insufficient quality, most likely due to a bad contact between a sensor and the skin. There was no other potential cause of the distortions in ICG signals. We do not think that the patients' condition could influence the quality of ICG examination and therefore our results. All grades of HF were represented in our study population. None of the patients had unstable HF - a condition which can influence the quality of ICG examination.

A limitation of our study is a small number of patients. Nevertheless, most of the previous studies concerning the correlation between ICG and echocardiography had a small number of participants. This might be a reason why the results are not ambiguous. Evaluation of left ventricular function was the subject in previous studies with ICG but none of the parameters we found associated with EF was previously regarded as a determinant of left ventricular systolic dysfunction. Systolic time ratio, however, was able to distinguish preserved from impaired EF [17]. Also, a close correlation between systolic time ratio and changes in EF was observed before and after treatment in patients with heart failure [18]. An association between systolic time ratio and EF was found in our study.

The following ICG parameters were suggested in another study as determinants of left ventricular systolic dysfunction: cardiac index, left cardiac work index and systolic vascular resistance index [19]. We could not confirm this.

The lack of association between cardiac index and EF found in our study confirms a lack of agreement between absolute values of cardiac output measured by ICG and by echocardiography [20]. We did not find any data about pre-ejection period or left ventricular ejection time as determinants of reduced left ventricular function.

According to the theoretical equation EF is a quotient of stroke volume and end diastolic volume, cardiac output is a product of stroke volume and heart rate. ICG was considered to be a reliable method to determine stroke volume [21]. Owing to these facts, we hypothesized that stroke index and cardiac index would be determinants of left ventricular systolic function and would be associated with EF. ICG was a validated method for measuring cardiac output [22]. Cardiac output by ICG was significantly correlated with a thermodilution method as a gold standard even in patients with heart failure [23,24], which strengthened our hypothesis.

No association between stroke volume index or cardiac output index and EF was found in our study.

EF is commonly used to describe cardiac contractility [25]. We expected to find an association between EF and ICG parameters which describe contractility: velocity index, acceleration index and Heather index. Heather index by ICG has been suggested as the determinant of reduced left ventricle systolic function [26]. No association between EF and those parameters was found in our study.

## Conclusions

The possibility to determine left ventricular function by ICG makes the method attractive for use in patients with HF in primary health care. The association which we found between EF and ICG parameters was not reported in previous studies.

We found no association between EF and ICG parameters which were suggested previously as the determinants of reduced left ventricular systolic function. We do not think that knowledge concerning explanation of hemodynamic parameters measured by ICG that is available nowadays is sufficient to adopt the method in practice and use it to describe reduced left ventricular function.

## Abbreviations

HF: Heart failure; EF: Ejection fraction; ICG: Impedance cardiography.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

EK participated in the design of the study, carried out the data collection, helped with data interpretation and drafted the manuscript. SS helped with the design of the study, data collection and draft of the manuscript. HO helped draft the manuscript. AH designed the study, performed the statistical analysis, handled the data set, interpreted the data, participated in

drafting the manuscript. All the authors read and approved the final manuscript.

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# Paper III





RESEARCH ARTICLE

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# Heart failure and levels of other comorbidities in patients with chronic obstructive pulmonary disease in a Swedish population: a register-based study

Elzbieta Kaszuba<sup>1,2\*</sup>, Håkan Odeberg<sup>2</sup>, Lennart Råstam<sup>2</sup> and Anders Halling<sup>2,3</sup>

## Abstract

**Background:** Despite the fact that heart failure and chronic obstructive pulmonary disease (COPD) often exist together and have serious clinical and economic implications, they have mostly been studied separately. Our aim was to study prevalence of coexisting heart failure and COPD in a Swedish population. A further goal was to describe levels of other comorbidity and investigate where the patients received care: primary, secondary care or both.

**Methods:** We conducted a register-based, cross-sectional study. The population included all people older than 19 years, living in Östergötland County in Sweden. The data were obtained from the Care Data Warehouse register from the year 2006. The diagnosis-based Adjusted Clinical Groups Case-Mix System 7.1 was used to describe the comorbidity level.

**Results:** The prevalence of the diagnosis of heart failure in patients with COPD was 18.8 % while it was 1.6 % in patients without COPD. Age standardized prevalence was 9.9 and 1.5 %, respectively. Standardized relative risk for the diagnosis of heart failure in patients with COPD was 6.6. The levels of other comorbidity were significantly higher in patients with coexisting heart failure and COPD compared to patients with either heart failure or COPD alone. Primary care was the only care provider for 36.2 % of patients with the diagnosis of heart failure and 20.7 % of patients with coexisting diagnoses of heart failure and COPD. Primary care participated furthermore in shared care of 21.5 % of patients with the diagnosis of heart failure and 21.7 % of patients with coexisting diagnoses of heart failure and COPD. The share of care between primary and secondary care varied depending on levels of comorbidity both in patients with coexisting heart failure and COPD and patients with heart failure alone.

**Conclusion:** Patients with coexisting diagnoses of heart failure and COPD are common in the Swedish population. Patients with coexisting heart failure and COPD have higher levels of other comorbidity than patients with heart failure or COPD alone. Primary care in Sweden participates to a great extent in care of patients with diagnoses of heart failure alone and coexisting heart failure and COPD.

**Keywords:** Heart failure, Chronic obstructive pulmonary disease, Diagnosis, Registries, Comorbidity, Primary care, Delivery of health care

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## Background

Worldwide, chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases with overall prevalence of 7.6 % [1] and a heavy economic burden [2]. Patients with COPD are a group where chronic cardiovascular diseases including heart failure occur more frequently than in the general population [3]. The risk of developing heart failure in patients with COPD is 4.5 times higher than in age-matched controls [4]. Coexisting heart failure and COPD can be overlooked due to similarities in symptoms and signs, which is an important clinical implication. The main clinical manifestation of COPD and heart failure is dyspnea, which in turn is one of the most common causes of consultations in both primary and secondary care, especially among elderly patients [5].

The prevalence of undiagnosed heart failure in patients with COPD older than 65 years in primary care is approximately 20 % [6]. A review of previous studies showed that the prevalence of heart failure in patients with COPD varied between 10 and 46 % [7].

The prevalence of COPD in patients with heart failure is also about 20 % [8, 9]. The prevalence and burden of heart failure and COPD correlate with an aging population. The proportion of elderly in Sweden is the highest in the world with 17.4 % of persons aged  $\geq 65$  years and is expected to increase until the year 2020 [10]. Management of heart failure and COPD is going to be a challenge in both primary and secondary care. Despite the fact that heart failure and COPD often occur together and have serious clinical and economic implications, both diseases have so far been mostly studied separately, especially on the population level. There is no Swedish data about prevalence of coexisting heart failure and COPD.

The aim of this study was to examine the prevalence of the diagnosis of heart failure in patients with the diagnosis of COPD in the Swedish population. A further aim was to describe the levels of other comorbidities and investigate where patients with coexisting heart failure and COPD receive care: primary, secondary care or both.

## Methods

This was a register-based, cross-sectional study. All the study population included people older than 19 years, living in Östergötland County in Sweden. The data used for the study was not openly available and was obtained after permission from the Östergötland County council. We used data from the Care Data Warehouse register [11]. The register collects data concerning consultation and diagnosis transferred every month from all public and private health care units in both primary and secondary care. Diagnoses were recorded according to the Swedish Version of International Statistical Classification of Diseases

and Related Health Problems version 10 (ICD 10). We used data from the year 2006. We identified an individual as having heart failure or COPD if the diagnosis code I50 or J44 was recorded on at least one consultation in primary or secondary care including hospitalization.

The code I50 covers: I50.0-chronic heart failure including congestive heart failure, right heart failure secondary to left heart failure, I50.1-left ventricular failure with or without lung oedema and asthma cardiale, I50.9 heart failure, unspecified.

The code J44 comprised the following: J44 chronic obstructive lung disease, J44.0 chronic obstructive lung disease with acute infection in lower airways, J44.1 chronic obstructive lung disease with acute exacerbation, unspecified, J44.8 other specified chronic obstructive lung disease including chronic bronchitis with emphysema.

The diagnosis-based Adjusted Clinical Groups (ACG) Case-Mix System 7.1 was used to describe comorbidity [12, 13]. Comorbidity on an individual level was measured when the diagnoses I50 and J44 were excluded and it is referred to as the level of other comorbidity.

Each individual was assigned one of six comorbidity levels called resource utilization bands (RUB) graded from 0 to 5.

When identifying the place where patients received care we used information where the diagnosis of heart failure and COPD was made: primary, secondary care or both.

## Statistics

Data were analyzed in the STATA version 10 (Stata Corporation, Texas, USA). Descriptive data were presented in tables. Differences in proportions between the groups were tested using the Chi square test. A  $p < 0.05$  was considered significant. Results for prevalence of heart failure and COPD are given for the whole study population. Thereafter direct standardizing for age was made. Individuals aged 60 and above were chosen arbitrarily as a standard population.

## Ethics

The study has been approved by the Research Ethics Committee at Linköping University No 147/05 and 29/06.

## Results

The study population consisted of 313,977 individuals. The diagnosis of heart failure was registered in 1.8 % and the diagnosis of COPD was registered in 1.2 % of the study population. The mean age in patients with the diagnosis of heart failure was 78.4 years (CI 78.0–78.7). The mean age of patients with the diagnosis of COPD was 70.5 years (CI 70.2–70.9). The prevalence of both diagnoses increased with age (Table 1). The prevalence of the

**Table 1 Prevalence of diagnoses COPD, heart failure and coexisting COPD and heart failure in the study population**

Variable	20–39 years	40–59 years	60–79 years	>80 years	Total
Women	47,419	53,539	41,359	16,386	158,703
Men	52,020	55,164	38,443	9647	155,274
COPD in total population	31 (0.03 %)	536 (0.4 %)	2280 (2.8 %)	889 (3.4 %)	3736 (1.2 %)
Heart failure in total population	34 (0.03 %)	328 (0.3 %)	2132 (2.6 %)	3045 (11.6 %)	5539 (1.89 %)
Heart failure in patients with COPD	0 (0 %)	26 (4.6 %)	367 (16.1 %)	307 (34.5 %)	700 (18.8 %)
Heart failure in patients without COPD	34 (0.03 %)	302 (0.3 %)	1765 (2.3 %)	2738 (10.9 %)	4839 (1.6 %)

diagnosis of heart failure in patients with the diagnosis of COPD was 18.8 and 1.6 % in patients without COPD. After standardizing for age the prevalence was 9.9 and 1.5 %, respectively. Standardized relative risk for the diagnosis of heart failure in patients with COPD was 6.6.

The prevalence of the diagnosis of heart failure increased with age in women and men in both groups and reached 35.7 % in men with COPD ≥80 years (Fig. 1). The prevalence of the diagnosis of heart failure was significantly higher in both women and men with COPD

comparing to women and men without COPD in all age groups apart from the age group 20–39 years.

The most common comorbid condition in all three groups of patients: heart failure alone, COPD alone and coexisting heart failure and COPD was essential (primary) hypertension coded with either I10 or I10.9. The latter code is used only in secondary care. The comorbid diagnoses are summarized in Table 2.

The levels of other comorbidity were significantly higher in patients with coexisting heart failure and COPD comparing to patients with heart failure or COPD alone (Table 3).

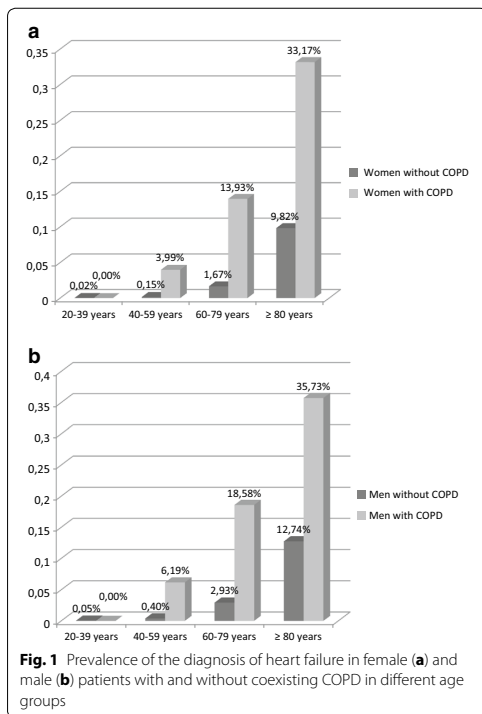
The proportion of individuals with higher levels of other comorbidity (RUB 3–5) was 95 % in the group with coexisting heart failure and COPD, while in the group with heart failure alone it was 90.7 % and in the group with COPD alone it was 73.3 %.

Primary care was the only care provider to 36.2 % of patients with the diagnosis of heart failure and 20.7 % of patients with coexisting heart failure and COPD. Furthermore, primary care participated in shared care of 21.5 % of patients with the diagnosis of heart failure alone and 21.7 % of patients with coexisting diagnoses of heart failure and COPD.

The share of care given by primary and secondary care varied depending on levels of other comorbidity both in patients with heart failure without COPD and patients with coexisting heart failure and COPD (Fig. 2). The higher the level of other comorbidity the larger the participation of secondary health care was. Among patients with the highest level of other comorbidity (RUB 5) in the group with coexisting heart failure and COPD 11 % received care only in primary care, 29 % received shared care and 60 % received care only in secondary care.

**Discussion**

We found that the prevalence of the diagnosis of heart failure in patients with the diagnosis of COPD was significantly higher than in patients without COPD. The levels of other comorbidity were significantly higher in patients with coexisting heart failure and COPD comparing with





**Table 2 Summarizing of the most common diagnostic codes**

Patients with COPD n = 3736	Code	Number (%)	Patients with heart failure n = 4839	Code	Number (%)	Patients with COPD and heart failure n = 700	Code	Number (%)
Essential (primary) hypertension	I10, I10.9	1196 (32)	Essential (primary) hypertension	I10, I10.9	2303 (47.6)	Essential (primary) hypertension	I0, I10.9	284 (40.6)
Observation for suspected disease or condition	Z039	628 (16.8)	Observation for suspected disease or condition	Z03.9	1472 (30.4)	Observation for suspected disease or condition	Z03.9	251 (35.9)
Heart failure, unspecified	I50.9	526 (14.1)	Atrial fibrillation and atrial flutter, unspecified	I48.9	1380 (28.5)	Atrial fibrillation and atrial flutter, unspecified	I48.9	199 (28.4)
Unspecified acute lower respiratory infection	J22	383 (10.3)	Type 2 diabetes mellitus, without complications	E11.9	958 (19.8)	Old myocardial infarction	I25.2	166 (23.7)
Type 2 diabetes mellitus, without complications	E11.9	350 (9.4)	Atrial fibrillation and atrial flutter, unspecified	I48.9	931 (19.2)	Type 2 diabetes mellitus, without complications	E11.9	149 (21.3)
Atrial fibrillation and atrial flutter, unspecified	I48.9	312 (8.4)	Chronic ischaemic heart disease, unspecified	I25.9	910 (18.8)	Chronic ischaemic heart disease, unspecified	I25.9	136 (19.4)

**Table 3 Distribution of levels of other comorbidity measured by RUB (resource utilization band) in the study population**

	Total	Patients without COPD		Patients with COPD		p value*
		No heart failure	Heart failure	No heart failure	Heart failure	
RUB 0	102,071 (32.51 %)	101,835 (33.34 %)	81 (1.65 %)	150 (4.49 %)	5 (0.71 %)	0.000
RUB 1	44,126 (14.05 %)	43,855 (14.36 %)	86 (1.78 %)	181 (5.96 %)	4 (0.57 %)	0.001
RUB 2	65,322 (20.8 %)	64,533 (21.13 %)	282 (5.83 %)	481 (15.84 %)	26 (3.71 %)	0.000
RUB 3	89,042 (28.36 %)	84,602 (27.7 %)	2514 (51.95 %)	1603 (52.80 %)	323 (46.14 %)	0.000
RUB 4	10,383 (3.31 %)	10,383 (3.31 %)	1234 (25.50 %)	434 (14.30 %)	203 (29 %)	0.000
RUB 5	3033 (0.97 %)	2065 (0.68 %)	642 (13.27 %)	187 (6.16 %)	139 (19.89 %)	0.000
Total	313,977 (100 %)	305,402 (100 %)	4839 (100 %)	3036 (100 %)	700 (100 %)	0.000

\* p value describes differences between groups with and without COPD

patients with heart failure or COPD alone. Primary care alone delivered care to 20.7 % of patients with coexisting heart failure and COPD and to a further 21.7 % who simultaneously received care from primary and secondary care.

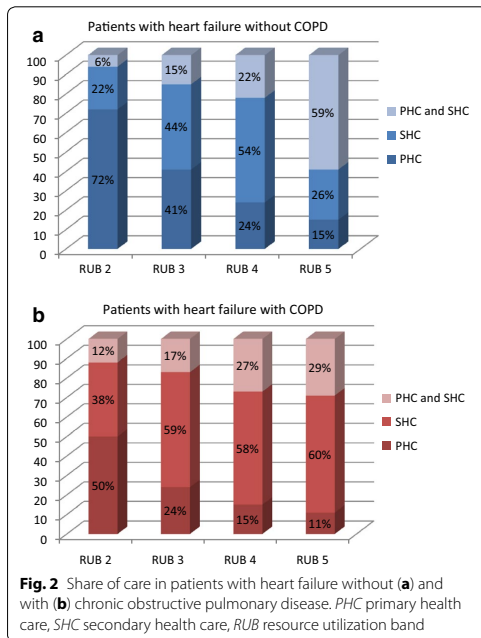
**Completeness and accuracy of data**

The Care Data Warehouse Register comprised data from the whole population in the Östergötland County, which is the strength of our study. All consultations were recorded in electronic charts and the diagnosis was required at each consultation. We analyzed data from both primary and secondary care. A previous study showed usefulness of data from the Care Data Warehouse register in Östergötland in estimating the prevalence of chronic diseases such as diabetes, hypertension, ischemic heart disease, asthma and COPD and showed that the longer period of analysis corresponded to better

capturing of cases [14]. The limitation of our study is a short period we analyzed. Our choice was anchored in Swedish clinical practice. In Swedish primary care patients with chronic diseases are actively checked at least once a year. Patients with COPD are summoned for a nurse-led follow-up and the presence of a specially educated asthma/COPD nurse is a requirement for each primary health care centre.

Nurse-led follow up of patients with heart failure is common in Swedish secondary care [15]. Östergötland was the leading county in Sweden in structured heart failure management in primary care [16].

A previous study showed that the diagnosis of COPD from a register in Sweden has an acceptable validity for being used in epidemiological research [17]. COPD in Sweden is usually diagnosed in primary care according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [18]. Spirometry as a gold standard



in diagnosing COPD is widely available in primary care [19, 20]. Echocardiography as a gold standard in diagnosing heart failure is not as much accessible to general practitioners as spirometry and requires referral to specialized care. A previous Swedish study showed that echocardiography was performed only in about 30 % of patients with suspected heart failure [21]. Östergötland County was a leader in Sweden in use of natriuretic peptides in patients with suspected heart failure in primary care [22]. The limitation of our study was that, due to ethical reasons, we could not validate recorded diagnoses against the original medical records. At the same time we have no premises to suspect that the diagnoses registered in the Care Data Warehouse were non-accurate.

### Interpretation of the results

We found that the diagnosis of heart failure occurred in 1.8 % of the study population.

This is exactly the same as the crude prevalence reported in a recently published Swedish register study [23]. According to this study the estimated prevalence of heart failure in Sweden was 2.2 % in year 2010. Estimation made about 15 years ago was 2.5 % [24].

The prevalence of the diagnosis of COPD was 1.2 %. Our result is considerably lower than prevalence of

COPD in the general population in Sweden estimated at about 6 % [25]. The discrepancy was expected because epidemiological studies regarding COPD used to be performed in individuals aged at least 40 years due to the onset of the illness, while we included individuals aged 20 and older in order to study the whole adult population. After excluding younger patients aged  $\leq 40$  years the prevalence of COPD was 1.7 %, which did not change our results considerably.

We searched only for the diagnostic code J44, while in studies from other countries chronic bronchitis and emphysema J40–J43 were also included [26]. By that choice we wanted to decrease a risk of the non-accurate COPD diagnosis. In view of present guidelines for the diagnosis of COPD in Sweden the diagnostic code J44 is expected to be used for patients with COPD after doing the spirometry. This code is expected even in patients with emphysema caused by COPD. We think that prevalence of COPD in our study was underestimated due to poor registering of the diagnosis code in medical records.

Prevalence of the diagnosis of heart failure increased with age in patients without and with COPD as reported in previous studies [27, 28]. In our study the prevalence of the diagnosis of heart failure in individuals  $\geq 80$  years in the general population was approximately 11 % and was comparable with previously reported data from epidemiological studies, but differed from the recent Swedish register study where it was about 19 % [23]. A difference between genders was reported in a Swedish epidemiological study. A report from 2001 [29] showed that heart failure was more prevalent in men up to 80 years of age, thereafter, heart failure was more prevalent in women. Our data from 2006 showed no significant difference between women and men even aged  $\geq 80$  years. The newer study [23] with data collection up to 2010 showed, in contrast to the first study, that prevalence was higher in men in groups 80–89 and 90–99.

Women dominated slightly in the group  $\geq 100$  years. The populations in all three studies were large enough to venture to assert that the age limit for healthy survivals has moved during one decade to centenarians, probably thanks to improved strategies in heart failure management in Sweden.

The diagnosis of heart failure occurred in 18.8 % of patients with COPD while in patients without COPD it occurred in 1.6 %. Due to differences in age between groups with and without COPD standardizing for age was made and standardized prevalence was 9.9 % in patients with COPD and 1.5 % in patients without COPD. Previously reported prevalence of heart failure in patients with COPD varied between 10 and 46 % [7]. These data were obtained in different settings and different procedures were used to make the diagnosis of heart failure, ranging

from clinical symptoms, standardized chronic heart failure score, the use of natriuretic peptides for assessment of left and right ventricle function by ventriculography or echocardiography. The highest prevalence was reported in emergency setting among patients with symptomatic dyspnea [30]. The diagnosis of heart failure in this study was established by assessment of left and right ventricle function by radionuclide ventriculography. The prevalence of the diagnosis of heart failure found in our study (18.8 %) is in agreement with the prevalence of heart failure in patients with COPD (20.5 %) found in the Dutch study conducted in primary health care setting [6]. The diagnosis of heart failure in that study was made by using echocardiography. In our register-based study we could not trace how the diagnosis of heart failure was made.

Differences in frequency of the diagnosis of heart failure between individuals with and without COPD were significant in all age groups except the age 20–39. Calculations in this age group were affected by 0 % prevalence of heart failure diagnosis in individuals with COPD.

Comorbidity in patients with heart failure and COPD is well-known and widely reported [31–37]. The most common comorbid condition in all three groups of patients in our study: COPD alone, heart failure alone and coexisting heart failure and COPD was essential (primary) hypertension coded with either I10 or I10.9. The latter code is used only in secondary care.

The next common diagnosis code in all three groups was Z03.9 Observation for suspected disease or condition, unspecified. This code does not allow identifying of disorder. If the register data should be available as a source of research e.g. prevalence studies, more specific diagnosis codes are desirable. Comorbidity should be considered as an important factor when analyzing needs for health care resources. ACG Case Mix is able to describe comorbidity in a quantitative way and is used in the Swedish health care system for calculation of payment rates. When analyzing comorbidity levels we excluded the main diagnoses of heart failure and COPD. This was done in order to study the importance of other comorbidity that otherwise would be hidden by the heavy burden connected with the diagnosis of heart failure or COPD. The levels of other comorbidity calculated in this way were significantly higher in patients with coexisting heart failure and COPD. That implies a greater need for health care and more extensive resource utilization than in patients with only heart failure or COPD.

The delivery of care to patients with coexisting heart failure and COPD has not been studied previously. When presenting our results in Fig. 2 we omitted groups with the lowest levels of other comorbidity (RUB 0 and

1) due to a small number of patients in those groups. As expected, the higher the levels of other comorbidity the greater participation of secondary care. We did not trace what kind of care patients got in secondary health care units. It might be hospitalizations or consultations in specialized outpatient clinics. Taking into consideration the heavy burden of both heart failure and COPD the participation of primary care was large in our opinion. Half of the patients with coexisting heart failure and COPD and lower levels of other comorbidity (RUB 2) received care only in primary care. In the group with the highest level of other comorbidity (RUB 5) and coexisting heart failure and COPD primary care was involved in almost 40 % of patients, either alone or together with secondary care. In the case of patients with heart failure without COPD the percentage was even higher (74 %). Shared care can be explained by organization of the Swedish health care system and established co-operation between primary and secondary care units concerning chronic diseases.

It is noteworthy that a considerable part of patients with the highest level of other comorbidity (RUB 5) received care only in primary care. A possible explanation might be that the patients were optimally treated and requirement of secondary care was unnecessary during one year period we analyzed. It might also be a matter of the terminal phase of illness and palliative care where primary care plays a central role.

## Conclusion

Our study showed that the prevalence of the diagnosis of heart failure in patients with the diagnosis of COPD is common in the Swedish population. Patients with coexisting heart failure and COPD have higher levels of other comorbidity than patients with heart failure or COPD alone. Primary care in Sweden participates to a great extent in care of patients with heart failure and coexisting COPD as well as without COPD.

## Abbreviations

COPD: chronic obstructive pulmonary disease; ACG: adjusted clinical groups; RUB: resource utilization band; PHC: primary health care; SHC: secondary health care.

## Authors' contributions

EK participated in the design of the study, statistical analysis, data interpretation and drafted the manuscript. HO and LR helped draft the manuscript. AH designed the study, performed the statistical analysis, handled the data set, interpreted the data and participated in drafting the manuscript. All the authors read and approved the final manuscript.

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**Competing interests**

The authors declare that they have no competing interests. We do not have any financial relation with the commercial identities mentioned in the paper.

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# Paper IV





# Impact of heart failure and other comorbidities on mortality in patients with chronic obstructive pulmonary disease

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## Abstract

**Background** Multimorbidity has already become common in primary care and will be a challenge in the future. Primary care in Sweden participates to a great extent in care of patients with two severe, chronic conditions: chronic obstructive pulmonary disease (COPD) and heart failure. Both conditions are characterized by high mortality and often coexist in one individual. Age, sex and comorbidities are considered to be the major predictors of mortality in patients with COPD and heart failure alone.

**Aim** To study how coexisting heart failure influences the mortality in patients with COPD and describe the impact of age, sex and other comorbidities on mortality in patients with coexisting heart failure and COPD.



**Methods** A register-based, prospective cohort study conducted in Blekinge County in Sweden with about 150 000 inhabitants. The study population comprised people aged  $\geq 35$  years.

The data about diagnoses of COPD and heart failure came from the health care register for the year 2007. Date of death was collected from January 1<sup>st</sup>, 2008 – August 31<sup>st</sup>, 2015 and obtained from the Blekinge County council. The diagnosis-based Adjusted Clinical Groups (ACG) Case-Mix System 7.1 was used to describe comorbidity. Each individual was assigned one of six comorbidity levels called resource utilization bands (RUB) graded from 0 to 5 where 5 means very high morbidity and need for care.

**Results** Estimated mortality in patients with COPD and coexisting heart failure was 7 times higher than in patients with COPD alone - odds ratio 7.06 (95% CI 3.88-12.84). Adjusting for age and male sex resulted in odds ratio 3.75 (95% CI 1.97-7.15). Further adjusting for other comorbidity resulted in odds ratio 3.26 (95% CI 1.70-6.25).

The mortality was strongly associated with the highest comorbidity level – RUB 5 where odds ratio was 5.19 (95% CI 2.59-10.38).

## Conclusion

Heart failure has an important impact on mortality in patients with COPD. The mortality in patients with COPD and coexisting heart failure is strongly associated with age, male sex and other comorbidities. Of those three predictors only other comorbidities can be influenced. Heart failure and other comorbidities should be recognized early and properly treated in order to improve survival in patients with coexisting COPD and heart failure.

### *Keywords*

Chronic obstructive pulmonary disease, heart failure, mortality, age, sex, comorbidity.

## Background

Today general practitioners seldom encounter patients with only one disease.

Population ages and patients of higher age are more likely to have two or more coexisting chronic disorders [1]. Multimorbidity has already become a norm and will be a challenge to future primary care. Our previous study showed that primary

care in Sweden participates to a great extent in the care of patients with two severe, chronic conditions: chronic obstructive pulmonary disease (COPD) and heart failure [2]. Both conditions are common in the Swedish population [3-5]. Prevalence of COPD is still high despite decreasing prevalence of smoking in Sweden [6]. COPD is predicted to be the third most common cause of death and disability worldwide by 2030 [7]. High mortality is not caused by respiratory failure which from the pathophysiological point of view can be considered a natural consequence of COPD due to disturbances in gas exchange [8]. Respiratory failure was a leading cause of death only in patients with advanced COPD and could explain mortality in only one-third of these patients [9]. The major independent predictors of mortality in COPD were comorbidity and sex [10-12]. Heart failure occurs with high prevalence in patients with COPD [13]. Although the strategies in management of heart failure have improved during last decades, prognosis remains poor [14-16]. Comorbidities, age and sex are independent indicators for the prognosis in heart failure [17, 18]. Despite increasing understanding that COPD and heart failure often coexist [19] they have earlier mostly been studied separately. It is a matter of course that the more disorders an individual has the worse the outcome will be. However, it is not clear if one plus one makes two in medical practice. The aim of this study was to find how much coexisting heart failure increases probability of death in patients with COPD and describe the impact of age, sex and other comorbidities on mortality in patients with coexisting COPD and heart failure. Thereby we wanted to find what coexisting heart failure and other comorbidities mean for the survival of an individual with COPD, which is of special importance in primary care where the patient is the focus.

## Methods

This was a register-based, prospective, observational study. The study was conducted in Blekinge County in Sweden with about 150 000 inhabitants. The study population comprised people aged  $\geq 35$  years.

The data were obtained from the Blekinge County council health care register which collected data concerning diagnosis at each consultation in all public and private health care units in both primary and secondary health care. Diagnoses were recorded according to the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD 10). We analyzed data from January 1<sup>st</sup> till December 31<sup>st</sup>, 2007.

An individual was identified as having COPD if the diagnosis code J44 was recorded on at least one consultation in primary or secondary care including hospitalization. The code J44 comprised the following: J44 chronic obstructive lung

disease, J44.0 chronic obstructive lung disease with acute infection in lower airways, J44.1 chronic obstructive lung disease with acute exacerbation, unspecified, J44.8 other specified chronic obstructive lung disease including chronic bronchitis with emphysema. The register did not contain information on the severity of COPD.

Coexisting heart failure was identified if the diagnosis code I50 was recorded.

The code I50 comprised: I50.0- chronic heart failure including congestive heart failure, right heart failure secondary to left heart failure, I50.1- left ventricular failure with or without lung oedema and asthma cardiale, I50.9 heart failure, unspecified. Occurrence of other diagnoses in medical records is referred to as other comorbidities.

The diagnosis-based Adjusted Clinical Groups (ACG) Case-Mix System 7.1 was used to measure other comorbidities [20, 21]. Each individual was assigned one of six comorbidity levels called resource utilization bands (RUB) graded from 0 to 5, where 5 means very high morbidity and need for care.

The date of death was collected from January 1<sup>st</sup>, 2008 –August 31<sup>st</sup>, 2015 and was obtained from the Blekinge County council. Individuals who left the Blekinge County during the observation time were excluded from the study.

## Statistics

Data were analyzed in the STATA version 13 (Stata Corporation, Texas, USA).

Distribution of categorical variables was presented as numbers. Distribution of continuous variables was presented as a mean and 95% Confidence Interval (CI).

Univariate analysis was used to calculate odds ratios of mortality for different variables. Logistic regression was used to calculate adjusted odds ratios step-by-step. Thereafter multiple logistic regression was performed in order to adjust the estimated odds ratio for the influence of age, sex and other comorbidities.

## Ethics

The study has been approved by the Research Ethics Committee at Lund University No 2015/169.

## Results

The study population consisted of 91 227 individuals aged  $\geq 35$  years of which 51.07% were female and 48.93% were male. The diagnosis of COPD was registered in 1011 individuals of which 27 (2.67%) moved and were excluded from the study. The final analyses were made on data from 984 individuals of which 53% were female and 47% male. The mean age in patients with the diagnosis of COPD was 71.1 (95% CI 70.4-71.8). The mean age for women was 69.4 (95% CI 68.5-70.4) and for men 72.9 (95% CI 72.0-73.8).

Comorbidity levels described by RUB were distributed as follows: RUB 3- 71.14 % (n=700), RUB 4 -21.65% (n=213), RUB 5 -7.22% (n=71).

We found the diagnosis of heart failure in 10.06% (n=99) of patients with the diagnosis of COPD.

Univariate analysis resulted in odds ratio of mortality in patients with COPD and coexisting heart failure 7.06 (95% CI 3.88-12.84). The highest level of other comorbidities was the next important variable which influenced mortality (Table 1).

Adjusting for age resulted in odds ratio 3.76 (95% CI 1.98-7.16) and for age and male sex in odds ratio 3.75 (95% CI 1.79-3.26 (1.70-6.25)). Further adjusting for other comorbidity resulted in odds ratio 3.26 (95% CI 1.70-6.25). Adjusted odds ratios are presented in Table 2.

Multiple logistic regression showed that the mortality was associated with age and male sex but the strongest risk factor for mortality was the highest comorbidity level – RUB 5 where odds ratio was 5.19 (95% CI 2.59-10.38) (Table 3).

## Discussion

We found that the odds of mortality in patients with COPD and coexisting heart failure were 7 times higher than in patients with COPD alone. Other comorbidities influenced mortality in patients with COPD and coexisting heart failure more than age and sex. Our study was register based. The primary source of information in the register was the patient's medical record. Because of the listing system in primary care in the Blekinge County we could study the whole population, which is a strength of our study. Each inhabitant was either actively or passively listed with a primary health care centre. Furthermore we collected data from both primary and secondary care. The limitation of our study is validity and completeness of diagnoses of COPD and heart failure in the medical record. Previous studies, however, showed that both diagnoses in Swedish registers had acceptable validity for being used in epidemiological research [22, 23]. Heart failure was previously

reported as the most common comorbidity noted in deceased patients hospitalized with COPD exacerbation [24]. Our study confirmed that coexisting heart failure considerably increases the probability of death in patients with COPD in general population. This is not surprising when taking into consideration that COPD is associated with an increased risk of cardiovascular diseases [25] due to smoking as a common risk factor and systemic inflammation, oxidative and physiologic stress and vascular dysfunction as a common mechanism [26]. Age and male sex were associated with higher mortality in patients with COPD and coexisting heart failure as expected when taking into consideration data on heart failure [17] and COPD alone [24]. A wide spectrum of comorbidities was previously reported as factors associated with mortality for patients with heart failure and COPD alone. Comorbidities with highest impact on mortality in patients with heart failure were: COPD, stroke, renal disease, anemia, diabetes [16] and for patients with COPD: respiratory failure, pneumonia, heart failure, ischaemic heart disease, hypertension and lung cancer [27]. The most common comorbid diagnosis in our material was hypertension, other common comorbidities were atrial fibrillation, diabetes type 2 and ischaemic heart disease. We think that those chronic and treatable conditions were the most important for comorbidity levels and mortality in our study population. The importance of comorbidity for mortality was shown in a Swedish study in patients with severe COPD treated with long-term oxygen therapy [28]. We showed the same effect of comorbidity in a whole population of patients with COPD and coexisting heart failure.

Comorbidity in our study was calculated as an individual measure using diagnoses analyzed with the ACG Case Mix system. The severity and chronicity of the different diagnoses in an individual led to a higher level of comorbidity (RUB). RUB is a categorization of the individual patient's morbidity and describes the sum of all comorbidities in an individual. We showed that the higher the level of comorbidity the higher odds ratio of mortality even when presence of heart failure was adjusted for. Odds ratio of mortality adjusted for age and male sex in the group with the highest level of other comorbidity was 5 times higher. This means that other comorbidities are an important independent predictor of mortality which should be recognized when treating patients with COPD and coexisting heart failure. Identifying and proper management of other comorbidities may decrease the odds of mortality in these patients.

# Conclusion

Coexisting heart failure increases considerably the odds of mortality in patients with COPD.

The mortality in patients with COPD and coexisting heart failure is strongly associated with age, male sex and other comorbidities. Of those three predictors only other comorbidities can be influenced. It is important to early recognize and adequately treat other comorbidities in patients with COPD and coexisting heart failure since they significantly influence survival.

**Table 1.**

Odds ratios of mortality in patients with COPD – univariate analyse of different variables used.

Univariate	OR (95%CI)
Heart failure	7.06 (3.88-12.84)
Age	1.13 (1.11-1.14)
Male sex	1.78 (1.38-2.30)
RUB 4	2.03 (1.48-2.78)
RUB 5	4.78 (2.61-8.74)

**Table 2.**

Odds ratios (OR) of mortality in heart failure in patients with COPD adjusted for different variables used.

Variables	OR (95%CI)
Heart failure	7.06 (3.88-12.84)
Heart failure, age	3.76 (1.98-7.16)
Heart failure, age, male sex	3.75 (1.97-7.15)
Heart failure, age, male sex, other comorbidities	3.26 ( 1.70-6.25)

**Table 3.**

Importance of different variables for mortality in patients with COPD. Odds ratios (OR) were adjusted for all other variables.

Variables	Adjusted OR (95%CI)
Heart failure	3.26 (1.70-6.25)
Age	1.12 (1.10-1.14)
Male sex	1.37 (1.02-1.85)
RUB 4	1.82 (1.26-2.65)
RUB 5	5.19 (2.59-10.38)

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