Left Ventricular Systolic Dysfunction in 75-year-old Men and Women

A Community-based Study of Prevalence, Screening and Mitral Annulus Motion for Diagnosis and Prognostics

PÄR HEDBERG
Dissertation presented at Uppsala University to be publicly examined in Aulan, Gamla värdfgymnasiet, Västerås, Saturday, June 4, 2005 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Reduced performance of the left ventricle to eject blood – left ventricular systolic dysfunction (LVSD) – is a common predecessor of the heart failure syndrome. With or without symptoms, LVSD is associated with a poor prognosis. However, with adequate treatment, the development or progression of symptoms, the need for hospitalisation and mortality can all be reduced. In the present work, the occurrence of LVSD was evaluated by echocardiography in a community-based sample of 75-year-old men and women (n = 433). LVSD was a common condition, with a prevalence rate of 6.8%. In nearly half the participants with LVSD, there was no clinical evidence of heart failure.

Community-based screening for asymptomatic LVSD has been proposed as a strategy to reduce the incidence of heart failure. Because of the high costs and low availability, echocardiography is not a suitable screening tool. The plasma concentration of B-type natriuretic peptide (BNP) has been the most advocated screening tool. Another alternative is the standard 12-lead electrocardiogram (ECG). Both the ECG and BNP were effective in excluding LVSD in our 75-year-old community-based sample. However, compared with BNP, the ECG had considerably better specificity. In screening for LVSD, BNP had a diagnostic value in addition to the ECG, but only in individuals with abnormal ECGs.

The left ventricular ejection fraction (LVEF) measured by echocardiography is a well-established index for describing left ventricular systolic function. The wall motion index (WMI) and the amplitude of mitral annulus motion (MAM) are suggested as alternative echocardiographic methods. Compared with MAM, the WMI had a more favourable agreement with the LVEF in our 75-year-old participants. Nonetheless, MAM was a strong predictor of mortality. MAM predicted the risk of all-cause and cardiac mortality independently of other risk factors. In addition, when it came to cardiac mortality, the predictive ability of MAM was independent of the LV function measured as the WMI.

Keywords: Aged, Heart Failure, Ventricular Function, Prevalence, Echocardiography, Electrocardiography, Natriuretic Peptide, Mortality

Pär Hedberg, Centre for Clinical Research, Centrallasaretet, Uppsala University, SE-72189 Västerås, Sweden

© Pär Hedberg 2005

ISSN 1651-6206
ISBN 91-554-6247-2
urn:nbn:se:uu:diva-5793 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-5793)
To my family
Marie, Johan, Ida and Amanda

Nog finns det mål och mening i vår färd, 
men det är vägen som är mödan vård.

Ur "I rörelse"
Karin Boye
List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.


*Articles reprinted with permission*
Contents

Introduction...................................................................................................11
Heart failure..............................................................................................11
Left ventricular systolic function .............................................................14
B-type natriuretic peptide (BNP) .............................................................17
Screening for left ventricular systolic dysfunction...................................19

Aims..............................................................................................................23

Methods ........................................................................................................24
Study population ......................................................................................24
Echocardiography.....................................................................................25
Electrocardiography (ECG).......................................................................28
Exercise testing ........................................................................................28
B-type natriuretic peptide.........................................................................29
Clinical evaluation....................................................................................29
Follow-up ..................................................................................................29
Statistics ...................................................................................................30
Definition of LV systolic dysfunction......................................................32

Results...........................................................................................................33
Baseline characteristics ............................................................................33
Left ventricular systolic function .............................................................34
Electrocardiography...................................................................................35
Exercise testing ........................................................................................35
B-type natriuretic peptide.........................................................................36
Follow-up ..................................................................................................37
Prevalence of LV systolic dysfunction (Paper I)......................................38
BNP and ECG in screening for LV systolic dysfunction (Paper II).........40
MAM compared with WMI in assessment of LVEF (Paper III)..............42
MAM as a predictor of mortality (Paper IV) ...........................................44

Discussion.....................................................................................................48
Prevalence of LV systolic dysfunction.....................................................48
Screening for LV systolic dysfunction.....................................................51
MAM for diagnosis and prognostics.........................................................54

Conclusions...................................................................................................58
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Angiotensin-converting-enzyme inhibitor</td>
</tr>
<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>ASE</td>
<td>American Society of Echocardiography</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type (or brain) natriuretic peptide</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range, i.e. 25th to 75th percentile</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MAM</td>
<td>Mitral annulus motion</td>
</tr>
<tr>
<td>MAM-LVEF</td>
<td>Left ventricular ejection fraction calculated from mitral annulus motion</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RNA</td>
<td>Radionuclide angiography</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristics</td>
</tr>
<tr>
<td>Simpson-LVEF</td>
<td>Left ventricular ejection fraction calculated according to the modified Simpson’s rule based on the disc summation method</td>
</tr>
<tr>
<td>WMI</td>
<td>Wall motion index</td>
</tr>
<tr>
<td>WMI-LVEF</td>
<td>Left ventricular ejection fraction calculated from wall motion index</td>
</tr>
</tbody>
</table>
Introduction

Heart failure
Heart failure is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the heart to fill with or eject blood.\(^1\) The syndrome involves compensatory, sometimes deleterious, mechanisms, which increase blood volume and raise cardiac filling pressures, heart rate and cardiac muscle mass to maintain the pumping function of the heart and cause redistribution of blood flow.\(^2\) The cardinal symptoms of heart failure are breathlessness, fatigue and oedema. Because of the non-specific nature of the symptoms, the diagnosis is often difficult, especially in mild disease.\(^3,4\) In a pragmatic definition of heart failure, recommended by the European Society of Cardiology (ESC), two of the following criteria have to be fulfilled: 1) symptoms of heart failure and 2) objective evidence of cardiac dysfunction.\(^5\)

Symptoms of heart failure
Exercise intolerance, usually ascribed to breathlessness or fatigue, is the major manifestation of heart failure. The main difference between exertional dyspnea in healthy subjects and in patients with heart failure is the degree of physical activity necessary to induce the symptoms.\(^2\) In mild heart failure, exertional dyspnea can simply appear as an aggravation of the breathlessness that occurs in healthy persons during activity. As the heart failure progresses, the degree of physical activity that causes breathlessness declines progressively. In severe heart failure, there is often breathlessness at rest. The degree of exertional symptoms in chronic heart failure has little or no relation to markers of central hemodynamic disturbances.\(^6,7\) Instead, it appears that peripheral factors, such as changes in skeletal and respiratory muscles and disturbances in ventilatory control reflexes, play an important role in limiting exercise.\(^7\)

Sudden breathlessness when lying down, referred to as orthopnea, is a more specific type of dyspnea reported in heart failure patients.\(^8\) This phenomenon has been attributed to the displacement of blood from the lower extremities and abdomen into the thoracic compartment in a recumbent position. The resulting increase in the load on the failing left ventricle causes an increase in pulmonary venous and capillary pressure, interstitial oedema and dyspnea.\(^2\) Although orthopnea is more specific to heart failure than
effort dyspnea, it is present in only 25% of heart failure patients. Oedema in heart failure patients, often presented as swelling of the ankles and feet, is mainly attributable to the activation of the renin-angiotensin-aldosterone system causing fluid retention. Weight gain, pleural effusion, hepatomegaly and ascites are other manifestations of this fluid retention.

Cardiac dysfunction

Impairment of the left ventricle (LV) to empty, i.e. LV systolic dysfunction, is the most common objective evidence of cardiac dysfunction found in patients with typical symptoms of heart failure. In two studies of incident cases of heart failure, 67-84% of the patients had reduced LV systolic function. In cross-sectional community-based data, approximately half the individuals defined as having heart failure also had reduced LV systolic function. This also implies that a significant percentage of patients with heart failure have an apparently normal LV systolic function. It is widely presumed that the majority of these individuals have a filling disorder of the myocardium and are consequently diagnosed as having diastolic heart failure. However, recent studies have questioned the presence of an intrinsic myocardial diastolic dysfunction in the majority of patients with “diastolic heart failure”. Nevertheless, heart failure patients with preserved LV systolic function have increased morbidity and mortality. In this thesis we focus on LV systolic dysfunction which, for prognostic and therapeutic reasons, is a predecessor of heart failure of the utmost importance.

It should be emphasised that cardiac dysfunction, such as LV systolic dysfunction, is not equivalent to heart failure. LV systolic dysfunction can be found in persons without any symptoms or signs of heart failure. In 1997 (i.e. at the start of the present study), community-based descriptions of the prevalence of LV systolic dysfunction, with or without a clinical suspicion of heart failure, were scarce and this was therefore an objective of our work (Paper I).

The progressive nature of heart failure – cardiac remodelling

It is widely accepted that heart failure is a progressive disorder. In response to damage to the myocardium (no matter whether it is acute damage, such as an acute myocardial infarction, or gradual damage, such as pressure or volume overload), a complex cascade of hemodynamic, neurohormonal and genetic mechanisms is activated to preserve cardiac function. This process – referred to as cardiac remodelling – may take place even in the absence of new identifiable damage to the heart. The pathophysiology of cardiac remodelling encompasses a number of mechanisms, including programmed cell death (apoptosis), hypertrophy of cardiac myocytes, destruction of the collagen struts that hold the individual myocytes together and growth of the interstitial matrix. These mechanisms are thought to converge and
ultimately modulate the size, shape and stiffness of the heart, leading to progressive LV dysfunction and heart failure.

The burden of heart failure

Heart failure is a common, costly and deadly disorder. In Sweden, the overall prevalence rate of heart failure has been estimated to be approximately 2-3%, corresponding to a total of 180,000-280,000 individuals. The prevalence increases with age. In the Framingham study, estimated prevalence rates in the age groups 50-59, 60-69, 70-79 and > 80 years were 0.8%, 2.3%, 4.9% and 9.1% respectively. The annual incidence rate of heart failure has been reported to be 1-4/1,000 in population-based studies. In Sweden, an estimated 30,000 individuals are newly diagnosed every year. As expected, there is an increase in incidence rates with age. In a suburb of London, the annual rate of new cases was 0.02/1,000 in those aged 25-34 years and 11.6/1,000 in those aged 85 years and over. In that study, the median age at presentation was 76 years.

A different type of incidence data comes from reports of hospital admissions related to heart failure. These data have to be interpreted with some caution because of their retrospective nature and variations in coding practices. In a registry-based study covering 19 counties in Sweden, Schaufelberger et al. reported that the age-adjusted first-time admission rates for men and women, with heart failure as the principal diagnosis, were 237 and 171 per 100,000 inhabitants respectively, in 2000. Re-admission rates of up to 44% within six months after the first hospitalisation for heart failure have been reported. In a recent European multicentre survey of patients hospitalised for heart failure, 20% of the patients were re-admitted within 12 weeks.

Considering the high hospitalisation rates for heart failure, it is not surprising that the management of heart failure requires a significant amount of health care expenditure. Heart failure is reported to consume 1-2% of health care costs in the USA and several European countries. The total annual treatment costs for heart failure in Sweden have been estimated at approximately 2,000-2,600 million Swedish kronor, corresponding to nearly 2% of the Swedish health care budget. The largest component was care in hospitals and nursing homes, constituting 65%-75% of the total cost of heart failure.

Heart failure is a highly lethal disorder. In the Framingham cohort, the age-adjusted five-year mortality rate was 59% for men and 45% for women diagnosed with heart failure during the period of 1990-1999. Slightly lower age-adjusted five-year mortality rates for men but similar for women (50% and 46% respectively), were reported from a community-based study of individuals diagnosed with heart failure during 1996-2000 conducted in Olmsted County, Minnesota. As expected, higher mortality rates have been reported for subjects with heart failure requiring hospitalisation. In a study of
hospitalisation for heart failure or cancer in Scotland, Stewart et al. reported a 75% five-year mortality rate for both men and women after the first hospitalisation for heart failure. With the exception of lung cancer in both men and women, and ovarian cancer in women, heart failure had the poorest age-adjusted survival outcome in comparison to the most common types of cancer.

Left ventricular systolic function

The ability of the LV to eject blood, referred to as the systolic function, is a complex process involving co-ordinated contractions of subendocardial, midwall, subepicardial and papillary muscle fibres. The muscle fibres of the midwall LV are arranged mainly circumferentially, whereas subepicardial, subendocardial and papillary fibres are arranged mainly in a longitudinal and/or oblique fashion. The shortening of muscle fibres results in a thickening of the ventricular walls, as well as a movement of the mitral annulus towards the LV apex. In addition, the oblique fibres produces a twisting movement of the LV. These events result in a volume reduction of the LV lumen and the generation of the stroke volume. The interaction of the LV, the other cardiac chambers and the entire vascular system results in the cardiac output, which is the product of stroke volume and heart rate.

Determinants of LV systolic performance

The forces acting on the myocardium during filling and contraction are important determinants of LV systolic performance. These forces are affected by chamber size and shape and can be described according to the concept of wall stress. The law of Laplace states that the stress in the walls of a cylinder is directly proportional to the transmural pressure and the radius of the cylinder and inversely proportional to the thickness of the cylinder walls. Although the geometry of the LV is far more complex than that of a cylinder, the fundamentals of the law of Laplace are important in describing the function of the LV. For instance, an increased radius of the LV, i.e. dilatation, causes increased stress on the chamber walls, if the transmural pressure and wall thickness are constant. By increasing the wall thickness (i.e. LV hypertrophy), the wall stress can be reduced.

The wall stress acting to stretch the non-contracting muscle in diastole can be viewed as preload. An increase in preload produces an increase in stroke volume by lengthening the fundamental contractile units – the sarcomeres – in the myocyte (the length-tension relationship). This phenomenon was first described in the frog heart by Frank in 1895 and in the mammalian heart by Starling in 1914. It is therefore often referred to as the Frank-Starling mechanism. The myocardial wall stress built up during the
systolic contraction can be viewed as afterload. In addition to chamber size and wall thickness, this wall stress depends on the peripheral vascular resistance, arterial compliance and intraventricular pressure. An increase in afterload reduces the myofibre shortening velocity, resulting in a decrease in stroke volume. Last but definitely not least, contractility is the fundamental quality of cardiac muscle that determines the systolic performance independent of loading conditions. Increased contractility produces a greater rate of contraction to reach a greater peak force. Exercise, adrenergic stimulation, digitalis and other inotropic drugs are factors that increase contractility.

**Echocardiographic assessment of left ventricular systolic function**

The ideal non-invasive assessment of LV systolic function would be a pure index of the inherent capacity of the myocardial fibres to contract independent of load, i.e. contractility. In isolated heart muscle preparations, the relationships between length and tension and length and shortening velocity are well described. When evaluating the contractile performance of the intact LV in vivo, these relationships are extrapolated, substituting volume for length and pressure for tension. Moreover, to obtain an adequate intraventricular pressure registration, an invasive approach is necessary and a non-invasive evaluation of LV function therefore requires additional extrapolation. Because of these unavoidable extrapolations and the close interrelations between contractility, preload and afterload in vivo, a load-independent non-invasive index of contractility would be very difficult to achieve.

**Left ventricular ejection fraction (LVEF)**

The LV ejection fraction (LVEF), expressed as stroke-volume normalised for LV end-diastolic volume, is the most commonly used index of systolic function. The firmly rooted use of the LVEF in clinical practice and research can be explained by its strong prognostic properties in many types of heart disease. Although clinically useful, it must be remembered that the LVEF is dependent not only on contractility but also on load and heart rate. There are a number of echocardiographic techniques to quantify the end-diastolic and end-systolic LV volumes needed to calculate the LVEF. These techniques are based on more or less sophisticated geometrical assumptions. Among the two-dimensional approaches, the biplane disc-summation method according to the modified Simpson’s formula (Simpson-LVEF) is least dependent on LV shape. Simpson-LVEF is a recommended echocardiographic method for both clinical and research purposes.

**Wall motion index (WMI)**

Wall motion scoring is based on a systematic visual judgement of the LV wall motion. In each echocardiographic imaging plane, the LV wall is
divided into several segments. Segmental models involving between five and 20 segments have been described. Each segment is assigned a numerical value that indicates the degree of wall contraction. In previous recommendations the endocardial motion of a segment was the only property to be rated. However, in recent recommendations from the American Society of Echocardiography (ASE), the systolic thickening of a segment, in addition to its endocardial motion, should be evaluated. The ASE standard assigns a score of 1 for normal contraction, 2 for hypokinesia, 3 for akinesia, 4 for dyskinesia and 5 for aneurysmal bulging. Berning et al. proposed a reverted scoring system in which a lower score indicated worse function and, in addition, they included a score for hyperkinetic motion and excluded the aneurysmal score (+3 = hyperkinesia, +2 = normokinesia, +1 = hypokinesia, 0 = akinesia, -1 = dyskinesia). A global wall motion score, referred to as the wall motion index (WMI), can be calculated by averaging the readings in all the segments.

The WMI has shown good correlation with the LVEF as measured by radionuclide angiography (RNA) or contrast ventriculography and the agreement with the reference method has been comparable with that for Simpson-LVEF or visual estimations of the LVEF. Several studies have reported a strong prognostic performance by the WMI (obtained according to ASE or Berning) in terms of mortality or cardiac events in patients with heart failure or acute myocardial infarction.

Mitral annulus motion (MAM)
The mitral annulus is part of the fibrous skeleton of the heart and consists of a ring of collagenous tissue that surrounds and supports the left atrioventricular orifice. It forms the attachment of the mitral valve leaflets and myocardial fibres of the LV and left atrium. The contraction of longitudinal/oblique LV myocardial fibres pulls the mitral annulus in a caudal direction towards the apex. In a recent study of healthy persons, this annular excursion was shown to explain 19% of the stroke volume. Moreover, the myocardial tissue volume is regarded as non-compressible and the total volume of the heart is fairly constant during the entire heart cycle. The displacement of myocardial tissue towards the apex caused by long axis shortening will therefore inevitably cause a volume reduction of the inner LV diameter, in addition to the volume reduction caused by the annular excursion.

The long axis shortening of the LV can be evaluated by M-mode echocardiography as the maximum amplitude of mitral annulus motion (MAM). Measuring MAM is easy to learn and rapid to perform, even in patients with poor image quality, and it has advantageous reproducibility. Previous studies have shown reduced MAM in acute myocardial infarction, coronary artery disease (with or without previous myocardial infarction), chronic heart failure and LV hypertrophy. MAM is also reduced in atrial
fibrillation as an expression of the loss of atrial contribution to the annular motion.\textsuperscript{76} The amplitude of MAM is load dependent, which has to be considered when it is used for evaluations of LV systolic function.\textsuperscript{77}

Early studies of the maximum amplitude of MAM revealed a high correlation with the LVEF and MAM was therefore proposed as an LVEF surrogate.\textsuperscript{71,78} However, in a study of patients with LV hypertrophy, Wandt et al. found a very weak correlation between MAM and Simpson-LVEF.\textsuperscript{75} Moreover, in a meta-analysis of 434 patients, Emilsson et al. reported a non-linear relationship between MAM and the LVEF.\textsuperscript{79} The relationship between MAM and the LVEF in less selected populations has never been evaluated and this was therefore an aim in our work (Paper III).

MAM is a strong predictor of mortality in acute myocardial infarction\textsuperscript{80} and in patients with heart failure.\textsuperscript{72} In a group of patients with stable coronary artery disease and relatively well-preserved LV systolic function, MAM was associated with increased mortality, while the LVEF was not.\textsuperscript{81} The prognostic performance of MAM in less selected populations has not previously been examined. We sought to evaluate the long-term prognostic value of MAM in our community-based sample (Paper IV).

B-type natriuretic peptide (BNP)

\textbf{History}

The family of natriuretic peptide hormones is a group of vasoactive peptides with many important physiological properties. In 1981, de Bold reported that an injected extract of atrial tissue into rats caused a powerful increase in sodium excretion and urinary volume.\textsuperscript{82} The active factor, atrial natriuretic peptide (ANP), was identified in 1984.\textsuperscript{83} Four years later, a compound was isolated from pig brain and found to cause natriuretic and diuretic responses similar to ANP.\textsuperscript{84} Although initially found in the brain, consequently called brain (or B-type) natriuretic peptide, its primary site for synthesis is the ventricular myocardium.\textsuperscript{85} A third member of the natriuretic peptide family, called C-type natriuretic peptide, was isolated from pig brain in 1990.\textsuperscript{86}

\textbf{Synthesis, release and actions of BNP}

BNP is synthesised as an amino-acid precursor protein and undergoes an intracellular modification to a prohormone. When released from the myocyte, the prohormone is cleaved into a 76 aminoacid N-terminal segment (NT-proBNP) and a 32 aminoacid active hormone.\textsuperscript{87} The principal stimulus of BNP release is myocyte stretch.\textsuperscript{88,89}

Three natriuretic peptide receptors (A, B and C) have been identified in mammalian tissue. When binding the natriuretic peptides, receptors A and B induce the generation of the second messenger cyclic guanosine
monophosphate (cGMP), which mediates most of the biological effects of the natriuretic peptides. Receptor C is a clearance receptor for the active peptides.87

ANP and BNP appear to exert a similar action on the target cells. In the kidney they increase glomerular filtration and inhibit sodium re-absorption, causing sodium excretion and diuresis. They also inhibit the secretion of renin and aldosterone. In the vascular system, the natriuretic peptides cause arterial and venous dilatation, leading to reduced blood pressure and ventricular preload. In addition, natriuretic peptides act in the central nervous system to reduce sympathetic tone and also appears to reduce salt appetite and thirst.87

**Diagnostic use of BNP**

Increased plasma concentrations of BNP have been reported in patients with various forms of heart disease, such as LV systolic dysfunction,90-93 hypertensive heart disease,94 valvular heart disease95-97 and atrial fibrillation.98 In patients with LV systolic dysfunction, BNP levels increase with the symptomatic severity of the disease, as assessed by the New York Heart Association classification.99 Compared with other neurohormones, BNP correlates in a superior way with pulmonary capillary wedge pressure and LV end-diastolic pressure in patients with LV systolic dysfunction.100 In dialysis patients, as well as in patients with lesser degrees of renal insufficiency, the BNP plasma levels are increased.101-103 However, in a recent study of 112 patients with end-stage renal disease requiring dialysis, the BNP levels were not elevated in a subgroup free from LV hypertrophy or cardiovascular diseases.101 The elevation of BNP levels in patients with renal insufficiency thus appears to reflect the high prevalence of cardiovascular co-morbidity.

**BNP in acute dyspnea**

Observational studies have suggested that BNP may be useful in establishing or ruling out the diagnosis of heart failure in patients with acute dyspnea.104,105 Mueller et al. evaluated the effect of measuring BNP levels in the emergency diagnosis of patients with acute dyspnea in a controlled randomised study.106 They found that the use of BNP levels in conjunction with other clinical information reduced the time to the initiation of the most appropriate therapy, the need for hospitalisation and intensive care, the time to discharge and the total cost of treatment. In that trial, heart failure was considered unlikely if the BNP plasma concentration was < 100 pg/ml, whereas, in concentrations of > 500 pg/ml, heart failure was considered the most likely diagnosis. When intermediate levels were found, the protocol recommended the use of clinical judgement and possible further diagnostic testing to rule out stable baseline LV systolic dysfunction and other conditions as the real cause of acute dyspnea.
BNP in primary care settings

In primary care settings, heart failure is commonly misdiagnosed. In one possible cause is the non-specific symptoms of heart failure, especially in mild disease. Misdiagnoses can lead to unacceptable delays in the treatment of heart failure and to excessive referrals for evaluating LV function by echocardiography. In a study of 126 general practice patients with clinically suspected heart failure, a BNP concentration with a cut-off value of 10 pg/ml had sensitivity and specificity rates of 0.92 and 0.18 respectively, to diagnose LV systolic dysfunction. A better diagnostic performance by BNP was reported by Smith et al. in a random sample of general practice patients. With a BNP cut-off value of 18.7 pmol/l, sensitivity and specificity rates were 0.92 and 0.65 respectively. A similar diagnostic value for BNP was reported by Krishnaswamy et al. in 400 patients referred for evaluation of LV function by echocardiography.

BNP in healthy individuals

In healthy individuals without diabetes, cardiovascular, pulmonary and renal disease, plasma concentrations of BNP vary according to gender and age. Women display higher BNP levels than men, while the levels increase with age in both sexes. This suggests that gender and age should be taken into consideration when defining a normal reference range of BNP for a given patient.

Screening for left ventricular systolic dysfunction

The burden of heart failure on the individual patient and on society has resulted in efforts to prevent heart failure by identifying persons at risk and treating them before symptoms develop. There are a number of criteria that should be fulfilled before a disorder is screened for: (1) the condition that is sought should be a precursor of an important health problem, (2) the natural history of the condition, including development from latent to manifest disease, should be adequately understood and the latent stage should be recognisable, (3) there should be an accepted treatment for patients with recognised disease, (4) there should be an acceptable screening test and (5) the cost of case finding and treatment should be balanced economically in relation to possible expenditure on medical care as a whole.

The natural history of asymptomatic LV systolic dysfunction

There is convincing evidence that persons with asymptomatic LV systolic dysfunction run a considerably increased risk of developing heart failure and death. In the community-based Framingham study, the annual incidence of
heart failure was 9.6% in persons with asymptomatic LV systolic dysfunction (LVEF < 40%) during a total of 12 years of follow-up.\textsuperscript{26} The incidence rate corresponded to an almost eight-fold increase in the risk of heart failure in comparison to subjects without LV systolic dysfunction when adjusted for age, gender and clinical risk factors. Even in persons with mild asymptomatic LV systolic dysfunction (LVEF 40-50%) there was an increased risk of heart failure (more than three-fold), with an annual incidence rate of 3.9%. In the placebo group in the SOLVD Prevention trial (LVEF < 35%), the annual incidence rate of heart failure was 9.7%.\textsuperscript{113}

The annual all-cause mortality rates for individuals with asymptomatic borderline (LVEF 45-54%) and definitive (LVEF < 45%) LV systolic dysfunction were 5.1% and 8.9% respectively, in the Cardiovascular Health Study.\textsuperscript{20} As compared with individuals without LV systolic dysfunction, these mortality rates corresponded to increased adjusted mortality risks of 25% and 83% respectively. Similar annual mortality rates (around 5-10%) have been reported in other population-based studies,\textsuperscript{26,114} as well as in the placebo groups in randomised, controlled trials.\textsuperscript{113,115}

In the Framingham study, the median survival time free of heart failure for persons with asymptomatic moderate-severe LV systolic dysfunction was 5.9 years, suggesting a latent phase during which these persons could be identified and treated.\textsuperscript{26} For the individuals with asymptomatic mild LV systolic dysfunction, the median survival time free of heart failure was 10.3 years.

**Treatment for asymptomatic LV systolic dysfunction**

There are consistent data from the SOLVD Prevention Study and the SAVE and TRACE studies that patients with asymptomatic LV systolic dysfunction will develop less heart failure and be hospitalised for heart failure to a lesser degree if they are treated with angiotensin-converting-enzyme inhibitors (ACE-I).\textsuperscript{113,115,116} In addition, the SAVE and TRACE studies showed significant reductions in mortality rates in the prevention groups. The patients included in the above-mentioned studies had LVEF levels of < 35-40%. The effect of treatment on patients with lesser degrees of LV systolic dysfunction has therefore not actually been clarified. Nonetheless, the American College of Cardiology and the American Heart Association (ACC/AHA) recommend treatment with ACE-I in patients with an asymptomatic reduction in LVEF, without giving any specific threshold for LVEF.\textsuperscript{1} However, they state that “patients with an LVEF < 40% are generally considered to have LV systolic dysfunction”. In guidelines from the ESC, ACE-I treatment is recommended when the LVEF is < 40-45%.\textsuperscript{5}

In addition to ACE-I treatment, the ESC recommends beta-adrenoreceptor antagonists (beta-blockers) in patients with asymptomatic LV systolic dysfunction following an acute myocardial infarction.\textsuperscript{3} This recommendation is mainly based on the CAPRICORN study, where carvedilol given to
patients with acute myocardial infarction and an LVEF of < 40% (regardless of symptoms) reduced the frequency of mortality and recurrent myocardial infarction compared with placebo.\textsuperscript{157} Although controlled data are lacking, the ACC/AHA recommends beta-blockers in asymptomatic patients with reduced LVEF, whether or not they have experienced a myocardial infarction.\textsuperscript{1}

**Screening tests for LV systolic dysfunction**

A screening test should have high accuracy, be quick and easy to perform and be inexpensive.\textsuperscript{112} The preferred diagnostic test to confirm or reject the diagnosis of LV systolic dysfunction is echocardiography.\textsuperscript{1,5} However, because of low availability and relatively high costs, it is unlikely that echocardiography would be a suitable primary screening tool, except possibly in certain risk groups with high prevalence rates of LV systolic dysfunction. In community-based screening, comprising subjects with a relatively low prevalence of cardiac dysfunction, other strategies have been sought. One alternative would be to screen using an inexpensive test, target individuals with positive screening tests for diagnostic testing by echocardiography and then treat those with confirmed LV systolic dysfunction.\textsuperscript{118}

Among possible primary screening tests, the plasma concentration of BNP has attracted interest in previous reports. In community-based studies, using BNP to screen for LV systolic dysfunction, the overall accuracy of the test has been reported to be between 0.61 and 0.88, measured as areas under the receiver-operator-characteristics (ROC) curves.\textsuperscript{92,119-121} As expected, the sensitivity and specificity rates have been highly variable with various cut-off values. One consistent finding has been high negative predictive values and low positive predictive values for the BNP as a screening test in the community-based studies. The strength of the BNP therefore appears to be in ruling out LV systolic dysfunction rather than in confirming the diagnosis.

Another possible screening test is the standard 12-lead electrocardiogram (ECG). It has been reported to have sensitivity rates and negative predictive values above 0.90 in screening for LV systolic dysfunction in various patient groups.\textsuperscript{122-124} To our knowledge, community-based evaluations of the ECG as a screening test for LV systolic dysfunction have not previously been performed. We aimed to study the ECG and BNP as screening tools for LV systolic dysfunction in our community-based sample (Paper II).

**Cost effectiveness of screening for LV systolic dysfunction**

Recently, a computer-simulated analysis of the cost effectiveness of community-based screening with BNP was presented.\textsuperscript{125} The study was based on previously published data relating to BNP-characteristics and the prevalence rates of LV systolic dysfunction from community cohorts and data relating to treatment benefits from randomised trials. The authors found
that, for every 125 men screened, one year of life would be gained at a cost of $23,500 and they then compared this with the estimated $16,000 cost per life year gained by annual mammograms for women aged 50 to 79 years. The costs for women in screening for LV systolic dysfunction were higher, mainly because of a lower prevalence rate. The conclusion was that screening with BNP followed by echocardiography in those with an abnormal test was economically attractive for 60-year-old men and possibly for women. To date, there have been no controlled studies of the cost effectiveness of screening for LV systolic dysfunction in the community.
Aims

This thesis presents the results of studies of LV systolic dysfunction in a community-based random sample of 75-year-old men and women, focusing on prevalence, screening and characteristics of mitral annulus motion.

The specific objectives of the studies are:

- to determine the prevalence rate of left ventricular systolic dysfunction, with or without clinical suspicion of heart failure, in 75-year-old men and women from the community

- to evaluate the 12-lead resting electrocardiogram and the plasma concentration of B-type natriuretic peptide as screening tools for left ventricular systolic dysfunction

- to compare the maximum amplitude of mitral annulus motion and the wall motion index, obtained by echocardiography, in the assessment of the left ventricular ejection fraction

- to evaluate the maximum amplitude of mitral annulus motion as a predictor of mortality in 75-year-old men and women from the community. A secondary objective was to compare the prognostic performance of mitral annulus motion with left ventricular function measured as the wall motion index.
Methods

Study population
In 1997, we invited a random sample of 618 men and women from the general population of all 75-year-old persons, living in the city of Västerås, Sweden. The invitation was accepted by 433 subjects (210 men and 223 women), corresponding to a response rate of 70.1%. The reasons for non-participation were that the person could not be reached (n = 29), had died before the investigation procedure was initiated (n = 2), had a language problem or logistical problem (n = 26), had a locomotive impairment (n = 28), was unwilling to participate because of heart disease already under medical surveillance (n = 13), had some other disease (n = 41) or the reason was unknown (n = 46).

All 433 participants and 62 (33.5%) of the 185 non-participants completed a questionnaire about previous diagnoses of cardiovascular and pulmonary disease, medication and smoking habits. Smoking habits were analysed as current smokers versus non-smokers (including previous smokers), unless otherwise stated. The 62 non-participants are referred to in the text as the sample of non-participants.

All the subjects gave their informed consent and the study was approved by the research ethics committee at the University of Uppsala, Sweden.

Paper I
The study population in Paper I consisted of the 433 subjects who accepted the invitation. A reference subgroup (n = 108) was defined as participants who did not fulfil any of the following criteria:

- use of regular cardiovascular or pulmonary medication
- self-reported history of myocardial infarction (confirmed from medical records), angina pectoris, hypertension, atrial fibrillation, diabetes mellitus, asthma or chronic obstructive pulmonary disease
- Minnesota code 1.1, 1.2, 1.3, 7.1, 4.1-4.4, 5.1-5.3, or 8.3 on the 12-lead resting ECG (i.e. Q-waves, left bundle branch block, ST-segment depression, T-wave inversion or atrial fibrillation/flutter)
- abnormal exercise ECG (see Exercise testing)
• echocardiographic findings: aortic peak flow velocity > 2 m/s or more than slight valve regurgitation.

Paper II
Twenty-six subjects were excluded from the original study group of 433 participants because of poor echocardiographic image quality rendering an evaluation of left ventricular systolic function unfeasible (n = 21), poor quality of the ECG (n = 2), pacemaker rhythm (n = 2), or missing BNP values (n = 1). As a result, a final sample of 407 (202 men and 205 women) remained to be analysed in Paper II.

Paper III
From the original study population of 433 subjects, participants with atrial fibrillation (n = 22) and pacemaker rhythm (n = 2) were excluded. The remaining 409 participants (188 men and 221 women) comprised the study population in Paper III.

Paper IV
From the original 433 participants, we excluded 25 persons in whom mitral annulus motion was not possible to obtain. A final sample of 408 (201 men and 207 women) therefore remained to be analysed in Paper IV.

Echocardiography
The echocardiographic studies were performed using an Acuson XP 128 system (Acuson Co., Mountain View, CA, USA) with all the participants in the left lateral recumbent position. Respiration and 1-channel ECG were registered simultaneously. The same physician (P.H.), who was blinded to the participants’ clinical data, performed all the studies. M-mode, two-dimensional mode, colour flow mapping and spectral Doppler investigations were performed and recorded on videotape.

LV systolic function was evaluated in three ways: (1) the LVEF was calculated on line, (2) the amplitude of mitral annulus motion was registered and (3) a scoring analysis was performed on the LV wall motion.

In detail, the on-line calculation of the LVEF was performed using the disc summation method according to Simpson’s rule (Simpson-LVEF) from the apical four- and two-chamber views. The disc summation method technique assumes that the two-dimensional slices pass directly through the central axis of the LV three-dimensional volume. A foreshortening of the LV axis will inevitably lead to the underestimation of the true volume. To avoid a shortening of the true major LV axis, the images representing the largest possible cavity length were used. Simpson-LVEF was not calculated in
participants in whom less than 60% of the endocardial borders could be detected.

MAM was registered by M-mode at four sites of the mitral annulus corresponding to the lateral, septal, anterior and posterior walls of the LV from apical four- and two-chamber views. The maximum amplitudes of MAM in the four registered sites were measured from three different heart cycles (Figure 1). In atrial fibrillation, five heart cycles were used. All measurements were made during expiration, as close as possible to end expiration. The mean of the values from the four sites was calculated and applied in the analysis.

Figure 1. Registration of mitral annulus motion (MAM) using the two-dimensional guided M-mode. In the four-chamber view, the cursor was placed in the lateral region of the mitral annulus, perpendicular to the direction of movement. In the M-mode echocardiogram, MAM was measured as the vertical distance between the point of the annulus most distant from the apex and a point closest to the apex, as indicated. Measurements were obtained from three to five heart cycles. The procedure was repeated in the septal region of the mitral annulus in the four-chamber view and in the posterior and anterior regions in the two-chamber view. The mean of the measured MAM at the four registered sites was calculated and used in the analysis.

The WMI was obtained using a method first described by Heger et al. and subsequently modified by Berning et al. The LV was divided into nine segments examined in five standard projections (i.e. one longitudinal and two short-axis views from the parasternal window and the apical four- and
two-chamber views; Figure 2). Each segment was assigned a score of +3 for hyperkinesia, +2 for normokinesia, +1 for hypokinesia, 0 for akinesia and –1 for dyskinesia, based on the degree of systolic wall thickening. A segment is often visible in two or three views. If the score for a segment differed between views, the scores were averaged. The average score for the nine segments constituted the WMI.

Figure 2. The nine-segment model used to obtain the wall motion index. Each of nine segments was assigned a score of +3 for hyperkinesia, +2 for normokinesia, +1 for hypokinesia, 0 for akinesia and –1 for dyskinesia. The average score for the nine segments constituted the wall motion index.

Measurements of MAM and the WMI were made off line from the video recording by the initial examiner. To avoid potential bias, these measurements were made at least one month after the calculation of Simpson LVEF.

Valvular abnormality was defined as a peak flow velocity of > 3.0 m/s across the aortic valve or at least moderate regurgitation of the aortic or mitral valves.

Intra- and interobserver reproducibility was tested by having the initial examiner and another physician at our laboratory re-measure Simpson LVEF, MAM and the WMI in 14 randomly chosen participants. On Simpson LVEF, the mean difference and coefficient of variation were 1.4 LVEF% (SD = 6.5) and 10.8% respectively, for the same observer, and 0.7 LVEF% (SD = 6.8) and 11.5% respectively, between the two observers. When it came to MAM, the mean difference and coefficient of variation were 0.2 mm (SD = 0.6) and 4.6% respectively, for the same observer, and 0.4 mm (SD = 1.0) and 8.3% respectively, between the observers. The mean
difference and coefficient of variation on the WMI were 0.02 (SD = 0.11) and 5.4% respectively, for the same observer, and 0.12 (SD = 0.14) and 7.1% respectively, between the two observers.

**Electrocardiography (ECG)**

A standard 12-lead electrocardiogram (ECG) was registered after a minimum 10-minute rest period. Blinded to the participants’ data, two physicians coded the standard 12-lead resting ECGs according to the Minnesota coding system. If the coding differed between the physicians, a new coding was made in consensus.

**Major abnormality** in the ECG was defined as the presence of Minnesota code 1.1-1.2, 4.1-4.4, 5.1-5.3, 7.1-7.2, 8.3 or 9.2 (i.e. abnormal Q-wave, ST-segment depression, T-wave inversion, left or right bundle branch block, atrial fibrillation or ST-segment elevation).

**Minor abnormality** was defined as code 1.3, 2.1, 3.1-3.2, 6.1-6.3, 7.3 or 7.6 (borderline Q-wave, left axis deviation, high R-wave amplitude, atroventricular block, incomplete left or right bundle branch block).

**Left ventricular hypertrophy** was defined as the joint occurrence of code 3.1 (high R-wave amplitude) in combination with either 4.1-4.4 (ST-segment depression) or 5.1-5.3 (T-wave inversion).

**Ischemic heart disease** was defined as a self-reported history of myocardial infarction (confirmed from medical records), angina pectoris or evidence of myocardial infarction (i.e. abnormal Q-waves) on the resting 12-lead ECG (Minnesota code 1.1-1.3 in Paper I and 1.1-1.2 in Paper IV).

**Exercise testing**

In the present study, the sole purpose of the exercise testing was to evaluate the exercise ECG as a criterion in the definition of the reference subgroup. On a bicycle ergometer, a symptom-limited exercise test was performed with 30 W as the initial load and with 10 W increments every minute. A 12-lead ECG was registered continuously during exercise and during the four minutes of the recovery phase. In addition, the 12-lead ECG was continuously computer-averaged during the exercise and recovery phases. ST-segment deviation was measured every minute from the incremental averaged ECG at 60 ms after the J point.

**Abnormal exercise ECG** was defined as ≥ 1 mm ST-segment depression in at least two adjacent precordial leads on the exercise ECG at the maximum work load or within four minutes during the recovery phase.
B-type natriuretic peptide

Venous blood was sampled in the morning from participants who had rested in a recumbent position for at least five minutes. The blood was collected in a 10 ml ice-chilled tube containing ethylenediamine tetraacetic acid (EDTA). The tube was turned five to 10 times, placed on ice again and then centrifuged at 4°C for five minutes at 2,000 g. The separated plasma was then put into polypropylene tubes (3 ml in each tube) and frozen at -70°C.

BNP analyses were performed at the Western Infirmary, Glasgow, Scotland. Plasma BNP concentrations were measured using a two-site monoclonal antibody immunoradiometric assay (Shionoria BNP kit, Shionogi & Co, Ltd., Osaka, Japan). The within- and between-assay coefficients of variation were 3.7% and 7.5% respectively.

Clinical evaluation

A consultant cardiologist (I.L.) performed the physical examinations. The consultant, who was the same for all participants, looked for signs associated with congestive heart failure, such as leg swelling, dilated neck veins, hepatomegaly, pulmonary rales, third tone gallop and murmurs. In the same session, he evaluated the self-reported history and symptoms of the participants. He was allowed to review the resting 12-lead ECG but was blind to the echocardiographic findings and the results of the exercise test. Based on these findings, without using any specific scoring system, the consultant classified the participants into the following groups: (1) no suspicion of heart failure, (2) slight to moderate suspicion of heart failure and (3) strong suspicion of heart failure. In the analysis, participants without a clinical suspicion of heart failure refer to group no (1) and participants with a clinical suspicion of heart failure refer to groups nos (2) and (3).

Follow-up

The participants and the sample of non-participants were followed until death or 1 March 2004, at which time they were censored. One participant was lost to follow-up after 6.6 years because of emigration. Causes of deaths were obtained from the Swedish National Cause of Death Register and classified according to the 10th revision of the International Classification of Disease (ICD-10). Cardiac death was defined as the ICD-10 codes I05-I09, I11, I20-I25 and I30-I50. Causes of death were missing in two of the deceased participants.
Statistics

The statistical tests were performed using the SPSS 10.0 for Windows (SPSS Inc., Chicago, Illinois, USA) in Papers I-III and Stata 8.0 for Windows (StataCorp, College Station, Texas, USA) in Paper IV. All receiver-operator-characteristics (ROC) analyses were performed using MedCalc 7.4 for Windows (MedCalc Software, Mariakerke, Belgium). Comparisons between groups were performed on the basis of the unpaired t-test for continuous variables and Pearson’s $\chi^2$ test or Fisher’s exact test for dichotomised variables as appropriate. For non-normal distributed variables (WMI and BNP) group comparisons were performed using the Mann-Whitney U test. Pearson’s correlation coefficient was used to quantify the linear association between two variables. The total accuracy of a continuous variable in predicting the presence or absence of LV systolic dysfunction was described by the area under the ROC curve.128

Multivariable logistic regression was used to evaluate the unique contribution of potential predictors of LV systolic dysfunction. The model included gender, smoking habits, myocardial infarction, angina pectoris, hypertension, diabetes, a clinical suspicion of heart failure, major ECG abnormalities and BNP.

Construction of cut-off values (Paper II-III)

The optimal cut-off value for MAM or the WMI to predict a Simpson-LVEF below a pre-specified value was defined as either 1) the value giving the highest accuracy (i.e. minimum false-negative and false-positive results) in a ROC analysis (Paper II), or 2) the value giving the highest inter-rater agreement (Cohen’s kappa, Paper III).

Two cut-off values of BNP for the detection of LV systolic dysfunction were derived from ROC analyses as: 1) the BNP concentration giving the highest specificity rate at a sensitivity rate of > 95% and 2) the BNP concentration giving the highest accuracy (Paper II). To avoid over-fitting, the ROC analyses were performed in a 10-fold cross-validation procedure.120 The cases in the data file were randomised into 10 blocks of roughly the same size. Each block in turn was excluded and the cut-off levels for the predictor variable were obtained (in the ROC analysis) from the cases in the remaining blocks and tested in the excluded block. Cut-off levels, sensitivity rates, specificity rates and negative and positive predictive values were calculated from the combined outcome of the 10 iterations.

Agreement between echocardiographic methods (Paper III)

The agreement between echocardiographic methods in estimating LV systolic function was analysed according to Bland and Altman.130 To perform the Bland-Altman analysis, LVEF values, on the basis of MAM (MAM-LVEF) and the WMI (WMI-LVEF), had to be calculated. To
optimise the fit in these relationships, we decided to calculate $R^2$ in different regression models. The models with the highest $R^2$ were used to calculate MAM-LVEF and WMI-LVEF. The pre-selected regression models and their equations were as follows: linear ($Y = a + bX$), logarithmic ($Y = a \cdot \ln(X)$), quadratic ($Y = a + bX + b_2X^2$), cubic ($Y = a + bX + b_2X^2 + b_3X^3$), curvilinear ($Y = e^{a + bX}$), and exponential ($Y = a \cdot e^{bX}$) where $Y$ = the dependent variable (i.e. LVEF), $X$ = the independent variable (i.e. MAM or WMI), $a$, $b$, $b_2$, $b_3$ = regression coefficients, $\ln$ = the natural logarithm and $e = 2.71828$ (the base for the natural logarithm).

**Survival analysis (Paper IV)**

The univariate association between a variable and mortality was evaluated by Cox proportional hazard ratios (HR). To avoid the loss of information, the MAM and WMI were analysed as continuous variables instead of being categorised. The assumption of linearity was validated by first- and second-degree fractional polynomials according to Royston and Altman. There were no significant deviations from linearity except for the model of all-cause mortality as a function of MAM, where a reciprocal transformation of MAM had a significantly improved fit (deviance 966.1 vs. 972.6, $p < 0.011$). The reciprocally transformed MAM (re-scaled by multiplication by $-100$) was subsequently used in the multivariable analysis relating to all-cause mortality.

Multivariable Cox proportional hazard regression was used to determine the unique contribution of MAM or WMI in combination with other factors potentially associated with mortality. Basic models were constructed separately for all-cause and cardiac mortality based on the following variables: gender, current smoking, hypertension, diabetes, atrial fibrillation and ischemic heart disease. Eligibility for inclusion in the basic models was evaluated in the univariate models, where a $p$-value of $< 0.20$ by the Wald test was the threshold criterion for inclusion. The MAM and WMI were subsequently introduced, separately or jointly, into the basic models. The assumption of proportional hazards was checked by including time-dependent covariates in the model. There were no violations of the proportionality assumption (as indicated by $p$-values of $< 0.05$ in the Wald tests of the time-dependent covariates). No apparent collinearity was identified among the covariates used in the multivariable analysis. All the variance inflation factors were $< 2$, well below the threshold of 10 used to indicate potential collinearity.

Survival curves were constructed for a baseline MAM of $\leq 9$ mm and $> 9$ mm (i.e. the lowest decile vs. the nine upper deciles of MAM) using the Kaplan-Meier method. The survival curves were compared using the log-rank test.
Definition of LV systolic dysfunction

Paper I
Left ventricular systolic dysfunction was statistically defined as cut-off values for Simpson-LVEF and the WMI, based on the distribution of these variables in the reference subgroup. When estimating the prevalence rate of left ventricular systolic dysfunction, we aimed to avoid borderline cases where there could be doubts about the clinical significance. The cut-off value for Simpson-LVEF was therefore set at the mean minus 3 SD in the reference subgroup (instead of the conventionally used mean minus 2 SD). In the reference subgroup, the mean Simpson-LVEF was 62% (SD 6.3; range 47-73). The mean minus 3 SD corresponded to a Simpson-LVEF of 43%.

As Simpson-LVEF could only be measured in 280 (65%) of the participants, whereas the WMI could be obtained in 95%, the WMI was chosen as the primary variable to define left ventricular systolic dysfunction. The construction of a cut-off value for the WMI was complicated by the skewed distribution in the reference subgroup, even after several transformation attempts. We therefore used the 0.5th percentile for the WMI as an approximate correspondent to 3 SD below the mean. The median WMI in the reference subgroup was 2.0 (IQR 2.0-2.1; range 1.7-2.7) and the 0.5th percentile was 1.7. Left ventricular systolic dysfunction was thus defined as a WMI of < 1.7.

Paper II
In Paper II, we started from a Simpson-LVEF of < 40% as a cut-off value for LV systolic dysfunction. The WMI had an area under the ROC curve of 0.998 (95% CI 0.983-0.999) in predicting a Simpson-LVEF of < 40%. Among possible cut-off values, a WMI of < 1.7 had the best accuracy (i.e. the smallest number of false positive and false negative cases) in predicting a Simpson-LVEF of < 40% with a sensitivity rate of 95% (95% CI 77-99) and a specificity rate of 99% (95% CI 97-100). Consequently, LV systolic dysfunction was defined as a wall motion index of < 1.7.
Results

Baseline characteristics

Table 1 shows the baseline characteristics of the participating 75-year-old men and women in comparison with the sample of non-participants.

<table>
<thead>
<tr>
<th></th>
<th>Participants (n = 433) n (%)</th>
<th>Non-participants (n = 62) n (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>210 (48)/223 (52)</td>
<td>24 (39)/38 (61)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>182 (42)</td>
<td>23 (38)</td>
<td>0.59</td>
</tr>
<tr>
<td>Current smoker</td>
<td>45 (10)</td>
<td>17 (28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>41 (9)</td>
<td>4 (7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>56 (13)</td>
<td>7 (12)</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypertension</td>
<td>122 (28)</td>
<td>16 (27)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (8)</td>
<td>6 (10)</td>
<td>0.61</td>
</tr>
<tr>
<td>Emphysema</td>
<td>17 (4)</td>
<td>6 (10)</td>
<td>0.049</td>
</tr>
<tr>
<td>Medication†</td>
<td>205 (47)</td>
<td>35 (56)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Participants vs non-participants
† Regular cardiovascular or pulmonary medication

There were no significant differences between the participants and the sample of non-participants when it came to gender, previous diagnoses of cardiovascular disease, diabetes and regular cardiovascular or pulmonary medication. There were significantly fewer current smokers and previous diagnosis of pulmonary emphysema among the participants. Ischemic heart disease (i.e. history of myocardial infarction, angina pectoris or abnormal Q-wave in the 12-lead resting ECG) was found in 83 (19%) of the participants.
Left ventricular systolic function

Simpson-LVEF

Simpson-LVEF could be obtained in 280 (64.7%) of the 433 participants. There was a significantly higher proportion of men in the group of 280 with a measurable Simpson-LVEF than in the non-measurable group (54.3% vs. 37.9%, p = 0.001). BMI differed significantly between these groups for both men (24.8 vs. 26.3, p = 0.001) and women (24.8 vs. 28.5, p < 0.001). No significant difference was noted between the groups in terms of history of myocardial infarction, angina, hypertension, diabetes, current or previous smoking and systolic and diastolic blood pressure.

Among the 280 participants in whom the Simpson-LVEF could be obtained, the mean LVEF was 59% (SD 10, range 16-86, Table 2). The mean Simpson-LVEF in the reference subgroup was 62% (SD 6, range 47-73).

Table 2. Echocardiographic evaluation of left ventricular systolic function in all the participants (n = 433) and in the reference subgroup (n = 108).

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Reference subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Simpson-LVEF (%)</td>
<td>280</td>
<td>59 (10)</td>
</tr>
<tr>
<td>Wall motion index</td>
<td>412</td>
<td>2.0 (2.0-2.1)</td>
</tr>
<tr>
<td>Mitral annulus motion (mm)</td>
<td>408</td>
<td>11.8 (2.1)</td>
</tr>
</tbody>
</table>

*Values are median and interquartile range

Wall motion index (WMI)

The WMI could be obtained in 412 (95.2%) of the participants, including all the 280 participants in whom Simpson-LVEF was measurable. The apical segment could not be scored in 15 participants (3.7%); for the other eight segments, scoring was not possible in three to six participants (0.7-1.5%).

The median WMI in the total study group was 2.0 (IQR 2.0-2.1, range 0.4-2.8, Table 2). Reduced wall motion (i.e. a wall motion score of < 2.0) in at least one segment of the LV was registered in 54 (13.1%) of the participants. In the reference subgroup, the median WMI was 2.0 (IQR 2.0-2.1, range 1.7-2.7). Reduced wall motion in at least one LV segment was noted in two men (WMI 1.7 and 1.9 respectively) and one woman (WMI 1.8) from the reference subgroup.

Mitral annulus motion (MAM)

MAM was possible to measure in 408 (94.4%) of the participants. The lateral, septal, anterior and posterior sites of MAM were not possible to
assess in nine (2.1%), 12 (2.8%), 20 (4.6%) and 22 (5.1%) of the participants respectively.

The mean MAM in the total study group was 11.8 mm (SD 2.1, range 3-19, Table 2). In the reference subgroup, the mean MAM was 12.6 mm (SD 1.3, range 10-15). MAM did not show any significant correlations with gender, height, weight, BMI, heart rate, systolic and diastolic blood pressure, or smoking habits in the reference subgroup.

Electrocardiography
The 12-lead resting ECG was of sufficient quality to be interpreted in all but two participants. In addition, there were two participants with pacemaker rhythm and no further interpretation was made in these ECG’s. Major ECG abnormalities were found in 108 (25.2%) of the 429 participants with fully interpretable ECGs (Table 3). Minor ECG abnormalities and completely normal ECG results were found in 86 (20.0%) and 277 (64.6%) respectively.

Exercise testing
Exercise testing was possible to perform in 387 (89.4%) of the participants. The mean maximum heart rate during the exercise tests was 137 ± 21 bpm. An exercise heart rate of at least 116 bpm (i.e. 80% of the predicted maximum heart rate calculated as 0.8 x [220 - age]) was reached in 332 (76.7%) of the participants. The mean maximum work load, normalised for weight, was 1.67 W/kg (SD 0.40) for men and 1.40 W/kg (SD 0.38) for women. An abnormal exercise ECG was registered in 58 (15%) of the 387 participants. The exercise ST-segment reaction was judged to be inconclusive in 32 (8.3%) because of pacemaker rhythm, left bundle branch block, digitalis medication or significant ST-segment depression at rest.

In the reference subgroup (n = 108), 80% of the predicted maximum heart rate (i.e. 116 bpm) was reached in 105 (97.2%), whereas the remaining three persons reached a maximum heart rate of 105 to 115 bpm. The mean maximum work loads for the men and women in the reference subgroup were 1.82 (SD 0.30) and 1.65 (SD 0.35) W/kg respectively.
Table 3. *Electrocardiographic findings in the 75-year-old participants with fully interpretable electrocardiograms (n = 429)*.

<table>
<thead>
<tr>
<th>Major ECG abnormalities</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>22 (5.1)</td>
</tr>
<tr>
<td>Complete left bundle branch block</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Complete right bundle branch block</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Abnormal Q-wave</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>45 (10.5)</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>60 (14.0)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy*</td>
<td>21 (4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor ECG abnormalities</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular block</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Incomplete left bundle branch block</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Incomplete right bundle branch block</td>
<td>14 (3.3)</td>
</tr>
<tr>
<td>Borderline Q-wave</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>High R-wave amplitude</td>
<td>45 (10.5)</td>
</tr>
</tbody>
</table>

*Left ventricular hypertrophy defined as high R-wave amplitude (Minnesota code 3.1) in combination with either ST-segment depression (code 4.1-4.4) or T-wave inversion (code 5.1-5.3).*

**B-type natriuretic peptide**

There was one missing BNP value among the 433 participants. The distribution of the BNP plasma concentration was positively skewed, with a median of 27 pg/ml (IQR 13-50, range 2-1639). In the reference subgroup, the median BNP concentration was 19 pg/ml (IQR 12-33, range 2-88) and it was higher in women than in men (22 pg/ml vs. 16 pg/ml, p = 0.02). The logarithm of the BNP plasma concentration showed no significant correlation with length, weight, BMI, heart rate, systolic and diastolic blood pressure, or smoking habits among the persons in the reference subgroup.
Follow-up

The median follow-up time among the participants (n = 433) was 7.2 years (range 0.5-7.2) corresponding to 2,844 person-years. During follow-up, 87 participants died (rate 3.1/100 person-years). The mortality rate was higher in men than in women (4.3 vs. 2.0 per 100 person-years, log rank \( \chi^2 \ 13.7, \ p < 0.001 \)). Table 4 shows the registered causes of death in the participating men and women. Cardiovascular deaths were registered in 40 participants (rate 1.4/100 person-years) and 27 of these deaths (rate 0.9/100 person-years) were from cardiac causes (i.e. acute myocardial infarction and heart failure).

Table 4. Causes of death in the participating 75-year-old men and women (n = 433).

<table>
<thead>
<tr>
<th></th>
<th>Men n (% of deaths)</th>
<th>Women n (% of deaths)</th>
<th>Total n (% of deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>26 (46)</td>
<td>14 (47)</td>
<td>40 (46)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>8 (14)</td>
<td>4 (13)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (14)</td>
<td>7 (23)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Ruptured aortic aneurysm</td>
<td>5 (9)</td>
<td>0 (0)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>2 (4)</td>
<td>2 (7)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>3 (5)</td>
<td>1 (3)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>20 (35)</td>
<td>8 (27)</td>
<td>28 (32)</td>
</tr>
<tr>
<td>Other causes</td>
<td>10 (18)</td>
<td>7 (23)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57 (100)</strong></td>
<td><strong>30 (100)</strong></td>
<td><strong>87 (100)</strong></td>
</tr>
</tbody>
</table>

Mortality in the non-participants

In the sample of non-participants (n = 62), the median follow-up time was 7.2 years (range 0.2-7.2), corresponding to 351 person-years. During the follow-up, 25 of the non-participants died. The all-cause mortality rate was significantly higher in the non-participants than in the participants (7.1 vs. 3.1 per 100 person-years, log-rank \( \chi^2 \) statistics 15.9, \( p < 0.001 \)).
Prevalence of LV systolic dysfunction (Paper I)

The prevalence rate of LV systolic dysfunction (i.e. a WMI of < 1.7) was 6.8% (95% CI 4.6-9.7, n = 28), with a significantly higher rate in men than in women (10.2% vs. 3.4%, p = 0.006).

Clinical suspicion of heart failure

In the clinical evaluation, 29 (6.7%, 95% CI 4.5-9.5) of the 433 participants were classified as having findings indicating heart failure. The prevalence rate of suspected heart failure was higher in men than in women (9.5% vs. 4.0%, p = 0.022). Of the 29 participants with suspected heart failure, the WMI could be obtained in 28, 15 of whom (54%) had LV systolic dysfunction. The prevalence rates of LV systolic dysfunction with and without a clinical suspicion of heart failure were 3.6% (95% CI 2.1-5.9) and 3.2% (95% CI 1.7-5.3) respectively. Consequently, in 46% of the participants with LV systolic dysfunction, a clinical suspicion of heart failure was absent.

Medication

Of the 28 individuals with LV systolic dysfunction, treatment with ACE-I and beta-blockers was being administered in 13 (46%) and 14 (50%) respectively. Among the 15 persons with LV systolic dysfunction combined with a clinical suspicion of heart failure, 12 (80%) and nine (60%) were on ACE-I and beta-blockers respectively. Treatment with ACE-I and beta-blockers was being administered in one (8%) and five (39%) respectively of the 13 individuals with LV systolic dysfunction combined with no clinical suspicion of heart failure.

Factors associated with LV systolic dysfunction

Table 5 shows some characteristics of the participants according to the presence or absence of LV systolic dysfunction. Previous history of myocardial infarction was very frequent in participants with LV systolic dysfunction (79%), but it was fairly infrequent in those without it (5%). Other co-morbidities significantly associated with LV systolic dysfunction were angina pectoris, hypertension and diabetes.

Persons with LV systolic dysfunction had significantly more frequent major ECG abnormalities. Left bundle branch block was more frequent in participants with LV systolic dysfunction than in those without it (11% vs. 0.3%, p = 0.001), whereas right bundle branch block was not more frequent (3.6% vs. 3.7%, p = 0.73). ST-segment depression and ST-segment elevation had prevalence rates of 61% and 14% respectively in participants with LV systolic dysfunction, compared with 7% and 1% respectively in participants without LV systolic dysfunction (p < 0.001 for both).
Table 5. Characteristics of the participants according to the presence or absence of LV systolic dysfunction (LVSD): univariate analysis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LVSD present no./total no. in subgroup (%)</th>
<th>LVSD absent no./total no. in subgroup (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>21/28 (75)</td>
<td>184/384 (48)</td>
<td>0.006</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4/28 (14)</td>
<td>40/384 (10)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>23/28 (82)</td>
<td>56/378 (15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22/28 (79)</td>
<td>18/383 (5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>14/28 (50)</td>
<td>39/383 (10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13/27 (48)</td>
<td>103/383 (27)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6/27 (22)</td>
<td>27/384 (7)</td>
<td>0.015</td>
</tr>
<tr>
<td>Valvular abnormality</td>
<td>3/28 (11)</td>
<td>14/384 (4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Clinical suspicion of heart failure</td>
<td>15/28 (54)</td>
<td>13/384 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Major ECG abnormalities</td>
<td>27/28 (96)</td>
<td>78/380 (21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5/28 (18)</td>
<td>16/382 (4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>4/28 (14)</td>
<td>15/380 (4)</td>
<td>0.034</td>
</tr>
<tr>
<td>Abnormal Q-wave</td>
<td>6/28 (21)</td>
<td>9/380 (2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ST-segment change</td>
<td>19/28 (68)</td>
<td>30/380 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>20/28 (71)</td>
<td>38/380 (10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>9/28 (32)</td>
<td>12/380 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)†</td>
<td>108 (74-173)</td>
<td>25 (13-47)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

†Values are median (IQR)

In a multivariable logistic regression model, myocardial infarction (OR = 64.3, 95% CI 9.7-426.0, p < 0.001), BNP (increase by 100 pg/ml, OR = 4.9, 95% CI 1.5-15.8, p = 0.008), major ECG abnormalities (OR = 16.5, 95% CI 1.8-155.3, p = 0.014), and a clinical suspicion of heart failure (OR = 7.1, 95% CI 1.1-45.3, p = 0.039) remained as independent predictors of LV systolic dysfunction.

Consequently, in this community-based sample of 75-year-olds, LV systolic dysfunction was prevalent in 6.8%. The condition was three times more common in men than in women. In 46% of the persons with LV systolic dysfunction there was no clinical evidence of heart failure.
BNP and ECG in screening for LV systolic dysfunction (Paper II)

There was a considerable overlap of BNP plasma concentrations between persons with and persons without LV systolic dysfunction (Figure 3). The median BNP concentration was 108 pg/ml (IQR 74-177) in persons with LV systolic dysfunction and 25 pg/ml (IQR 13-47) in persons without the condition (p < 0.001).

Figure 3. Distribution of BNP plasma concentration in the 75-year-old men and women with or without LV systolic dysfunction (LVSD).

Construction of cut-off values for BNP

The area under the ROC curve for the plasma concentration of BNP in screening for LV systolic dysfunction was 0.88 (95% CI 0.80-0.96), with no significant difference between men and women (0.86 vs. 0.93, p = 0.20). Among possible cut-off values, the ROC analysis (through a 10-fold cross-validation) showed that a BNP of > 28 pg/ml gave the highest specificity rate at a sensitivity rate of > 95% when it came to detecting LV systolic dysfunction. The highest accuracy rate was achieved with a BNP plasma concentration of > 73 pg/ml. Of the 407 participants, 197 (48.4%) had a BNP of > 28 pg/ml and 64 (15.6%) a BNP of > 73 pg/ml.

Diagnostic characteristics of BNP and ECG

A BNP plasma concentration of > 28 pg/ml showed a slightly lower sensitivity rate (0.93) than major abnormalities in the ECG (0.96) in detecting LV systolic dysfunction (Table 6). The specificity rate was considerably higher for the ECG. The higher cut-off level for the BNP (i.e.
> 73 pg/ml) exhibited a higher specificity rate but failed to detect six (21%) of the 28 participants with LV systolic dysfunction. With a BNP cut-off value of > 28 pg/ml, the men had sensitivity and specificity rates and negative and positive predictive values (95% CI) of 0.91 (0.71-0.97), 0.56 (0.49-0.63), 0.98 (0.93-1.00) and 0.19 (0.13-0.28) respectively. The corresponding values for the women were 1.00 (0.65-1.00), 0.54 (0.47-0.61), 1.00 (0.97-1.00) and 0.07 (0.04-0.14) respectively.

Table 6. Diagnostic characteristics of the 12-lead ECG and BNP in screening for left ventricular systolic dysfunction in the 75-year-old men and women (n = 407).

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ECG abnormalities*</td>
<td>0.96 (0.82-0.99)</td>
<td>0.79 (0.75-0.83)</td>
<td>1.00 (0.98-1.00)</td>
<td>0.26 (0.18-0.35)</td>
</tr>
<tr>
<td>All ECG abnormalities</td>
<td>0.96 (0.82-0.99)</td>
<td>0.69 (0.64-0.73)</td>
<td>1.00 (0.98-1.00)</td>
<td>0.18 (0.13-0.26)</td>
</tr>
<tr>
<td>BNP &gt; 28 pg/ml†</td>
<td>0.93 (0.77-0.98)</td>
<td>0.55 (0.50-0.60)</td>
<td>0.99 (0.97-1.00)</td>
<td>0.13 (0.09-0.19)</td>
</tr>
<tr>
<td>BNP &gt; 73 pg/ml‡</td>
<td>0.79 (0.60-0.90)</td>
<td>0.89 (0.85-0.92)</td>
<td>0.98 (0.96-0.99)</td>
<td>0.34 (0.24-0.47)</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide, ECG = electrocardiogram, NPV = negative predictive value, PPV = positive predictive value.

*Major ECG abnormalities defined as atrial fibrillation, left or right bundle branch block, abnormal Q-wave, ST-segment change, or T-wave inversion.

†Cut-off value defined as best specificity at a sensitivity of > 0.95 from ROC analysis (derived and tested in a 10-fold cross-validation).

‡Cut-off value defined as best accuracy from ROC analysis (derived and tested in a 10-fold cross-validation).

Among the 302 participants without major ECG abnormalities, only one had LV systolic dysfunction (Table 7). Of the participants with major abnormalities in the ECG, the prevalence rate of LV systolic dysfunction was higher in participants with BNP plasma concentrations of > 28 pg/ml than in those with concentrations of ≤ 28 pg/ml (35% vs 3%, difference 32, 95% CI of the difference 16-44).
Table 7. Probability of LV systolic dysfunction in different combinations of findings in the resting 12-lead ECG and BNP in the 75-year-old men and women (n = 407).

<table>
<thead>
<tr>
<th>Combinations of findings</th>
<th>No. with LVSD/no. with combinations of findings</th>
<th>Prevalence (%) of LVSD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ECG* + BNP ≤ 28 pg/ml</td>
<td>1/179</td>
<td>0.6 (0.1-3.1)</td>
</tr>
<tr>
<td>Normal ECG* + BNP &gt; 28 pg/ml</td>
<td>0/123</td>
<td>0.0 (0.0-3.0)</td>
</tr>
<tr>
<td>Abnormal ECG† + BNP ≤ 28 pg/ml</td>
<td>1/31</td>
<td>3.2 (0.6-16.2)</td>
</tr>
<tr>
<td>Abnormal ECG† + BNP &gt; 28 pg/ml</td>
<td>26/74</td>
<td>35.1 (25.2-46.5)</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide, ECG = electrocardiogram, LVSD = left ventricular systolic dysfunction.

*ECG normal or with minor abnormality.
†ECG with major abnormality (abnormal Q-wave, ST-segment change, T-wave inversion, left or right bundle branch block, or atrial fibrillation).

Diagnostic characteristics in participants without clinical evidence of heart failure

Of the 407 participants, 379 (93%) were classified as being free from suspicion of heart failure in the clinical evaluation and 13 of them had LV systolic dysfunction. Among the participants without suspected heart failure, major abnormalities in the ECG had sensitivity and specificity rates and negative and positive predictive values (95% CI) of 0.92 (0.72-0.98), 0.81 (0.77-0.84), 1.00 (0.98-1.00) and 0.14 (0.09-0.22) respectively, in diagnosing LV systolic dysfunction. The corresponding figures for a BNP of > 28 pg/ml were 0.85 (0.62-0.95), 0.57 (0.53-0.61), 0.99 (0.97-1.00) and 0.06 (0.04-0.10) respectively.

Consequently, the ECG was a more effective primary screening tool for LV systolic dysfunction than BNP, mainly because of better specificity. BNP had an additional diagnostic value to the ECG, but only in participants with an abnormal ECG.

MAM compared with WMI in assessment of LVEF (Paper III)

Simpson-LVEF, MAM and the WMI could be obtained in 262 (64.1%), 386 (94.4%) and 390 (95.4%) respectively of the 409 included participants. All three echocardiographic methods were applicable in 261 participants. The prevalence rates of a Simpson-LVEF of < 50% and < 40% were 11.1% (n = 29) and 6.9% (n = 18) respectively.
Agreement between echocardiographic methods

The linear correlation coefficient between MAM and Simpson-LVEF was 0.61 (p < 0.001). The linear, logarithmic, quadratic, cubic, curvilinear and exponential regression models had $R^2$ values of 0.36, 0.41, 0.43, 0.43, 0.49 and 0.39 respectively, in the relationship between MAM and Simpson-LVEF. The equation for the curvilinear model thus had the highest $R^2$ and was therefore used to calculate MAM-LVEF.

In the relationship between the WMI and Simpson-LVEF, the linear correlation coefficient was 0.83 (p < 0.001) and the linear, logarithmic, quadratic, cubic, curvilinear and exponential regression models had $R^2$ values of 0.69, 0.65, 0.70, 0.72, 0.67 and 0.77 respectively. The exponential regression model thus gave the highest $R^2$ value and was therefore used to calculate WMI-LVEF.

In the Bland-Altman analysis, the mean difference between the calculated MAM-LVEF and Simpson-LVEF was $-2.4 \text{ LVEF}\%$ (SD = 7.9), yielding limits of agreement (mean difference ± 1.96 SD) from $-17.8$ to $+13.1$ (Figure 4A). The mean difference between the calculated WMI-LVEF and Simpson-LVEF was $0.3 \text{ LVEF}\%$ (SD = 6.4), giving limits of agreement from $-12.3$ to $+12.9$ (Figure 4B).

Figure 4. Analysis of agreement between the LVEF according to Simpson’s rule (Simpson-LVEF) and the LVEF calculated from (A) mitral annulus motion (MAM-LVEF) and (B) wall motion index (WMI-LVEF) (n = 261).
Ability to predict a Simpson-LVEF below a certain value

The areas under the ROC curves for MAM and WMI when predicting a Simpson-LVEF of < 50% were 0.892 and 0.998 respectively. The difference between the areas was 0.106 (95% CI of the difference 0.062-0.149). When predicting a Simpson-LVEF of < 40%, the areas of the ROC curves for MAM and WMI were 0.955 and 0.998 respectively, with a difference of 0.043 (95% CI of the difference 0.017-0.069).

The values for MAM with the highest inter-rater agreement (Cohen’s kappa) to detect participants with a Simpson-LVEF of < 50% and < 40% were 10 mm and 9 mm respectively. When it came to the WMI, the corresponding values were 2.0 and 1.7 respectively. The ability of MAM and WMI to predict a Simpson-LVEF of < 50% and < 40% respectively is shown in Table 8.

Table 8. The ability of mitral annulus motion (MAM) and wall motion index (WMI) to predict participants with a left ventricular ejection fraction (LVEF) of < 50% and < 40% (n = 261).

<table>
<thead>
<tr>
<th>LVEF &lt;50%</th>
<th>Optimal cut-off values</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAM &lt;10 mm</td>
<td>0.48 (0.31-0.66)</td>
<td>0.98 (0.95-0.99)</td>
<td>0.94 (0.90-0.96)</td>
<td>0.74 (0.51-0.88)</td>
<td></td>
</tr>
<tr>
<td>WMI &lt;2.0</td>
<td>1.00 (0.88-1.00)</td>
<td>0.98 (0.95-0.99)</td>
<td>1.00 (0.98-1.00)</td>
<td>0.85 (0.70-0.94)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEF &lt;40%</th>
<th>Optimal cut-off values</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAM &lt;9 mm</td>
<td>0.72 (0.49-0.88)</td>
<td>0.99 (0.97-1.00)</td>
<td>0.98 (0.95-0.99)</td>
<td>0.87 (0.62-0.96)</td>
<td></td>
</tr>
<tr>
<td>WMI &lt;1.7</td>
<td>0.94 (0.74-0.99)</td>
<td>0.99 (0.97-1.00)</td>
<td>1.00 (0.98-1.00)</td>
<td>0.90 (0.69-0.97)</td>
<td></td>
</tr>
</tbody>
</table>

NPV = negative predictive value, PPV = positive predictive value.

Thus, MAM was poorly correlated with Simpson-LVEF, with wide limits of agreement. In contrast, the WMI had a better correlation and narrower limits of agreement. The ability to predict a pre-specified Simpson-LVEF value was more favourable with WMI than with MAM.

MAM as a predictor of mortality (Paper IV)

The median follow-up time for the 408 participants included in the study was 7.2 years (range 0.5-7.2). During follow-up, 83 of the 408 participants died (rate 3.1/100 person-years) and 26 (rate 1.0/100 person-years) of these deaths were from cardiac causes.
Unadjusted mortality risk
The all-cause mortality rate for participants within the first decile of baseline MAM (3-9 mm) clearly diverged from the participants within the upper nine deciles (Figure 5A). There were no cardiac deaths during follow-up among the 115 persons with an MAM of > 13 mm (Figure 5B). The unadjusted Cox proportional hazard ratios for the associations between various risk factors and mortality are shown in Table 9.

Figure 5. Rates of all-cause (A) and cardiac (B) mortality according to baseline mitral annulus motion (MAM) divided into deciles. The lowest decile corresponds to an MAM of ≤ 9 mm and the upper nine deciles to an MAM of > 9 mm.

Table 9. All-cause and cardiac mortality in relation to various risk factors in the 75-year-old men and women: univariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.26</td>
<td>1.43-3.56</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.26</td>
<td>1.31-3.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.77</td>
<td>1.14-2.76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.52</td>
<td>0.76-3.04</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.81</td>
<td>0.84-3.93</td>
</tr>
<tr>
<td>IHD</td>
<td>2.14</td>
<td>1.34-3.40</td>
</tr>
<tr>
<td>WMI (increase of 0.1)</td>
<td>0.89</td>
<td>0.84-0.94</td>
</tr>
<tr>
<td>MAM</td>
<td>0.86*</td>
<td>0.81-0.92</td>
</tr>
</tbody>
</table>

Values are unadjusted Cox proportional hazard ratios (HR) and 95% confidence intervals (95% CI).

IHD = ischemic heart disease; MAM = mitral annulus motion; WMI = wall motion index.

*Decrease of 100 mm⁻¹ (reciprocal transformation of MAM)
†Increase of 1 mm (linear version of MAM)
The all-cause mortality rates for participants with an MAM ≤ 9 mm and an MAM of > 9 mm were 8.0 and 2.6 per 100 person-years respectively (log rank \( \chi^2 \) 21.9, \( p < 0.001 \), Figure 6A). The corresponding cardiac mortality rates were 4.6 and 0.6 per 100 person-years respectively (log rank \( \chi^2 \) 37.5, \( p < 0.001 \), Figure 6B).

![Figure 6. Kaplan-Meier plot showing cumulative all-cause (A) and cardiac (B) mortality according to baseline mitral annulus motion (MAM).](image)

**Independent predictors of mortality risk**

Gender, current smoking, hypertension, atrial fibrillation and ischemic heart disease fulfilled the inclusion criterion (i.e. p-values < 0.20 in the univariate Cox proportional hazard ratio analysis) to be retained in the basic model for all-cause mortality. Hypertension, diabetes, current smoking and ischemic heart disease were retained in the basic model for cardiac mortality. When analysed separately in the basic multivariable models, MAM and WMI independently predicted both all-cause and cardiac mortality (Table 10). The combined inclusion of MAM and WMI excluded them both as independent predictors of all-cause mortality. However, MAM remained as an independent predictor, when analysed jointly with the WMI in the basic model for cardiac mortality.

MAM thus predicted the all-cause and cardiac mortality independently of other potential risk factors. When it came to cardiac mortality, this predictive ability was also independent of LV function measured as the WMI.
Table 10. Multivariable Cox proportional hazard models for all-cause and cardiac mortality in the 75-year-old men and women.

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Cardiac mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic model + MAM</td>
<td>Basic model + WMI</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAM (per 100 mm(^{-1}) decrease)</td>
<td>0.91</td>
<td>0.85-0.98</td>
</tr>
<tr>
<td>WMI (per 0.1 increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAM (per 1 mm increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMI (per 0.1 increase)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are Cox proportional hazard ratios (HR) and 95% confidence intervals (95% CI).
IHD = ischemic heart disease; MAM = mitral annulus motion; WMI = wall motion index.
Discussion

Prevalence of LV systolic dysfunction
LV systolic dysfunction was a common finding in our study population (Paper I). The overall prevalence was 6.8% and it was three times higher in men than in women. In 46% of the participants with LV systolic dysfunction, there was no clinical suspicion of heart failure. In echocardiographic community-based studies, the reported prevalence rates of LV systolic dysfunction have varied between 1.8-11.3% (Table 11).20,22,25,132-136 The variation in prevalence rates can be explained primarily by four factors: the selection of the study population, the response rate of the invited population sample, the echocardiographic method and the choice of cut-off values.

Study population
The age of the selected study population is a strong determinant of the occurrence of LV systolic dysfunction. We aimed to investigate a well-defined, community-based group of individuals with an age relevant to the clinical reality. The relevance of selecting persons who are 75 years old is supported by the finding that the median age at presentation of heart failure was 76 years in a study investigating the incidence of heart failure in a London suburb.35 Numerous studies have shown that the prevalence rate of LV systolic dysfunction rises with increasing age (Table 11).22-25,134,135 McDonagh et al. reported a prevalence rate of 5.6% in the oldest subgroup (65-74 years) in a community-based study from Glasgow.22 In subgroups 65-74 and 75-84 years of age, Davies et al. found prevalence rates of 2.9% and 3.7% respectively.25 Identical to our finding, a prevalence of 6.8% was found in the subgroup aged 70-79 reported by Raymond et al.135

One common feature of the summarised studies in Table 11 is the gender difference, with the male prevalence of LV systolic dysfunction being at least twice and up to seven times as high as that of the female prevalence.
Table 11. The prevalence of LV systolic dysfunction and the prevalence of LV systolic dysfunction without clinical evidence of heart failure: echocardiographic community-based, cross-sectional studies.

<table>
<thead>
<tr>
<th>Country (authors)</th>
<th>n</th>
<th>Mean age (range)</th>
<th>Definition of LVSD</th>
<th>Prevalence of LVSD (%)</th>
<th>Prevalence of LVSD without heart failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (McDonagh et al.)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1467</td>
<td>50 (25-74)</td>
<td>LVEF &lt; 0.30 (BpS)</td>
<td>4.0 2.0 2.9 1.4</td>
<td></td>
</tr>
<tr>
<td>Spain (Cortina et al.)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>351</td>
<td>60 (&gt; 40)</td>
<td>LVEF &lt; 0.50 (Tz)</td>
<td>- - 3.1 1.1</td>
<td></td>
</tr>
<tr>
<td>USA (Devereux et al.)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>3184</td>
<td>61 (45-74)</td>
<td>LVEF &lt; 0.40 (Tz)</td>
<td>4.7 1.8 2.9 -</td>
<td></td>
</tr>
<tr>
<td>UK (Davies et al.)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>3960</td>
<td>61 (&gt; 45)</td>
<td>LVEF &lt; 0.40 (MpS, Ve)</td>
<td>3.0 0.7 1.8 0.9</td>
<td></td>
</tr>
<tr>
<td>USA (Redfield et al.)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2036</td>
<td>63 (&gt; 45)</td>
<td>LVEF ≤ 0.40 (Ve)</td>
<td>3.6 1.0 2.0 1.0</td>
<td></td>
</tr>
<tr>
<td>Netherlands (Mosterd et al.)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2267</td>
<td>66 (55-95)</td>
<td>FS ≤ 0.25</td>
<td>5.5 2.2 3.7 2.9</td>
<td></td>
</tr>
<tr>
<td>USA (Gottdiener et al.)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>5532</td>
<td>- (&gt; 65)</td>
<td>LVEF &lt; 0.45 (Ve)</td>
<td>5.9 1.8 3.5 2.5</td>
<td></td>
</tr>
<tr>
<td>Denmark (Raymond et al.)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>764</td>
<td>- (50-89)</td>
<td>LVEF ≤ 0.40 (WMIc)</td>
<td>7.6 2.6 4.7 1.6</td>
<td></td>
</tr>
<tr>
<td>Sweden (present study)</td>
<td>412</td>
<td>75 (75)</td>
<td>WMI &lt; 1.7</td>
<td>10.2 3.4 6.8 3.2</td>
<td></td>
</tr>
<tr>
<td>UK (Morgan et al.)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>817</td>
<td>76 (70-84)</td>
<td>At least mild (Ve)</td>
<td>12.8 2.9 7.5 2.6</td>
<td></td>
</tr>
<tr>
<td>Finland (Kupari et al.)&lt;sup&gt;36&lt;/sup&gt;</td>
<td>476</td>
<td>80 (75-86)</td>
<td>FS ≤ 0.25</td>
<td>- - 11.3 9.0</td>
<td></td>
</tr>
</tbody>
</table>

BpS = biplane Simpson method, FS = fractional shortening, LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, MpS = monoplane Simpson method, Tz = Teichholz method, Ve = visual estimation, WMIc = calculated from wall motion index
Response rate

The response rate in our study was reasonably high (70.1%). However, the drop-outs may have led to an underestimation of the prevalence rate of LV systolic dysfunction, as it is conceivable that diseased people are less likely to participate. Although the rate of self-reported cardiovascular diseases did not differ between the participants and the sample of non-participants, there were significantly more current smokers and self-reported diagnoses of emphysema among the non-participants. In addition, the all-cause mortality rate was significantly higher among the sample of non-participants in comparison to the participants. In the light of these facts, it is likely that the prevalence of LV systolic dysfunction in the present study is a lower bound estimate.

In the summarised prevalence studies in Table 11, the response rates (where available) varied from 47% to 88%. It is conceivable that some of the variation in the prevalence rates of LV systolic dysfunction could be explained by differences in response rates.

Echocardiographic methods

A range of echocardiographic methods is being used in clinical practice and research to describe LV systolic function. One commonly used index is the volume-based LVEF, which can be obtained in a number of different ways. The disc summation method based on Simpson’s formula has been recommended as the method of choice, when LVEF is obtained by echocardiography for research purposes.53 In the majority of previous prevalence studies, the Simpson-LVEF was not used as the primary index to define disease. High dependence on image quality in the apical views, resulting in missing observations, and the considerable time required for examination are possible explanations for the low use of Simpson-LVEF. In our population, Simpson-LVEF was possible to obtain in 65% of the participants.

Visual estimation of the LVEF, as used in several of the prevalence studies, and the WMI, as used in our study, are methods that are less dependent on image quality and faster to perform than the disc summation method. On the other hand, visual estimation of the LVEF and wall motion scoring are considered to be less objective methods, with a higher degree of dependence on the executor. Nonetheless, these methods have been shown to have a diagnostic performance similar to Simpson-LVEF, when compared with RNA or contrast ventriculography.59

Fractional shortening and LVEF according to Teichholz are echocardiographic methods based on M-mode measurements restricted to basal points of the LV anterior and posterior walls. In the presence of regional wall motion abnormalities these methods are not reliable in estimating global LV systolic function.137
Cut-off values
Different cut-off values in the definition of LV systolic dysfunction are an obvious explanation for differences in prevalence rates between various studies. However, between centres, even the same cut-off value can correspond to different levels of LV systolic dysfunction. Findings have been reported, indicating systematic differences between centres in echocardiographic measurements of LVEF, suggesting a need for locally defined reference values.\textsuperscript{138} These findings are supported by the considerable difference in mean LVEF derived in our reference subgroup and in a subgroup free from apparent cardiovascular disease in a Glasgow survey\textsuperscript{22} (mean LVEF 62\% vs. 48\%). In the Glasgow study, an LVEF cut-off value of 30\% was used to define LV systolic dysfunction, which corresponded to approximately 3 SD below the mean in their reference group. In comparison, 3 SD below the mean in our reference subgroup corresponded to an LVEF of 43\%.

Screening for LV systolic dysfunction
LV systolic dysfunction is a common and treatable precursor of heart failure. In community-based data, 35-80\% of subjects with LV systolic dysfunction have been reported to be asymptomatic.\textsuperscript{20,22-25,132-136} Community-based screening for asymptomatic LV systolic dysfunction has been suggested as a potential strategy to reduce the incidence of heart failure.\textsuperscript{139} In our study population, the prevalence rate of LV systolic dysfunction in combination with clinical evidence of heart failure was 3.6\% This symptomatic condition is obviously found and treated without any screening programmes, as indicated by the fairly high rate of ACE-I treatment (80\%, n = 12) in this subgroup. In contrast, if not screened for, the majority of the 3.2\% of the study population who were found to have LV systolic dysfunction without suspicion of heart failure (corresponding to asymptomatic LV systolic dysfunction) would probably have lost the chance of early treatment with prognostic advantages - in this subgroup only one person (8\%) was on ACE-I treatment.

Echocardiography is an accepted, and the most commonly used, method to reach a definitive diagnosis of LV systolic dysfunction. However, because of low availability and relatively high costs, echocardiography will probably never be a cost-effective primary screening tool for LV systolic dysfunction in community-based populations. We evaluated the resting 12-lead ECG in comparison with the plasma concentration of BNP as screening tools for LV systolic dysfunction (Paper II). The ECG was more effective than BNP as a primary screening tool, mainly because of better specificity. BNP had an additional diagnostic value, but only in participants with abnormal ECGs.
ECG as a screening tool
In previous reports, based on various patient groups, sensitivity rates and negative predictive values of at least 0.90 have been reported for the ECG in screening for LV systolic dysfunction. These studies agree with our findings, i.e. the ECG was an effective tool for excluding LV systolic dysfunction, keeping the number of false-negative cases low. In contrast, Sandler et al. reported lower sensitivity and specificity rates for the ECG in detecting LV systolic dysfunction in patients referred for echocardiography. In that study, the mean LVEF was 48% in the patients with LV systolic dysfunction, compared with 32% in our study. A higher degree of myocardial damage in the affected group could account for the higher sensitivity rate of the ECG in detecting systolic dysfunction in our study.

The Minnesota code was utilised to interpret the ECGs in the present study. The use of another coding system, such as computer-based automated interpretation, could perhaps have yielded a different diagnostic performance by the ECG. However, fully automated computer ECG interpretations have been reported to have reduced accuracy when compared with expert electrocardiographers. On the other hand, manual ECG interpretation by a cardiologist, assisted by a computer interpretation, can reduce the number of false positive readings and give better agreement with an expert electrocardiographer consensus panel.

BNP as a screening tool
The plasma level of BNP has become a useful tool in ruling out heart failure in patients presenting with dyspnea. Its role in community-based screening remains to be further clarified. In accordance with previous reports, we noticed a considerable overlap of BNP plasma concentrations between participants with and without LV systolic dysfunction (Paper II). This wide distribution could not be explained by age variations (the participants were all 75 years of age). Participants with hypertension, LV hypertrophy or atrial fibrillation were not excluded and could therefore possibly account for raised BNP levels, despite normal LV systolic dysfunction. Moreover, medication is a possible explanation for low BNP levels in persons with LV systolic dysfunction.

One consistent finding in previous community-based studies, as well as in the present study, has been high negative predictive values and low positive predictive values for BNP as a screening test for LV systolic dysfunction. This finding is not surprising, considering the high dependence of the predictive values on prevalence rate. From a public health view, LV systolic dysfunction is common, but from a screening perspective the prevalence is low. Even if a screening test would yield fairly high sensitivity and specificity rates, a low prevalence rate results in high
negative and low positive predictive values. Based on these findings, both BNP and the ECG appear to be tests that are suitable for the exclusion of LV systolic dysfunction.

Should we screen for left ventricular systolic dysfunction?

The strategy of performing community-based screening for asymptomatic LV systolic dysfunction complies with many of the necessary requirements proposed for a screening programme. The condition is a widely accepted precursor of heart failure and is therefore a pre-clinical stage of an important health problem. The natural history of asymptomatic LV systolic dysfunction is well-documented and comprises significant morbidity and mortality. In addition, the natural history contains a latent phase, rendering time for discovery and treatment before possible development to overt heart failure. There are widely accepted treatment policies for asymptomatic LV systolic dysfunction, although controlled studies regarding treatment for mild LV systolic dysfunction (LVEF 40-50%) are lacking.

However, there are still important issues to be addressed before a screening programme could be recommended. A screening strategy and its cost effectiveness have to be established. The success of a screening programme is critically dependent on the prevalence of the disorder that is being screened for. Clearly, it would not be cost effective to screen the entire population for LV systolic dysfunction. The disorder is confined to certain risk groups who are older, with evidence of ischemic heart disease. Another risk group that has recently been identified comprises patients with clinical manifestations of non-cardiac vascular diseases. In populations with high prevalence rates of LV systolic dysfunction, it is possible that direct screening with echocardiography could be a cost effective strategy. However, in less selected populations with lower prevalence rates, a simple and inexpensive screening test to target persons for echocardiographic evaluation is probably required. Our findings suggest that the 12-lead ECG, possibly in combination with BNP, is a possible alternative (Paper II). With the ECG as a primary screening tool, the number of echocardiograms in our study could have been reduced by 74% (105 instead of 407), still managing to detect 96% of the participants with LV systolic dysfunction. In an alternative scenario, if BNP analyses were to be performed on participants with abnormal ECGs and subsequent echocardiography were to be performed only on subjects with an increased BNP plasma concentration, the number of echocardiograms could be reduced by 82% (74 instead of 407). This procedure would detect 93% (26/28) of the individuals with LV systolic dysfunction.

The only definitive way to establish the benefits of a screening programme is to perform a prospective controlled randomised trial, evaluating the cost effectiveness of screening versus no screening.
question of whether screening for LV systolic dysfunction in the community is an important activity to reduce the incidence of heart failure therefore remains to be evaluated.

MAM for diagnosis and prognostics

The muscle fibre orientation of the LV is mainly longitudinal/oblique in the subendocardial and subepicardial layers and circumferential in the midwall. The motion of the mitral annulus towards the apex is due to the shortening of the longitudinal/oblique fibres. This motion can be measured by M-mode echocardiography in terms of amplitude or by tissue Doppler echocardiography in terms of velocity. The long axis shortening of the LV is a reflection of the longitudinal/oblique muscle fibre function. Acute myocardial ischaemia causes a reduction in the amplitude of long axis shortening. In patients with stable coronary artery disease, long axis shortening is often reduced, even in the absence of overt myocardial ischaemia. Furthermore, abnormal long axis function may revert to normal after successful revascularisation.

One important advantage of assessing LV systolic function by MAM amplitude is the low dependence on image quality, mainly because of the distinct echoes from the mitral annular tissue. Additionally, the method is easy to learn and demonstrates an advantageous intra- and inter-observer reproducibility. A fixed LV apex is an important assumption for the M-mode technique to be valid as a measurement of LV long axis shortening. Several authors have reported that the epicardial part of the apex is almost stationary during the heart cycle. Nonetheless, Rodriguez et al. found that the apical motion represented approximately 20% of the total LV long axis shortening in an invasive sheep model. However, they also found that MAM measured with a fixed-apex assumption was more closely correlated with a load-insensitive index of global LV systolic function than was the long axis measurement including the apical motion.

MAM in the assessment of LVEF

The most commonly used index for LV systolic function, the LVEF, is based on the volume reduction caused by both long axis and circumferential shortening of the LV. In contrast, the amplitude of MAM is not a volume-based index and it is not directly affected by the contraction of the circumferential fibres. In healthy persons, the maximum amplitude of MAM declines significantly with age. This is in contrast to the LVEF, which is largely unchanged with age. Despite these differences between the LVEF and MAM, early studies in various patient groups demonstrated a strong
correlation between MAM and LVEF. Consequently, MAM was proposed as a surrogate for the LVEF. The maximum amplitude of MAM showed a poor correlation with Simpson-LVEF in the present study (Paper III), with wide limits of agreement. In predicting a Simpson-LVEF with a pre-specified value, MAM yielded a low sensitivity as a reflection of the overestimation that MAM had in relation to Simpson-LVEF in the lower range of LVEF levels. A curvilinear equation had the best fit to describe the relationship between MAM and Simpson-LVEF in our 75-year-old men and women, which is consistent with a previous meta-analysis of 434 patients. The particular population that is selected could be a reasonable explanation of the differences in the relationships between MAM and LVEF in various studies. It is conceivable that disturbances in regional wall motion or electrical conduction have an effect on the correlation between MAM and LVEF. In a group of patients with marked LV hypertrophy, Wandt et al. demonstrated that there was no significant correlation between MAM and LVEF. A higher correlation might occur if patients with LV hypertrophy, bundle branch block or LV aneurysm were excluded.

Our findings confirm the data from other recent studies in that MAM is not interchangeable with the LVEF, suggesting that MAM should be used as a direct index of LV function as a complement to LVEF, instead of converting it to an LVEF value.

The disc summation method as a reference

We used the disc summation method according to Simpson’s formula as a reference method. RNA and cardiac magnetic resonance imaging are regarded as the in vivo “gold standard” methods for assessments of LVEF. However, because of the high costs and low availability these methods were not possible to use in the present study. Moreover, when it came to RNA, exposing a community-based sample to radiant diagnostics would have been questionable from an ethical point of view. Previous studies have reported fairly wide limits of agreement between RNA and the disc summation method in the evaluation of LVEF. However, with a few exceptions, the mean differences between these two methods were close to zero (Figure 7). For echocardiographic assessments of LVEF in clinical trials, the disc summation method is the recommended approach whenever good apical views can be obtained.

Unfortunately, the Simpson-LVEF could only be obtained in 65% of our participants because of reduced endocardial detection. The ultrasound machine in our study was not equipped with second harmonic imaging technology. This kind of technology measurably improves the quality of the two-dimensional image and probably makes it possible to obtain Simpson-LVEF in a larger number of persons.
Figure 7. Limits of agreement (mean difference ± 2 SD) between radionuclide angiography and the echocardiographic biplane disc summation method in the assessment of LVEF. Results from previous studies. *Operator no. 1. **Operator no. 2.

MAM as a predictor of mortality

The present study (Paper IV) is the first to evaluate the prognostic value of MAM in a community-based sample. MAM predicted cardiac mortality independently of other potential risk factors, including LV function measured as the WMI. Its predictive ability for all-cause mortality was similar to that of the WMI.

Previous data on MAM amplitude as a predictor of prognosis are scarce. In 181 heart failure patients with a mean age of 76 years, Willenheimer et al. reported a significant relationship between all-cause mortality and the maximum amplitude of MAM.\textsuperscript{72} In the patients with an MAM of $\geq 10$ mm and $< 10$ mm, the one-year mortality rates were 0% and 25.3% respectively. The same group recently reported that MAM was a strong predictor of mortality in a group of 271 patients with acute myocardial infarction.\textsuperscript{80}

MAM mainly arises from the contractions of longitudinally directed myocardial fibres. In contrast, the LVEF and WMI probably reflect the contractions of both longitudinal and circumferentially directed fibres. The subendocardial, longitudinal fibres are more prone to ischemic damage than the mid-wall, circumferential fibres,\textsuperscript{163} which is a basis for the speculative hypothesis that the MAM would be a more sensitive marker of prognosis than the LVEF. This hypothesis was supported by the finding that MAM, but not LVEF, was significantly related to cardiac mortality in a recent study of 333 patients with stable coronary heart disease.\textsuperscript{81} It is noteworthy that MAM,
but not the WMI, remained as an independent predictor of cardiac mortality when forced together with the WMI in the multivariable analysis in our cohort. Indeed, this finding supports the above-mentioned hypothesis, but it should be interpreted with caution. The WMI is not necessarily interchangeable with the LVEF. Although the WMI showed considerably better agreement than MAM with the Simpson-LVEF in our participants (Paper III), it is possible that the Simpson-LVEF would have performed better than the WMI in the multivariable analysis. However, the Simpson-LVEF could only be obtained in 65% of our participants, whereas the WMI was available in the vast majority. To avoid systematic misrepresentation of the population by using only 65% of the sample, we decided to use the WMI instead of the Simpson-LVEF.

The prognostic value of MAM could possibly depend on the method used to measure the longitudinal shortening. The traditional method of measuring MAM, as used in the present study, is based on the total amplitude of MAM, irrespective of the temporal appearance of the nadir and the peak excursion. A proposed new method involves measuring the amplitude in the systolic ejection phase alone. In most healthy persons, the peak excursion occurs in end systole, i.e. adjacent to aortic valve closure. However, in ischemic heart disease and in hypertensive patients with LV hypertrophy, the peak excursion can be delayed and appear after aortic valve closure. This so-called post-systolic shortening could over-rate the long axis function in diseased individuals, if measured in the traditional way. The traditional method also includes the pre-systolic atrial contraction wave, which would be excluded if MAM were only measured in the systolic ejection phase. The question of whether there is an improvement in the prognostic value when using the above-mentioned suggested new method for measuring the MAM amplitude remains to be evaluated.
Conclusions

LV systolic dysfunction was a common condition in our 75-year-old men and women. In this community-based sample, the overall prevalence rate was 6.8%. The condition was more likely to affect men than women. In nearly half the 75-year-olds with LV systolic dysfunction, there was no clinical suspicion of heart failure.

Both the ECG and the plasma concentration of BNP were highly effective in excluding the presence of LV systolic dysfunction. However, compared with BNP, the ECG yielded a considerably better specificity. In screening for LV systolic dysfunction, BNP had an additional diagnostic value to the ECG, but only in individuals with an abnormal ECG. The findings suggest that the ECG and BNP should be included as important tools in screening programmes for LV systolic dysfunction.

The performance of the WMI in estimating the LVEF was more favourable than that of MAM in our community-based sample of 75-year-old men and women. The findings suggest that the WMI is preferable to MAM in estimating the LVEF and that the conversion of an MAM estimate into an LVEF value should be avoided.

LV function, as measured by MAM, predicted the risk of all-cause and cardiac mortality independently of other potential risk factors. When it came to cardiac mortality, this predictive ability was also independent of LV systolic dysfunction measured as the WMI. MAM may prove to be a valuable method in the assessment of mortality risk in less selected populations.
Acknowledgements

I would like to express my sincere gratitude to everyone who has contributed in different ways to the work involved in this thesis.

First of all, I would like to thank the two people who followed the progression of the work most closely, Tommy Jonason and Ivar Ringqvist. Tommy, my supervisor and colleague at the Department of Clinical Physiology in Västerås, for continuously sharing your in-depth knowledge and experience, for your never-ending support and patience, for always respecting my ideas and for good friendship throughout the years. Ivar, my co-supervisor, for giving me the opportunity to discover the interesting world of clinical physiology by offering me employment a decade ago, for providing an excellent scientific environment during your years as head of the Department of Clinical Physiology, for your support, valuable discussions and constructive criticism.

Egil Henriksen, head of the Department of Clinical Physiology and co-author, for maintaining the excellent scientific environment at the department, for generously sharing your in-depth knowledge in and fascination with echocardiography, for your pioneering ideas, advice and support, especially in Paper III, and for fruitful discussions (not least on how to renovate an attic).

Göran Nilsson, co-author, for your extraordinary enthusiasm and positive attitude, for valuable discussions and respect for my ideas and for your thorough processing of the manuscripts.

Ingemar Lönnberg, co-author, for excellent collaboration. Without your impressive effort clinically to evaluate the participants in the study, it would not have been possible to accomplish this work.

Kenneth Pehrsson, co-author, for rendering your expertise in fruitful discussions and for your thorough processing of the manuscripts.

Stefan Sörensen and John Öhrvik for excellent statistical advice.

Jeanette Kliger and Leslie Shaps for excellent linguistic revision.
The staff at the Centre for Clinical Research in Västerås and especially Marie-Louise Engström, for help with data collection, for escorting the BNP samples to Glasgow and for invaluable support when it came to the preparatory formalities of this dissertation, Petra Wahlén and Marja-Leena Ojutkangas, for thorough data collection, and Jerzy Leppert, head of the centre, for valuable support.

Co-workers and colleagues at the Department of Clinical Physiology in Västerås, for all your support and encouragements and for providing a stimulating and pleasant working atmosphere.

My wife Marie and my children Johan, Ida and Amanda for being my beloved family, for all your patience and encouragement, and for reminding me of what is important in life.

Last but not least, many thanks to all the 75-year-old men and women who willingly participated in the study.

This work was supported by the County Council of Västmanland and the Västmanland research foundation against cardiovascular disease.
References


Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 39

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine").