Cardiovascular aspects on chronic obstructive pulmonary disease

- with focus on ischemic ECG abnormalities, QT prolongation and arterial stiffness

The Obstructive Lung Disease in Northern Sweden (OLIN) studies, thesis XIX

Ulf Nilsson
“I love to watch the ravens  
Making spirals in pairs  
Its feathers and faith meeting the grace of the invisible air  
They just fling themselves wide open  
And jump into the sky  
It’s a radical trust that gives us the freedom to fly”

Amy Martin
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>i</td>
</tr>
<tr>
<td>Abstract</td>
<td>iii</td>
</tr>
<tr>
<td>Enkel sammanfattning på svenska</td>
<td>vi</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>x</td>
</tr>
<tr>
<td>Original papers</td>
<td>xii</td>
</tr>
<tr>
<td>Preface</td>
<td>1</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
</tr>
<tr>
<td>Historical perspective</td>
<td>2</td>
</tr>
<tr>
<td><em>Ischemic heart disease</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Electrocardiogram and the Minnesota code</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Prolonged QT interval</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Arterial stiffness</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Chronic obstructive pulmonary disease</em></td>
<td>3</td>
</tr>
<tr>
<td>Overview of cardiovascular disease and COPD</td>
<td>5</td>
</tr>
<tr>
<td><em>Ischemic heart disease</em></td>
<td>5</td>
</tr>
<tr>
<td><em>QT-interval</em></td>
<td>6</td>
</tr>
<tr>
<td><em>Arterial stiffness</em></td>
<td>9</td>
</tr>
<tr>
<td><em>Chronic Obstructive Pulmonary Disease</em></td>
<td>11</td>
</tr>
<tr>
<td><em>Cardiovascular comorbidity in COPD</em></td>
<td>14</td>
</tr>
<tr>
<td><strong>Aims of the thesis</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Materials and methods</strong></td>
<td>17</td>
</tr>
<tr>
<td>Study design</td>
<td>17</td>
</tr>
<tr>
<td><em>The OLIN studies</em></td>
<td>17</td>
</tr>
<tr>
<td>Study population</td>
<td>20</td>
</tr>
<tr>
<td>Data collection and definitions</td>
<td>20</td>
</tr>
<tr>
<td><em>Electrocardiogram</em></td>
<td>20</td>
</tr>
<tr>
<td><em>Arterial stiffness</em></td>
<td>21</td>
</tr>
<tr>
<td><em>Lung function tests</em></td>
<td>24</td>
</tr>
<tr>
<td><em>Structured interview and biometric data</em></td>
<td>24</td>
</tr>
<tr>
<td><em>Statistical methods</em></td>
<td>25</td>
</tr>
<tr>
<td><strong>Ethical considerations</strong></td>
<td>27</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>28</td>
</tr>
<tr>
<td>Prevalence of ischemic heart disease among subjects with COPD and NLF (paper I)</td>
<td>28</td>
</tr>
<tr>
<td>Ischemic ECG abnormalities and mortality among subjects with COPD and NLF (paper II)</td>
<td>30</td>
</tr>
<tr>
<td>QTc interval and COPD (paper III)</td>
<td>31</td>
</tr>
<tr>
<td>Arterial stiffness among subjects with and without COPD (paper IV)</td>
<td>33</td>
</tr>
<tr>
<td><strong>Discussion on Methodology</strong></td>
<td>34</td>
</tr>
</tbody>
</table>
Abstract

Background

Chronic Obstructive Pulmonary disease (COPD) is an under-diagnosed disease with a prevalence of approximately 10%, highly dependent on age and smoking habits. Comorbidities are common in COPD and of these, cardiovascular diseases (CVD) are the most common. COPD is the fourth leading cause of death globally, and CVD probably contribute to the high mortality. Within CVD, Ischemic Heart Disease (IHD) is the most common. It is highly clinically relevant to identify signs of ischemic heart disease, other cardiac conditions, and risk factors for CVD in COPD. Electrocardiogram (ECG) is a simple but still major diagnostic tool in clinical cardiology, including disturbances in the electric conduction system and ischemia. Due to the under-diagnosis of COPD, there is limited knowledge regarding the prevalence and prognostic impact of ECG abnormalities in COPD. Arterial stiffness is a risk factor for CVD, which has raised an increased interest, however not evaluated in population based studies of COPD.

Aim

The overall aim was to describe cardiovascular aspects on COPD, with a specific focus on arterial stiffness, prevalence and prognostic impact of ischemic ECG abnormalities and prolonged QT interval, by comparing subjects with and without obstructive lung function impairment in a population-based cohort.

Methods

The thesis is based on the Obstructive Lung Disease in Northern Sweden (OLIN) COPD study; a population-based longitudinal cohort study. During the years 2002-2004, all participants in clinical examinations from previously recruited large population-based cohorts were invited to re-examination including spirometry and a structured interview. All subjects with obstructive lung function impairment (n=993) were identified, together with 993 age and sex-matched referents without airway obstruction. The study population (n=1986) has been invited to annual examinations since 2005 including spirometry and structured interview. Papers I-III are based on data from 2005 when electrocardiogram (ECG) was recorded in addition to the basic program. All ECGs were Minnesota coded and QT-time was measured. Paper IV is based data from 2010 when non-invasive measurements of arterial stiffness, assessed as pulse wave velocity (PWV), was added to the program. Spirometric
data were classified as normal lung function (NLF), restrictive spirometric pattern (RSP) and airway obstruction (COPD). The following spirometric criteria for COPD were used: post-bronchodilator FEV1/VC<0.70 (papers I-IV, in paper III labelled GOLD-COPD) and lower limit of normal, LLN (LLN-COPD) (paper III). Spirometric classification of COPD severity was based on FEV1 % predicted as a continuous variable or according to the Global Initiative for Obstructive Lung Disease (GOLD), divided into GOLD 1-4.

Results

The prevalence of ischemic heart disease (IHD), both self-reported and assessed as probable and possible ischemic ECG abnormalities (I-ECG) according to the Whitehall criteria, was similar among subjects with NLF and COPD. The prevalence of both self-reported and probable (I-ECG) according to Whitehall increased by GOLD grade. Among those with COPD, self-reported IHD was associated with disease severity, assessed as FEV1 % predicted also after adjustment for age and sex (paper I).

In both COPD and NLF, those with I-ECG had a higher cumulative mortality over 5 years than those without I-ECG (29.6 vs. 10.6%, p<0.001 and 17.1 vs. 6.3 %, p=0.001). When analysed in a multivariate model, the Mortality Risk Ratio (MRR, 95%CI) was increased for subjects with COPD and I-ECG (2.4, 1.5-3.9), and non-significantly so for NLF with I-ECG (1.65, 0.94-2.90), when compared to NLF without I-ECG. When analyzed separately among subjects with COPD, the increased risk for death associated with I-ECG persisted independent of age, sex, BMI-class, smoking habits and disease severity assessed as FEV1 % predicted (1.89, 1.20-2.99). The proportion without reported IHD was high among those with I-ECG; 72.4% in NLF and 67.3% in COPD. The pattern was similar also among them; I-ECG was associated with an increased risk for death in COPD and non-significantly so in NLF (paper II).

Mean corrected QT-time (QTc) and prevalence of QTc prolongation was higher in RSP than NLF but similar in NLF and GOLD-COPD. The prevalence of borderline as well as prolonged QTc increased by GOLD grade (test for trend p=0.012 for both groups). Of those with GOLD-COPD, 52% fulfilled the LLN-criterion (LLN-COPD). When comparing LLN-COPD and NLF, the pattern was similar as when comparing NLF and GOLD-COPD. The cumulative mortality over 5 years was higher among subjects with borderline and prolonged QTc than those with normal QTc in subjects with GOLD-COPD and LLN-COPD but not in NLF and RSP (paper III).
Arterial stiffness, assessed as PWV, was higher in GOLD 3-4 compared to non-COPD (10.52 vs. 9.13 m/s, p=0.042). Reported CVD and age >60 were both associated with significantly higher PWV in COPD as well as in non-COPD. In a multivariate model, GOLD 3-4 remained associated with higher PWV when compared with non-COPD, also when adjusted for sex, age group, smoking habits, blood pressure, reported CVD and pulse rate (paper IV).

**Conclusion**

In this population-based study, the prevalence of ischemic ECG abnormalities was similar among subjects with normal lung function and COPD, but increased by disease severity among subjects with COPD. Ischemic ECG abnormalities were associated with an increased mortality among subjects with COPD, independent of common confounders and disease severity, also among those without known heart disease. Whilst the prevalence of QTc prolongation was similar in NLF, COPD and LLN-COPD, it was associated with an increased mortality only in the COPD-groups. ECG is a simple non-invasive method and seems to identify findings of prognostic importance among subjects with COPD. Central arterial stiffness, a known risk factor for cardiovascular disease, was increased among subjects with severe and very severe COPD when compared to subjects without COPD independent of common confounders.
Enkel sammanfattning på svenska

Bakgrund

Kroniskt obstruktiv lungsjukdom (KOL) är en av våra folksjukdomar som förekommer hos cirka 10% av befolkningen. KOL är en underdiagnostiserad sjukdom, man räknar med att enbart cirka var tredje individ av alla med KOL är identifierade inom hälso- och sjukvården. De främsta riskfaktorerna för KOL är tobaksräkning och stigande ålder. Hosta, slem och andfåddhet är vanliga symtom, och vid misstanke om KOL skall man göra lungfunktionsmätning. Hos personer med KOL visar lungfunktionsmätning luftvägsostruktions, d.v.s., förträngning av luftrören. KOL klassificeras enligt de internationella GOLD-riktlinjerna i fyra svårighetsgrader; 1) lindrig, 2) medelsvår, 3) svår och 4) mycket svår sjukdom. KOL-sjukdomen kan inte botas, men den kan behandlas. Rökstopp är den absolut viktigaste åtgärden, och läkemedelsbehandling kan lindra symtom samt förebygga försämringsperioder. Personer med KOL har ofta även andra sjukdomar, så kallad komorbiditet, där de vanligaste är hjärt-kärlsjukdomar och cancer. KOL är den fjärde vanligaste dödsorsaken i världen, och hjärtskjukdomar bidrar troligen till den ökade dödligheten hos dem med KOL. Bland hjärtskjukdomar vid KOL är ischemisk hjärt sjukdom (kransväderpunktsjukdom) den vanligast förekommande. För att kunna behandla ischemisk hjärt sjukdom på ett effektivt sätt måste den upptäckas i tid. EKG är en enkel och för patienten smärtfri undersökning där man kan upptäcka störningar i hjärtatets retledningssystem och ischemi (syrebrist) i hjärtmuskeln. Till följd av underdiagnostiken av KOL är kunskapen dock begränsad vad gäller både förekomst av EKG-förändringar och om EKG-förändringar har någon betydelse för prognosen hos personer med KOL. Förstyrvning av de stora artärerna i kroppen, så kallad artærystyvhet eller arterial stiffness, är en känd riskfaktor för utveckling av hjärt- och kärlsjukdomar. Kärlstyvhet har med åren väckt ett ökat intresse, men har inte tidigare studerats bland KOL i någon befolkningsstudie. På grund av den betydande underdiagnostiken av KOL är befolkningsstudier nödvändiga för att kunna öka kunskapen om riskfaktorer för, förekomst av och prognos vid hjärt- kärlsjukdomar hos personer med KOL.
Syfte med studien

Det överbegripande syftet med avhandlingen var att i en beskriva kardiovaskulära aspekter på KOL, med specifikt fokus på artärstryhett, förekomst och prognostisk betydelse av ischemiska EKG-förändringar samt förlängd PQ-tid, genom att jämföra personer med och utan KOL i en befolkningsstudie.

Metod


Resultat

Delstudie I

Ischemisk hjärt sjukdom (IHD), både självrappor terad och baserat på EKG-fynd enligt minnesotakodning var lika vanligt bland personer med NLF och KOL, men förekomsten ökade med ökad svårighetsgrad av KOL. Bland
personer med KOL ökade förekomsten av självrapporiterad IHD med svårighetsgrad av KOL oberoende av ålder och kön.

**Delstudie II**

Både personer med KOL och NLF som hade ischemiska förändringar på EKG enligt minnesotakodning (I-ECG) hade en högre dödlighet (mortalitet) under en femårsperiod än dem som inte hade I-ECG (29.6 vs. 10.6%, p<0,001 och 17.1 vs. 6.3 %, p=0,001). Den ökade risken för död bland personer med KOL och I-ECG jämfört med NLF utan I-ECG var statistiskt säkerställd och oberoende av ålder, kön, rökvanor och BMI. Risken var även förhöjda för personer med NLF och I-ECG, men var inte statistiskt säkerställd. Vid analyser enbart bland personer med KOL hade de med I-ECG ökad risk för död oberoende av ålder, kön, BMI-grupp, rökvanor och svårighetsgrad av KOL. Det var en hög andel personer utan tidigare rapporterad ischemisk hjärt sjukdom bland den som hade ischemiska EKG-förändringar, 72.4% bland dem med NLF och 67.3% bland dem med KOL. Även bland dessa individer var mönstret detsamma, I-ECG var förknippat med en signifikant ökad risk för död bland dem med KOL, medan den ökade risken bland NLF inte var statistiskt säkerställt.

**Delstudie III**


**Delstudie IV**

Arteriell kärlstyvhet, definierat som PWV, var högre hos personer med svår och mycket svår (GOLD 3-4) jämfört med personer utan KOL (10,52 m/s jämfört med 9,13 m/s). Både bland dem med och utan KOL hade de med självrapporiterad hjärtkärlsjukdom och ålder över 60 år högre PWV. Svår och mycket svår KOL (GOLD 3-4) hade högre PWV än dem som inte hade KOL,
oberoende av ett flertal andra olika riskfaktorer såsom åldersgrupp, kön, rökvanor, blodtryck, självrapporterad hjärtkärlsjukdom och pulsfrekvens.

**Sammanfattning**

Denna avhandling visar att ischemisk hjärt sjukdom och ischemiska EKG-förändringar var lika vanligt bland personer med normal lungfunktion och personer med KOL, men andelen med ischemisk hjärt sjukdom och EKG-förändringar ökade med svårighetsgrad av KOL. Ischemiska EKG-förändringar ökade risken för död bland personer med KOL, oberoende av svårighetsgrad av KOL och ett flertal andra riskfaktorer. Även personer utan känd hjärt sjukdom, men med ischemiska EKG-förändringar, hade en ökad risk för död. Förlängd QTc var vanligare bland RSP än NLF men lika vanligt bland NLF och KOL. och andelen med förlängd QTc ökade med svårighetsgrad av KOL. Bland dem med KOL, men inte bland dem med RSP eller NLF, hade de med förlängd QTc högre dödlighet än dem med normal QTc. EKG är en enkel diagnostisk metod som förefaller kunna identifiera förändringar som har betydelse för prognosen vid KOL. Arteriell styvhet var ökad hos personer med svår och mycket svår KOL jämfört med personer utan KOL, oberoende av ett flertal andra riskfaktorer.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>Angina pectoris</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CABG</td>
<td>Coronary artery bypass graft</td>
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<td>CHF</td>
<td>Chronic heart failure</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume during 1 second</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>GOLD</td>
<td>Global initiative for chronic obstructive lung disease</td>
</tr>
<tr>
<td>I-ECG</td>
<td>Ischemic ECG abnormalities</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
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<td>LLN</td>
<td>Lower limit of normal</td>
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<td>LQTS</td>
<td>Long QT syndrome</td>
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<td>MC</td>
<td>Minnesota code</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
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<td>NLF</td>
<td>Normal lung function</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity</td>
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<td>QT</td>
<td>Interval between the start of the Q-wave and end of the T-wave</td>
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<td>QTc</td>
<td>Heart-rate-corrected QT-interval</td>
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<tr>
<td>RR</td>
<td>Interval between the peak of one QRS complex to the next</td>
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<tr>
<td>RSP</td>
<td>Restrictive spirometric pattern</td>
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<td>SVC</td>
<td>Slow vital capacity</td>
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<tr>
<td>TdP</td>
<td>Torsade de Pointes</td>
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<td>VC</td>
<td>Vital capacity</td>
</tr>
</tbody>
</table>
Original papers


Preface

This thesis is about cardiovascular disease in chronic obstructive pulmonary disease. In my clinical role as a Registered Nurse working in a cardiac care unit for more than 18 years, I have met numerous patients with cardiovascular disease and concomitant pulmonary diseases. When the opportunity to start an epidemiological PhD research project involving heart and lung was given, it presented an opportunity to take a step back from the individual patient care to gain a broader perspective.

As a nurse in the clinical setting, focus is always on the whole patient, to treat each patient as an individual, with his or her specific needs and health in focus. In epidemiology, focus is not on the individual, but on the population. This may sound contradictory for a nurse, but the tools within epidemiology have an important role to play within nursing, as well as in medicine, to create an understanding for public health challenges, prevention of disease and how to promote health in a broader sense. As a matter of fact, one of the first epidemiologists, and the one who introduced advanced graphs in presentation of statistical data, was a not totally unfamiliar British nurse, Florence Nightingale.

Cardiovascular disease is a broad term covering several different diseases and conditions. In this thesis, the focus is set on electrocardiographic abnormalities; findings related to ischemic heart disease and prolonged QT-interval, along with measurements of arterial stiffness. The basis of this thesis is an epidemiological study on chronic obstructive pulmonary disease, COPD. With my background in cardiology, and to highlight the cardiovascular aspects, the cardiovascular areas of interest are presented ahead of the pulmonary.
Introduction

Historical perspective

The development of modern medicine has a long and winding history. This section will give a short historical background in relation to the current topics.

Ischemic heart disease

The oldest known findings of ischemic heart disease date 3,500-4,000 years back in time and were found when CT-scans were performed on mummies (1, 2). It was not until the late 15th century that the exploration of human anatomy began by, among others, Leonardo Da Vinci. William Harvey, a British physician, is credited with the discovery of the circulation of blood through the heart and lungs during the 18th century (3). William Hebeerden was in the mid-18th century the first to describe the classical symptoms of angina pectoris, i.e. stress-triggered central chest pain, but the understanding of the angina symptoms remained unclear until James B Herrick in 1919 concluded that the narrowing of coronary arteries may cause the symptoms.

Electrocardiogram and the Minnesota code

The Dutchman Wilhelm Einthoven received the Nobel Prize in 1924 for the invention of the electrocardiogram (ECG). The ECG revolutionized the diagnostics of cardiac disease, especially ischemic heart disease, early in the 20th century (4). ECG made it possible to detect both disturbances in the electric conduction system and ischemia, and is still a major diagnostic tool in clinical cardiology. Since the 1970s, ECG is also frequently used in clinical and epidemiological studies, thanks to the development of a standardized classification system presented during the 1960s. This system developed over the years, and the first version of The Minnesota Code Manual of Electrocardiographic Findings was published in 1982 (5). The Minnesota code (MC) makes it possible to compare and quantify standardized ECG abnormalities between individuals and groups, and also to follow the dynamics of ECG abnormalities over time (5).

Prolonged QT interval

Although the ECG was invented late in the 19th century and further developed and fine-tuned ever since, it was not until half a century later that prolongation of the QT-interval attracted attention. Whilst recognized early in the ECG-era, QT was first considered as of minor importance. In 1957 Jervell
and Lange-Nielsen described a family where four out of six children had fainting attacks, deafness and prolonged QT interval related to sudden death (6). This hereditary combination of symptoms was later labelled Jervell-Lange-Nielsen syndrome. During 1963 and 1964, Romano and Ward independently described children without deafness, but with fainting attacks, prolonged QT intervals and sudden death (7, 8). This hereditary combination was later labelled the Romano-Ward syndrome. The discovery of the rare hereditary long QT syndrome (LQTS) puts the focus on prolonged QT per se. In the population, different causes of acquired prolonged QT have been described over the years, for example increasing age, structural heart disease and different drugs (9, 10).

**Arterial stiffness**

The exploration of the blood vessels function began around 1710 when Stephen Hales made experiments measuring blood pressure on his horse. The development of technical devices to register the arterial pulse waves started in Europe from mid nineteenth century and continued until the Second World War. After the war, the interest for arterial haemodynamics continued, but at this time mainly in the US. The development was in the beginning driven by physiologists, but later, when the potential clinical use of arterial stiffness was recognised, also clinicians became involved (11).

**Chronic obstructive pulmonary disease**

In 1679, when the Genevan physician Bonet documented findings of “voluminous lungs” found during autopsy studies, he was one of the first to describe what would later be labelled emphysema (12). Almost ninety years later, in 1767, the anatomist Morgagni described the lungs of a deceased 40-year old man as “very turgid with air” and having black spots here and there (13, 14) In 1793, Baillie documented observations from a post mortem examination of a deceased man with a long history of difficulty breathing (15):

“....The lungs are sometimes, although I believe very rarely, formed into pretty large cells, so as to resemble somewhat the lungs of an amphibious animal. These cells, in the only instance which I have seen of this disease, were most of them of the size of a common garden pea, and some few were so large as to be able to contain a small gooseberry.....”

Later, after more observations, he related these “cells” to accumulation of air in the lungs, which could lead to further increase in the size of the “cells”.
One of the first written descriptions of inflammatory symptoms in the airway was made by Sydenham in 1683 (16). In 1800, Cullen tried to systematically summarize a definition of the previous fragmented descriptions of a condition called "dyspnæa catharralis"; frequent coughing that brings up mucus from the airways (17). The physician Badham in London was, in 1814, the first to use the term bronchitis for the previously more or less anecdotal descriptions of inflammation in the airways (18).

In 1821, Laennec, the inventor of the stethoscope, gave a detailed description of the auscultatory findings of the emphysematic lung. He also concluded that there was a connection between findings of “catarrh”, sputum, in the small airways and the development of emphysema (19).

An important landmark for the understanding and diagnosis of respiratory diseases was reached on May 29, 1844, when John Hutchinson for the first time demonstrated his invention, the spirometer, at the Society of Arts in London. The demonstration was mentioned in the June issue of The Lancet the same year, but it took a long time for the spirometer to become a diagnostic tool in clinical practice (20). At first, it was only used to measure slow vital capacity. Approximately 100 years later, the French inventors Tiffenau and Pinelli further developed the use of the spirometer by adding forced expiratory volume in 1 second (FEV1) and the forced vital capacity (FVC) (21). These measurements became pivotal in the diagnostics of several respiratory conditions, including obstructive pulmonary diseases.

For many years there was no real consensus among physicians on how to clinically define emphysema and chronic bronchitis. There are two important landmarks: the CIBA guest symposium in 1959, where chronic bronchitis and emphysema were defined (22), and the American Thoracic Society Committee on Diagnostic Standards in 1962, where “excessive amounts of sputum” was added to the definition of chronic bronchitis, and further, stated that the diagnosis was prevalent provided that other respiratory conditions were excluded (23). These definitions of chronic bronchitis and emphysema are still in use today. However, the term Chronic Obstructive Pulmonary Disease (COPD) was not used at these meetings. The first time COPD is believed to have been used was by William Briscoe at the ninth Aspen Emphysema Conference in 1965 (24).


Overview of cardiovascular disease and COPD

In this section, terminology/definitions, pathophysiology and epidemiology will be briefly described for the cardiovascular aspects of interest, and COPD.

Ischemic heart disease

Terminology/definitions

Ischemic Heart Disease (IHD), or Coronary Artery Disease (CAD), includes stable angina pectoris and acute coronary syndromes. Acute coronary syndromes by definition include unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) (25). Ischemic heart disease is a common cause of heart failure, especially in the western world (26). ECG is a simple non-invasive diagnostic method, and is, together with other clinical examinations, an important tool for detection and monitoring of myocardial ischemia (27).

Pathophysiology

Ischemic heart disease may be acute or chronic. Chronic IHD is characterized by stable symptoms over the course of months or years. It can be the first emerging sign of IHD, or it can be the residual symptom after an acute event. Ischemic heart pain, known as angina pectoris, is the most common symptom related to IHD. Angina pectoris is the result of transient episodes of myocardial ischemia. This is usually caused by the presence of arterial calcifications and stenoses that reduce the supply of oxygenated blood in relation to the oxygen demand in the coronary muscle (27). Pain is a late symptom of myocardial ischemia, but myocardial ischemia can also be present without any experienced pain, “silent ischemia” (28). In rare cases the blood flow can also be reduced by transient vasospastic constriction (27). Another cause of stable angina may be ischemic cardiomyopathy. Important risk factors for angina include smoking, obesity, hypertension, dyslipidaemia and diabetes (29). The underlying pathophysiological mechanisms including changes in the myofibres polarization, changed direction of repolarization and myocardial necrosis are associated with characteristic ischemic ECG abnormalities (30).

Epidemiology

Cardiovascular diseases (CVDs) cause more than 3.9 million deaths in Europe each year, whereof 1.8 million within the EU, making them the leading cause
of mortality (31). Within Europe there is a substantial variation; the burden of CVD is higher in central and eastern countries compared to northern, western and southern countries. The most common form of CVD is IHD. In 2015, the incidence of IHD in Europe was 5.75 million cases, whereof 2.97 million among men (31). In Sweden, the annual incidence of acute myocardial infarction in 2015 was 27,932 cases, whereof, 61% men (32). The mortality caused by IHD the same year was 124/100,000 inhabitants, to be compared to an all over mortality of 929/100,000 (33). However, according to the WHO MONICA project in northern Sweden, a decrease has been observed in diagnosed myocardial infarction events from 1985 and the following 20 years (34).

**QT-interval**

**Terminology/definitions**

The QT-interval represents the duration of the electric depolarization and repolarization of the ventricles in the heart to be completed. A prolonged QT interval correlates to a prolongation of ventricular repolarization, which results in an increase in the absolute refractory period and may be potentially arrhythmogenic, in its worst form leading to sudden death by a polymorph ventricular tachycardia, Torsade de Pointes (TdP) (35). The QT-interval is measured from the beginning of the Q-wave until the point where the end of the T-wave reaches the isoelectric line (figure 1). The QT-interval is related to the heart rate, defined as the interval between the R-waves (R-R interval) in the same lead as the QT-interval is measured. To compensate for this variability, the QT can be corrected for heart rate; corrected QT or QTc, using one of several existing formulas. The most commonly used formulas are the Bazetts (36) and Fridericias (37). These can be used in parallel, since the Bazetts formula can give inaccurate results at slow heart rates, <60 bpm (overcorrection) and fast heart rates, >90 bpm (under correction), and the Fridericia formula may be more correct at fast heart rates (38).
Pathophysiology

The QT-interval on the ECG is a graphic presentation of the cardiac ventricles’ depolarization and repolarization in the myocardium over time. The QT-interval is determined by the excitation time and the duration of the action potential of the myocytes in the ventricular region that repolarize last.

In a cardiac muscle cell, there is a potential gradient across the cell membrane called the resting potential. This gradient is caused by the predominance of extracellular Na\(^+\) ions, and the predominance of intracellular K\(^+\) ions leading to a negatively charged inside of the cell membrane compared to the outside. The action potential is divided into five phases (0-4) (figure 2), and made possible by transient ionic currents through ionic channels in the myocyte cellular membrane. The action potential is generated by the opening of voltage-gated sodium channels that allow Na\(^+\) ions to enter fast through the cell membrane. This results in a quick depolarization (phase 0) of the cell, during which the cell goes from a negative to positive charge. Immediately after depolarization, Na\(^+\) channels are closed and voltage-gated potassium channels open, allowing K\(^+\) ions out of the cell (phase 1). Slightly after, the slower working calcium channels open, letting Ca\(^{2+}\) ions into the cell, which prolong the positively charged phase (phase 2). When Ca\(^{2+}\) channels are closed, and K\(^+\) ions continue to diffuse from the cell, repolarization begins (phase 3). The end of phase 3 concludes when the action potential of the cell reach its resting potential (phase 4). The refractory period, which includes phases 0-3, must be completed before the muscle can be stimulated again (38).
Long QT syndrome (LQTS) can be congenital or acquired. LQTS is a result of a prolongation of the excitation time and/or the duration of the action potential in the ventricular muscle. In its congenital form, it can be hereditary or idiopathic. There are several different genetic mutations that can cause LQTS; mutations in genes connected to potassium and sodium channels representing more than 90% of LQTS mutations (39). Acquired prolonged QT may have several different causes, whereof drug-induced is the most common (40). Antiarrhythmic drugs, but also a large spectrum of non-cardiac drugs, may cause drug-induced prolonged QT. A frequently updated evidence-based list of drugs affecting QT may be found at http://www.crediblemeds.org.

![Figure 2. Phases of the cardiac action potential.](image)

**Epidemiology**

Prolonged QT is a condition that often goes without presenting any symptoms and therefore remains undetected. When clinical symptoms occur, they appear instantly and often lead to sudden death. Prolonged QT has over time been considered an extremely rare condition. With increased awareness and screening, the prevalence is estimated to rise, although prevalence estimates of QT prolongation vary greatly depending on characteristics of the study population, type of ECG recording, procedure of measurement, type of heart rate adjustment formula and the cut-off values used. The QT-interval is longer among females, caused by a QT shortening among men during puberty (41), therefore different cut-off values are commonly used for men and women.

The prevalence of congenital QT prolongation is estimated at 1:2,000. In a study on 43,080 infants, n=28 (0.06%) had a QT between 460 and 470 ms and n=31 (0.07%) had a QT >470 ms (42).
Prevalence and incidence of acquired LQTS have rarely been described. A QT-interval >500 ms is associated with ventricular arrhythmias, most frequently Torsade de Pointes (TdP), which may lead to recurrent syncope or sudden death. TdP is a rare condition and drug-induced TdP prevalence in the general population is hard to determine (43). Due to the rapid onset and fatal progress, it is most probably largely underreported. However, there have been reports of approximately 1:700 cases of TdP in the Swedish pharmacovigilance database. Of the total 88 TdP-cases, 74% involved cardiac drugs (44).

**Arterial stiffness**

**Terminology/definitions**

Increased central arterial stiffness has long been considered an early marker of atherosclerosis (45), and increased arterial stiffness is associated with cardiovascular mortality (46). There are a number of different methods to assess stiffness of the arteries in humans. Each method tries to find a surrogate measure for the arterial compliance in the aorta; Augmentation Index (AIx), Systemic Arterial Compliance (SAC), Stiffness Index (SI) and Pulse Wave Velocity (PWV).

\[
PWV = \frac{\Delta L}{\Delta t}
\]

*Figure 3.* The formula for calculating crude pulse wave velocity (PWV).

Carotid-femoral PWV is considered to be a reproducible method and it is the ‘gold standard’ for estimating arterial stiffness (47). PWV consists of two entities, \(\Delta L\) and \(\Delta t\). The first, \(\Delta L\), is the anatomical distance between measuring sites of the carotid and femoral arteries. The second, \(\Delta t\), is the pulse transit time (figure 3). The pulse waves used for calculation of the PWV are the mean waves based on a series of consecutive registered waves. The \(\Delta t\) is the time in between the carotid and femoral pulse waves, and is measured at the foot of each pulse wave. There was no established standardized method for measuring PWV, until 2012, when an expert consensus of a standardized measurement method was published (47).
Pathophysiology

The pathophysiological mechanisms behind arterial stiffness are many and complex. This section will only provide a brief introduction.

The large arteries consist of three main layers of elastic tissue. The thin inner layer, the intima, is made up of endothelial cells. The second layer, the media, is the thickest layer and consists of elastin, smooth muscle cells and collagen. The third and outermost layer, the adventitia, is a thin layer of collagen fibres, blood vessels and nerves (11). The elastic features of the arteries make them compliant to blood pressure changes; they expand during systole, and recoil in diastole, helping to propel the blood further towards peripheral arteries. At lower pressures, the distension takes place in the flexible elastin fibres, while with higher pressures, and by that a wider distension, gradually more tension is put on the stiffer collagen fibres (48). Arterial walls naturally get stiffer with aging, due to several structural and mechanical changes in the arterial wall (49). This leads to a gradually increasing speed of the reflecting wave. Until the ages of 50-60 years, the reflecting wave reaches the heart in diastole. With increased velocity, due to stiffer arteries, the wave is gradually reflected toward the heart at an earlier time of the cardiac cycle, i.e. in systole. This phenomenon puts even more strain on the arterial wall with more tension on collagen fibres, and elevates the systolic pressure (11).

There are many different possible mechanisms behind the development of arterial stiffness. One central cause is hypertension, which in itself can be caused by different complex mechanisms. Systemic inflammation is associated with arterial stiffness and may be involved in the pathophysiological mechanisms. Also elevated serum levels of metalloproteinases (MMPs) -2, 9 and 12 have been shown to independently correlate with increased arterial stiffness, probably due to their ability to degrade extracellular matrix, for example elastin (50-52).

Epidemiology

Increased central arterial stiffness is, as discussed above, considered an early marker of atherosclerosis (45) and has been associated with an increased risk for cardiovascular events and mortality (53). Furthermore, it is considered an important independent predictor for hypertension, ischemic heart disease (54) and cardiovascular mortality (46). It is difficult to find epidemiological data on arterial stiffness, but reference values for PWV, based on data from subjects without hypertension and other cardiovascular risk factors from eight European countries, were published in 2010 (55). In June 2015, the application of these normal values in a Portuguese population were published
(56), and a higher proportion than expected, every third subject among those aged 40 and below, had signs of early vascular aging.

Chronic Obstructive Pulmonary Disease

Terminology/definitions

Spirometry and spirometric classification of COPD

One of the cornerstones in the definition of COPD is airflow limitation due to airway obstruction. There have been several different definitions of airway obstruction over the years, but they have some common traits; the use of the ratio between FEV₁ as numerator and SVC, FVC or VC as denominator.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria, a post-bronchodilator fixed ratio FEV₁/FVC<0.70, was launched in 2001, and is the same in all subsequent updates of the document (57). The fixed ratio is a generally accepted definition of airway obstruction in the clinical settings. However, a fixed ratio will overestimate airway obstruction among elderly, and may underestimate COPD in younger people (58, 59). In 2005, and with a follow up in 2011, a ERS Task Force published guidelines recommending the Lower Limit of Normal (LLN) criteria for epidemiological research, which set the cut-off at a post-bronchodilator ratio of FEV₁/FVC below the fifth percentile of the reference value (60, 61). Since the outcome of LLN is dependent of reference values, it is important that the reference values used are representative for the population under study (62).

Reference values

Reference values have traditionally been used to define the degree or the severity of lung function impairment. Several different sets of reference values have been presented over the years. The European Coal and Steel Community reference values (63) have commonly been used throughout Europe until 2012, when the ERS taskforce the Global Lung function Initiative (GLI) presented their multi-ethnic reference values (64). The use of the GLI reference values is now endorsed by several respiratory societies.

Besides international reference values, there are also numerous national and regional values. In Sweden two main sets have been in use; the Berglund reference values (65) which were published in the 1960s, and the Hedenström values (66, 67), introduced in 1980s. The Swedish Respiratory Society recommends the Hedenström reference values for clinical practise. In epidemiological research, it is important to use reference values
representative for the population under study. In 2015, the OLIN studies published their own set of reference values based on in total 501 respiratory healthy non-smoking Caucasians living in the county of Norrbotten, Sweden (68).

Disease severity

Assessment of COPD disease severity includes spirometric classification of airway obstruction. The spirometric classification of disease severity is most often based on FEV1 percent of predicted reference value (FEV1 % predicted), and in the GOLD document it is divided into four levels. The specific FEV1 cut-points have been the same since the first version published in 2001, and in all subsequent versions of the GOLD document (table 1), even though the nomenclature has varied; stage I, IIA, IIB and III, stage 1-4, grade 1-4 or simply GOLD 1-4. In the last updates, including the 2017-update the classification of airflow limitation in COPD is labelled GOLD 1-4 (57).

Table 1. Classification of airflow limitation severity in COPD according to GOLD.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Post-bronchodilator FEV1,</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>FEV1 ≥80% predicted</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>50% ≤ FEV1 &lt;80% predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>30% ≤ FEV1 % &lt;50% predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>FEV1 ≤30% predicted</td>
</tr>
</tbody>
</table>

Besides spirometric classification of airflow limitation, assessment of disease severity is also based on burden of respiratory symptoms, exacerbations and comorbidities. There are validated questionnaires for assessment of symptoms. The most commonly recommended are the modified Medical Research Councils (mMRC) scale (0-4) for assessment of dyspnoea (69), and the COPD Assessment Test (CAT) for assessment of burden of symptoms (70), but there are also other questionnaires, for instance the Clinical COPD Questionnaire (CCQ) (71).

Pathophysiology

COPD is characterized by an irreversible airway obstruction and an enhanced inflammatory response to airway irritants; particles and gases, for example
from combustion of biomass fuel, and tobacco smoking, where the latter is of particular importance for development of COPD (57).

Tobacco smoke causes inflammation, oxidative stress and an imbalance of protease and antiprotease in the airways of all smokers. Oxidative stress contributes to an imbalance of proteases and antiproteases by stimulating increased release of proteases, for example several MMP:s and/or an inactivation of antiproteases, for example alpha 1-antitrypsin. This leads to destruction of lung tissue (72). There are also rare cases of inherited lack of anti-protease, such as Alpha-1-antitrypsin deficiency, associated with emphysema (73).

These pathological processes lead to physiological manifestations such as increased mucus secretion (bronchitis) and parenchymal destruction (emphysema). The inflammation is also manifest in the small airways, causing bronchiolitis and narrowing of the airways. The destruction of alveolar walls also leads to loss of the lungs’ elastic recoil. The following obstruction of airways leads to air trapping during expiration, causing hyperinflation. The hyperinflation reduces the inspiratory capacity in the lungs which causes breathlessness and reduces exercise capacity.

**Epidemiology**

Accurate morbidity data on COPD are difficult to obtain, mostly due to diversity in definitions, and a massive under diagnosis. Under-diagnosis is common, especially during earlier stages of disease, when symptoms can go undetected or are not perceived as signs of a disease (74, 75). Some reports are based on symptoms, others on physician diagnosis or spirometric data. Still, when prevalence estimates are based on spirometry, the results are dependent on if the procedure is performed pre- or post-bronchodilation, and also on the used definition of airway obstruction, the fixed ratio or the LLN.

The most important predictors of COPD prevalence are age and smoking habits of the population under study, together with the used spirometric criterion. The prevalence increases by age, up to 50% of elderly smokers fulfil the spirometric criteria for COPD (76). Also, second hand smoking is associated with COPD (77), and globally exposure to biomass fuel combustion for cooking and heating purposes are other important risk factors. The prevalence of COPD ranged between 10-25% between study centres in the multinational Burden of Obstructive Lung Disease (BOLD) study (78). However, when using the LLN spirometric criteria instead of the fixed ratio, the prevalence was reduced by 30-50% (79). Furthermore, using pre- instead
of post-bronchodilator spirometry will increase the prevalence by roughly 25% (80).

The under diagnosis of COPD is substantial, and varies globally (81). In Sweden, it has been estimated that approximately every third individual with COPD has been identified by health care (82). However, recent data from the OLIN studies indicate that the under diagnosis may have decreased, especially among those with severe and very severe disease (83).

In 2014, COPD was the fourth leading cause of death globally according to WHO, and is estimated to become the third leading cause by 2030 (84). Since co-morbidities are common in COPD, misclassification of causes of COPD-related death will, together with under diagnosis, lead to an underestimation of the burden of mortality among subjects with COPD (85). Due to the under diagnosis, epidemiological studies are necessary to understand the true burden of COPD in the society.

**Cardiovascular comorbidity in COPD**

**Pathophysiology**

COPD and CVD share common risk factors as age and smoking. The pathophysiological connection between COPD and CVD is complex and largely unknown. Both conditions have an inflammatory component and systemic inflammation has been suggested as a common link (86, 87). In COPD, the local airway inflammation is believed to spill over to create a systemic inflammation that involve, amongst all, TNF-α and IL-6, which in turn may trigger atherosclerosis and coronary artery disease (88). The local process in the lungs with MMPs breaking down the elastin in pulmonary tissue has also been suggested to spill over to a systemic inflammatory process leading to degradation of elastin in the arterial walls, and thereby causing increased arterial stiffness.

A few studies have addressed the pathophysiological connection between prolonged QT-interval and COPD. It has been suggested that the autonomic neuropathy related to lung disease and hypoxia, may affect the duration of cardiac repolarization, which is reflected by a prolonged QT-interval (89, 90).

**Epidemiology**

Comorbidities are common in COPD. CVD is the most common, and may amount up to 70% of the total burden of comorbidities (91). CVD most probably also contribute to the increased mortality observed among subjects
with COPD (91). Among cardiovascular diseases IHD is of specific interest, contributing to > 7.5 out of the estimated 17 million deaths in 2012 according to WHO (84).

In a review published in 2015, 29 studies describing different aspects of prevalence and/or incidence of cardiovascular comorbidity in COPD were identified. Only eight of these studies were population-based, and used spirometric classification of COPD (92). In two of these studies the prevalence of IHD was reported; in the Copenhagen City Heart Study, the prevalence was 14%, based on ischemic ECG abnormalities (93), and in the geriatric population of the SaRA study, the prevalence of IHD was 15%, based on interview data (94).

Most guidelines for diagnostics and treatment of COPD recommend that you should consider concomitant cardiovascular disease. ECG is a simple and cheap diagnostic tool in the diagnosis of heart disease, including assessment of arrhythmias, ischemic abnormalities and also measurement of QT interval. However, to the best of our knowledge there are no previous population-based studies evaluating the prevalence and the prognostic impact of ischemic ECG abnormalities and/or QT-interval among subjects with COPD, defined by post-bronchodilator spirometry.

Increased arterial stiffness is a well-known marker of atherosclerosis and a risk factor for cardiovascular diseases, not least IHD (45). Studies on selected COPD populations indicate that arterial stiffness is increased among subjects with mainly severe and very severe COPD (95, 96). When identifying risk factors of cardiovascular disease among subjects with COPD, it has even been suggested that non-invasive measurement of arterial stiffness should be implemented in daily clinical practise (97). However, there is a lack of population-based studies on arterial stiffness in COPD.

It has been suggested that individuals with COPD may have an altered cardiac repolarization, which may cause a prolonged QT-interval. Among 91 subjects with COPD, a third had a prolonged QTc compared to 12.5% among matched controls (90). In a recently published population-based study, 218 subjects with COPD were included. Those with COPD had a non-significantly increased risk for prolonged QTc when compared to those without (OR 1.84, 95% CI 0.94-3.62) (98). Still, there is limited population-based data on the prevalence and clinical impact of prolonged QTc in COPD.
Aims of the thesis

The overall aim was to describe cardiovascular aspects on COPD, with a specific focus on arterial stiffness, on prevalence and prognostic impact of ischemic ECG abnormalities and prolonged QT interval, by comparing subjects with and without obstructive lung function impairment in a population-based cohort.

Specific aims in the papers I-IV are as follows:

I. To estimate the prevalence of self-reported ischemic heart disease and ischemic ECG changes among subjects with COPD, and by COPD disease severity in comparison with subjects without obstructive lung function impairment, divided into normal lung function and restrictive pattern on dynamic spirometry.

II. To assess the impact of ischemic ECG abnormalities on long term mortality among subjects with COPD compared to subjects with normal lung function.

III. To estimate the prevalence of prolonged QTc among subjects with normal lung function, airway obstruction based on the fixed ratio (GOLD) and LLN criteria, and restrictive pattern on dynamic spirometry. A secondary aim was to evaluate if QTc was associated with prognosis, assessed as mortality over a five-year period, in any of the groups.

IV. To analyse cross-sectional data for comparison of central arterial stiffness measurements in subjects with and without COPD and also in relation to COPD disease severity. A secondary aim was to evaluate whether productive cough was associated with increased central arterial stiffness.
Materials and methods

Study design

The OLIN studies

The Obstructive Lung disease In Northern Sweden (OLIN) studies are an epidemiological research program ongoing since 1985 in Norrbotten, the northernmost county in Sweden. Over the years, several cohorts have been identified and followed longitudinally; in total approximately 60,000 persons, from children to elderly living in the county of Norrbotten, have participated in postal questionnaire surveys and clinical examinations. The OLIN studies have four research programs; 1. Asthma and allergy among children, 2. Asthma and allergy among adults, 3. COPD, and 4. Health economics. This thesis is based on the longitudinal OLIN COPD study included in the COPD research program.

The OLIN COPD study

The OLIN COPD study is a prospective longitudinal population-based cohort study. In 2002-2004 all previous participants in clinical examinations from four population-based adult cohorts, whereof two including random samples, and two including age-stratified samples, were invited to re-examination. Approximately 4,200 subjects participated in examinations including amongst all structured interview and dynamic spirometry. All subjects fulfilling the spirometric criteria for obstructive lung function impairment (FEV1/VC <0.70) were identified (n=993) together with age- and sex matched referents without obstructive lung function impairment (99). The study population (n=1986) has been invited to annual clinical examinations from 2005 including structured interview, dynamic spirometry with reversibility test and questionnaires for assessment of health status. In addition to the basic program, 12 lead ECGs were recorded in 2005 and, in 2010, non-invasive measurement of central arterial stiffness was performed.
The gadgets you need when doing some serious Minnesota coding!
Figure 4. Recruitment and participation of the study population.

a Missing spirometry or ECG. b Missing PWV. c Including 36 subjects with PWV measurements from beginning of 2011.
Study population

This thesis is based on data from participants at the clinical examinations in 2005 (paper I-III) and 2010 (paper IV). Papers I and IV are cross-sectional (2005 and 2010 respectively), and papers II and III are longitudinal (follow up of mortality data from 2005 until December 31st 2010). Figure 4 presents the study population, recruitment and participation, and Table 2 presents an overview of data, definitions of spirometric classification and ECG variables used in these papers.

Data collection and definitions

Electrocardiogram

Standard 12 lead ECG’s were recorded using 25 or 50 mm/s paper speed before spirometry on subjects in supine position and after sufficient rest.

Ischemic heart disease on ECG

All ECGs were coded according to the Minnesota code (MC) by two independent coders, blinded to lung function data and medical history. The definitions of ischemic ECG abnormalities used in papers I and II are presented in table 2. In paper I, ischemic ECG-abnormalities were classified according to the Whitehall criteria (100).

QT-interval

QT-measurements were performed manually with a calliper of a 0.01 mm resolution by an observer blinded to clinical data. A second observer measured a random sample of the ECG’s, and the inter-individual agreement was considered good. Subjects were excluded if they had ECG-abnormalities which could interfere with measurements of the QT-interval; 52 subjects with atrial fibrillation (MC 8.3.1), 14 subjects with electronic pacemakers (MC 6.8) and 73 subjects with complete left- or right bundle branch block (MC 7.1.1 and 7.2.1). In another 6 subjects it was impossible to measure the QT interval due to poor-quality ECG or frequent supraventricular and/or ventricular ectopic beats). The QT interval was measured in 3 consecutive ECG complexes in lead II, V5 and V6. The mean QT-interval of each lead was calculated, and the R-R interval was measured in the lead with the longest mean QT interval. To identify the end of the T-wave, the “tangent method” was used (38, 101). Corrected QT intervals (QTc) were derived using the Bazett formula (36) for heart rates <90 bpm, and the Fredericia formula for heart rates ≥90 bpm (37).
Prolonged QTc was defined as ≥450 ms in men and ≥460 in women (102). Borderline QTc was defined as 430 - 449 ms in men and 440-459 ms in women.

**Arterial stiffness**

Central arterial stiffness was measured as pulse wave velocity (PWV) using the non-invasive Vicorder® system (Skidmore Medical Ltd., Bristol, UK). PWV was measured after 20 minutes of rest. ΔL was measured as the direct distance between the cuffs placed over arteries carotis and femoralis, with patient in supine position, and a slight head of bed elevation. Recording was performed three times within 5-10 minutes. At least two recordings within a 0.5 m/s range were required for the recordings to be considered reproducible; if not, recordings were repeated up to a total of five times. The median PWV was calculated for each individual. Blood pressure was measured manually in the left arm with the subjects in the supine position after 20 minutes of rest, prior to the measurement of PWV (figure 5).

**Figure 5.** Illustration of cuff placement for measurement of central arterial stiffness. Red line indicates ΔL.
Table 2. Presentation of papers I-IV; overview of included data, lung function classification, cardiovascular examinations and key questions at interview.

<table>
<thead>
<tr>
<th>Included data</th>
<th>Lung function classification</th>
<th>Cardiovascular examinations</th>
<th>Key interview questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examinations:</td>
<td>NLF: FEV1/VC ≥0.70 &amp; VC &gt;80%</td>
<td>ECG, Minnesota coded</td>
<td>IHD:</td>
</tr>
<tr>
<td>Cross-sectional data 2005</td>
<td>of predicted</td>
<td>Whitehall probable IHD:</td>
<td>AP, MI, CABG, PCI</td>
</tr>
<tr>
<td></td>
<td>RSP: FEV1/VC ≥0.70 &amp; VC &lt;80%</td>
<td>Major Q/QS (MC 1-1, 1-2) plus</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>COPD: FEV1/VC &lt;0.70</td>
<td>LBBB (MC 7.1.1)</td>
<td>Smoking habits</td>
</tr>
<tr>
<td></td>
<td>Disease severity:</td>
<td>Whitehall possible IHD:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GOLD stage based on FEV1 % predicted1</td>
<td>Minor Q/QS (MC 1-3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To be included in the analyses</td>
<td>ST-segment depression (MC 4-1 – 4-3 plus T-wave (MC 5-1–5-3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>participants had to fulfil same spirometric criteria at recruitment in 2002-04 and in 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference values: OLIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper II</td>
<td>NLF: same as paper I</td>
<td>ECG, Minnesota coded</td>
<td>IHD:</td>
</tr>
<tr>
<td>Examinations:</td>
<td>RSP: same as paper I</td>
<td>Major Q/QS wave: (MC 1-1, 1-2)</td>
<td>AP, MI, CABG, PCI</td>
</tr>
<tr>
<td>Cross-sectional data 2005</td>
<td>COPD: same as paper I</td>
<td>Major isolated STT abnormalities: (MC 4-1, 4-2, 5-1, 5-2)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Mortality:</td>
<td>Disease severity: GOLD stage</td>
<td>Minor Q/QS wave plus major ST-T: (MC 1-3 plus 4-1, 4-2, 5-1, 5-2)</td>
<td>Smoking habits</td>
</tr>
<tr>
<td>From examination in 2005 until 31st December 2010</td>
<td>based on FEV1 % predicted1 and FEV1 % predicted1 used as a continuous variable</td>
<td>Minor isolated Q/QS wave: (MC 1-3)</td>
<td></td>
</tr>
</tbody>
</table>
### Paper III

<table>
<thead>
<tr>
<th>Examinations:</th>
<th>ECG, measured QTc interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional data 2005</td>
<td>Prolonged QTc: &gt; 450 ms (men), &gt;460 ms (women)</td>
</tr>
<tr>
<td>Mortality:</td>
<td>Borderline QTc: 430-449 ms (men), 440-459 ms (women)</td>
</tr>
<tr>
<td>From examination in 2005 until 31st December 2010</td>
<td></td>
</tr>
<tr>
<td>NLF: same as paper I</td>
<td></td>
</tr>
<tr>
<td>RSP: same as paper I</td>
<td></td>
</tr>
<tr>
<td>COPD: same as paper I &amp; LLN¹</td>
<td></td>
</tr>
<tr>
<td>Disease severity: GOLD stage based on FEV₁ % predicted</td>
<td></td>
</tr>
<tr>
<td>Classification based on spirometry in 2005</td>
<td></td>
</tr>
<tr>
<td>Reference values: OLIN</td>
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</table>

### Paper IV

<table>
<thead>
<tr>
<th>Cross-sectional data 2010</th>
<th>Non-COPD: FEV₁/VC ≥0.70</th>
<th>Central arterial stiffness</th>
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<tbody>
<tr>
<td>COPD: same as paper I</td>
<td>Pulse wave velocity (PWV) m/s</td>
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<tr>
<td>Disease severity: GOLD stage based on FEV₁ % predicted</td>
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<tr>
<td>Classification based on spirometry in 2010</td>
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<tr>
<td>Reference values: Berglund</td>
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¹Based on best values before or after bronchodilation

Lung function tests

Lung function tests were performed in accordance with the American Thoracic Society guidelines (103), with the exception that all subjects were standing instead of sitting. Spirometry was performed following ECG registration. The spirometers used for all examinations were a set of dry volume spirometers, the Vicatext 5 (Gebr. Mijnhardt B.V., Odijk, The Netherlands) (figure 6). The spirometers were calibrated daily with a 3.0 l syringe. Vital capacity (VC) was defined as the highest value of forced vital capacity (FVC) and slow vital capacity (SVC). Reversibility test was performed with Ventoline® 4x0.2mg if FEV₁/VC<0.70 or FEV₁<80% predicted.

Based on the best values of VC and FEV₁ pre- or post-reversibility test, COPD was defined as FEV₁/VC<0.70 (papers I-IV) and by the LLN criterion, FEV₁/FVC below the fifth percentile of the reference value (paper III). Disease severity among subjects with COPD was classified according to the GOLD spirometric criteria into GOLD 1-4 based on FEV₁ % predicted (57) Non-COPD, defined as FEV₁/VC≥0.70, was further divided into normal lung function (NLF), FEV₁/VC≥0.70 and VC≥80%, and restrictive spirometric pattern (RSP), FEV₁/VC≥0.70 and VC<80%. The locally derived OLIN reference values based on respiratory healthy non-smokers (68) were used in paper I-III, while the Berglund reference values (65) were used in paper IV.

Structured interview and biometric data

Data on respiratory symptoms, smoking status, medical history, including cardiovascular and pulmonary disease and current medication were obtained by a structured interview. The questions regarding respiratory conditions and symptoms were adapted from the revised version of the British Medical Research Council questionnaire (104). The questions are well-validated and have been used in several national and international studies (105-107). In addition, questions regarding smoking status, comorbidities, including CVD, and medication were included. The definitions for IHD and CVD used in the different papers are presented in table 2.

Weight and height was measured in ordinary indoor clothing without shoes. Body Mass Index (BMI) was calculated weight (kg)/height (m)², and divided into four groups; underweight <20, normal 20-24.9, overweight 25-29.9 and obesity ≥30. Smoking habits were classified as non-smoker, ex-smoker (>12 months) and current smokers, and the number of pack-years was calculated; (number of cigarettes per day/20) x number of years smoking.
**Statistical methods**

The statistical software Statistical Package for The Social Sciences (SPSS) (IBM, Armonk, NY, USA), versions 22-23, were used for statistical analyses. Due to a low number of participants in GOLD 3 and 4, they were grouped together.

Chi-square test for independence was used for bivariate comparisons of categorical variables. Chi-square test goodness of fit was used for comparison of the observed sample distribution with an expected. Mantel-Haenszel test for trend and Fischer’s exact test was used where appropriate. Independent samples t-test and ANOVA were used when comparing means for continuous variables. Odds ratios (ORs) were calculated for risk assessment of dichotomous variables by using multivariate logistic regression models (paper I), and beta-coefficients were calculated for risk assessment of continuous variables by analyses in multivariate linear regression models (paper IV). Survival was illustrated by Kaplan Meier curves (paper II and III), and risk for death, expressed as Mortality Risk Ratio (MRR), was estimated by using multivariate Poisson regression models (paper II). A p-value of <0.05 was considered statistically significant for all tests, and 95% confidence intervals (CI) were additionally used for evaluation of significance for OR, beta-coefficient and MRR estimates.
Figure 6. One of the two Vicatest 5 spirometers that was used throughout the study
Ethical considerations

All papers in this thesis are based on the OLIN COPD study, which has been approved by the Regional Ethical Review Board at Umeå University, Sweden, approval number 04-045 M, with additions for ECG in 2005 and arterial stiffness in 2010. The study has been performed in accordance with the Declaration of Helsinki.

All included subjects gave their informed written consent to participate in the study. They were informed about the aim, that participation and all collected data were handled with confidentiality and that each subject had the right to withdraw from the study. All subjects received a study specific ID-code and the code key was stored within the OLIN studies premises. Data files distributed to researchers were de-identified and included only the study specific ID-code to guarantee confidentiality and anonymity for the study subjects. The participants received no financial compensation.

The participants were informed regarding lung function test results and if clinically relevant ECG abnormalities were present. As the results of arterial stiffness measurement could not be translated to clinically relevant outcome on an individual basis, the participants were informed that the aim was to evaluate arterial stiffness (a known risk factor for cardiovascular disease) among subjects with and without COPD and COPD disease severity on a group level. Thus, no information on individual results of arterial stiffness was presented to the participants.

In epidemiological studies, subjects with previously unknown disease may be identified, and information regarding a previously undiagnosed disease may be perceived negatively. However, the benefit of early diagnosis and possible treatment is expected to exceed the possible harm of information regarding previously undiagnosed disease. Responsible physicians within the OLIN studies have assessed pathological findings, and when appropriate, subjects have been informed and offered referral to adequate level of public health care for further consultation and/or follow-up.
Results

Prevalence of ischemic heart disease among subjects with COPD and NLF (paper I)

This paper was based on cross-sectional data from 2005 including structured interview and ECG. Spirometric classification was based on spirometry at baseline and in 2005. The study population included 1188 subjects whereof 576 fulfilled the spirometric criteria for COPD, and 612 subjects had normal lung function (NLF) both at baseline and in 2005. The distribution of COPD by GOLD grade was: GOLD 1 38.4%, GOLD 2 53.5% and GOLD 3-4 8.2%. The prevalence of IHD based on self-reported data did not differ when comparing subjects with NLF and COPD (12.6% vs. 16.1% p=0.08).

The prevalence of ischemic ECG abnormalities was similar in the NLF and COPD groups both when the ECG abnormalities were divided into major, intermediate or minor, and when grouped together according the Whitehall criteria.

Prevalence of self-reported IHD and ischemic ECG abnormalities were compared between subjects with NLF and COPD by GOLD grade. The prevalence of self-reported IHD was higher in GOLD 2 than NLF, and the test for trend showed an increased prevalence of self-reported IHD (p=0.007) (figure 6a). When the prevalence of ischemic ECG abnormalities were analysed by NLF and GOLD grades, the test for trend was significant for Whitehall probable (p=0.042) (figure 6b) but not for Whitehall possible (p=0.355) (figure 6c). Among subjects with COPD, FEV1 % predicted was associated with self-reported IHD and probable, but not possible, Whitehall criteria. FEV1 % predicted remained associated with self-reported IHD, but not probable Whitehall criteria after adjusting for age and sex.
Figure 6. Ischemic heart disease categorized as (A) Self-reported IHD and (B) Ischemic ECG changes according to Minnesota coding categorized as probable Whitehall criteria and (C) Possible Whitehall criteria among subjects with normal lung function (NLF), COPD GOLD 1, 2 and 3–4, with 95% confidence intervals. Significance is shown with **p ≤ 0.01 (NLF compared with GOLD 1, 2 and 3–4, respectively). Observe that a, b and c have different scales on the y-axis. From: Nilsson et al. BMC pulmonary medicine (2015) 15:156
Ischemic ECG abnormalities and mortality among subjects with COPD and NLF (paper II)

This paper was based on cross-sectional data from 2005 and follow-up of mortality data until December 31st, 2010. The study population included 786 subjects with NLF and 635 subjects fulfilling the spirometric criteria for COPD, whereof 40.7% in GOLD 1, 51.1% in GOLD 2 and 7.8% in GOLD 3-4. The cumulative mortality was higher among those with than those without ischemic ECG abnormalities (I-ECG); in NLF 17.1 % and 6.3% (p=0.001), and in COPD 29.6% and 10.6% (p=0.001) respectively. In the COPD group, the cumulative mortality increased by disease severity, both among subjects with and without I-ECG.

The survival among subjects categorized as NLF and COPD, with and without I-ECG is illustrated by Kaplan–Meier curves in figure 7. In a multivariate Poisson regression model adjusting for age, sex, smoking habits and BMI classification, the risk for death, expressed as Mortality Risk Ratio (95%CI), was increased among COPD with I-ECG (MRR 2.4 95%CI 1.5-3.9), and non-significantly so among NLF with I-ECG (MRR 1.65 95%CI 0.94-2.90), when compared to NLF without I-ECG.

Figure 7. Kaplan–Meier curves illustrating survival among subjects with NLF or COPD with and without ischemic ECG abnormalities (I-ECG) using log-rank; \( p=0.001 \). Abbreviation: NLF, normal lung function. From: Nilsson et al. International Journal of COPD (2017) 12
When analysed among subjects with COPD, I-ECG was associated with an increased MRR, independent of age, sex, smoking habits, BMI classification, and disease severity assessed as FEV1% predicted. Among subjects with COPD, 67.3% had no previously reported heart disease, and also among them, the cumulative mortality was higher among those with than without ischemic ECG abnormalities (25.8 % vs. 8.8, p=0.001). The pattern was similar among those with NLF. A multivariate subgroup-analysis was also performed among subjects without reported ischemic heart disease. Those with COPD and I-ECG had an increased risk for death (MRR 3.01, 95%CI 1.59-5.71), while the risk for death among subjects with NLF and I-ECG was non-significantly increased (MRR 1.95, 95%CI 0.94-4.06), when compared with NLF without I-ECG.

**QTc interval and COPD (paper III)**

Paper III was based on cross-sectional data from 2005 and follow-up of mortality data until December 31st, 2010. The study-population included 1480 subjects; 734 with NLF, 175 with RSP and 571 with FEV1/VC<0.70 (GOLD-COPD), whereof 41.0% GOLD 1, 51.7% GOLD 2 and 7.4% GOLD 3-4.

Mean QTc was longer, and the prevalence of prolonged QTc was higher in RSP than NLF. Sex-stratified analyses revealed a similar pattern among men, while the corresponding analyses among women yielded no significant differences.

When comparing NLF and GOLD-COPD, mean QTc and prevalence of prolonged QTc were similar, while the prevalence of borderline QTc was higher in GOLD-COPD than NLF. In analyses stratified for sex, the pattern was similar among men, but no significant differences were observed among women. The prevalence of borderline as well as prolonged QTc increased by GOLD grade (test for trend 0=0.002 for both groups), and the prevalence’s were higher in GOLD 2 and GOLD 3-4 than in GOLD 1. In the sex-stratified analyses the pattern was similar among men. Also among women, the pattern of prevalence of borderline QTc was similar, while there were few cases with prolonged QTc.

Among those with GOLD-COPD, 299 subjects (52%) fulfilled the spirometric criteria for LLN-COPD. When comparing mean QTc duration and prevalence of QTc prolongation in LLN-COPD and NLF the relationships were similar as when comparing GOLD-COPD and NLF. This was also the case for increasing mean QTc, and prevalence of borderline and prolonged QTc by GOLD grade.
The cumulative all-cause mortality was similar when comparing normal with borderline and prolonged QTc respectively, among those with NLF as well as those with RSP. Among subjects with COPD, both GOLD-COPD and LLN-COPD, the mortality was higher among subjects with borderline and prolonged QTc than those with normal QTc, however, non-significantly so for prolonged QTc in LLN-COPD (table 3). The worse survival associated with QTc prolongation among subjects with COPD was illustrated by Kaplan Meier curves in paper III; QTc prolongation was associated with decreased survival among subjects with COPD, regardless of whether the GOLD or the LLN spirometric definition was used.

**Table 3.** Comparing cumulative mortality among subjects with normal QTc and borderline QTc respectively prolonged QTc by group; normal lung function, restrictive spirometric pattern, GOLD-COPD and LLN-COPD. n (%). From Paper III

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Borderline</th>
<th>(P^a)</th>
<th>Prolonged</th>
<th>(P^b)</th>
<th>(P^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NLF</strong></td>
<td>39 (6.4)</td>
<td>8 (10.0)</td>
<td>0.236</td>
<td>5 (10.4)</td>
<td>0.289</td>
<td>0.155</td>
</tr>
<tr>
<td><strong>RSP</strong></td>
<td>17 (13.1)</td>
<td>3 (12.0)</td>
<td>1.000</td>
<td>2 (10.0)</td>
<td>1.000</td>
<td>0.695</td>
</tr>
<tr>
<td><strong>GOLD-COPD</strong></td>
<td>41 (9.4)</td>
<td>17 (17.3)</td>
<td><strong>0.023</strong></td>
<td>8 (20.5)</td>
<td><strong>0.030</strong></td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td><strong>LLN-COPD</strong></td>
<td>20 (9.1)</td>
<td>12 (21.8)</td>
<td><strong>0.009</strong></td>
<td>5 (20.0)</td>
<td>0.090</td>
<td><strong>0.012</strong></td>
</tr>
</tbody>
</table>

\(P^a\) comparing normal QTc and borderline QTc

\(P^b\) comparing normal QTc and prolonged QTc

\(P^c\) test for trend
Arterial stiffness among subjects with and without COPD (paper IV)

This paper was based on cross-sectional data from 2010. The study population included 947 subjects with complete data on spirometry, structured interview and measurements of arterial stiffness, whereof 36 subjects were examined in the beginning of 2011. Out of 947 subjects, 416 fulfilled the spirometric criteria for COPD and 531 were non-obstructive (non-COPD). Among those with COPD the distribution of disease severity was 63.1% GOLD 1, 32.9% GOLD 2 and 3.1% GOLD 3-4. The prevalence of self-reported cardiovascular disease (CVD) was similar in COPD and non-COPD. Among subjects with COPD, those with productive cough had a close to significant higher PWV compared to those without productive cough (p=0.052). In bivariate analyses, arterial stiffness, assessed as pulse wave velocity (PWV), was associated with age over 60 years, self-reported CVD and GOLD 3-4. When analysed in four different multivariate models with a baseline adjustment for age, sex, smoking habits, and stepwise including systolic BP (model A), diastolic BP (model B), systolic, and diastolic BP (model C), and systolic BP and CVD (model D), GOLD 3-4 remained associated with increased PWV throughout all models, when compared with non-COPD. (Model D: beta-coefficient 1.518, 95%CI 0.494 - 2.543. p <0.010). Productive cough was not associated with PWV when included in the model.
Discussion on Methodology

In discussion on Methodology a few important concepts in epidemiological research are defined along with a discussion of the methods used in this thesis.

Definitions

Bias

When designing a study, the possibility of bias, or systematic errors, must be considered, and as far as possible be addressed. There are several different biases that can occur, depending on type of study and research question. Bias can be divided into selection bias, information bias and confounding (108).

Selection bias

If the study population differs from the target population of interest in some way, selection bias is present. This may be caused by different reasons, e.g. by convenience sampling or exclusion criteria used. One common cause of selection bias is non-participation, which may contribute to lack of generalizability, i.e. the study participants do not represent the intended population. In both cross sectional and longitudinal epidemiological studies, non-responding and non-attendance are important factors to consider. These “non-participants” can contribute to skewed data and it is crucial to keep these at a minimum to minimize the risk for selection bias. In a longitudinal study, mortality over time will gradually lead to a healthy survivor effect, i.e. subjects with heavy disease burden will die and the results must be interpreted in view of the fact that the residual population has a lower disease burden. This is a natural development, but needs to be considered.

Information bias

Information or misclassification bias may occur whenever inaccuracy in a measurement is present, for example in this thesis when collecting data by interview or when performing ECG-recordings or lung function testing.

When information is gathered in a large epidemiological study, there may be a number of events where errors can occur. In data collection there may be a misclassification bias, caused in physical examinations, for example by poor performance during lung function testing, or faulty or wrongfully calibrated medical equipment. Recall bias is another important factor, participants may give erroneous answers during the interview or when filling in questionnaires,
on purpose or by mistake. Observer bias may occur if the observer or interviewer knows the disease status of the subject, as it may influence the collected data.

**Confounding**

Confounding is a distortion of the results in a study which occurs when the association between exposure and the measured outcome is affected, entirely or in part, by an external factor, apart from the investigated variable (108). Confounding can be controlled in different ways, where matching in case-control studies is one common approach. Matching on specific variables will adjust for the confounding effect of these variables. (108).

**Validity**

Validity is a term used in epidemiological research to assess to what degree the collected information answers to the research question. Validity may be impaired by different bias.

**Internal validity**

Internal validity is the degree to which the observed findings are considered correct. If a study provides correct information, is able to measure what was the intention of the study, and reflects the true situation in the study population, it can be said to have high internal validity. This can be impaired by selection bias, confounding, information bias or small study samples.

**External validity**

The external validity describes if, and to what extent, the results can be generalized to the population that the study population is intended to represent. If, for example, the study by design is to strictly controlled with rigid inclusion and exclusion criteria, the selection of the study population will yield results not applicable to the general population. The sampling and selection of study population and participation rate are important factors affecting the external validity.

**Reliability**

Reliability refers to the consistency of the results; to which extent the study can be repeated and still give the same results. Factors that affect reliability are degree of standardized and robust biometric measurements, use of well-
validated questionnaires and the calibration of measurement instruments. Inter-individual variation among research assistants’ data collection may also affect reliability.

**Study population and participation**

Due to the well-known under diagnosis, population-based studies are needed to understand the clinical picture and burden of COPD. The COPD-cohort was, as described in the method section, identified from re-examination of population-based cohorts (99). The distribution of disease severity was similar to what has been described in other population-based studies (93, 109), including a majority of GOLD 1 and 2, but only a few cases with GOLD 3-4. The external validity is considered good and the results are expected to be generalizable to COPD in the population. However, the low number of GOLD 3-4 in a population-based study will affect the statistical power and may contribute to a lack of statistical significance when comparing this group with e.g. GOLD 1, GOLD 2 or subjects without airway obstruction.

The reference population without obstructive lung function impairment was pairwise matched 1:1 by age and sex to the COPD group. After inclusion was completed, the pairwise connection was removed. As previously described, matching is common in research, as it will allow a smaller study population, and may also reduce risk of confounding. In the OLIN COPD study, the matching remained fairly intact in 2005 (99). However, the basic matching was affected when the non-obstructive reference population was divided into NLF and RSP. The matching was also affected by other factors, for example when ECG data were used as selection criteria. This may have had a negative impact on the power of certain analyses as adjustment for age and sex may be needed when the original matching was affected.

The participation rate has been over all high in the OLIN COPD study, 94% in 2005, and 80% in 2010. Non-participation at examinations can be divided into eligible (declining participation or not able to participate) and not eligible (due to death). Subjects not able to participate at the physical examinations any of the years were invited to a telephone-interview using the same questionnaire as at examinations (figure 1). However, for the aim of the papers included in this thesis, participation in physical examination was crucial to obtain data on spirometry, ECG and arterial stiffness.

In a longitudinal cohort study, a selection bias contributing to a healthy survivor effect is expected to emerge. Previously published data from the OLIN studies on incident COPD revealed that death was the major cause of
non-participation at follow up. Low lung function and smoking were also associated with non-participation at follow up, further supporting an assumption of a healthy survivor effect (110).

No selection bias of importance was expected in papers I-III, due to the high participation rate and low number of deceased since baseline. In paper IV, based on examinations in 2010, a non-participation analyse was included; baseline data from 2002-04 were compared between those who died before examination and those who participated at examination in 2010. The proportion of men was higher among the deceased, they were older and had a higher prevalence of COPD and heart disease at baseline. In summary, the data support a healthy survivor effect.

**ECG-registration, coding and measurement**

ECGs were recorded on several different ECG-machines, the majority with the Swedish standard 50 mm/s paper speed and a smaller number was recorded with the paper speed 25mm/s, which is common internationally. All ECG-machines were calibrated according to international standards (5). The difference in paper speed can potentially affect the resolution of time dependent details on ECG recordings, e.g. width of the QRS complex or duration of PQ-time. In this thesis, the ECG-reading was performed using a 10x resolution scale loupe designed for ECG reading, in combination with a standard ECG ruler, and a high-resolution calliper. The use of two different paper speeds was thus not considered to affect the outcome of the ECG readings.

To minimize the risk for observer bias, all ECG-reading and -coding were blinded for the coders, with regard to disease status of the participants. Minnesota coding (paper I and II) was performed by two independent experienced coders and, upon disagreement consensus was reached. A trained medical student performed measurements of QT interval, when compared to a random sample of ECGs examined by a second assessor, the inter-individual agreement was good (paper III).

The use of ECG in epidemiological studies has its limitations. Standard 12-lead ECG only provides a short glimpse, approximately four to ten beats, during 10 seconds of the hearts activity, why intermittent abnormalities rarely are recognized. Further, ECG has limited sensitivity and specificity for detecting ischemic myocardial events (111), as these abnormalities can be dynamic and fluctuate over time (112, 113). However, this phenomenon most
probably affected cases and referents similarly in papers I and II, thus not affecting the observed differences between groups.

Recognizing the end of the T wave can be difficult when measuring the QT interval. Whereas the QRS onset is sharp and easily identified, the end of the T wave gradually merges with the baseline, is not always clearly demarcated and can also be distorted by the appearance of a U-wave. The “tangent method”, a common method to define the end of T waves, was used in paper III. This method has a high reproducibility which enables good intra-individual measuring consistence, but is considered to give systematically shorter QT intervals compared to other measuring methods (114). This may contribute to an underestimation of the QT-interval and prevalence of prolonged QT in paper III, compared to other studies.

The QT interval is affected by the heart rate. There are several different formulas to correct QT-interval for heart rate (QTc). Even though the Bazett formula (36) has been questioned (115, 116), it is one of the most commonly used (98), and provides an adequate correction for heart rates ranging from 60 – 90 bpm. However, the Bazett formula underestimates the QTc duration at lower, and overestimates the QTc at higher heart rates. The Fredericia formula reflects a more accurate correction at high heart rates and was used for heart rates ≥90 bpm, but carries the same limitations as the Bazett formula at slow heart rates (117). Thus, the QTc interval among subjects with heart rates <60 bpm might have been underestimated.

Gender-specific limits for QTc prolongation recommended by several professional organizations were used in paper III (102), Still, since other definitions are also used in the literature, the definition of prolonged QTc must be considered when comparing the results between studies (118, 119). There is no established gold standard to define borderline QTc, and the used limits were chosen based on a compilation of limits in different studies on prolonged QTc.

**Arterial stiffness**

In paper IV, we used the pulse wave velocity (PWV) as a measure of central arterial stiffness. PWV is considered to be the gold standard for assessing the stiffening of the larger arteries (120). The measurements were performed with the Vicorder® system following a strict protocol. As specified in the methods section, we used the crude direct-measured distance between the cuffs placed over carotid and femoral arteries.
There has been a lack of standardization for the technical performance of measuring PWV, complicating comparisons between studies. In 2012, an expert consensus document was published regarding standardization of the measurement method, and discussed a cut-off limit at 10 m/s increased PWV (47). The direct measure of carotid-femoral distance may overestimate the true anatomical distance, and it is now recommended to correct the direct measured carotid-femoral distance by multiplying by 0.8 (47). Differences in measurement methods and corrections of carotid-femoral distance may cause a significant difference in PWV (11, 47), affecting the external validity of the results. Thus, the absolute values of PWV in our study may be higher than expected, however, the observed differences between groups are still considered valid. Different devices for measuring central arterial stiffness may also contribute to differences in PWV (97). In this study, we used the Vicorder® that has been well validated in comparison with other devices, as for example the SphygmoCor® (121, 122). Vicorder® is less operator-dependent than the SphygmoCor® and is thus considered to be more suitable for epidemiological fieldwork (121, 122).

**Spirometry and spirometric criteria for COPD**

Definition of airway obstruction by a post-bronchodilator fixed ratio, FEV₁/FVC, has been generally accepted since the launch of the first version of the GOLD document around the shift of the millennium. The OLIN COPD study was designed shortly thereafter and the fixed ratio was used to define airway obstruction. The fixed ratio is also used by many guidelines, including the Swedish national guidelines, for diagnosis and treatment of COPD (123, 124) and is thus highly clinically relevant. However, the fixed ratio will overestimate the prevalence of airway obstruction among elderly, and may include also elderly non-smokers without respiratory symptoms (59). This has to be taken into account when interpreting the results.

In large epidemiological studies, also pre-bronchodilator fixed ratio has been used to define airway obstruction (93, 125), but the pre-bronchodilator ratio will overestimate the prevalence of COPD by around 25% (80). The GOLD document uses the FVC as denominator when estimating the ratio, but also acknowledges VC as denominator. In the OLIN COPD study, the best value pre- or post- bronchodilator was used to obtain the most accurate value possible for each subject, and also the highest value of FVC and VC as denominator when calculating the ratio with FEV₁ as nominator. The use of VC instead of FVC as denominator may generate higher prevalence of airway obstruction (126).
The LLN-criterion is considered to be a more physiological definition of COPD. A task force report from the European Respiratory Society, ERS, was published a few years ago, recommending the use of post-bronchodilator LLN to define airway obstruction in epidemiological studies (61). There are also national treatment guidelines for COPD based on the LLN-criterion (123). However, the LLN-criterion is highly dependent on representative reference values for the population under study (62), and when the LLN-criterion was used in paper III the locally derived OLIN reference values were used (68). Different definitions of airway obstruction will undoubtedly affect the prevalence of airway obstruction (74, 126).

According to GOLD, spirometric classification of disease severity in COPD is commonly based on FEV₁ % predicted (57). Different versions of the GOLD document have been referred to in the papers I-IV. The specific FEV₁ cut-points for the four levels of airway obstruction, GOLD 1-4, have been the same in all versions of the GOLD document since first launched just after the shift of the millennium, and all subsequent versions thereafter. It is of importance that the used reference values are representative for the population under study. The Swedish Berglund reference values (65) for FEV₁, which conforms well to individuals in northern Sweden without airway symptoms (127) were used in the chronologically first publication, paper IV. The later published, locally derived, OLIN reference values based on smoking free respiratory healthy subjects (68) were used for FEV₁ in the chronologically later published papers I-III, and also, as mentioned previously, when using the LLN criterion for airway obstruction in paper III.

**Questionnaire and interview**

The structured interviews and lung function tests were performed by the same staff. They had extensive training in interview technique and regular follow-ups for method control with the aim to reduce inter-individual bias. The self-reported data on smoking, medication and cardiovascular comorbidities may be affected by recall bias for individual subjects, but is unlikely to be systematic (128, 129). Interview data have not been compared with medical records, however, self-reported data and medical records data on cardiovascular disease have fairly good agreement (129)
Discussion of main results

The overall aim of this thesis was to describe the prevalence of cardiovascular disease in COPD, with focus on ECG abnormalities (ischemic abnormalities and QT prolongation) and arterial stiffness, comparing subjects with and without obstructive lung function impairment in a population-based study sample. ECG abnormalities were also evaluated in relation to prognosis, assessed as mortality.

The well-known under diagnosis of COPD is related to disease severity and contributes to an underestimation of especially GOLD grade 1 and 2 in the society (75). Population-based studies using methods in accordance with diagnostic criteria for COPD, i.e. post-bronchodilator spirometry, identify subjects otherwise undiagnosed. The distribution of disease severity in the COPD cohort within the OLIN COPD study is comparable to what has been shown in other population-based studies; including predominantly subjects with GOLD 1 and 2 and few subjects with GOLD 3-4. The participation rate was high in the 2005-examinations, thus, excluding a selection bias of importance. Standardized and well validated methods were used. Altogether, this supports an assumption of a high external and internal validity, and that the observed results are representative for subjects fulfilling the spirometric criteria for COPD in our society. In paper IV, based on data from examinations performed in 2010, analyses of non-participation supported a healthy survivor effect, to be further discussed below.

Prevalence of Ischemic heart disease

According to a review published a few years ago, the prevalence of ischemic heart disease among subjects with COPD varies considerably between studies, from 4 up to 64% (92). The large differences in prevalence were dependent on definitions of disease, data sources used and selection of study populations. However, population-based studies on COPD, including evaluation of cardiovascular diseases with diagnostic methods such as ECG are scarce (92, 130). In our population-based study (paper I), self-reported ischemic heart disease was equally common among subjects with COPD and NLF. Ischemic ECG abnormalities were also equally common in COPD and NLF, both when analysed separately classified by Minnesota coding, and when grouped together according to the Whitehall criteria. However, the prevalence of IHD increased by COPD severity, both when defined as self-reported IHD and as Whitehall probable ischemic ECG abnormalities. The Copenhagen City Heart study (93) reported a lower prevalence of self-reported heart disease, as well as of ischemic ECG-findings. Differences may be explained by their use of pre-
bronchodilator spirometry values, which may overestimate the prevalence of airway obstruction. They also used a more conservative definition of ischemic ECG abnormalities than the Whitehall criteria, and had a higher burden of current smoking. Besides our study (paper I), there are hardly any comparable population-based studies on ischemic ECG abnormalities, in which COPD has been defined according to guidelines based on post-bronchodilator spirometry. The prevalence of IHD was highest in GOLD 3-4, and in accordance with studies on hospital based populations including more severe stages of COPD (131-133). However, the low number of subject with GOLD 3-4, which comes with the population-based study design, contributed to a low statistical power when comparing GOLD 3-4 with other GOLD-grades and NLF.

Ischemic heart disease and mortality

Cardiovascular comorbidity is, together with cancer, recognized as a major cause of mortality in COPD (134). In paper II, we presented that ischemic ECG abnormalities (I-ECG) were associated with increased crude mortality in both COPD and NLF groups. When adjusted for confounders, the increased risk for death associated with I-ECG persisted, significantly so for COPD but not NLF when compared with NLF without I-ECG. The results indicate that I-ECG may be of greater importance among subjects with COPD. Large trials, whereof several performed in selected COPD populations, have shown that ischemic heart disease is a common cause of death in COPD (130, 134), and ischemic heart disease may be the cause of higher mortality in COPD patients than COPD itself (135). Among subjects with COPD, I-ECG almost doubled the risk for death when compared to those without I-ECG (paper II). Although minor changes in ST-T wave on ECG can be unspecific to ischemia, major changes, such as Q/QS waves, T waves and/or ST-segment depression, strongly suggest an underlying ischemia (30, 136). In paper II, minor ischemic ECG abnormalities, in accordance with the Minnesota code classification (5), were excluded, except for minor Q/QS wave, with the aim to reduce the impact of possible non-ischemic changes in the analyses.

Of importance, a majority of subjects with I-ECG, both among those with and without COPD, reported no previous ischemic heart disease. Yet, this group had an increased mortality in comparison with those without I-ECG. Thus, the present data suggest that ECG may be sensitive enough to detect ischemic abnormalities of prognostic importance. Recall bias affecting self-reported data of IHD may be a contributing factor to the observed findings, but underlying undetected or silent ischemia may also contribute. The prevalence of silent ischemia is ranging from 0.5% to more than 20% in different studies.
(137), and among diabetic patients even up to 40% to 50% (138). One large study, using myocardial perfusion Single-photon emission computed tomography (SPECT) to identify ischemic myocardium, reported that among subjects with no previous history of ischemic heart disease, the annual “cardiac event” rate (cardiac death and nonfatal MI) was 3.1% among those with >7.5% ischemic myocardium, compared to 0.4% (p<0.001) for subjects with <7.5% ischemic myocardium (137). The prevalence of silent myocardial ischemia in COPD is largely unknown, but may contribute to the increased mortality observed in paper II. Clinical guidelines for diagnosis and treatment of COPD recommend evaluation of cardiovascular comorbidity and cardiovascular risk factors among subjects with COPD, and our results suggests that further evaluation of ECG as a screening tool could be of value.

Prolonged QT-interval and COPD

The prevalence of hereditary long QT syndromes (LQTS) was about 1:2000 when assessed in a large screening program among infants (37) and, most probably, LQTS does not affect the results in our study. Acquired prolonged QTc is more common, but often goes undetected in the general population. Besides age and sex, there are several drugs that affect the QT interval (123).

There were no differences in mean QTc or prevalence of prolonged QTc when comparing NLF and GOLD-COPD, but the prevalence of both borderline and prolonged QTc increased by GOLD grade. Autonomic neuropathy is associated with prolonged QTc and mortality among subjects with COPD (122). This pathophysiological mechanism may contribute to the observed association between COPD disease severity and increased QTc prolongation, if we assume that neuropathy increases by disease severity. Differences in medication due to the severity of COPD may also contribute to the increased prevalence of QTc prolongation by increasing GOLD grade, but unfortunately cannot be evaluated as data on specified medication are lacking.

Established gender-specific limits for QTc prolongation were used in paper III (102), but there is no established gold standard to define borderline QTc. However, the definition of borderline QTc used in paper III seems to identify a population with increased mortality among those with COPD.

QTc prolongation is generally considered more common among women (36, 124). The size of the study population in our study entails limited statistical power for subgroup analyses. Thus, the results of the gender-specific analyses must be interpreted with caution, even though the results indicate that QTc prolongation, in contrast to the referred studies, may affect men to a greater
extent than women. Yet, supportive of our results, a significant association between lower lung function and longer QTc was reported among men, but not women, in a recent publication (125).

In the GOLD-COPD population, 299 subjects (52%) fulfilled the LLN-criterion. It has been reported that the LLN-criterion may reduce the prevalence of COPD by 30-50% when compared to the fixed ratio criteria (79, 139). The proportion fulfilling the LLN-criteria in our study can thus be considered rather high, to which the age distribution in the study population may have contributed. The outcome of the LLN criterion is also dependent on using normal values representative of the studied population (62), which was met by using the locally derived OLIN reference values (68).

In the sensitivity analysis using the LLN-criterion, the results showed a similar pattern as with the fixed ratio, even though the size of the population affected the statistical power to demonstrate statistical significance. The survival curves (Kaplan-Meier) illustrated that QTc prolongation was associated with worse survival than normal QTc among subjects with COPD, but not NLF or RSP. Not only prolonged, but also borderline QTc, as defined in our study, seems to be of prognostic importance in COPD.

**COPD and Arterial stiffness**

Increased central arterial stiffness is a well-known risk factor for cardiovascular diseases, not least IHD, and arterial stiffness is known to be increased in severe and very severe COPD (96, 140). However, population-based studies on arterial stiffness in COPD are scarce. Increased arterial stiffness was associated with higher age and GOLD 3-4 when compared to non-COPD, also when adjusted for confounders in multivariate models (paper IV). The non-participation analyses from the 2010 examinations supported a healthy survivor effect. Despite this healthy survivor effect, the results were strong enough to show a significant association between increased central arterial stiffness and GOLD 3-4. Even though the observed associations are considered valid, the absolute values of PWV have to be interpreted taking the method used into account; the later published standardized measurement method recommending adjustment of direct measured carotid-femoral distance (47) was not used in our study. Thus the absolute values of PWV may be higher than in studies using adjustment of the carotid-femoral distance. The used measurement methods should be considered when comparing results between different studies, and they will also affect the ability to compare measured values with reference values and suggested cut off levels defining increased PWV.
The increased prevalence of IHD in the more severe stages of COPD, reported in paper I and II of this thesis, may be associated with an increased central arterial stiffness. However, the cross-sectional design of this study of arterial stiffness could only provide associations and not evaluate causality. The study was further limited by the fact that no detailed data of medication was included in the analyses. Measurement of arterial stiffness is not yet a fully established clinical method, and the interpretation of PWV values for individual patients is not entirely clear. Still, a recent review suggested that non-invasive measurement of arterial stiffness should be included as a screening method for cardiovascular disease among subjects with COPD in clinical practice (97). However, further studies are needed to evaluate arterial stiffness as a clinical tool for risk factor assessment of cardiovascular disease.

**Restrictive spirometric pattern**

The original reference population in the OLIN COPD study was non-obstructive, defined as FEV1/VC≥0.70, and thus included also subjects with restrictive spirometric pattern (RSP). In this thesis, subjects with RSP have been excluded from the analyses in paper I and paper II, addressed separately in paper III and was included in the non-COPD group in paper IV. The aim of this thesis was not to evaluate RSP in relation to cardiovascular disease, but the importance of RSP within this topic is here briefly described.

RSP is related to an increased prevalence of CVD and risk factors for CVD. Subjects with RSP have a higher prevalence of myocardial infarction, angina pectoris, hypertension diabetes and a higher BMI (83, 141, 142). They also have an increased mortality than subjects with normal lung function (143). The cause of restrictive patterns on dynamic spirometry is heterogeneous, and may be due to for example thoracic deformity, obesity, neuromuscular disease, cardiac insufficiency, pleural fluid and interstitial lung disease (144). Due to the diversity in underlying causes of RSP, true restrictive lung function impairment needs to be confirmed by a reduced total lung capacity on static spirometry.

The exclusion of RSP from non-COPD in papers I and II, gave the opportunity to compare COPD to a reference population without the increased burden of CVD in RSP. In paper III, non-COPD was divided into NLF and RSP for the same reason, and they were also compared. RSP had a longer mean QTc-interval, as well as higher prevalence of prolonged QTc-interval than NLF. The population with RSP was rather small, contributing to low statistical power. The current study is, however, as far as we know the only one addressing QTc
in relation to RSP, and further studies are needed to understand the impact of QTc prolongation among subjects with RSP.

In paper IV, arterial stiffness was compared between subjects with and without COPD, and RSP was included in non-COPD group. Based on the known increased burden of CVD in RSP (141-143), the inclusion of RSP in the non-COPD group probably affected the observed differences in PWV. Substituting non-COPD with NLF in the comparison with COPD may have revealed an even greater difference in PWV. According to a recently published study, RSP increase the risk for increased arterial stiffness (145), which support this assumption.
Conclusions

In this population-based study, ischemic heart disease was equally common among subjects with COPD and those with normal lung function (NLF). In COPD, the prevalence of self-reported ischemic heart disease and ischemic ECG abnormalities (I-ECG) increased by disease severity. I-ECG was associated with a higher mortality over a five-year period, both among subjects with NLF and COPD. Both subjects with COPD and NLF with I-ECG had an increased risk for death when compared to those with NLF without I-ECG, however significantly so only for COPD. Among those with COPD, the almost doubled risk for death associated with I-ECG was independent of disease severity. Furthermore, I-ECG was associated with an increased risk for death also among subjects without previously reported heart disease. The results indicate that I-ECG may be of greater importance among subjects with COPD than NLF. The findings further suggest that a simple resting ECG may be a valuable tool in the clinical setting to detect ischemic abnormalities of prognostic value among subjects with COPD, independent of previously known heart disease.

The prevalence of prolonged QTc was higher in RSP than NLF, while the prevalence was similar among those with GOLD-COPD and NLF. The prevalence of prolonged QTc increased by disease severity in COPD. Among those with GOLD-COPD, but not RSP and NLF, prolonged QTc was associated with an increased crude cumulative mortality over five years when compared to normal QTc. Among those with GOLD-COPD 52% fulfilled the spirometric criteria for LLN-COPD. In general the pattern was similar in GOLD-COPD and LLN-COPD, also when compared to NLF. The results suggest that prolonged QTc is of prognostic value among subjects with COPD. Based on this assumption, prolonged QTc observed in the clinical setting should lead to consideration if there are possible underlying contributing causes that can be addressed and modified, such as medication.

Central arterial stiffness assessed as PWV was increased among subjects with severe and very severe COPD when compared to non-COPD subjects. Subjects with COPD and productive cough had a close to significant increased PWV when compared to those without productive cough. However, severe and very severe COPD, but not productive cough, remained associated with an increased risk for increased central arterial stiffness compared to non-COPD when adjusted for possible confounders. The use of arterial stiffness estimates is still not established in clinical practice and the clinical relevance of the observed findings needs to be evaluated.
Future perspectives

One of the charms of research is that every answered question leads to new questions. This thesis addressing cardiovascular comorbidity in COPD is no exception to that. The results presented in this thesis have, amongst all, generated the following research questions.

Cardiac troponin has previously been shown to be a prognostic marker of mortality in COPD. Is the observed increased prevalence of ischemic ECG abnormalities associated with increased serum levels of cardiac troponin?

All-cause mortality was increased among subjects with ischemic ECG abnormalities. Are ischemic ECG abnormalities and elevated troponin risk markers of mortality independent of each other, or do these risk factors interact, and if so, how?

Besides ischemic ECG abnormalities, also prolonged QT interval was related to increased all-cause mortality. What was the cause of death among the deceased? Was prolonged or borderline QTc associated with sudden death?

PWV was related to GOLD 3-4 in our cross sectional study. What is the prognostic impact and clinical relevance of elevated PWV in COPD?

In addition to these questions, a deeper knowledge of the pathophysiological mechanisms are of importance for understanding the relationship between cardiovascular disease and COPD. This is also important in order to identify possible preventive measures for cardiovascular disease in COPD.
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